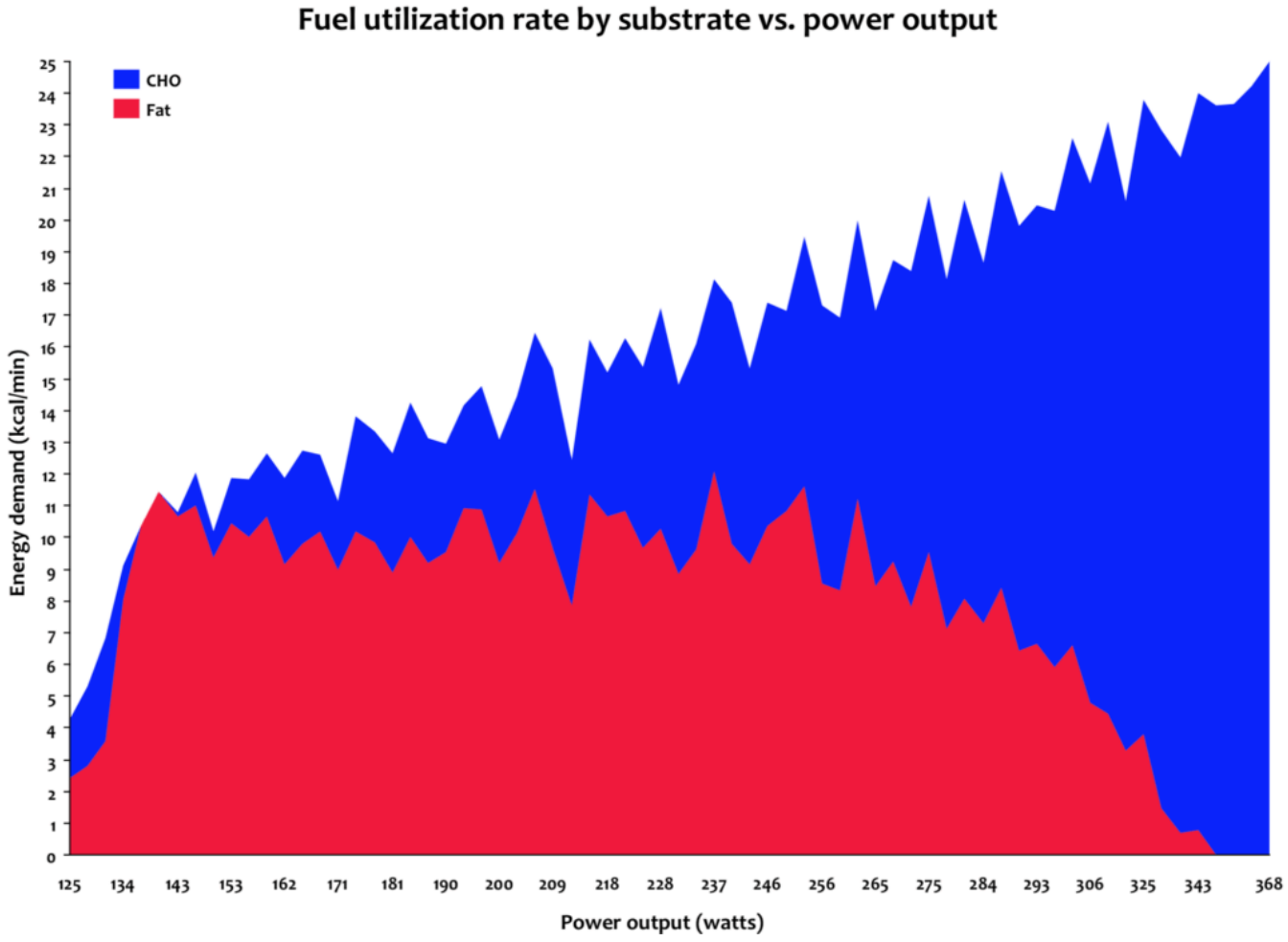
#73 - AMA #9: NAD & metformin, fat-burning zone, creatine, estrogenization of men, emergency kit for cold & flu, and more

PA peterattiamd.com/ama09

Peter Attia September 30, 2019



In this “Ask Me Anything” (AMA) episode, Peter answers a wide range of questions from subscribers. Bob Kaplan, Peter’s head of research, asks the questions. If you’re not a subscriber and listening on a podcast player, you’ll only be able to hear a preview of the AMA. If you’re a subscriber, you can now listen to this full episode on your private RSS feed. You can also watch (or listen) to this full episode on our website at the AMA #9 show notes page. If you are not a subscriber, you can learn more about the subscriber benefits here.

We discuss:

- The story of how Peter almost worked for Theranos [2:00];
- The trend of lower testosterone and higher estrogen in men: Why is it happening and what to do about it? [10:00];
- Takeaways from Peter’s recent hunting trip in Hawaii [14:45];

- What books are you currently reading/listening to? [21:30];
- What advice would you give to the 25 year-old Peter? [24:00];
- What is your emergency protocol if you start getting sick? [27:45];
- How have your thoughts changed on NAD precursors, and also on metformin, in the past year or so? [30:30];
- What are your thoughts on "fat burning" zones for cardio workouts? — A lesson in relative vs. absolute fat combustion [34:15];
- What mental models do you use and how do you go about solving problems and approaching difficult questions? [49:00];
- Creatine supplementation—Yay or nay? Why? [49:30]; and
- More.

§
NAD & metformin, fat-burning zone, creatine, estrogenization of men, emergency kit for cold & flu, and more

§

Show Notes

The story of how Peter almost worked for Theranos [2:00]

⇒ For a primer on Theranos and why this is even interesting…

- Give the wiki page a quick read
- Also, check out this HBO documentary
- Or the best selling book by John Carreyrou

An offer from Theranos

- In 2006, Peter was working at McKinsey & Company in Palo Alto
- Theranos contacted him and he was offered their Chief Medical Officer position
- He met with Elizabeth Holmes
- They looked at the black box machine together and discussed business and technology

Decided not to take the job for several reasons

- First, someone Peter trusts did not say anything good about one of the investors in Theranos
- Secondly, loved his job at McKinsey
- Third, wasn't convinced that what you could test in a box that size was interesting

> "*I knew enough about diagnostics and…chemistry that I knew that there was…not going to be anything you could do on a drop of blood, in a box that size, that was clinically interesting.*"

8 years later

- In 2014, 8 years after declining the job, Forbes valued Theranos at $9 billion
- Calculated the money he would be worth if he had taken the job, “life changing money”

In 2015

- Peter was at a fundraising event where Elizabeth was the top speaker (ahead of Mark Zuckerberg)
- Elizabeth saw Peter and remembered him from 9 years prior
- They exchanged contact info and kept in touch for a while
- 2 days after this event, John Carreyrou put on an article in the WSJ exposing some of the fraud going on at Theranos

Cognitive dissonance

- Here is Elizabeth as the headliner at this “who’s who” event
- Simultaneously, she knows her world is about to get super messy was the WSJ article releases
- From a psychology standpoint, Peter says he doesn’t believe that Elizabeth ever *thought* she was doing anything wrong
- Which is not for a moment to say, she shouldn’t be held accountable for what happened
- She should be absolved of the responsibility of what she’s done
- But it’s a very important distinction… you can be so delusional that you really believe that the lies you’re telling are for the better good

Did Peter ever suspect fraud from Elizabeth and/or Theranos?

> “*I never suspected [fraud]. . .I just thought it was the world’s most uninteresting business in the history of civilization. Like point of care testing in a drug store for Chem-7, and CBC? I would have more interest in a business that specialized in removing hangnails and nose hairs.*”

The trend of lower testosterone and higher estrogen in men: Why is it happening and what to do about it? [10:00]

Lower T, Higher E

- If you took blood samples from a group of men in the 1950s, and did the same for a similar group of men today…
- You would notice that, in today’s men, **testosterone is lower, and their estrogen is higher**

The question is, WHY?

1 Increase in obesity

- Because, obesity obviously implies more adipose tissue.
- Adipose tissue is where we’re going to see more of the enzyme called aromatase (which turns testosterone into estrogen)

- If you have more adipose tissue and potentially more aromatase, you will undergo that chemical reaction more of turning the testosterone into estrogen.

2 Chemicals that can mimic the effects of estrogen (or increase the production of estrogen)

- Lots of plastics have been proposed to do this
- Examples,

- Food stored in plastic tupperware
- Drinking coffee in cups with plastic lids
- Especially off plastics that are going to have any high temperature with them

Things Peter does personally to combat this:

- Use glass containers at home
- He also washes all plastics by hand instead of in the dishwasher

Anecdote from a patient:

- He was drinking tons of coffee from plastic cups daily
- Switched to non-plastic and reported to feel 100 times better
- (Obviously, this could be placebo)

How much of a difference does any of the stuff make?

> I have absolutely no idea if this is making a difference or not, says Peter

Furthermore, when doing blood tests…

- We don't even know what we're measuring
- A lab test that's measuring estrogen, first of all, you're usually just measuring estradiol (rarely measure estrone or estriol in men)
- And then there could be a whole bunch of pseudo estrogens that are floating around that are exerting other biologic effects, that are "estrogen-izing"
- But you can't measure them in the serum.

Anyone know of an expert on this topic?

- Peter says he only knows a little bit on this topic
- All suggestions are welcome for who the expert is on the topic

Takeaways from Peter's recent hunting trip in Hawaii [14:45]

Peter recently went to Hawaii to hunt axis deer

Takeaways from the actual hunt

- The shot, which is incredibly difficult and takes years of practice to even have a chance, is the **easiest** part

- Being able to spot an axis deer, literally just see one, is ridiculously hard
    Their sense of sight, hearing, and smell are preternatural (they can smell you from a hundred yards away)
- Stalking them is nearly impossible without expert guides
    - About the hardest terrain you're going to find in North America
    - Very cool, also difficult and frustrating
- Harvest them quickly and efficiently
    If you manage to find them, stalk them, get in position to shoot them, and accurately hit them, you then have to harvest them properly
- In summary,
    - Peter gained an enormous appreciation for the expertise that goes into being able to actually get in a position to even take this shot…
    - Without that kind of knowledge [from the guides], "*you'd be twiddling your thumbs for days, hiking 16 miles a day, not even seeing an animal*"

Feeding on a truly wild animal

- Many people discuss the difference between farmed cow and grass-fed cow
- There are differences, says Peter…
    - Namely their diet (farmed cow mostly corn)
    - Less antibiotics
    - Less hormones
- H*owever*…
    - The grass fed cow is not living in a natural environment
    - And it's still subject the unnatural stress (tremendous amount of stress at the time it's killed)
- *This is in *stark contrast* to how the axis deer are killed

Axis deer

- They are not natural to Hawaii (they're natural only to India)
- They are an invasive species to Hawaii
- These are animals that are dying instantly because of how swiftly the kill happens (and from a great distance away)
- "*To me, that's the absolute apex of what the best meat could possibly be like.*"
- You can just taste the difference
- Venison has a reputation as being a kind of "gamey" meat, but axis deer is not remotely gamey in this fashion
- In other words,
    - you don't have that lactate surge, which is what happens when an animal is injured
    - You don't have that cortisol surge, which is what happens when an animal is stressed

Peter's new aspiration: *Could I get to the point in life where I don't need a single animal that I didn't kill, or a friend of mine didn't kill?*

What books are you currently reading/listening to? [21:30]

Coddling of the American Mind by Jonathan Haidt and Greg Lukianoff

- As a parent, it's good to make sure we catch ourselves from doing too much coddling, says Peter
- The book explains the harmful level of political correctness going on using the example of the bubbles existing within the 20 most elite schools in the country
- "*It just provides an incredible level of head shaking.*"

⇒ Example,

- The dean of students at Claremont McKenna College was forced to resign over an email that was deemed bigoted/racist
  (Sam Harris did an entire podcast on this)
- You should feel disgust at how this woman was treated
- And then more importantly, feel a need to examine the underpinning of how it could happen

The Coddling of the American Mind talks about how this environment basically came to fruition around 2013

- And we're now seeing the far extremes of this political correctness
- And hopefully it sort of it comes back to the middle

Do you always listen to audiobooks nowadays or do you read paper copies as well?

- Mostly listen
- Sometimes will also get a hard copy to take notes

What was the last paper copy book Peter read?

- The Second Mountain by David Brooks
- Peter wrote about this book in a Sunday email: David Brooks and the quest for a moral life

What advice would you give to the 25 year-old Peter? [24:00]

- During a recent talk Peter gave on mental health, a woman asked the question: "*What can you say to somebody who's in need of this type of help?*"
- Peter's answer: "*Sadly, I don't know what you can say to somebody who isn't sort of cracked open a little bit and willing to hear what you have to say.*"

Change comes from the inside

- Just like someone who needs to eat better, exercise more, sleep more…
- You can't impose that on people
- It's the same when someone needs to "unscrew themselves emotionally"

- They have to **want** to change

Peter said the 25-year old him wouldn't have listened to his advice

- Because the 25 year old me wasn't broken
- He hadn't hit a relative rock bottom
- There was no way he was going to listen…
- He's a total stubborn, maniacal focused human being that's not going to hear it from anybody until the pain gets great enough

Christmas Carol analogy:

- Scrooge was only able to change when he saw the ghost of Christmas future
- You really need to **see** what is going to happen if you continue on a certain path
- It's almost like you need a crystal ball

What is your emergency protocol if you start getting sick? [27:45]

Two Things Peter Keeps on Him All the Time

1 Tamiflu

- In case you are coming down with the flu, you need Tamiflu
- But you can't wait until you're in the middle of it or it's too late
- It only works if you catch the influenza right on the update
- Peter points out that the flu vaccine isn't efficacious every year (in 2018 it was "basically a placebo")
- So you could still get the flu even if you get the shot
- If Peter even starts getting a fever, he will *assume* its the flu and take the tamiflu

2 Amantadine + Aleve

- Amantadine is for treating the regular, garden variety, pain in the ass cold
- The protocol is…
    - Take the given dose of amantadine in combination with two Aleve a day, for five days
    - Start taking it the second you have the onset of symptoms
- The Aleve is for SIRS (Systemic Inflammatory Response Syndrome) **which is why you feel bad with a cold**
- SIRS is the body's immune response to:
    - The toxins that are being released by the virus, and
    - more importantly, the immune cells themselves actually gearing up each other

> "I don't think the data would support the use of amantadine [for the common cold], but it's a very well tolerated drug. If it gives me some placebo effect, I'll take it."

How have your thoughts changed on NAD precursors, and also on metformin, in the past year or so? [30:30]

NAD precursors: Something Peter is more *bullish* on today versus a year ago

- A year ago I was completely dismissive of NAD precursors such as nicotinamide riboside (NR) and NMN
- Thought it was just a great marketing story
- Anecdotally people would frequently tell Peter they have more energy, better sleep, etc.
- But Peter attributed at least some of those benefits to a placebo effect
- That said, Peter is still very convinced that **intravenous NAD** is nonsense (mostly just a scam)
- Today, Peter says that some of the oral NAD precursors (NR, NMN) may actually have some efficacy
- This is despite the fact that Josh Ribinowitz's group published a paper showing how most of that oral NR is actually being taken up in the liver
- But we still don't know how much goes into the liver
- And it's also unknown as to whether there is an upside to the liver itself increasing its concentration of NAD

⇒ For more on NAD

- Episodes of The Drive with David Sinclair episode (Part 1 and Part 2)
- Episode of The Drive with Chris Masterjohn

Metformin: Slightly more bearish on Metformin for longevity in otherwise "healthy" people

- Today, Peter says he's a "*bit more tempered in my enthusiasm around metformin use in the healthiest of people*"
- He remains incredibly optimistic about the use of metformin in people who are metabolically anything other than very healthy
- But when you take that tiny subset of people who are like 9 out of 10 in terms of health… "*it's possible metformin is not helping them, and it's even possible that metformin is detracting a little bit.*"

What are your thoughts on "fat burning" zones for cardio workouts? — A lesson in relative vs. absolute fat combustion [34:15]

==> For more on this topic, check out Peter's blog post (and lecture) from 2013

***Absolute* versus *relative* fat combustion**

- The respiratory quotient (RQ) is used to measure the **relative amount** of fat oxidation versus glucose oxidation

- To do this:
  - Put someone on a treadmill
  - Put a mask over their mouth (and plug their nose) that is measuring
    - i) the oxygen leaving (computer subtracts that from the oxygen coming in) and this calc is called the VO2
    - ii) The CO2 exiting (CO2 going in is effectively zero) so we now know the VCO2
- The ratio of these things—VCO2 to VO2—is called respiratory quotient (RQ)
- And that ratio tells you *where your fuel is coming from*

The RQ range

- When that ratio is in the 0.7 range, virtually all of your energy is coming from **fat**
  Why? ⇒ It's just stoichiometry… it's just telling you that when your CO2 production is only 70% of your oxygen consumption so you are producing long hydrocarbons
- When the ratio reaches 1.0, what that means is your VCO2 is equal to your VO2
  - (your production of carbon dioxide is equal to your consumption of oxygen)
  - In other words, all your energy is coming from glucose and nothing from long hydrocarbons (i.e., fat)
- W*hat does this tell you*?
  It tells you your RELATIVE amount of fat versus glucose

At 60% of your max heart rate…

- A reasonably fit person is still closer to 0.7 versus the 1.0
- However, a highly insulin resistant person, who is both de-conditioned and highly metabolically inefficient, will have a very high respiratory quotient even (An RQ north of 0.9!)
  - That person is never going to get well without **fasting and exercise**
  - You just have to be able to **drive glycogen depletion**

Let's talk about ABSOLUTE fat combustion

To understand absolute fat combustion, you must know the *absolute* level of VO2, and the *absolute* level of VCO2.

- To understand total energy expenditure, we can use the Weir equation
- Energy expenditure equals = 3.94 x VO2 + 1.11 x VCO2

How the testing process works

- During a test, the computer can spit out your VO2 and VCO2 every 15 seconds onto a spreadsheet
- The computer will spit out at 15 second intervals into an excel spreadsheet
- We then use that to determine **total energy expenditure**
- Then you look at the **ratio of VO2 to VCO2** to determine how much of my *energy came from fat oxidation versus glucose oxidation*

Results from Peter's self testing on a bicycle:

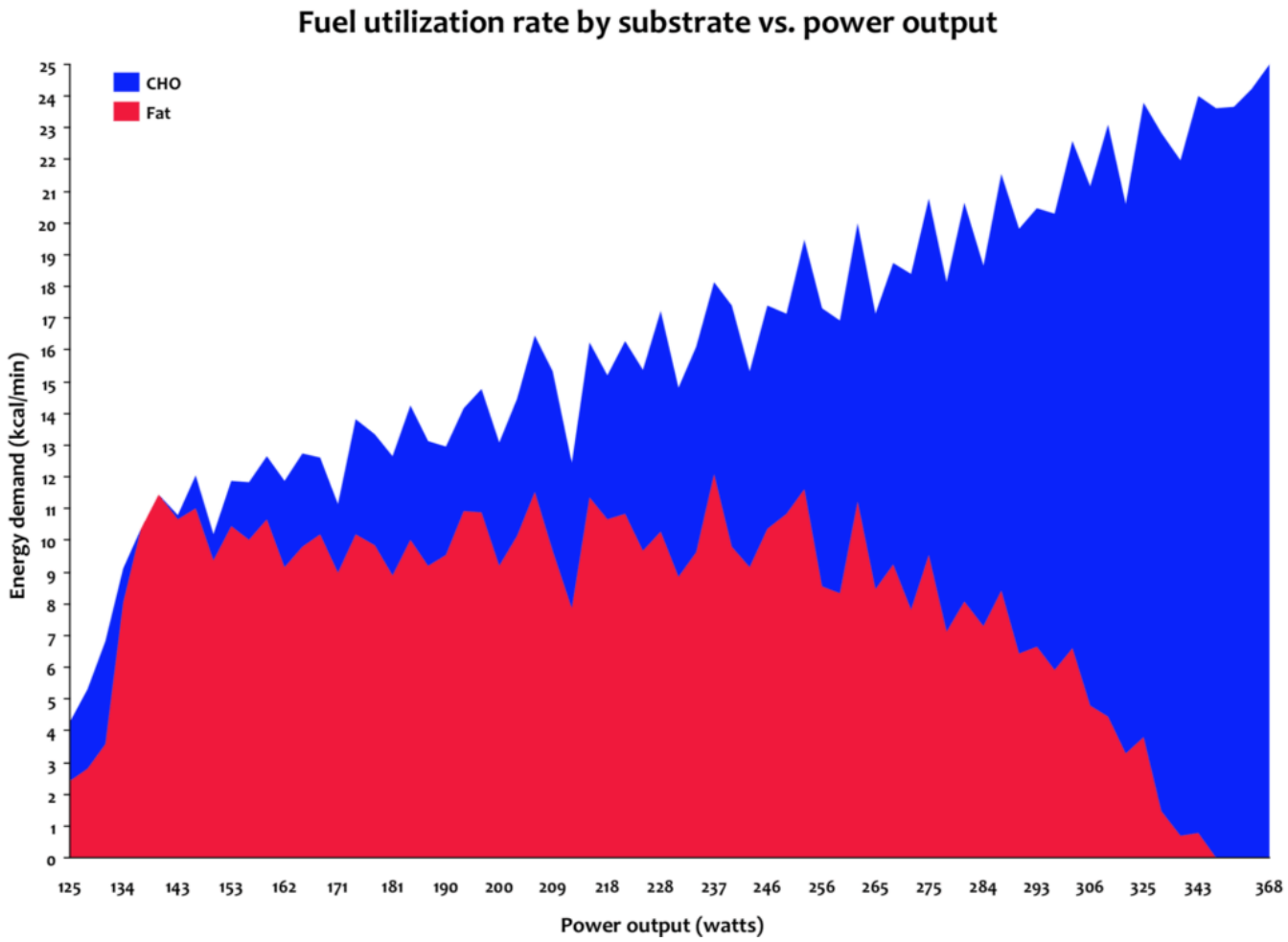


Figure 1. Results from Peter's VO2 max test showing fuel utilization by substrate vs. power output.

Results from the test show

- As your energy level goes up…
- Your total calories expended per minute goes up
- But your ***relative*** contribution of fat goes down
- But the ***absolute*** value of fat peaks somewhere in the middle (and then comes down)
- Where your absolute fat oxidation is peaking is a function of i) your fitness, and ii) your fuel (food)
    - On a ketogenic diet, for example, Peter's fat oxidation will peak at about 1.6 to 1.8 grams per minute (higher than when not on a keto diet)

So…*is training at 60% of max heart rate ideal for burning fat?*

- At 60% of your maximum heart rate…
- you may be burning your *highest percentage of fat*
- but you are absolutely not even coming close to burning your *highest amount of fat*
- Looking at percentage of fat oxidation can lead to ridiculous ideas such as "you burn more fat while sleeping and than while exercising"

*Really important point = **Exercising at 60% of maximum heart rate is *too low in intensity***

- This is considered being in “zone 1”
- It’s not harmful in any way, shape, or form
- It’s just not the best use of your time
- **Zone 2** is a better place to be

Heart rate zones

- Zones are based on heart rate
- Divided into five zones
- What is Zone 2?
    - 75 to 80% of maximum heart rate
    - So with a max HR of 180, your zone 2 would be a HR of 135-144
    - This is the **sweet spot to be spending your “cardio time”**
    - You are right at the threshold of the mitochondria
    - Just being on the cusp of really crossing over into anaerobic work.
    - *The fitter you get*, the higher that number gets
    - Also, it might be that when you’re starting out, 60% of your max HR is indeed your zone 2

Tip of the day

- You can use *subjective level of exhaustion* to estimate zone 2
- In zone 2, you could carry out a basic conversation but it is a little uncomfortable
- Talking is strained enough that the person you’re talking to knows you’re exercising
- Above zone 2, it’s too uncomfortable to have a conversation
- Below zone 2, you can be “chatty Cathy”
- Your goal while doing cardio is to find that zone 2 either using a HR monitor or the “conversation” test

What mental models do you use and how do you go about solving problems and approaching difficult questions? [49:00]

- Peter is going to “punt” this question for now
- He wants to get Shane Parrish on the podcast to discuss this topic
- Check out this NY Times article on Shane

Creatine supplementation—Yay or nay? Why? [49:30]

What is creatine?

> Creatine is this molecule in our body that is a phosphate donor

What’s phosphate?

- ATP is a phosphate donor

- ATP has three phosphates
- Anytime you need energy, you're basically turning ATP into ADP…it's the liberation of the third P that is the energy that we use to do things
- We breathe to provide oxygen to the electron transport chain to generate ATP from ADP

We actually have *three* energy systems (not two)

- Most people think we have these two energy systems
    - Aerobics, where we make ATP in the presence of sufficient oxygen at a low enough rate
    - Anaerobic when we can make ATP, once we've exceeded the level of sufficient cellular oxygen using pyruvate and turning it into lactate
- The *third* energy system called the **creatine phosphate system**
    - We use creatine as a direct donor of phosphate
    - In an all out energy burst, this is the energy system we are using for the first 3-4 seconds

History of creatine supplementation

- About 30 years ago, it became really popular for athletes to supplementing with creatine phosphate
- At the beginning, it was common to "load" so 20 g per day for 5 days, then do a maintenance phase at 5 g per day (or something close to that)
- You would gain a ton of weight
- You definitely got stronger
- It was a legitimate performance enhancing supplement

Today, we have learned…

- Creatine *phosphate* provides no benefit… you can just use the creatine *monohydrate* and you'll pick up the phosphates in your body
- The loading phase is unnecessary

Current recommended way to take creatine?

- Take 5 g per day of creatine monohydrate
- *Peter's preferred brand: Biosteel Creatine Monohydrate

What to expect when taking it?

- Gain some weight (mostly water weight)
- Some increase in strength

Who would it help?

- Peter wonders is creatine would help with performance in his tabatas on the AirDyne bike

- They decide probably not since he would burn through the creatine so quickly
    Tabata tangent…
    - we really have no ability to go “all out” even for just 20 seconds
    - Even if you think you are going 100%, you’re actually pacing yourself
    - Check out Peter’s tabata protocol in AMA #5
- Sprinters? ⇒ maybe
- Competitive cyclist? ⇒ probably not, because by the time you are “sprinting” you are at the end stages of the race and you’ve already used up that creatine
- Athletes looking for strength and performance gains? ⇒ probably
- Average Joe looking to better results in the gym? ⇒ A coin toss
- Chris Masterjohn says creatine might even help marathon runners

Is it safe?

If you’re using a pure product (like Biosteel), it is incredibly safe

⇒ For more on creatine, check out Peter’s interview with Chris Masterjohn starting at 2:10:15

§

Selected Links / Related Material

The HBO documentary about Theranos: The Inventor: Out for Blood in Silicon Valley | (hbo.com) [2:00]

The book detailing the story of Theranos: Bad Blood: Secrets and Lies in a Silicon Valley Startup by John Carreyrou | (amazon.com) [2:00]

The WSJ article by John Carreyrou that first revealed the shenanigans inside Theranos: Hot Startup Theranos Has Struggled With Its Blood-Test Technology | John Carreyrou (wsj.com) [7:00]

Book Peter recently finished: The Coddling of the American Mind: How Good Intentions and Bad Ideas Are Setting Up a Generation for Failure by Jonathan Haidt and Greg Lukianoff | (amazon.com) [21:30]

Story about overly PC culture forcing the dean of students to resign at Claremont McKenna College: Dean at Claremont McKenna College Resigns Amid Protests | Ian Lovett (nytimes.com) [22:00]

Sam Harris podcast episode where he discusses the forced resignation of the dean of students at Claremont McKenna College: #137 Safe Space-A Conversation with Jonathan Haidt | (samharris.org) [22:00]

The last book that Peter actually bought the paper copy so he could take notes: The Second Mountain: The Quest for a Moral Life by David Brooks | (amazon.com) [23:50]

Peter’s Sunday email about this book: David Brooks and the quest for a moral life

Analogy Peter used to describe how Peter almost need a crystal ball to see how their future will turn out if they don't change their actions/behavior: A Christmas Carol | (wikipedia.org)

What Peter takes if he feels the flu coming on: Tamiflu | (goodrx.com) [27:45]

What Peter takes if he feels the common cold coming on: Amantadine | (goodrx.com) [28:45]

> Note he takes this in tandem with Aleve

Josh Ribinowitz's paper showing how most of that oral NR is actually being taken up in the liver: Quantitative Analysis of NAD Synthesis-Breakdown Fluxes (Liu et al., 2018) [31:30]

For more on NAD precursors: [32:00]

- *Episodes of The Drive with David Sinclair*:
  - #27 – David Sinclair, Ph.D.: Slowing aging – sirtuins, NAD, and the epigenetics of aging
  - #70 – David Sinclair, Ph.D.: How cellular reprogramming could slow our aging clock (and the latest research on NAD)
- *Episode of The Drive with Chris Masterjohn*: #46 – Chris Masterjohn, Ph.D.: Navigating the many pathways to health and disease – NAD and sirtuins, methylation, MTHFR and COMT, choline deficiency and NAFLD, TMAO, creatine and more

Peter's blog post on RQ, ketosis, and fuel utilization during exercise: My Quantified Self, Part I

NY Times article about mental models by Shane Parrish: How a Former Canadian Spy Helps Wall Street Mavens Think Smarter | Shane Parrish (nytimes.com) [49:00]

Peter's tabata protocol: #50 – AMA #5: calcium scores, centenarian olympics, exercise, muscle glycogen, keto, and more

Paper suggesting to take 5 g per day of creatine monohydrate: International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine (Kreider et al., 2017) [54:00]

Peter's preferred brand of creatine monohydrate: Biosteel Creatine Monohydrate | (biosteel.com) [54:15]

For more on creatine, check out Peter's interview with Chris Masterjohn (starting at 2:10:15): #46 – Chris Masterjohn, Ph.D.: Navigating the many pathways to health and disease – NAD and sirtuins, methylation, MTHFR and COMT, choline deficiency and NAFLD, TMAO, creatine and more

§

People Mentioned

- Tom Brady (a decent football player) [1:45]
- Elizabeth Holmes (founder of Theranos) [4:45, 5:45, 6:00, 6:30, 7:30, 8:15, 8:45]
- Mark Zuckerberg (second fiddle speaker to Elizabeth Holmes at charity event) [5:45]
- Tim Ferriss (invited Peter to charity event where he reconnected with Elizabeth Holmes) [6:00]
- John Carreyrou (wrote the story that revealed the fraud at Theranos) [7:00]
- Bradley Cooper (a handsome man) [8:00]
- Adolf Hitler (bad guy) [8:15]
- Robin Hood [15:15]
- Rob Lustig [21:30]
- Jonathan Haidt (author of Coddling of the American Mind) [21:45]
- Sam Harris (podcast episode about the dean of students being forced to resign at Claremont McKenna College) [22:15]
- David Brooks (Canadian-born American political and cultural commentator who writes for The New York Times) [23:45]
- Galileo Galilei (Italian astronomer, physicist and engineer) [26:30]
- Charles Dickens (author of Christmas Carol) [26:45]
- Ebenezer Scrooge (protagonist in A Christmas Carol) [27:15]
- Josh Ribinowitz (paper showing most of oral NR is actually being taken up in the liver) [31:30]
- David Sinclair (NAD) [32:00, 32:30]
- Chris Masterjohn (NAD, creatine) [32:00]
- Travis Denson (show notes contributor for The Drive podcast) [41:00]
- Andrew Coggan (zones for cyclists) [45:30]
- Shane Parrish (mental models) [49:15]
- Usain Bolt (sprinter) [53:30]

§