

## Dr. Peter Attia: Exercise, Nutrition, Hormones for Vitality & Longevity | Huberman Lab Podcast #85

My guest this episode is Dr. Peter Attia, M.D., who trained at Stanford University School of Medicine, Johns Hopkins Hospital and the National Institutes of Health (NIH). Dr. Attia is host of The Drive podcast and is a world expert on behavioral approaches, nutritional interventions, supplementation and pharmacological techniques to improve lifespan, healthspan and athletic performance. We discuss how best to evaluate your health status using routine blood work, body scans and regular tests of physical strength and endurance. Dr. Attia explains what he uses with his patients to “back-cast” their health goals as a way to design their exercise and nutritional programs. We also discuss hormone modulation and replacement therapy for both men and women. We explain how cholesterol and related factors contribute to cardiovascular disease risk and how to monitor and mitigate that risk. Dr. Attia details various supplementation, nutrition, exercise and prescription approaches useful to people in every decade of life to improve vitality, reduce their risk of disease and increase the number of years sustaining peak cognitive and physical health.

#HubermanLab #PeterAttia #Longevity

Thank you to our sponsors

AG1 (Athletic Greens): <https://athleticgreens.com/huberman>

Thesis: <https://takethesis.com/huberman>

InsideTracker: <https://insidetracker.com/huberman>

Helix Sleep: <https://helixsleep.com/huberman>

Supplements from Momentous

<https://www.livemomentous.com/huberman>

Social & Website

Instagram: <https://www.instagram.com/hubermanlab>

Twitter: <https://twitter.com/hubermanlab>

Facebook: <https://www.facebook.com/hubermanlab>

TikTok: <https://www.tiktok.com/@hubermanlab>

Website: <https://hubermanlab.com>

Newsletter: <https://hubermanlab.com/neural-network>

Dr. Peter Attia

Website: <https://peterattiamd.com>

The Peter Attia Drive Podcast: <https://peterattiamd.com/podcast>

Newsletter: <https://peterattiamd.com/newsletter>

Twitter: <https://twitter.com/PeterAttiaMD>

Instagram: <https://www.instagram.com/peterattiamd>

YouTube: <https://www.youtube.com/c/PeterAttiaMD>

Facebook: <https://www.facebook.com/peterattiamd>

## Articles

Strength & longevity: <https://peterattiamd.com/ama27>

VO2 max & longevity: <https://peterattiamd.com/how-does-vo2-max-correlate-with-longevity>

## Timestamps

00:00:00 Assessing Health Status & Improving Vitality

00:02:51 Momentous Supplements

00:03:46 Thesis, InsideTracker, Helix Sleep

00:07:29 Lifespan: Bloodwork & Biomarkers Testing, The “4 Horseman of Disease”

00:11:51 Healthspan: Functional Testing, Cognitive & Emotional States

00:13:59 Blood Testing: Best Frequency

00:16:01 DEXA Scan: Lean Mass & Fat, Bone Mineral Density & Osteoporosis

00:22:33 Bone Mineral Density & Age-Related Decline, Strength Training,  
Corticosteroids

00:29:24 Osteopenia & Osteoporosis Diagnosis, Strength Training

00:31:03 AG1 (Athletic Greens)

00:32:16 Back-casting: Defining Your “Marginal Decade”

00:38:31 All-Cause Mortality: Smoking, Strength, VO2 max

00:44:43 Attia’s Rule of Supplementation, “Centenarian Decathlete” Physical Goals

00:49:24 Importance of Exercise, Brain Health, MET hours

00:55:23 Nicotine & Cognitive Focus

01:03:12 Menstruation, PMS & Menopause  
01:10:10 Hormone Replacement Therapy, Menopause & Breast Cancer Risk  
01:22:06 Estrogen, Progesterone & Testosterone Therapies in Women  
01:26:35 Hormone Replacement Therapy in Men, SHBG & Testosterone, Insulin  
01:37:23 Clomid, Pituitary, Testosterone & Cholesterol, Anastrozole, HCG  
01:47:46 Fadogia Agrestis, Supplements, Rapamycin  
01:52:06 Testosterone Replacement Therapy & Fertility  
01:59:26 Total Testosterone vs. Free Testosterone  
02:02:51 Cholesterol & Dietary Cholesterol, Saturated Fat, LDL & HDL, Apolipoprotein B  
02:17:42 Apolipoprotein B, Diet, Statins & Other Cholesterol Prescriptions  
02:25:15 Cardiovascular Disease, Age & Disease Risk  
02:28:53 Peptides, Stem Cells, BPC157, PRP (Platelet-Rich Plasma), Injury  
Rehabilitation  
02:37:40 Metabolomics & Exercise  
02:40:44 GLP-1 & Weight Loss  
02:47:06 Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors,  
Momentous Supplements, Instagram, Twitter, Neural Network Newsletter, Huberman  
Lab Clips

The Huberman Lab Podcast is for general informational purposes only and does not constitute the practice of medicine, nursing or other professional health care services, including the giving of medical advice, and no doctor/patient relationship is formed. The use of information on this podcast or materials linked from this podcast is at the user's own risk. The content of this podcast is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Users should not disregard or delay in obtaining medical advice for any medical condition they may have and should seek the assistance of their health care professionals for any such conditions.

Title Card Photo Credit: Mike Blabac - <https://www.blabacphoto.com>

- Welcome to the Huberman Lab Podcast, where we discuss science and science-based tools for everyday life. I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today my guest is Dr. Peter Attia. Dr. Attia is a physician who's focused on nutritional, supplementation-based, behavioral,

prescription drug, and other interventions that promote health span and lifespan. His expertise spans from exercise physiology to sleep physiology, emotional and mental health and pharmacology. Today we talk about all those areas of health, starting with the very basics, such as how to evaluate one's own health status and how to define one's health trajectory. We also talk about the various sorts of interventions that one can take in order to optimize vitality, while also extending longevity, that is lifespan. Dr. Attia's uniquely qualified to focus on the complete depth and breadth of topics that we cover. And indeed, these are the same topics that he works with his patients on in his clinic every day. Dr. Attia earned his Bachelor of Science in mechanical engineering and applied mathematics, and his MD from Stanford University School of Medicine. He then went on to train at Johns Hopkins Hospital in general surgery, one of the premier hospitals in the world, where he was the recipient of several prestigious awards, including Resident of the Year. He's been an author on comprehensive reviews of general surgery. He spent two years at the National Institute of Health as a surgical oncology fellow, at the National Cancer Institute, where his work focused on immune-based therapies for melanoma. In the fields of science and medicine, it is well understood that we are much the product of our mentors and the mentoring we receive. Dr. Attia has trained with some of the best and most innovative lipidologists, endocrinologists, gynecologists, sleep physiologists and longevity scientists in the United States and Canada. So the expertise that funnels through him and that he shares with us today is really harnessed from the best of the best, and his extensive training and expertise. By the end of today's episode, you will have answers to important basic questions such as should you have blood work? How often should you do blood work? What specific things should you be looking for on that blood work, that are either counterintuitive or not often discussed, and yet that immediately and in the long-term influence your lifespan and health span? We talk about hormone health and hormone therapies for both men and women. We talk about drug therapies that can influence the mind as well as the body. And of course, we talk about supplementation, nutrition, exercise, and predictors of lifespan and health span. It is an episode rich with information. For some of you, you may want to get out a pen and paper in order to take notes. For others of you that learn better simply by listening, I just want to remind you that we have timestamped

00:02:51 Momentous Supplements

all this information so that you can go back to the specific topics most of interest to you. I'm pleased to announce that the Huberman Lab Podcast is now partnered with Momentous supplements. We partnered with Momentous for several important reasons. First of all, they ship internationally, because we know that many of you are located outside of the United States. Second of all, and perhaps most important, the quality of their supplements is second to none, both in terms of purity and precision of the amounts of the ingredients. Third, we've really emphasized supplements that are single ingredient supplements, and that are supplied in dosages that allow you to build a supplementation protocol that's optimized for cost, that's optimized for effectiveness, and that you can add things and remove things from your protocol in a way that's really systematic and scientific. If you'd like to see the supplements that we've partnered with Momentous on, you can go to [livemomentous.com/huberman](https://livemomentous.com/huberman). There you'll see those supplements, and just keep in mind that we are constantly expanding the library of supplements available through Momentous,

00:03:46 Thesis, InsideTracker, Helix Sleep

on a regular basis. Again, that's [livemomentous.com/huberman](https://livemomentous.com/huberman). Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is, however, part of my desire and effort to bring zero cost to consumer information about science and science-related tools to the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is Thesis. Thesis makes custom nootropics that are designed for your unique needs. Now, to be honest, I'm not a fan of the word nootropics, because nootropics means smart drugs, and, to be honest, there is no such thing as a smart drug, because there's no neural circuit for being smart. There are neural circuits rather for being creative or for task switching or for focus. And as we all know, different sorts of demands, whether or not they're cognitive or physical, require different types of cognitive and physical abilities. Thesis understands this and has created a kit of custom nootropics that are tailored to your needs. To get your own personalized nootropic starter kit, you can go to [takethesis.com/huberman](https://takethesis.com/huberman). Take their three minute quiz, and Thesis will send you four different formulas to try in your first month. That's [takethesis.com/huberman](https://takethesis.com/huberman), and use the code Huberman at checkout to get 10% off your first box of custom nootropics. Today's

episode is also brought to us by InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body and help you reach your health goals. I've long been a believer in getting regular blood work done, for the simple reason that many of the factors that impact your immediate and long-term health can only be assessed from a quality blood test. And nowadays, with the advent of modern DNA tests, you can also analyze, for instance, what your biological age is, and compare it to your chronological age. And obviously it's your biological age that really matters. The challenge with a lot of blood tests and DNA tests, however, is that you get information back about metabolic factors, hormones, and so forth, but you don't know what to do with that information. InsideTracker makes it very easy to know what to do with that information to optimize your health. They have a personalized platform, it's a dashboard that you go to. You can click on the level of any hormone, metabolic factor, lipid, et cetera, and it will tell you the various sorts of interventions based on nutrition, supplementation, et cetera, that you can use to bring those numbers into the ranges that are ideal for you. If you'd like to try InsideTracker, you can visit [insidetracker.com/huberman](https://insidetracker.com/huberman), to get 20% off any of InsideTracker's plans. That's [insidetracker.com/huberman](https://insidetracker.com/huberman), to get 20% off. Today's episode is also brought to us by Helix Sleep. Helix Sleep makes mattresses and pillows that are of the absolute highest quality. They also have some really unique features, because they are customized to your unique sleep needs. I've talked over and over again on this podcast and on other podcasts, about the fact that sleep is the foundation of mental health, physical health, and performance. There's just simply no other substitute for a quality night's sleep on a regular basis. I've been sleeping on a Helix mattress for well over a year now, and it's the best sleep that I've ever had. And that's in large part, because the mattress was designed for me. What you need to know, however, is what's the ideal mattress for you. And you can do that by going to Helix's site. You can take their brief quiz which will ask you do you sleep on your side, your back, your stomach, or maybe you don't know, or maybe all three, do you tend to run hot or cold in the night, maybe you know, maybe you don't. At the end of that short quiz, they will match you to the ideal mattress for you. I matched to the dusk, the D-U-S-K mattress, but again, that's what I need. That's not necessarily what you need in order to get your best night's sleep. But if you're interested in upgrading your mattress, go to [helixsleep.com/huberman](https://helixsleep.com/huberman), take their two minute sleep quiz, and they'll match you to a customized mattress for you, and you'll get up to \$200 off any mattress order and two free pillows, they have terrific pillows. And

you get to try out that mattress for 100 nights risk-free. They'll even pick it up for you if you don't love it, but I'm certain you will. Again, if you're interested you go to [helixsleep.com/huberman](https://helixsleep.com/huberman),

00:07:29 Lifespan: Bloodwork & Biomarkers Testing, The "4 Horseman of Disease"

for up to \$200 off your mattress order and two free pillows. And now for my discussion with Dr. Peter Attia. Peter, thanks for joining me today. - Thanks for having me, man. - I've been looking forward to this for a very long time. - [Peter] As have I. - I'm a huge fan of your podcast. I know that you went to Stanford and worked with a number of people that are colleagues of mine. So for me, this is already a thrill, just to be doing this. - Yeah, well, it's likewise. - I have a ton of questions, but I want to start off with something that I wonder a lot about, and that I know many other people wonder about, which is how to assess their current health and their trajectory in terms of health and wellbeing, specifically as it relates to blood work. So what are your thoughts on blood work? Is it necessary for the typical person? So this is somebody who's not dealing with some acute syndrome or illness. And at what age would you suggest people start getting blood work? How frequently should they get blood work? How often do you get blood work done, et cetera? - Yeah, there's a lot there. I mean, the way I talk about this with patients is, first, taking everything back to the objective. So what's the thing we're trying to optimize? So if a person says, look, I'm trying to break 10 hours for an Ironman, I don't know that blood work is going to be a game-changing aspect of their trajectory and their training. You know, they're going to benefit much more from sort of functional analyses of performance. So I'm assuming, based on the question, that you're really coming at this through the lens of living longer and living better through the lifespan health span lens? - Mostly, yeah. I think most people have some sense of their vitality or lack of vitality, but I think everyone wonders whether or not they could feel better, and whether or not blood work will give them a window into how they might go about feeling better. - Yeah, I think it does to some extent, but I also think that it has a lot of blind spots. So I kind of break things down into the two vectors that make up longevity, which are lifespan and health span. So lifespan is the easiest of those vectors to understand, because it's pretty binary. You're alive or you're not alive. You're respiring or you're not. You make ATP or you don't, end of story. So what gets in the way of lifespan is essentially the four horsemen of disease, right? So atherosclerotic disease, cancer, neurodegenerative

disease, and metabolic disease, which directly isn't the cause of many deaths, but basically creates the foundation to all of those other diseases. So, you know, if you're a non-smoker, what I just rattled off is about 80% of your death. So how does blood work help address those? It varies. So on the atherosclerotic standpoint, it's a very good predictor of risk, if you know what to look for. So primarily ApoB would be the single most important lipoprotein that we care about. I can explain what that means in a second. And then also, other markers of inflammation, endothelial health, and metabolic health. When it comes to cancer, you know, blood testing in the sense of biomarkers is not particularly helpful, outside of knowing that the second leading environmental or modifiable cause of cancer is metabolic ill health, after smoking. So we don't actually know a lot about cancer in the sense of what causes it. It's really stochastic, and it's a lot of bad luck. So we know that smoking drives it, and we know that, even though epidemiologically we say obesity drives it, what it really means is metabolic poor health. It's probably the hyperinsulinemia that comes with obesity that drives it. So biomarkers help with that, but there's still an enormous blind spot to cancer. We could talk about liquid biopsies aside, 'cause those aren't really biomarker studies, but put that away. On the neurodegenerative side, you know, I don't think we have a lot of insight that comes to understanding Parkinson's disease, but when it comes to dementia, particularly Alzheimer's disease, which is the most prevalent form of dementia, I think the biomarkers can be quite helpful. They overlap a lot with the atherosclerotic diseases. So the same things that drive the risk of heart disease are driving the risk of dementia. And then there's some novel stuff as well, if you include genetic testing, which you can get out of a blood test. We get a whole suite of genes, not just APOE, but far more nuanced stuff than that, that can also play a role. So you can stratify risk in that sense. So in aggregate, I would say, you know,

00:11:51 Healthspan: Functional Testing, Cognitive & Emotional States

blood testing of biomarkers provides pretty good insight into lifespan. When you get into health span, you have kind of the cognitive, physical, emotional domains. I think here the biomarkers are far less helpful, and here we kind of rely more on functional testing. So when it comes to sort of the cognitive piece, you know, you can do cognitive testing. In terms of long-term risk, a lot of the things that imply good cognitive health as you age, are in line with the same things that you would do to reduce the risk of dementia. So all



the biomarkers that you would look to improve through dementia risk reduction, you would be improving through cognitive health. On the physical side, I mean, outside of looking at hormone levels and things which we look at extensively, and understanding how those might aid in or prevent some of the metrics that matter, it really is, this is a biomarker aside thing. I mean, I'd be much more interested in a person's DEXA, CPET testing, VO2 max testing, you know, zone two lactate testing, fat oxidation. Those are what I would consider more functional tests that give me far more insight into that. And then of course the emotional piece, which depending on who you are, might be the single most important piece, without which none of this other stuff matters, right? If you're a totally miserable human being, your relationships suck, I don't think any of this other stuff matters. And certainly there's nothing that I'm looking at in biomarkers that's giving me great insight into that. - Do you ask about emotional state, or do you try and assess emotional state indirectly when you do an intake with one of your patients? - Probably not so much in the intake, because I think it takes a while to form a relationship with a patient before that starts to become something that they're necessarily going to want to talk with you about. But I definitely think of it as an important part of what we do. And I think without it, none of this other stuff really matters. Again, the irony of thinking about how many years I spent sort of in pursuit of fully optimizing every detail of everything, without any attention being paid to that dimension, is not lost on me. And look, there are some patients who, that's just not something that, that's something that's compartmentalized. Maybe they're, you know,

00:13:59 Blood Testing: Best Frequency

they're doing well in that department, or maybe they aren't, but they just aren't willing to engage on that yet. - In terms of frequency of blood testing, if somebody feels pretty good and is taking a number of steps, exercise, nutrition, et cetera, to try and extend lifespan and improve health span, is once a year frequent enough, and should a 20-year-old start getting blood work done just to get a window into what's going on? Assuming that they can afford it or their insurance can cover it. - Yeah, I mean, look, I certainly think everybody should be screened early in life because if you look at, like, what's the single most prevalent genetic driver of atherosclerosis, is Lp[a]. So unfortunately most physicians don't know what Lp[a] is, and yet somewhere between eight and 12% of the population has a high enough, and depending on who you, you

know, I had a recent guest on my podcast who suggested it could be as high as 20%, have a high enough Lp[a], that it is contributing to atherosclerosis. So to not want to know that, when it's genetically determined, right, this is something that, you're born with this and you only need to really check it once, why we wouldn't want to know that in a 20-year-old, when it can contribute to a lot of the early atherosclerosis we see in people. It's leaving money on the table, in my opinion. The frequency with which you need to test really comes down to the state of interventions. I don't think it makes sense to just do blood tests for the sake of doing blood tests. There has to be kind of a reason. Is something changing? You know, a blood test is, for the most part, a static intervention. It's a look at a window in time. And there's benefit in having a few of those over the course of a year, if you're unsure about a level. So if something comes back and it doesn't look great, yeah, it might make sense just to recheck it without reacting to it. But typically, you know, in patients, we might check blood two to four times a year, but we're also probably doing things in there to now check, like hey, you know, we gave this drug, did it have the desired outcome? You put on three pounds of muscle

#### 00:16:01 DEXA Scan: Lean Mass & Fat, Bone Mineral Density & Osteoporosis

and lost three pounds of fat, did it have the desired outcome? - Speaking of tracking weight and fat, lean mass percentages, is that something that you recommend your patients do pretty often? I know people that step on the scale every day, I know people like myself that frankly, I might step on the scale three times a year. I don't really care. I pay attention to other things that are far more subjective. Maybe I'm making a huge mistake. What are your thoughts about quantitative measurements of weight, BMI, for the typical person? - I think they're pretty crude. I think a DEXA, I'd rather take a DEXA annually, and then maybe follow weight a little bit more closely to get a sense of it. And so with a DEXA you're getting, at least the way we look at the data, four pieces of information. Now, most people when they do a DEXA, should I explain what that is, I'm? - Yeah, I think some people might not know what DEXA is. In fact, I confess, I have a crude understanding of what it is. Tell me where I'm wrong, and hopefully where I'm at least partially right. My understanding is that there are a number of different ways to measure lean mass to non-lean mass ratio, and there's one where they put you underwater. There's one where they put you into some sort of non-underwater chamber. There's caliper. And then there's the looking in the mirror and pinching and changing

the lighting. - You know, it's funny, if you've done it enough, you can, I can sort of tell my body fat by my abs, right. So I can sort of tell by, you know, how good the six pack or how bad the six pack is, what the leanness is. And that's actually not a terrible way to do it. A bodybuilder, for example, which I've never been, can tell you the difference between being 6%, 7%, 8%, 10%, just based on the degree of visibility within the abs. But basically, a DEXA scan is an x-ray. So it's the same principle as just getting a chest x-ray, where ionizing radiation is passed through the body. And there's a plate behind the body that collects what comes through. And the denser the medium that the electrons are trying to go through, the less of them that are collected. So when you look at an x-ray, as everybody's probably seen an x-ray, that which is white is most dense. So if you had, you know, a piece of metal in your pocket, it would show up as a bright white thing. That's why ribs and bones show up as white, and the things that are the least dense, like the lungs, where it's just air, are the blackest. And everything is a shade of gray in between. So a DEXA is just doing that effectively, but it's a moving x-ray. So you lay down on a bed and it takes maybe 10 minutes, and this little, very low power x-ray kind of goes over your body. And the plate beneath it is collecting information that is basically allowing it to differentiate between three things, bone mineral content, fat, other. And the other is quantified as lean body mass. So that's organs, muscles, everything else. So when most people do a DEXA, they get the report back, and the reports are horrible. I've yet to see one company that can do this in a way that isn't abjectly horrible. We've created our own templates, so we have our own dashboard for how we do this, 'cause we've just given up on trying to use theirs. But the first thing most people look at is what's my body fat. And this is the gold standard outside of like MRI or something, that's only used for research purposes. So a DEXA is going to produce a far better estimate of body fat, than calipers or buoyancy testing, or things like that, provided the machinery is well-calibrated, and the operator knows how to use it. I've heard some people argue that in the hands of like the guy who's been doing calipers his whole life, it could probably be comparable with calipers. But nevertheless, for an off-the-shelf tech, DEXA is amazing. Of the four things that get spit out of the DEXA, we think that the body fat is the least interesting. And so I would rank that as fourth on the list of what's germane to your health. The other three things that you get spit out are bone mineral density, visceral fat, and then the metrics that allow you to compute, like to basically compute what's called appendicular lean mass index and fat-free mass index. And so those three metrics are significantly more important than body fat. And the reason is as follows, right? So, bone

mineral density basically speaks to your risk of osteoporosis and osteopenia. And that doesn't sound very sexy to people our age, you know. 50-year-old guys listening to this, it's like, yeah, big deal. But for a 50-year-old woman, this is a huge deal, right? A woman who's just about to go through menopause, or has just gone through menopause, is at an enormous risk for osteopenia, and then ultimately osteoporosis, because estrogen is the single most important hormone in regulating bone mineral density. And we can come back and talk about why that's the case, but it's very interesting how the biomechanics of bones work, and why estrogen specifically is so important. And this is a huge cause of morbidity, right? So, you know, if you're over the age of 65 and you fall and break your hip, your one year morbidity is about 30 to 40%. Which again, just to put that in English, if you're 65 or older, you fall and break your hip, there's a 30 to 40% chance you're dead in a year. - [Andrew] Wow. - Bones matter. So we want to really get a sense of where you stack up for your age, for your sex. And if you're anywhere off the pace, we have to ramp up our strategy and be super aggressive about how to increase that, or at a minimum, prevent any further decay. - And are there age-related charts for these sorts of things? - Yeah, this all gets spit out into what's called a Z-score. So when you're looking at your BMD, it's going to give you a Z-score. So a Z-score of zero means, and you understand this, but it's like, a Z-score referring to a probability distribution in a standard mode. So Z-score of zero means you're at the 50th percentile for your age and sex. A Z-score of plus one, you're one standard deviation above, minus one, below, et cetera. There's also a T-score, which is doing the same thing, but comparing you to a young person. And so the T-score is technically used to make the diagnosis of osteopenia or osteoporosis. We tend to look more at the Z-score, and basically say, look, if your Z-score right now is minus one, in four years I want your Z-score to be zero. Not necessarily because you've increased that entire way, but maybe you've increased slightly

00:22:33 Bone Mineral Density & Age-Related Decline, Strength Training, Corticosteroids

while it's expected that you would've declined. - I see. What are some things that we can do to improve bone mineral density at any age? - So it turns out there's a real critical window in which we are malleable. So depending on the age at which someone's listening to us discuss this, you know, if you're under 20, 25, you are still in that time of

your life when you are able to reach your potential. So it turns out that strength training is probably the single best thing you can do. And this was a surprise to me, 'cause we, you know, we did an AMA on this topic a little while ago, and that's when I got really deep on this with our analysts. My assumption was running must be the best, like some sort of impact must be the best thing you can do. You know, I assumed running would be better than swimming and cycling. But it turned out that power lifting was probably the best thing you could do. And I think once you understand how bones work, it became more clear, which is, you know, power lifting is really putting more of a sheer force from the muscle via the tendon onto the bone, and that's what the bones are really sensing. They're sensing that sheer force that's being applied through the bone, in a compressive way, depending on the bone of course. And that's what's basically activating the osteoblasts, which are the cells that are allowing bone to be built. So this turns out to be probably more important for females, because how high you can get during that period of development, say till you're 20 or 25, basically sets your trajectory for the rest of your life. So where we get into real trouble is with patients who, for example, used large amounts of inhaled steroids during that period of their life, 'cause let's say they had really bad asthma. Or patients who needed large amounts of corticosteroids for some other immune-related condition. So during their critical window of development, they were taking a drug that was impairing this process. So, you know, we have some patients like that in our practice and that's just an enormous liability that we're working really hard to overcome, with nutrition, with hormones, with drugs, with training. And, you know, it's just something you have to be aware of. - I wasn't aware that inhalants for asthma and things of that sort can impair bone mineral density. - If they're steroid-based. Some of them of course are just beta-agonists, and they're fine. - So anything corticosteroid like? - Yep. - Interesting. And then I always get asked this question, and I always reflexively want to say no, but I don't really know the answer so I don't reply. What about topical corticosteroid? You know, people will put cortisone cream. To me, it seems almost inconceivable that it would have a systemic effect, but then again, what do I know? - It's all dose and time-related. So, you know, if you're talking about like I've got a little rash under my skin, I'm going to put corticosteroids on, probably not. But certainly, with enough of it put on, I mean it is absorbed, so it could be an issue. But that's not typically what we're concerned with. I mean, we're mostly concerned with people that are taking even modest amounts of prednisone for months, years at a time. Or, like I said, kids that are using steroid inhalers for years and years and years. Again, I'm not suggesting that if

your kid's on a steroid inhaler they shouldn't be. You have to solve the most important problem, and if asthma is the most important problem, so be it. I think you just want to turn that into, okay, well, how much more imperative is it that our kid is doing things that are putting a high amount of stress on their bones, via their muscles, to make sure that they're in that maximal capacity to build. - Do you think that somebody in their 30s or 40s or 50s could still benefit from strength training in terms of bone mineral density and longevity, as it relates to bone mineral density, given that there's this key window earlier, they might have missed that one. - Oh yeah, no, no, this is essential for the rest of life because you're now trying to prevent the fall off. So basically the way it works is you're sort of, from birth to say 20 you're in growth. From 20 to 50, you plateau. At 50, men start to decline, but it's really small. Women start to decline and it's precipitous. - And it's related to the drop in estrogen associated with menopause or premenopause? - [Peter] Correct. - And can we get into any of the broad contours of what that strength training looks like? We had Dr. Andy Galpin on the show, he talked a lot about ways to build strength versus hypertrophy versus endurance, et cetera. I think there's pretty good agreement across the fields of physiotherapy, et cetera, of physiology and medicine, in terms of how to do that. But my understanding is fairly low repetition ranges, so this is anywhere from one to six repetitions. Typically not aiming for a pump hypertrophy, that sort of thing. But heavy loads that are hard to move, 80% of one repetition maximum or more, done with long rest periods, two to three times a week type thing, is that about right? - Yeah, if you look at the literature on this, it's going to tell you, it's going to differentiate power lifting from weightlifting. In other words, yeah, you do need to be kind of moving against a very heavy load. Now again, that can look very different depending on your level of experience. Like I really like deadlifting. Now, I mean, I can count the number of days left in my life when I'm going to want to do sets over 400 pounds. But, you know, I'll pick and choose the days that I do. But, you know, I grew up doing those things, I'm comfortable with those movements. If I had a 60-year-old woman who's never lifted weights in her life, who we now have to get lifting, I mean, we could get her to deadlift, but I think, I wouldn't make perfect the enemy of good. I'd be happy to put her on a leg press machine and just get her doing that. You know, it's not as pure a movement as a deadlift, but who cares, right? We can still put her at a heavy load, for her, and do so safely. So, now that said, I mean, there was a study that was done in Australia, and I'm, you know, hopefully we can find a link to it. There's a video on YouTube that actually kind of has the PI sort of walking through the results. I could send

it to you. - [Andrew] Okay, yeah we'll track it down. - And it's just amazing. They took a group of older women. They looked like they were in their 60s or 70s, who had never lifted weights in their life, who had osteopenia, and some probably already had osteoporosis, and they basically just put them on a strength training protocol. And it is remarkable to watch these women. They're doing good mornings. They're doing dead lifts. They're picking heavy things up off the ground. I think one woman was picking up, God, I want to say she was like picking like 50, 60 kilos up off the ground. I mean, just staggering sums of weight for these women who have never done anything. And their bone health is improving at this age. So the goal, frankly, is to just, you know, never get to the point where you have to do this for the first time. Strength training is such an essential part of our existence

00:29:24 Osteopenia & Osteoporosis Diagnosis, Strength Training

that it's never too late to start, but you should never stop. - I love that advice. Is it a systemic effect or a local effect? So, for instance, let's say that, well, my mother's in her late 70s. She actually used to be really strong when we were kids. She could move this fish tank that was in my room long before I could move it, and I was always, she's really strong. Over the years, I wouldn't call her frail by any means, but I certainly think she could benefit from some strength training. Let's say she were to start doing some leg presses or start even with air squats and maybe work up to some pushups, are the effects all local, meaning if she were to just train her legs or just do pushups, would it only be the loads applied to the limbs and muscles and tissues that were involved? - I think that's where the bulk of it is, yeah. - Okay. - Yeah. - [Andrew] So you need to train the whole body, essentially. - Yeah, now keep in mind, the diagnosis of osteopenia and osteoporosis is based on only three locations, the left hip, the right hip, and the lumbar spine. So, you know, that's just the convention by which we make the diagnosis. And I think part of that has to do with that's where the majority of the insults occur. Now not all of the insults, I've seen people that have, you know, because of horrible bone density, they're fracturing ankles and tibia, fibula, like they're having low tib fib fractures just walking. So clearly bone density outside of those regions does matter. But much of it is really focused on, and, by the way, you know, you fall, you break a wrist, so this is a systemic issue. But the majority of the response is a local response, 'cause it really comes down to putting a load

00:31:03 AG1 (Athletic Greens)

directly on that bone, and then having that bone, in kind, respond by laying down more bone. - Before we continue with today's discussion, I'd like to just briefly acknowledge our sponsor Athletic Greens, now called AG1. Athletic Greens, aka AG1, is an all-in-one vitamin mineral probiotic drink that also has adaptogens and digestive enzymes. I've been taking Athletic Greens since way back in 2012, so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and the reason I still drink Athletic Greens twice a day is that it supplies total foundational coverage of my vitamin mineral needs, and it supplies important nutrients that I need to support my gut microbiome. The gut microbiome, as many of you know, supports the immune system. It also supports the so-called gut brain access, which is vital for mood, for energy levels, for regulating focus, and many other features of our mental health and physical health that impact our daily performance and high performance in any endeavors we might be involved in. If you'd like to try Athletic Greens, you can go to [athleticgreens.com/huberman](https://athleticgreens.com/huberman), and claim a special offer. They're giving away five free travel packs plus a year's supply of vitamin D3 K2, with every order. And of course, vitamin D3 K2 are vital for all sorts of things like hormone health and metabolic health, and K2 for cardiovascular health and calcium regulation.

00:32:16 Back-casting: Defining Your "Marginal Decade"

Again, you can go to [athleticgreens.com/huberman](https://athleticgreens.com/huberman) to claim that special offer. You mentioned falling and the problems with falling and breaking things, and mortality related to that. I wonder whether or not there are also health-related effects of just having weak bones that are not just about falling and breaking a bone, and dying a year later. That's obviously very severe. Because I think when people hear about that, some people might think, well, I'll just be more careful. I'll just move more slowly. I'll sit in a wheelchair if I need to, even though I might be able to walk, if it keeps me from falling. Some people I think adopt that mentality. What are some of the benefits of having high bone mineral density for men and women, that are perhaps independent of risk of injury? - Well, I think it's actually the inverse of what you just said, right? It's sort of like, you have to sort of be able to articulate what it is you want in your marginal decade. So we use this thing in our



practice called the marginal decade. Marginal decade is the last decade of your life. So everyone will have a marginal decade. That's the only thing I can tell you with absolute certainty, right? - I believe you. - There's no immortality. There's no hidden elixir that's going to help us live to be, you know, whatever. I mean, we're all going to be in our last decade at some point. And outside of people who die suddenly or through an accident, most of us know when we're in that marginal decade. You might not know the day you enter it, but most people, you know, who are old enough, if you tell them, are you in the last decade of your life, they probably have a sense that they are. So I think the exercise that we like to go through with our patients very early on is have them, in exquisite detail, more detail than they've ever considered, so we have to prompt them with like 50 questions, lay out what their marginal decade should look like. - Wow, that's a serious exercise. - It's a very serious exercise, right? Like what, tell me everything that is going to happen in your marginal decade. I don't know when it's going to be, Andrew, it could be 87 to 97 if we're doing well, right? It might be 79 to 89, I don't know. But, you know, it would really be a very nuanced exploration of that topic. And I think until you do that, all of this other stuff is just abstract and kind of nonsense. Until a person can tell you what it is that they want to be doing in that last decade, you can't design a program to get them there. I mean, think about it. Someone wants to do an Ironman, we take it for granted that we know what the objective is. I have to be able to swim 2 1/2 miles. I have to be able to get out, take my wetsuit off, hop on my bike, ride 112 miles, get off my bike, take the bike shoes off, put the run shoes on, run 26.2 miles. Like we get it, we know what the objective is. And only by knowing that can you train. Can you imagine if I said to you, Andrew, I'm going to have you do an athletic event in a year, start training. I'm not going to tell you what it is, just do it. Could be playing basketball. You know, it could be swimming to Catalina Island. It could be running 100 miles. You wouldn't be able to do it. So similarly, if we don't know what our marginal decade is meant to be, there's no way to train for it. - Do you think this is a good exercise for anyone and everyone to do on their own, regardless of age here? I'm hearing this - Absolutely. - and I'm thinking, I need to think about when my last decade might be and what I want that to look like. - Absolutely, I mean, when I say we do it with our patients, that's only because that's the population I work with. But there's simply no reason everybody shouldn't be going through this exercise. - And then you sort of back script from there, figure out what people should be doing, given their current health status. - Exactly right, we call it back casting. So the first step we do is, once we've really delineated what the objective function looks like, we

then say, okay, how do you break down that into metrics that we can measure? So, you know, you described doing a whole bunch of things. Okay, just to let you know, to do that will require a VO2 max of 30 milliliters of oxygen per minute per kilogram. And the person will say, okay, what does that mean? We'll say, well, that's a measure of your maximal uptake of oxygen, and that declines at about 8% to 10% per decade. So if you have to be at 30, and let's just assume you're going to be doing that at 90, so what do you need to be at 80, 70, 60, 50. Okay, here's what it would need to be at 50. Okay, what are you now? Ah, there's a big gap. You're below where you need to be now. So you're obviously higher than 30 now, but if you're only at 42 now and you need to be at 30 and 40 years, you're not going to cut it. You have to be a lot fitter. Okay, now let's do the same exercise around strength and stability. And without exception, most people, when they do this exercise, will find out they're well below where they need to be. So the gravity of aging is more vicious than people realize, and therefore the height of your glider needs to be much higher than you think it is when you're our age, if you want to be able to do the things we probably want to be able to do when we're 90. - I absolutely love this approach. I've never done it in terms of my health. I've always thought about what I want to accomplish in the next three to six months or next year or so. - And by the way, that's a great approach. That's forecasting. Forecasting is fantastic. Forecasting is really good at short-term things. It doesn't work for long-term things. Long-term, you have to do back casting. - This back casting approach really appeals to me because in my career, well, I never anticipate, excuse me. I never anticipated I'd be podcasting. But that's what I did at some point as an undergraduate, I looked at professors, I'm like, that looks like a pretty good life. They seem pretty happy, I talked to a few of them, and then I figured out what I need to do at each stage in order to get to that next rung on the ladder, and just kind of figured it out in a back casting kind of way, as you refer to it. I think this is incredibly useful because it puts all the questions about blood work and how often to get blood work and what to measure, in a really nice context that's a highly individualized. I've never heard of this before, so. - And I should give a nod to Annie Duke. I used to always refer to this as reverse engineering, but in Annie Duke's book, she wrote about this exact thing and called it back casting, and I was like, I like the term back casting better. I think it's more intuitive than reverse engineering. - Yeah, there's a real genius to it and I think it,

00:38:31 All-Cause Mortality: Smoking, Strength, VO2 max

'cause it sets so many things into the appropriate bins and trajectories. I've heard you talk before about some of the prime movers for longevity and all-risk mortality. And I'd love for you to review a little bit of that for us. I think we all know that we shouldn't smoke because it's very likely that we'll die earlier if we smoke nicotine. I'm neither a marijuana nor a nicotine smoker, so I feel on stable ground there. But anytime we see smoking nowadays, people really want to distinguish between cannabis and nicotine. So I am curious about any differences there in terms of impact on longevity. But in that context, what are the things that anyone and everyone can do, should do, to live longer basically? - How long you got? - Well, you tell me. You tell me. I'd like to live, to be, I'd like my final decade to be between 90 and 100. - Oh no, I meant how long do you, yeah yeah. - No no, I'm just kidding. I'm just kidding. - And will we spend from now until you're 90 talking about this? - Well, there's a risk of that. But top contour is fine, I know you've done a lot of content on this, and we will give people links to some of that more in depth content. But, you know, let's say we were on a short flight from here to San Diego, we're in Los Angeles now, and we got take off and landing, and we don't want to kink our neck too much by doing this thing. So if I just said, hey, you know, gimme the extended version of the three by five card. What does that look like? - So, let's start with a couple of the things that you've already highlighted. So smoking, how much does smoking increase your risk of all-cause mortality? And the reason we like to talk about what's called ACM, or all-cause mortality, is it's really agnostic to how you die. And that doesn't always make sense. I mean, if you're talking about, you know, a very specific intervention, like a anti-cancer therapeutic, you really care about cancer-specific mortality or heart-specific mortality. But when we talk about these sort of broad things, we like to talk about ACM. So, you know, using smoking, smoking is approximately a 40% increase in the risk of ACM. - What does that translate to in, that means I'm shortening my life by 40%? - No, it means at any point in time, there's a 40% greater risk that you're going to die relative to a non-smoker and a never smoker. - Got it. - Yeah. So it's important to distinguish. It doesn't mean your lifespan is going to be 40% less. It means at any point in time, standing there, your risk of death is 40% higher. And, by the way, that'll catch up with you, right? At some point that catches up. High blood pressure. It's about a 20 to 25% increase in all-cause mortality. You take something really extreme, like endstage kidney disease. So these are patients that are on dialysis, waiting for an organ. And again, there's a confounder there because there's what's the

underlying condition that leads you to that. It's, you know, profound hypertension, you know, significant Type II diabetes that's been uncontrolled. You know, that's enormous, that's about 175% increase in ACM. So the hazard ratio is like 2.75. Type II diabetes is probably about a 1.25 as well. So a 25% increase. So another question is like, how do you improve? So what are the things that improve those? So now here we do this by comparing low to high achievers on other metrics. So if you look at low muscle mass versus high muscle mass, what is the improvement? And it's pretty significant. It's about three X. So if you compare low muscle mass people to high muscle mass people as they age, the low muscle mass people have about a three X hazard ratio, or 200% increase in all-cause mortality. Now, if you look at the data more carefully, you realize that it's probably less the muscle mass fully doing that, and it's more the high association with strength. And when you start to just tease out strength, you can realize that strength could be probably 3 1/2 X as a hazard ratio, meaning about 250% greater risk, if you have low strength to high strength. - And high strength is the ability to move loads at 80 to 90% of one repetition? - It's all defined by given studies. So, the most common things that are used are actually, they're used for the purposes of experiments that make it easy to do. And I don't even think they're the best metrics. So they're usually using like grip strength, leg extensions, and like wall sits, squats, things like that. So how long can you sit in a squatted position at 90 degrees without support, would be a great demonstration of quad strength. A leg extension, you know, how much weight can you hold for how long, relative to body weight, things like that. You know, we have a whole strength program that we do with our patients, we have something called the SMA. So it's the strength metrics assessment. And we put them through 11 tests that are really difficult, you know, like a dead hang is one of them. Like how long can you dead hang your body weight, stuff like that. So we're trying to be more granular in that insight, but tie it back to these principles. If you look at cardio respiratory fitness, it's even more profound. So if you look at people who are in the bottom 25% for their age and sex, in terms of VO2 max, and you compare them to the people that are just at the 50th to 75th percentile, you're talking about a two X difference roughly, in the risk of ACM. If you compare the bottom 25% to the top 2.5%, so you're talking about bottom quarter to the elite, for a given age, you're talking about five X. - Wow! - 400% difference in all-cause mortality. That's probably the single strongest association I've seen for any modifiable behavior. - Incredible. So when you say elite, these are people that are running marathons at a pretty rapid clip. - Not necessarily. It's just like what the VO2 max is for

that, like my VO2 max would be in the elite for my age group. My VO2, but again, I'm training very deliberately to make sure that it's in that. So I wouldn't consider myself elite at anything anymore, but I still maintain a VO2 max that is elite for my age. - I consider you an elite physician and podcaster. And guy all around. But true. But in terms of, okay, so- - But the point is like, you don't have to be a world class athlete

00:44:43 Attia's Rule of Supplementation, "Centenarian Decathlete" Physical Goals

to be elite here, yeah. - Got it. So maybe we could talk a little bit about the specifics around the training to get into the top two tiers there, because it seems that those are enormous positive effects of cardiovascular exercise, far greater than the sorts of numbers that I see around, let's just say supplement A or supplement B. - Well, and that's, you know, like this is my whole pet peeve in life, right? It's like, I just can't get enough of the machinating and arguing about this supplement versus that supplement. And I feel like you shouldn't be having those arguments until you have your exercise house in order, you know. You shouldn't be arguing about this nuance if you're carnivore diet, versus this nuance if you're paleo diet, versus this nuance if you're vegan diet, like, until you can deadlift your body weight for 10 reps. Like then you can come and talk about those things, or something like, let's just come up with some metrics. Like until your VO2 max is at least to the 75th percentile and you're able to dead hang for at least a minute, and you're able to wall sit for at least two, like we could rattle off a bunch of relatively low hanging fruit. I wish there was a rule that said like you couldn't talk about anything else health-related. - We can make that rule. - [Peter] No one'll listen to it. - I don't know about that. We can make whatever rules we want. We can call it Attia's rule. One thing I've done before on this podcast, and on social media is, just borrowing from the tradition in science, which is it's inappropriate to name something after yourself, unless you were a scientist before 1950. But it's totally appropriate to name things after other people. So I'm going to call it Attia's rule. Until you can do the following things, don't talk about supplements. - Please refrain from talking about supplements and nutrition. - There it is, hereafter, thought of, referred to, and referenced as Attia's rule. I coined the phrase, not him. So there's no ego involved, but it is now Attia's rule. Watch out. Hashtag Attia's rule. - Oh God! - Wikipedia entry, Attia's rule. In all seriousness, and I am serious about that. Dead hang for about a minute seems like a really good goal for a lot of people. At least- - That's our goal. I think we have a minute and a half is the goal

for a 40-year-old woman. Two minutes is the goal for a 40-year-old man. So we adjust them up and down, based on age and gender. - Great. And then the wall sit, what are some numbers? - We don't use a wall sit, we do just a straight squat, air squat at 90 degrees. And I believe two minutes is the standard for both men and women at 40. - Great. And then, because for some people thinking in terms of VO2 max is a little more complicated, they might not have access to the equipment to measure it, et cetera, what can we talk about, think about, in terms of cardiovascular. So run a mile at seven minutes or less, eight minutes or less? - Oh, that's a good question. So there are really good VO2 max estimators online, and you can plug in your activity de jure, so be it a bike, run, or rowing machine, and it can give you a sense of that. And I don't, I used to know all of those. - Oh, that's okay. - But now that I just actually do the testing, I don't recall them. But it's exactly that line of thinking, like, can you run a mile in this time. If you can, your VO2 max is approximately this. - [Andrew] Great. - And I think, somewhere in my podcast realm, I've got all those charts posted of like, this is by age, by sex. This is what the VO2 max is in each of those buckets. - Terrific, we'll provide links to those. We'll have our people find those links. And then you mentioned deadlifting body weight 10 times. - I just made that one up. That's not one that we include, but- - [Andrew] Something like that? - We use farmer carries. So we'll say for a male, you should be able to farmer carry your body weight for, I think we have two minutes. - [Andrew] Great. - So that's half your body weight in each hand. You should be able to walk with that for two minutes. For women, I think we're doing 75% of body weight or something like that, yeah. - Great. I love it. As indirect measures of how healthy and, - Yeah. - we are. And how long we're going to live. - It's basically grip strength, it's mobility. I mean, again, walking with that much weight, for some people initially, is really hard. You know, we use different things like vertical jump, ground contact time if you're jumping off a box, things like that. So it's really trying to capture, and it's an evolution, right? Like I think the test is going to get only more and more involved as we get involved, 'cause it took us about a year. Beth Lewis did the majority of the work to develop this. Beth runs our strength and stability program in the practice. And, you know, basically I just tasked her with like, hey, go out to the literature and come up with all of the best movements that we think are proxies for what you need to be like the most kick-ass, you know, what we call centenarian decathlete, which is the person living in their marginal decade at the best. - Well, what I'm about to say is certainly

00:49:24 Importance of Exercise, Brain Health, MET hours

a mechanistic leap, but if you look at the literature on exercise-related neurogenesis in mice, or brain atrophy or brain hypertrophy, et cetera, in animal models, it's very clear that the best way to get a nervous system to atrophy, to lose neurons, shrink neurons, and or lose connections between neurons, is to stop that animal from moving. Or to de-enrich its environment, deprive it of some sensory input or multiple sensory inputs. And the best way to enhance the size of neurons, the number of connections between neurons, and maybe even the number of neurons, is to enrich its environment and get it moving while enriching that environment. - You know, Andrew, I think it's very difficult for me to say that the same is not true in humans. And so the first time this became clear to me was in 2014, I had an analyst, Dan Pelletier, and I said, Dan, I'm going to give you a project that is vexing me to no end, which is, I want you to look at all of the literature that we have, both mechanistic and clinical trial data, that talks about Alzheimer's prevention. And I want to know every single type of input. And I want to have a clear sense of via what mechanism does it offer what mode of protection? And it took Dan, and this was obviously, we iterated a lot on this together. And he came back with kind of an amazing presentation that took, I don't know, nine months to a year of work. And what amazed me was when he came back to it, he said, the single greatest efficacy we can point to is exercise. And I was like Dan, that's got to be nonsense, dude. There's no way exercise is the single best thing you can do for the brain. There has to be some drug you've missed. There has to be some other thing that you've missed. And he's like, no, like this is hands down the best thing 'cause you're, you know, it's not just what it's doing to BDNF. It's not just what it's doing to vascular endothelium. It's not just what it's doing to glucose disposal and insulin signaling and all these things. It's just touching every aspect of the brain. And I was very skeptical for about six months, kind of really pushed on him and I was like, I think you're missing something, Dan, I think you're missing something. And then finally in the end, looped in Richard Isaacson, who's a neurologist that we work with really closely on Alzheimer's prevention. And you know, ultimately it turned into a paper that we wrote basically, you know, about this topic, and a few others. 'Cause again, I thought, oh, are you sure it's not EPA and DHA? Like that's got to have a bigger impact. And again, there are a lot of things that I think do matter and there's a whole host of things that we do for Alzheimer's prevention. But I think you're absolutely right. There's not one thing that I'll tell patients is more important than exercising. And by the

way, it's not the sort of pathetic recommendations that are made. Like it's, you have to exercise a lot more if you want to get this maximum benefit. You will get, you know, the maximum benefit comes going from nothing to something. So if you go from being completely sedentary to doing 15 MET hours per week, you'll get probably a 50% reduction in risk. - Wow. - So a MET hour, a MET, just for people who don't know, is a metabolic equivalent. So we're exerting about 1.3 METs sitting here talking. If we were sitting here being quiet, it would be about one MET. Walking really briskly would be about five METs. So 15 MET hours per week would be three one hour really brisk walks. That's not a lot of work. But just going from doing nothing to doing that would give you 50% of the benefit that you would get from going all the way. Now I, again, I think, I'm personally a little skeptical of how much that's, I think it's probably a bit less than that. I think there's more upside than people appreciate. But the studies, I don't think, can truly capture that. But look, you know, there's no reason to not be exercising more than that, and capture more benefit, even though the rate at which you accrue it is less. And it also speaks to the health span side of this, which is not necessarily captured in those data. The health span gets back to the functional piece we opened with, which is what do you want to be doing in your marginal decade? Do you want to be able to pick up a great-grandkid, if they come running at you? Do you want to be able to get up off the floor? Do you want to be able to play on the floor with a kid and then get up on your own? - And I think most people are thinking final years of life, they're trying to think, you know, how can they take themselves to the bathroom? They're thinking, how can they sit up off the toilet? I mean you have like really base, vegetative type functions, right, at some level. I love this, again, this idea of marginal decade and using that as a way to back cast, to actual methods and behaviors and protocols that one should be doing on a daily basis. I'll use anecdotal, as it's now called, to cite just, I know three Nobel prize winners, which doesn't mean anything except that they did beautiful work. But the point is that they're all in their 90s. So I'll name them 'cause I'm complimenting them for what they've done. Not just their work, but what I'm about to describe. So Eric Kandel at Columbia. Nobel prize winner for work on memory. Torsten Wiesel, work on neuroplasticity. And then Richard Axel, who's also at Columbia, Nobel prize winning work for molecular biology of smelling and molecular biology generally. All three of them still alive, Richard's younger compared to the other two. All three of them either swim, jog, or play tennis, or racquetball I think is Richard's thing, multiple times per week. They're all cognitively still extremely sharp, still interested in the arts, doing science, curious about science, running laboratories, writing



books, going on podcasts. I mean, it's incredible. Again, that's anecdotal. But I was kind of surprised to learn that colleagues that were so intellectually strong were also so obsessed with exercise. I mean, they really are obsessed with their exercise routine and early on linked that to their, some of their intellectual vigor over time. I want to just also use that as a jumping off point to ask about one kind of niche thing, but it comes up.

00:55:23 Nicotine & Cognitive Focus

I don't think I'm going to get out which one of those told me this, but one of those three individuals chews an excessive amount of Nicorette. Used to be a smoker and I asked him why and he said because, in his estimation, it's protective against Parkinson's and Alzheimer's, or at least the nicotinic acetylcholine augmentation of nicotine, 'cause nicotine is an acetylcholine receptor obviously, is known to create a state of focus and neural enhancement. What are your thoughts about not smoking, let's just, I just want to be really clear, people, don't smoke nicotine, vape nicotine, it's going to shorten your life. Just terrible idea, addictive, et cetera, in my opinion. But what are your thoughts about augmenting acetylcholine, through the use of nicotine, in order to keep the brain healthy and focused? Again, this is one Nobel prize winner, so it's truly N of one, but he's so convinced that this matches up with the mechanistic data on acetylcholine and cognition, that I'd love to hear your thoughts on it. - So I can't speak to the AD prevention component of it. I'd have to run that by a couple of my colleagues who I collaborate with on that. But I can definitely speak to the cognitive enhancement piece of it. And I actually did an AMA on this, probably a year ago, where I went into all of the gory details of it and talked about my own use of nicotine, which I'll cycle on and off, I've been doing it for the last 10 years. I haven't- - What form do you take it in? - I used to use the gum. I don't like the gum anymore, so now I like these little lozenges that, and I'll tell you a funny story about this. So our mutual acquaintance, David Sinclair, mentioned a company to me a year ago. He's like, hey, have you heard of this company? And I forget the name of the company, but he gave me some name. So I go online and it's like this company selling nicotine. And I'm like, I wonder why he's asking me to do this. Well, I'll just order a bunch and then we'll figure out why, 'cause we were, you know, there was some reason we were doing this potentially through investment. So I get a, like literally order like a lifetime supply of this stuff. And it's pretty good, it's actually, it's a really nice little patch, 'cause I, the thing I didn't like about the gum was I hated just the taste of it. So then the next week

I'm talking to David and I'm like, by the way, I ordered all that nicotine stuff you told me about. He's like what? And he goes, oh, the company's name was something else. It was totally unrelated. It's like, oh God. So the short answer is, I think this stuff is absolutely a concentration-enhancing substance. It is addictive and people need to be wary of that. Now it's not addictive to everybody. I personally experience no addiction to it whatsoever. So I can, I could do it every day for 30 days and stop and experience no withdrawal. I could forget about it, it doesn't really seem to matter. You have to be careful with the dose, truthfully. I mean, remember one cigarette is about one milligram of nicotine, and a lot of these lozenges will plow four to eight milligrams into you in one shot. And for someone who is, you know, naive to that, like I am, four milligrams is a lot of nicotine in one bolus. So you just have to be very mindful of it. I got a lot of flack when I did this AMA, for obvious reasons, but people were like, how can you, as a doctor, encourage people to use nicotine. And I was like, first of all, I'm not encouraging anybody to use it. I just want to be able to talk about the biochemistry of it. And if disclosing that I use it from time to time is an endorsement then I apologize for that. But on the list of things that you can do to make your brain a little more focused, I would consider this infinitely safer than what a lot of people are doing, which is using stimulants. I mean, to me, you know, I just tell patients outright, like we are under no circumstance prescribing stimulants. I mean, yeah, we're not giving anybody Adderall. We're not giving anybody Vyvanse, or any of these things. Not to say they don't have an appropriate clinical use, but they should be prescribed under the care of somebody who's really monitoring the use case for it. And using that as a tool to enhance, you know, concentration in cognitive performance is not something we're comfortable doing.

- Yeah, it's rampant on college campuses. - [Peter] I can only imagine. - Armodafinil, modafinil which are slightly different, of course, but, so non-clinical use, not prescribed for ADHD, but just, it's rampant. Recreational use, study-based use. - But the data I've seen on modafinil suggests that it only really provides a nootropic benefit. in someone who is deprived of sleep. Is there data that in a totally well-rested person, there is a nootropic benefit of modafinil? - I don't know. I have one experience with armodafinil, where I took a half a recommended dose, this was prescribed by a doctor. I went to give a talk. This was in Hawaii and I'm four hours into the talk. My co-speaker came up to me and just said, well, first of all, you got a little bit of spit in the corner of your mouth. And second of all, you haven't blinked in three minutes. And third, there's only two people left in the audience. I was so lazered in that I kind forgot the context. Now I'm a little bit of a,

kind of a tunnel vision, OCD-type anyway, but one, that was all it took, I never took any more of it. It was a powerful stimulant. I take 300 milligrams of Alpha-GPC now and again, before some cognitive work, sometimes before workouts, and I do subjectively feel that it narrows my focus in a nice way. But I don't take it more than once or twice a day, and more than once or twice a week. - See, this is an example of where, you know how we're talking about exercise versus sort of nutrition and supplements for longevity. I think there may be a whole bunch of things that are kind of interesting around focus, but nothing would compare to changing our environment. Like I think that if I compare my focus today to my focus when I was in college, there's no comparison. Like in college, I was truly a robot. But I think a large part of it was, there was no distraction. There's no email. There's no social media. There's no internet. I mean, I was in college when Mosaic launched in the early '90s. Like I, you know, and you had to walk like a mile to get to the computer lab on a big Sun workstation to do anything in, you know, some computer code language. So when you're sitting in your room studying, there was no distraction. And I think that's a far greater component of what it means to be focused, than the challenges we have today. So, you know, my thoughts on this would be, if we really wanted to return to a state of focus, we're going to have to individually do something about, you know, our environment. And I don't know what the answer is. Like, I've tried every little trick I can think of, like closing my browsers when I'm writing and stuff, but, you know, I'm just not strong enough willed. Like I'll pick up my phone every 20 minutes to look and see if I missed a text message or something stupid. - That's pretty infrequent. I did an episode on habits and looking at the data. It seems that people are getting interrupted or interrupting themselves about once every three minutes in the typical workplace, now that typical has changed with a lot more people working at home. I do put my phone away when I try and work, but nothing focuses me like a deadline. A little bit of fear-based urgency. That's it, grant deadlines, you know, drop deadlines as I call them, or podcasts we're going to record today, that nothing works quite like it. But such is life. Well, thanks for that offshoot about nicotine. Again, you're not recommending it, I'm not recommending it, but it's clear that augmenting the acetylcholine system, which is what nicotine does in its various forms, and some related type pharmacology, does enhance focus and pretty potently. So I think it's going to be an interesting area for real clinical trials and things of that sort.

01:03:12 Menstruation, PMS & Menopause

Love to chat about hormone therapies, and hormones generally. When Robert Sapolsky came on the podcast, we talked a little bit about menopause and the data around menopause. He's very interested in these findings that, I think I'm going to get this right, that whether or not women benefit from estrogen therapy to offset menopause really depends on when that therapy is initiated. I don't know if you're aware of those data, but he claimed that if they begin estrogen therapy in the middle to tail end of menopause, the outcomes can be quite bad. Whereas if they initiate those estrogen therapies as they enter menopause or even before menopause, then the outcomes can be quite good. I don't know what percentage of the patients you treat are male versus female, and what ages those patients are of course, but what are your thoughts about estrogen therapy for women, menopause, and hormone therapies generally for women, maybe even testosterone therapy, you hear about that these days, and then we'll talk about men. - So our practice is probably 70 30 male female. So we have lots of women, and this is a very important topic. It's also probably, let me think. I just want to make sure I'm not being hyperbolic when I say this. Yeah, I don't think I am. It's hands down the biggest screw up of the entire medical field in the last 25 years. Now, again, it's possible in the next hour I'll think of, nope, there's a bigger screw up. - Another giant screw up. - Yeah, but I don't think I will. I'm pretty confident that I won't be able to think of a bigger act of incompetence than what happened with the women's health initiative in the late '90s and early 2000s, which is effectively the study that turned the entire medical field off hormone replacement therapy for women. So it's important, I think, to explain what this study looked at. So this was a study that was conducted in response to the widely held belief in the '70s and '80s that women should be placed on hormones as they're going through menopause, right? Menopause is, I guess maybe I'll even take a step back. I don't know how much your audience is familiar with how estrogen progesterone work. Is it worth going into that stuff? - Yeah probably worth mentioning a bit of the top contour. Some of them might be familiar with it, we've done episodes on estrogen testosterone, but frankly, as I think back to those, we didn't really go into the biology of estrogen testosterone enough. - Yeah, so, I mean, actually an interesting aside that I always tell my female patients who get a kick out of this. When you look at a woman's labs, you'll see her estrogen, her progesterone, her FSH, her LH, her testosterone, her sex hormone binding globulin, and all these things. But based on the units they're reported in, it's a very distorting picture of what the most common androgen is in her body. If you

actually convert them to the same units, she has much more testosterone in her body than estrogen. - Interesting. - Yeah. - I did not know that. - Yeah. - Then again, I've never been a woman getting my hormone profile. - Yeah, yeah. So even though a woman's testosterone is much less than a man's level, it's still more than she has estrogen in her body. - [Andrew] Wow! - So phenotypically, right, estrogen is the hormone that's dominating and test, so it's the, she has much higher estrogen than a man and much lower testosterone than a man, but in absolute amounts, she has more testosterone than estrogen. Just worth pointing that out. - [Andrew] Incredible. - So, you know, what's happening to a woman from the age she starts menstruating until she goes through menopause, outside of pregnancy and birth control and stuff like that, is she has this cycle, you know, roughly every 28 days, but it can vary, where at the beginning of her period, we call that day zero, her basic, her estrogen and progesterone are very low. You can't measure them. And then what happens is the estrogen level starts to rise, and it rises in response to a hormone called follicle stimulating hormone, FSH, that is getting her ready to ovulate. And she ovulates at about the midpoint of her cycle. So if we're just going to make the math easy, on day 14 she's going to release a follicle from one of her ovaries. And the estrogen level is sort of rising, rising, rising. We love to measure hormones on day five, because I want to have a standardized way in which I measure her hormones. So our women know if we're in the business of trying to understand her hormones, the day her period starts, even if it's just a day of spotting, that becomes our benchmark, and then day five, I want to see every hormone on that day. And if everything is going well, I know what her FSH, LH, estradiol and progesterone should be on that day. So the estrogen rises, starts to come down a little bit as she ovulates, and then the luteinizing hormone kicks on because it's now going to prepare her uterus for the lining to accommodate a pregnancy. So now you start to see estradiol go back, but now, for the first time, progesterone goes up. So progesterone has been doing nothing for 14 days, and now it starts to rise. And actually progesterone is the hormone that's dominating the second half, which is called her luteal cycle. So the first 14 days is the follicular cycle. Second is the luteal cycle. So once you get to about the halfway point of that, which is now, just to do the math, 21 days in, the body has figured out if she's pregnant or not. And again, most of the time she's not going to be pregnant. So the body says, oh, I don't need this lining that I've been preparing, I'm going to shed it. So now progesterone and estrogen start crashing, and the lining is what is being shed, and that is the menses. By the way, it's that last seven days of that cycle, that in a susceptible

woman is what creates those PMS symptoms. So it's the, actually, this is something that you would probably have a better understanding of than me. There is something about this in a susceptible woman, where the enormous reduction of progesterone so quickly is probably impacting something in her brain. So this is a legitimate thing, right? I mean, you know, it's not like, oh, she's crazy because she's having all these PMS symptoms. No. We know that that's the case because if you put women on progesterone for those seven days, those symptoms go away. - [Andrew] Interesting. - So if you can stabilize their progesterone during the last half of their luteal phase, and sometimes we would just do it for the entire luteal phase, just put them on a low dose of progesterone, all PMS symptoms vanish. - Very interesting. I'll have to look up where the progesterone receptors are located in the brain. The Allen Brain Institute now has beautiful data of in situ hybridization, which for, 'cause they don't understand is, looking at RNA and sort of where genes and proteins ought to be expressed in the human brain, by using actual human brain tissue sections as opposed to just mice. So I'll take a look, I think- - Yeah, I'm really curious, yeah. - Some insight into what that progesterone emotionality link might be, and where it might exist, neural circuit wise. - So then, when the estrogen and progesterone reach their nadir again, that starts the cycle. So that just, that cycle is happening over and over and over again.

#### 01:10:10 Hormone Replacement Therapy, Menopause & Breast Cancer Risk

Okay, so it became well known in the '50s that, okay, a woman's going to stop menstruating at some point, her estrogen goes down. Why don't we just give her estrogen? 'Cause that's clearly going to help with some of the symptoms of menopause. So what do women experience when they go through menopause? The first symptoms are what are called vasomotor symptoms. So this is usually in the form of night sweats, hot flashes. So, and depending on the woman, this can be really significant, right? These are women who can have a hard time sleeping. They can be having hot flashes during the middle of the day. They can wake up soaked in a pool of sweat. Those tend to pass after a couple of years, and then they get into sort of the more long-term complications of menopause. So what we call vaginal atrophy, vaginal dryness, and then the stuff that we talked about a while ago, which is the osteopenia osteoporosis. A lot of women will complain of brain fog. So, I mean, clearly this was an issue and it was recognized 70 years ago. Why don't we give women estrogen back to replace that hormone? And so

that went on for a couple of decades, maybe less, maybe a decade, and then it was realized, wait a minute, we were driving up the risk of uterine cancer. And the reason for that is if you just give estrogen with no progesterone to antagonize it, you will thicken the endometrium endlessly and you will increase the risk of hyperplasia. Well, you'll definitely undergo hyperplasia, and then ultimately dysplasia. Dysplasia is precancerous, and ultimately we were seeing that. So people figured out, well, actually, if you want to give estrogen to a woman who still has her uterus, you have to give her progesterone as well. You have to be able to have a hormone to oppose the estrogen. And then that became effectively in, call it the 1970s-ish, the standard for HRT. So in the early 1990s the NIH said, look, we haven't really studied this. We have a ton of epidemiology that says giving women hormones seems to be doing really good things. They feel better, so all their symptoms go away. They seem to have lower risk of heart disease, lower risk of, you know, cardiovascular, pardon me, lower risk of cardiovascular disease, lower risk of bone fractures. Everything seems to get better. Lower risk of diabetes. But we haven't tested this in a randomized prospective trial, so let's do this. So that became the WHI. And it randomized, it had two parallel arms. So it had a group for women who did not have a uterus. So these are women that had undergone hysterectomy for some other reason. And then it had a group for women that did have their uterus. In the first group, there was a placebo arm and then an estrogen only arm. And in the other group, there was a progesterone plus estrogen versus a placebo. Everything about the way this study was done is a bit wonky. Some of it is justifiable, but it's important to understand. First, the women were all way outside of menopause. So none of these women were started when you would normally start HRT. And there were probably several reasons for that, but one of them is, and I think this is a legitimate reason, they wanted hard outcomes. They wanted to know death rates. And if you're doing this on women in their 50s, you just weren't going to get it, right. You couldn't- - Wait too long. - Yeah, you got to wait too long. And this was only going to be like a seven to 10-year study. So they had to do this on women who were much older. They also disproportionately took much sicker women. I believe the prevalence, and again, I'm going to get some of these numbers wrong and people are going to get all phosphorylated, but, you know, I mean, I'm in the ballpark, right? Something like 30, 40% of these women were smokers. The prevalence of obesity, diabetes was enormous. So they really disproportionately picked the most unhealthy population they could, that was pretty advanced in age. And again, I think part of that was to say, look, we want to make sure that after seven years, we really know if

there's a difference in these causes of death. The other thing is, this is kind of weird, although again, I understand their rationale for it, but this is a great example of be very careful when you look at a clinical trial, that it remotely represents the patients you're interested in treating. So they also treated no patients who were symptomatic. The rationale being, if we include in the study patients who are symptomatic, those who are randomized to placebo will drop out. - Okay, it makes sense in terms of study design, makes no sense if the study design is intended to mimic the real world. - That's right. So now let's just keep track of the three issues. We have a disproportionately unhealthy patient population who are not symptomatic, and we're starting them more than 10 years after menopause. The next thing that they did, which again, I understand why they did it, but it's now the fourth strike against this study, is, and I've spoken with the PI of the study and asked this question point blank. I'm actually going to have her on my podcast at some point soon to go over this in more detail, is why did you use conjugated equine estrogen, an MPA, which is a synthetic form of progesterone. - [Andrew] Horse- - Yes. - estrogen? - It's horse urine, is they collect horse urine, so they're getting, it's- - Horses do urinate a lot. Or at least when they urinate, it seems like a large volume of urine, from what I've observed. - [Peter] You have a lot of experience with this? - No, but, you know, my sister rode horses for a little while, my high school girlfriend had a horse, and that thing, I mean the pees were legendary. It's a male horse. - Yeah. - Yeah. - So, yeah, so the conjugated equine estrogen is the estrogen that's collected from female horses. And then it's a synthetic progesterone. And I said to the person, I said, well, why didn't you use what we use today, which is bio-identical estrogen in progesterone. Like today, when we put women on estrogen, we use a, it's an FDA product called the Vivelle-Dot. So it's a patch that you just put on, and it's estradiol, but it's bio-identical estradiol. And we use what's called micronized progesterone. So bio-identical progesterone. And she said, well, at the time we just wanted to test what was currently being used. And I said, totally makes sense. But again, now you have four considerations that you have to keep in mind, okay. So despite those four considerations, and I'm going to make a case for you why I think the MPA created a real problem in that study, the synthetic progesterone, when the preliminary results were first made available, but not yet peer-reviewed and not yet published, there was a huge fiasco, huge press announcement about it, suggesting that the women receiving the CEE plus MPA, in the group with the uterus, had a higher incidence of breast cancer. And that basically became the headline that never went away, though it turned out not to be true. Let's talk about the numbers.



What was the increase in the risk of breast cancer in that group? Which gets to one of my, you know, if you ever listen to me on a podcast rail on something. - Listen, I have about 3,800 pet peeves and counting. My laboratory staff know these, know a good number of them. So, you do not have - Here, I'll add to one of them. - to apologize for having many pet peeves. Because as long as they have experience in data to support them, it provides- - So one of my biggest pet peeves is, and my team knows this 'cause sometimes they'll occasionally, you know, they'll do this and I'll have to remind them, you never talk about a relative risk change without an absolute risk accommodating it, right. So, what does that look like? So the relative risk increase of breast cancer in the estrogen plus MPA group versus the placebo was 25, 27%. And that became the only headline. HRT increases risk of breast cancer by 27%. Now, I don't think that's true at all today, but let's even look at the data. What was the ARR? What was the absolute risk increase? It was a difference between five cases per thousand and four cases per thousand. So the ARR was 0.1%, one case in a thousand. And it's true, going from four in a thousand to five in a thousand is a 25% increase, but it's a completely inappropriate context. - I agree, and I feel like headlines of that sort, which have come up recently around various dietary interventions, we won't go there, at least not for the time being, are nothing short of criminal because they really distort people's thinking. But also they steer the course of science and medicine for, as you pointed out, for decades, if not longer. And they can really take us off our health track in serious ways. - So I'll bring this meandering to a close, which is to say, even though I could spend the next hour talking about all of the ways in which this study was flawed, and all of the very unethical things that were done by a number of the investigators who went out of their way to mask the truth of this study from the world, I'll tell a woman today, we're going to start you on this when you're going through menopause. We're using bio-identical hormones. And if your upper bound risk of breast cancer is one case in a thousand, you should at least weigh that against all of the other benefits, which I'll talk about. Now, there's something else I want to say, because a moment ago I alluded to the fact that I think the MPA might have been the biggest issue in that study. So there were two findings in that study that were negative. One was the small increase in the risk of heart disease, and the small increase in the risk of breast cancer. But consider the other group, we forgot about the group that didn't have a uterus. 'Cause remember, those women got estrogen only versus placebo. What was the difference in breast cancer there? Well, this is interesting 'cause it didn't reach statistical significance, but its P value was 0.06 or 0.07. So it came very close, but

it was in the opposite direction. It was a 24% risk reduction, about one in a thousand as well. So when you had estrogen plus MPA, you had a barely statistically significant, the P value was 0.05, so it just hit statistical significance, one in a thousand cases for breast cancer. And then you had one in a thousand cases, but P value of 0.07, for reduction of risk of breast cancer. Which to me suggests that the MPA, the synthetic progesterone, was playing more of a role than anything else. The second thing I point out is oral estrogen, which we no longer use, does increase coagulability. It does increase the ability of the blood to clot a little bit. And when we look at the more recent data on HRT, using topical estrogen or patches of estrogen, we don't see that at all. In fact, we see the opposite now. So now we see the risk of heart disease going down in women with estradiol. - And some women will be arriving to those treatments with mutations and things like Factor V Leiden and other clotting factors. Is it appropriate to say that everyone, both male and female, should know whether or not they have mutant forms of Factor V Leiden? - You know, we don't typically test people for Factor V. My wife actually has it, but we didn't learn it until she had HELLP syndrome giving birth to our first daughter. But, you know, we kind of look for more family history reason to be testing things like that. We take a pretty detailed family history,

01:22:06 Estrogen, Progesterone & Testosterone Therapies in Women

so we'll kind of look for clotting issues there. - What about, so your reflex nowadays is to put women on these topical estrogen therapies? - Well it's to basically have the discussion, right? So here's where we still struggle, right, is, you know, if it were up to me, I'd prefer for a woman's HRT to be provided by her GYN, because we want to be able to work in partnership with the GYN who we would like to see an endometrial ultrasound done every year. That's, you know, some would argue that's overkill, but we think she should be having a pap smear every year as well. So if we're looking at the cervix, we want to look at the endometrium, we want to make sure the lining isn't too thick. The other thing I should say, Andrew, is today, we now realize that not all women can tolerate estrogen, pardon me, progesterone. So you have to be careful. So assuming, again, a woman still has her uterus, the estrogen solves most of the problems, but then you have to decide, can she tolerate the progesterone? And it needs to be, if given systemically like a hundred to 200 milligrams. And for some women, that is a lifesaving intervention. I mean, they start sleeping better, their hair gets thicker, they feel better.

But for some women, it literally drives them crazy. It's probably the reciprocal of what we were seeing in the case of women with PMS. So in those situations we say, great, we're done with oral progesterone. We just use a progesterone coated IUD. So then you get the local progesterone in the uterus for protection, and the systemic estrogen. - Fascinating. What about oral contraception in women? So the use of estrogen chronically through people's, you know, college years or 20s, 30s, maybe even teens, who knows. What's known about the long-term effects, if any? - I got to be honest with you, I don't think I know enough to comment on it. It's not something that really impacts my patient population. At least in what I see, more women are using IUDs for contraception than OCs. I mean, we use OCs sometimes in women who are premenopausal, for symptomatic control, but we'll typically use like a low low estrin, so a very low synthetic estrogen, which I don't like using these very much. But if it's the only thing that we can get to control certain symptoms, and we'll use it like half her cycle. But it's typically not something we're that experienced with. - What about testosterone, because you mentioned that, you know, nanogram per mill, when you said everything to the same, you know, I guess it's nanogram per deciliter, - Yeah yeah. - as it would be to kind of normalize everything. - Versus picogram per ML. - Right, yeah. And so, what Peter was pointing out before is that you look at your charts and they're all in these different measures, and so when you normalize, testosterone is actually higher than estrogen in women. That's a surprise to me. Do you prescribe testosterone therapy to women ever? - We do sometimes, but I do it with much more caution because I don't have the data, right. So where I'll, you know, what we'll say is, look, I mean, we're now really outside of an area where I can point to a lot of data. Like when it comes to estrogen and progesterone, I'll happily go toe to toe with anybody who wants to make the case that it's dangerous. Similarly, when it comes to using testosterone in men, I'll spend all day, and I can go through that literature until the other person cries and wants to just call uncle, right. When it comes to- - And then you prescribe them testosterone. - When it comes to estrogen in, testosterone in women, don't have that data. And I'd love to see that trial done. So what's the sweet spot, how do we reconcile that? So it's not something I consider standard. And basically, if a woman is, if her testosterone, first of all, is staggeringly low, and again, even though her testosterone's low compared to a male, we still have a range. So if it's really at the bottom of that range, she's really having difficulty putting on muscle mass and really complaining of low libido, I think in that situation, we'll go ahead and use topical testosterone, and, you know, replace her to

a level that is still physiologically normal. - Yeah, that's key because when people hear HRT, they think about, super physiological seems to be the term. - Yeah, like I've never seen a single symptom in a single woman that I've put testosterone on, in terms of like acne, body hair, things like that. Like those are real symptoms that you have to be aware of, but, you know, like clitoral enlargement and things like that, like that doesn't happen under physiologic normal conditions.

01:26:35 Hormone Replacement Therapy in Men, SHBG & Testosterone, Insulin

- I'd love to talk a little bit about hormone replacement therapy in men. When one looks on social media and the internet, there seems to be a younger and younger cohort of guys and people in their teens and 20s, showing up to the table thinking that injecting testosterone cypionate or taking Anavar, whatever it is, is going to be the right idea. They mainly seem to be focused on cosmetic effects. I'm not a physician, so I can't say whether or not they were actually hypogonadal et cetera, but it seems to me, again, correct me if I'm wrong, but it seems to me that similar to the Attia's rule as it relates to longevity, that we could come up with a broad contour rule in which if a male of any age is not trying to get decent sleep, exercise appropriately, appropriate nutrition, minding their social connections, et cetera, et cetera, the idea of going straight to testosterone seems like a bad idea. That said, just like with depression and antidepressants, there is a kind of a cliff after which low enough testosterone, or low enough serotonin, prevents people from sleeping, exercise, social connection, et cetera. So I do want to acknowledge that. But with that in mind, how do you think about, and perhaps occasionally prescribe and direct your patients in terms of hormone replacement therapy in men, person in their 30s, person in their 40s, who's doing almost all the other things correctly. What sorts of levels do you think are meaningful? Because the range is tremendous in terms of blood tests. 300 nanograms for deciliter, I think on the low end now in the U.S., all the way up to 900 or 1200, that's an enormous range. What are some of the other hormones you like to look at, estrogen, DHT and so on? - So, a lot to unpack there. So, let's start with the ranges, right? So the ranges you gave are for total testosterone, of course, and we don't spend a lot of time looking at that the way we, you know, I used to spend more time looking at total and free when I used more tricks to modulate it. So I'm actually far more simple in my manipulation of testosterone today than I was six or seven years ago. Six or seven years ago, I mean, we were, you know,

we would use a micro dose of Anavar to lower SHBG in a person who had normal testosterone, but low free testosterone. - What was a low dose of Anavar in that context? - 10 milligrams subling two to three times a week. - Anavar basically being DHT. Oxandrolone- - Yeah, oxandrolone, yeah exactly. - And again, we're not recommending this. This actually, if you're playing a competitive sport, can get you banned from that sport. - No no, yeah yeah. This is- - It can also get you banned from having children if you do it incorrectly. - Yeah, so a micro dose of this has to be small enough that it doesn't impair your body's ability to make testosterone. But Anavar has such a high affinity for SHBG, that it basically distracts your SHBG from binding your testosterone. - Freeing up testosterone. - That's exactly right. So the goal was, how do I just give you more free testosterone? So if a patient shows up and they've got a total testosterone of 900 nanograms per deciliter, which would place them at, you know, depending on the scale you look at, the scale we look at, that would place you at about the 70th percentile. But your free testosterone is, you know, eight nanograms per deciliter. So that's pretty bad. That means you're less than 1% free. A guy should be about 2% free T. So that dude should be closer to 16 to 18 nanograms per deciliter. So in that situation that I just gave you, his SHBG is really high. His SHBG is probably in the 80 to 90 range. - That's very high. 'Cause I think the upper range is somewhere around 55, 56. - Exactly. - Yeah. - So we would first back stall for what's driving his SHBG. So there's basically three hormones, so genetics plays a huge role in this. There's no question that just out of the box, people have a different like set point for SHBG. Mine is incredibly low. My SHBG is like kind of in the 30s, 20s to 30s. But from a hormone perspective, there's basically three hormones that run it. So estradiol being probably the most important, insulin and thyroxine. So we're going to look at all of those and decide if any of those are playing a role. So insulin suppresses it. So this is actually the great irony of helping a person get metabolically healthy, is in the short run, you can actually lower their free testosterone, all things equal. Because as insulin comes down, SHBG goes up, and if testosterone hasn't gone up with it, you're lowering free testosterone. - So somebody who goes on a very low carbohydrate diet in an attempt to drop some water and drop some weight, is going to increase their SHBG? - Yeah, if their insulin goes down enough. - Bind up testosterone, less free testosterone. I can tell the carnivore diet people are going to be coming after me with bone marrow in hand. But then again, after this discussion extends a little further, I'm sure the vegans will be coming after me with celery stalks, so it's a. - So then the same as with estradiol. So except in the opposite direction. So higher

estradiol is higher SHBG. So again, occasionally you'll see a guy with normal testosterone, but he's a very high aromatase activity person. So he has a lot of the enzyme that converts testosterone into estradiol. You can lower estradiol a bit with an aromatase inhibitor, and that can bring down SHBG. Now, again, these things individually are rarely enough to move the needle. The last is thyroxine. So if you have a person whose thyroid is out of whack, you have to fix that before you, if their T4 is out of whack, you're going to interfere with SHBG. There are also some supplements which I think you've probably talked about these on the podcast. I feel like I've heard you talk about these on the podcast. - Yeah, there are a few that will adjust, you know, there's this idea now there's a much better review, it just came out, I'll send it to you, I'd love your thoughts on it, and I've been perusing it line by line. But I love input from experts like you on the use of Tongkat Ali for reducing SHBG. In my experience, it does free up some testosterone. By which mechanism it isn't exactly clear. And the effects aren't that dramatic. Right, they're probably multiple effects. For all we know, it increases libido, and it does, generally, by way of increasing estrogen slightly, which can also increase libido in some individuals. So we don't know the exact mode of action. So we've talked about a few. The one that a few years back people were claiming could reduce SHBG was stinging nettles. - Stinging nettles, yeah. - Stinging nettle, well I'll just, urinating seems to be coming up multiple times on this podcast, for whatever reason. Stinging nettle extract, I took, the most pronounced effect of that was you could basically urinate over a car when taking SHBG. What the underlying mechanism of that was, I do not know. I took it for a short while, it didn't drop my SHBG very much, but it did drop my DHT sufficiently so that I stopped taking it. - You felt that, yeah. - I do not like anything that impedes DHT. I don't care if my hairline retreats, I don't care about any of that. DHT to me is something to be coveted and held onto because you feel so much better when your DHT is in the appropriate range, and I'd love your thoughts on that. - Yeah, again- - At some point too. - It really depends on the guy, and it depends on what risk you're trying to manage, right. So prostate size starts to become one of the issues with DHT. - Luckily my prostate-specific antigen is low, and DHT, the things that I know can reduce it are things like finasteride, Propecia, things like, yeah, right. Things that people take to try and avoid hair loss can dramatically reduce DHT and lead to all sorts of terrible sexual side effects, mood-based side effects, et cetera. But yeah, so I'm not aware of anything that could be taken in supplement form that can really profoundly drop SHBG. - Yeah, we don't spend much attention on it anymore. Basically, I used to have a much more

complicated differential diagnosis eight years ago. Like, I mean it was, I would drive patients nuts with the whiteboard diagrams I would draw for them, when in the end, I think they were just like, dude, just, what do I need to take? Today we take a much more simple approach. So the first question is, should you or should you have your free testosterone being higher? That's the metric I care about, is free testosterone is the first, most important, the second most important is estradiol. - And sorry to interrupt, you said, if you look at your total testosterone, you want the free T to be about 2% of your total. - Well, it should be, right. Now I can't, I might not change that anymore. So in other words, if a guy's at 1%, then I know I have to really boost his total testosterone. If he's only going to get one to 1 1/2% of it converted to free, I need to boost him. And that's why I don't care if he's outside the range. Like, I'll have a guy who's free T, I might have to get a guy's total T up to 1500 to get his free T to 18. - I see, so free T is the target. I like this approach. - Free T is what we treat. - And do you still use Anavarax, - I don't use - oxandrolone, sorry, to try and lower SHBG. - I don't, no. - Because it's too potent? - No, because it's just too complicated for patients. It's a drug that can't be taken orally, so you have to take it under the tongue. - Like a troche or something. - Right, but then, you know, I had one patient once who, even though we told him about 87 times that, he was like swallowing the Anavars and his liver function, and he was like, we're talking 10 milligrams three times a week is a tiny dose, and three months of him, or whatever, two months of him swallowing that every time tripled his liver function test. So it's like, I was like, you know, it's just not worth the hassle of doing this for, you know, perfection. In reality, we can fix this another way. So the first order question is, do we believe clinically you will benefit from normalizing your free testosterone, or taking it to a level, let's call it 80th to 90th percentile. So upper normal limit of physiologic ranges. That's the first order question. And that's going to come down to symptoms, and that's going to come down to some biomarkers. I think there's, two years ago, was it two years ago or maybe a year ago, very good study came out that looked at pre-diabetic men, you've probably talked about this study, and looking at insulin resistance and glucose disposal with and without testosterone. And the evidence was overwhelmingly clear. Testosterone improves glycemic control. Testosterone improves insulin signaling. This shouldn't be surprising by the way, given the role muscles play as a glucose reservoir and a glucose sink. So now I include that as one of the things that we will consider as a factor for using testosterone. Now, again, it's not the only one. So you can accomplish that with exercise, you can accomplish that with these other things, but then you get into a little bit of the vicious

cycle of will having a normalized testosterone facilitate you doing those things better. So let's just assume we come to the decision that this person is a good candidate for testosterone replacement therapy. The next question is, what's the method we're going to do. Are we going to do it indirectly or directly? Now we used to use a lot of Clomid in our practice.

01:37:23 Clomid, Pituitary, Testosterone & Cholesterol, Anastrozole, HCG

And have you talked about Clomid on the pod? - Haven't talked too much about it. No, we've talked a little bit about the fact that some people taking things like anastrozole to reduce aromatase activity, can potentially run into trouble because they think, oh well, more testosterone, good, lower estrogen, bad, and then they end up with issues like joint pain, memory issues, and severe drops in libido. And I think a lot of the reason why - And even fat accumulation. So if estrogen is too low, you can develop adiposity in a way that you wouldn't otherwise. There was a great New England Journal paper, it's probably 10 years old now, that looked at, I believe it was five different doses of testosterone cypionate. So these men were chemically castrated and divided into 10 groups. It's pretty remarkable - [Andrew] That somebody signed up for this study. - Yeah, so you were with and without anastrozole and five doses of testosterone. So now you basically had five testosterone levels, plus or minus high or low estradiol. And the results were really clear that the higher your testosterone and the more your estradiol was in kind of that 30 to 50 range, the better you were. So if estrogen was too low, even in the presence of high testosterone, the outcomes were less significant. - And this is 30 to 50 nanograms per decile, not 30 to 50% of one's testosterone. Okay, great. No, we haven't talked, but Clomid is, you know, we have not talked a lot about Clomid. I'd love to get your thoughts on Clomid. - So Clomiphene is a fertility drug. It's a synthetic hormone. It's actually two drugs, M Clomiphene and I forget the other one. And it tells the pituitary to secrete FSH and LH. So you, and so the advantage of Clomid is it's oral, and it's meant to be taken orally. So, you know, a typical starting dose would be like 50 milligrams three times a week. And if you do that, you'll notice, in most men, especially young men, FSH and LH goes up. In any man, the FSH and LH go up, but if a man still has testicular reserve, he'll make lots of testosterone in response to that. 'Cause that's the first order question we're trying to answer is do you, is your failure to make testosterone central or peripheral? - Yeah, and I think, just want to point out, again, correct me if I'm wrong, but



my understanding is that a lot of the drugs that we're talking about, the synthetic compounds, testosterone, estrogen, things related to growth hormone, et cetera, were discovered and designed in order to treat, and excuse me, in order to isolate and treat exactly these kinds of syndromes, whether or not it was the hypothalamus, the pituitary, or the target tissue, the ovaries or the testes. Correct? - Correct, yeah. I mean, I think, the easiest way to go about doing this is just give the hormone that's missing, without attention to where the deficiency is. Why this becomes relevant is if you have a 35-year-old guy whose testosterone is low, but you can demonstrate that it's low because he's not getting enough of a signal from the pituitary, why would you bother giving him more testosterone when he has the Leydig cells and the Sertoli cells to make testosterone. He just needs the signal. Sometimes, though not always, just a course of Clomid can wake him up, and he's back to making normal testosterone. - So he'll do this three times a week, 50 milligrams, three times a week, for a short course, and then? - Yeah, we would do that for eight to 12 weeks and then we reevaluate. - And estrogen and testosterone will increase in parallel. - Yes. And again, it depends, you know, aromatase activity is dependent on how much body fat you have and genetics. And if estradiol gets too high, we think if it gets over about 55, 60, we will give micro doses of anastrozole. But it has to be real micro doses. I mean, you cannot pound people with anastrozole. To give you perspective, the sort of on-label use, like if you just go to a pharmacy and order anastrozole, you're going to get one milligram tablets. Like we can't give anybody a milligram. - [Andrew] They'll feel like garbage. - We have to have it compounded at 0.1 milligrams, and we might give a patient 0.1, two to three times a week. That would be a big dose of anastrozole. - Yeah, I think that the typical TRT clinic out there is giving 200 milligrams per mil, one mil, 200 milligrams of testosterone once every two weeks, and then hitting people with multiple milligrams of anastrozole, and they're all over the place. - I've never really understood, I mean, I guess I shouldn't be surprised, but it kind of blows my mind that these TRT clinics are up all over the place, given how bad. I mean, I see the results, 'cause I have patients that come from them, and I don't understand like why they're so incompetent. - I actually think it's worse than that. I think that they simply don't understand and don't care, because it's a pill mill and it's a money mill. I think that nowadays it seems almost everybody who's doing TRT is taking lower doses more frequently every other day, or twice a week, dividing the dose, and being very, very careful with these estrogen or aromatase blockers. - Most of our patients do not take aromatase inhibitors. It's not needed. It's really only the high aromatasers that need it.

And so yeah, when we'll talk about testosterone, we'll talk about dosing there, 'cause I agree. The more frequently you can take it the better, and frankly, you don't need to go more frequently than twice a week. - Because it's so slow-acting. - The half-life, yeah, the half life of the drug is, I think it's about 3 1/2 days, is the plasma half-life or something like that. I could be off a little bit, but twice week dosing is really nice. So if you go to like a testosterone clinic that's giving you 200 every two weeks, 50 twice a week is the same total dose, which, by the way, is a physiologic dose. That's not going to give somebody any of the side effects you would see. You're not going to get acne with that. You're not going to get gynecomastia. You're not going to get anything. The only real side effect you get from that is you will get testicular atrophy. It is enough to suppress. - Yeah, to maintain fertility, what do you typically do for? - Well, so this is where, so I'll finish the story on Clomid, 'cause we currently do not use Clomid, and that's due to a really interesting observation that we made, that I don't think has been reported in the literature yet, which is that Clomid was increasing levels of a sterol that we also happen to measure called desmosterol. - [Andrew] I'm not familiar with that. - So, and the way that cholesterol is made, it's made by, there's two pathways that make cholesterol. So it starts like with two carbon sub units, like Acetyl-CoA, and it kind of marches down a pathway, bifurcates, and cholesterol is the finished product of both. But in one of those pathways, the molecule right before cholesterol is called desmosterol, in the other pathway it's called lathosterol. So we constantly measure lathosterol and desmosterol, because we want to know how much cholesterol is being synthesized in the body. Not just what your cholesterol is. We want to know how much cholesterol you reabsorb. And those markers are really important to us when we're looking at cardiovascular disease risk. So when we gave patients Clomid, we were noticing a almost universal rise in their desmosterol levels. Now, the most obvious explanation for that, though the last time I looked, I couldn't find clear explanation for this in any of the clinical, like the clinical trials that led to the approval of Clomid. So I don't know if it was described. In fact, maybe it wasn't known. I suspect it is inhibiting the enzyme, which I think is called delta-24 desaturates, that turns desmosterol into cholesterol. Makes sense if you inhibit that enzyme, you're going to see a rise in desmosterol. This wouldn't have been a concern to me, if not for the fact that Tom Dayspring, who's one of the physicians we work with, who's one of the world's experts in lipids, pointed out a very obscure story, which was that the very first drug ever approved to treat cardiovascular disease, at least to treat hypercholesterolemia, was a drug that attacked the same enzyme. So this is in the early

1960s I believe, maybe the mid '60s. This drug was approved and it lowered cholesterol. And it was approved on the basis of lowering cholesterol. Now today, no drug for ASCVD is approved on the basis of it lowering cholesterol. That's not a high enough bar. You have to reduce events. Actually have to show that you're preventing heart attacks and death. But at the time it was like, hey, it lowers cholesterol, it's got to be good. Well, in the late '60s it was pulled from the market because events were going up. So cholesterol was coming down, events were going up. How could that be? We don't know. What we are suspecting is that desmosterol, which is still a sterol, was potentially more damaging and created more oxidative stress in the endothelium, in the sub-endothelial space than cholesterol. - [Andrew] I see. - Which would at least suggest to us, and again, we're taking a lot of leaps here, that maybe having high desmosterol, very high desmosterol, is not a good thing. And so once we kind of pieced all that together a few years ago, we were like, yeah, we're just not going to prescribe Clomid anymore. And we then switched to HCG, which we used to use sometimes instead of Clomid, but it's more cumbersome to work with. It needs to be refrigerated, it's a much more fragile molecule. - Yeah, I think we talked about this once. It's almost like if you accidentally knock over the little bottle, it's basically gone bad. - Yeah yeah. - Travel with it is very challenging. - Can't travel with it. It's a needle, you know, it's an injection, Sub-Q. So easy to administer, it's not IM or anything like that, but it's just more of a hassle factor. But that said, it has the benefit that Clomid does, which is it preserves testicular function. It preserves testicular volume. So, you know, body builders will often use this in their post-cycle therapy, as a way to kind of recover function. And we would just use it now as ongoing therapy for a guy who still has testicular reserve. - So on its own, no testosterone, no aromatase inhibitor, nothing. Just a way to crank out a bit more testosterone from the testes. Maybe some additional estrogen also? - Yeah, and HCG is a different model. HCG is just an analog of luteinizing hormone. So it's basically like giving them luteinizing hormone. - So it's going to crush endogenous luteinizing hormone levels, right, because it's- - Actually, yeah. You don't really see much of an impact on LH,

01:47:46 Fadogia Agrestis, Supplements, Rapamycin

but you do see endogenous testosterone production go down. Actually, no, I correct that. Both FSH and LH will go down on a high enough dose. Yep. - Just as a mention, and

here I'm not making recommendations, but one supplement I've talked a lot about publicly is Fadogia agrestis, which is this weird Nigerian shrub that- - You talked about this on Tim's podcast. - On Tim's podcast and Joe's podcast, and, you know, there was a bit of a backlash because it does turn out that at high doses, in rodent studies, it can cause some toxicity of the testes. But at lower doses, it does seem to increase luteinizing hormone. And after talking about this, a number of people went out there, did pre and post blood work, and the consistent effect seems to be an increase in luteinizing hormone. There's a noticeable effect on testicular size and volume. So a lot of people take this and be like, oh, you know, their balls are getting bigger, and so they get all excited that something good is happening. But we don't know the long-term safety and efficacy of something like Fadogia, whether or not it needs to be cycled- - Yeah, this is why I'm also very leery of the supplements in this space, because at least when we're using HCG, or testosterone, like we have so many years of data. You have to remember how many women are using this stuff for reproductive medicine. So, you know, I think the FDA has a lot of faults. I think I have an entire podcast devoted to the corruption of the FDA and all of the mistakes that have been made with respect to their oversight in, especially generic drugs. But it's way more regulated than the wild wild west of nutty supplement land. - Absolutely. I think that the reason we're talking about things like Tongkat and Fadogia was to provide some intermediate discussion between doing all the correct things, but no supplementation or hormone therapy, and then going straight to hormone therapy. - Yeah, I- - It's sort of like the leap from, I can't focus very well, to Ritalin, right, without a real diagnosis of ADHD to, oh well, maybe some things like Alpha-GPC low doses of nicotine, right? But I agree entirely. I mean, the sourcing is important. The dosages are worked out empirically on an individual basis. And there aren't randomized control trials. There just aren't. - Yeah, and, you know, have kind of like a seven, this is another Peter Principle, right. So I got a lot of patients that come into the practice and, you know, during our intake, we go through what drugs and supplements are you taking right now? And, you know, a lot of people come in, I'm not taking anything, Peter, I just, you're in charge now, like tell me what you think. And then you get a lot of people that come in and they're like, are going to need an extra few pages for this part of the documentation. - Right, the people who travel with a suitcase that you can hear as they walk through the airport from all the pills rattling. - So I give these patients a little homework exercise, which is you have to answer these seven questions for every supplement you take, and here's the spreadsheet and let's talk about

it. And it basically just runs through like, you know, it's basically walking you through the logic of why do you take this molecule? And I think for many people, it's when they do that, it's very sobering, right. They kind of, a lot of them will come back and be like, you know what, I don't think I can come up with any reason along this really rigorous line of thinking as to why I'm taking 80% of this stuff. - Well, I know people, and actually we know some of the same people, who are fanatic about like red light on the testes, sunning their testes, putting ice packs on their testes. It's kind of all over the place. The number of things that people are trying and doing in order to increase testosterone output from their testes is pretty remarkable. And that said, among some of the women I know, the number of things that they're doing to try and promote longevity and fertility, and in particular skin health, hair health and nail health, is also kind of outrageous. Everything from collagen to red light therapies, which may actually have some efficacy in certain cases. But. - As an interesting aside. - There's a hunger there, right? - Oh for sure. One of the things that I hope gets a lot more attention is the use of rapamycin for preserving ovarian health. So the animal literature on this is pretty impressive, right? So in mouse models, rapamycin will preserve ovarian life. And so- - Interesting. - It makes sense, right. I mean, it totally makes sense why the most potent GRo protective molecule we have would also preserve and extend ovarian life, at least in mice. So I'd love to see the clinical trials done in women to test this hypothesis. - I definitely want to come back to this, 'cause that's a key thing.

#### 01:52:06 Testosterone Replacement Therapy & Fertility

I know that a lot of people are interested in female fertility out there, including their male partners. So going back to, so now I understand why you don't prescribe clomiphene, because of this desmesterol, potential desmesterol link. What about testosterone therapy? So less, - Yeah. - less frequent, lower doses, less or no estrogen inhibition or aromatase inhibition. - Yeah, only, we're only using an aromatase blocker, and we use Arimidex when we do. It's just to get that estradiol into the range we want. I like to see it between 30 and 50. That's the sweet spot. And I don't know, I would say like a third, maybe a, not even a third, I'd say probably 20% of men require a micro dose of anastrozole to get into that range. Most do not. And I'd rather err on the side of being a little high than a little low. So I never really want to be below 25, unless sometimes it's just below 25 and it is, it is what it is, that's fine. But if we're suppressing it to below 25, I

never want to be in that zone. And then yes, so TRT is ultimately, you know, giving testosterone cypionate is usually what we use. - Injectable, so as opposed to cream or pellet. - Correct. I used to use pellets with women, for some who were really adamant about the convenience of it, but for a bunch of reasons I just, I'm mostly not doing that and I've never been a fan of pellets in men. - You can't control the dosages, once it's in, right? - Well, even if you know the dose, yeah, that's obviously a problem. But I don't think, there's a big difference between putting a pellet into a man and a woman. So when you're putting a estrogen pellet into a woman, it's like, it's that big. When you're putting enough pellets into a man for six months of testosterone, it's two sums of pellets that are longer than my fingers. So you're putting like a V-shape. - [Andrew] Where are you putting this? - You're putting it into the gluteal fat. So it's just a more morbid procedure, and I don't think it's necessary. I think if you know how to manage it, you know, through sort of the injections, and now- - [Andrew] Injections are no big deal. - Yeah, well especially now if you're doing, we're having them do Sub-Q injections anyway. So it's not IM, they're using five-eighths inch to a one inch 25 gauge needle, which is about the smallest needle you can push the oil through, once to twice a week, depending on. And by the way, if they're real needle-phobes we use Xyosted, which is a preloaded pen. - And are you having all men take HCG to maintain fertility and testicular size? - Only if they want to. - Got it. - And by the way, we do not like to use TRT in men who, we don't like to use testosterone specifically in men who still want to maintain fertility. We just steer them away from that. - Because total sperm count goes down. - Yeah, we just say, why risk it. Like we'd rather use HCG. - [Andrew] Yeah, just on its own. - Yeah, just wait till you're done reproducing. Bank sperm, wait till you're done reproducing before we go to testosterone. - What are some of the benefits, and what are some of the cautionary notes with appropriate TRT, meaning the kind of contour that we're talking about here. A lower dose with the yes or no low estrogen control. People, what did generally people report, how do they feel? What does it allow them to do that they couldn't do or feel before? And then in terms of what are the markers to look for? Is it LDL, blood pressure, water retention, acne, those kinds of things. Are there some other things as well? - Yeah, it depends on the doses, right? I mean, again, we're using these in really low doses, so it's pretty rare that we'd have a patient on more than a hundred milligrams a week of testosterone. I think for comparison, like a bodybuilder could easily take 500 to a thousand during a high growth phase. - I know some of these guys, they go ballistic, or they're doing moderate levels of testosterone cypionate, but they're also taking

Dianabols, Nandrolone, you know, SARMs, and a bunch of other things. I mean, their stacks are kind of ridiculous. I mean, no disrespect to that sport, but I mean, people are dying like crazy in that sport right now. - [Peter] It's outside of physiology. - Yeah, and I think for 99% of people listening, they look, they hear bodybuilder and they just go, like, why would somebody do that anyway? - [Peter] Right. - I think that's the typical response. - So the point is, a lot of, but we owe those guys a great deal of gratitude 'cause they've shown us the boundaries. - Including the women. - That's right, yeah, yeah. And so, those bodybuilders have taught us a lot about like what happens. And so yeah, the bloating, the water retention, acne, hair loss, hair growth, all of those things we understand. The truth of it is, we just don't see those things in our patients. - But a hundred milligrams per week is a very low output. My understanding- - But it's a physiologic dose. I mean, the reality of it is it's enough for most people. I mean there's, probably the highest we've ever had to go is maybe 70 twice a week. - What's the youngest patient you've ever had to put on TRT? - Actual testosterone? - Mm hmm. - Probably, that's a good question, I'm thinking about. Maybe 40. - I think that's great for people to hear, 'cause I know that a lot of guys in their 20s are thinking TRT is the way to go, and I would argue unless you're doing everything else right and you're still hypogonadal and you're really struggling, put that time off. Because also the fertility issue you want to delay, delay, delay. - Well, again, it depends if, when we say TRT, if you're in your 20s and there's no other way, I would hope you would be steered toward HCG to at least preserve testicular function. Now again, we don't actually know if after being on HCG for 10 years, your pituitary will still work. - Right, you won't be able to make your own luteinizing hormone. - Exactly. So, it might be the case that you're going to need something upstream of that, like Clomid, to kick start it, and then we're, but again, I don't want anybody who's listening to this who's using Clomid for fertility, to think that there's anything wrong with it. I was, my concern over this became like, if you're going to be on this for 10 years, is it problematic? Not if you're using this for a course of IVF or something like that. So, again, if we felt that someone's pituitary was not working, I would be happy to put three months of Clomid on them to kind of try to see if we could blast it back. - Do you have men cycle on and off testosterone at these low dosages? Are they taking a month vacation from it every once in a while? - Yeah, totally depends. You know, I was talking to a patient yesterday where we're going to do, we just decided to change his cycle, eight weeks on, then eight weeks on HCG, eight weeks on, then eight weeks on HCG. So that's going to be a cycle that maintains his testosterone level,

but fluctuates between endogenous, exogenous, endogenous, exogenous. Sometimes we'll just do testosterone on, off, on, off. And there it's like, how much can he replenish naturally, but understanding his T will dip during those off cycles. - Seems to me there's a tremendous incentive for somebody to develop a molecule that can directly target SHBG, besides Oxandrolone and Anavar, right? If one could just drop SHBG just the tiniest bit, it seems like one could adjust the free T in a way that would be great. I don't know why that molecule's so hard to target, but somebody ought to do it. The chemistry can't be - Yeah, it's funny. - that hard. - I talked with Patrick Arnold about this many, many years ago. I wish I could remember what his ID, he had a comment about this that at the time made sense, and I don't remember what it was, 'cause I had that thought too, like man. Especially for that subset of guys who have normal testosterone, but they're just over binding it. - I'm really glad that you brought up this issue

#### 01:59:26 Total Testosterone vs. Free Testosterone

of total testosterone versus free T, and the reason is, ever since going on podcasts and talking about this stuff, and talking about it on this podcast, people will send me their numbers. They'll send me their charts and then they'll send photos of themselves, and I can tell you, while I'm not a clinician and I haven't done fancy statistics on it, there's very little correlation between someone's absolute testosterone and how they appear. I mean, some of these guys look, you know, really lean, really strong, and they'll say, oh, total testosterone is 550, 480, right. And then other people, you know, testosterone is 860, but you look at them and you think, oh, they kind of have kind of a dough-y look to them. And so it's got to be this free testosterone thing, plus estrogen, et cetera. And so cosmetically- - Well, but also training and nutrition too, right. - Yeah, absolutely. - I mean, I just think, I think for all this talk about testosterone, which I enjoy talking about and, you know, I enjoy talking about the data on, you know, long-term health consequences of testosterone, 'cause it's another controversial topic, I also think people kind of overstate its importance. - [Andrew] I agree. - And I think there's a group of people who think if I could just fix my testosterone, everything will be better. And it's sort of like, no, actually that's not true at all. Really, the only purpose in my mind of fixing testosterone is to give you the capacity to work harder. It's really going to help you recover more from your workouts. This should just give you a greater ability to experience muscle protein synthesis. So, you know, if I just give you a bunch of testosterone and you sit on the



couch and your nutrition doesn't change and you're not exercising anymore, you're not going to experience any benefits of this thing. I mean, my testosterone level has fluctuated quite a bit throughout my life. And when I think about as an adult, not sort of including when I was sort of a fanatical teenager, but as an adult, when was I at my absolute most insane physique, like my best performance on a DEXA scan, would've been, I was 38-years-old, by DEXA I was 7% body fat. My fat free mass index was like 23.2, 23.3 kilograms per meter squared. I mean, I was huge, strong, and totally ripped. My testosterone was in the toilet. I was over-training like crazy. I was, you know, exercising probably 26 hours a week, killing it in the gym, swimming like a banshee, cycling like my life depended on it, grossly over-trained, low T, but, you know, I mean physically looked like twice the guy I am today. You know, today my T's probably twice as high as it was then. So, you know, now you could say, well, Peter, what if you took T back then? How much better could you have been? Sure. But, again, I think the take home is just giving somebody T doesn't do much of anything. It probably helps on the insulin resistance front, without any other thing. But to me that's a waste, like that's squandering the gift that it is giving you, which is the ability to do more work and, you know, capture the benefit of it via muscle protein synthesis. - I agree, and I think that the psychological effect of testosterone, whether or not it's exogenous or endogenous, is it makes effort feel good. - Yeah. - At some level it really seems to do that. And Sapolsky tells me the main reason, or mechanistically the main reason that it can do that is by adjusting levels of activity in the amygdala. - Interesting. - And so there's some interesting imaging there.

02:02:51 Cholesterol & Dietary Cholesterol, Saturated Fat, LDL & HDL, Apolipoprotein B

I'd love to chat more about the cholesterol pathway, and I know this is a huge landscape as well, but I think we're doing a good job of diving in deep, but not getting stuck in the underlying currents at all. There's tremendous debate about whether or not dietary cholesterol directly relates to, or does not relate to, serum cholesterol, LDL and HDL. Here's my- - Is there? - I think, well, let me put it this way. There are people that argue, I'm certainly not arguing. - Yeah, yeah, yeah. - There are people that argue that if one eats a ton of saturated fat, that LDL goes up and HDL goes down. - Oh, okay, but that's not dietary cholesterol per se. - No, not dietary cholesterol per se, but, and then there are people that argue that, you know, any increase in saturated fat intake is going to be

bad, that you already synthesize enough cholesterol for hormone production, et cetera. I'd like to talk about this in terms of how one should read their charts. My LDL is in what I'm told is healthy range. My HDL is in what I'm told is healthy range. I do try and not overeat things like butter, cheese, and red meat, but I do eat some of those things and I feel pretty good. But most people are operating under the assumption that eating saturated fat is bad, and you only do it insofar as you want to taste it. And then of course there's a small group of people that love to eat organs and meats, and really pack cholesterol, and would argue that it doesn't matter if your LDL is 870, it's not going to impact your health. What's the reality around LDL, HDL, dietary cholesterol, saturated fat, at least in your view? - So first let's differentiate between cholesterol and fat, just for the listener, 'cause we use them, you know, I want to make sure people understand. So, cholesterol is a really complicated molecule. So it's a ringed molecule. God, I used to know exactly what its structure was, but like it could have 36 carbons, for all I remember. It is a lipid, so it is a hydrophobic molecule that is synthesized by every cell in the human body. It is so important that without it, if you look at sort of genetic conditions that impair cholesterol synthesis, depending on their severity, they can be fatal in utero. So in other words, anything that really interferes with our ability to produce cholesterol, is a threat to us as a species. And the reason for that is cholesterol makes up the cell membrane of every cell in our body. So, you know, as you know, but maybe the listeners don't, even though a cell is a spherical thing, it has to be fluid, right? It's not just a rigid like sphere, like a, you know, a blow up ball, right? It's got to be able to kind of move in this way to mesh with other cells. It also has to accommodate having porous structures that traverse its membrane to allow ions and things like that to go across. And it's cholesterol that gives the fluidity to that membrane. It's also, as you're alluding to, the backbone of some of the most important hormones in our body. Estrogen, progesterone, testosterone, cortisol. So we have this thing, super important. Okay. Then let's talk about, can you get cholesterol in your diet? Yes, you can eat foods that are rich in cholesterol. What was known in 1960, but somehow escaped everybody's imagination until finally the American Heart Association acknowledged this a few years ago, is that the cholesterol you eat does not really make it into your body. And the reason for that is it's esterified. So we have, and not to get too nerdy, but I think people, I really think it's important people understand how this thing works. So we have cells in our gut, and enterocytes, they're the endothelial cells of our gut. They have, each one of them has basically two transporters on them. So the first is called the Niemann-pick C1-like 1 transporter. The

second is called the ATP-binding cassette G5/G8. Okay. The Niemann-pick C1-like 1 transporter will bring in any sterol, cholesterol, zoosterol, phytosterol. Any sterol that fits through the door will come in. Virtually all of that is the cholesterol we produce that gets taken back to the liver, that the liver packages in bile and secretes. So that's what aids in our digestion, which is another thing I should've mentioned earlier. In addition to using cholesterol for cell membranes and hormones, we wouldn't be able to digest our food without cholesterol, because it's what makes up the bile salts. So our own cholesterol is basically recirculated in a pool throughout our body, and this is the way it gets back into the body. It's through this Niemann-pick C1-like 1 transporter. When it gets in there, the body, this is the checkpoint of regulation. This is where the body says, do you have enough cholesterol in the body, yes or no? If yes, I will let that cholesterol make its way into the circulation. So it'll go off the basolateral side of the cell, not the luminal side, into the body. Alternatively, the body says, you know what? We have enough cholesterol. I'm going to let you poop this out. And now the ATP-binding cassette will shoot it out, it'll go back into the luminal side, and away it goes. So all of the cholesterol in our body is not esterified. And it doesn't have that big, bulky side chain attached to it. The cholesterol you eat is esterified, and an esterified cholesterol molecule simply can't physically pass through that Niemann-pick C1-like 1 transporter. Now, we probably manage to de-esterify 10 to 15% of our dietary cholesterol. So in other words, there are small amounts of dietary cholesterol that do make their way into our circulation, but it represents a small fraction of our total body's pool of cholesterol. Again, this was known, even by Ancel Keys, the guy who turned fat into the biggest boogeyman of all time. Ancel Keys acknowledged this in the 1960s. Dietary cholesterol plays no role in serum cholesterol. Again, it took the American Heart Association another 60 years to figure that out. But even now they acknowledge that. Dietary cholesterol has no bearing. - So why is it that it's pretty easy to find studies, or at least people who are highly credentialed from good institutions, claiming that eating saturated fat- - [Peter] Saturated fat's different. - Saturated fat and red meat, things that are rich in cholesterol, to be more specific, is bad for us in terms of our eventual LDL. - So this is two different things. So saturated fat consumption in many people will erase LDL cholesterol. So it's important to differentiate between the, what is saturated fat? So saturated fat of course is a fatty acid, just so people understand. Totally different molecule from cholesterol. Cholesterol is this very complicated ring structure, multiple rings stuck together. SFA, saturated fat, is just a long chain fatty acid that is fully saturated, meaning it has no double bonds, and it can exist in

isolation. It can exist in a triglyceride, triglycerides, or, you know, a phospho lipid, or all sorts of things like that. So when we eat foods that contain fat, basically there are three distinctions for that fat. Is it saturated, is it monounsaturated, one double bond, or is it polyunsaturated, two or more double bonds? The observation that eating saturated fat raises cholesterol is generally correct. But again, now it makes, because if we're going to start talking about LDL, we have to explain what LDL is. This is another one of those things that's just so grossly misunderstood, that it's, it makes having discussions about this very complicated. Let's go back to the cholesterol problem, right? So every cell in our body makes cholesterol, and almost without exception, they make enough. There are a handful of times, however, when a cell needs to borrow cholesterol from another cell. Okay, so how would you do this, right? So if you're sort of, if you're playing God for a minute and you want to design a system, you have to be able to transport cholesterol from one cell to another. The most logical place you would transport this is through the circulation. And the problem with circulation is it's water. Plasma is water. So now you have this problem, which is, I want to transport cargo that is hydrophobic, in a hydrophilic medium. Can't do it. So if you think about all the things that we transport in our blood, sodium, electrolytes, glucose, things like that, they're water soluble. It's easy. They just move back and forth in our blood with no chaperone. But when you want to move cholesterol, you have to package it in something that's hydrophilic. That something is called a lipoprotein. So we have these spherical molecules that are lipid on the inside, protein on the outside, lipoprotein, and inside they contain cholesterol and triglycerides. So now you've got this spherical thing, triglyceride, cholesterol on the inside, and it's chaperoned by a hydrophilic molecule that allows it to move through our circulation. And those lipoproteins exist in different densities. So if you run these out on a gel electrophoresis plate, you'll identify different densities. The density is a function of how much protein and how much lipid is in it. So the highest density of this is called a high density lipoprotein, and the lowest density of this is called a very low density lipoprotein, a VLDL. And then next to that you have an LDL, a low density lipoprotein, and then next to that you have an IDL, an intermediate density lipoprotein. So, you know, it actually goes VLDL, IDL, LDL, but anyway. So when people say my LDL is high, or my LDL is 100, what are they saying? They're saying the cholesterol concentration of my LDL particles is a hundred milligrams per deciliter. So the total cholesterol concentration you have in your circulation is that number that says total cholesterol. So if someone's blood panel says my total cholesterol's 200, it means that if you take all the lipoproteins in their

circulation, bust them open and measure the cholesterol content, it's 200 milligrams per deciliter. And for all intents and purposes, because the IDLs are so short-lived, that's basically the sum of your LDL cholesterol, your VLDL cholesterol, and your HDL cholesterol. Those three things sum to your total cholesterol. - What about LDL little a that you mentioned earlier? - [Peter] LP little a is another- - LP, excuse me. - Yeah, yeah, he's another actor. He is a special type of LDL that, again, in sort of 10 to 20% of the population, is a really bad actor. So that's an LDL that has another apolipoprotein on it called apolipoprotein little a. - [Andrew] Got it. - The other thing I'll just say on this, because earlier I mentioned ApoB. There are two broad families of lipoproteins. There are those that are wrapped in ApoBs, and those that are wrapped in ApoAs. The ApoA family is the HDL family. The ApoB family is the VLDL, IDL, LDL family. - I see. So for somebody who let's say their total cholesterol is, let's just stay with 200 for simplicity. What do you like to see in terms of the HDL LDL ratio? - Couldn't care less. I only care about ApoB. I only care about ApoB. I care about the causative agent of atherosclerosis. ApoB is the thing that drives atherosclerosis. - And what levels are attractive or repulsive for you when you see levels of ApoB that are blank, you get really concerned? - It depends on the person's objectives. So again, we take a very different view. I mean, we have. - Vitality now, and I want to live to be a hundred. - Yeah, so if you see- - And I'm assuming some taper. - If you tell me you want to live to be a hundred, you're going to need to keep your ApoB below 30 milligrams per deciliter. - Let's say I want to live to be a hundred, but I also, well, how about, I don't care how long I live, but I want to feel great while I live. - Again, it depends, right? Like anybody who's had a heart attack is going to be compromised in their ability to feel well after. Right, so. - I guess, I say it that way, because if you're going to tell me that in order to achieve that live to a hundred level, I'm going to have to give up my personal life and my- - No no, to get- - and my brain functioning, then I'm not really interested. - Sure, but to get LDL levels, and really, again, people think of it as LDL, it's really ApoB, right? ApoB is this total concentration of LDL and VLDL. And that's what matters. Those are the big atherogenic particles. LDL also includes the Lp[a], although the concentration of Lp[a] is relatively speaking so small that it doesn't generally show up as much in the ApoB. So we treat ApoB, and basically what it comes down to is you want ApoB to be as close to the level as it was when you were born. So we start developing heart disease when we're born. That's just the way it is. The autopsy studies make this abundantly clear. When you look at autopsies of young people who are dying in their 20s, and this was first done in the 1970s, it was again

repeated. Again, it's always done after we have a war, right? So in the 1970s, it was done on people, you know, who died in Vietnam. In the early 2000s it was done on mostly young men, but some young women, who were, you know, dying in Iraq and Afghanistan. And we saw without any ambiguity that cardiovascular disease is already taking hold in people who are 18, 19, 20-years-old. - [Andrew] Wow! - And to be clear, they aren't going to die of atherosclerosis at that age. They're still 40, 50 years away from it. But this is a lifelong disease. And we also know that the disease can't really develop until ApoB reaches a certain threshold. And that's the threshold that most of us get to by the time we're sort of in our teens. So it's this really young ApoB level of kind of 20 to 30 milligrams per deciliter, that makes it impossible to get atherosclerosis. So ApoB is necessary, but not sufficient to develop ASCVD. Now that, go ahead. - Oh, I'm sorry, I was just going to ask,

02:17:42 Apolipoprotein B, Diet, Statins & Other Cholesterol Prescriptions

what are some of the top behavioral nutritional supplementation, if any, based, and prescription drug-based ways to target ApoB? - Well, nutritionally, you basically have two big tools, right? And it depends on what's driving up ApoB. So ApoB, remember, is the concentration of LDL and VLDL particles. And what do they carry? Cholesterol and triglycerides. So anything that reduces cholesterol and reduces triglycerides, is going to reduce ApoB. Triglycerides are generally driven by carbohydrate intake. So more insulin-resistance, more carbohydrate intake, more triglycerides. So we, I mean clinically, this is readily apparent to anyone who treats patients. If you restrict carbohydrates, you will reduce triglycerides. That just happens all day long. But if you reduce triglycerides by raising fat intake so much, it can still raise ApoB. So you have to be able to think about it. So in an ideal world, it's can you lower saturated fat, which tends to be the one that is most driving ApoB, while lowering carbohydrate, and then see what you can get. But here's the reality of it is, there's nobody with dietary intervention that's going to get to a level of 30 milligrams per deciliter. I mean, I've never seen anything. - Pure dietary intervention. - Yeah. - So what are the other things that- - [Peter] It's got to be pharmacologic at this point. - Statin type interventions? - Well, now you have multiple classes of drugs. So the tried and true is the statin. So statins work by inhibiting cholesterol synthesis, and the net effect of that is that the, so the liver is really sensitive to cholesterol levels. It doesn't want too much, it doesn't want too little. When you inhibit

cholesterol synthesis, the liver says, I want more cholesterol. So it puts more LDL receptors on its surface, and it pulls the LDL out of circulation. That's what lowers the LDL in the circulation. So, you know, again, nine statins in use today, we typically use four of them. The side effect profile, contrary to kind of all the sort of statin-hating propaganda out there, very benign, right? 5% of people experience muscle soreness, which reverses upon cessation. - Cognitive effects? - Again, I think it's, in terms of actual comparing it in a placebo, no effect whatsoever, right. So does that mean that you put a patient on it, they won't complain of something? No, but if you look at clinical trials, there's no evidence whatsoever that statins impair cognition. There's also no evidence in clinical trials that they accelerate the risk of neurodegenerative disease. In fact, it's the opposite. Now we will, there's a very nuanced case we make, Andrew, which is we'll look at patients with highly suppressed desmosterol levels. We will back off. We do want to maintain desmosterol above a certain level, because of some evidence that is still, I think, very preliminary, but enough for us that we say, why take the chance? We have so many other tools to lower cholesterol, why would we over-suppress synthesis in a susceptible individual? So the next tool you look at is a drug that blocks the absorption, or the reabsorption of cholesterol. Remember that Niemann-pick C1-like 1 transporter? So that guy has a drug called ezetimibe that just mechanically blocks it. So in people, and that's why I mentioned earlier, we measure all those sterols in people, so we also measure things called phytosterols. And the phytosterols give us an indication of how active that transporter is. So the higher your phytosterols, the more likely you are to respond to ezetimibe. Next class of drugs is a drug that blocks cholesterol synthesis, but only in the liver. So the statin does it globally. This other drug called bempedoic acid does it only in the liver. So it has a very similar mechanism to statins. Different enzyme. Not quite as potent, but way fewer side effects. So any patient that's having a response to statins that's adverse, we'll try this other thing. - What's it called, one more time? - [Peter] Bempedoic acid. - Bempedoic acid. - The most potent drug of the lot is the PCSK9 inhibitor. So PCSK9, it's a protein that was discovered in the late '90s, I believe, is responsible for the degradation of LDL receptors. This was first discovered in people who had a condition called familial hypercholesterolemia, or FH. So these are people that have incredibly high cholesterol. Typically their total cholesterol level is 300. Their LDL cholesterol is typically, you know, north of 200 milligrams per deciliter. This is a disease that is defined by the phenotype, not the genotype. So the phenotype has a very clear definition, which I basically just gave you. The genotype is, there's a million paths

to get there. There's over 3000 mutations that are known to produce that phenotype. This was discovered to be one of them. In people who had hyper functioning PCSK9, this protein was just constantly hammering and destroying the LDL receptors. And so their LDL would be huge. And by extension, their total cholesterol would be. So in 19, no sorry, in 2006, Helen Hobbs and colleagues discovered an opposite group of population. People who had LDL cholesterol naturally of 10 to 20 milligrams per deciliter, which would be an ApoB of about 20 milligrams per deciliter, and who never got heart disease. They were immune to heart disease, no matter how long they live. And they had the opposite, they had hypofunctioning PCSK9. And so that was 2006 in the "New England Journal of Medicine." That basically got a whole bunch of drug companies hot on the trail of producing a drug to mimic it. So now we have these antibodies, and they're wildly effective. - What percentage of your patients over 45 do you have on either a statin or on one of these other classic compounds? - Well, often it's in combinations, and I would say 80%. - [Andrew] Eight zero? - Well you have to remember what our objective is. Like, we're in the business of trying to make sure people live as long as possible. And you have to take a sort of world view of this, right? If you, like what's the most prevalent cause of death globally? - [Andrew] Say cardiovascular disease. - Yeah, and like, how close is it? So the last year before COVID, COVID kind of messes up these numbers a little bit, but if you go to 2019, 18.6 million people died of heart disease. Number two, cancer, 10 million. Like nothing's in the zip code of atherosclerosis. And if you remember what I just said, if you took everybody in their 20s and reduced them to a level of that of a child, you'd make ASCVD an orphan disease. - So. - So the question is can you do that? - Why don't we hear more, why don't we hear more about this? I realize there's some nuance. It's not straightforward, it's not as simple as saying, eat less cheese, red meat and watch your LDL, get on a statin. But why do we hear so little about ApoB, in the general discussion? Social media is such a skewed landscape, as we know. People shouting into tunnels of varying clarity. Some are beautiful bronze tunnels with clean walls and others are sewer lines, right. And they all converge in the same place. - Yeah. - Right, as we know. But why do we hear so little about this? I mean, I'm not on a statin, but now I'm beginning to think that maybe that might be a good idea to consider one of these other compounds. I don't know the last time I looked at my ApoB specifically, I'm guessing my physician did. But why don't we hear more about this?

02:25:15 Cardiovascular Disease, Age & Disease Risk



This sounds so important. It sounds like the most important conversation, 'cause all the hormone stuff and all the stuff about smoking, and head injuries, and ADHD and all the rest, I mean, is irrelevant if you're dead, right? - Yeah. It's a great question, I don't think I have a great insight as to why this isn't more front and center. I think the bigger problem is why don't we even understand how to think about it? I mean the, and there's a whole chapter in my book I'm working on that really gets to this problem of, why aren't we looking at atherosclerosis in terms of treating the causative agent? Instead, we look at modifying 10-year risk. So that's the fundamental difference between what I call medicine 2.0 and medicine 3.0. Medicine 2.0, which is what we're generally practicing today, when it comes to ASCVD says, look, we will treat you, we will lower that LDL cholesterol, they still don't talk about ApoB, but that's a very American thing. If you go outside of the United States, everybody's talking about ApoB, it's in the guidelines in Europe and Canada, and everywhere else. The United States is very stubborn on this, and it's due to a couple of really weird personalities in the lipid world. But the paradigm is, when your 10-year risk reaches 5%, when there's a 5% chance that you're going to have a heart attack, stroke, or die in the next 10 years, now it's time to treat you. Medicine 3.0 says that's not the way to think about it. You treat the causative agent. If there's a causative agent, you treat it. If blood pressure raises the risk of heart disease, you lower blood pressure. If smoking raises the risk of something, you treat smoking. And the reason that the risk model is so bad when you're looking at 10-year risk, is age is the biggest driver of risk. I mean bar none, right? So if you take a 70-year-old with perfect lipids and perfect blood pressure and perfect everything, their 10-year risk of ASCVD is probably four to five times higher than the most unhealthy 30-year-old. It's not even close. - It's a lot like eye disease. You know, there are exceptions, of course, but we always say that the biggest risk factor for going blind from glaucoma is being an older person, frankly. - So if you could identify what the risk factors are for glaucoma, imagine if the paradigm was, we're only going to treat it when your risk of blindness reaches 5%, which isn't triggered until you're old enough anyway. Wouldn't you rather know that when you're 30? - Absolutely. - And say, wait, if maybe being in the sun without sunglasses, or, you know, using this type of eye drop or something like that, has a negative impact, I would rather know that sooner. So that's the fundamental difference. It's a philosophical difference, with respect to prevention. And I will acknowledge that in one element of prevention, I make no consideration. I am only coming at this through the lens of the

individual. I am never coming at this through the lens of society. That makes my life easier, and it makes the problem I'm solving easier. I don't have to answer the quality adjusted life year problem. I don't have to ask the question, is it economical to treat people at 30? I don't know the answer to that question. But I also know that when you're trying to solve really complicated problems, the more you can simplify the better. So I've just acknowledged openly, not solving that, if you want to criticize me for it, that's fine. Let's be transparent. But all I care about is the person I'm sitting across from, and in that situation, it's really their decision if they can justify the cost of treatment.

02:28:53 Peptides, Stem Cells, BPC157, PRP (Platelet-Rich Plasma), Injury Rehabilitation

- An esoteric question, and then a less esoteric question. The esoteric question relates to something that I think is a little bit niche, but not necessarily so, which is, peptides and stem cells and PRP. I don't want to go off on too much of a tangent on rehab, but I know you've done a number of posts on social media recently that were, I have to just tell you were really thoughtful, and I really appreciate that you're willing to share your own tissue rehabilitation experience, and point people to that, because this is a landscape that a lot of people are in and they don't know how to navigate it. And a mutual friend of ours, not to be named, sent me a text and said, I'm going to be talking to Attia, and what do you know about studies on things like BPC-157, this gastric peptide that anecdotally, again, anecdotally, people report getting injections of this into the shoulder, knee, et cetera, and feeling so much better, so much faster, but there really aren't good studies, controlled studies. And you hear all the same sorts of things about platelet-rich plasma, PRP, which, if someone tells you there are a lot of stem cells in them, they're lying. There are not a lot of stem cells in them. And you also hear about stem cells, which are not FDA approved, at least in this, for most uses in this country, but are certainly, people are flying down to Colombia and getting injections. And what is your understanding or experience with things like BPC-157, specifically, 'cause peptides is a huge landscape. We should probably do a whole episode on peptides. Things like PRP. PRP is now approved for, I mean, women are getting injections of this into their ovaries to improve follicle count. We know this. People are getting injections of PRP into every tissue and organ and, hell, men are getting injected into their penis, so I hear, for all sorts of reasons that are unclear to me. What's the deal with PRP, BPC-157, and stem cells? Do

you ever see interesting effects? Are you curious about these compounds? Do you prescribe or direct people towards these? The FDA approved ones of course. - Yeah, so short answer is, I'm definitely curious about them and I'd love to see the work done, but I also think this is about as wild wild west as it gets. PRP less so, but certainly stem cells and peptides. And, you know, I just think, if you're going to do something without a clinical trial, you got to show up with a lot more data, right? So let's use rapamycin as an example, right? I'm a huge proponent of rapamycin. And you can say, well, Peter, how can you take or prescribe rapamycin for GRo protective effects, when we do not have a human clinical trial demonstrating that it lengthens life? And the answer is, because I have 84 other pieces of data that all point in the same direction across every model organism going back more than a billion years. And that's really different from, Joey, Sammy, and Sally did this thing, and I think it works. And they just can't be compared. Now I have no idea if stem cells work. I have no idea if BPC-157 works. I have no idea, frankly, if PRP even works, though it might seem to have some efficacy and some indications. For example, maybe when it comes to early hair loss. Maybe when it comes to, you know, certain joint issues. But the reality of it is like, I think we just have to accept the fact that everything we do has an opportunity cost, and that opportunity cost is sometimes financial. But I actually find a lot of times it's in time and effort and energy that goes into something. Now, when I was, you know, waiting to get my shoulder surgery, this is an injury that I've had forever, right? This is an injury, you know, this injury was actually probably the greatest source of discomfort I had swimming the Catalina Channel the last time in 2009. So that tells you how long I've had this injury. But, you know, I sort of knew at some point, like, I'm going to have to have it fixed. And I sort of went down this rabbit hole like, hey, is there anything I can do to avoid having surgery? You know, would infusing a million stem cells into it work? And in speaking with as many orthopedic surgeons as I could, the answer was kind of unambiguously no. And by the way, it doesn't mean you wouldn't feel better if I injected a bunch of stem cells into your shoulder. There are a lot of reasons that might make you feel better. Just like there are a bunch of reasons you can feel better if somebody injects saline directly into your joint. So the question is, is it going to fix the underlying problem, and if so, will it do so by what mechanism? So I'm pretty sure that if you took a thousand people with my particular injury, and injected them with stem cells, it wouldn't do a thing, because of the nature of my injury. I had a complete labral tear. Are there some injuries that might benefit from it? Yeah, possible. So the question is, how would you design the trial to

narrow down your patient population correctly, so that you might see a signal? 'Cause the other risk of doing a trial is you have too much of a heterogeneous patient population. You don't know what the heck you're really doing, and you get meaningless results. You get a null result, when in fact there's a small signal, but you were underpowered to pick it up because, you know, you only had 10% of your patient population that was the right patient population to get that. So, you know, will we ever get there? I don't know, because I don't see what the incentive is, right. You have people who are making money hand over fist, doing procedures on the basis of I'm not sure what, what would their motivation or incentive be to sort of see this legitimized? You'd really have to be able to say, well, there really needs to be sort of a pharma angle to this. It's sort of one of the wishes I had, right? Like if I was a billionaire, I feel like the way I would probably waste all of my money would be running clinical trials on stuff nobody cared about. - Yeah. - It would just be- - Likewise, I will join you, because that would be, yesterday we recorded a sit down with somebody from Caltech who works on aggression and rage, and other things related to that, and has identified peptides that are approved the FDA for other reasons that seem to adjust anxiety, might even adjust aggression and pathologic aggression, and went off on to a long description of why none of these drugs exist on the market for the treatment of psychiatric illness, and yet probably would work. And what's missing is a billionaire, or a billion dollar company, that is willing to invest in something that very likely will work, but the market value isn't quite there. Or it failed in a previous trial, and so no one wants to touch it with a 10-foot pole. Hopefully someone listening to this will be incentivized to provide this sort of a venue for that. The kind of work that we're talking about. I have to ask. - But I want to make one other point, Andrew, which is, to me, the problem with a lot of these things is it gets, it's a crutch. You know, it's sort of like what we talked about with like, hey, just fix my T man, and everything's going to be fine. And it's like, no, that's just the beginning. You know, what I worry about when I see people who are clamoring for this stuff is a lot of times they don't realize that, whether it's psychologically or otherwise, they sort of say, well, now that I've had this thing done, I don't have to do the hard work of the real rehab. I mean, if I've learned anything through my shoulder surgery, and I'm now 3 1/2 months out. - How does it feel? - Amazing. I mean, look, I still can't do a lot of stuff. It's going to be, you know, a while. I haven't even been able to shoot a bow yet. And it'll probably be a year before I'll go back to, you know, long dead hangs and heavy deadlifts. I mean, I dunno, maybe nine months. But it's, you know, I'm not there yet. But what I learned

through a really amazing prehab and rehab process is, like you just got to do the work, and it's freaking hard. Shoulders are the most tedious, boring thing in the world. I mean, three days a week I am doing, four days a week I am doing one hour of just dedicated stuff for this shoulder, that is super uncomfortable, super boring, super frustrating. But, I mean, I have faith in the methodology, right. And I think a lot of people are saying, just shoot the stem cells into me and I don't have to do any of that stuff. And the reality of it is, I think that's a very dangerous place to be. - Have you ever tried BPC-157? - Yeah, we tried it. We had, you know, again, maybe seven, eight years ago, we had a bunch of patients ask about it, so, you know, my view is, okay, I was pretty convinced that there was no safety downside to it so I was like, well, I wouldn't prescribe it to a patient unless I tried it myself. So me and another doc in the practice, Ralph, we did it for, I don't know, a couple months. I didn't notice a single thing. - Interesting.

#### 02:37:40 Metabolomics & Exercise

Well, thank you for that. Shifting to a less esoteric, but, and I think probably more important topic overall. Metabolomics. We're talking about this before we sat down to record. What is, what are metabolomics? Why should we be thinking about them? I have some idea of what it might be about, but most people I think are not thinking about metabolomics at all. And for those that are, I'm sure they could learn more. So tell us about metabolomics and what you'd like to see more of in the world of metabolomics. - Yeah, so omics is just the term that we use to describe the study of something. So genomics right, is like the broad study of genes, and, you know, proteomics, the broad study of proteins and things like that. So metabolomics is just study of metabolites, and metabolites, unlike a lot of these other things, they're a relatively finite number of these things, many of which are known, but some of which are not known. So glucose is a metabolite. Acetyl-CoA is a metabolite. Lactate is a metabolite. And so the question is, what do we know about these things and how they work? And more importantly, what do we know about certain physiologic states, and the metabolomic profile that results from them? So let's use two extreme examples, like exercise. Everybody understands, the data are unambiguously clear, exercise produces about the most favorable phenotype imaginable. So if you wanted to take a genomics approach to understanding that, you might look at, is there a change in the genome when you exercise? And the answer is probably not, but maybe if you looked at the methylation patterns and epigenome, you

could look at epigenomic studies. But you might instead look at kind of the proteomic side of that. Like, what is gene expression doing? And there you would see a lot of changes. Well, what I don't think people are really understanding, although there was a very interesting paper that just came out two weeks ago that looks for novel metabolites that are changing, is they're a huge signal in a metabolomic profile that looks different in the state of exercise versus non-exercise. And could that represent part of how exercise is transmitting its benefit through the body? You know, people always talk about the holy grail of metabolomics would be can you find a pill to mimic exercise? And I think the answer to that question is going to be undoubtedly no. For a couple of reasons. One, even if you could mimic the longevity sort of lifespan parts of it, you could never mimic the health span parts of it. But what if you could do both, right? What if there were small molecules that can replicate some of the protective benefits of exercise, and you could combine those with exercise? What if those could be treatments for other disease states, like diabetes, things like that? So that's why I think this field of metabolomics is relatively untapped, and I think potentially the next sort of frontier.

#### 02:40:44 GLP-1 & Weight Loss

- Speaking of frontiers, I hear a lot nowadays about GLP-1 and pharmacology, that prescription drugs that mimic or increase GLP-1 directly, glucagon-like peptide. People are talking about this as the blockbuster obesity drug. I haven't heard this much talk about a drug to adjust human body weight favorably, since the discussions of fen-phen when I was in college, and then of course fen-phen was pulled from the market because people were dying. Not left and right, but enough people died that they pulled it from the market. - Which, by the way, is an interesting story. You know, it was the enantiomer that they chose to use that was the wrong enantiomer. And what it resulted in was, God, I think it was like. - Was it mitral valve prolapse? - It was an MVP, yeah, it was something in the mitral valve. Yeah, I think the chordae tendineae were rupturing in the mitral valve, and it was mostly young women I think were getting, you know, horrible pulmonary disease as a result of it. Probably pulmonary hypertension or something like that. But there were, you know, there were two enantiomers of the drug, and had they just used the other one, this issue wouldn't have happened. And there was a stupid reason why they made the choice to use the one they did. And it's one of those things where once you make the mistake, you're never going back. It's not like that company

could say, okay, wait, we want to do over, but we're going to do it with the right version. So it's a tragic outcome. But you're absolutely right. I think the GLP-1 agonists have more efficacy, and, you know, for all intensity and for everything we can see, certainly seem safer. - Are you excited about them? - Yeah, I am, yeah. I mean, I think we're just seeing the kind of tip of the iceberg. They're not miracle drugs, right. They come with problems, right, which is, you know, they're catabolic across the board. So patients are losing fat, but they're losing muscle as well. So, you know- - You just sent all the gym jockeys running from [indistinct], that's all you have to say. All you have to say nowadays about something is that it's going to drop testosterone, lower fertility, change someone's skin, hair or nails, and it's like people, it could extend life to being 250-years-old and people are gone. Humans are humans. That's a neuroscience and psychology issue, not a biology medicine issue. But I'm pleased to hear that you're excited by them, 'cause I hear a lot of excitement. I haven't heard anything disastrous about them. - It takes a while to get people up to dose. So if you're looking at semaglutide, the dose that was studied, so did a one-year trial, or maybe it was a little over that, maybe 60 weeks. But it took about 16 weeks to get the patients comfortably up to 2.4 milligrams weekly, which was the dose that they ultimately stayed on. In our experience, when we use it, we don't even usually go up to 2.4 milligrams. We can usually get enough benefit between one and two milligrams. And we usually move people along a little bit quicker. But we've definitely had our share of patients who can't tolerate it due to the nausea. - Interesting. - Which might be part of how it's working, right, is the sort of suppression of appetite, which, if taken to an extreme can produce nausea. - Interesting. - Yeah, I think most of the effect of semaglutide is central, not peripheral. - Huh. So I don't know, I saw one paper that GLP-1 is acting both on cells in the periphery, to cause gut distention in some ways, or sort of make people feel full, through promotion of literally mechanical receptors that make people feel as if their stomach is distended, even though their stomach is empty. And then perhaps some central hypothalamic effects. Is that what- - Yeah, I think it's doing, I would bet 80% of it's in the hypothalamus. It is also improving insulin sensitivity in the periphery, but I don't think that that's accounting for much of its benefit. - Super interesting. - And there's next gen versions of these that seem to be more long-lasting. So right now, if you look at coming off semaglutide, you're going to see a weight regain. So there's newer versions that seem to preserve the weight loss, even off the drug. So it begs the ultimate question, which is like, what's the total use case for this going to be? Is this going to be a drug you cycle on and off? Or is it going to be a drug

that a person has to stay on indefinitely, and if so, will they become tachyphylactic? Will they gain resistance to it? So it's still super early days on these things. - My hope is that it would be a little bit like the way that you describe testosterone and estrogen therapies, that it would allow people to do more of the behavioral work that's absolutely required for health span and lifespan. - Yep, and we've also seen, on the flip side of that, you can cheat through semaglutide, right? You can drink a lot of calories, and sort of get around the drug. So, you know, for example, like, you know, we always encourage patients who want to lose weight to really just eliminate alcohol. That's like, that's the cheapest, easiest trick to lose weight. And so if you're still drinking a lot of alcohol, which is incredibly caloric, and just drinking a lot of caloric stuff, we've seen that that's less, this is just anecdotal with our patients, but we've seen that that's, it's easier to get around the benefits of the drug that way. - Interesting. I so appreciate your answers today. First of all, they were incredibly thorough and pointed towards real world application. I also just want to thank you more broadly for the work that you do, because obviously you have this incredible clinical experience and patient population that you work very closely with. But I see you really as one of the few, both clinicians, and I realize you're an MD, did you do a PhD as well? No, but I consider you a scientist clinician, a clinician scientist is the appropriate wording of that of course, in the way that you really still drill into studies in detail. I know a lot of clinicians, not all of them do that for sure. And the fact that you're so hungry for the new incoming knowledge, as well as the old literature. So, it's an incredibly rich data set in that brain of yours, and I really appreciate you sharing it with us, both in your podcast, in the upcoming book, which I think that we'll certainly have you on here again in anticipation of that. But I know I, and a ton of other people, are really excited for the book. And in the way that you approach social media and your podcast and going on podcasts. So thank you so much. I learned a ton, I know everyone learned a ton. - Thanks Andrew. Great to be here, man. - Thank you.

02:47:06 Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors, Momentous Supplements, Instagram, Twitter, Neural Network Newsletter, Huberman Lab Clips

Thank you for joining me today for my discussion with Dr. Peter Attia, all about the things that we can do in order to maximize our lifespan and health span, I highly recommend people check out Dr. Attia's podcast, "The Drive" is excellent, as you can imagine, based



on today's conversation, and it's easily available on Apple Podcast, Spotify, Overcast, and Google. Please also check out Dr. Attila's website. It's [peteratillamd.com](http://peteratillamd.com). There you can find links to his podcast episodes as well as a signup for his excellent weekly newsletter. That newsletter provides terrific information related to health that anyone can benefit from. If you're learning from and or enjoying this podcast, please subscribe to our YouTube channel. That's a simple zero cost way to support us. Please also subscribe to the podcast on Spotify and Apple, and on both Spotify and Apple, you have the opportunity to leave us up to a five star review. If you have questions or comments or suggestions about topics you'd like us to cover, or guests you'd like us to interview on the Huberman Lab Podcast, please put those in the comment section on YouTube. We do read all those comments and we do take them to heart. Please also check out the sponsors mentioned at the beginning of today's podcast, and check out Momentous supplements, our new partners in the supplement space, and check out Athletic Greens. That's the best way to support this podcast. If you're not already following us on social media, please do so. We are [hubermanlab](#) on Twitter, and we are also [hubermanlab](#) on Instagram, and both places I cover science and science-related tools, some of which overlap with the content of the Huberman Lab Podcast, but much of which is unique from the content covered on the Huberman Lab Podcast. Again, that's [hubermanlab](#) on Instagram, and [hubermanlab](#) on Twitter. Please also check out our Neural Network monthly newsletter. This is a newsletter that has summaries of podcast episodes. It also includes a lot of actionable protocols. It's very easy to sign up for the newsletter. You go to [Hubermanlab.com](http://Hubermanlab.com), click on the menu, go to newsletter. You supply your email, but we do not share your email with anybody. We have a very clear and rigorous privacy policy, which is we do not share your email with anybody. And the newsletter comes out once a month, and it is completely zero cost. Again, just go to [Hubermanlab.com](http://Hubermanlab.com) and go to the Neural Network newsletter. I'd also like to point out that that the Huberman Lab Podcast has a clips channel, so these are brief clips anywhere from three to 10 minutes, that encompass single concepts and actionable protocols related to sleep, to focus, interviews with various guests. We talk about things like caffeine, when to drink caffeine relative to sleep, alcohol, when and how and if anyone should ingest it relative to sleep, dopamine, serotonin, mental health, physical health, and on and on. All the things that relate to the topics most of interest to you. You can find that easily by going to YouTube, look for Huberman Lab clips in the search area, and it will take you there. Subscribe, and we are constantly updating those with new clips. This is especially useful, I believe, for

people that have missed some of the earlier episodes, or you're still working through the back catalog of Huberman Lab Podcast, which admittedly can be rather long. And last, but certainly not least, thank you for your interest in science.