EP\_1245\_NICK\_NORWITZ\_AUDIO

**Dave:** [00:00:00] The calories in calories out hypothesis,

**Nick:** I feel like it's just a way to shame fat people [00:00:05] because it doesn't usually work. It's technically accurate and practically useless. The thing about calories in [00:00:10] calories out is it's not a model of obesity in the first place. It is just describing what [00:00:15] has happened.

There are a group of

**Dave:** people who say that all you have to do to lose weight is [00:00:20] exercise more and eat less. And I did this for 18 months straight in my early 20s. I never [00:00:25] lost a pound. Most

**Nick:** people are not overweight because they have a slow metabolism. They [00:00:30] have a slow metabolism because they're

**Dave:** overweight.

What are the top three blood [00:00:35] markers that you think are most important for people metabolically? You're listening to [00:00:40] the human upgrade with Dave Asprey.[00:00:45]

This episode is going to be a lot of fun because you're going to get. Some new [00:00:50] information on papers that just came out and our guest today is Dr. [00:00:55] Nick Norwitz, who's a PhD researcher, educator, and [00:01:00] just an absolute OG when it comes to metabolic health, [00:01:05] valedictorian at Dartmouth and PhD in metabolism from Oxford, [00:01:10] little things like that, getting his MD at Harvard.

And I'd say we [00:01:15] share that mission of making metabolic health. Something that we all think about because [00:01:20] metabolism powers energy, which powers longevity, which [00:01:25] powers willpower, and which powers just being kind to other people. [00:01:30] Nick, welcome to the show. Thanks for having me on, Dave. So many [00:01:35] things. I want to get the latest updates on stuff you're excited about.

We're going to, we're going to get there in a second, [00:01:40] including some stuff about hair loss and some stuff about Alzheimer's. [00:01:45] But first, if you could only have one pharmaceutical to extend [00:01:50] your life or give you superpowers, what would it be?

**Nick:** Like an existing pharmaceutical? Can I just get like

**Dave:** [00:01:55] Stormbreaker from the MCU or something?

I like the MCU answer. However, I'm [00:02:00] looking for a real pharmaceutical today. You're like, wow, that thing has some benefits.

**Nick:** I think it's, I don't know [00:02:05] if, I'm sorry to cop out, but I don't know if I can answer that question because it's so context dependent. It's like, what does an [00:02:10] individual need, hey, there's something for me.

**Dave:** I [00:02:15] don't think I need any pharmaceuticals. I didn't say need, you're talking about to be better than [00:02:20] you would have been without it. That I don't have access to? Well, no, you have access to whatever pharmaceutical you want. I [00:02:25] mean, you have friends. You're in medical school. No cognitive enhancers, no longevity drugs, nothing.

[00:02:30] You're, you're like that. Not drugs per se. Testosterone? [00:02:35] Nothing?

**Nick:** No, actually my testosterone is weirdly high. The last year it's been running around 1100. [00:02:40] I have no idea why. What's your free testosterone look like? Um, [00:02:45] I don't remember what the number was, but it's also high. I mean, my SHBG runs high too.

That tends to happen when [00:02:50] you're lean and low farb, but my free AMI total is pretty high. Beautiful, and how

**Dave:** old are

**Nick:** you? [00:02:55]

**Dave:** 20, I turned 29. Well, that's why it's high, because, you know, you've You still have your [00:03:00] DHEA and, uh, pregnant alone.

**Nick:** It jumped actually after I finished. I was on a really [00:03:05] stressful rotation on like night shifts.

Oh, that'll, that'll do it. Using around like 400, and then I, uh, [00:03:10] went off of that. I started a new relationship, so a couple variables there. [00:03:15] And it jumped from like 4 to 1100. It's been sitting there since.

**Dave:** Yeah, having some female [00:03:20] pheromones in the environment around you is actually well correlated with increases in [00:03:25] testosterone.

**Nick:** It's interesting because it's like, you know, that question I was asking a urologist around about [00:03:30] this actually the other day on Instagram while I was like, could, you know, sexual activity increase [00:03:35] testosterone levels? And on the one hand, there's not anything on PubMed, like I know how to do a literature search.

But then again, you have [00:03:40] to think about like the methodology and things like. Sexual [00:03:45] sex quality might matter, and how to actually do that

**Dave:** study, you know what I mean? The best in the world at [00:03:50] that is John Gray, from the Mars and Venus books. [00:03:55] And he's got really good research around the testosterone drop in the [00:04:00] 24 hours after ejaculation, along with a big increase in prolactin.

[00:04:05] and There are ways to mitigate that, of course, but what, [00:04:10] what does happen is that just the presence of women who are ovulating [00:04:15] Does increase testosterone. In fact years ago when [00:04:20] I was like, this would be really good from a longevity perspective, you can buy pheromones [00:04:25] called copulins and just sprinkle them around your house.

And then your body knows that there might be fertile [00:04:30] women in the environment and it raises testosterone. And if you're in an environment [00:04:35] with no pheromones after a while, your body's like, what's the point? That stops making testosterone because you got nothing to do with [00:04:40] it. Noted. I'll thank my girlfriend for my metabolic boost.

[00:04:45] Now, for listeners who are unfamiliar with your work, and you've built a name for yourself in the keto [00:04:50] world and the metabolism world, why did you get into it? I know you had a health problem. Just kind of walk us through your [00:04:55] basic journey there so people understand why you are so passionate.

**Nick:** Well, I grew up [00:05:00] always wanting to do medicine and science.

I come from a medical background, or medical [00:05:05] family, so both my parents are physician scientists, and it's what I've wanted to do my whole life. [00:05:10] So I studied cell biology and biochemistry in college and then went off to do my [00:05:15] PhD at Oxford in metabolism with a plan to come back, do medical school. It's a very standard [00:05:20] academic physician path, MD, PhD, residency fellowship, all that.

Oh yeah. [00:05:25] Along the way, I, uh, started dealing with my own health issues, in my case it was inflammatory bowel [00:05:30] disease. I hit pretty hard at the end of college and then during grad school to the point that I was like in, out of, uh, [00:05:35] ICU level care. And it was really jarring for me because it went, you know.[00:05:40]

Within a couple of years, I went from being a high performing athlete, like, I was sub 3 [00:05:45] marathoner, winning push up competitions, top of my class in school, to being like, [00:05:50] you know, physically fragile, laying in a bed, mind not there, social [00:05:55] life just corroded, and it makes you think, like, you know, how fast you can [00:06:00] fall, and it was definitely very humbling, and I think I reached a point that a lot of people reach, [00:06:05] which is desperation, and when you're desperate, you'll try anything, so.

You know, even at that point in time, I had a [00:06:10] lot of faith in conventional medicine. I use, a word I don't [00:06:15] use lightly, faith, because I think of faith as like, kind of like a blind belief. But that's, [00:06:20] in effect, what it was, because it needs to be, right? Like, no individual can have [00:06:25] a full picture and a full understanding of why we do what we do in conventional medicine.[00:06:30]

Growing up the son of two doctors and having access to the best medical systems in the [00:06:35] world and having some sense. of what the training is like and how much there is to learn and what [00:06:40] the art of medicine is. I have a lot of respect, and I still do, for conventional medicine. So, it almost [00:06:45] seemed arrogant to be like, I can fix this myself.

Like, what do I know? I'm in my early [00:06:50] 20s. Like, I haven't done. I haven't paid my dues that all my brilliant physician, you [00:06:55] know, caretakers have. So, it almost seemed arrogant to try to take control of my own [00:07:00] metabolic health journey. But, I got to this place of desperation and then you're like, I'll try anything.

I just need [00:07:05] this to stop. So, you know, after conventional treatments hadn't worked [00:07:10] effectively, I started trying metabolic health interventions. I didn't call them that at that point, I just called them things like [00:07:15] diet, and I just started tweaking my diet. So I went through every diet you can imagine. [00:07:20] Um, the standard ones for IBD, inflammatory bowel disease, and IBS as well.[00:07:25]

Are things like low FODMAP, specific carbohydrate, tried those, did the whole plant based [00:07:30] thing. Ouch. That didn't help, did it? Uh, it didn't, no. Uh, did you get a sore [00:07:35] whack? I went on a similar path, okay. It was in my scope of awareness. As something I [00:07:40] thought of at the time is healthy, and for some people it might work.

I'm not saying for some people it wouldn't, but that did not work.

**Dave:** [00:07:45] Hey, breatharian might work for some people too, we can always hope. Yeah, I saw someone post the other day about how he [00:07:50] lost 60 pounds on a sunlight diet. I'm like, dude,

**Nick:** that's fasting. But anyway, that [00:07:55] aside, I tried a bunch of different diets and eventually got to a ketogenic diet.

And [00:08:00] I want to be clear, I tried it not out of expectation, but out of desperation.

**Dave:** Me [00:08:05] too.

**Nick:** Why not, right? You have nothing to lose. It's like, all right. I cut out some carbs for a little [00:08:10] while, whoop dee doo, I'm already feeling like death, and a light bulb went [00:08:15] off in me in every way, shape, and form. Yes. My energy got better, my inflammatory [00:08:20] markers dropped to the lowest they'd been, and I just came back to life.

And then, [00:08:25] actually, when I got my X colonoscopy, I was in biopsy proven remission. Beautiful. So this [00:08:30] was feelings, biomarkers, and biopsy on colonoscopy remission. [00:08:35] And, you know, it was really striking for me. And at that time, I [00:08:40] thought I was just what one calls a medical zebra. So there's a saying in medicine when you hear [00:08:45] hoofbeats, saying horses, not zebras, and the zebras are the outliers, the weird ones.

And so even now I'm like, [00:08:50] I'm happy I'm healthy, but this is weird because there's no like controlled trials on this. [00:08:55] This isn't a quote evidence based therapy, but it did pique my interest enough. [00:09:00] To start to, one, delve into the literature deeper on metabolic health, and then, two, delve into the [00:09:05] community.

And what I found, and this is what I like to say most often [00:09:10] about my journey, is the most amazing thing about my journey is it's not at all [00:09:15] unique. No, it's so common. So, there's this, yeah, there's this motif where people struggle [00:09:20] with some metabolic health problem. It could be obesity, it could be diabetes, it could be [00:09:25] autoimmune or inflammatory condition.

You know, standard approaches don't work, so they try something that is [00:09:30] considered by society to be out there, to be extreme. Say, a ketogenic diet or fasting, [00:09:35] and they have remarkable success. And so, that's really [00:09:40] what shaped my journey going into medical school and my perspective, because I started to think about, [00:09:45] you know, incentive structures and how we do medicine, and there's a lot I've realized, but one thing I kind of want to point [00:09:50] out to people is this idea that absence of evidence is an evidence [00:09:55] of absence.

And what I mean by that is, I can't tell you [00:10:00] that it's proven in a human randomized control trial that a ketogenic or carnivore diet [00:10:05] will help in inflammatory bowel disease. There's no study, rigorous study showing that, as there are for [00:10:10] some pharmaceuticals. However, it doesn't mean that it might not work or might not be [00:10:15] the most potent approach for some people.

It's just we've never asked the question, and why haven't we asked the [00:10:20] question? Well, because the business model for doing these studies isn't very clear. So who's going to fund it? [00:10:25] And if we're not going to fund the trials, we're not going to get done. We're not going to have it as quote, evidence based [00:10:30] medicine.

So this idea that we have now in the Western world of conventional [00:10:35] evidence based medicine, on the one hand, it's good because we do want an evidence based, on the other hand, it's lacking [00:10:40] because the research infrastructure is not built to examine metabolic health [00:10:45] interventions that we need for the metabolic diseases that are plaguing us, which is so [00:10:50] obvious when you see it.

But it took a personal experience

**Dave:** for me to see

**Nick:** that.

**Dave:** I went through a [00:10:55] period early on where I was actually angry because no [00:11:00] one had told me about the keto diet. And when I was about [00:11:05] 25, 26, I found out about Robert [00:11:10] Atkins. His first book was published the year I was born. And I [00:11:15] lost 50 pounds in three months and a lot of my gut issues went away.

The other 50 [00:11:20] pounds took me 10 plus years. That's why I wrote the Bulletproof diet. The first like Keto's clean Keto [00:11:25] cyclical intermittent fasting diet because I'm like, here are the things that we're [00:11:30] missing. In order to get my metabolism all the way working. It's more than just go keto all the time and don't [00:11:35] eat any carbs ever.

Cause that, that usually doesn't end well for people if they're not paying [00:11:40] attention to all the other variables. But along that way, I'm like, why did no one tell me it would have been [00:11:45] so easy, right? Did you go through a period of value? Like I've had IBS all this [00:11:50] time. If someone had just fricking told me to eat the butter instead of the rice, it would have been [00:11:55] better.

Or did you skip that phase?

**Nick:** I don't think I was ever angry because there was nobody to be [00:12:00] angry at. It's like

**Dave:** I wasn't angry at anyone, I was just angry in general. Like, why? It's not fair. Why wasn't the [00:12:05] information out there? Like, like, everyone needs to know this is a tool, at least. Right? [00:12:10] So, I've gotten angry at

**Nick:** the reality of things, especially as I've gone through medical school [00:12:15] and seen patients be mistreated.

Because I'm someone with an incredible amount of [00:12:20] resources. Not only having parents that can support me in medicine, having access to the best healthcare system in the world, [00:12:25] the skill set to actually delve into the literature, develop protocols, [00:12:30] most people don't have that. That is profound privilege.

And even with that, it took me multiple [00:12:35] years to get to a point where I had a solution. So, we are not [00:12:40] serving the public with respect to metabolic disease. That is very clear. And to me now, it's kind of [00:12:45] obvious some basic things that we could do. And yet we're stuck in this [00:12:50] dysfunctional system doing things that just make absolutely no sense when you can see [00:12:55] them.

And to shift that, we'll take like a large societal shift, and I'm eager for [00:13:00] that to happen. This is what I've, I say I'm eager for it to happen, but I acknowledge the realities of where we're [00:13:05] at. So I'm working for it to happen. And there are moments when I see people being, [00:13:10] you know, I think given advice that is not helpful, and then they Spin their [00:13:15] wheels and put a ton of effort and energy into trying to recover.

It's a futile effort, and I feel like we could [00:13:20] serve people better. It's just, you know, the reality is it'll take a little while, but to, to [00:13:25] get there, it's gonna take a shift in social psyche, which I think we are seeing. But [00:13:30] it's just gonna take time.

**Dave:** If you are working on fixing your metabolism, [00:13:35] and you could either exercise for an hour a day or more, [00:13:40] Or, eat an appropriate diet and get good sleep the way [00:13:45] biohackers do, which would you choose?

Oh, the

**Nick:** latter. Without question, I mean, I [00:13:50] think the potty needs some sort of activity input, but like, yeah, no, I think diet [00:13:55] and sleep are paramount, especially if you're someone who's trying to say, like, lose weight, reverse diabetes, [00:14:00] obesity, then it's diet first. It doesn't mean, it shouldn't be either or, obviously.

It's not either or. [00:14:05] An hour at the gym is not going to save you. No.

**Dave:** I believe that really strongly. I did 90 minutes a [00:14:10] day, 6 days a week for 18 months, in my early 20s, trying to lose the weight and fix my [00:14:15] metabolism, and it didn't work. And man, you can get tired and over trained that way. [00:14:20] And it leads to all kinds of problems.

So I, I just want people to understand it's food first, it's lifestyle [00:14:25] second, and the appropriate amount of exercise third, you got to do all three.

**Nick:** Yeah. [00:14:30] And realize that it might be a long journey. I don't know if you saw that, um, epigenetic memory of [00:14:35] obesity paper that came out. Is this the

**Dave:** multi generational one?

**Nick:** No, no, no. So there was a [00:14:40] paper that came out where, um, they were looking basically at sat cells [00:14:45] and this included, it included animal models, but it included human studies. Where they [00:14:50] wanted to see, you know, if someone has had obesity, but then lost weight, do their fat [00:14:55] cells have some sort of memory of the obesity as compared to the lean person?

And so, this was new [00:15:00] 2024 data. They took biopsies from people before and after bariatric surgery, before they lost at least a [00:15:05] quarter of their body weight, and compared the before and after biopsies to always lean people. And what they [00:15:10] found is that even two years after the surgery, The fat cells from the people who had obesity [00:15:15] had this epigenetic memory.

So they tended to have down regulation of [00:15:20] pathways related to metabolism and up regulation of pathways related to inflammation. Now, I did a [00:15:25] video on this and at the end I said, Do you find this pessimistic? Because it kind of [00:15:30] sounds like, oh, no, I've like had obesity but I've recovered but I'm always going to be behind the eight ball.

I don't see [00:15:35] it like that. Me

**Dave:** either.

**Nick:** This is how I see it. And this is the reason I brought it up. The [00:15:40] body takes time to adjust. Now, this paper was two years after [00:15:45] surgery. So only two years, and also, the weight loss was presumably progressive after [00:15:50] surgery. So it's not like they were lean as soon as they got surgery, it took two years.

I [00:15:55] believe, this is a speculation, but what I would believe is that Over time, what you could call the [00:16:00] metabolic scar of obesity would fade. But the reason I bring it up, and the reason it was forefront of [00:16:05] mind, is you said, you know, the first 50 pounds for you came off in a few months, and then it took a long [00:16:10] time for the rest to recover.

And what I would say to people on this journey is like, you know, [00:16:15] the investment, the motivation at the beginning, it's really meaningful, but I think things [00:16:20] get easier as you go along the journey. And it is a chronic [00:16:25] grass is greener on the other side scenario. which I see as very uplifting, not [00:16:30] pessimistic.

**Dave:** And if you look at how often fat cells get [00:16:35] replaced, only about 10 percent of fat cells get replaced each year. So if [00:16:40] you change the epigenetic environment, in other words, all the stuff in your [00:16:45] body, when those 10 percent of cells get turned over and they're in a healthy [00:16:50] metabolism, they're likely to do it.

And what that means, if an individual [00:16:55] fat cell Lives for eight to 10 years. It's going to take a while to fully recover. [00:17:00] I've been Relatively lean as in under 12 14 percent body [00:17:05] fat for 20 years now, even though I weighed 300 pounds and I am at 4. 8 [00:17:10] percent body fat right now. And I'm not trying to be lean.

I'm actually trying to put fat back on and it's [00:17:15] difficult because my body's just used to this. It's funny how that works. Yeah, I know. Right. And there's [00:17:20] people going, Dave, you know, shut up, but I'm, I'm serious. This is something that's relatively new to [00:17:25] me or I'm going, can I love to have like three pounds of fat added to my frame just so I could use it [00:17:30] for longevity purposes.

And I'll get there. The idea though is, is you can train the [00:17:35] body to do these things. So, what do you think about cycling keto [00:17:40] versus just continuous keto? There's some debate about that.

**Nick:** Yeah, I would [00:17:45] say all things being equal, to me it makes sense. There are different levels at which you can dissect [00:17:50] this.

One is just the, some people like to take the evolutionary perspective, like we weren't [00:17:55] adapted as a species to be in ketosis all the time. So there's that. I think, you know, maybe the [00:18:00] more evolved way to think about it is, in general, like [00:18:05] biology and nature in general works in cycles, catabolic, anabolic cycles, not going at [00:18:10] the same time.

You want to break down, renew, and then you want to build [00:18:15] up. So, actually, if you look at some of the data, like, say, the neuroscience data, and this is some of the work of [00:18:20] Mark Mattson out of, uh, Johns Hopkins, what you find is, you know, there's like, signs [00:18:25] of enhanced learning, long term potentiation in fasting feeding cycles during the refeed, because during the [00:18:30] refeed, you're, you know, getting a boost of growth hormones that [00:18:35] help with things that are beneficial.

So, you really do want a balance of a balance. [00:18:40] Anabolism building up and metabolism building down. So, I think keto [00:18:45] cycles make sense. Again, all things being equal. But I caveat that with, I also [00:18:50] don't think chronic ketosis is per se harmful. So, if you have [00:18:55] a metabolic condition like I do, say inflammatory bowel disease, where this is therapeutic for me, [00:19:00] then by all means, stay in ketosis.

All the nine. I don't think we have any data to suggest it's [00:19:05] truly harmful. There's one paper on cellular senescence and, quote, zombie cells that I've gone [00:19:10] over. But, I think for the most part, the data would say it's largely safe if you have a [00:19:15] metabolic condition. But I'm, I'm pro Tito's Cycling if it works [00:19:20] for someone.

But, again, if it's the kind of thing, adding that car which makes you fall off the bandwagon and gain back weight, [00:19:25] then don't do it. It's very individualized in that way.

**Dave:** Yeah, if it doesn't work, don't do it, would be really good advice [00:19:30] for everyone. Make yourself

**Nick:** do it. If you're like, I know I'm gonna gain weight, back, And, you know, [00:19:35] my own diabetes and obesity are going to come back if I add back the carbs, but I really want a keto cycle just because, then, you know, [00:19:40] you don't need to.

**Dave:** My advice after interacting with tens of thousands of people [00:19:45] personally, and my own thing is, be in ketosis, and then [00:19:50] Saturday morning, Have the pancakes, but without the gluten made out of things that [00:19:55] don't give you a disease like IBD and don't trigger you So it could just be a piece of fruit. It could [00:20:00] be scarves just dip out and the reason for this has to do with acromantia [00:20:05] Because acromantia as you know, I'm just educating listeners.

It's a [00:20:10] generally beneficial Probiotic that lives in your gut, but if you don't have [00:20:15] enough carbs to make mucus lining for the gut It will actually poke holes in [00:20:20] your gut and it is then associated with Parkinson's. So it's one of those things where [00:20:25] you got to get some kind of ability to make mucus. You could also take soluble [00:20:30] fiber that keeps you in ketosis.

I made one years ago that quadrupled my number of [00:20:35] species in the gut. So it's possible to have a healthy microbiome and be in [00:20:40] ketosis, but different prebiotics work differently for different people. And since you're at IBS, it might be different. [00:20:45] What do you think of that perspective? Stay in ketosis, but take some soluble fiber that goes to butyrate [00:20:50] and just don't worry about it.

**Nick:** Yeah. I mean, the thing with the microbiome research in general is a lot [00:20:55] of it is really black box. We can speculate and generate protocols and, and, [00:21:00] and. You know, we could be right, we could be wrong. I think there's a [00:21:05] lot we don't know about the microbiome, and this is in large part because it's so [00:21:10] dynamic.

There's so much inter and intra individual variability that's a really hard thing to [00:21:15] measure. Right now, I see things moving towards a more metabolomics focused [00:21:20] approach, so rather than saying, You know, what gut bugs do we have, we look at what is [00:21:25] being produced by the gut bugs. Because different bugs can serve different functions in different people.

So, [00:21:30] a lot of the pre existing data, what we call gut bugs, good or bad, are based on [00:21:35] large scale studies of populations who are on mixed diets. So, it's really hard to [00:21:40] generalize to people on very low carbohydrate diets because then things change. Your compositions are going to change. [00:21:45] The rules different bugs take are going to change.

And you're going to have other molecules [00:21:50] serving different functions like beta hydroxybutyrate, which obviously can fuel, you know, intestinal cells as [00:21:55] opposed to butyrate, which might be made by the fermentation of certain fibers. So, [00:22:00] it's not easy. I would say, in general best [00:22:05] practice for most people and I'd actually put myself in the exclusion group.[00:22:10]

But yeah, I think eating generally a more diverse diet, [00:22:15] including fermented foods, things like sauerkraut, kimchi, kefir [00:22:20] is, is gonna do well for your gut. I, I put myself [00:22:25] out as an exception because like with all things, it's very individual. So there's data that [00:22:30] came out of Stanford, I think it was a sonograph paper, Showing that, for example, fibers in about one third [00:22:35] of people were pro inflammatory.

**Dave:** Yes, especially inulin. [00:22:40] People say that, oh, inulin's so healthy for you. It's almost as inflammatory as gluten for a large [00:22:45] number of people, so I tend to steer away from it.

**Nick:** Well, the point being in this study, like, you know, there was a portion of [00:22:50] people that had an anti inflammatory response to fiber, and a portion had a pro inflammatory response to fiber.[00:22:55]

Now, I will also caveat that, that the pro inflammatory response Subgroup tended to have [00:23:00] less diversity, which begs the question, could you build them up to the point where then they had the positive [00:23:05] response, but then we come back to what I'm saying before, whereas like we don't have good protocols on this.

There's [00:23:10] so many cool things we could do like fecal matter transplants or a whole nother like topic, which could be very [00:23:15] cool and therapeutic, but we haven't developed clinical protocols. So it's very difficult to say, [00:23:20] but if you tolerate things like, you know, ferment low carb, like fresh fermented [00:23:25] foods.

I can only see a potential upside to including them rather than [00:23:30] downsides, but if you don't tolerate them, they don't have them.[00:23:35]

**Dave:** I went through a long phase [00:23:40] as I was fixing my metabolism where I would eat fermented foods, [00:23:45] some of them, but not all of them, and I would just get the worst response. I would just get profoundly [00:23:50] tired and like sugar cravings and just felt awful. It turns out a lot [00:23:55] of them make histamine. And histamines are neurotransmitter and it has [00:24:00] effects throughout the body.

So if you're sensitive to histamine, you're going to eat these things and feel like crap. [00:24:05] And you're going to think you're crazy because sometimes you feel good. Sometimes you don't. And the bottom line is that batch of [00:24:10] kimchi is different than that batch of kimchi. Right. So it's okay to just [00:24:15] say you got to do what works and to your point there, there's pretty good evidence that you'll figure out [00:24:20] something.

The best data set that I know of is a biome has a million samples now that [00:24:25] include RNA to figure out what your gut bacteria is doing and correlating it with with a [00:24:30] spit and blood. So I think sometimes I'm like, you know what? Our data set [00:24:35] shows you might try this food and this one's probably not going to work.

That's a good starting point to see how [00:24:40] you feel. Yeah. There are probably other tests as well.

**Nick:** And I think the whole idea of starting point is [00:24:45] really key because What we're talking about now is mechanism and you can speculate all day, but at the end of the day, it's [00:24:50] about trying what works for you, having a hypothesis, implementing that on yourself and seeing [00:24:55] how you feel.

And you can correlate those feelings to any mechanism [00:25:00] and you could be right or you could be wrong. But at the end of the day, you probably just care about how you [00:25:05] feel and how you're functioning. So as long as an individual is willing to go on this journey, [00:25:10] test their hypotheses on themselves and iterate, they generally can get to a good place.

Whether or [00:25:15] not they're right or wrong about the mechanism of what's going on in their body is kind of irrelevant at the individual level, [00:25:20] much as I love mechanism.

**Dave:** I'm so happy you said that. I'm with you. Mechanisms are great [00:25:25] stories that help us understand how to solve problems. One of my favorite stories about that [00:25:30] is from Candace Pert, the discoverer of the opioid receptor.

[00:25:35] And in her memoir, she talks about traveling down and meeting [00:25:40] shamans in South America. And she got all excited and she explained how all [00:25:45] these receptors work and neurotransmitters. And the shamans started laughing and [00:25:50] she goes, why are you laughing? She's like, you think those things exist, [00:25:55] right? And it's not that the shamans didn't have a working model for solving problems.

It's just an [00:26:00] entirely different one. And neither story is accurate because [00:26:05] underneath all that is some kind of quantum stuff we barely understand. And if we aren't looking at it, it probably doesn't even work [00:26:10] that way. Like it does, it doesn't even work in our brains. So understanding both stories are [00:26:15] valid.

I am also a mechanistic guy, right? I love your perspective, but end of the day, like you [00:26:20] said, it either works or it doesn't. And if your story is wrong, who cares? You got the, you got the win. At the [00:26:25] individual level. Yeah. Let's talk about some news. You and I are both fans of intermittent [00:26:30] fasting. The Bulletproof Diet is a major intermittent fasting book that's been around for a long [00:26:35] time.

So one of the warnings that I've had about [00:26:40] fasting enough of a warning that I wrote a second book on fasting to talk about this is that you can [00:26:45] increase cortisol if you fast too much. And if you fast too much, that [00:26:50] increase in cortisol hits women before it hits men. And the order of [00:26:55] operations is number one, your sleep quality goes down.

So you wake up more at night, you [00:27:00] don't get as much deep sleep. Something's not right. Number two is [00:27:05] you start waking up without a morning kickstand. Or if you're a woman, your cycle [00:27:10] starts to become irregular, if you have a cycle. And then, the third thing that happens [00:27:15] is hair thinning in both men and women.

And that was driven by cortisol, but there may be other effects. There's a [00:27:20] new study, though. Tell me about the new study on fasting and hair loss. Right. This just came out a [00:27:25] couple days

**Nick:** ago. Um, I was actually reading it this morning. and It [00:27:30] describes the mechanism whereby fasting, intermittent fasting actually does lead to hair loss.

So, [00:27:35] basically the mechanism is that when you fast, leptin goes [00:27:40] down. Leptin is released from fat tissue and while it goes down, like while it's a chronic [00:27:45] hormone, it also can drop acutely. So, during a fast it can drop quite acutely and that activates the [00:27:50] brain, the hypothalamus. to activate the hypothalamic pituitary adrenal axis.[00:27:55]

The adrenals kick out cortisol and epinephrine. [00:28:00] Now, what cortisol and epinephrine are good at doing is simulating fat burning. [00:28:05] And this is what's really interesting. So, your body is [00:28:10] actually built up of all these little metabolic pockets. They're called niches. And in the [00:28:15] dermis, area of the skin, You have these hair follicle stem [00:28:20] cells.

And the stem cells are surrounded by fat cells, they're called [00:28:25] dermal adipocytes. And the epinephrine and the cortisol stimulate the [00:28:30] dermal adipocytes to release free fatty acids. In fact, the burning of fat [00:28:35] in the dermis skyrockets the free fatty acid levels above what it is in the [00:28:40] blood. So in this metabolic niche, around the stem cells, in the dermis that give rise to [00:28:45] hair follicles, There's this drop in free fatty acids and what happens is it [00:28:50] causes the stem cells to burn them fatty acid oxidation And at such a [00:28:55] high rate that actually there's an increase in oxidative stress, reactive oxygen species, that [00:29:00] overwhelms the antioxidant capacity leading [00:29:05] to basically poisoning and apoptosis, programmed cell death of these stem [00:29:10] cells.

And so, hair growth slow. So they showed in this new study, you know, longer [00:29:15] fasts had a more potent effect. And that actually the effect, you know, if it was [00:29:20] applied chronically, at least in the animal models. led to, basically, deaths of the hair [00:29:25] follicle. It wasn't something that got adapted to, the hair follicle died.

And they did these experiments. If you go to the paper, it's [00:29:30] really cool because they did like shave the mice naked and they saw how long the hair will go back so [00:29:35] you see these like little rows of like naked mice slowly growing hair back and it's really interesting [00:29:40] because it's even dose dependent where it's like the mice that ate on a 12 12 schedule they grew the hair back the [00:29:45] quickest, 16 8 slower, 18 6 slower, and slower and slower and slower.

So, [00:29:50] it does appear that fasting impairs hair follicle growth, and this is also [00:29:55] correlated with a human randomized trial. They pulled data, it was something like [00:30:00] 49 young healthy adults, and she had a little patch of hair, had some undergo [00:30:05] intermittent fasting and the hair grew back about 18 percent slower.

So it's really [00:30:10] interesting. What I will say is this was not like a fasting is bad paper. [00:30:15] It's so much cooler than that because a lot of other metabolic benefits were identified in the [00:30:20] mice. Better glucose control, other markers of better metabolic health. Actually lower [00:30:25] oxidative stress systemically.

So the, the dermis oxidative stress does not [00:30:30] correlate with the systemic oxidative stress. But this is just an example of how beautiful the body [00:30:35] is at, like, partitioning resources. In fact, other stem cells, including in [00:30:40] the epidermis, which is important for the barrier function, were totally fine. [00:30:45] And muscle stem cells and gut stem cells, all these might have had positive effects, but you can think of it as, like, [00:30:50] the dermis is martyring itself, the dermal stem cells, and you don't grow hair.

So, it's actually [00:30:55] very adaptive, it makes a lot of sense. And one thing they did in the study on [00:31:00] the mice, which is they said, Okay. This is the mechanism. The free fatty acid [00:31:05] overload is causing oxidative stress and overwhelming antioxidant capacity. What if we just put some [00:31:10] topical antioxidants on, so they put some vitamin E on, and it helped?

One of the things they [00:31:15] said in the paper is like, next step is like Does topical vitamin E protect against hair loss in [00:31:20] humans doing intermittent fasting? For a few, that's a concern. If you look at my eyebrows, evidently it's not a concern for me, [00:31:25] but, Uh, very cool paper. Very cool mechanistic paper with some

**Dave:** essential [00:31:30] action items.

I love that. You can, you can do so much better than vitamin [00:31:35] E. A lot of the researchers are still using synthetic vitamin E. And one of [00:31:40] the other strategies for hair loss is you increase mitochondrial function, which [00:31:45] means the mitochondria make their own antioxidants more easily. Topical aspirin, [00:31:50] topical caffeine.

there's, there's a long list of things that, that [00:31:55] seem to help. And something that isn't in that paper that I'm aware of. [00:32:00] But is important is that when people get that activation of their stress [00:32:05] response and I don't care if it's from too many cold plunges from fasting for too long and [00:32:10] inappropriately or from, you know, over exercising because you think it's going to [00:32:15] make you healthy until you die at a normal age, which is some of the advice that's out there.[00:32:20]

I'm kind of looking to go beyond a normal age and I'm willing to exercise as much as is necessary and no more. [00:32:25] So all these things are about stress response and you can have, [00:32:30] okay. Cortisol that goes up, you can have adrenaline that goes up, but the [00:32:35] unsung partner to adrenaline is noradrenaline or epinephrine or norepinephrine [00:32:40] because epinephrine and adrenaline are the same thing just for listeners.

So, what are your [00:32:45] thoughts on fasting and norepinephrine and can, can you walk our listeners [00:32:50] through that hormonal conversation?

**Nick:** Well, norepinephrine is, as you know, a [00:32:55] precursor to epinephrine. They're all on the same catecholamine pathway.

What

**Dave:** exactly is [00:33:00] your, your question with respects to, there's a ratio of [00:33:05] epinephrine or of, of epinephrine to norepinephrine.

That, that you are [00:33:10] looking for in people are not particularly stressed. So if you're working [00:33:15] at a nice, calm pace is four to one. In my mid twenties, when I was metabolically [00:33:20] dysregulated, it was 45 to one for me. So I, I was entirely [00:33:25] stress hormone dysregulated and norepinephrine, it [00:33:30] actually prolongs the resting phase of hair stem cells.

So [00:33:35] they wait longer and it inhibits activation of follicle [00:33:40] cells, follicle stem cells. So understanding that your stress response may be [00:33:45] different than someone else, And that it might've been possible to [00:33:50] use some hormone blockers that block stress hormones, like a beta blocker topically [00:33:55] in your hair. So I'm, I'm all over this.

It's so interesting. Yeah. And so what [00:34:00] do I do? I do a variety of things that involve antioxidants and [00:34:05] mitochondrial stimulation. In the hair and I use a little bit of [00:34:10] topical minoxidil and I'm a little bit sketched out by a [00:34:15] finasteride because that whole idea of chemically neutering yourself for a decade or [00:34:20] so to have better hair.

The reason you probably wanted better hair was so that [00:34:25] you wouldn't. Have the effects of being chemically neutered so that seems like a bad risk to [00:34:30] take but that's just me Thoughts on that strategy or anything else you'd like to add about hair.

**Nick:** Nothing about hair It's [00:34:35] not really been something I thought about a lot to be honest This is a this is like I love the mechanism.

So I read the paper [00:34:40] also a professor of mine Mentor of mine ironically the day this paper came [00:34:45] out. He said he was trying his first prolonged fast and he falls So I'm [00:34:50] like, good thing you're bald already.

**Dave:** That's funny. You gotta give those professors some crap. [00:34:55] It

**Nick:** was coincidental timing.

**Dave:** Another area of interest that we share is [00:35:00] Alzheimer's.

I wrote a big cognitive function book and that C8 MCT [00:35:05] oil that I popularized when I was running Bulletproof. In phase two [00:35:10] trials, C8 MCT has a beneficial effect on Alzheimer's disease. I can [00:35:15] never say that. So I'm like, I'll just get everyone to drink coffee and do some MCT and it's going to help [00:35:20] Alzheimer's.

MCT, as I think most listeners know, leads to mildly elevated [00:35:25] ketones. But there's a new paper out about Alzheimer's and [00:35:30] protein. Talk to me about that.

**Nick:** Yeah, so, this came out of the Buck Institute, [00:35:35] um, I Madhaven was the first author. Other people you might know, Brianna Stubbs. who you [00:35:40] know was an author on the paper.

She actually did her PhD in the same lab I did at Oxford. A couple years [00:35:45] before me. And so this paper was about protein misfolding. So as people may or [00:35:50] may not know, neurodegenerative diseases in general, not just Alzheimer's, but Parkinson's, ALS, [00:35:55] Huntington's, they're diseases of proteins misfolding pathologically.

And, you know, [00:36:00] Biology 101 is structure determines function. So if something misfolds, [00:36:05] As a wrong structure, it has a wrong or pathological function. So things like amyloid [00:36:10] plaques that you might have heard about, tau tangles, the hallmarks of Alzheimer's are basically from protein [00:36:15] misfolding. And so, you know, in an ideal world, what you do is get [00:36:20] these misfolded proteins out of the brain.

And there's a lot of things ketones can do [00:36:25] that are beneficial for brain health, but this new study shows how they can actually target [00:36:30] misfolded proteins. Help them transition from a soluble to an insoluble form and get them [00:36:35] cleared out of the brain, which is really incredible. so basically when the proteins misfold, the [00:36:40] ketones bind to this now exposed pocket on the proteins and then help them get cleared.

Exactly [00:36:45] how, the, uh, carphagy or the proteasome isn't really isn't really aware, isn't really, [00:36:50] uh, known yet, although that'll be the next step in research, but it was really cool. [00:36:55] And just fascinating to me because I was looking at it and I'm like, [00:37:00] wow, isn't nature incredible? Because it's like ketones are this simple molecule and yet not [00:37:05] only are they clearing these proteins out, but bear in mind that they're not just clearing proteins willy nilly, they can [00:37:10] actually identify, this simple molecule can identify the misfolded proteins [00:37:15] based on the binding pockets that are exposed when they misfold and get them cleared out of the brain.

So the [00:37:20] analogy I used in a video I have coming up on this paper was [00:37:25] It's kind of like if your brain is a really messy apartment, and trash is just building up everywhere all over the [00:37:30] apartment. What you want to do is get the trash from the trash bin. So ketones [00:37:35] can somehow go around and clean up all the trash and put it in the trash bin.

And not only that, they can then [00:37:40] take the trash bin and dump it into the garbage chute. Which is amazing. Actually, there's a great quote in the paper by the [00:37:45] authors themselves when they say something to the effect of Ketones are like the [00:37:50] janitor of the brain. It was really brilliant. So we'll have coverage coming out on that.

And, uh, the [00:37:55] first author of the paper was kind enough to give his two cents. So I'll include that as well.

**Dave:** You always have the [00:38:00] best reporting on the latest papers. I appreciate how you explain it for people. It's [00:38:05] fun. It's, it is fun. It's an unusual skill to be able to do

**Nick:** that. I'm new to it. And I [00:38:10] think we.

It's just, there's a lot of opportunity that opens up. I like to teach about it, but I realize [00:38:15] now I can be a bridge to the authors being like, you know, hearing from the horse's mouth. So in upcoming [00:38:20] videos, we have a few where after I give my two cents, it's like, and here's what the [00:38:25] authors had to say on like, why is this exciting and what is the next stage in the research?

And [00:38:30] just to kind of plug some initiatives we have going, you know, we're both excited about making metabolic [00:38:35] health mainstream. I can talk to the general public, but I'd really like to get my claws into the [00:38:40] next generation of doctors. So, I'm actually working with, um, a company called [00:38:45] Exam Crackers.

They're a bunch of companies that help people prep for medical school in the MCAT. Exam Crackers is one of the [00:38:50] companies, and now we are providing MCAT medical school exam and entrance [00:38:55] exam style passages free with a lot of these paper breakdown videos so students can [00:39:00] prepare for the MCAT with free resources.

And We're going to be moving [00:39:05] towards actually getting some of my videos. And content CME accredited. So current [00:39:10] physicians get continuing medical education credits. Yeah. Nice job, Nick. It's going to [00:39:15] be fun. I'm working with a metabolic health initiative on that. It's a Dom D'Agostino, Victoria [00:39:20] Fields, really great people.

So we're going to drop a pilot on that. I'm covering [00:39:25] some research on a food addiction virus, which is another topic, but there's just so much bull stuff [00:39:30] coming out in metabolic health space. And it's just about awareness because. [00:39:35] I know there is interest in the topic, we just need to kind of like, [00:39:40] stimulate this interest, especially in the next generation.

**Dave:** It's so cool when physicians [00:39:45] learn how to do the systems biology stuff the way that it seems like you [00:39:50] think. Suddenly sometimes things just become apparent. Like when I, I heard [00:39:55] about the Alzheimer's and protein folding paper, my mind goes [00:40:00] to HDACs or histone deacetylase chemicals. [00:40:05] And a lot of the stuff in the Bulletproof Diet and in Head Strong, the Cognitive [00:40:10] Enhancement book, like there's benefits to ketosis that go beyond just [00:40:15] losing weight or having more energy.

And it's funny because both [00:40:20] coffee and ketosis can change HDACs [00:40:25] and they are what regulate gene expression around [00:40:30] folding and unfolding or we'll say refolding proteins and they [00:40:35] stack incredibly well with heat shock proteins, which means that if you're [00:40:40] intermittent fasting or you have a keto diet and you have a cup of coffee, And you hop in your [00:40:45] sauna, or you hop in a hot tub that's hot enough.

Then you're kind of [00:40:50] doubling down on your body's ability to potentially remove or at least prevent [00:40:55] plaques. Thoughts on that?

**Nick:** I would say that the, the HDACs, the HDACs and [00:41:00] orgy misfolding, they're, they're distinct, I would say, but parallel. So [00:41:05] in terms of folding or unwinding, there's things like the protein [00:41:10] misfolding that we talked about and heat shock proteins, which help with protein folding.

So you're right. If you go in a [00:41:15] sauna, basically you can increase the expression of these proteins at. Make your protein folding system more [00:41:20] robust. And then there are HDACs. So histone deacetylases, as their [00:41:25] name suggests, deacetylate histones. Which brings the question, what are histones? [00:41:30] Histones are protein complexes around which DNA is wound.

So, it's not as much [00:41:35] folding but winding of genes. So the DNA kind of [00:41:40] string folds around these histones. And by changing the histone deacetylase function, [00:41:45] you can wined or unwined sections of your chromosome, your DNA, to change how [00:41:50] genes are read into mRNA, which is read into protein. So that's more [00:41:55] about gene expression than protein misfolding per se [00:42:00] So there's a winding and unwinding I see all those things can get conflated but the HDACs aren't actually [00:42:05] helping in protein folding.

**Dave:** Interesting. So they're they're helping to define the protein as it comes [00:42:10] off, as it's read from the DNA.

**Nick:** which will then develop into a protein, but it's I guess you could say [00:42:15] that his, the histambucillases are helping define what proteins your body [00:42:20] makes and then you want to make sure they get folded properly.

**Dave:** The interesting thing is that [00:42:25] inhibiting HDAC reactivates heat shock [00:42:30] folding protein. And we have a couple papers now that show when you're in a [00:42:35] sauna and you have those high temperatures, your body will unfold misfolded [00:42:40] proteins and then refold them. So there's a kind of cool mechanistic dance. I don't think we understand all of [00:42:45] it.

And thanks for the little lesson on HDACs. It's been a little while since I [00:42:50] wrote a chapter on that. so do you do heat therapy with your ketosis? Do you do cold therapy? [00:42:55]

**Nick:** I have been very resistant to cold exposure because I, of all the [00:43:00] things that I don't, like, you know, it's like, there's a lot of things you can do for your health.

You all know we're healthy. [00:43:05] But everybody has that one or two thing that is like, I just hate this so much. That it's not worth it to me. Cold [00:43:10] therapy has been that. I'm pulling the trigger and Gonna do some experiments on it, but historically, like, [00:43:15] you know, I'd, I'd rather run a marathon on a broken foot than get into cold [00:43:20] water.

I just hate it so much, but I love saunas. Like, I like heat, so I've always enjoyed [00:43:25] that. Honestly, for me My, let's say, metabolic health protocol has not been optimized the [00:43:30] last little while, largely because of where I am in life. Being an PhD researcher and medical student, [00:43:35] and young person trying to make it in Boston with current real estate prices, while managing social [00:43:40] media is not the most conducive to always taking care of yourself in every moment.

[00:43:45] So I'm aware of that, and I try to be transparent about that, but It

**Dave:** could further optimize, for sure. [00:43:50] Can I share a section of my new book that comes out next year called [00:43:55] Heavily Meditated with you? That'll make you like your cold plunge? Sure.

**Nick:** There was paper I was just reading on, [00:44:00] um, Well, I was looking into reasons why or why not to cold plunge.

And what I've come to is like, [00:44:05] you don't cold plunge for fat loss or calorie burning. It's just not efficient. There's actually a new [00:44:10] study that came out on, um, this. Not

**Dave:** efficient on calorie burning?

**Nick:** It's not. So, for example, this new [00:44:15] study came out where they exposed people to cold water in a, um, [00:44:20] Like a, a wetsuit, enough to induce shivering.

But the way [00:44:25] that they'd, uh, defined, like, the threshold was actually 50 percent above you know, [00:44:30] resting energy expenditure, so basically 1. 5 met. Uh, by comparison, [00:44:35] walking at 3 miles per hour is like 3 met. So if you want to burn calories, like, [00:44:40] you can go for a walk, and the amount of time you spend walking is probably going to be more efficient than cold exposure.[00:44:45]

For the most part, and there doesn't appear to be a significant afterburn effect, in fact [00:44:50] after a 10 day exposure Really? That like flies in the

**Dave:** face of a lot of papers I've seen, wow.

**Nick:** No, [00:44:55] so, and after a 10 day exposure there was no change in like fat mass. And this intervention [00:45:00] I will say, I mean, there's some studies showing like increased metabolic rate, but it's also like these people were swimming [00:45:05] in freezing water for multiple hours.

I'm like, yeah, that's different than like sitting in your cold [00:45:10] punch for 15 minutes. So I don't think it's an efficient way to burn calories. [00:45:15] Yes. You need to maintain your body heat. So while you're sitting in the cold water, your energy expenditure is going to go up, [00:45:20] but the amount that goes up. It's not like you're like turning your brown fat on, you're going to get [00:45:25] a six pack from cold, so don't do it for that reason.

**Dave:** It, and also when you're in the [00:45:30] water isn't when a lot of the calorie increase that I've read about comes. [00:45:35] It's in the next couple hours afterwards as you warm yourself back up. But again, it's not the [00:45:40] same as going for a bunch of exercise. It's

**Nick:** not that much, but there's other reasons. So the, the [00:45:45] spike in dopamine that happens is about a greater than 250%.

[00:45:50] Spike in dopamine that happens after a cold water explosion. This was a paper published in 2000. [00:45:55] And they looked at least into the one hour recovery period. There's a big jump in dopamine. I [00:46:00] will say a caveat with that paper, because you might have talked about it, people talk about it, is they are [00:46:05] measuring plasma dopamine, and dopamine does not cross the blood brain barrier.

So we don't know what's happening with [00:46:10] brain dopamine. I do think it's just intuitively obvious that there's [00:46:15] a central nervous system activation. And people feel great after cold plunging. To the [00:46:20] degree to which the serum dopamine is actually, like, predicting anything going on in the brain is, or to [00:46:25] what degree it's correlating is another story.

But I think a re a reason to cold plunge is one, the mental health [00:46:30] benefits, and then there's things like anti inflammatory benefits. So, have you heard of a mericin? No. [00:46:35] I think there was a paper in 20. 2 on mericin. And basically, so, it's [00:46:40] made by Oh, oh, they're S they're SPMs. Uh, yes. So Okay, I take that.

It's actually derived [00:46:45] from DHA. It's a, it's a DHA derivative and if you [00:46:50] are exposed to cold a cold exposure, then your fat cells turn the DHA into these [00:46:55] mericins, which signal to your liver and systemically to reduce inflammation. So [00:47:00] there's probably anti inflammatory benefits to cold plunging via literal hormones [00:47:05] that are released from fat tissue.

So I think cold plunge is very [00:47:10] interesting. I just wouldn't do it for calorie burning purposes. And also, just from the anti inflammatory thing. [00:47:15] You probably mentioned this to your audience before, but like do a cold plunge right after you worked out because you [00:47:20] actually want a post workout inflammatory response.

So people say like, when should you [00:47:25] cold plunge? I say, when should you not cold plunge? Not after a workout and not right before bed.

**Dave:** Well, you want [00:47:30] to do it, before you work out. And there are some people where the mammalian dive [00:47:35] reflex helps them sleep better with a cold plunge. And there's that temperature drop.

That helps you go [00:47:40] to sleep, but then your body will become warmer afterwards, which may affect deep sleep. So it's kind of [00:47:45] a double edged sword. I think it's very mixed before the, the new concept in heavily [00:47:50] meditated is something that I called bicep and it's not, it's not this [00:47:55] one. It's a brief actually just got my first tattoo.

Oh, nice, sweet. What does it [00:48:00] say there? Stay curious. Mine is similar. Do you recognize it? Oh, [00:48:05] uh, it's a little fuzzy on my screen. Which hormone is it? It's trimethylxanthine. Ah. [00:48:10] Caffeine. It

**Nick:** was dangerous to try to guess the,

**Dave:** the molecules on somebody's tattoo. It is dangerous, especially when [00:48:15] you can't see what, what molecules are on it.

I'm like, is that

**Nick:** a nitrogen? I can't tell.

**Dave:** Bicep is [00:48:20] brief, intentional, conscious exposure to pain. And it turns out that [00:48:25] doing something painful for a minute every day, Changes dopamine [00:48:30] receptor sensitivity and cold plunge counts. So does whipping yourself the [00:48:35] way monks used to or getting a tattoo, which a lot of people do if they're depressed.

And [00:48:40] it turns out that throughout the rest of the day, it takes less [00:48:45] stimulus for you to benefit from the dopamine levels that you have. So for [00:48:50] people with ADHD or attention issues or just a lot of stress or people who just want [00:48:55] to be able to expend less willpower to do what they want to do, That one minute of painful [00:49:00] stuff, which can include a cold plunge, it benefits you psychologically and from a [00:49:05] motivation perspective, entirely different than the endorphins you get, entirely different than the [00:49:10] cold shock proteins, all those other biohacking benefits.

This is a new benefit in cold plunge [00:49:15] or, frankly, getting a spanking. Doing something that hurts, as long as it doesn't hurt you, [00:49:20] is totally fine.

**Nick:** Is the book in its final, uh, has it been? Is it [00:49:25] complete, or can you add a reference? Because I have a reference that you were gonna

**Dave:** love me for. I might be able to add a reference.

If [00:49:30] it's not already in there, tell me about it.

**Nick:** So, this is a paper published in Cell Metabolism. It was [00:49:35] entitled, Physical Exercise Mediates Cortical Synaptic Protein [00:49:40] Lactalation to Improve Stress Resilience. I can send you the link, it's 2024, [00:49:45] September 3rd, 2024, Sound Metabolism, by Jan et al. And what they [00:49:50] show, alright, high level, I think they'll probably agree exercise is [00:49:55] good for anxiety.

And they show a mechanism for how this might work, so let's [00:50:00] go back to the histone deacetylases. What they're doing is they're removing a functional group called an acetyl group [00:50:05] from proteins. Now, protein function can be determined by putting tags on and [00:50:10] taking tags off. Histone deacetylases are removing a tag.

A tag [00:50:15] that is relatively newly identified is lactate itself. So lactate can [00:50:20] attach to proteins and change their function. And what they show in this [00:50:25] study is that physical exercise, especially high intensity exercise that is boosting [00:50:30] lactate levels, will boost lactate levels in the prefrontal cortex of the brain.

The [00:50:35] lactate can then act as a tag on different proteins, including one at the synapses between [00:50:40] neurons. I think it was called SNAP91. And in so doing, the lactate changes [00:50:45] the protein function to change the neuron function to actually have anti anxiety effects. [00:50:50] So the lactate molecule itself is changing brain [00:50:55] function to reduce anxiety.

I had a video on it. It wasn't very popular. But [00:51:00] I can send you that as well. That's

**Dave:** interesting. How cool is that, right? Yeah, [00:51:05] there are so many things that we don't quite know about yet. Probably [00:51:10] the way I would approach that as a biohacker is I would do something from the last book called [00:51:15] blood flow restriction.

Are you familiar with that?

**Nick:** I have BFR bands. I [00:51:20] just never have used them. I use them

**Dave:** on occasion. I go through phases. So a BFR bands what [00:51:25] these do is they increase lactate levels dramatically in the tissues where some blood flow, but [00:51:30] not all blood flow is cut off. And presumably after you release the bands, you get a wave [00:51:35] of lactate that goes through the body and then does good things to the brain.

So, so there you go. If, if you're feeling [00:51:40] anxious and, or depressed, maybe you should try some BFR bands. They're very affordable on Amazon [00:51:45] and maybe it'll work. Maybe it won't. Do what works. Yeah, I know. Super cool. All right, let's [00:51:50] talk about cholesterol. My advice has been for 15 years, if it's harming you, your LP [00:51:55] PLA2 levels should go up, because that's an enzyme released from damage to the lining of your [00:52:00] arteries.

Or your CRP, which is a marker of inflammation risk. Or your [00:52:05] homocysteine levels are the things I pay attention to, regardless of cholesterol. [00:52:10] But, different people have very different opinions. Tell me where you are with [00:52:15] cholesterol versus inflammation. Teach me something. As discussed

**Nick:** in public settings, it's [00:52:20] very devoid of nuance.

So we're gonna talk about some things, LZL, ApoB, insulin [00:52:25] resistance, statements like lower is better, and what I want To be clear [00:52:30] on is none of these things are things to take [00:52:35] as definitives. So, when I talk a lot, let me start with more of the devil's advocate [00:52:40] conventional viewpoint. things like ApoB and LDL particles.

Some people say they're causal [00:52:45] in heart disease, and then people bucket that idea. No, they are. They're part of the causal pathway. They are [00:52:50] necessary for the cascade of heart disease. So that's a totally [00:52:55] appropriate state. So is breathing, yes. Yeah, so, so, however, [00:53:00] just because, I think people get wrapped up in the terminology, so things like causal, when they say [00:53:05] Causal, they necessarily think important, and then they jump from that to, like, it needs to be pharmacologically [00:53:10] treated.

These are not the same thing. Something can be part of a causal pathway, and [00:53:15] mechanistically, it can make sense to undermine the disease process by knocking out something that's necessary in the [00:53:20] disease process. However, at the individual level, it's not quite so simple. Because [00:53:25] something can be causal, but how much risk is it actually [00:53:30] providing?

So you can have elevated cholesterol, and at an individual level, [00:53:35] you know, the relationship between the exposure and say plaque accumulation can [00:53:40] be very weak. So if you actually think about it like just a simple graph of like, y [00:53:45] axis is plaque accumulation and also heart risk, and x axis is cholesterol exposure, [00:53:50] let's say LDL particle or ApoB, like milligram per deciliter years, The question is [00:53:55] not, is it a positive slope, the question is, how positive is it?[00:54:00]

Because if it's like a straight up line, very steep, then yeah, you're accumulating [00:54:05] plaque really quickly for an exposure and you should do something about it. And you can measure that. Yeah, and if it's really shallow, then [00:54:10] it's like, well is it worth intervening on if your risk is increased [00:54:15] 0. 001%? It's still, quote, increased, but it's very different than it being increased [00:54:20] by, you know, 20%.

So, like, by goofy analogy, I use [00:54:25] this on a thumbnail in my video, it's like, the Geico Gecko and Godzilla, they're both [00:54:30] lizards. They both constitute a lizard threat. But they're very different. In terms of their [00:54:35] magnitude. And you might want to drop a nuke on Godzilla, you don't want to drop a nuke on the Geico Gecko to deal [00:54:40] with that problem.

So, you know, it's in [00:54:45] a word or two, context dependent. Like, your LDL [00:54:50] level, let's just say. The risk it presents is highly context dependent on [00:54:55] other metabolic factors, your metabolic milieu, your family and genetic background. So it's [00:55:00] impossible based on a single marker to say you should do X, Y, Z. [00:55:05] And, and that is a totally, I think anybody listening can be like, yeah, that's [00:55:10] obvious and kind of totally reasonable.

And also the art of medicine, a doctor is going to work with their patient, hopefully to [00:55:15] figure out what works best for them. But in the public sphere, what I see happening is these [00:55:20] gross oversimplification. So you get statements like you might've heard of the lower is better. Well, you [00:55:25] know, a commercial is talking about LZL or Applebee.

And I'm like, well, what the [00:55:30] reason they say this, at least the reason I think they say it, and they can feel free to correct me is. They're [00:55:35] worried about giving an inch and having a mile taken and they'd prefer to present the most conservative [00:55:40] stance so people don't do things that they perceive as risky with their health.

Now, the [00:55:45] problem I see with that is first, lore is better as a garbage statement because [00:55:50] it's devoid of nuance. Lower, better for what? All cause mortality or [00:55:55] just cardiovascular disease? And also, what are you doing to get the lowering effect? Because you can't just [00:56:00] isolate one biomarker and snap your fingers like magic and lower it.

You're affecting other things. [00:56:05] Are you changing your diet? Are you taking medication? And what are the acute and chronic effects [00:56:10] of those interventions? So, it's grossly oversimplistic. And [00:56:15] the problem I have as a scientific communicator is I [00:56:20] understand The concern about the people potentially getting confused and doing something [00:56:25] dangerous.

That's a legitimate concern, I hear that. However, people [00:56:30] are also very good at knowing when they're being patronized to and condescended to, and [00:56:35] they hate that, understandably, so then they rebel. So in presenting these [00:56:40] overly simplistic messages and trying to be dogmatic about it, things like lower is better.

You are [00:56:45] actually creating the rebellion that you're pretending to fight against. And so the best thing I think we can [00:56:50] do is approach these topics with nuance and say, Look, yes, LDL [00:56:55] particles, Applebee particles, are part of the causal cascade. Quote, all things being [00:57:00] equal, lowering it could lower your cardiovascular risk.

But what is your [00:57:05] presumed absolute risk, and what are we going to do, and what other effects might this have? Then [00:57:10] let's make a global, reasonable, Determination of what we're actually going to do. [00:57:15] And in some people, a statin might be appropriate therapy. I think these medications have their [00:57:20] place. But in other people, even those with very high cholesterol, it might be, you know, [00:57:25] maybe we're going to monitor you with coronary CT angiography and see how things progress rather than [00:57:30] jumping to a medication.

And there's a lot we don't understand right now about, in [00:57:35] particular, people who are very metabolically healthy. We do have very high [00:57:40] cholesterol. That's where our research is on these so called lean mass hyper responders, because they're just [00:57:45] a new population that hasn't been studied. In medicine 101, you should be very cautious about [00:57:50] generalizing from population X to population Y.

So if you have this new population that's [00:57:55] never been studied, where you have a metabolic response to low carb diets where cholesterol [00:58:00] goes up, that's unlike any other population, because it's not, as far as we know, a genetic [00:58:05] defect, like familial hypercholesterolemia, and these people are metabolically healthy.

Then all we can [00:58:10] say with respect to risk is we don't know, but we need to do more research, which is [00:58:15] where we're at now. So in terms of practical quote advice, [00:58:20] I would say, you know, functional markers will always be [00:58:25] biomarkers. So like for me, what I'm doing is. I'm monitoring with imaging. [00:58:30] So, you know, there's coronary CT and geography.

You can look at which has its [00:58:35] value and then also C CTA, coronary, coronary artery calcium scan, [00:58:40] CAC, and then also C CTAs. You can have a discussion with your doctor, but like [00:58:45] Monitoring how much plaque is actually in your vessel is valuable. So, like, if you're a, you know, [00:58:50] 60 year old woman, and this is a case I'm aware of, someone very close to me in my family, I might call her mom.[00:58:55]

I have permission. But she's had high cholesterol all her life. She's also a Z class hyper responder, so, [00:59:00] you know, she's had something on the order of 10, 000 mg per deciliter [00:59:05] years. She doesn't want to risk her heart health, so she gets an imaging, and her arteries are perfectly clean. [00:59:10] Now, after 60 years on this Earth, Very high cholesterol exposure, and she has [00:59:15] no plaque progression.

Chances are it's not going to crop up in the next two years, so should she [00:59:20] go on a medication? Her doctor talks, and it's like, look, based on your imaging, you as an [00:59:25] individual may not need medication. Someone else, if she had gotten that scan and she had a ton of plaque, then [00:59:30] maybe she would have adopted some sort of therapy, but what we can say is, [00:59:35] there's a ton we don't know, and there's a bunch of individual [00:59:40] variability, so don't go to the internet and try to get your advice there.

[00:59:45] Compile the picture of what you are as a metabolic

**Dave:** organism and then have it Even from your page, we shouldn't go [00:59:50] there? It seems like there are some reliable sources on the internet.

**Nick:** But not, not for generalities though. Oh

**Dave:** [00:59:55] yeah, okay.

**Nick:** Like you, we, we, one can't say, I can't say you listeners should do X [01:00:00] because I don't know your family history.

I don't know your genetics. I don't know your metabolic state. I don't know [01:00:05] your personal priorities and preferences. So, given all that I [01:00:10] think you can listen to people and say, Oh, I took this interesting tidbit [01:00:15] away from X, Y, and Z person. I'm not saying the internet isn't reliable, I'm saying you should [01:00:20] not take academic information and arguments as gospel for your [01:00:25] health.

You should integrate it into a consideration, a deep [01:00:30] consideration, hopefully with, you know, Medical support on what to do. [01:00:35] And understand that all these options are appropriate. People who [01:00:40] say statins are rat poison know they have their place. People who say if you have high cholesterol you need to treat it and you [01:00:45] need your LDL under 40.

I don't agree with that either. It's like, these things [01:00:50] aren't simple matters, and in being dogmatic about it, we all just lose, and people get put in dangerous situations.[01:00:55] [01:01:00]

**Dave:** I love the nuance there, and I don't think that there's [01:01:05] a cause for panic for almost any of those results. It's like, oh, here's something that's [01:01:10] trending in a direction I don't want, so I'm going to figure out what are the levers I can pull. [01:01:15] And for listeners, you can go to axo. health, A X O dot health.[01:01:20]

And you can order a lab test that's very affordable, no insurance [01:01:25] company conversations ever have to happen there, which is why it's affordable. And [01:01:30] you can get your APOB and you can get your cholesterol and your triglycerides and [01:01:35] your CRP LPPLA2 and all those things and just know where you are. [01:01:40] And if you don't like some of those numbers, there's easy stuff to do to manipulate most of those.[01:01:45]

And that means maybe you should go get a soft plaque scan like a clearly or one of the scans you [01:01:50] talked about. But if those numbers are pretty good, you probably don't have to pay [01:01:55] attention to that with your, your energy right now because you may have something else like cognitive function to [01:02:00] focus on.

So it's like, should you pay more attention? Those seem like good markers. [01:02:05] What are the top three blood markers that you think are most important for [01:02:10] people metabolically? Metabolically, overall. I can guess [01:02:15] one of them. What are you thinking? HbA1c.

**Nick:** Yeah, I [01:02:20] mean, that, that, in the context of also like a home IR and insulin.

Like as you know, [01:02:25] HbA1c does not tell all. It's your average blood sugar, so you want that low, but you can also be on [01:02:30] the road to developing diabetes where your body is compensating. for [01:02:35] hyper for insulin resistance by producing more insulin. So let's say an [01:02:40] HbA1c and either a fasting insulin or HOMA IR.

So a marker of insulin [01:02:45] resistance and a marker of blood sugar. And then beyond [01:02:50] that, let, I mean, it's going to be very individual. It would be a treadless ride, a fasting treadless [01:02:55] ride. I can't think of anything good that would come from a very high fasting treadless ride, and I think it can be the canary in the coal [01:03:00] mine.

I'll caveat it's a noisy marker. So like, you know, say you fast for [01:03:05] it for a very long time, it can go up. You just worked out, it can either be up or [01:03:10] down. Make, the best way to do it is like 12 to 14 hours water only [01:03:15] fasted, so not even coffee. But I would say, if you have a high AHOMA IR, a [01:03:20] high, or a bad HOMA IR, like a high fasting insulin, high A1C, or high [01:03:25] triglycerides, Something's probably awry.

And those are all very basic. So those like [01:03:30] esoteric tests you can get, but like I would say most people should know those markers. Yeah.

**Dave:** Yeah. I like to [01:03:35] do those every three to six months in my own journey and just making it [01:03:40] easy to do so someone comes to my house and draws it. has been life changing.

That's [01:03:45] why Axo Health does that as well. And by the way, if, if you're curious. Guys, [01:03:50] it's 80 to have someone come to your house or you can just go into a lab and save 80 bucks, [01:03:55] but it's not a huge amount of money compared to the time you save. And the idea [01:04:00] that you should have to go to your doctor and beg to get these markers is offensive to me.

So now you [01:04:05] can go to your doctor when you have the markers and have the conversation and just save a ton of time. Yeah, [01:04:10] no. There are more and more companies putting data in people's hands. It's a human right to know [01:04:15] what's going on in your body. I don't think so. If you, if you want.

**Nick:** I talk to people, I'm like, my doctor won't get a fasting insulin.

I'm like, [01:04:20] why? They're like, why do I? They're like, because it's not, quote, actionable. Like, they're not going to change your medication scheme. [01:04:25] I'm like, but it's information that the patient wants. Order the freaking tests.

**Dave:** At a certain point, I'm like, [01:04:30] Doctor, I'm paying you for your prescription pad [01:04:35] to give me the data that I want.

And you set up the system along with the AMA in order [01:04:40] to make sure that you're in the loop, and I respect that. So please do what I paid you for [01:04:45] this appointment for, which is I wanted my information. And you're part of my care team. So like, let's work together. I [01:04:50] understand

**Nick:** there are limited resources. I do.

So I, I'm not a fan of like, just like, testing willy nilly, [01:04:55] but like. But if it's valuable to the patient and it can inform lifestyle change, [01:05:00] then I consider something like, you know, the cost of an insulin test pretty

**Dave:** Well, I mean, if the patient's [01:05:05] bearing the cost, okay. I agree if it's going to be paid for by a [01:05:10] socialized medicine or the equivalent, which is an insurance company.

There's [01:05:15] all kinds of bureaucratic stuff, but if you're like, Hey, some people want to go out and spend 100 on drinks. [01:05:20] I want to spend 100 on getting my lab work done. Okay, more power to ya, right? Yeah,

**Nick:** it's [01:05:25] such an inefficient system, it's absolutely grotesque. Yeah. And I'm not gonna pretend I [01:05:30] understand all medical economics, but like, there are just some things you see and I'm like, I don't understand why we're spending money on

**Dave:** [01:05:35] this.

Jeez, we could go on for, for probably Several hours about that. [01:05:40] I want to talk about something interesting. There are a group of people who say that all you have [01:05:45] to do to lose weight is exercise more and eat less. And I did this for 18 months straight in [01:05:50] my early twenties. I never lost a pound. I maxed out all but two of the machines at the gym [01:05:55] and I never lost a belt size.

Yes, I had more muscle and less fat, but I was still [01:06:00] fat. And I was eating low calories or starving all the [01:06:05] time. It was, it was hellish. So I consider that advice to be [01:06:10] mean spirited from people who never had to deal with obesity. Or if they did deal with obesity, [01:06:15] they had a working metabolism and bad habits.

but if you have something dysregulating you, [01:06:20] no amount of effort is going to work until you unblock some pathways. So I came [01:06:25] up with several use cases that disprove the calories in calories out thing. [01:06:30] including you can't eat uranium and gain weight. And they said, well, you can't metabolize that. Oh, [01:06:35] so metabolism matters.

And then you say, Oh, there's a drug called ziralinone. They give to cows that get [01:06:40] some fat on 30 percent less calories. If you have that drug, eating less might not [01:06:45] work, but there's also a contagious type [01:06:50] of obesity. And there's a couple cases I wrote about in the Bulletproof Diet, a guy gets [01:06:55] scratched by a chicken.

And there's a certain virus that causes rapid [01:07:00] obesity. That's infectious, and so there's another case, but there's some new stuff [01:07:05] about food addiction in a virus. Tell me what you found out about that.

**Nick:** Yes, [01:07:10] so, um, this was a paper that came out of a Spanish group a little while [01:07:15] ago, and, uh, basically what they did is they were looking at this phenomenon of food addiction.[01:07:20]

Which isn't technically in the DSM, which is like a manual of [01:07:25] psychiatric diagnoses. However, it can be classified based on just a [01:07:30] substance use disorder. So the criteria of a substance use disorder, and measured using something, the [01:07:35] most common is called the Yale Food Addiction Scale or, uh, Yale Food Addiction Scale 2.

0. So, it's a [01:07:40] clinical phenomenon, people have basically substance use disorder for food. Generally like [01:07:45] processed foods and sugar, and then, you know, the thought is what causes it? Is it just [01:07:50] habitual? I would say, you know, anybody who's kind of a biological materials like [01:07:55] me, know it's like there's something biological going on here, and what they did was they were [01:08:00] looking for, uh, fingerprints of this food addiction phenomenon in [01:08:05] the microbiome, and in particular, the microvirome.

So, your microbiome [01:08:10] is the microorganisms in your body. But that's not just bacteria, it's also [01:08:15] viruses, which is kind of underappreciated. So they were able to identify a one [01:08:20] family of virus in particular called microviridae. And within there, there is a [01:08:25] particular virus called the Gokusho virus. And what they found was [01:08:30] it was strongly associated with food addiction in multiple [01:08:35] cohorts, including a validation cohort.

And that the mechanism appeared [01:08:40] to be, and they used animal models to demonstrate the mechanism, but changes [01:08:45] in the metabolism of the serotonin and dopamine precursors. So, [01:08:50] um, uh, seen, or tryptophan and tyrosine respectively for serotonin and [01:08:55] dopamine. And basically by binding to, or by infecting, they're called [01:09:00] bacteriophage viruses, bacteria, and then changing the, the bacterial metabolism, they [01:09:05] changed Dopamine and serotonin precursor metabolism to then change brain function, which they could [01:09:10] see on functional magnetic resonance imaging in association with changes in food [01:09:15] addiction score.

So basically they identified a virus that appears to, at least to some degree, [01:09:20] contribute to, one could even say cause, food addiction phenomenology. [01:09:25] Which is freaking fantastic! Or, I mean, not for the people who add it, but it's very, very [01:09:30] interesting. And just as another layer, it's the idea that Even with respect [01:09:35] to, quote, behavior and call food addiction a behavior, as opposed to just, [01:09:40] say, metabolism at the level of oedipocyte and fuel partitioning with insulin, this [01:09:45] idea of obesity is so, so complex, and I'm on the same wavelength with you, [01:09:50] Dave, as far as Calories in, calories out being such a gross [01:09:55] oversimplification that it offends my sensibilities to even here eating eat less, [01:10:00] move more at our current stage.

We can delve more into that, but that was the literature you were asking [01:10:05] about.

**Dave:** Is there an easy way to determine if someone has that virus? I don't think that's a [01:10:10] clinically available test.

**Nick:** No, this is brand new research and generally research is well ahead of, uh, [01:10:15] a clinical Diagnostics. So, no, I can't like say, here's a test, go get [01:10:20] to see if you have microviridae, yada yada.

**Dave:** So the, the biohacker approach, if you have food [01:10:25] addiction that isn't trauma based and doesn't make any sense and you've tried everything and you [01:10:30] think it's a possibility and you can't order the test and you've exhausted everything else. You [01:10:35] could try something like a broad spectrum antiviral like [01:10:40] Cytoflavir.

And you'd look at the side effects and decide if they're worth it. I have no idea what they are. [01:10:45] And go, hmm, maybe it's gonna work. And if you try it for a week, you're like, holy crap, something changed. [01:10:50] Great, but your doctor's probably not gonna want to do that, but you still might want to.

**Nick:** I wouldn't recommend going that [01:10:55] far yet.

I think there's probably other empiric things you can toy with. I don't know a lot of people with food addiction if they [01:11:00] try cutting out all sugar. Or even going keto, that could help before eating [01:11:05] pharmaceuticals. I'm, you know, I'm not going to tell you what you should do. I do think they'll probably be, people will [01:11:10] be very eager to figure out how you can diagnose and treat this in humans.

But until that one.

**Dave:** Yeah, lab [01:11:15] tests will come. Until then you should try a gram of animal protein per pound of body weight. Intermittent [01:11:20] fasting, keto diets. You know, I have a whole book about all this. You have a whole YouTube channel [01:11:25] full of stuff. You can try a lot of things that affect food cravings.

And if you're like, no, I've done [01:11:30] everything. And I know people like that. I, I got to that point where I've done everything. That's supposed to work. And I'm going to have to try the [01:11:35] crazy stuff because I'm desperate and I'm still 300 pounds. so just the, the way of thinking [01:11:40] about, Hmm, if that might be a variable, what are the odds that that's your variable?

They're low, right? And if you've [01:11:45] exhausted everything else, Hey, now you know there might be something. And the idea that it's possible. It's just [01:11:50] yet another hole in the target that is the calories in calories out [01:11:55] hypothesis. I feel like it's just a way to shame fat people because it doesn't [01:12:00] usually work.

And if it does more power to you, but you might try fasting, which is different than calorie [01:12:05] reduction and get a totally different result because of ketones.

**Nick:** Yeah. Well, on the calories in calories out, I [01:12:10] think something to point out is that it's It's technically accurate and [01:12:15] practically useless. And people need to understand why you can reconcile, quote, [01:12:20] calories in, calories out with things like the carbohydrate insulin model.

[01:12:25] Because the thing about calories in, calories out is, no, it's not a wrong [01:12:30] model. It's not a model of obesity in the first place, biologically speaking. It is [01:12:35] just describing what has happened. When there's been a weight change, [01:12:40] post hoc. And you can even see this how people like describe us like, Oh, you know, [01:12:45] this person ate 6, 000 calories and their estimated needs were 3, 000 but they didn't gain weight.

And [01:12:50] people are like, well their energy expenditure must have been higher. I'm like, great, you just post hoc like [01:12:55] rationalized your model. Or, you know, you could do the vice versa. This person was restricting, but they didn't gain [01:13:00] weight and they were predicted to by their Harris Benedict equation. Oh, well.

Their basal metabolic rate went down. It's still [01:13:05] calories. I'm like, but yeah, now it's practically useless. So we need to understand the whole idea of [01:13:10] calories in, calories out. It applies, but it is not the independent [01:13:15] variable. It is the dependent variable. It is what is resulting from other [01:13:20] interventions, other variables, like how you partition fuel in your body.

If you have a hormonal [01:13:25] milieu, say very high insulin level, that's calling your body, I'm going to partition the calories I take in [01:13:30] into fat tissue. What happens downstream of that is more hunger, [01:13:35] which leads to more energy intake, and less energy expenditure, too. So your body will [01:13:40] finagle the calories in, calories out, to get the outcome it wants in the chronic sense.

[01:13:45] which I would differentiate from the acute sense, because yes, you can slam 10, 000 calories a day for a few [01:13:50] days and acutely gain weight, but that doesn't tell you anything about the actual chronic development of [01:13:55] obesity in the real world setting. So, calories in, calories out, is [01:14:00] Not even a, a, a model of obesity.

And just for kicks and giggles, cause I saw this on [01:14:05] threads the other day, there was a guy who put out a thread, and I usually don't respond to these [01:14:10] things, I usually don't, but this one was just so dumb I needed to. He [01:14:15] said, Most people are not overweight because they have a slow metabolism. [01:14:20] They have a slow metabolism because they're overweight.

And this guy, [01:14:25] what, LeanLyfeCoach, just like a, you know, the standard, [01:14:30] like, young 20 something flexing his six pack. Which is like, to your point, I think people [01:14:35] who really parrot the calories in calories out model, one major reason [01:14:40] they do it is because It's a self serving bias. If [01:14:45] you're a chronically lean person, or you're just a person who's like, even currently lean, [01:14:50] if your world model is, this is a function of basically, you know, [01:14:55] eat less, move more, then there's a virtue, like literally a, a, a [01:15:00] positive human quality to being able to exert the, quote, willpower needed to get that outcome.[01:15:05]

And so, it serves you to have a very, very basic, simplistic understanding of, [01:15:10] I have high willpower which means I can eat less and move more. you know, and rather than challenge [01:15:15] what does this actually mean, does this model actually make sense? And so you get people like these, quote, this [01:15:20] guy's a coach, or he calls himself a coach, saying, Most people are not overweight because they have a slow metabolism.

They [01:15:25] have a slow metabolism because they're overweight. Which, if you stop and think about it, is so stupid. Now, if people [01:15:30] want to know what I replied, I said, Most influencers don't make up nonsense because [01:15:35] they're influencers. They're influencers because they make up nonsense. Now, if this individual is trying to [01:15:40] suggest that fat tissue burns less energy at rest than muscle tissue, he should have chosen better terminology, as [01:15:45] stated.

The thread as is, is empty calories for the mind. Anyway, [01:15:50] I love that. That's one thing that does get under my skin, the calories in, calories out. I'm going to call it nonsense, [01:15:55] because what it is, is nonsense.

**Dave:** Thank you. Uh, we're in agreement. And I, I do [01:16:00] invite guests on the show who disagree on it, because I, I'm curious, what, what am I missing [01:16:05] here?

But between Gary Taubes, you so many Metabolic experts and lung [01:16:10] cavity doctors, it's just become clear that manipulating calories isn't that [01:16:15] powerful yet. Manipulating timing of calories and type of [01:16:20] calories and the whole ketosis thing and amount of proteins and specific [01:16:25] aminos. Those seem to move the needle in a way that just [01:16:30] radically restricting calories with diet coke that you can cancel out with a Snickers bar.

It just [01:16:35] doesn't work.

**Nick:** It's, it's, it's defted because it might, again, the acute doesn't equal [01:16:40] chronic. If you fast, which is extreme caloric restriction, although you're also going into ketosis and carbohydrate [01:16:45] restricting, so there's complaining variables there, it could lose weight, but obviously that's not sustainable.

So, [01:16:50] the, you know, diet Coke and special K diet that might work for a week, it [01:16:55] will inevitably fail as your metabolism slows, the energy output goes down, your your [01:17:00] hunger goes up, and then you'll fail, and the system in common knowledge, the way it is, we'll say you [01:17:05] fails. Rather than, this approach was doomed to fail in the first place.

[01:17:10] So, yeah, no, I think, the calories in, calories out, Psyche needs to [01:17:15] die. Not just because I'm attached to some other academic model, But because it's hurting [01:17:20] people. Like, you see it in the world around you, where, People want to treat their obesity, [01:17:25] And, this is what they get told, some version of calories in, calories out, Eat less, move more, [01:17:30] Then they try it, they put a tremendous amount of will in, and they do, And then when it [01:17:35] fails, They blame themself, and you have your cycle go on enough, [01:17:40] and people end up with learned helplessness.

**Dave:** Mm hmm.

**Nick:** And, you know, like a dog that's been [01:17:45] shopped too many times. And then, what do you do? And I think as a society, one of the things that's [01:17:50] happening, and I might get in trouble for saying this, but this is how I think it's manifesting and coming out, is, you end [01:17:55] up with movements like, healthy at any size.

Where people start to excuse it, [01:18:00] and I really feel, because I see the learned helplessness, and I'm like, You were pushed here, and I [01:18:05] understand why, because you put all this effort in, you genuinely did, but down a misdirected path.

**Dave:** [01:18:10] I've been to that point where it doesn't matter what I do. Like, I'm sitting here, I'm [01:18:15] eating less than five of my friends combined, and I'm working out more than all of [01:18:20] them, and I'm still fat, and I'm like, it's a helpless thing.

It is a, it [01:18:25] is a terrible thing. So you're saying, well, this is just normal, it's my state. It just means that you haven't [01:18:30] found what works yet. But if you just. Deceive yourself and say no, this is healthy. [01:18:35] That's not what your labs say and I want you to feel good all the time [01:18:40] And I want you to be actually healthy instead of identify as healthy.

It's not okay to do that [01:18:45]

**Nick:** I will also caveat that like I do think BMI is like a crappy metric and just [01:18:50] because you're in the cool overweight Category doesn't mean you're unhealthy But I'm, I'm like, the [01:18:55] distinction here is like, look, we can go beyond BMI. We could say there are definitely different body types and because [01:19:00] somebody's heavy set doesn't mean they're unhealthy, but at the same time, it's not [01:19:05] appropriate to have somebody who's metabolic markers are screwed up with a BMI of 48, excess [01:19:10] visceral adiposity, and say, quote, healthy at any size as an excuse, because that's just hurting [01:19:15] that person.

Yeah, it's mean. It's not their fault. Like they need support. Or [01:19:20] health, but it's not helping society. It's not helping that person.

**Dave:** If it [01:19:25] makes you feel better listening to this, my BMI is still a little too high. [01:19:30] So if I get my avatar on one of those fitness apps, it actually has me as round [01:19:35] around the middle.

I'm 4. 8 percent body fat, but my bone density is like [01:19:40] Wolverine. I have exceptionally dense bones because of my biohacks. So they're saying, well, you must [01:19:45] be fat. I'm like, this is just a nonsense variable. What I do look at [01:19:50] is total fat mass in the body. And when you come into upgrade labs, [01:19:55] we have medical grade gear that measures that you can also get it with a Dexa.

[01:20:00] And that doesn't, doesn't change even percent body fat. You want to drop your [01:20:05] percentage body fat, drink a gallon of water, hopefully with electrolytes and magically. [01:20:10] Now you have more water so your percentage body fat drops because there was more water in your body so don't poop [01:20:15] and drink a lot of water and get your Percentage body fat and feel good about yourself until you go to the [01:20:20] bathroom and pee I'm sure the yeah impacted feces is

**Nick:** equivalent metabolic weight of muscle [01:20:25] mass Biohackers [01:20:30] Eddie Hall, do you know Eddie Hall?

He's one of the world's strongest men. Won carnivore for three months [01:20:35] and just came out with his results. He went in three months on carnivore, but down [01:20:40] from 27 percent body fat to 19 percent on dexa.

**Dave:** Wow.

**Nick:** And his strength, [01:20:45] he only, and look, I think, like, that was He's almost entirely, well, it [01:20:50] was entirely fat mass that he lost, but he's, he's now 19 percent body fat at something like 350 [01:20:55] pounds and 19 percent on dexa, not like alloper, like that is bananas and that [01:21:00] kind of drop my goodness.

So, that was bananas. That's a really cool. He was [01:21:05] eating. 9 to 10, 000 calories per day. Oh yeah. Yeah, it's not about number of calories. [01:21:10] An absurd amount of body fat over 3 months, eating 000 calories per day. So [01:21:15] yeah, thank you, calories in, calories out. I did a video on his one month progress and I [01:21:20] had like a dietary record from him, so I was like, he's eating 10, 000 calories, and I'm like, let's just put his age, [01:21:25] sex, weight into like Harris Benedict, and his, his, based on my bulk, it was like [01:21:30] 3, 000 calories.

And I'm like, so he's somehow losing weight on top of like [01:21:35] a maintenance deficit of 7, 000. And there were some of the comments like, [01:21:40] yeah, but he like exercises a lot. I'm

**Dave:** like, not that much. That was not that much. [01:21:45] Like, no, like this is just Nick. I did, I did something similar before. I published the [01:21:50] Bulletproof diet the big, uh, cyclical clean keto, intermittent fasting book.

[01:21:55] That it's almost a million copies sold at this point. Wow. Uh, I [01:22:00] was like, I want to stress test this. So I decided that for a month I was going to eat at least [01:22:05] 4, 500 calories a day. I was going to do my recommendation. So this was [01:22:10] the equivalent of carnivore. It was [01:22:15] steak and meat and butter. I did have coffee and butter.

Some people say that's not [01:22:20] carnivore. Most people are okay with those things. And I would have possibly one [01:22:25] serving of broccoli a day. And that was it. And 4, 500 calories. I said, and to [01:22:30] make sure I stacked the deck against myself, I will sleep less than five hours a night and I'll [01:22:35] stop exercising. Okay.

And my goal was I'm going to gain three pounds, but all the [01:22:40] science says I should have gained 20 pounds to say it's not possible. I lost weight. I ended up [01:22:45] doing this for months, and I grew a six pack and posted a picture of it. It was insane.

**Nick:** [01:22:50] I've tried doing similar things over a feeding experience. At some point it becomes self limiting.

I couldn't do it for months, [01:22:55] but like, I've done 5, 000 calories for a month, and if people see me, I'm small. I'm like [01:23:00] 5'8 BMI's, never tops 22. 5, and even [01:23:05] that at 5, 000 calories? For a month on a strict keto, I will [01:23:10] not gain a pound. I just won't. I will notice other things happening. My body temperature goes [01:23:15] up.

My heart rate goes up. I bounce around like a like a pogo stick. [01:23:20] I can't stop it. But my body is just like in this state. It's just like, I don't want you to be [01:23:25] fat. Like, go away, NMG, go away. And it just, you, you don't gain weight. It's kind [01:23:30] of bananas. I'm not saying it'll happen with everyone, but it is.

It's also not good for you from a longevity perspective. [01:23:35] No! Definitely not. Impossible, too. Like, I didn't sleep well. It's like, it's not [01:23:40] fun. It, it, people think it sounds fun. It's, it's fun for like

**Dave:** two days, and then you're like, er. I, I [01:23:45] wish that I had done it less in retrospect. I just did it for a while because I used the extra energy to [01:23:50] start the biohacking movement while I was working full time and had a new baby, so.

You know, I, I [01:23:55] burned the energy one way or another, but I don't think it, it was beneficial for longevity. But for listeners, [01:24:00] both of us have eaten stupid amounts of calories and not gotten fat, which is yet another [01:24:05] piece of anecdotal evidence that says just cutting calories, being hungry all the time, probably [01:24:10] isn't going to make you get your metabolic gains.

Okay. Nick, your work [01:24:15] is fascinating and I, I'm grateful that you're one of, are [01:24:20] up and coming people talking about metabolism in a meaningful way. You've got great academic [01:24:25] credentials and more coming your way. You've become a really good communicator at [01:24:30] frankly, relatively young age. It takes a while to learn how to communicate the way you do.

So whatever you [01:24:35] did, you did it right. And so you're making a big difference [01:24:40] and you're setting yourself up To continue carrying the torch [01:24:45] of upgrading ourselves just with real science instead of with this [01:24:50] dogmatic belief in whatever Kellogg's told us. So thank you.

**Nick:** I appreciate it. It's [01:24:55] been a really fun journey.

I'm at that stage in my life that listeners, if they're older than me, might [01:25:00] remember where you're like, Huh, this is what I actually want to do. You know, I grew [01:25:05] up thinking what the right thing to do was. And recently I kind of made a leap towards. [01:25:10] I'm really passionate about metabolic health, teaching, I want to figure out how to do this.

We're living in a really [01:25:15] exciting time especially for me as like a young academic where like I have access to communicate directly [01:25:20] with people, get creative in how I provoke discussions in ways that prior [01:25:25] generations just didn't have access. So like when I'm frustrated because people won't talk about research I [01:25:30] think's important, I don't have to just like say, oh crumbs, I will like, you know, [01:25:35] go spend the next seven years doing residency, fellowship, training, get this grant, that branch.[01:25:40]

I'm like, no, I'm going to do a freaking n equals one experiment where I eat Oreo cookies to lower my cholesterol and [01:25:45] then force this discussion to happen because I can't. And because there's [01:25:50] a game that I think is important and appropriate to play currently in [01:25:55] where we are with academia and social media just In this [01:26:00] incursion, this collision where you kind of have to acknowledge the rules of the game and the [01:26:05] engagement and use it to provoke deep discussions and [01:26:10] ask hard questions and have these nuanced dialogues.

That [01:26:15] push us to progress important science [01:26:20] and push people to think in a way that can benefit their health. And it's a really [01:26:25] complex art, but I'm having a lot of fun with it along the way. So, I'm looking [01:26:30] forward to the next several decades of doing this.

**Dave:** Is that it? You got more than a several decades.

**Nick:** [01:26:35] Alright, many decades. I don't want to be too, uh, predictive, uh, too, uh, anyway, [01:26:40] cocky about it, but yeah. I'm missing at least 70 years. I'm making another 70 years. It's [01:26:45] my veteran, my, uh,

**Dave:** rookie year. If you have the impact that you can have, [01:26:50] it's at least 10 decades, but I'll race.

**Nick:** Hopefully, hopefully, we'll see.

It's gonna [01:26:55] be, I mean, it's funny, because this has ramped up so fast, like, I started getting serious about social [01:27:00] media in 2024, this year. While a full time researcher and a [01:27:05] medical student and it's ramped up this fast. So like in five years The things that are [01:27:10] happening right now Like I got flown out to India like a little week ago First time to [01:27:15] India like based on some stuff that happened on social media Wow, which is like, you know I went from in a [01:27:20] couple periodical months like eating crappy hard boiled eggs like in the hospital [01:27:25] cafeteria to being like You know, first class guitar air at some really cool parties.

[01:27:30] Like, you know, partying with famous rappers and talking to like Royal families about [01:27:35] Metavel. It's the most bizarre thing. I'm still wrapping my head around it. It's super bizarre. Life is [01:27:40] changing really quickly and I'm just enjoying the ride right now. Well, thank you. I probably shouldn't have said all that [01:27:45] happened.

I don't know how I'm going to get in trouble for it, but it probably will.

**Dave:** You won't get in trouble

**Nick:** for it. You're fine. Thank you. [01:27:50]

**Dave:** See you next time on the human upgrade [01:27:55] podcast.