Frail Proof

Safely Yet Reliably Optimize Your Hormones to Live a Longer, Stronger, and Healthier Life

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Questions, suggestions, and comments should be directed to feedback@frailproof.com.

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Chapter 1: Introduction

As of 2020 it was projected that up to 4% (1) of US men over the age of 40 are receiving testosterone therapy (most commonly known as Testosterone Replacement Therapy, or TRT), a percentage that has more than tripled just in the last decade and continues to increase. Even so, this represents only a small fraction of the men who could benefit from this type of treatment: Almost 40% of men begin showing symptoms of hypogonadism or "Low T" by age 45 (2).

Meanwhile the percentage of women receiving hormone therapy (most commonly known as Hormone Replacement Therapy, or HRT) has dropped by 50% over that interval and continues to decline. Extrapolating from these trends, TRT will become more common than HRT within the next few years if indeed the crossover has not already occurred. This is despite the fact that approximately 100% of women over the age of 45 could benefit from some form of this treatment.

This situation seems to me an ideal domain for a biohacking approach. Biohacking, the use of scientific and/or technological interventions to improve the functioning of the human body, is clearly human destiny: Every year new treatments are developed and more science is done that helps us know how and when to apply them. While the term technically includes bionics (things like artificial joints, pacemakers, and cochlear implants) and indeed most drugs used to treat chronic conditions, it really comes into its own when applied to individual efforts to increase one's quality or length of life, individual effort that is necessary because the medical profession has lagged behind the available science and technology. Biohacking is therefore a client-driven system where *we* are fully involved in defining and executing our treatment and our doctor's role is mostly to sanity-check our recommendations, make sure we haven't overlooked something, and to ensure that we're implementing the treatment correctly. This book will review the state of the art in the area of hormone supplementation and recommend ways to remove the practical and institutional roadblocks that are preventing much wider use, and more optimal use, of these life-altering therapies, especially for women.

While we'll touch on the usual grist for mill of the health, anti-aging, and menopausal treatment fields (diet, exercise, supplements, stress reduction, etc.), make no mistake: None of those other things can hold a candle to hormones and pharmaceuticals when it comes to actually dealing with disease and age-related decline in physical and

mental health. The path proposed here is therefore a sort of middle ground between the wishful thinking we get from proponents of "natural" treatments (which rely primarily on the placebo effect, or even just on convincing people to accept their suffering because it's "normal"), and the "Big Pharma" approach of using real science to create a patentable drug for every little thing that ails you, their ultimate goal being to have everyone taking a wide variety of expensive and side-effect inducing drugs that are designed to prolong life (thereby meeting insurance company requirements) without regard to our well-being.

The recommendations in this book were developed using a combination of peer-reviewed journal papers (references included), protocols used by specialists in this area (functional medicine, integrative medicine, and anti-aging, commonly running practices classified as "concierge telemedicine"), "broscience" (the vast collection of anecdotal reports that can be found on web sites and forums, including reports on effective dosing from transsexuals, women taking these hormones to improve fertility, in-vitro fertilization (IVF) surrogates, postmenopausal women receiving HRT, andropausal men receiving TRT, and men and women using hormones for bodybuilding), and the personal experience of the authors (my wife and myself).

Although we are not medical doctors, one of us does have a PhD (in experimental psychology) and we both have way too much time on our hands: we cashed out and retired from our main careers as software engineers and entrepreneurs in our early 40s, almost 20 years ago. These characteristics provide us with the ability to separate the wheat from the chaff in all of these published reports. Not being physicians also frees us from the constraints imposed by medical boards or the legal profession which would be quick to turn any recommendations like these into weapons in a malpractice lawsuit even if there is no scientific basis for doing so: In fundamental conflict with the design of our legal system, the real world is a probabilistic place and sometimes bad things happen without any individual or act being responsible.

Although you will need a doctor to prescribe most of the hormones recommended here, you'll probably sense a high level of skepticism, if not outright disdain, of doctors in this presentation. It's well earned: The third leading cause of death in the US is "medical errors". These are events that generally fall short of outright malpractice, but could have been prevented if either the doctor, staff, or patient was paying proper attention. The third leg of that support system is you: You have an obligation to know what your condition is, what the appropriate

treatment for it is, and whether or not you are properly receiving that treatment. My wife and I have always been relatively healthy, but even we've had a dozen examples of doctors (or more rarely nurses or other staff) making the wrong diagnosis, prescribing an inappropriate treatment, or botching the implementation of it. Our experience has been that when it comes to hormone therapies, the odds of these kinds of failures greatly increases.

There are many sources for these failures, simple incompetence being one of the most common: As is the case with any profession, there are good doctors and bad ones. Unfortunately, unlike, say, restaurants or products on amazon.com, the review system for doctors is severely broken, making it very difficult to tell in advance which kind you're working with, even if they've been "your doctor" for years and you've never had any problems before. As above, part of the problem is with the legal and malpractice insurance systems, which forces doctors to be overly conservative and resort to conventional treatments even when they aren't the state of the art (or science).

And part of it is that most doctors don't keep up with the journals in their fields and so just aren't aware of what the state of the art is. This problem is compounded by the pharmaceutical industry, which unfortunately is the major source of information for most doctors, but which is highly biased toward ever-newer treatments that are recommended not because they're best for the patient, but merely because they make more money for the drug manufacturers and distributors.

Again, the antidote for all of these things is for you to be an informed consumer of these products and services, and for you to speak up, get a second opinion, or switch doctors when you don't believe you are receiving the absolute best treatment for you. It may take a bunch of emails and phone calls to find a doctor that will work with you to optimize your health, and you might have to commute a longer distance or pay more out of pocket for one, but they're out there and worth the effort to find.

And to complete the disclaimers, you should keep in mind that unlike nearly everyone else working in this field we're not hawking a product, a seminar, or paid private consultations, nor trying to get on TV to facilitate any of the above. We do not have any direct financial interest in any company that provides the recommended products or services. The nominal prices charged for this book on Amazon are merely a practical necessity to qualify for the full support of Amazon's marketing and distribution system. Free versions of the book and the appendices are currently available on https://www.frailproof.com/, but note that we reserve the right to withdraw these free versions if a

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Frailproof.com is not a business, nor even one of our main extracurricular activities. Our goals are primarily altruistic (we want you to have the best life that you can), although we would confess to being motivated by one tiny bit of self-interest: The more people who join us in using these protocols, the easier and cheaper it will be for us to continue to use them. We also hope to build up political capital to be used to protect and promote our continued use of these protocols should medical boards or regulatory agencies come after the doctors or pharmacies we need.

This book is primarily composed of specific recommendations and the justifications for them with relatively little of the "filler" (general background information, personal anecdotes, encouragement/commiseration, etc.) that is used to bulk up books from mainstream publishers so that they'll look good on the shelves of a bookstore or library. If you want or need that other stuff, we've included mini-reviews of the most popular menopause and anti-aging books on Amazon in an appendix to help guide you. But note that none of them are cited as references in this book which gives you some idea as to our overall opinion of their value: All of the references in this book are to papers in peer-reviewed journals and include HTTP links: You are strongly encouraged to at least try to read the source material in areas of particular concern.

This book is structured as a series of rules followed by the justification and implementation suggestions for each. In the spirit of biohacking, which is at its heart an engineering rather than a scientific discipline, the implementation details provided here are more like what you'd call "guidelines" than actual rules. Like any other type of engineering there are certain techniques and calculations that are standards, but oftentimes customization is required to make the protocol better fit the situation at hand.

Chapter 2: The philosophy

Hormone optimization is not the same thing as hormone replacement.

The philosophical goal of TRT is merely to raise levels until any symptoms of low testosterone are alleviated. The same symptom-alleviation goal is also generally true of HRT for women. With optimization, a more suitable domain for biohacking, the goal is to increase levels until the maximum benefits (improved physical fitness and condition (skin, bones, hair, muscles), mood, libido and sexual performance, etc.) without incurring significant side effects (water retention, acne, increased risk of cardiovascular disease or cancer, etc.). For sex hormones this generally means blood serum levels near the top of the "normal" range reported on the lab tests (for women, averaged over the monthly menstrual cycle). While TRT dosing is typically in the range of half the optimization dose, HRT dosing is typically 25% or less of the optimization dose, which in turn is only a fraction of the peak levels experienced by younger women at various points in their menstrual cycles or when pregnant.

Another key distinction here is between physiological and pharmacologic dosing, the former leading to serum levels around the "normal" average (albeit the average is usually calculated using the levels from a wide range of ages), and the latter being anything above that. Hormone "replacement" is (at most) the realm of the former, "optimization" generally being the latter.

Hormone therapy is not "natural", but then neither is living to age 50.

We are a species that has evolved to meet the requirement that individuals only need to survive until their 40s: Just long enough to reproduce and maybe help take care of the grandkids until they're old enough to fend for themselves. There is a minor selected-for bonus for having a few extra years at the end to transfer the skills and knowledge we have gained over our lifetimes to our descendants. Note that apes, and therefore presumably our common ancestors, don't need to do this which is why apes don't undergo menopause.

Women in prehistoric societies didn't even have to worry as much about taking care of their own children in their 40s because they

underwent menopause significantly earlier than modern women do: Depending on their health and available resources, as early as their late 30s. Being pregnant at 40 in a subsistence-level society would be extremely risky, and death in childbirth an enormous waste of scarce resources. Evolution therefore provided those extra few years for "information transfer" in those environments by initiating menopause earlier.

The upshot of all of this is that if you do anything to ensure that you live beyond your 40s you are essentially gaming the system, evolutionarily speaking. Any argument that taking hormones is somehow unacceptable because it's "unnatural" should be treated with the same disdain as if someone asked you to stop brushing your teeth, taking any sort of dietary supplement, exercising (at least when you're not out gathering food or skirmishing with a neighboring band/tribe), eating a balanced diet instead of whatever you crave or have access to at the moment, or reading about ways to improve your health, all of which are equally unnatural. All of these techniques therefore fall squarely in the realm of biohacking.

Your body evolved to function best with relatively high levels of hormones, the levels we have in our 20s and 30s. Because almost all of our prehistoric ancestors were dead by their late 40s, what happens to our bodies after that age generally wasn't subject to evolutionary selection at all. The result is that we older people haven't benefited from any of the optimization that evolution can provide. This being the case the only reasonable approach, indeed the only "natural" approach, is to try to retain as much of the function our bodies had during our 20s, a goal that *requires* supplementation of hormones, in most cases by the time we reach our mid-40s. To not use them is to accept "deficiency" as the normal state of being.

A similar argument also applies when discussing "replacement" vs. "optimization" protocols: It's important to keep in mind that when discussing potential treatments with your doctor that this is a philosophical issue, not a medical or safety issue. If your doctor is not on board with the "optimization" philosophy and that's what you want (or indeed need), in most cases there's no point in engaging in a philosophical debate. Your best option is to find, and if need be pay out of pocket for, a doctor who has embraced the philosophy that medical intervention to slow the physiological decline associated with aging is appropriate.

The appropriate criteria for assessing medical treatment relate to quality of life, not quantity.

Imagine you're 80 years old and are offered the choice of two treatment protocols. Under protocol 1 you will (continue to) lose strength and will soon be confined to a wheelchair. By 85 (on average) you will be bedridden with the TV, your caregiver, and your bedsores as your only companions. You'll live until you're 90 (on average) under these conditions, then probably die in a hospital after hundreds of thousands of dollars have been spent trying to keep your frail body alive.

Under protocol 2 you will *gain* strength and mobility, look and feel younger, and have much improved sexual performance, but will die by age 85 (on average), possibly of cancer or a heart attack, but more likely by being hit by lightning while out playing golf, contracting an exotic disease while traveling in Africa, being hit by a car while riding your bike, or falling into a volcano you just had to see up close, ground tremors be damned. Which protocol would you chose?

Nearly everyone would chose protocol 2, and yet the guidelines of all the major medical organizations are formulated such that protocol 2 is essentially prohibited. In fact it's rare that testing protocols for treatments even *measure* quality of life, let alone assign it to be the primary objective. Instead, reducing "all causes" mortality is set as the primary goal, with quality of life or even patient preference being of little concern.

But our current situation is actually worse than that: There is no quality evidence that hormone therapy, when carried out properly, does in fact shorten life. Certainly the fiasco that was the Women's Health Initiative (WHI) study that almost single-handedly resulted in an over 50% drop in HRT use over the last decade can be completely discounted: They used the wrong doses (too low) of the wrong hormones (they only evaluated oral synthetics, and omitted testosterone) on an inappropriate population (most were overweight or obese, half were current or former smokers (3)) and then used the wrong criteria to judge the results (they completely discounted the minimal quality of life information that they collected and they never even asked the women about their preferences). Indeed, they piled insult on top of injury by prematurely discontinuing the HRT arm of that trial even though their own data showed that it *reduced* all causes mortality, at least for hysterectomized women, albeit with increases in some particular causes (4).

If you won't optimize your hormones for yourself, do it for those who will be responsible for your care if you don't.

Some of the most effective advertising for diabetes drugs and in anti-smoking campaigns plays off of parents' concern for their children: Take care of yourself so that you can be there for your children. The same philosophy should apply as you get older: You have an obligation to your children (and indeed the rest of us) to take care of yourself so that you don't become a burden on us. Choosing the "natural" path of constant decline to decrepitude is therefore an act of self-indulgence morally equivalent to refusing to quit smoking or insisting on riding your motorcycle without a helmet. While the same claim could be made to many other "lifestyle choices" the case of aging is different because there is not even any addiction or natural drive (as is the case for eating) that might be difficult for you to fight. Choosing to forgo treatment for hormone deficiency is purely a matter of ignorance or laziness (i.e., aging isn't a "lifestyle choice" at all and so not something that the rest of us are obligated to allow you the freedom to enjoy without our nagging you to take better care of yourself). Low level supplementation is even covered by insurance in most cases, removing the financial burden, although it may be some time before full optimization-level protocols are covered by insurance.

Sex hormones are only part of the health optimization process which for most people will also include at least measuring and if necessary correcting for suboptimal serum levels other hormones such as insulin, thyroid, and vitamin D (which is actually a hormone, not a vitamin), nutrients (vitamins and minerals), and dealing with other health and lifestyle issues (diet, exercise, stress, being overweight, high blood pressure, blood lipids, sleep apnea, smoking, etc.)

For example, if you've got a TSH over 2.0 and *any* of the symptoms of hypothyroidism (and the list is quite impressive, including fatigue, weakness, weight gain or increased difficulty losing weight, coarse or dry hair, hair loss, dry or rough or pale skin, brittle nails, cold intolerance or cold extremities, muscle cramps or aches, constipation or irregular bowel movements, depression, irritability, memory loss or confusion, and decreased libido) you need to have a

full thyroid workup and most likely some sort of supplemental thyroid hormone therapy. Since few doctors who are not anti-aging or functional medicine specialists will do this with a TSH less than 3.0 (many won't even do this with a TSH up to 4.5, some even higher!), you need to take responsibility for learning about the condition (see the appendix for references) and seeking out a doctor who will properly treat it. And this doesn't even address the fact that TSH is a crude and, in our considered opinion, obsolete way to assess thyroid function: I only include it in this rule because it is still the "standard of care" for most doctors, and the only test most of them will order as part of an annual physical. More on thyroid dosing below, in the section on lab testing.

Same rule applies if you've got an A1c over 5.7 (indicating prediabetes) and yet haven't been prescribed metformin. Most doctors won't do this, even though the current NIH "guiding principles" document on diabetes now recommends it (5). Metformin has lately taken on the aura of a miracle cure or preventative for a wide variety of diseases including many different forms of cancer, making taking it even if you don't have high A1c a reasonable thing to do. But it's pretty much a no-brainer if your A1c is elevated.

High blood lipids (cholesterol) can be dangerous, but using blood tests to diagnose or tune treatment is at best a very crude tool: Many people with normal lipid levels have heart attacks or strokes, and many people with high lipids are actually not at elevated risk and so should not be treated. Especially not with statins which can cause a wide range of other dysfunctions, including reducing testosterone (i.e., they're a whack-a-mole treatment, where taking one drug causes a problem that requires yet another treatment to address).

Instead, the gold standard for risk assessment is a Coronary Artery Calcium (CAC) scan, preferably one done with an Electron Beam Tomography machine which has much higher precision and yet only exposes the subject to a fraction of the radiation of a conventional CAT scanner. If neither of these is available to you or the cost is prohibitive, a carotid artery ultrasound is a reasonable second choice: Because these tests measure actual plaque buildup rather than relying on imperfect correlations, they're much more reliable predictors of who is actually at risk. If your doctor remains concerned about high lipid levels or hypertension (high blood pressure), only consider treatment for those *after* you've got any hormone deficiencies squared away: Hormone supplementation interacts with both blood pressure and lipid levels and you may not need to treat either of them if hormone levels are returned to healthy levels.

As for sleep apnea, it's a hidden epidemic, with significant consequences for those who suffer from it, including many of the symptoms of hypothyroidism (and indeed hypothyroidism itself!), high blood pressure, and teeth grinding or loose teeth. Hormone supplementation, because it facilitates deeper and more restful sleep, can cause or worsen apnea.

While the gold standard for diagnosis is a sleep study, those can cost over $1000 USD and are often not covered by insurance. Fortunately there are inexpensive biohacks for this. The easiest diagnostic aid is if a partner says you snore, stop breathing, grind your teeth, or thrash around during sleep. Another easy first step is a snore-assessment app (for your smartphone or tablet), such as "SnoreLab": If you're in the "green" on that, you probably don't have apnea. In the yellow or above, you'll need an oxygen monitor test to confirm the diagnosis, or to move directly to treatment.

Inexpensive recording pulse oximeters are available that in our experience give comparable results to sleep studies done by medical professionals (and at a small fraction of the cost, and you can repeat the tests and share the device with friends or family members so that they can check themselves). If using one of these confirms apnea or if you decide to skip getting a firm diagnosis, the next step is to try a mandibular adjustment device (MAD), commonly known as an antisnore mouthpiece or mouthguard. There are a wide range of these, which fortunately matches up to the very wide range of individual differences in mouth size and shape. A money-back guarantee is a very useful feature of these: You will probably have to try several to find the one that works best for you. Unfortunately if none of them solve the problem, you're left with far more expensive and intrusive options (custom-fit MADs, oxygen concentrators, CPAP machines, surgery, etc.) which will require the participation of a licensed medical professional.

The reason it's necessary to treat all of these issues together is that there are interactions between them: The harm from not addressing any two of them may be greater than the sum of those two considered individually, and interactions between treatments designed to address symptoms (rather than actually cure or prevent the underlying condition) can lead to a never-ending process of whack-a-mole where trying to treat one thing causes something else to go wrong. While hormone therapy should not be the first step in this process, it can be a useful component of it, particularly if any of the steps require behavior modification: Testosterone in particular can help boost personality characteristics that can be of great assistance in

the very difficult task of changing habits (mood, self-esteem, persistence, "grit", etc.) (6)

While management of a wide range of additional hormones (cortisol, adrenals, HGH/IGF-1, EPO, serotonin, melatonin, etc.) and subclinical dysfunctions (particularly things like Low Dose Naltrexone (LDN) for autoimmune disorders) could potentially be part of an optimization protocol, there is a definite priority order: sorting thyroid hormones and insulin (A1c) must be the top priority, followed closely by sex hormones which must form the core of any anti-aging or optimization protocol. Only after all of the above are well managed should additional projects even be considered: In many cases these other hormone deficiencies and disorders will resolve without targeted therapy once the main hormone and lifestyle issues have been dealt with.

If a man is on hormone therapy his postmenopausal wife should be too.

It seems positively cruel to me that we currently allow or even encourage men to use hormone therapy to improve their strength, mood, libido, and sexual performance while their wives are denied these things. Are we *trying* to break up these relationships? A stable romantic relationship is key to most people's quality of life, and providing *both* partners with what they need to be fully engaged in the sexual component of that relationship would seem to me to be a practical necessity.

And why do we as a society deny this treatment? The fact that, unlike TRT trials for men, there has never even *been* a study that attempted to measure the long term effects of recreating premenopausal levels of sex hormones in postmenopausal women I think provides unambiguous evidence: Although we have made great strides in accepting nontraditional gender and sexual orientations, preserving sexuality in women into their 70s or 80s is apparently still just too big a leap for most of us to accept, especially if you consider the asymmetry between the way we treat them and men of the same age. While a 70-something year old man pairing up with a 20-something year old women might get teased about "robbing the cradle" or getting a "trophy wife", pair a 20-something year old man with an 70-something year old women and the reaction is shock, disgust, revulsion. It's been over 50 years since ***Harold and Maude*** was released, and yet the premise of that movie retains every bit of its punch.

This attitude is so ingrained and so prevalent across cultures and across generations that my theory is that it's been genetically programmed into us: A man who "sows" his seed in an older women is not just wasting his own time and effort, he's squandering a precious genetic resource that we seem to collectively believe we have an interest in preserving. Except that we don't need to do this anymore: As part of the advancement of civilization we've largely rejected this "replism": The idea that our behavior should be governed by emotions and biases programmed into us by our genes because that aided propagation of those genes in prehistory (for more on how this problem pervades all aspects of our societies, see my other project, the Matchism Manifesto).

The vicious overreaction from the medical profession to Suzanne Somers' hormone therapy proposal (a derivative of the Wiley Protocol) I believe provides another example. Even though her recommended protocols are technically flawed (as you'll see in the next chapter), they're actually very similar to the protocols used by the vast majority of those doctors who are her most vociferous critics. Their criticism of her proposals is therefore bafflingly hypocritical: They lack the very scientific proof that hormone therapies are dangerous that they claim that she doesn't have that they're safe. What's really going on here, besides the normal paternalism that is endemic among doctors, is that they're reacting at an emotional level to Somers' philosophy that women should not accept aging as inevitable and should fight it with every tool that they have.

Given the "quality over quantity" rule above, the fact that the data on the *overall* risks associated with hormone therapies are equivocal at best, and yet that there is no significant debate on the issue of their effectiveness (even the most vocal critics will concede that they work, and very well), it should be clear that the onus is on the medical profession to *prove* that they're dangerous before they deny access to them to *anyone*. To do otherwise is simply inhumane.

Of course the converse to this rule should also be a rule: A postmenopausal woman with testosterone levels restored to premenopausal levels needs a man that can keep with up her and in many if not most cases that means her husband will also need therapy.

It's never too late to start hormone therapy, or switch to this protocol.

Most prescribing guidelines propose to limit HRT to women under the age of 60 (whereas no such limits are ever applied to men). But

there is no scientific basis for these guidelines, albeit there is very little research on women starting treatment after age 60. It is not unreasonable to for a woman to start hormone therapy at age 70 or even 80, but extra care must be taken to ensure that you're starting with a clean slate (i.e., you should have a clear mammogram and uterine ultrasound, or have already had those organs removed): Properly dosed, the hormones recommended here won't cause a new cancer to form, and may indeed even prevent that, but they can stimulate an existing cancer to grow or spread.

To switch from a different hormone protocol, especially one where you have been underdosed progesterone (as indicated by having an endometrial stripe thicker than 8mm or if blood spotting has occurred), it would be a good idea to induce a period to clear out any accumulated precancerous cells. Humans (like all other mammals) can resorb endometrium, but we are relatively unusual in how thick the endometrium can become and it can take months to complete that process unless a period occurs. To induce a period, stop any current estrogen and progesterone treatment, wait a week or so for serum levels to drop, then give a single large injection of OHPC (at least 250mg/1ml, scaled by lean body mass (7)) to induce a period (8). Start this new ***FP*** (Frail Proof) Protocol after that process is complete. Note that just stopping P will likely fail to trigger a period, especially if it has been underdosed (which of course it surely has been or the endometrium wouldn't have thickened in the first place).

Chapter 3: The hormones

For men, sex hormone therapy must include at least two compounds, testosterone and hCG. For women, at least three compounds are required, analogs of estrogen, progesterone, and testosterone.

Although it is very commonly omitted, I, along with most male hormone specialists, firmly believe that hCG (human chorionic gonadotropin) is a necessary component of any sex hormone protocol for men. Without it, testosterone supplementation causes the pituitary to stop producing luteinizing hormone (LH), leading to the testis shutting down and shrinking, reduction of sperm production (reduced ejaculate), and in some cases infertility. LH also has direct effects on mood and libido. hCG is a LH analog, used instead of LH because it has a much longer half-life (LH's half-life is only about 20 minutes).

For women, it's the testosterone that is most commonly omitted, but that too has crucial roles in women's mood, libido, and sexual function, as well as having beneficial effects in strength and body composition (decreasing fat and increasing muscle mass). Testosterone production by the ovaries drops in parallel with estrogen production during menopause, leading to substantial testosterone deficiencies in most women by the time that process has completed (9).

There are many analogs of each of the three of the main sex hormones, molecules that activate the same receptors, but to different degrees and with different levels of cross-activation to other types of receptors. The body has the capability to change many of these forms into others. For example there are three natural forms of estrogen, estradiol (E2), estriol (E3), and estrone (E1), and the body can convert between them. Testosterone can be changed into estradiol, and both actually originally come from progesterone. There are many analogs of progesterone, so many that there's a separate term used to refer to them collectively: progestins (or sometimes "progestogens") (10). Without going into a master class in hormone chemistry, the take home message is that the exact analog used for supplementation matters a lot less than overall levels and what efforts are taken to manage the activation of other types of receptors and the body's

natural tendency to convert one form into another (a process generically referred to here as "metabolism").

While bioidentical forms of hormones are to be preferred when appropriate, it is crucial to recognize and discount the "appeal to nature" fallacy.

Note that when choosing among various forms of hormones, bioidentical forms are better not merely because they're "natural", but because they tend to have fewer side effects because they activate the same receptors and are processed by the same physiological pathways as endogenous (internally produced) hormones. If you read anyone promoting them over synthetic analogs based on some claim that they're "natural" without providing any scientific (evidence-based) proof, definitely just ignore them or indeed make a conscious decision to do the opposite of what they propose.

This of course also applies to anyone promoting any sort of dietary-focused protocol, especially if they recommend specific foods or "herbal" supplements that are claimed to boost hormone levels: The vast majority of time supplements are just a waste of time and money (because they are not regulated many of them contain little or none of the substance they claim to), but in significant percentage of the time they are actively harmful, either because they contain adulterants or because the source material itself is harmful because it is unrefined and so contains compounds that interfere with the "natural" functioning of the body.

Due to the need for hCG (for men), progesterone (for women), and testosterone (for both) there is only one suitable method for sex hormone therapy: injection.

There is no oral or transdermal (applied to the skin) form of hCG or any other LH analog. Enough said: Men *must* receive at least some injections to achieve hormone optimization.

Bioidentical testosterone taken orally is toxic to the liver and so should be avoided. Transdermal application of the quantities required for optimization in men requires that extremely high (irritation causing) concentrations, perhaps even blended with accelerants such as DMSO, be applied two or more times a day. As is the case for women and progesterone. Assuming transdermal even worked reliably: A view commonly expressed in the scientific literature is that topical application of hormones is simply an inappropriate therapy because

dosing is so difficult to regulate and often results in low blood serum levels, the result being that underdosing, at least periodically, is almost universal (11), (12), (13), (14), (15), (16). Which is one reason why the Wiley Protocol (which is all transdermal) and the derivative of that recommended by Suzanne Somers is problematic.

Many practitioners attempt to get around the low-serum-levels problem by using saliva or blood-spot testing, but even the creators of these tests cannot explain why blood serum levels are so much lower, nor do they even claim that underdosing is not occurring even when the hormones do show up on these other tests (17) (16). While this outcome is unfortunate in the case of testosterone, underdosing progesterone results in a vast increase in the risk of endometrial (uterine) cancer because it fails to prevent endometrial proliferation and hyperplasia (the primary, but far from only, role of progesterone analogs (progestins) in hormone therapy) (18). And few of the doctors that continue to prescribe transdermal progesterone order the kind of tests (uterine biopsy or ultrasound) that would be necessary to confirm that proliferation is not occurring. Instead they rely on blood spotting or other extreme side effects, and then usually just discontinue therapy or order a hysterectomy when they occur rather than attempting to correct the underdosing problem.

While there has been some research on sublingual/transbuccal (putting a wafer or troche under the tongue or between the cheek and gum) and transvaginal or transrectal application of progesterone as alternatives, our experience has been that neither is acceptable (tastes bad, messy, inconvenient (the compounds must be refrigerated), very expensive (several times the price of injectable hormones), and as with transdermal, it is difficult to impossible to properly regulate dosages).

Oral progesterone (sometimes called oral micronized progesterone or OMP) is also particularly pernicious: When progesterone is taken orally more than 90% of it is metabolized by the digestive system or liver into at least 30 different chemicals that do not activate progesterone receptors (14). While many of these compounds have known side effects, extreme sleepiness being only the most common, we really have no idea what the long term effects of exposure to most of these metabolites are. The need to minimize these side effects usually results in significant underdosing, again vastly increasing the risk of endometrial cancer and other negative side effects of "estrogen dominance". Probably because of this, taking OMP has been shown to be significantly more risky than oral MPA (Provera), a full synthetic (19).

The same kind of "foreign substance" problem is found with Premarin, the most commonly prescribed oral estrogen: Not even counting what the liver does to them during digestion, the majority of the compounds supplied in Premarin are found only in horses, not humans. This is yet another reason why the WHI study was such an epic fail.

Pellet therapy, in which multi-month doses are inserted through an incision in the skin, is not an option for hCG or progesterone at endometrium-protecting levels, ruling this mode out even if the surgery, much greater expense, and the non-reversible Russian-roulette dosing is not a sufficient disincentive.

Injection has none of these disadvantages: Dosing is precisely controlled, is easily reversible or adjusted if negative side effects occur, there is no first-pass metabolizing by digestive system, and there is no unexplainable difference in serum vs. saliva levels. And as long as you're injecting the hCG or progesterone anyway, adding the other necessary compounds to the protocol is an insignificant burden.

Given the need for an injectable form, there is at present only one suitable progestin for hormone optimization in women, hydroxyprogesterone caproate (OHPC).

Despite the fact that there is exactly zero recently published research on OHPC for continuous (vs cyclic) HRT (let alone hormone optimization), there is a decades-long history of use of this compound as a contraceptive, as the form of progesterone used in transsexual therapy, for IVF, and for pregnancy support (as in the branded form of the compound, Makena) that has proven that it is safe and effective. Millions of Chinese women use it as a component of "Chinese Injectable #1", one of the most widely used contraceptives in China, for example.

While OHPC is not, strictly speaking, "bioidentical" it is the synthetic progestin most similar to natural progesterone in structure and effect. The same is true of the other two compounds recommended for the ***FP*** Protocol: testosterone cypionate (sip-PIE-oh-nate) and estradiol cypionate (estradiol, also known as E2, is the most active form of estrogen). Both of these, like OHPC, are the natural molecule with small added components (esters) that make them more stable and resistant to metabolizing (the half-lives of the natural hormones are in the range of minutes to hours, whereas these esters all have half-lives of about a week).

T-cyp and E-cyp have the additional advantage of being "prohormones" of the natural substances. That is, they activate the targeted receptors directly, but the first step in their metabolism is the snipping off of the cypionate ester, leaving the bioidentical compound to continue activating those receptors and also to show up on blood tests which allows us to use these results to adjust dosing. OHPC metabolism doesn't work this way, since the enzyme that operates on it cleaves it in two, leaving metabolically inactive metabolites. Unfortunately no usable prohormone of progesterone has ever been synthesized, and it is likely that this is even theoretically impossible. At least we're lucky that OHPC metabolism is not like that of oral compounds which metabolize into biologically active compounds that cause significant side effects.

If you are in one of the countries where it is available (notably not including the US), dydrogesterone (Duphaston) oral would be a reasonable alternative. If neither of these is available to you, a distant third-best alternative would be medroxyprogesterone acetate (MPA, brand name Depo-Provera and the progestin component of Prempro), but only the injectable form: oral MPA has a much shorter half-life, leading to cyclical underdosing unless dosed multiple times per day. And for reasons that no one seems to understand, oral MPA is metabolized in a way completely different from injected MPA, potentially a very serious problem in itself.

MPA in any form is also much more likely to be associated with thrombosis (blood clots) and neurological side effects, such as causing or worsening depression, due to its much stronger affinity for glucocorticoid receptors (3 times greater than progesterone (15) or OHPC (20)). It is notable that oral MPA was the only compound assessed in the WHI study, and they found exactly what was predicted based on previous studies including those for its initial FDA approval: A doubling of blood clot risk and a significant increase in risk of breast cancer, effects that have not been reported with progesterone or OHPC.

If testosterone cypionate or estradiol cypionate are not available, one of the other esters (such as testosterone enanthate or estradiol valerate) can be substituted, but dose size and frequency will need to be adjusted to account for the different bioactivity and metabolization rate. The cypionate ester is always to be preferred because it results in more stable serum levels than the others and is less likely to cause other side effects.

Chapter 4: The dosing

If you can feel the difference an individual dose makes, you're not dosing frequently enough.

This common-sense recommendation is widely ignored by doctors in all fields for all types of drugs. Instead, they follow manufacturer's recommendations which are designed to promote sales rather than optimal effectiveness and where moderate side effects are acceptable so long as they're not so bad that the drug is discontinued.

Unless dramatically varying serum levels are an essential component of the protocol, a primary goal should be to maintain serum levels within at least a factor of two. Doses should therefore be scheduled no longer than the half-life of the compound, with twice that frequent being optimal (more often than that and the law of diminishing returns sets in). Since the half-lives of the hormones recommended here are about a week, this means injecting at least once a week, with twice a week being preferred. This pairs well with hCG for male hormone optimization because it too must be injected at least twice a week due to its shorter half-life. It also makes easier to tolerate the injections since each shot is only half the volume of a weekly injection: A 0.5ml injection (half a syringe) is usually very well tolerated and causes little or no pain or bruising. Go larger than that and the likelihood of these problems increases exponentially unless you divide the dose up into multiple areas (i.e., give two or three shots at the same time, at which point you've only saved a little prep time over doing twice-weekly injections).

While sequential/cyclic dosing may be considered during perimenopause, only continuous dosing should be considered for the long-term in intact women.

During perimenopause, the last few of a woman's reproductive years, hormone levels can fluctuate dramatically, causing the symptoms that most people associate with menopause, particularly the dreaded "hot flashes". While these will eventually resolve by themselves as the ovaries shut down and hormone levels drop to low and stable levels, most women at least consider using HRT at this time to alleviate this discomfort.

Many physicians will prescribe hormone supplements for this interval with the goal of alleviating only these symptoms and the plan to discontinue treatment as soon as they resolve. They usually choose a regimen where a low dose of an estrogen analog is given continuously and a progestin given for only part of the month (usually less than 2 weeks of a monthly cycle, though sometimes a single large dose is given at the beginning of the cycle, as is commonly prescribed with injectable contraceptives). These protocols usually alleviate the hot flashes and can also stabilize the menstrual cycle which can become irregular during perimenopause, but because the doses are so low they do little to provide the other benefits of these hormones with respect to body composition, bone density, libido and sexual function, etc.

In the spirit of biohacking (i.e., "use whatever works") cyclic protocols must be considered acceptable in women have had a hysterectomy or in intact women so long as a regular bleed occurs. OHPC can be used in these protocols by simply giving a single large injection (e.g., the dose used for Chinese Injectable #1 and the standard dose for amenorrhea which is 250mg/1ml) 2 weeks after the last period (8).

Where problems with cyclic protocols arise is when the expected bleed fails to occur, where breakthrough bleeding occurs at any other point in the cycle, or if there has been any history of endometriosis (endometrial cells present anywhere outside the lining of the uterus). These constitute serious and potentially very dangerous breakdowns in the protocol because in most cases it means that endometrial proliferation may be occurring with no means of flushing out the accumulation of potentially precancerous cells, vastly increasing the risk of endometrial cancer (like, orders of magnitude greater risk, not the typical few-percent increase that is found in most clinical trials) (18).

Proponents of cyclic protocols, like proponents of herbal supplements, have generally fallen under the spell of the "appeal to nature" fallacy. Again, because the human body evolved to only last until its 40s, any claim that "mother nature knows best" applied to anyone older than that deserves at least extreme scrutiny but more likely only ridicule as a statement of pseudoscientific or antiscientific philosophy.

Worse, they don't even have the "natural" part right: Extrapolating from research on small scale societies, where people live in conditions more similar to those of our ancestors during the Era of Evolutionary Adaptation, it's clear that these "cycles" (including menstrual periods) should actually be relatively rare because women spend the majority

of their lives either pregnant or nursing during which these cycles are suppressed. Most of them therefore only had a few periods in their entire lives. Viewed in this light, menstrual periods should be seen more as an "emergency eject" mechanism to deal with a buildup of endometrial tissue in the relatively rare event that a pregnancy doesn't occur. It's therefore a mechanism that you don't want to be pushing every month, especially when you don't need to. The "natural" state of women is therefore much more similar to what is achieved with continuous protocols: Relatively high levels that slowly grow over 9 months of pregnancy followed by lower and more stable levels for approximately 3 years during nursing (E2 levels during nursing are in the same ballpark as the median level over the menstrual cycle albeit somewhat lower for some women (21)).

This is another strike against the Wiley Protocol (WP), which attempts to recreate the wide range of serum hormone levels found in premenopausal monthly hormone cycles in postmenopausal women under the theory that young women don't get cancer or heart disease and it must be the *fluctuations* in the hormones that are protecting them as opposed to just the average levels. Unfortunately although there has never been a study that compares WP with other cyclic protocols, when compared with continuous protocols *all* cyclic/sequential protocols have been shown to be far more risky (22) (19): Risk of endometrial cancer was reduced by up to 50% with a continuous protocol in the first study, almost 95% in the second.

Strike three is that WP is also a very burdensome protocol with twice a day applications of very specific amounts of estrogen and progesterone creams, and high levels of them, which are commonly associated with all of the usual menstrual-cycle effects (bloating, mood changes, cramps, etc.). And of course because it's transdermal you must be very careful that none of the applied cream ever makes contact with kids, pets, or lovers.

Strike 4 (yeah, the metaphor is breaking down) is that because it relies on expensive compounds that can only be acquired from approved compounding pharmacies WP is a very expensive protocol costing anywhere from 2 to 4 times as much as the injection-based protocol recommended here, an extra $500 to $1500 USD a year.

Strike 5 (in for a penny, in for a pound!) is that Wiley claims that testosterone is not a necessary component of hormone therapy and in general will not prescribe it. Her book even claims that it causes breast cancer, which should mean that premenopausal women should be getting that left and right because their testosterone levels are several times higher than those of postmenopausal women.

Strike 6 (this is getting ridiculous!) is that Wiley claims that an important reason why a cyclic protocol is necessary is that hormone receptors show a "tolerance" effect where long term continuous exposure causes them to desensitize. If this were the case then continuous protocols would require ever-increasing dosages to achieve the same effect. Unfortunately for Wiley this sort of tolerance effect has never been reported in the peer-reviewed literature or even in the broscience for TRT or HRT, probably because tolerance effects *in general* only occur where dosing is far above physiological levels. The only use comparable to that in the domain of hormones is that of anabolic steroids in bodybuilding where typical doses are at least double the amounts necessary to achieve serum levels near the top end of the physiologic range reported on lab tests (or the calculated equivalent dosing for substances that don't register on lab tests), and in which, indeed, tolerance effects are frequently reported, leading to the practice of "cycling"

The only advantages of a cyclic protocol are that the induced period in a cyclic protocol serves a backstop to address endometrial hyperplasia even if the overall progestin dose is too low to prevent it from occurring in the first place. It also reduces the number of office visits required if the hormones are supplied via doctor-supplied injection (the progestin shots typically only have to be given once a month, or for MPA only once every three months).

But these are very minor benefits when compare with the huge main advantage of a continuous protocol, the fact that there is no monthly period with its associated inconvenience and side effects. Which is why nearly all women prefer continuous to cyclic protocols when they're given a choice. Continuous protocols are also much less likely to be discontinued due to blood spotting: Irregular bleeding is the #1 reason for stopping HRT, and also the most common initiator of the chain of events that leads to hysterectomy. No woman should ever have that procedure unless a diagnosis of untreatable cancer has been confirmed, and never merely prophylactically to spare the doctor the trouble of figuring out why the progestin has been underdosed. Hysterectomies are unfortunately still incredibly common because most doctors either can't or won't do that.

But it is worth repeating: it is *essential* in a continuous protocol to ensure that serum levels of the progestin remain high enough at all times to prevent endometrial proliferation/hyperplasia since there is no bleed that would flush out any that develops. This is something that just cannot be guaranteed by oral, transdermal, transvaginal, or sublingual protocols but can easily be ensured with injections.

Therefore the only acceptable protocol for long term hormone optimization in intact women, and the recommended protocol even for perimenopause and women who have undergone hysterectomy, is continuous dosing of both estrogen analogs and a progestin, with testosterone included as needed. The protocol recommended here in most cases will suppress endometrial proliferation, ovulation, and menstruation within weeks of starting it, although the protocol should be started immediately after a period to ensure that as few potentially precancerous cells are present in the uterus before menses are suppressed.

Given the need for injections and for frequent (twice weekly) intervals, the only viable delivery method for sex hormones is by self-injection.

Going to the doctor every week for an injection seems to me to be ridiculously inconvenient, yet many TRT patients do exactly that. But twice a week?

As for the argument that self-injection is somehow too dangerous or burdensome for the average adult to master, one should consider the fact that the average juvenile diabetic learns to self-inject their insulin by the age of 11. Does diabetes somehow make kids superhuman, or is this just another example of how so many in the medical profession prefer to treat adults like children who are incapable of even understanding let alone participating in their diagnosis and treatment?

The injections generally cause only slight discomfort (comparable to a flu shot, albeit without the day-long ache those sometimes cause), but occasionally the needle tip will end up near a nerve and it'll sting a bit for a minute or two. Ice packs and/or menthol-infused alcohol prep can help prevent or alleviate this. Any location with a thick enough fat pad ("pinch an inch") is suitable, so if you get a stinger more than once in a particular location, just avoid it in the future.

Although most of these hormones come with instructions to inject them intramuscularly ("IM") the scientific literature and broscience all concur that this is an obsolete method: IM injections are much more painful (both during the injection and in many cases for hours or days afterward), much scarier (they require a long, thick needle), much riskier (you may hit a vein and cause an embolism), and results in significantly lower serum levels (meaning you're just wasting a significant amount of the injected hormones). A good example of this is the comparison between the IM and SC versions of Depo-Provera

(MPA): The standard 3 month dose for the Depo SubQ Provera is 104mg whereas the equivalent IM product requires 150mg to achieve the same result.

If you do decide to inject IM, be sure to draw back after inserting the needle to check for blood to make sure you haven't hit a vein: Even though an oil embolism is only likely to cause chest pain, shortness of breath, and/or a coughing fit (unlike an air embolism, which can cause a heart attack or stroke), it's not a pleasant experience. Again, this is something that is extremely unlikely or maybe even impossible with SC injections, depending on an individual's body composition and vasculature and the length of the needle used.

For women, OHPC can be combined in the same syringe with T-cyp and E-cyp, so you only have to do one shot once or twice a week. Detailed instructions for preparing and using the mix can be found in Appendix 3. For men, note that hCG is water based and so shouldn't be combined with the testosterone cypionate injection. You can use a much smaller (e.g. 31 gauge) needle for hCG, but men will need two separate injections as opposed to just one for women.

My wife and I inject each other: We're undergoing the treatment as much for each other as for ourselves and we've found that injections are less uncomfortable if you're distracted (by the TV or your phone or whatever) while receiving them, something that is not possible when self-injecting. You can also inject into places (back of the upper arm, top of the buttocks) that aren't accessible via self-injection.

Although there is little actual research to back this up (and it's not something that even comes up in most medical practices), and despite the fact that the broscience consensus is that medical professionals would be adamantly opposed to the practice, I consider it safe to draw multiple doses into a syringe and reuse it: We and many other biohackers have done this for years without problems (it saves time, effort, money, and environmental impact). If you choose to implement this biohack, the following rules must be followed:

1) Never share a syringe with another person (who may have different diseases and/or microbiome than you).
2) Keep the partially-filled syringe safe: Although a child or pet is unlikely to suffer permanent damage if they were to eat or inject it, they would likely be very sick, maybe for days.
3) Never insert a used syringe back into a vial: The compounds do contain preservatives but that is only to protect against weak assaults such as from stuff in the air that you inject prior

to drawing a dose, not all the contaminants that would be on a used needle.

4) Use the partially-filled syringe for the next dose: There have been broscience claims that the injectable compound, especially oil-based compounds, can damage the rubber in a syringe so you don't want to leave them in there for more than a few days. And of course keep them away from heat and sunlight.
5) If multiple people in a household are doing this, be sure to mark the syringes well. I use a purple permanent marker to color my wife's plunger.
6) Note that the needle will get duller each time you insert it (into a vial, or into skin), but there should be no problem getting several insertions out of one needle.

There's a special version of this hack that's particularly appropriate for hCG which must be kept refrigerated and which is relatively unstable when subject to vibration (which is why the instructions tell you never to shake the vial). I've personally experienced weakened potency when travelling with hCG in a vial. Plus, the instructions that come with hCG often specify that it must be used within 30 days of reconstituting (you must add bacteriostatic water to the lyophilized (freeze dried) powder before you can use it). Yet a 12,000 IU vial should last you at least 3 months.

Note that hCG can be mixed in two strengths, 1000IU/ml or double strength at 2000IU/ml. I usually make the latter, which gets me 4 doses in each 1/ml syringe.

To preserve the potency of my hCG what I do is draw all of a freshly reconstituted vial into syringes and freeze them (draw in 9% of air to allow room for expansion, position them needle up to freeze, and then store them in a sealed freezer bag). hCG is much more stable when frozen than as a liquid, and even if it does thaw and get bumped while you're travelling, at worst you've only reduced the potency of what you're carrying rather than a whole vial. I put the prefilled syringes in a short piece of sprinkler pipe with duct-taped ends, which is unlikely to attract the attention of the TSA (at least if it's in your checked bag) or hotel staff who might be cleaning your room or restocking your fridge. Even so, you should carry the box with the printed prescription label on it with the syringes, just in case. Your other injections can be carried with the hCG: oil-based compounds can (but don't need to be) refrigerated or even frozen, but be sure to let them come to room temperature and that they're well mixed before injection (draw a

little air into the syringe and invert it a few times to let the air bubble stir it up to make sure, then push the air back out).

Chapter 5: The metrics

Treat the labs, and the patient.

"Treat the patient, not the labs" only became a cliché because doctors frequently base treatment on the wrong labs or wrong target levels, such as assuming that because a patient's levels are in the lab "normal" ranges that there isn't a problem. Most serious and chronic conditions can and should be diagnosed and treated long before the patient exhibits any symptoms. Waiting until they do only guarantees that significant damage will be done, damage that could have been prevented had proactive measures been taken based on the labs. A patient that shows symptoms that aren't reflected on the labs generally only means that the right tests haven't been done or that they've been interpreted incorrectly. "Optimization" generally *requires* treating to the labs, the goal being to prevent degradation, not merely react to it.

For example if you start thyroid therapy and your doctor insists on adjusting dosing based on TSH (an indirect measure of thyroid function), that's a non-negotiable signal that it's time to find a new doctor because it means that your current doc intends to significantly underdose you. The only lab results that should be used to inform thyroid dosage are Free T3 (FT3) and the FT3:Reverse T3 (RT3) ratio, FT3 being the active form of the hormone, and RT3 being the inhibitory form. Which means that if your RT3 is high relative to FT3, you'll suffer the symptoms of hypothyroidism *regardless* of what your TSH or T4 (the storage form of the thyroid hormone) levels are (which are the levels most doctors dose to).

Target levels for FT3 (defined to be where most people feel at their best and yet with minimal risk of the effects of hyperthyroidism) should be around the 2nd to 3rd tertile break in the lab range (i.e., about 66%). So, for a lab range of 2.0 - 4.4 pg/mL, your initial target should be about 3.5 pg/mL. Target for RT3 should be below the middle of the range (16 ng/dL for a range of 9-24), and FT3 should be adjusted to keep the two proportional. FT3 is regulated by overall dosage, whereas RT3 is regulated by the T3/T4 ratio in the supplemental hormones, although it may respond to other treatments as well (stress reduction, reduction in inflammation, etc.). Which means that if your doc insists on prescribing a T4-only hormone

(Synthroid/levothyroxine) and your RT3 is above 16 you will never achieve a proper balance because more of the T4 will just be converted into RT3, making your symptoms *worse*. The only way to deal with high RT3 is to supplement with a compound that contains both T3 and T4, such as the various animal-derived products (Armor, Nature-throid, Westhroid, etc., aka Natural Desiccated Thyroid (NDT) or Desiccated Thyroid Extract (DTE)). If even those don't provide sufficient T3, a custom-compounded liothyronine/levothyroxine (T3+T4) mixture may be required.

Stop taking your thyroid supplement the evening before testing: While some doctors recommend taking them 2-4 hours before the draw, this would result in measuring peak, rather than average or trough, values and would almost certainly result in underdosing. Tissue levels (effect on heart rate, blood pressure, etc.) correspond to average levels, not the peaks.

If your doctor expresses concern about osteoporosis due to a suppressed TSH, that's a sign that they're uninformed about the state of the science (as unfortunately most are): T3 has to be near or above the top end of the normal range (which generally causes TSH to drop below 0.1) to increase the risk to the bones (23) (24) or cause of any of the other symptoms of hyperthyroidism (restlessness, heart rate issues, etc.). If your doctor expresses skepticism about using RT3 as a target because the science is still not clear on its role, while that's technically true, it's of no consequence: Whether RT3 is the cause of "euthyroid sick syndrome" or merely a correlate, NDT lowers RT3 so either way it is actually addressing the issue even if it is not clear yet exactly how.

As for the lab tests for thyroid antibodies, while they may provide evidence of Hashimoto's, knowing you have that is pretty much only of academic interest. You shouldn't use them to adjust dosing or to trigger other protocol requirements (changing diet, etc.): With appropriate T3+T4 supplementation (and of course supplementation with other hormones) the load is taken off the thyroid and Hashimoto's will most likely spontaneously resolve (i.e., you don't need to treat Hashimoto's any differently than any other type of hypothyroidism: You treat to achieve target lab values and relieve your symptoms, not based on the diagnosis).

Dosing men:

What target lab values to use for the sex hormones? For men this is relatively easy: Optimization is keeping Free Testosterone levels near the top of the lab range for the immunoassay version of the test (don't bother with the more sensitive and more expensive LCMS version). For estrogen (E2), try to keep it at least above the middle of

the lab range of the "sensitive" version of the test (usually LCMS), but do allow for tweaking based on how you feel (I retain water and get kind of "weepy" with E2 above the top of the lab range). Too low is definitely worse than too high as that can make your joints ache and impact mood and sexual function. If just a little high, men might be able to adjust it down using only supplements (e.g., DIM and calcium d-glucarate), but in some cases an aromatase inhibitor (AI) will be required. Men should adjust dosing of their AI, which regulates the body's conversion of testosterone to estradiol, very slowly and carefully again keeping in mind that underdosing is almost always better than overdosing.

While you can get compounded AI capsules in any strength, they're very expensive and it's troublesome to manage your supply that way, especially when you have to adjust the dosage (which for most people is a regular occurrence). Then there's all the FDA and broscience reports of compounded capsules having the wrong dose (sometimes orders of magnitude too high or low), having adulterants or contaminants in them, or an individual reacting to the fillers used (the same can happen with compounded injectables, of course, but at least the level of quality control on those has to be much higher for obvious reasons and the compounder generally only has to deal with a single recipe when producing an entire batch rather than a custom recipe for each customer). My considered opinion is therefore that overall it's better to manage your own dosing starting with factory-produced full-strength tablets rather than compounded capsules despite the additional hassle.

After reviewing the broscience and performing some experiments of my own, my preferred solution to the AI dose-adjustment problem is to dissolve a 1mg tablet of anastrozole in 1ml of vodka, then draw into a 1ml syringe with a large (e.g., 18 gauge) needle (same type we use to make the E:T:P mix). With this method it is easy to squirt my current 0.1ml dose into a beverage.

Recently there has been some debate about whether AIs are ever necessary and you may read claims that E2 should be left alone to float with T levels. While this is probably not overly dangerous, don't be fooled: The studies the major proponents of this protocol (specifically Dr. Neal Rouzier) cite do *not* provide any assurance of this. The problem is with the definition of "high" or "elevated" E2: The studies being cited use a standard where anything over the top of the lab range is defined to be "high" whereas the levels experienced in testosterone optimization are frequently double or even triple those levels. We really have no idea what the long-term effects of levels that high will be, but do have plenty of evidence from the use of anabolic

steroids for bodybuilding that they can cause significant side effects (mood instability, water retention (often to the point of serious edema developing), and gynecomastia (man boobs)). I personally have experienced the first two because my uncorrected E2 is around 80, which is more than twice the top of the lab range and in the same ballpark as the median levels experienced by premenopausal women.

Unless the side effects are so bad as to require considering discontinuing hormone therapy, I generally recommend against trying to tweak dihydrotestosterone (DHT) levels which tend to increase with testosterone levels via the action of the 5α-reductase enzyme in both men and women. DHT is at least partially responsible for many of the negative effects of testosterone supplementation (acne, body hair growth, and male pattern baldness and benign prostatic hyperplasia (BPH)), but it also promotes muscle growth, mood, and sexual function in both men and women. Although there are herbal supplements (saw palmetto) and prescription drugs (finasteride) that will block the conversion of testosterone to DHT, they are associated with serious side effects (25), some of which may persist long after the drugs are discontinued. Reducing the odds of having the occasional pimple is simply not worth the risk of complete and irreversible erectile dysfunction. A middle-ground treatment for male pattern baldness is topical minoxidil (Rogaine), which locally reduces DHT without the systemic side effects.

Dosing women:

For women, the hormone target ranges vary more, because there are larger individual differences in metabolism and preference. For free testosterone a target around the top of the lab range is a good starting point, though most women can go substantially above that without experiencing significant side effects. For the other two a reasonable starting point is to target the average monthly values experienced by premenopausal women, which are about 100pg/ml for estradiol and at least 5ng/ml or the calculated equivalent of another progestin. These happen to coincide with the levels found just past ovulation in the menstrual cycle, the time of the month when most women feel at their best (see Figures 1 and 2, both derived from the data in (26), noting that average values are somewhat above the median values shown).

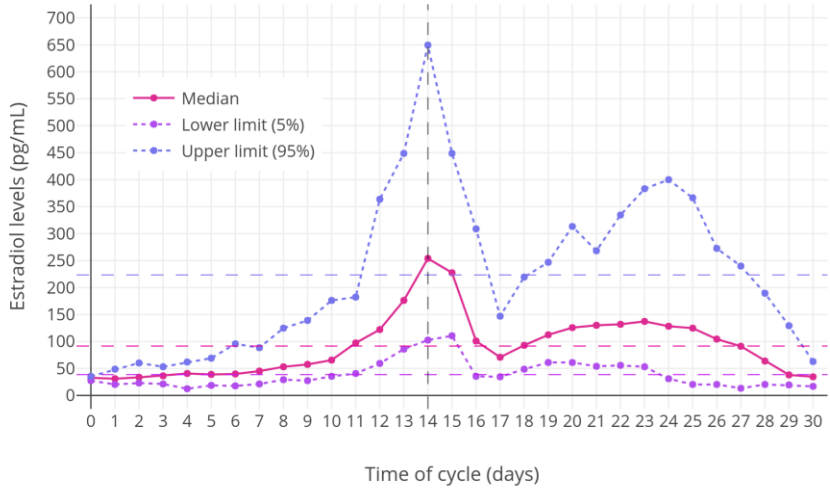

Figure 1: Estradiol levels over the menstrual cycle

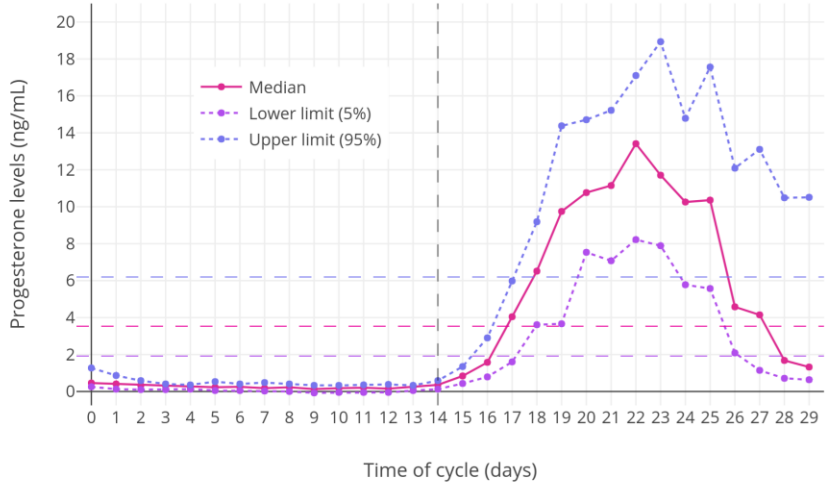

Figure 2: Progesterone levels over the menstrual cycle

Note that sequential/cyclic protocols can't offer this benefit: While in most of them estradiol levels don't vary (albeit are usually substantially lower than the levels recommended here), their prescribed progesterone doses result in serum levels varying nearly as much as in premenopausal women, which as every woman knows causes water retention and frequently causes cramps, irritability, and the wide range of other systems often associated with Premenstrual

Syndrome (PMS). The protocols that do vary estrogen, such as the Wiley Protocol, result in a large peak in estrogen which can also have negative effects on mood, especially increased anxiety, and increase susceptibility to migraines and flare-ups of autoimmune diseases.

The P to E ratio in the targets specified above is about 50:1 (note that E2 is generally reported in pg/ml whereas progesterone in the 1000 times as large ng/ml). Although many physicians target a 100:1 or even 200:1 ratio, this can only be achieved by seriously underdosing estrogen (common) or trying to achieve P levels that will render the patient painfully bloated or perhaps even comatose: At 200:1 for even a relatively modest 100pg/ml level of estrogen, P levels would have to be 20ng/ml, which is well above even the highest peak in premenopausal women and would require an oral micronized dose of over 1g a day, 5 times the usual 200mg/day dose that already causes sleepiness in most women. Since there is no evidence that serum P levels above 5ng/ml provide additional endometrial protection (at least when given continuously), these ratios seem mostly designed to compensate for the frequent underdosing that occurs in oral and transdermal progesterone protocols due to individual differences in absorption and metabolism.

If supraphysiological levels of hormones result in increased benefits with no significant side effects, they should be considered acceptable. For example most women can significantly benefit from supraphysiological levels of testosterone without risk of negative side effects. They can actually *reverse* the effects of aging and gain stronger muscles and bones, younger-looking skin, increased libido, more satisfying orgasms, and improved mood at levels far lower than would cause side effects like deepening voice, hair growth, or megaclitoris which only occur at levels many times higher than the normal physiological range (27), (9).

For men, the standard TRT dose is usually considered to be 100mg/wk, whereas the optimization dose will be significantly higher *plus* the boost due to the hCG. My T-cyp dose of 160mg/wk plus 1000 IU/wk of hCG keeps me right at the top end of the lab range for free testosterone, a level I maintain without experiencing any significant side effects. Closing in on age 60, I'm stronger than I've ever been before, partly because I have more time and motivation to work out than I did when I was younger, but mostly because my testosterone levels are significantly higher than they were even in my 20s and more than double what they were before I started biohacking them. I also require a tiny dose (0.2mg/wk) of anastrozole to keep my estrogen at the optimal level, just above the middle of the lab range.

My wife's doses keep her at the optimal (i.e., near median premenopausal) level for lab-measured E2 and calculated progesterone-equivalent OHPC levels, and at the top of the "normal" range for free testosterone, also without significant side effects and while maintaining an optimal 4mm endometrial stripe. And she too is stronger than she was at any earlier age and looks, acts, and feels half her age.

Be sure your doctor adjusts dosing using "free" and not "total" testosterone: Especially in men and women over 50, most of the testosterone is bound up by SHBG (Sex Hormone Binding Globulin) and so is not available for the cells to use. This leads to underdosing if only total testosterone is measured. SHBG also binds estradiol, but less aggressively than testosterone, so dosing based on total estradiol is usually acceptable. But do be sure to order the lab test for SHBG, especially during the initial phase of your treatment: SHBG will change in response to your hormone supplementation (in men it typically goes down due to the effects of testosterone, allowing you to reduce your dose, whereas in women it generally increases slightly due to the effects of estrogen).

Any concerns about testosterone increasing aggression in either women or men (as in "roid rage") is completely misplaced: The science shows that increasing testosterone can actually *increase* social behavior in humans and other social primate species (28), at least short of the massive doses that some bodybuilders take. This has also been our experience, confirmed by a vast number of broscience reports. And of course women (or men, for that matter) don't have to worry about unintentionally ending up looking ripped: That takes years of daily multi-hour workouts and rigorous dieting. If you accidentally start showing a six pack, eat a few donuts and sufficient body fat will return to hide those new muscles.

Note that OHPC doesn't show up directly on standard progesterone lab tests, so following the ratios given above, which are based on a broad survey of dosing and dose-response reports, is essential. To ensure this you should include a uterine ultrasound in the testing protocol. The optimal endometrial thickness is that of premenopausal women at the start of their cycles, 4 to 5mm (29): Less than that indicates underdosing estrogen, more than that underdosing the progestin. Although most HRT protocols allow for endometrial thickness of up to 11mm, my considered opinion is that this is primarily to allow for underdosing progesterone to minimize application inconvenience and/or side effects. Risk of endometrial cancer is proportional to thickness (30) (31) and there is no reason to take on this additional risk when it can be avoided entirely by using an

appropriate progestin and delivery mode (i.e. one, like OHPC injection, that provides stable and reliable dosing without dose-dependent side effects).

If your doctor won't order the labs you think you need, order them yourself.

There are lots of internet sites that allow you to order lab tests, usually at a significant discount off the list prices. The blood draws are done at independent facilities, not hospitals or doctor's offices, and by technicians who specialize in that procedure and so are usually quite skilled at it. If your doctor, or even a general staff member in that office, is doing their own blood draws, that's a good sign that it's time to start shopping for a new doctor.

If you're with an HMO or other managed-care plan you may find it especially difficult to convince a doctor to order the full slate of tests necessary to properly diagnose chronic conditions (hypothyroidism being one very commonly underdiagnosed condition, for example). The problem here is one of simple economics: The fewer conditions you are diagnosed with, the more money the HMO makes. As with hormone therapy, one solution to this problem is to pay out of pocket for a integrative or functional medicine specialist. But is also often the case that if a doctor is presented with labs that you've paid for that clearly show a disease in progress they will relent and agree to treat it. And of course they can then bill that part of your treatment to insurance or get covered by the HMO rather than you having to pay out of pocket for not only the consultations but also any drugs or maintenance testing you will require.

Another example of that kind of undertesting is that ferritin is not included in the standard "comprehensive metabolic panel" (CMP, or CMP-14), leading to failure to detect a wide range of very dangerous conditions (hemochromatosis, infections such as hepatitis, and several types of cancer). Be sure to ask your doctor to include this test the next time they order a CMP for you. Then be sure you get a copy of the test results and evaluate them yourself rather than take the doctor's word for it that there's no problem.

Take lab values and ranges with a grain of salt.

Third party testing has shown that different labs report significantly different values when sent the exact same samples. Even the same lab won't report the same values on the same samples if they offer two versions of a test (for hormones usually a cheaper

immunoassay test and a more expensive LC/MS (Liquid Chromatography/Mass Spectrometry, sometimes labeled as a "sensitive", test). They all also have serious test/retest reliability problems even when redoing the same test. And these labs all use different lab ranges and no one ever seems to be sure how those ranges are set (they seem to be "trade secrets", but are they based on all samples they get? Only samples for people who aren't "sick"? Some theoretical calculation?).

One example of when and why it's reasonable to ignore lab ranges is ferritin levels (a measure of iron storage), frequently ordered when assessing thyroid function. The top end of the lab range specified for women is generally half (or less) the level specified for men, but this seems to be due to the fact that menstruating women are almost universally slightly anemic, not because there is any inherent physiological benefit to having lower levels (32). Therefore when assessing ferritin levels for women on hormone therapy use the range for males (typically 12-300 ng/mL, although some labs specify 500 as the top end of the range) rather than the one specified for females (12-150). Then, the optimal level will be near the middle of the range, as is the rule of thumb for most tests, although you should use the top of the range (or even slightly over) for substances that tend to decline with aging and/or have anti-aging properties. In the case of ferritin this means that most women, even most postmenopausal women, are iron deficient even though they don't show any overt symptoms. Fortunately this condition tends to resolve itself with thyroid and sex hormone supplementation. If ferritin levels exceed even the male range order a full iron panel in your next set of tests to make sure there's not something more serious going on (although the symptoms are generally worse with men, women can have hemochromatosis too).

An additional complication with lab levels is that even with continuous dosing, the serum levels actually vary substantially within an individual based on the time between your last dose and the blood draw together with many factors that influence metabolization rates: Any changes in diet, exercise, sleep, or being sick can make it impossible to compare one result with another.

Bottom line, don't obsess over lab values. As long as you're within 50% of the lab range of the desired target you're doing OK. But do at least try to sample at the same point in your dosing cycle (conventionally, just prior to a scheduled dose).

Chapter 6: The small stuff (diet and exercise)

You don't need to do weight bearing exercise when optimizing hormones but doing so doubles the effect on strength increases and changes in body composition.

The combination of optimizing hormones (especially testosterone) plus strength training probably won't cause you lose weight, but the changes in body composition will make you look like you did (muscle is about 20% denser than fat). The extra exercise will of course help you lose weight if you're not currently lifting weights regularly.

Including generous quantities of testosterone in hormone therapies can initiate "virtuous cycles": Increasing strength increases the amount of weight you can lift, which feeds back and increases strength even more. Increased strength expands the range of activities you can engage in, again increasing strength of other muscles that further expand your choice of activities. Increasing your exercise options also makes it easier to maintain motivation because it helps prevent getting into a rut. Increasing testosterone also speeds healing, which makes any muscle soreness or injuries resolve more quickly, which will make possible to resume exercising sooner (33). Testosterone has also been shown to be protective against autoimmune disorders including rheumatoid arthritis (34) which may also explain why women, and especially postmenopausal women, are several times more likely to get these than men. And most of these diseases severely impact the ability to exercise, leading to a downward spiral in both quality and length of life.

Addition of sufficient exercise to your life does not take anywhere as much time as most people think (or now spend). There are countless studies that back this up: Unless you're rehabbing an injury or working up to the ability to do more vigorous exercise, spending an hour or more on a treadmill or stationary bike is simply a waste of time. It doesn't build strength, accelerate weight loss, or help achieve any other optimization goal. Instead, spend 15 minutes every other day doing weight-bearing exercise at a level that raises your heart rate to within 80% of its maximum value (High Intensity Interval Training, or HIIT). You'll know you're doing it right if you're out of breath and sweating by the end of your workout. This is a small enough time

commitment that you can almost certainly squeeze it in just before you take a shower (and you'll need one afterward ;-)

This also means it'll be hard to justify traveling to a gym or rec center for your workouts. Instead, invest in a good quality set of weights, or if your budget and available space allows it, a functional trainer (cable machine), a system that will allow you to perform the major compound exercises (squats, deadlifts, bench press, pulldowns, wood chops, etc.) reliably and efficiently. A 15-minute run or fast bike ride a couple of times a week is a good supplement to these, particularly if you can interleave it into the days you don't lift weights.

You've heard it since you were a kid: Eat right! But don't expect miracles even if you do.

Not to beat a dead horse, but don't fill your body with crap that you know damn well is not good for you. That said, expecting any significant improvement in health merely by changing your diet is almost certainly a waste of time and effort. Although supermarket tabloids and TV health shows are jam-packed with anecdotal reports of miraculous "cures" when some food is added (or deleted) from a diet, the scientific literature is remarkable in the almost complete absence of evidence-based support for any of these claims, at least exclusive of known and easily distinguishable diseases (like celiac).

The primary concern with diet in the first world is simply eating too much. Portion control should therefore be your first line of defense: Use a bowl instead of a plate to measure out your meal. If you go out to a sit-down restaurant, eat half what they serve and take the rest home for lunch the next day. Avoid buffets. Limit calories consumed in beverages (sodas, coffee with cream and/or sugar, high alcohol content craft beer, etc.) which are not satiating and so make you crave more.

This doesn't mean you have to deprive yourself of the things you love to eat. If you really like French fries, eat a (small) pack a couple of times a month. If sweets are your thing, eat a donut after a (low carb) Sunday dinner, or a piece of dark chocolate after any meal. But keep in mind that only get a limited amount of willpower each day and so you must spend it wisely. Using a little to avoid buying that big bag of potato chips is a much better investment than committing yourself to using some every day for the next week to try to limit yourself to only consuming a one-ounce serving.

On the subject of diet, a rule about "food sensitivities": Scientific evidence that "food sensitivities" in general and "gluten sensitivity" in

particular is even a real thing at all is very weak (35) (36) (37). To the extent that they do exist in most cases they're the result of failures of the digestive system to function properly *in general*, not something like allergies which are caused by reactions to specific chemical compounds. Treating food sensitivities by trying to avoid specific foods, as many people attempt to do with protocols like a "gluten free" or "paleo" diet, is a game of whack-a-mole that you can never win: With a poorly functioning digestive system (commonly referred to as "leaky gut syndrome") you will eventually become "sensitive" to *any* food you eat regularly.

So instead of expensive and yet unreliable testing and/or exhaustive (and exhausting) elimination trials, you should treat the underlying condition, most commonly a hormonal deficiency such as undiagnosed or undertreated hypothyroidism (free T3 below the middle of the normal range): Hypothyroidism causes a slowing of bodily functions in general including slowing the flow of material through the gut. This can lead to disorders such as small intestinal bacterial overgrowth (SIBO) a primary cause of leaky gut syndrome. Supplemental thyroid hormone, especially T3 +T4 combinations (Armor, Nature-throid, etc.), can quickly, and in some cases miraculously, resolve a large number of different digestive issues.

Another common problem is with sugar metabolism for which metformin (an insulin modulator) can be a solution: One of the main effects of metformin is to change the climate for the gut microflora (microbiome), which may explain the digestive upset that occurs during the first week or so of metformin therapy. The reformulated microbiome in many cases is more compatible with human physiology and so can allow a leaky gut to heal and resume normal processing of whatever food is consumed.

Finally, oral medications, including antibiotics, NSAIDS, and oral hormones used for HRT, can themselves cause leaky gut syndrome. More on this below.

To lose weight, the best diet is the one you can stick to.

The average American is 30 pounds overweight, an amount that has serious health, life span, and quality of life implications. Which means that for most of us going on a diet is going be part of the optimization process. The first step in that process is to check your BMI using a BMI table (search for that on the Internet). If your BMI is over 30, you're obese and getting under 30 should be set as one of your primary goals in life. Look at a BMI table to find your initial target weight, which is for a BMI of 30 for your height. Subtract that from

your current weight and you'll have a rough estimate of the number of weeks your initial diet will last: It is very difficult to lose more than 1 pound per week consistently because if you try your body will go into starvation mode and start hoarding calories and fat.

If your BMI is under 30 (good for you!) the urgency abates and the goal shifts: Although the current recommendations are to maintain a BMI under 25, that's a very crude measurement because it doesn't account for body type. It is especially likely to be off for those who are working out (as you should/will be) and so have higher lean body (muscle) and bone mass. So instead of a target BMI you should use a target body fat percentage.

There are many ways to measure body fat: Skin calipers, body composition scales, hydrostatic weighing, the "Bod Pod", or a DEXA scan. But because you really only need a rough measure you should use whatever is convenient and within your budget. Two places where you might get an inexpensive or free measurement are your gym (most of which have a body composition scale and/or a staff member trained to use calipers), or doctor's office (ask for a fat percentage when you get a DEXA scan to measure your bone density as part of a physical exam). You might also do an Internet search for an "Inbody" nearby, a very accurate system that many health clubs and functional medicine specialists make available to the general public for a small fee.

For men over 50 the target fat percentage should be under 20%, for women, 25%. To calculate your target weight, first compute your lean mass:

LM = current weight * (100 – current fat percent) / 100

Then compute your target weight:

TW = LM / (100 – target fat percentage) * 100

There are enormous individual differences in how well a particular diet will work, but there are certain trends that are useful to know about. Fasting diets such as the 5:2 or 16-hour diet are very effective and the easiest to stick to for most people, probably because they don't come with the feelings of deprivation that other diets tend to cause (they're the type my wife and I use when we periodically need to cut a few pounds). High fiber/high protein/moderate fat/low carb/very low sugar diets (Atkins, keto, paleo, etc.) tend to be easier to stick to than traditional "low calorie" diets (and diet foods) that tend to cause hunger pangs after high-glycemic carbs are consumed.

The good news is that getting your hormones sorted first will make losing weight a lot easier: T3+T4 thyroid hormones, metformin, and testosterone all facilitate fat burning, although you will still need to tweak diet and exercise to achieve a significant result.

A couple of specific food recommendations that I've found helpful, especially on 500-calorie fasting days:

1) Milk tea (50/50) made with Fairlife (low sugar) milk, and tea sweetened with sucralose (Splenda) and/or stevia.
2) Bai drinks. Not cheap, but they taste better and are far more satisfying than diet sodas.
3) Beef jerky and quality nuts (e.g., pistachios) and cheeses to snack on.
4) Protein bars: I only need to have half of one with a glass of milk tea to make a satisfying breakfast.
5) Sugar free chocolate (e.g. Hershey's Special Dark): Relatively high in fat and calories, but the lack of sugar allows them to satisfy a chocolate craving without taking you out of ketosis (fat burning) mode.

Good food is cheap compared with health care, or even gym memberships. Like life in general make your food consumption about quality rather than quantity.

Voice of experience: Don't be tempted to try the hCG diet. Although hCG is recommended above as a component of hormone optimization for men, it is not an effective appetite suppressant nor does it provide any muscle-sparing capability when paired with an extremely low calorie diet. You will lose weight on the hCG diet, just as you would on any 500-calorie-a-day diet, but you'll be tired, hungry, and half the weight you will lose will be muscle, lean mass that will be very difficult to gain back. About the only thing useful about the hCG fad is as a source of creative recipes that can be used with a 5:2 diet.

Dietary supplements in most cases are not necessary, but can provide marginal improvements in quality and/or length of life.

A full slate of quality supplements costs as much as hormone therapy, has an even greater potential for side effects, and yet provides only a small fraction of the potential benefits. A proper diet will provide you with all of the nutrients you need, and supplementing with a single senior/mature multivitamin will almost always be sufficient to prevent any overt deficiency.

Note that the "treat the patient" directive above especially doesn't apply to lab reports of nutrient levels for supplementation: In most cases there is no perceptible effect from any of these, so getting to the high normal or slightly over lab level is the appropriate target. Be careful not to overdose: Most commonly available supplement

strengths actually result in megadosing, which can cause more problems than it prevents, particularly when taking one supplement interferes with the absorption or utilization of another or of the nutrients in your normal diet. And if you take a supplement that contains biotin, be sure to stop at least a few days prior to any blood draws: It interacts with many tests, leading to inaccurate results.

If you decide you want that extra few percent of optimization, here are the supplements I recommend, in priority order:

1) Vitamin D3 + K2 and B12 + folate: These are the vitamins most likely to be low in older individuals, mostly due to relatively lower absorption especially if you're taking other drugs that interfere with that (like statins or metformin). Be sure to do lab tests to determine need and appropriate dosing, redoing labs after supplementing for a month to ensure that you have achieved target levels.
2) Calcium, Magnesium, Zinc, Selenium, and Boron: These 5 minerals work as a team to provide strong bones and cellular function. If you think you need one, I recommend supplementing all 5 to preserve the balance. Be careful with magnesium some formulations of which can have a laxative effect. Magnesium bisglycinate is the compound least likely to cause problems. And don't take calcium supplements, and especially not with Vitamin C, if you're prone to calcium oxalate kidney stones or have a family history of them.
3) DHEA and/or pregnenolone: May help with mood and to help "back fill" the hormone pathways, leading to more efficient utilization of injected hormones. Check your labs, though: Most supplements provide way too much. To maintain levels near the top end of the lab range my DHEA dose is 25mg/day, my wife's only 10mg whereas the most popular products provide 100mg. Overdosing can lead to side effects, especially sleepiness, or even interfere with maintaining serum levels of other hormones. These supplements by themselves are not reasonable substitutes for taking the other hormones recommended in this protocol since they will have only a small percentage of the effect.
4) DIM, fish oil, CoQ10, aspirin, and other antioxidants and anti-inflammatories: These generally have little effect on quality of life, but may prolong it by reducing the risk of cancer and/or heart disease.

Note that high doses of vitamins A, C, E or B-complex are not on this list, nor are there any purely herbal supplements or probiotics. The science has shown that they simply aren't effective, or have

disqualifying risks or side effects. Even the above list probably has things on it that will eventually prove to be of no value or are actively harmful. If in doubt, leave it out.

Two substances that are not normally considered "supplements" but can have great benefits for both quality and duration of life are fiber (especially if your diet is deficient) and D-mannose, which can have an almost miraculous effect on curing and preventing urinary tract infections (UTI), which tend to become chronic conditions in postmenopausal women.

Chapter 7: The bottom line

Be very wary if your doctor prescribes drugs to treat conditions that are more easily and reliably resolved with hormones or to address side effects from other drugs, or prescribes antibiotics for infections that haven't been positively identified.

Big Pharma loves it when your doctor prescribes expensive patented drugs to address high blood pressure, high cholesterol, osteoporosis, depression, autoimmune diseases, and high blood sugar, particularly when these treatments requires *additional* drugs to mitigate side effects. They reward this behavior with free swag, conference trips and excursions, and sometimes even direct financial compensation. There is *constant* pressure on doctors to prescribe these things.

Yet hormonal therapies can resolve many of these issues far more reliably, less expensively, with fewer side effects, and with many additional benefits. Again, if your doctor won't prescribe hormone therapy as the first-line treatment for these kinds of conditions, your best option is to find a doctor who will. Only after all hormonal deficiencies are addressed should additional drugs be considered to treat any remaining issues.

Antibiotics are a special case: Life-saving medicines when prescribed optimally, they seldom are, with prescriptions written for viral infections, for infections that can be treated by other means (such treating or preventing UTIs with D-mannose), or when the individual will most likely be able to clear the infection on their own. There are two main problems with overprescribing antibiotics. The first is that this provides an evolutionary pressure toward creating "superbugs" that are resistant to antibiotics. The second is the devastating impact they have on gut flora (your microbiome), the consequences of which can extend to all aspects of a person's life and health, including causing food sensitivities, nutrient deficiencies, opportunistic infections, autoimmune diseases, and a wide range of other health problems.

Only take antibiotics when you're sure that the proper antibiotic has been prescribed for the exact bacterial infection you have. Then be

sure to take the full recommended course: You don't want *your* body to be the place where the next superbug evolves.

Ask your doctor if you have a choice of injectable or intravenous antibiotics vs. oral and choose the former if available: These may still have negative effects on the gut, but it's far less likely than if the antibiotic is introduced directly to where the microbiome is living. This is especially true if you'll need an extended course of antibiotics (more than 2 weeks): It takes over a month for your gut to recover from a short course of oral antibiotics, but it may never recover if you take them longer than that, or if you take probiotics after using antibiotics (as many doctors currently mistakenly recommend) (38). And because you'll be an expert on SC administration, it will generally be preferred to do SC vs IM injections for the antibiotics too (39). And if you have any new gut issues after a course of antibiotics, especially when treating a gut infection like Clostridium difficile (C-diff), look into fecal microbiome transplant (FMT), an elite biohack.

Hormone optimization is not cheap and is not covered by most insurance, but most people who've done it consider it well worth the cost.

Figure on spending up to $3000 (USD) the first year, and at least $1000 a year for the rest of your life for the necessary lab tests, consultations, supplements, supplies, and the hormones themselves. The first year will be much more expensive because you need extra testing and consultations: I recommend the first lab tests 6 weeks after starting the protocol, and up to every 3 months after that for the first year until you and your doctor are sure you've got the protocol right. An ultrasound, if necessary, should be done at 3-6 months, or both then and at the start of treatment if you are currently using an HRT protocol with a low (or zero) dose of a progestin such that it does not cause a monthly period, or if you've ever had breakthrough bleeding on whatever dose you're on.

It will probably take several months of adjustments to get your dose dialed in because there are huge differences in individual responses to these treatments. Most people experience both positive and negative effects during this process, with both being more pronounced the longer their bodies have been deprived of these hormones before starting treatment. One might think of this adjustment as a "second puberty", albeit one that is much shorter in duration, much more controllable, and free of all the drama.

But trust us: If you're in the target demographic (anyone who as a result of aging has noticed a significant decline in their strength or the quality of their skin, hair, or sex life) you'll appreciate the benefits of these treatments more than anything else you'd spend that kind of money on (new car payments, shoe collection, cosmetic procedures, barista-prepared coffee, etc.) and will find that dealing with the side effects as you tweak your dosing is a very small price to pay.

It may be hard to find a doctor who will prescribe OHPC, but then again, it's hard to find a doctor who will competently deal with any hormone issues.

It's been our experience that it's very unlikely that a Primary Care Physician (PCP)/General Practitioner (GP) will even properly treat a thyroid issue, let alone supervise an overall hormone optimization protocol. But it doesn't hurt to ask, and to ask for a reference to a functional/integrative/anti-aging specialist if your PCP/GP is only comfortable with treating symptoms. You probably don't want a referral to an endocrinology specialist, which in our experience (backed up by hundreds of broscience anecdotes) isn't likely to do the job right either.

So most likely you're going to have to rely on internet searches to find a doctor willing and able to take on this project. You might also watch for local ads from hormone specialists, even those that focus mainly on thyroid or male sexual health. Gynecologists are another likely source, especially if they've taken anti-aging or integrative workshops. I haven't contacted any of them (and so obviously can't vouch for them), but Suzanne Somers maintains a list of possible candidates at https://www.foreverhealth.com/

I generally recommend using a local doc over Internet-based "concierge telemedicine" practices, although it's more work to find one and it may not even be possible in some areas. I had to contact a couple of dozen doctors in this area (Boulder/Denver) to find 3 who would prescribe OHPC, to give you some idea of the scale of the problem. It probably helps to be able to say "hydroxyprogesterone caproate" (e.g., look up those two words and "pronounced" on YouTube) and to tell them that it's the chemical name for Makena, which they've probably heard of.

If a candidate is willing to even consider prescribing OHPC, definitely follow up: This is a new protocol and most likely you'll have to be an advocate as part of the process. If a doctor that otherwise seems suitable is on the fence about OHPC, consider starting with oral

micronized progesterone or even transdermal instead of going straight to OHPC (I'd still recommended injection for e-cyp and t-cyp, though, which should be no problem to get approved). But do watch that endometrial stripe: Reliable dosing of estrogen is not such a great feature when paired with an unreliable or underdosed progestin. If you think it would help, send me (feedback@frailproof.com) contact information for the doctor and I'll send them a copy of this book. It might also help to volunteer to sign an "informed consent" form which will provide the doctor cover from legal claims. An Internet search for "hormone treatment informed consent form" will turn up many of these.

Assuming you even have a choice, pricing for these specialists is often difficult to compare. Some practices are "all inclusive" and charge a flat monthly fee that covers all testing, consultations, and in some cases even the drugs and hormones you'll need. They can seem expensive, but can actually be a good deal, especially for the first year or so while you're tweaking your protocol. Other doctors charge flat rate for consultations and have contracts with labs and compounding pharmacies so that you can get discounts from these. But keep in mind that compounding pharmacies are almost always going to be more expensive than buying factory-produced products from your local grocery store pharmacy with a coupon from goodrx.com (anywhere from twice to ten times the price). Conversely, Internet lab testing sites will often beat the discounts the labs offer to your local (low volume) doctors.

This is probably not the ultimate hormone therapy protocol, but it's the best we can derive using the information and compounds currently available.

The OHPC levels recommended in this book and protocol guide are almost certainly higher than required: Many studies have shown that endometrial protection can be achieved with even relatively low serum levels, especially of synthetics. The problem is that there are very large individual differences in sensitivity and metabolism: Unless you're doing a biopsy every few months, where individual cells are examined to determine their state, you can't *know* that endometrial proliferation is not occurring and therefore that cancer risk is increasing. Even an ultrasound is only an indirect measure of this, but is more than sufficient if a robust continuous level is maintained, something that can easily be achieved with OHPC without incurring significant side effects. Indeed, there may even be additional benefits

to running higher-than-needed levels of a progesterone analog (mood, bone health, healing speed, etc.). Direct serum-level tests for OHPC have been developed (Covance has one), but at this point they're only available to clinicians running large-scale studies, mostly of using Makena for pregnancy support. Perhaps if enough people adopt this protocol Quest or Labcorp will make such a test available to the general public.

Even better would be if someone were to synthesize a prohormone of progesterone, one with a half-life of at least a week. As an alternative, sustained-release versions of progesterone such as Prosphere (progesterone microspheres encapsulated in cholesterol) have been developed, but none are available in the US. In any case it would be years before either of these will have been proven to be as safe and reliable as OHPC.

What we *should* be doing is conducting large scale studies to try to assess this variability and optimal dosing. Unfortunately, since all of the hormones recommended here are long off patent, there is no incentive for drug companies to conduct or fund research into their use. And given the medical profession's insistence on using "all causes mortality" (or worse, particular relatively-small risks such as for breast cancer) as the primary criteria for judging the suitability of medical interventions it's also unlikely we'll see any large-scale research on hormone optimization in the near future. But these protocols do work and those who have used them are generally extremely satisfied with them and plan to continue to maintain them for as long as possible. Other protocols, especially those that omit key elements, have very limited benefits (primarily symptom relief) and so are usually discontinued after a relatively short period of time.

Fortunately there has recently been a thawing in the medical community's blanket prohibition on HRT, with an increasing awareness that the details matter. A lot. Some researchers are even thinking even farther ahead, proposing to replace even more of the substances that the ovaries produce (40).

A significant percentage of men receiving testosterone treatment are actually already on doses that should be considered "optimization" rather than just TRT. Virtually no women are receiving this level of treatment, however. This is partly because of a systematic bias in women's health treatment (another example of that being that women are significantly more likely to die after having a heart attack than men (41)). There also seems to be even greater reluctance on the part of even hormone specialists to prescribe treatments that require self-injection to women. But much of the problem is a consequence of the lack of research and practical information on suitable compounds for

use in these protocols. Hopefully this book will contribute to addressing all of these issues.

Conclusion: Your body is your most precious possession. Step up to your obligation to take care of it.

You cannot trust anyone else, least of all whatever doctor you've ended up with, to make the healthcare decisions necessary to optimize your health. I hope that some of the ideas presented here help you on your path toward a long and healthy life.

Appendix 1

The Frail Proof Buyer's Guide

Mini-reviews of books on menopause, andropause, HRT, TRT, and anti-aging, with links to other background material

This section, which is also available as a stand-alone book, is provided as supplement to Frail Proof. It contains links to background material on what hormones are and what they do and on the many benefits that accrue from optimizing them.

For background on the general philosophy that justifies biohacking and other anti-aging protocols, start with the science behind to our evolution-derived bodies and behavior. ***The Selfish Gene*** by Richard Dawkins is a great introduction to the evolutionary processes involved, but any of the popular recent books on evolutionary psychology, including Sapolsky's ***Behave*** and Wright's ***The Moral Animal***, will also serve as great sources of inspiration and motivation: The bodies and brains of human beings are incredibly imperfect contraptions and keeping them in good condition and "fixing" them when necessary is an individual obligation and our collective destiny.

There are a wide range of Internet sites related to the topics covered in ***FP***. Unfortunately they vary a lot in quality and signal-to-noise ratio. For thyroid issues I recommend https://stopthethyroidmadness.com/ as a good starting point, their emphasis on T3+T4 treatment being especially informative and in conflict with what most doctors currently recommend.

There are also lots of sites that cover TRT and men's health, but unfortunately the majority of the content on them is of the "broscience" variety: Anecdotal reports that you have to read hundreds or thousands of to have any hope of digesting down to a reasonable awareness of the state of the art. Mostly what you'll develop is a great sympathy for the vast number of men who are suffering what can only be considered abuse at the hands of their incompetent doctors (e.g., only dosing testosterone once every two or three weeks, dosing testosterone without hCG, or receiving no assessment or treatment of estrogen levels, etc.).

Unfortunately I also can't recommend any current Internet site that specializes in hormone therapy for women: So few

postmenopausal women are currently maintaining optimal (or even "normal") levels of hormones, or indeed even receiving all three required hormones, that there is very little broscience (or would that be "sisscience"?) to rely on in this domain. Keep in mind that any site or book that exclusively or even primarily recommends oral (synthetic or bioidentical) or cyclic delivery modes is not a viable source of quality information because they're tied to protocols that are obsolete, ineffective, and frequently even dangerous. This applies to almost all of the hormone-related information you'll find in FaceBook groups, most of which have the additional problem of overt, even proud, censorship of any information that conflicts with the biases of the moderators. For example, anyone who posts links to peer-reviewed research that conflicts with the recommendations of the Wiley Protocol will get banned from WP-oriented groups, a policy that denies the members of those groups the facts they need to make informed decisions.

The same unfortunately applies to the current crop of books on menopause, the overall sense one gets from reading more than a few of them is that hormone optimization is only in its "stone knives and bearskins" stage, a stage where leeches and trepanation (cutting holes in the skull to let the evil spirits out) could be standard treatment: It's rare to find two of them that even partially overlap in their recommended protocol, to the extent they even specify a protocol and target hormone levels at all.

Nevertheless I'll review the most popular of those books here to help ensure you don't waste time on those that you wouldn't benefit from reading. They are most likely to be useful if you've failed to keep up with the continuous stream of health fads covered in the popular media (regarding diet, exercise, effects of stress, etc.) and so will find their coverage of these topics informative.

The common theme of most of these books is they primarily appeal to placebo effects and the human characteristic that "misery loves company". Which is not to say that those things have no value, especially if there aren't any alternative treatments. But the whole point of ***FP*** is to show that viable alternative treatments do exist, and if you implement them you will no longer benefit from hearing about other people's suffering and whatever philosophies they offer up that might make that suffering more bearable.

A good litmus test to apply to any book you're considering reading is the author's opinion on the quality and general applicability of the outcome of the Women's Health Initiative (WHI) study. If they support it, my considered opinion is that not only does this disqualify them from being considered an expert in the field, it should disqualify them

from practicing medicine at all because it indicates an irredeemable preference for the status quo and a willful ignorance of anything that challenges that, regardless of what is in the best interests of their clients.

Which brings us to Wikipedia, and in particular the WHI article (https://en.wikipedia.org/wiki/Women%27s_Health_Initiative): While Wikipedia can be an excellent source of background information in non-controversial domains, it has serious "foxes guarding the henhouse" problems elsewhere. The core of the issue is that self-selected "editors" with strong biases, or indeed direct conflicts of interest, can simply override any attempt to change (fix) articles when the state of the science or even the popular consensus has shifted (voice of experience here). While there are many ways to address this problem (such as designing a structured way to present multiple viewpoints, or having biases systematically examined by provably impartial juries), the organization has not implemented any of them. Which is why I no longer support Wikipedia financially or with my edits. Take anything you read on that site on a controversial subject, including HRT and hormone therapies in general, with your BS detector fully activated. And then be sure to check out other sources (such as the references provided in ***FP***, and/or some of the books listed below) before forming any strong opinions on the matter.

A second good test to use when judging the quality of books and other sources of information is the reliance on anecdotes over peer-reviewed published research. They take the form of "Person W had problem X which was treated with protocol Y and the outcome was Z". The best of these is where "W" is you: Only then can you be sure that Y was the only change you made and that there is a good chance that Y usually or always achieves Z. Second best is where W is a patient of a doctor, in which case the anecdote becomes a "case study". You're still not sure if Y was the only intervention, or indeed the Z actually occurred or that it wasn't just a result of the placebo effect. Worst is where W is your wife's cousin's Facebook friend, in which case we call it "fake news". The same is generally true if you're hearing the story on TV or reading it in a supermarket-checkout-line tabloid: The main purpose of stories in those forums is to sell advertising, not help you optimize your health.

Almost all of these books on menopause make a fundamental error when describing the relative risks associated with different forms of the hormones. Most gloss over these differences, citing research that only tested one particular substance and generalizing that to all others in the same category, implying that there is no significant difference between them. The rest (mostly those that endorse "bioidentical"

hormones) imply the differences are far larger than they actually are, ignoring the fact that even doubling a negligible risk usually results in a still-negligible risk. The truth is somewhere in between: While there are significant differences in risk as a function of the particular hormone analogs you use, these differences are small compared with differences in risk that result from under or overdosing as the result of dose size (particularly the E to P ratio), timing (relative to half lives, and cyclic vs. continuous protocols), and how they are administered (oral, transdermal, injection, pellets, etc.). Unlike ***FP***, none of these books makes any serious effort to objectively explore these issues.

I've included a few books on this list that cover hormones or anti-aging in general because there is a lot of overlap in these fields. I've also included a few that focus on testosterone and TRT, most of these being clearly superior to the books on menopause if only because they almost all take an optimization/biohacking approach vs. assuming that alleviating symptoms is enough. Women can benefit from reading them because there are large areas where the issues and protocols overlap and to get steeped in the biohacking ethic.

The primary metric used to rank these books is their utility for biohacking: The specificity of the protocol recommended and the quality of the evidence used to support those recommendations. You'll have to read the descriptions if you're looking for something else.

1. ***Dr. Colbert's Hormone Health Zone: Lose Weight, Restore Energy, Feel 25 Again! (5*)***

   Good overview of the issues, and with lots of specific recommendations.

   The good:

   - The best of the current crop of hormone books.
   - Well researched with lots of good references.
   - Good coverage of thyroid, adrenals, and cortisol, although the conclusion about the latter two is that it's seldom necessary to treat them specifically if you properly optimize the other hormone levels.
   - Lots of specifics on dosing and target hormone levels for both men and women, and all levels provided are for serum rather than saliva or urine.
   - Strong advocate of testosterone for women, and as pellets or injections.
   - Advocates for optimization rather than merely treating to address symptoms.

- Appropriately skeptical of doctors and their current prescribing (underdosing) regimens and of transdermal and oral protocols.

The bad:

- Way too many anecdotes and the author admits that many of them are "composites" (i.e., made up), although they are at least from his own practice.
- Way too many exclamation points!
- Overly fanatic of pellet therapy and doesn't address the issue of inability to reliably achieve target serum levels that plague that mode (most people are either over or underdosed on pellets, sometimes wildly so, something that just isn't a problem with injections, an alternative the book endorses only tepidly).
- Recommends only sublingual/buccal or oral progesterone, which is especially odd considering he recommends injections for T even for women.
- Fails to properly diagnose women having periods or blood spotting while on HRT: He recommends decreasing estrogen when the real problem is underdosing or inconsistently dosing an oral/sublingual/transdermal progestin (a problem that is *very* common).
- A little cavalier about recommending HGH supplementation: There are many peer-reviewed papers that link high IGF-1 to significantly increased risk of many forms of cancer, a risk he doesn't even mention.
- Minor formatting and consistency issues (e.g., the target serum levels are different in different sections!).
- Recommends Christianity as a part of the protocol and contains biblical citations throughout.

2. ***The Natural Superwoman (4*)***

Approachable overview of menopause and anti-aging with few glaring flaws.

The good:

- Strong advocate for HRT, including testosterone.
- Appropriately skeptical of old-school docs, oral hormones, synthetics, saliva testing, cyclic protocols, the WHI study, and herbal supplements.
- Relatively free of faddish recommendations and fake anecdotes.
- Reasonable transdermal protocol.
- Usable (if unconventional) list of references and index.

The bad:

- Emphasizes (E3) estriol, although doesn't require it.
- Doesn't provide target levels, although does mention optimization is to levels at age 20.
- No mention of injections.
- Weak on diagnosis and treatment of thyroid.
- Some redundancy in discussions of supplement benefits, and too much coverage of the standard "diet and exercise" recommendations.

3. ***The Good News About Estrogen (4*)***

A refresh of The Natural Superwoman that's unfortunately even weaker on how-to information.

The good:

- Strong advocate for HRT, including testosterone. More complete and updated E2 information than the previous book.
- Appropriately skeptical of old-school docs, oral hormones, synthetics, pellets, saliva testing, cyclic protocols, the WHI study, and herbal supplements.
- Relatively free of faddish recommendations and fake anecdotes.
- Reasonable transdermal protocol.
- Good list of references, but no footnotes so it's hard to tie specific claims to their supporting research.

The bad:

- Emphasizes (E3) estriol, although doesn't require it.
- Doesn't any dose or provide target levels, nor even any discussion of the difference between symptom relief protocols vs. optimization
- Misrepresents injection, relegating them to the most serious conditions.
- Weak on diagnosis and treatment of thyroid.
- Much redundancy in discussions of symptoms, and too much coverage of the standard "diet and exercise" recommendations.

4. ***The Testosterone Optimization Therapy Bible: The Ultimate Guide to Living a Fully Optimized Life (4*)***

The definitive guide, albeit with many flaws in the specific protocols it recommends.

The good:

- At least touches on everything you could possibly want to know about hormones (more like an encyclopedia than a bible, I'd say).

- Huge number of good references and links to informative websites.
- Abundant tables and graphs with recommended protocols, lab levels, etc.
- Appropriately critical of non-effective supplements and protocols, including testosterone "boosters" and transdermal/topical.
- Good coverage of supplements that *do* work, and recommended off-label uses of other beneficial drugs.

The bad:

- Over 600 pages, although if you can handle that it is the best route to mastery of the domain.
- Contains material (such as a section on spirituality) that readers may prefer to find elsewhere, or not at all.
- Good coverage of the benefits hCG, but lacking in endorsement that it should be a standard component of any male hormone optimization protocol.
- Recommends T3/T4 thyroid compounds for weight loss, a risky protocol that in the past caused many people to end up in the emergency room which is part of the reason why many doctors now refuse to prescribe these compounds at all.
- The chapter on hormone optimization in women is scattershot, with a lot of good information mixed in with anecdotes and bogus "appeal to nature" recommendations. The recommendation of a complex cyclic transdermal protocol (a derivative of the Wiley Protocol) fundamentally conflicts with the conclusions drawn elsewhere in the book and with the recommendations published in peer-reviewed journals.
- Expensive, albeit for much more material than in the MANual (the previous version of this book).
- Relatively low production values (sloppy editing, low quality illustrations, etc.), especially considering the price.
- As is the case with the MANual, you can't trust the reviews on Amazon because 5-star reviews are essentially being purchased via an appeal at the end of the book to get free swag in exchange for a good review.
- No index, and it's big enough to need one.
- Numerous problems with references and URLs including many typos and dead links. It's also annoying that there are no URL links in the references even though many of

the cited papers (or at least the abstracts) are available on the Internet.

5. ***The Menopause Manifesto: Own Your Health with Facts and Feminism (4*)***

   Great overview of the process and consequences of menopause but with weak protocol recommendations.

   The good:

   - Strong advocate of HRT including testosterone.
   - Strong sections on relative risks of treatments (and non-treatments).
   - Appropriately skeptical of the WHI "standard of care", herbal supplements, pellet-based therapies, and saliva testing.
   - Highly critical of other books/authors, particularly Suzanne Somers (**I'm Too Young For This**) and Christiane Northrup (**The Wisdom of Menopause**), the latter having been exposed by Covid to be an antivaxer.
   - Good set of references although there are no footnote markers so it's often hard to tie a claim to a particular reference.
   - Lots of mnemonics and rules of thumb that will make it easier to remember and apply what you've read.
   - A feminist perspective which while overbearing at times is a refreshing difference from other books in this field.

   The bad:

   - Blanket prohibition on transdermal P and makes claims about it that are not supported by the peer-reviewed literature.
   - Definitely slanted toward medical organizations and their standards and so is overly critical of compounding pharmacies and of functional/integrative/anti-aging docs.
   - Way too comfortable recommending exotic new drugs such as SERMs, although it does offset that with stories about how other new and shiny drugs ended up being disasters.
   - Provides standard dosing recommendations, but no target levels.
   - No coverage of thyroid, cortisol, or other hormones that may go off at this age.
   - Doesn't mention injections.
   - Needs better editing (typos, formatting errors, redundancy, etc.)

6. ***Screaming to be Heard: Hormone Connections Women Suspect…and Doctors Still Ignore (4*)***

   Overly long and somewhat out of date, but among the best overviews of the field.

   The good:

   - Strong advocate for HRT, especially for the E2 (estradiol) component.
   - Appropriately skeptical of doctors, herbal supplements, pellet-based therapies, and saliva testing.
   - Specifies a good target levels for E2 (90pg/ml) and recognizes that both Free T and Total T should be considered when dosing T.
   - Deep coverage of a wide range of health conditions and how HRT can be an essential part of the treatment for them.
   - Roughly balanced coverage of synthetics and bioidenticals (i.e., appropriately prefers the latter, but points out many cases where the former can be the more appropriate treatment).

   The bad:

   - Other than a few in-line references there are no references or footnotes to provide support for most of the claims made, and some of them really needed this support since they're most likely wrong or at least out of date.
   - Recommends oral testosterone which has been shown to put the liver at unnecessary risk.
   - Overly (and repeatedly) critical of progesterone supplementation and recommends against supplementing it at all for women who've had a hysterectomy or ablation.
   - Criticized injection-based protocols based on the deeply flawed assumption that only doctors can provide them. Which is ironic since a major theme in the book is women are treated as second-class citizens by the medical profession and yet most men are allowed to do their own TRT injections…
   - Weak coverage of thyroid issues, and recommends against NDT based on bogus claims that sensitivities will develop if they are used (we'd all be allergic to pork in general if those types of sensitivities were an actual thing).

7. ***Safe Hormone Smart Women (3*)***
   Extensively researched, but will be too pedantic for most.
   The good:
   - Page per page, the most extensively researched book on this list.
   - Extremely pro HRT with references to back up most of the claims.
   - Appropriately skeptical of oral hormones, herbal supplements, and saliva testing.

   The bad:
   - Only recommends transdermal protocol and doses provide are unsafe (P dosing of 20-40mg/day, which is only 20 to 50% of the minimum safe doses).
   - No target levels and weak coverage of thyroid.
   - No index, severely impairing its utility as a reference.
   - The lack of references for most of the controversial claims (those that don't appear in other books on this list) could prove dangerously misleading to readers who aren't paying close attention.
8. ***Happy Healthy Hormones: How to Thrive in Menopause (3*)***
   Good overview of the issues and set of references but weak on the specific protocol recommended.
   The good:
   - Easy to read and relatively comprehensive.
   - Unlike most of the other books on this list it has been kept up to date with regular revisions.
   - Appropriately skeptical of the WHI study, doctors, synthetic hormones, high-dose cyclic protocols (like the Wiley Protocol), and herbal supplements.
   - Good coverage of other hormones to consider (thyroid, cortisol, insulin, etc.)
   - A client-centered protocol which allows you to tune your own dosage.
   - Recognizes testosterone is a key component of an HRT protocol.
   - Good analysis of testing protocols including requiring regular transvaginal ultrasounds.
   - Includes an appendix with additional references with custom abstracts that explain their significance.

   The bad:
   - Primarily about symptom relief rather than optimization and recommends keeping doses as small as possible. Will

cut doses if high lab levels are reported, even if symptoms return.

- Recommends only expensive 24-hour urine testing rather than using the peer-review standard of serum (blood) levels.
- Recommends only oral and transdermal modes, and at relatively low doses with no target levels provided (you have to be a medical professional and sign up for the online program (at $50 a month) to gain access to this information). Doesn't mention injections or pellets at all.
- Significant number of anecdotes, although at least they're from the author's own practice.
- Treats the fact that 90% of oral micronized progesterone gets metabolized into non-bioidentical compounds by the liver as a "feature" (some of those compounds make you sleepy and a lot of women have trouble sleeping).

9. ***How to Achieve Healthy Aging (3*)***

State of the art on philosophy, but too few specific recommendations to be of much use.

The good:

- Strong advocate for HRT/TRT and to optimization levels including T for women.
- Appropriately skeptical of Big Pharma, the WHI study, doctors, and synthetic hormones.
- Good coverage of the need for thyroid supplementation in most people over age 50.

The bad:

- Superficial treatment of what hormones even are (e.g., generally uses the term "estrogen" and never even mentions the issue that there are many different estrogens).
- No discussion of the alternative modes, no dosing recommendations, no target levels.
- Little discussion of anti-aging or health maintenance in general: Doesn't cover vitamins or other supplements, the importance of diet and exercise, or required testing.
- No direct cites to references (though there are references in the back). No index.
- Considerably redundancy: could be trimmed by a third with proper editing.

10. ***The New Hormone Solution (3*)***
    Good overview of the issues, but very weak on references and the specific protocol recommended.
    The good:
    - Easy to read and relatively comprehensive,
    - Appropriately skeptical of the WHI study, doctors, synthetic hormones, and herbal supplements.
    - Good overview of the types of drugs doctors may try to prescribe instead of hormones (especially antidepressants) and why you shouldn't accept them as substitutes for real hormone therapy.
    - Includes a chapter on TRT for men.

    The bad:
    - No direct cites to references (though there are references in the back).
    - Primarily about symptom relief rather than optimization.
    - Abundant anecdotes, although at least they're from the author's own practice.
    - Recommends oral and transdermal modes, and at relatively low doses with no target serum levels specified.
    - Doesn't recommend testosterone for women.
11. ***The Estrogen Window (3*)***
    Strong advocate for estrogen therapy, but recommends only a very weak protocol.
    The good:
    - Very critical of the WHI.
    - Appropriately critical of doctors, although tries to shift the blame for their inadequate treatment to medical boards, professional organizations, and malpractice and health insurance companies.
    - Appropriately skeptical of compounding pharmacies, but mistakenly blames them for the problems with transdermal progesterone (which are primarily caused by large inter-individual/inter-area/inter-day variability in permeability and metabolism).
    - Strong proponent of regular assessments including of endometrial thickness, especially for cyclic (vs. continuous) progesterone protocols.
    - Recommends starting therapy at the first sign of menopause (the opening of the "Estrogen Window"), and at least open-minded about duration (no "10 year" limit, which I guess means that in many cases the "Window" never closes).

The bad:

- All about the estrogen with inadequate coverage of progesterone and negligible coverage of testosterone, thyroid, and other hormones.
- Overly eager to accept FDA-approved therapies, including for SERMs which have negligible safety records compared with almost all progestins.
- Despite the deference to the FDA, hypocritically promotes herbal supplements which are specifically recommended against by the FDA (and pretty much every other evidence-based organization), albeit with appropriate caveats.
- Primarily about symptom relief rather than optimization.
- Considerable redundancy: The length could be cut by at least a third with aggressive editing.

12. ***I'm Too Young For This (3*)***

Well researched, but fanatic about bioidentical hormones and so overlooks their limitations.

The good:

- Convincingly argues the goal should be improved quality of life rather than mere symptom relief.
- Comprehensive and well researched with a decent set of references.
- Approachable, albeit at some cost in the scientific and protocol details.
- Appropriately skeptical of doctors, the WHI study, saliva testing, oral dosing, conventional hormones (Premarin and MPA), and herbal supplements.
- Good section on how to find and evaluate a new doctor.

The bad:

- Only recommends transdermal protocols, and doesn't specify dosages or target serum levels (it's a modified version of the unproven Wiley Protocol although unlike the original it does at least recommend testosterone supplementation).
- Overly critical of synthetic analogs, making the recommendation for bioidenticals more of a religious argument than a scientific one.
- Recommends cyclic over continuous dosing and doesn't (couldn't) address more recent studies that have shown the latter is safer: The one study she does cite isn't relevant since it only covered oral synthetic progestins and only NETA was assessed in continuous protocols, NETA

overall being more risky than MPA, which in turn is significantly more risky than OHPC.
- Fails to recommend testing to monitor endometrial thickness which is a high risk area with both transdermal and cyclic protocols.

13. ***The Hormone Balance Bible (3*)***
Long-winded "archetype" model of hormone issues probably only useful for premenopausal women.
The good:
- Emphasizes that finding a good doc is the single most important part of the process.
- Relatively complete descriptions of the hormones, what they do, and the symptoms of deficiencies and excesses.
- Appropriately skeptical of pellet therapies.
- Recommends blood serum testing with urine testing as a backup where metabolism issues are suspected.

The bad:
- The "archetype" framework leads to massive redundancy making the book at least three times as long as it should be.
- Only recommends transdermal protocols, and doesn't specify dosages or target serum levels. Emphasizes symptom relief rather than optimization.
- Does briefly discuss injections but only very tepidly recommends them.
- Wastes enormous verbiage on Energy Integrators (without even explaining what they are), Yoga poses, chakras, and herbal supplement recommendations with no references provided to support any of this.
- Weak set of references and index (then again, this is highly correlated with the very low information density of the book overall).
- Most of the case studies are pre or perimenopausal women making it of very limited use postmenopause (only 1 of the 12 archetypes applies in this case).

14. ***Discovering Your truebalance with Bioidentical Hormones (3*)***
Very approachable, but poorly researched and with a weak protocol.
The good:
- Appropriately skeptical of "standard of care" doctors, Big Pharma, the WHI, oral hormones, and PremPro.
- Strong advocate for HRT, including testosterone for women.

- Flexible on synthetics and concedes that there are things that bioidenticals are just too weak to handle.
- Provides specific doses and target levels, though unfortunately they're way low (40pg/ml for E2, bottom of the lab range for T).

The bad:

- Major fanboy of estriol but provides no references to any research that supports any of the claims for it.
- No index and references lack article titles, making them very difficult to verify or to use this book as a reference.
- Very confusing about P, including target levels, cyclic vs. continuous protocols, saliva testing, and is apparently the source of the completely unsupported recommendation to withhold P one day a week to refresh receptors (and even admits that this may trigger a period every week, which it does in some women!). Misrepresents one of the key findings in this area: Transdermal doses less than 80mg/day do *not* provide endometrial protection.
- No mention of the requirement to have ultrasounds.
- Recommends injections for men, but only transdermal for women with no justification provided for this obvious sexual bias.
- Poorly edited with typos, multiple figures appear more than once, and significant redundancy.

15. ***Stay Young & Sexy with Bio-Identical Hormone Replacement: The Science Explained (3*)***

Anti-Prempro screed with a weak protocol prescription.

The good:

- Well researched with a decent set of references albeit primarily about how bad Premarin and Provera are.
- Good coverage of the history of HRT.
- Appropriately skeptical Big Pharma, saliva testing, oral dosing, conventional hormones, pellets, hysterectomies, high dose cyclic protocols (e.g., those that cause periods like the Wiley Protocol), and incompetent doctors.
- Few anecdotes and only uses them to illustrate failures (the section on broken bones and bone healing failures with Fosamax are particularly effective).
- Allows for testosterone although claims that most women don't need it.
- Good section on how to find and evaluate a new doctor.
- Includes a section for men, albeit without any specific protocol recommendations.

The bad:

- Heavily estriol-oriented (80% estriol Biest/Triest) protocol and claims that other forms of estrogen cause cancer. Ignores reports that estriol doesn't provide any of the benefits of estradiol on bone, heart, hair, skin, etc.
- Despite pointing out all the potential advantages of HRT recommends what is primarily a symptom-relief oriented protocol.
- Only recommends transdermal/transvaginal protocols, and doesn't specify dosages or target serum levels. Doesn't even mention injection protocols.
- Only recommends expensive and burdensome 24-hour urine testing that is difficult or impossible to compare with the results from the peer-reviewed literature which all uses serum testing.
- Overly critical of synthetic hormones, making the recommendation for bioidenticals more of a religious argument than a scientific one (e.g., there are now peer-reviewed papers that show that MPA/Provera is actually *safer* than Oral Micronized Progesterone).
- Accepts the quality of the WHI blaming the results all on the Premarin and Provera rather than on any flaws in the study design or implementation.
- Recommends cyclic over continuous dosing and doesn't (couldn't) address more recent studies that have shown the latter is safer.
- Fails to recommend testing to monitor endometrial thickness which is a high risk area with both transdermal and cyclic protocols.

16. ***The Miracle of Bio-Identical Hormones (3*)***

Minimalist book with a minimalist progesterone-based protocol.

The good:

- Strong endorsement that T3+T4 thyroid supplementation is an essential component of HRT, though unfortunately with no target levels, dosing recommendations, or coverage of RT3 or Hashimoto's.
- Recommends T as a standard component of HRT, and at a reasonable dose (5mg/day transdermal).
- Appropriately skeptical of Big Pharma, AMA "standard of care", antidepressants, and OMP.

The bad:

- Makes Dr Lee (***What Your Doctor May Not Tell You About Menopause***) look like hesitant about progesterone!

- Progesterone dose for protocol is 200mg/day transdermal, a massive overdose (approximately equivalent to 500mg/day OMP).
- Recommends against any estrogen supplementation.
- Doesn't supply target levels for P or T.
- Repeatedly makes misleading and provably false statements (even for 2007) about "estrogen" (vs. specific forms of it), synthetic hormones, and even about progesterone (it does *not* prevent osteoporosis, only E and T can do that).
- Goes off on various rants about how progesterone alone can cure ADHD, metabolic syndrome, and a host of other maladies, claims for which there is no peer-reviewed support.
- No references, a real deal breaker considering the claims.

17. ***Estrogen Matters (3*)***

Comprehensive review of the evidence that HRT is safe and effective, but not much else…

The good:

- Absolutely eviscerates the WHI study, and the researchers associated with it, especially those who continue to support its conclusions.
- Relatively free of anecdotes, with the bonus of being the only book on this list that explains in great detail why using anecdotes or other broscience to make individual or public policy decisions is just a really bad idea unless it's backed up by data from peer-reviewed journals.
- Provides evidence against transdermal application of hormones.
- If you have even a tiny shred of open-mindedness about HRT there is no way you could read this book and come away with any doubt that it should be the standard of care for nearly all women.

The bad:

- The cliché "beating a dead horse" comes to mind when reading it and at various points it becomes positively tedious: The WHI study was botched, we get it already!
- The level of technical detail may be overwhelming for many readers.
- It's a "one trick pony": It's essentially a pro-HRT propaganda piece with very little in the way of background information on what hormones are and what they do or

practical advice as to what treatments to use, how to use them, or how to assess their effects on the body.

- Primarily endorses Premarin as the form of estrogen and synthetic oral progestins with no real discussion of alternatives. No mention of testosterone at all.
- Repeatedly criticizes doctors about their unsupported biases without specifically advising their clients to educate themselves to enable them to take control of their treatment, nor does it even provide even open-minded doctors any information about appropriate therapies and testing protocols.

18. ***The Estrogen Question: Know Before You Say "No" to HRT. (3*)***

    Essentially a clone of "Estrogen Matters" with slightly more data but way milder criticism of the WHI and doctors and organizations that still follow its recommendations.

    The good:

    - Fully referenced with more studies some of which are newer than "Estrogen Matters" (because it was published a year later).
    - Recommends transdermal bioidentical E2, P and T over oral forms.
    - Relatively free of anecdotes.
    - Recommends starting HRT early, and not ever discontinuing.

    The bad:

    - Zero information on dosing or target levels.
    - Egregiously misinformed about HRT via injection protocols.
    - Claims to be written for lay people, but is clearly aimed at trying to educate doctors without insulting them and their allegiance to "standard of care". Its main flaw in comparison with "Estrogen Matters" is in fact that its criticism of the WHI and "standard of care" is way too muted.

19. ***The Definitive Testosterone Replacement Therapy MANual: How to Optimize Your Testosterone For Lifelong Health And Happiness (3*)***

    A good introduction to the "why" of TRT, with somewhat out of date coverage of the "how".

    The good:

    - Good section on diagnosis of low TRT.
    - Lots of appropriate references and links to informative websites.

The bad:

- Limited coverage of the management of thyroid hormones and insulin, although at least they are mentioned as variables. As with the "TOT Bible", recommends T3/T4 compounds for weight loss.
- Very expensive for the amount of content, a significant portion of which is "filler" such as interviews and testimonials.
- Amazon reviews are not reliable because the author/publisher is gaming the system by offering compensation for 5-star reviews.

20. ***Hormones and Your Health: A Smart Woman's Guide to Hormonal and Alternative Therapies for Menopause (3*)***
    Lots of facts but unfortunately draws many wrong conclusions from them.
    The good:
    - The most factually complete and best researched menopause book on this list.
    - Strong advocate of HRT.
    - Appropriately skeptical of the WHI (and other large-scale studies), doctors, saliva testing, Big Pharma, the media, oral hormones, and supplements, and backs these opinions up with lots of supporting references.
    - Strong advocate of avoiding hysterectomy, again with many references.
    - Well indexed, making it useful as a reference book.

    The bad:
    - The key elements of the recommended protocol aren't backed up with facts, or don't fit with the facts provided in the cited research (e.g., makes the ridiculous claims that testosterone supplements aren't needed because levels don't decrease in men or women as a result of aging, and that DHEA is an adequate substitute for testosterone).
    - May be too dense for most readers (albeit it does say it's for "Smart Women").
    - Mostly about symptom relief rather than optimization.
    - Significantly out of date. For example more recent research has shown that the recommended cyclic/sequential protocols are significantly more risky than continuous protocols. Even the research she cites should have been sufficient for her make this recommendation: For example she has good coverage of endometriosis but

fails to recognize that cyclic protocols are inappropriate for any women with a history of this condition.
- No coverage of other key hormones that need to be monitored in menopause (thyroid, cortisol, etc.)

21. ***Menopause: Your Management Your Way … Now and for the Rest of Your Life (2*)***
Well researched with lots of good references, but doesn't supply a specific protocol or even make specific recommendations in general.
The good:
- At least touches on every relevant topic.
- Excellent long-form table of contents and index.

The bad:
- Big fan of herbal supplements.
- Very weak discussion of thyroid issues.
- Little discussion of testosterone (calls it the "male" hormone).
- Fairly shallow discussion of most topics, seems to go out of its way to avoid strongly recommending or condemning any specific proposal.
- Overly accepting of saliva testing, the WHI, oral hormones, and "making up your own protocol".

22. ***Sex, Lies, and Menopause: The Shocking Truth About Hormone Replacement Therapy (2*)***
Bold protocol with weak to non-existent scientific backing.
The good:
- The best review of the history of HRT.
- The original "Wiley Protocol".
- Good analysis of the connections between hormone levels and cancer.
- Very skeptical of doctors, insurance companies, and Big Pharma, with a good analysis of how the patent system is abused by the latter.
- Appropriately skeptical of oral hormones, saliva testing, and herbal supplements.
- Strong advocate for HRT and includes very specific protocol recommendations with both dose and target serum levels.

The bad:
- Appears to be well referenced, but actually isn't: Many of the references are to non-peer-reviewed sources and the references to many of the peer reviewed articles (actually, all of the ones I checked!) misrepresent the conclusions of

those articles. But the most egregious example is that the reference for the key claim of the entire book, that cyclic/sequential protocols are superior to continuous protocols, is a circular reference to this book itself! That's like saying "It's true because I said so!".

- Relatively free of anecdotes, but stuffed with "just so" stories about everything from pagan rituals to the frequency of homosexuality. There's also a fair amount of mysticism (such as recommending timing periods to the phases of the moon and support for homeopathy).
- A "bioidentical" zealot, she massively overgeneralizes the characteristics of synthetic progestins.
- A "sequential/cyclic" zealot, she says that women need to be menstruating into their 90s, a claim she doesn't back up with any peer-reviewed research or even any anecdotes.
- Opposes testosterone supplementation and even claims it causes breast cancer, which is false. Worse, she ignores the fact that testosterone levels in premenopausal women are at least double what they are in postmenopausal women, this exact same type of difference in levels being the only evidence she cites that estrogen levels should be kept high after menopause (i.e., because young women don't get breast cancer).
- The protocol itself is extremely burdensome: Twice a day side-effect-inducingly high doses of estradiol and progesterone creams, *plus* a monthly period. Who's going to put up with that?

23. ***Age Healthier, Live Happier: Avoiding Over-Medication Through Natural Hormone Balance (2*)***

The founder of the BioTE pellet company promotes his products.

The good:

- Extremely skeptical of Big Pharma, synthetic hormones, and transdermal hormones.
- Big proponent of thyroid supplementation with NDT and correctly blames doctors for significantly underdiagnosing and undertreating hypothyroidism.
- Doesn't weigh in on the saliva/blood/urine testing debate, but in practice relies on blood testing.

The bad:

- Ginormously hypocritical: Goes on and on about the results of Big Pharma's withholding of information and misrepresentations of the benefits of their products and yet does exactly the same thing, promoting a system

where doctors are trained to insert pellets without understanding the risks, the underlying physiology, or even how to do proper follow-up, leading to negative outcomes for a large fraction of their customers and turning doctors into "pellet pushers".

- Unfairly critical of injections because it assumes IM injections done by doctors. In fact SC injections done yourself have none of the listed disadvantages and offer far more stable levels than pellets with an order of magnitude (or perhaps more) lower risks of infection/rejection/overdose/underdose (the book discloses (p105) that just the first two of those happen 6-8% of the time which is just an insanely high failure rate)
- The only specific dose or serum level target specified in the entire book is that Total Testosterone of 500ng/ml in men is the criteria to get a new pellet. In fact, depending on SHBG levels, that is already significantly deficient.
- Promotes only OMP without even mentioning the inadequate serum progesterone levels most women achieve with that, leading to significant underprotection of endometrium. Claims the sleepiness OMP causes is a benefit.
- "Anecdotes" are clearly fabrications.
- No references and no index, and the former being especially significant because many of the claims in the book are completely unsupported by the peer-reviewed literature.

24. ***Younger: A Breakthrough Program to Reset Your Genes, Reverse Aging, and Turn Back the Clock 10 Years (2*)***

    Broad survey of the anti-aging field, but weak on medical intervention (i.e. the stuff that works).

    The good:

    - The best coverage of the "diet and exercise" portion of an anti-aging protocol.
    - Well referenced and with lots of specific protocol recommendations, at least for non-medical interventions.

    The bad:

    - Very limited coverage of hormones and just passes the buck on them: Rather than educating the consumer, recommends you "ask your doctor about…" which only ensures undertreatment or perhaps failure to treat at all.
    - Very limited coverage of lab testing, an essential component of any anti-aging protocol.

- Recommends genetic testing as part of the process of refining a protocol, something that the science probably won't actually support for decades, if ever.

25. ***Younger Next Year for Women: Live Strong, Fit, and Sexy - Until You're 80 and Beyond (2*)***

    Run-of-the-mill "diet and exercise" book that unfortunately has the hormone story completely wrong.

    The good:

    - Chatty, friendly, and optimistic about your prospects as an old person.
    - Lots of lifestyle hacks to help you set goals and then keep up the motivation to achieve them.
    - Good motivator for taking on the "diet and exercise" part of an anti-aging protocol.

    The bad:

    - Has the hormone story completely wrong: Wholeheartedly and uncritically accepts the deeply flawed WHI study report, and claims that HRT and TRT are simply inappropriate and unnecessary therapies.
    - Repeats the (now widely discredited) claims that testosterone is simply the aggression hormone.
    - No mention of thyroid, insulin, metformin or any other medical factor associated with aging. Only mentions cancer a couple of times with zero information about how to prevent or treat it.
    - Way too many anecdotes, and no references.
    - About 3 times as long as it needs to be, unless it's the anecdotes you're really into.

26. ***The Wisdom of Menopause (2*)***

    A classic example of the Matthew Effect: A lousy book that sells well because it's popular.

    The good:

    - Fairly comprehensive survey of the field, with special emphasis on the most common protocol elements (diet, exercise, and stress reduction).
    - Appropriately skeptical of the WHI, synthetic hormones, doctors, Big Pharma, and supplements.
    - Good collection of quality references.
    - By far the most popular book on menopause, meaning it's the one your doctor and your friends are most likely to be familiar with.

The bad:

- Endorses HRT, but only tepidly. Contains lots of evidence about the benefits of HRT, but then only recommends relatively weak transdermal doses that will generally only achieve symptom relief instead of full optimization. Doesn't even provide target levels.
- Relies on "private communication" of unpublished research for key components of the protocol, including the single most important aspect: HRT delivery via oral vs. transdermal vs. pellets/injections (discussion of the latter is omitted entirely!)
- Endorses saliva testing, and makes the common mistake of assuming saliva levels correspond to physiological effects, a claim unsupported by the peer-reviewed research.
- Makes specific recommendation about diet and supplements but then admits "I don't have any evidence any of this works".
- Way too many anecdotes, and explicitly admits that some of them are fabricated (she calls them "composites").
- Almost useless coverage of thyroid issues with no target levels provided, no mention of RT3, thyroid antibodies, or Hashimoto's despite acknowledging that this is one of the most likely problem areas in menopause.
- Randomly mixes spiritual "evidence" (the "Divine", chakras, etc.) in with the real science, leading the reader to doubt her grasp of what "evidence based decisionmaking" really is.
- Way too long: at almost 750 pages it's about 3 times as long as most of the other books on this list. Unfortunately about a third of that is simple redundancy (e.g., the same recommendation against some common treatments are repeated multiple times). Another third are anecdotes, about her own life or those "composite" case studies. Properly edited this book would be similar in length to the others because it contains about the same amount of information overall.
- The index is weak. Part of this is because of the redundancy, part because the book simply lacks information on many crucial subjects, but beyond those things it simply lacks entries even for important things it does cover. This makes the book very hard to use as a reference, supposedly one of its selling points. If you still

want to have a copy I'd recommend buying the Kindle version where at least you can use full-text search.

27. ***Ageless: The naked truth about bioidentical hormones (2*)***
Expensive "concierge" doctors ramble on about their (now long out of date) unsupported theories.

The good:

- All in on the "most doctors don't know what they're doing" philosophy.
- Firm on the need for hormone therapy for both men and women.

The bad:

- Vastly inferior to her newer book (I'm Too Young For This), both in the quality of the writing and quality of the evidence.
- Accepts the findings of the WHI, but blames them on the fact that the hormones used were synthetics.
- Huge fan of transdermal cyclic protocols but supplies zero evidence for why they're better or even safe at all.
- No specific protocols or target serum levels.
- No references other than a bibliography of the books of the contributors.

28. ***What Your Doctor May Not Tell You About Menopause (2*)***
Significantly out of date, from a time when mere symptom relief was the standard.

The good:

- Extensive background information on what hormones are and what they do.
- Relatively free of anecdotes, appeals to nature, and reliance on the placebo effect.
- Good criticism of oral progesterone.

The bad:

- Overwhelming emphasis on symptom relief rather than hormone optimization.
- Endorses the WHI methods and conclusion.
- All about the transdermal progesterone, claiming that it's the appropriate treatment for nearly all women.
- Claims only 1/3 of women need estrogen, and even then only minimal (perhaps even negligible) doses. Which is kind of lucky because it's the only way the seriously underdosed progesterone regimen wouldn't be dangerous.
- Recommends saliva testing over serum testing, yet provides no theory explaining the discrepancies. Is particularly a fanboy of Zava/ZRT (the saliva-testing

company behind the bogus claims that you can only accurately measure transdermal hormones by saliva).
- No recommendation to test for effects (endometrial thickness, bone density, etc.)
- Does recommend testosterone, but only for some women, only very low doses, and only as a cream.
- Recommends changing diet and avoiding environmental toxins instead of taking thyroid hormone, a ridiculous prescription.

29. ***The Hormone Cure (2*)***

The "Gottfried Protocol" mostly relies on the "placebo effect". Avoid it.

The good:

- Good general background information on the issues, terminology, and references.
- Especially good overview of cortisol and thyroid pathways and treatments.
- Addresses hormone imbalances in all stages of women's lives, including in premenopausal women.

The bad:

- Infuriatingly hypocritical: It makes many claims of deference to the FDA and peer-reviewed journals, but then repeatedly makes strong recommendations to use the kinds of supplements and dietary protocols that those organizations specifically recommend against. Worse, it makes little or no mention of the issues concerning the quality, effectiveness, or side effects of most of those supplements.
- Relies heavily on anecdotes, although at least they are from the author's own professional experience ("The Gottfried Files").
- Mostly about symptom relief rather than optimization. The heavy reliance on herbal supplements also means that it's primarily a "placebo effect" protocol.
- Recommends only transdermal estrogen and oral micronized progesterone. Recommends against any sort of testosterone supplementation, and indeed is heavy on recommendations on reducing testosterone levels even further than their naturally-low postmenopausal levels.

30. ***Anticancer: A New Way of Life (2*)***

A "wishful thinking" prescription for anticancer/anti-aging.

The good:

- There undoubtedly is a connection between cancer and things like diet, exercise, and mental health, albeit at best a moderate one. This book could help one optimize these aspects of a health maintenance protocol (although there are many, many others do a better job of that).
- Very well researched, although most of the references are limited to the above topics.
- Optimistic tone could prove beneficial to those who are already fighting cancer.

The bad:

- How one could publish a book on cancer that doesn't even mention metformin is baffling.
- Extremely limited coverage of hormonal effects on cancer (and they're vastly larger than diet, exercise, and mental health combined). To the extent it mentions hormones at all it's about how to reduce them, which is exactly backwards: We need to managed them to achieve optimal levels, not fear them.
- Stuffed with personal anecdotes, appeals to nature, things that "work" due only to the placebo effect, and wishful thinking.

31. ***Mayo Clinic The Menopause Solution: A doctor's guide to relieving hot flashes, enjoying better sex, sleeping well, controlling your weight, and being happy! (2*)***

Mostly about accepting suffering or paying Big Pharma to alleviate it, the side effects be damned.

The good:

- A beautiful book, with top shelf layout and custom illustrations.
- Extensive survey of all the things that can go wrong with us as we age, which is especially useful if you happen to be from Mars.
- Appropriately skeptical of supplements and transdermal hormones.
- Good lists and descriptions of tests that older people should get with their physicals (bone density, colon health, etc.) albeit with very little information about how to evaluate the results.

The bad:

- More about working around or accepting suffering than about doing anything to address the underlying issues.
- Generally supports the WHI conclusions.

- Very little discussion of actual hormone protocols, and especially deficient in discussion of testosterone.
- No discussion of thyroid issues.
- Positively stuffed with recommendations for Big Pharma products including antidepressants, statins, and hypertension and osteoporosis drugs including a wide variety of cutting edge products most of which, if history is any guide, will eventually prove to be far more dangerous than hormones (not to mention being orders of magnitude more expensive).
- No references! At all!

32. ***Dr. John Lee's Hormone Balance Made Simple (1*)***

A lightweight digest of Lee's other books, probably not useful for anyone.

The good:

- Well, at least it's short. And cheap.
- It does specify a protocol, albeit a very weak one.

The bad:

- All of the flaws in his other book ("***What Your Doctor May Not Tell You About Menopause***") without any of the redeeming background information.
- Only targets symptom relief rather than health optimization.
- Primarily recommends progesterone, with many (bogus) warnings against supplementing estrogen or testosterone.
- Only recommends saliva testing and not serum levels nor for effects (bone density, endometrial thickness, etc.)
- No references.

33. ***Menopause Confidential (1*)***

Probably the worst of the books in this field, no references or protocol recommendations at all!

The good:

- Short, approachable overview of the issues.
- Appropriately critical of saliva testing.

The bad:

- Heavy emphasis on symptom relief rather than hormone optimization.
- Specifically avoids recommending particular protocols in an attempt to keep the book from becoming obsolete (which is not your problem), leading to vague and superficial coverage of this key issue.

- No references! “Approachable” is worthy goal, but not if it means leaving out crucial information and links to supporting data.

Appendix 2

The Frail Proof FAQ

Frequently Asked Questions about Hormone Therapies

These are the questions most frequently posted on social media with most of the answers digested from the book Frail Proof, which in turn was derived from the peer-reviewed research, popular books on menopause, and the answers posted to those questions on social media (which are collectively commonly referred to as being the "broscience"). Please refer to that book and the links on https://www.frailproof.com/ for more information and supporting references.

This list and the Frail Proof protocol in general is oriented toward US audiences. The hormones, lab tests, and protocols in other countries will vary somewhat although the underlying conditions and general solutions are the same. Prices shown are in USD.

In these questions and on social media in general, the following abbreviations are used:

T = testosterone
E = estrogen (all forms)
E1 = estrone, the "old woman" estrogen, produced by fat
E2 = estradiol, the most potent form, produced by the ovaries
E3 = estriol, the weakest form, doesn't protect bones/brain/skin
P = progesterone (also progestins and progestogens in general)
OMP = oral micronized progesterone (a P)
OHPC = hydroxyprogesterone caproate (generic Makena, a P)
MPA = medroxyprogesterone acetate (generic Provera, a P)
NETA = norethindrone acetate (generic Aygestin, a P)
GP = general practitioner (a family doctor)
PCP = primary care physician (same as GP)
NP = nurse practitioner (lowest certification to prescribe)
PA = physician's assistant (between NP and MD)
WP = Wiley protocol, a high-dose cyclic transdermal protocol
SS = Suzanne Somers a major proponent of WP-like protocols
SHBG = sex hormone binding globulin, disables T and E2
TSH = thyroid stimulating hormone
FT3, RT3 = Free T3 and Reverse T3
DIM = Diindolylmethane, a supplement to reduce "bad" estrogens
surmeno = Surgical menopause (having ovaries removed)

Units are most commonly omitted when quoting levels because most labs, and most notably both Quest and Labcorp, use the same units. Different labs do have different ranges, however, and you need those ranges to make the call about whether a level is high or low. To convert US units to European units (usually in nmol rather than pg or ng) divide by (roughly) 3. More precise conversion calculators can be found on-line.

1) Do I need hormone therapy? How will I benefit?

Every one of the current generation of books on menopause recommends it for postmenopausal women, although the specific protocol recommendations vary considerably (see http://www.frailproof.com/FPBG.pdf for the details). A more complete consensus is seldom seen in the medical field. For men the answer is more qualified: If you have any of the symptoms of low testosterone (weight gain, loss of strength or muscle mass, mood or motivational disorders, sexual dysfunction, and many others) and test low on Free T, you will almost certainly benefit.

And the benefits are primarily in quality of life, not just quantity. Beyond mere alleviation of the symptoms of menopause and andropause, hormone therapies simply make you look, feel, and act younger, slowing or in many cases even reversing the aging process.

2) Is hormone therapy safe?

It is definitely safer than doing without: Even in the most negative (albeit very poorly done) study of hormone therapies, the Women's Health Initiative, all-causes death was lower in the treatment group than for the women who did not receive hormones, albeit with increases in some specific conditions (blood clots and breast cancer in particular). And that data was collected more than 20 years ago: With more modern protocols, especially those that don't rely on fully-synthetic oral hormones like Premarin and MPA, risk is lower even for those conditions.

3) When should I start hormone therapy?

Women should start P therapy as soon as periods start to become irregular (perimenopause), cyclically/sequentially (14-21 days a month) if the goal is to regulate the periods or continuously if the goal is to stop them entirely. Because P declines first, women typically become estrogen dominant for up to a few years, leading to a greatly increased risk of endometrial proliferation/hyperplasia

which can cause blood spotting and breakthrough bleeding. This in turn is associated with a significant increase in the risk of cancer but more importantly of getting talked into having a hysterectomy when all they really need is P supplementation.

E2 and T decline more slowly: By the time menopause starts they have dropped by roughly half and can take years to drop down to postmenopausal (negligible) levels. Therefore E2 and T therapy can be started immediately with P, but with proportionately smaller doses: It is possible to go through menopause experiencing none of the side effects women typically report and to fully protect bone and muscle mass during the transition.

4) *Can I start after age X?*

There are no specific age restrictions on hormone therapies, neither for men nor women. Although there is relatively little data on women starting or continuing therapies after age 60, the data from studies on men even much older than that (even into their 90s) is encouraging: They gain strength, muscle mass, mental clarity, and "grit" and with a very low incidence of side effects and a *decrease* in risk of cancer and heart disease.

There's also no need to ever stop hormone therapies: The 10-year window old-school docs use is an archaic concept not supported by more modern research.

5) *Will hormone therapy cause weight gain?*

While supplementing E, P, and/or T can cause some water retention, and hence some weight gain, none of them should cause fat accumulation, and E2 and T supplementation will generally reduce existing fat mass. T when combined with weight-bearing exercise will generally result in increased muscle mass, again increasing weight but not fat. The one exception to this rule is that E2 and T both interact with thyroid hormones, causing or exacerbating hypothyroidism. A full thyroid panel should be done prior to starting HRT/TRT and retesting and thyroid hormone dosing adjusted within a few months of reaching a stable protocol. It's difficult to impossible to lose or even maintain a stable weight if you are hypothyroid.

6) *My doctor wants to prescribe X, which I don't want, or won't prescribe Y, which I do. What can I do?*

Change doctors. The "standard of care" in HT/HRT/TRT and for thyroid issues and diabetes is at least a decade behind the peer-reviewed science, and many doctors are even more backward than that. The odds of receiving appropriate hormone therapy from a General Practitioner (GP) are close enough to zero as to rule out even considering this. Odds are only slightly better with urologists, gynecologists, and endocrinologists who are not much more likely to even be aware of the state of the art in this field let alone be providing treatment at that level.

So, in most cases you'll need to find a "functional", "integrative", or "anti-aging" specialist or a clinic that specializes in hormone therapies. A good place to start is The American Academy of Anti-Aging Medicine (A4M) doctor locator: https://www.a4m.com/find-a-doctor.html, keeping in mind that many of these doctors will support clients without ever even seeing them ("concierge telemedicine"), using local providers for the physical exams. Or do an Internet search for those terms specifying your city or state/province. But even after you find a candidate, gather as much information about the therapies they prescribe before signing up for a consultation to ensure that they're a good fit and that you're not just wasting each other's time.

7) *Can I get insurance to pay for these therapies?*

In general, no. Most insurance plans, specifically including Medicaid and Medicare, do not cover state of the art treatments (including prescribing hCG for men and testosterone for women), in part because they are not FDA approved (i.e., modern hormone therapy relies heavily on off-label uses of hormones and other drugs). Trying to mix and match (trying to get a GP to order some of the tests and hormones that may be covered by insurance while having a specialist order the rest) generally only results in frustrating both doctors and yourself.

8) *How much will this cost?*

The cost varies a lot depending on the protocol you and your doctor choose. It also will cost two or three times as much the first year, while you are tweaking your protocol, as in subsequent years. The going rate for start-up consultations ranges from $250 to $500, with less expensive follow up consultations being required a few times a year to start and as little once a year ongoing. Blood

tests generally run about $250 per batch and must be done several times the first year, but probably only once or twice a year once you get your protocol down. If your doctor quotes significantly more than that for labs, order them yourself through one of the various on-line lab companies (e.g., https://www.ultalabtests.com/thyroidpharmacist/).

For the hormones, generic compounded creams and patches (transdermal application) and synthetic oral products are generally the least expensive, figure $200 to $400 a year. Injections generally run $300-$500 a year depending on whether you can use factory-produced compounds (e.g., Depo-Testosterone and Depo-Provera) or need compounded products (OHPC is only available compounded and many people have reactions to the carrier oils in factory-produced products). Note that at least some injections are required for men since hCG is only available by injection. Brand-name creams, such as for the Wiley Protocol (WP), generally run 2 to 3 times that much (up to $1000/yr). Pellets can be that much or more because they require minor surgery to insert, a procedure that must be repeated about 4 times a year, and because P can't be pelletized in endometrium-protective quantities you have to add in the cost of some other form of that. For both WP and pellets the cost will be more for women than men whereas for injection the costs will be similar (the cost of the hormones themselves and the total quantities injected are similar).

9) *Is T required for women?*

Although few of the current crop of menopause books specifically recommend this, the peer-reviewed literature and broscience are unequivocal: Insufficient T is nearly universal in postmenopausal women and supplemental T provides a great many benefits to them. It may not be necessary if mere symptom relief is the goal, but is an essential component of any optimization protocol where the goal is to preserve the muscle mass, mood, libido, and "grit" that are characteristic of younger adults.

10) *My T is X, is that good?*

It is essentially useless to test or quote total testosterone levels because the effective (available for your body to use) amounts depend on SHBG levels which vary tremendously between individuals and even over time depending on what treatments you are receiving. You really only need to know "Free T" and so should only test and quote that. The "good" levels, for both men and

women, are around the top of the lab range (4 to 5 for women for LabCorp and Quest). This provides maximum benefits with minimal risk of side effects. Note that this rule also applies to quoting E2 levels if you're not supplementing T: SHBG preferentially binds T, but if Free T is too low it will bind up more E2 making your symptoms correspond with a much lower value than your labs would indicate.

11) *What are the best target levels for E2 and P? What doses will achieve these?*

For symptom relief it is usually sufficient to raise E2 to 20 to 40 for both men and women. For women seeking to optimize levels to premenopausal levels to achieve maximum benefits in skin, hair, bones, heart, and libido, a target near the median level in premenopausal women is frequently used, around 100. Some cyclic protocols target much higher levels (in the hundreds), but only for part of the month after which a period will clear out any accumulated endometrial tissue.

According to the peer-reviewed research, P levels for women on continuous protocols must be at least 5 to provide endometrial protection, a level that drastically reduces the risk of uterine cancer. Most practitioners furthermore try to balance E2 with P, specifying ratios of 50:1 to 100:1 (accounting for the difference in units, a factor of 1000). So a P of 5 would correspond to an E2 of 100. For cyclic protocols, P needs to be raised high enough to trigger a premenopausal-quality period.

As for dosing, tor injections starting T-cyp doses for women are roughly 20mg/wk, dosed once or twice a week. For E-cyp and E-val, 1.5mg/wk is a reasonable starting dose. For bioidentical P, 10mg/day, for OHPC about 150mg/wk.

For transdermal note that these recommendations refer to the hormones themselves, not the volume or weight of the cream: If all you have is the volume, multiply the dose size in ml by the cream concentration in mg/ml to convert to mg. Note that You must ***always*** dose transdermal hormones twice a day: Half life of those is too short for anything less. Starting doses for T are 5mg/day. Starting E2 dose is 3mg/day, and for P 80mg/day is a minimum safe dose. Note that many doctors prescribe less P than this, but the peer reviewed research is unequivocal on this: Doses less than 80mg/day simply do not provide sufficient endometrial

protection vastly increasing the risk of spotting, bleeding, cancer, and hysterectomy.

Minimum safe OMP dose is 200mg day, split breakfast and dinner. Again, most docs underdose OMP and say to take it before bed. Again, the peer-reviewed research is unequivocal on this: It is simply unsafe to take OMP on an empty stomach or only once a day unless the dose size is vastly increased because absorption is so poor and the half-life is too short. Also note that you must order the LCMS version of the P lab test when using OMP: The standard test significantly overestimates level of protection because it reacts to P metabolites that do not provide endometrial protection. It is not safe to take T orally or as a troche: Most of it simply gets digested, but metabolites generated may be hepatotoxic (kills liver cells). It is not safe to take E2 orally because the majority of it metabolizes into E1 which increases the risk of breast and ovarian cancer.

Redo labs a month after every significant protocol change and adjust dosing as necessary to achieve target levels.

12) My TSH is X, is that good?

TSH is essentially useless as a means of diagnosing or monitoring treatment of thyroid issues (review the information on https://stopthethyroidmadness.com/ for why). Which of course will be news to most doctors because their standard of care is, again, decades behind the state of the art. TSH level is a very indirect measurement of thyroid function since TSH only stimulates the thyroid to produce T4 which then gets metabolized into T3, the active form of the hormone. And even most of that is bound up and so not active.

So you only need to test Free T3 and then adjust dosing to get it to around 3.5, roughly the 66th percentile of the lab range. Lower than that and you'll most likely experience symptoms of hypothyroidism, higher than that of hyperthyroidism. If T3 is low and you require treatment you should overwhelmingly prefer DTE/NDT (desiccated thyroid extract/natural dehydrated thyroid) such as Armour or Nature-throid over T4-only drugs (Synthroid). If your doctor won't prescribe one of them, see question #4 or at least insist on testing Reverse T3 (RT3), the inhibitory form of the active thyroid hormone: If it is elevated (above the middle of the lab range) no amount of T4 will alleviate your symptoms and it

may even make them worse because your body will just convert more of it to RT3 than to Free T3.

TSH under appropriate treatment will generally drop below the bottom of the lab range (0.4) but optimally should remain at or above 0.1. Note that most docs will attempt to reduce dosage to keep TSH above the lab range minimum of 0.4: If they do this, recognize that they are using obsolete information (e.g., some will try to convince you that it puts you at risk of osteoporosis which was shown many years ago to be a misconception so long as FT3 dose not go above 3.5) and again see question #4. Testing for thyroid antibodies (TPO and Thyroglobulin) to diagnose Hashimoto's is not strictly necessary as the treatment is the same regardless of whether you have it or not: The primary reason for including them is to help convince your doctor that treatment is necessary even though low Free T3 or high Reverse T3 should be sufficient to do so.

13) What's the best hormone protocol, oral, creams, patches, injections, suppositories, or pellets?

Make no mistake: Any treatment, even the "standard of care" low dose oral Prempro (equine estrogens with MPA), is safer and better than no treatment at all. Whether you can upgrade from that depends primarily on whether you can find and afford to pay for a progressive doctor.

There is much debate and yet no consensus on which protocol is best, neither on social media nor in the peer-reviewed research nor in the many books that have been published on menopause and hormone therapies. To some extent it depends on individual metabolism, motivation, available time and financial resources, tolerance for side effects (primarily associated with oral and pellets, pellets due primarily to the very common issues with dose regulation) and pain tolerance and squeamishness (associated with injections and pellets). Choosing a particular protocol yourself does obligate you to do the research necessary to compare all of the options, so one obvious answer is to choose a good doctor first and let them help you choose the protocol.

That said, injections have the reputation of being the "elite" protocol because they impose the greatest technical burden on the client but also offer by far the best control over dosing and the associated increase in safety and effectiveness and with the

smallest incidence of side effects. They're also significantly cheaper than pellets or name-brand transdermal (roughly 1/3 the cost). For men, the decision is easier: hCG can only be supplied by injection and most elite practitioners consider this an essential component of an optimization protocol. For women OHPC occupies a similar position. As long as you're doing one injection it only makes sense to get all your hormones that way. Second best would have to be transdermal/transvaginal/transrectal: Good level control and reasonable pricing, but with significantly more trouble (P must be dosed twice a day, the other hormones at least once a day). Pellets are a distant third: Expensive, poor level control, and a (relatively) high failure rate. Oral is fourth: Only acceptable if you can't get anything else.

14) Should I use "bioidentical" hormones, or are synthetics OK?

After an enormous amount of debate on this issue there is no clear picture other than that mode is vastly more important than the substance. For example 90% of oral micronized progesterone (ostensibly bioidentical) is metabolized by the liver and digestive system into roughly 30 different chemicals, many of which are not found in significant levels in untreated women, and many of which cause serious side effects (anxiety and sleepiness being two of the most common). This problem with "first pass" metabolism affects most other compounds when delivered orally, regardless of whether they started out as bioidentical or fully synthetic.

Any remaining differences between synthetic and bioidentical hormones are small by comparison, so it's generally better to choose them based on dosing reliability, frequency of side effects, or cost than being a stickler for detail on how they are produced. If oral micronized progesterone makes you groggy, troches or wafers for sublingual or transbuccal administration (dissolving under the tongue or between the cheek and gum) taste terrible to you, and/or you find the twice-a-day application of creams too burdensome, or if any of the above don't reliably keep your serum P level above 5, consider substituting an oral synthetic (even MPA) or OHPC injections which don't have any of these issues. All are safer overall than reducing the dose size of the bioidentical in an attempt to mitigate side effects.

One "bioidentical" to avoid is estriol (E3), and pills or creams that contain it (Biest or Triest, which contain E3 with some E2 and sometimes E1). Estriol is an extremely weak form of estrogen (30

to 100 times weaker than estradiol) and while it can help some with symptom relief it does not offer the same protection to bones/hair/skin as estradiol and so is not suitable as a component of an optimization protocol. Regardless of whether E3 is included in a protocol or not, E2 levels must be still optimized by dosing appropriately.

15) *Are cyclic/sequential protocols better than continuous protocols?*

There is also considerable disagreement on this issue in both the broscience and menopause books. The peer-reviewed research is much clearer, however: Continuous protocols have been shown to cut the risk of endometrial cancer by up to 50% over cyclic protocols such as the Wiley Protocol. The issue here is whether the dosing of P causes a sufficiently robust flushing and/or resorption of the endometrial tissue that grows during the low-P portion of the cycle. If it does not, the risk of endometrial cancer skyrockets in proportion to the amount of endometrial tissue: A stripe over 11mm thick is hundreds of times more likely to result in cancer than a stripe 5mm or less (for frame of reference this difference in risk is many times greater than that of smoking, drinking, high blood pressure, high cholesterol, and diabetes *combined*).

A fundamental misconception apparent in the proponents of cyclic protocols is that they're somehow more "natural" because they attempt to continue the monthly menstrual cycle in postmenopausal women. In fact, humans evolved in an environment where periods were very rare because women were either pregnant or nursing (both of which suppress menstruation) almost continuously. Looking at it from this perspective menstruation must be perceived as an "emergency eject" feature to be activated only in the relatively rare case where an egg released during ovulation did not get fertilized. The "natural" state of women is therefore much more similar to what is achieved with continuous protocols: Relatively high levels that slowly increase over 9 months of pregnancy followed by lower and more stable levels for approximately 3 years during nursing (E2 levels during nursing are in the same ballpark as the median level over the menstrual cycle albeit somewhat lower for some women). The second justification is that cyclic protocols somehow preserve or renew receptor sensitivity, a claim for which there is exactly zero support in the peer-reviewed research. This sort of "habituation" or

"tolerance effect" has never been reported in the TRT literature either.

16) I have blood spotting, should I be worried?

The short answer is "yes", but only a little: The greatest risk associated with blood spotting is not cancer, it's a doctor ordering an unnecessary hysterectomy: 600,000 of these procedures are performed in the US alone, at least 90% of which are unnecessary. There is a significant risk of cancer too, however, which is why the better-safe-than-sued doctors frequently try to take the easy way out rather than investing the time to figure out what's going wrong with your levels and/or protocol and fixing that.

Approximately 75% of cases of bleeding in postmenopausal women are caused by endometrial atrophy, where the endometrial lining is too thin (less than 4mm) due to a lack of estrogen and so is easily damaged. The second most common cause is endometrial proliferation/hyperplasia, where too much estrogen is available in relation to the level of a P that would check this growth. Although this tissue growth is caused by estrogen, the real problem is usually that the P level is not sufficient to suppress it. In both of these cases reducing E (unfortunately the approach most often chosen by doctors) is generally the exactly the wrong thing to do. Instead P must be increased, or possibly both P and E2 increased, either by increasing the dosage or changing the form, mode, or frequency of application. For example, transdermal P must be applied twice a day because dosing only once a day can cause a premature period: It is the drop in P level that causes a period and even the drop in level over 24 hours can be enough to do this. Note that this issue is particularly important to follow up on with continuous protocols or cyclic protocols that are not causing a premenopausal-quantity period each month, a robust period being a backstop that addresses the issue within a month of when the growth occurs.

Bleeding is also a sign that proper testing is not being done: A failure on the doctor's part, and a clear signal that it's time to shop for a new doctor. In addition to monitoring serum levels (or doing the dosing math correctly for synthetics) to ensure that a proper P to E ratio is being maintained, a uterine ultrasound should be ordered within 6 months of establishing a settled protocol. This simple, painless, and reasonably priced test (should be around $250) provides great peace of mind because of the vast increase

in risk of cancer associated with a thick endometrium (greater than 6mm), especially when there is also blood spotting.

Whatever else you do, do *not* adjust your P dosage in an attempt to minimize side effects or use those side effects to your advantage (e.g., many women inappropriately use OMP as a sort of sleeping pill, varying their dose based on how much sleep they need, grogginess being one of the most common side effects of OMP). This is a sure-fire way to end up with one of those unnecessary hysterectomies because it results in chronic underdosing.

17) Is there an injectable P?

Yes, but due to its short half-life (less than 24 hours) natural progesterone would have to be injected at least every day, with twice a day being preferred. And those shots can be very painful because the compound is an irritant at high concentrations. Fortunately there are two alternatives, MPA and OHPC.

Injectable MPA (Depo-Provera) has been used as a long-acting contraceptive since the 1980s. It's safe and effective and with fewer side effects than are associated with oral MPA (e.g., as the progestin component of Prempro). Even better is OHPC (hydroxyprogesterone caproate, generic Makena) the synthetic most similar to natural progesterone in structure and effect. In the US it is used primarily for pregnancy support, but it is used by millions of women in China as the P component of a once-a-month injectable contraceptive.

OHPC only needs to be injected once or twice a week, MPA only about once a month. SC/SQ (just under the skin) injections of these compounds are more effective and far less painful than old-school IM (deep into the muscle) injections.

18) Which is better, blood (serum) or saliva testing?

Although a couple of the current crop of menopause books recommend saliva testing, most don't and the peer-reviewed research is unequivocal: All recent published research uses serum testing, and the review/survey articles that discuss saliva testing universally report that it is not reliable enough to be used for diagnosis or treatment of any condition. Serum testing much more closely reflects the availability of hormones to all of the tissues of the body, not just the lymphatic system that is more selectively

involved in transdermal application and saliva or blood spot testing. Urine testing can also be accurate, but is more expensive than serum testing and many levels can't be measured that way.

19) I have symptom X, will supplement Y fix this?

In general, no, unless you're exceptionally susceptible to the placebo effect. While certain nutritional supplements (vitamins and minerals) can have very limited benefits in addressing overt deficiencies (see the section on supplements in **Frail Proof** for the details), herbal supplements in general have no place in an anti-aging or hormone optimization protocol. This is one area where the FDA and the medical profession have it right and their position is backed up by even the latest peer-reviewed research: Herbal supplements are at best ineffective (indeed, independent testing has shown that many of them contain little or none of the compound they're supposed to be providing!) and in most cases interfere with proper treatment, cause debilitating side effects, or even are directly harmful. Be especially skeptical if your doctor is selling the supplements they are recommending. If you're still inclined to try one be sure to first read the reviews of that supplement on sites such as https://labdoor.com/ and https://www.drugs.com/.

Appendix 3

The Frail Proof Protocol

This appendix describes how to prepare and use the 3-part hormone injection (OHPC + estradiol cypionate + testosterone cypionate) for postmenopausal women. The protocol for men and additional information on the protocol for women can be found in the full Frail Proof book. The key to the protocol for women is OHPC (hydroxyprogesterone caproate aka generic Makena), the progestin component. The book has more information on why it, and an all-injection protocol, is superior to all of the alternatives. The other two components are widely used in hormone therapies, with T-cyp being by far the most popular form of T for men on TRT.

There are lots of videos that show how to do subcutaneous (SC/SQ) injections: Search for "insulin injection video". And keep in mind that the average juvenile diabetic learns to self-inject their insulin by the age of 11: If they can do this, surely you can too. Hormones are about as easy to dose as insulin, but it takes slightly more time to draw and inject them: Insulin is water-based whereas these hormones are all dissolved in oil-based carriers. The recommended syringe is commonly known as an "allergy test syringe" (26 gauge 3/8" zero-deadspace), which is smaller and shorter than that used for a flu shot albeit a little larger diameter than typically used for insulin.

You can get E-cyp and T-cyp from most pharmacies, though it will be a special order for many of them. OHPC is generally only available (or at least only available cost-effectively) from mail-order compounding pharmacies (e.g., Talon Compounding and Vasco Rx) which are generally price competitive with local pharmacies for E-cyp and T-cyp too. If possible get 10ml vials of the hormones with an ethyl oleate carrier. 5ml vials will work, but tend to me more expensive per mg. Other carrier oils will work, but all are thicker than EO (slower to draw and inject) and some (particularly cottonseed and castor) are more likely to cause reactions (usually redness and itching) at the injection site. Factory-produced hormones tend to use those two problematic carrier oils, although they'll generally be cheaper than those produced by a compounding pharmacy. It's OK to mix different types of carriers: They'll all blend. The empty sterile vials and syringes are all available on-line at very reasonable prices or from pharmacies, though you may have to accept substitutes from the latter.

The concentrations recommended here are the most common and usually the least expensive per mg. Other concentrations can be used,

but the ratio of the components and the dose size will have to be scaled accordingly. Other esters can be used (e.g., testosterone enthanate or estradiol valerate), but again the concentrations will generally be different for those and so the formula will need to be changed to supply equivalent mg per dose. Contrary to standard dosing instructions, these alternative esters are all roughly equally effective and dosing in mg per kg of body weight should be the same. But half-lives matter: For example, E-val has a half-life of 4 days vs. 8 days for E-cyp, so you must inject it at least twice a week and you will end up injecting more (in mg) per week for equivalent effect. Note that even though E-val generally costs less per mg than E-cyp, the fact that you need to inject more and the much greater risk of side effects due to the higher peak values make for a poor cost/benefit tradeoff.

The ratio of the three compounds is 6:4:1 (OHPC:E-cyp:T-cyp. At the concentrations specified below). This recipe makes 11ml, which should last you 12-16 weeks. You can pay to have a compounding pharmacy make this mix for you, but it will be many times more expensive and involve a much longer delay than the $2 and 5 minutes it takes to do it yourself.

The resulting mix has the following concentrations: OHPC 136mg/ml, E-cyp 1.8mg/ml, T-cyp 18mg/ml. A good starting dose for a 120lb woman is 0.8ml of this mix per week, split into two injections (e.g., 0.4ml on Monday morning, 0.4ml on Thursday evening). Dosing should be scaled by body weight. If you're already injecting E-cyp or T-cyp, scale your dose size to match the mg/wk of whichever you're currently receiving. If you know you have particularly low or high SHBG, you could also take that into account (e.g., increase the dose if your SHBG is over 150, decrease it if it's less than 100). And note that you can easily change the dose size with every shot (unlike, e.g., with pellets where you'd be stuck with an incorrect dose for weeks or months) without risking inadequate endometrial protection because the P:E2 ratio is fixed.

Supplies for producing the mix:

vial of OHPC 250mg/ml
vial of estradiol cypionate 5mg/ml
vial of testosterone cypionate 200mg/ml
empty 10ml sterile vial
5 ml syringe with 17-21 gauge needle
Alcohol prep pad or alcohol-soaked cotton ball

Procedure:

1) Wipe tops of vials with alcohol pad/ball.
2) Draw 5ml of air into syringe with needle.
3) Insert needle into OHPC vial.
4) Push air into vial, and then draw out 6ml of OHPC.
5) Insert needle into empty vial and inject.
6) Draw 5ml of air from the mix bottle to relieve pressure.
7) Repeat steps 2-6 moving 4ml of the E-cyp.
8) Repeat steps 2-6 moving 1ml of the T-cyp.
9) Invert/swirl mix until completely smooth. Don't shake!

If you're using a smaller syringe you'll have to repeat the intermediate steps to move the compounds in multiple steps. If there's not enough hormone left in a source vial, you'll also need to use additional vials to get the right quantity moved into the new vial. Note that vials are usually overfilled, so you can usually get 6ml out of a 5ml vial if you work at it.

Supplies for injecting the mix:

Vial of mix
1ml syringe with 3/8" 26 gauge zero-deadspace needle
Alcohol prep pad or alcohol-soaked cotton ball

Procedure:

1) Swirl mix and check to make sure it's uniform.
2) Wipe top of vial with alcohol pad/ball.
3) Wipe target area of skin with alcohol pad/ball.
4) Draw (dose size) of air into syringe with needle.
5) Insert needle into mix vial.
6) Push air into vial, and draw out (dose size) of mix.
7) Lightly pinch some skin, then push needle in (quickly).
8) Slowly inject contents over several seconds.
9) Wait a second or two for the dose to diffuse.
10) Quickly remove needle.
11) Place (clean) finger (the one used to do alcohol wipe) on injection site and maintain light pressure for a few seconds to prevent leakage and help distribute mix away from injection site.
12) Remove finger and wipe up any leakage, or distribute it and call it "transdermal application", because that's what it is.

You can inject into any area that has a decent fat pad under the skin, but of course you probably also want to use a relatively

insensitive location. Most common is to inject into the belly fat or "love handles". The top of the buttocks is also a good choice although it will require having a partner do the actual injecting.

Do labs for E2 (estradiol) and Free Testosterone about a month after starting the protocol, and adjust dosing as required. Target values for E2 are about the average level in premenopausal women (about 100 for Labcorp and Quest: To get a ballpark estimate for other labs, add up the top and bottom of the ranges for the follicular and luteal phases and divide by 4). Free T should be near the top of the lab range (4-5 for Labcorp and Quest). Note that you may have to adjust your ratio if the E2 and T are not off by the same proportion, but you should maintain the 6:4 OHPC:E2 ratio unless a transvaginal ultrasound at 3-6 months shows an endometrial stripe thicker than 5mm which indicates that you need more of a progestin to suppress endometrial proliferation/hyperplasia. Similarly, if you're starting this protocol as the result of failure of a previous protocol (spotting/bleeding or an ultrasound that shows thickened endometrium) using a higher OHPC:E2 ratio may be warranted. The 6:4 ratio is fairly conservative (there should be more P than is necessary for adequate protection) due to the fact that underdosing has far more serious consequences than slightly overdosing and because side effects are rare for OHPC even with doses many times larger than required for postmenopausal hormone therapy (specifically, no sleepiness as is pretty much a standard side effect of OMP (Prometrium) due to the fact that 90% of the latter is metabolized by the digestive system into at least 30 different chemicals that are not progesterone).

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