Welcome to the Huberman Lab Podcast where we discuss science and science-based tools for everyday life.
I'm Andrew Huberman and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine.
Today marks the first Journal Club episode between myself and Dr. Peter Atia.
For any of you that are not familiar with Dr. Peter Atia, he is a medical doctor and MD who is an expert in all aspects of health and lifespan.
He is the author of a best-selling book entitled Outlive, which is a phenomenal resource on all things health span and lifespan.
And he is the host of the very popular podcast The Drive where he interviews various experts in all domains of medicine and scientists as well.
Today, Peter and I hold our first online collaborative Journal Club.
For those of you that aren't familiar with what a Journal Club is, a Journal Club is a common practice in graduate school and medical school
whereby students get together to discuss one or two papers to critique those papers
and to really compare their own conclusions of those papers with the conclusions of the authors and to highlight any key takeaways.
Peter and I have been wanting to do a Journal Club together for a very long time
and we decided to do that Journal Club and to record it for you.
So today you will be sitting in on the first Huberman Atia Journal Club.
By the way, it could just have easily been called the Atia Huberman Journal Club.
And we will discuss two papers.
First, Peter is going to discuss a paper on metformin, which is a drug that many people are interested in for its potential role in longevity.
I want to highlight potential there.
He's going to compare that paper to previous findings on metformin.
And by the end of that discussion, he will advise as to whether or not he himself would take metformin
and whether or not other people might be well advised or ill advised to take metformin based on the data in that paper and at this time.
Then I present a paper which is about the placebo effect.
I have to imagine that most of you have heard of the placebo effect.
But what's interesting about the paper that we discussed today is that it shows that the placebo effect can actually follow a dose response.
So it's not just all or none.
It actually is the case that you can scale the degree of placebo effect depending on whether or not you're thinking you're taking low doses, moderate doses or high doses of a particular drug.
And the particular drug that's discussed in the paper that I cover is nicotine.
So for those of you that are interested in cognitive enhancement by way of pharmacology or frankly for people who are simply interested in how our beliefs can shape our physiology,
I think you'll find that discussion to be very interesting.
So by the end of today's episode, you will not only have learned about two novel sets of findings, one in the realm of longevity as it relates to metformin and another in the realm of neurobiology and

placebos or placebo effects,
but you will also learn how a journal club is conducted.
I think you'll see in observing how we parse these papers and discuss them, even arguing in them at times,
that what scientists and clinicians do is they take a look at the existing peer-reviewed research
and they look at that peer-reviewed research with a fresh eye asking,
does this paper really show what it claims to show or not?
And in some cases, the answer is yes.
And in other cases, the answer is no.
What I know is for certain is that by the end of today's episode, you will learn a lot of science.
You'll learn a lot about health practices, some of which you may want to apply or avoid.
And you'll learn a lot about how science and medicine is carried out.
Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford.
It is, however, part of my desire and effort to bring zero cost to consumer information about science and science-related tools to the general public.
In keeping with that theme, I'd like to thank the sponsors of today's podcast.
Our first sponsor is Helix Sleep.
Helix Sleep makes customized mattresses to give you the best possible night's sleep.
Now, sleep is the foundation of mental health, physical health, and performance.
When we are sleeping well and enough, mental health, physical health, and performance all stand to be at their best.
One of the key things to getting a great night's sleep is to make sure that your mattress is tailored to your unique sleep needs.
Helix Sleep has a brief two-minute quiz that if you go to their website, you take that quiz and answer questions,
such as, do you tend to sleep on your back, your side of your stomach, do you tend to run hot or cold in the middle of the night?
Maybe you don't know the answers to those questions, and that's fine.
At the end of that two-minute quiz, they will match you to a mattress that's ideal for your sleep needs.
I sleep on the Dusk DUSK mattress, and when I started sleeping on a Dusk mattress about two years ago,
my sleep immediately improved.
So if you're interested in upgrading your mattress, go to helixsleep.com.
Take their two-minute sleep quiz, and they'll match you to a customized mattress for you,
and you'll get up to $350 off any mattress order and two free pillows.
Again, if interested, go to helixsleep.com.
for up to $350 off and two free pillows.
Today's episode is also brought to us by Levels.
Levels is a program that lets you see how different foods and behaviors affect your health by giving you real-time feedback
using a continuous glucose monitor.

One of the most important factors impacting your immediate and long-term health
is the way that your body manages its blood glucose, or sometimes referred to as blood sugar levels.
To maintain energy and focus throughout the day, you want to keep your blood glucose steady
without big spikes or dips.
Using Levels, you can monitor how different types of foods and different food combinations,
as well as food timing and things like exercise, combine to impact your blood glucose levels.
I started using Levels a little over a year ago, and it gave me a lot of insight into how specific foods were spiking my blood sugar
and then leaving me feeling tired for several hours afterwards,
as well as how the spacing of exercise and my meals was impacting my overall energy.
And in doing so, it really allowed me to optimize how I eat, what I eat, when I exercise, and so on,
such that my blood glucose levels and energy levels are stable throughout the day.
If you're interested in learning more about Levels and trying a continuous glucose monitor yourself,
go to levels.link.huberman.
Right now, Levels is offering an additional two free months of membership.
Again, that's levels.link.link.huberman to get two free months of membership.
And now, for my Journal Club discussion with Dr. Peter Atia.
Peter, so good to have you here.
So great to be here, my friend.
This is something that you and I have been wanting to do for a while,
and it's basically something that we do all the time,
which is to peruse the literature and find papers that we are excited about for whatever reason.
And oftentimes, that will lead to a text dialogue or a phone call or both.
But this time, we've opted to try talking about these papers that we find particularly exciting in real time
for the first time as this podcast format.
First of all, so that people can get some sense of why we're so excited about these papers.
We do feel that people should know about these findings.
And second of all, that it's an opportunity for people to learn how to dissect information
and think about the papers they hear about in the news,
the papers they might download from PubMed if they're inclined,
also just to start thinking like scientists and clinicians
and get a better sense of what it looks like to pick through a paper,
the good, the bad, and the ugly.
So we're flying a little blind here, which is fun.
I'm definitely excited for all the above reasons.
Yeah, no, this is you and I have been talking about this for some time.
And actually, we used to run a journal club inside the practice
where once a month, one person would just pick a paper
and you would go through it in kind of a formal journal club presentation.
We've gotten away from it for the last year just because we've been a little stretched then.
I think it's something we need to resume because it's a great way to learn and it's a skill.
People probably ask you all the time because I know I get asked all the time,

hey, what are the dos and don'ts of interpreting scientific papers?
Is it enough to just read the abstract?
No.
And usually the answer is, well, no.
But the how to is tougher.
And I think the two papers we've chosen today illustrate two opposite ends of the spectrum.
You're going to obviously talk about something that we're going to probably get into
the technical nature of the assays, the limitations, et cetera.
The paper, ultimately, I've chosen to present, although I apologize,
I'm surprising you with this up until a few minutes ago,
is actually a very straightforward, simple epidemiologic paper that I think has important
significance.
I had originally gone down the rabbit hole on a much more nuanced paper
about ATP binding cassettes in cholesterol absorption.
But ultimately, I thought this one might be more interesting to a broader audience.
By the way, I got to tell you this funny story.
So I had a dream last night about you.
And in this dream, you were obsessed with making this certain drink that was like your elixir.
And it had all of these crazy ingredients in it.
Supplements.
Tons of supplements in it.
But the one thing I remembered when I woke up, because I forgot most of them,
I was really trying so hard to remember them.
One thing that you had in it was dew.
Like you had to collect a certain amount of dew off the leaves every morning to put into this drink.
It was like just sounds like something that I would do.
And so, but here's the best part.
You had you had like a thermos of this stuff that had to be with you everywhere.
And all of your clothing had to be tailored with a special pocket that you could put the thermos into
so that you were never without the special Andrew drink.
And again, you know how dreams when you're having them seem so logical and real.
And when you wake up and you're like, that doesn't even make sense.
Like, why would he want the thermos in his shirt like that?
I would warm it up like, you know, all these, but boy, it was a realistic dream.
And there were lots of things in it, including dew, special dew off the leaves every morning.
I love it.
Well, it's not that far from reality.
I'm a big fan of Yerba mate.
I'm drinking it right now.
In fact, in its many forms, usually the loose leaf.
I don't tend to drink it out of the gourd.
My dad's Argentine.
So that's where I picked it up.

I started drinking it when I was like five years old or younger, which I don't recommend people do.
It's heavily caffeinated.
Don't drink the smoked versions either, folks.
I think that was potentially carcinogenic.
But this thing that you describe of carrying around the thermos close to the body, if you are ever in Uruguay
or if you ever spot grown men in a restaurant anywhere in the world carrying a thermos with them and to their meals and hugging it close, chances are they're Uruguayan.
And they're drinking Yerba mate.
They drink it usually after their meals.
It's supposed to be good for your digestion.
So it's not that far from reality.
I don't carry the thermos, but I do drink mate every day.
And I'm going to start collecting dew off the leaves.
Just a few drops every morning.
Some other time we can talk about dreams.
Recently, I've been doing some dream exploration.
I've had some absolutely transformative dreams for the first time in my life.
One dream in particular that allowed me to feel something I've never felt before
and has catalyzed a large number of important decisions
in a way that no other experience, waking or sleep, has ever impacted me.
And this was drug-free, et cetera.
And do you think you could have had that dream?
We don't have to get into it if you don't want to talk about it now.
But was there a lot of work you had to do to prepare for that dream to have taken place?
Oh, yes. Yeah.
At least 18 months of intensive analysis type work with a very skilled psychiatrist.
But I wasn't trying to seed the dream.
It was just I was at a sticking point with a certain process in my life.
And then I was taking a walk while waking and realized that my brain,
my subconscious, was going to keep working on this.
I just decided it's going to keep working on it.
And then two nights later, I traveled to a meeting in Aspen
and I had the most profound dream ever where I was able to sense something and feel something I've always wanted to feel as so real within the dream, woke up, knew it was a dream
and realized this is what people close to me that I respect have been talking about.
But I was able to feel it and therefore I can actually access this in my waking life.
It was absolutely transformative for me.
Anyway, sometime I can share more details with you or the audience.
But for now, we should talk about these papers.
Very well.
Who should go first?
I'm happy to go first.

This one's this one's this is a pretty straightforward paper.
So we're going to talk about a paper titled reassessing the evidence of a survival advantage in type two diabetics treated with metformin compared with controls without diabetes, a retrospective cohort study.
This is by Matthew Thomas Keys and colleagues.
This was published last fall.
Why is this paper important?
So this paper is important because in 2014, Bannister published a paper that I think in many ways kind of got the world very excited about metformin.
So this is almost 10 years ago.
And I'm sure many people have heard about this paper, even if they're not familiar with it, but they've heard the concept of the paper.
And in many ways, it's the paper that has led to the excitement around the potential for gyro protection with metformin.
And I should probably just define for the audience what gyro protection means.
And probably also sorry to interrupt what metformin is just for the uninformed.
That's a great point.
So I'll start with the with the latter.
So metformin is a drug that has been used for many years.
Depends, you know, where it was first approved, I think was in Europe.
But, you know, call it directionally 50 plus years of use as a first line agent for patients with type two diabetes.
In the US, maybe 40 plus years.
So this is a drug that's been around forever, trade name, Glucophage or brand name.
And but again, it's, you know, it's a generic drug today.
The mechanism by which metformin works is debated hotly.
But what I think is not debated is the immediate thing that metformin does, which is it inhibits complex one of the mitochondria.
So again, maybe just taking a step back.
So the mitochondria as everybody thinks of those as the cellular engine for making ATP.
So the most efficient way that we make ATP is through oxidative phosphorylation, where we take either fatty acid pieces or a breakdown product of glucose.
Once it's partially metabolized to pyruvate, we put that into an electron transport chain.
And we basically trade chemical energy for electrons that can then be used to make phosphates onto ADP.
So it's, you know, you think of everything you do.
Eating is taking the chemical energy and food, taking the energy that's in those bonds, making electrical energy in the mitochondria.
Those electrons pump a gradient that allow you to make ATP.
To give a sense of how primal and important this is, if you block that process completely, you die.
So everybody's probably heard of cyanide, right?
Cyanide is something that is incredibly toxic, even at the smallest doses.
Cyanide is a complete blocker of this process.

And if my memory serves me correctly, I think it blocks complex four of the mitochondria.
I don't know if you recall if it complex three or complex four.
I know a lot about toxins that impact the nervous system, but I don't know a lot about poisons.
But if ever you want to have some fun, we can talk about all the dangerous stuff that animals make and insects make and how they kill you.
Yeah, like detrototoxin and all these things that block sodium channels.
Alpha-lactrotoxin, bungrotox.
I really geek out on this stuff because it allows me to talk about neuroscience, animals, and scary stuff.
It's like combines it.
So we could do that sometime for fun, maybe at the end if we have a few moments.
So, you know, something like cyanide that is a very potent inhibitor of this electron transport chain will kill you instantly.
People understand that, of course, a drop of cyanide and you would be dead literally instantaneously.
So Metformin works at the first of those complexes.
I believe there are four of my memory serves correctly for electron transport chain complexes.
But of course, it's not a complete inhibition of it.
It's just kind of a weak blocker of that.
And the net effect of that is what?
So the net effect of that is that it changes the ratio of adenosine monophosphate to adenosine diphosphate.
What's less clear is why does that have a benefit in diabetics?
Because what it unambiguously does is reduces the amount of glucose that the liver puts out.
So hepatic glucose output is one of the fundamental problems that's happening in type two diabetes.
You may recall, I think we talked about this even on previous podcast.
You and I sitting here with normal blood sugar have about five grams of glucose in our total circulation.
That's it.
Let's think about how quickly the brain will go through that within minutes.
So the only thing that keeps us alive is our liver's ability to titrate out glucose.
And if it puts out too much, for example, if the glucose level was consistently two teaspoons, you would have type two diabetes.
So the difference between being metabolically healthy and having profound type two diabetes is one teaspoon of glucose in your bloodstream.
So the ability of the liver to tamp down on high glucose output is important.
Metformin seems to do that.
So can I just ask one question?
Is it fair to provide this overly simplified summary of the biochemistry, which is that when we eat, the food is broken down,
but the breaking of bonds creates energy that then our cells can use in the form of ATP.
And the mitochondria are central to that process.
And that metformin is partially short circuiting the energy production process.
And so even though we are eating, when we have metformin in our system, presumably there is

going to be less net glucose.
The bonds are going to be broken down.
We're chewing, we're digesting, but less of that is turned into blood sugar, glucose.
Well, sort of.
I mean, it's not depriving you of ultimately storing that energy.
What it's doing is changing the way the body partitions fuel.
That's probably a better way to think about it to be a little bit more accurate.
So, for example, like it's not depriving you of the calories that are in that glucose.
That would be, you know, fantastic.
But that was the that was the cholesterol.
Remember the cholesterol from the 90s.
Alestra folks, for those of you who don't remember.
By the way, if you ever ate the stuff, you'd remember because it was a fat that was not easily digested.
It had sort of in sort of analogous to plant fiber or something like that.
So it was being put into potato chips and whatnot.
And the idea was that people would would simply excrete it.
And I don't know what happened except that people got a lot of stomach aches.
And everyone got a fatter in the world.
We know that.
The anal seepage is what really did that product.
Anal seepage.
Only a physician, because after all, Peter's a clinician, a physician and MD and I'm not, could find it an appropriate term to describe what this is.
Yeah.
When you have that much fat malabsorption, you start to have accidents.
Wow.
And so that did away with that product.
Right.
It was either that or the diaper industry was going to really take off.
Okay.
That's why you don't hear about Alestra.
That's right.
So we've got this drug.
We've got this drug metformin.
It's considered a perfect first line agent for people with type two diabetes.
So again, what's happening when you have type two diabetes, the primary insult probably occurs in the muscles and it is insulin resistance.
Everybody hears that term.
What does it mean?
Insulin is a peptide.
It binds to a receptor on a cell.
So let's just talk about it through the lens of the muscle because the muscle is responsible for most

glucose disposal.
It gets glucose out of the circulation.
High glucose is toxic.
We have to put it away and we want to put most of it into our muscles.
That's where we store 75 to 80% of it.
When insulin binds to the insulin receptor, tyrosine kinase is triggered inside.
So just ignore all that, but a chemical reaction takes place inside the cell that leads to a phosphorylation.
So ATP donates a phosphate group and a transporter, just think of like a little tunnel, like a little straw goes up through the level of the cell.
And now glucose can freely flow in.
So I'm sure you've talked a lot about this with your audience.
Things that move against gradients need pumps to move them.
Things that move with gradients don't.
Glucose is moving with its gradient into the cell.
It doesn't need active transport, but it does need the transporter put there.
Glucose requires the energy.
That's the job of insulin.
By the way, I did not know that.
I mean, I certainly know active and passive transport as it relates to like neurotransmitter and ion flow.
But I'd never heard that when insulin binds to a cell that literally a little straw is placed into the membrane of the cell.
Yeah, glucose doesn't need a pump to move it in because there's much more glucose outside the cell than inside.
So it's just, but the energy required is to move the straw up to the cell.
So biology is so cool.
Yeah, it is.
So what happens is as and Gerald Shulman at Yale did the best work on elucidating this as the intramuscular fat increases.
And by intramuscular, I mean intracellular fat, triacyl and diacylglycerides accumulate in a muscle cell.
That signal gets interrupted.
And all of a sudden I'm making these numbers up.
You used to need two units of insulin to trigger the little transporter.
Now you need three and then you need four and then you need five.
You need more and more insulin to get the thing up.
That is the definition of insulin resistance.
The cell is becoming resistant to the effect of insulin.
And therefore the early mark of insulin resistance, the canary in the coal mine is not an increase in glucose.
It's an increase in insulin.
So normal glycemia with hyperinsulinemia, especially post-prandial, meaning after you eat

hyperinsulinemia,
is the thing that tells you, hey, you're five, ten years away from this being a real problem.
So fast forward many steps down the line.
Someone with type two diabetes has long passed that system.
Now not only are they insulin resistant where they just need a boatload of insulin,
which is made by the pancreas, to get glucose out of the circulation.
But now that system's not even working well.
And now they're not getting glucose into the cell.
So now their glucose level is elevated.
And even though it's continually being chewed up and used up because, again, the brain alone would account for most of that glucose disposal,
the liver is now becoming insulin resistant as well.
And now the liver isn't able to regulate how much glucose to put into circulation and it's overdoing it.
So now you have too much glucose being pumped into the circulation by the liver
and you have the muscles that can't dispose of it.
And it's really a vicious, brutal cascade because the same problem of fat accumulating in the muscle is now starting to happen in the pancreas.
And now the relatively few cells in the pancreas called beta cells that make insulin
are undergoing inflammation due to the fat accumulation within the pancreas itself.
And so now the thing that you need to make more insulin is less effective at making insulin.
So ultimately, way, way, way down the line, a person with type 2 diabetes might actually even require insulin exogenously.
Could you share with us a few of the causes of type 2 diabetes of insulin resistance?
I mean, one, it sounds like is accumulating too much fat.
Yeah, so energy imbalance would be an enormous one.
Inactivity or insufficient activity is probably the single most important.
Gerald Shulman was running clinical trials at Yale.
They would be recruiting undergrads to study, obviously, because you're typically recruiting young people.
And they would be doing these very detailed mechanistic studies where they would require actual tissue biopsies.
So you're going to biopsy somebody's quadriceps and actually look at what's happening in the muscle.
Well, I remember him telling me this when I interviewed him on my podcast.
He said, the most important criteria of the people we interviewed is because they were still lean.
These weren't people that were overweight, but they had to be inactive.
You couldn't have active people in these studies.
So exercising is one of the most important things you're going to do to ward off insulin resistance.
But there are other things that can cause insulin resistance.
Sleep deprivation has a profound impact on insulin resistance.
I think we probably talked about this previously.
But if you notice some very elegant mechanistic studies where you sleep deprived people,

you let them only sleep for four hours for a week, you'll reduce their glucose disposal by about half. Which is, I mean, that's a staggering amount.
You're basically inducing profound insulin resistance in just a week of sleep deprivation.
Hypercortisolemia is another factor and then obviously energy imbalance.
So when you're accumulating excess energy, when you're getting fatter,
if you start spilling that fat outside of the subcutaneous fat cells into the muscle, into the liver, into the pancreas,
all those things are exacerbating it.
Got it.
Okay.
So enter metformin, first line drug.
So most of the drugs, so every drug you give a person with type two diabetes is trying to address part of this chain.
So some of the drugs tell you to make more insulin.
That's one of the strategies.
So here are drugs like sulfonylureas.
They tell the body make more insulin.
Other drugs like insulin just give you more of the insulin thing.
Metformin tackles the problem elsewhere.
It tamps down glucose by addressing the hypatic glucose output channel.
GLP1 agonists are another drug.
They increase insulin sensitivity, initially causing you to also make more insulin.
So that's osempic.
Yes.
Yeah.
And is it true that berberine is more or less the poor man's metformin?
Yeah.
It's from a tree bark.
It just happens to have the same properties of reducing mTOR and reducing blood glucose.
Yeah.
And metformin, by the way, occurs from a lilac plant in France.
Like that's where it was discovered.
So metformin is also based on a substance found in nature.
So you need a prescription for metformin.
You don't need a prescription for berberine.
Correct.
But yeah, we can talk about berberine a little bit later.
I had a couple great experiences with berberine and a couple bad experiences.
Interesting.
Berberine.
Yeah.
So maybe taking one step back from this.
In 2011, I became very interested in metformin personally, just reading about it, obsessing

over it, and just somehow decided like I should be taking this.
So I actually began taking metformin.
I still remember exactly when I started.
I started it in May of 2011, and I realized that because I was on a trip with a bunch of buddies, we went to the Berkshire Hathaway shareholder meeting, which is the Buffett shareholder meeting.
And it's kind of like a fun thing to do.
And I remember being so sick the whole time because I didn't titrate up the dose of metformin.
I just went straight to two grams a day, which is kind of like the full dose.
And we went to this-
Is that characteristic of your approach to things?
Yes.
I think that's safe to say.
Next time, I'll give you a thermos of this dew that I collect in the morning.
Oh, really?
Yeah.
So I remember being so sick that the whole time we were in Nebraska or Omaha, I guess, I couldn't, we went to Dairy Queen because you do all the Buffett things when you're there, right?
Like, I couldn't have an ice cream at Dairy Queen.
You couldn't?
I mean, I couldn't.
I'm so nauseous.
Oh, because I would say if you've got metformin in your system, you're going to buffer glucose.
You could have four ice cream cones and it probably would go on.
I couldn't keep anything down.
I mean, I was so nauseous.
So clearly metformin has this side effect initially, which is a little bit of appetite suppression.
But regardless, that's the story on metformin.
There are a lot of reasons I was interested in it.
I wasn't thinking true giro-protection.
That term wasn't in my vernacular at the time.
But what I was thinking is, hey, this is going to help you buffer glucose better.
It's got to be better.
And this was sort of my first foray into self-experimentation.
Do you want to define giro-protection?
Yeah.
Yeah.
Geriatric giro.
Yeah.
So, yeah, giro from geriatric old protection, so protection from aging.
And when we talk about a drug like metformin or rapamycin or even NAD, NR, these things,

the idea is we're talking about them as giro-protective to signal that they are drugs that are not targeting a specific disease of aging.
For example, a PCSK9 inhibitor is sort of giro-protective.
But it's targeting one specific pathway, which is cardiovascular disease and dyslipidemia.
Whereas the idea is a giro-protective agent would target hallmarks of aging.
There are nine hallmarks of aging.
Please don't ask me to recite them.
I've never been able to get all nine straight.
But people know what we're talking about, right?
So decreased autophagy, increased senescence, decreased nutrient sensing or defective nutrient sensing, proteomic instability, genomic instability, methylation, all of these things, epigenetic changes.
So a giro-protective agent would target those deep down biologic hallmarks of aging.
And in 2014, a paper came out by Bannister that basically got the world focused on this problem.
By the world, I mean the world of anti-aging.
So what Bannister and colleagues did was they took a registry from the UK and they got a set of patients who were on metformin with type 2 diabetes, but only metformin.
So these were people who had just progressed to diabetes.
They were not put on any other drug, just metformin.
And then they found from the same registry a group of matched controls.
So this is a standard way that epidemiologic studies are done.
Because again, you don't have the luxury of doing the randomization.
So you're trying to account for all the biases that could exist by saying, we're going to take people who look just like that person with diabetes.
So can we match them for age, sex, socioeconomic status, blood pressure, BMI, everything we can.
And then let's look at what happened to them over time.
Now again, this is all happening in the future.
So you're looking into the past.
It's retrospective in that sense.
So let me just kind of pull up the sort of table here so I can kind of walk through.
And this is not in the paper we talked about, but I think this is an important background.
So they did something that at the time I didn't really notice.
I didn't notice what they did.
I probably did and I forgot, but I didn't notice this until about five years ago when I went back and looked at the paper.
And they did something called informative censoring.
So the way the study worked is if you were put on Metformin, we're going to follow you.
If you're not on Metformin, we're going to follow you.
And we're going to track the number of deaths from any cause that occurred.
This is called all cause mortality or ACM.
And it's really the gold standard in a trial of this nature or a study of this nature or

even a clinical trial.
You want to know how much are people dying from anything because we're trying to prevent or delay death of all causes.
Innovative censoring says, if a person who's on Metformin deviates from that inclusion criteria, we will not count them in the final assessment.
So how are the ways that that can happen?
Well, one, the person can be lost to follow up.
Two, they can just stop taking their Metformin.
Three, and more commonly, they can progress to needing a more significant drug.
So all of those patients were excluded from the study.
So think about that for a moment.
This is, in my opinion, a significant limitation of this study.
Because what you're basically doing is saying, we're only going to consider the patients who were on Metformin, stayed on Metformin, and never progressed through it.
And we're going to compare those to people who were not having type 2 diabetes.
So an analogy here would be, imagine we're going to do a study of two groups that we think are almost identical.
One of them are smokers, and the other are identical in every way, but they're not smokers.
And we're going to follow them to see which ones get lung cancer.
But every time somebody dies in the smoking group, we stop counting them.
When you get to the end, you're going to have a less significant view of the health status of that group.
So with that caveat, the Bannister study found a very interesting result, which was the crude death rate was, and by the way, the way these are done, this is also one of the challenges of epidemiology is the math gets much more complicated.
You have to normalize death rate for the amount of time you study the people.
So everything is normalized to 1,000 person years.
So the crude death rate in the group of people with type 2 diabetes who were on Metformin, including the censoring, was 14.4.
So 14.4 deaths occurred per 1,000 patient years.
If you looked at the control group, it was 15.2.
This was a startling result.
And I remember reading this in, again, 2014 and being like, holy crap, this is really amazing.
Could you explain why?
Because I hear those numbers and they don't seem that striking.
It's a difference of about a year and a half.
Now, of course, a difference of about a year and a half in life span is remarkable.
It doesn't even translate to that.
So taking a step back, type 2 diabetes on average will shorten your life by six years.
So that's the actuarial difference between having type 2 diabetes and not all comers.
But you're right.
This is not a huge difference.

It's only a difference of a little less than one year of life per 1,000 patient years studied.
And by the way, up here, just point out my math was wrong when I said about year and a half.
The point here is you would expect the people in the metformin group to have a far worse outcome, i.e. to have a far worse crude death rate.
And the fact that it was statistically significant in the other direction.
And it turned out on what's called the Cox proportional hazard, which is where you actually model the difference in lifespan.
The people who took metformin and had diabetes had a 15%, 15% relative reduction in all cause death over 2.8 years, which was the median duration of follow up.
Well, that seems to be the number that makes me go, wow, right, because could you repeat those numbers again?
Yeah.
So 15% reduction in all cause mortality over 2.8 years.
That's a big deal.
It is.
And again, there's no clear explanation for it unless you believe that metformin is doing something beyond helping you lower blood glucose, because the difference in blood glucose between these two people was still in favor of the non-diabetics.
So again, the proponents of metformin being a geroprotective agent, and I put myself in this category at one point, I would put myself today in the category of undecided, but at the time, I very much believed this was a very good suggestion that metformin was doing other things.
You mentioned a couple already.
Metformin is a weak inhibitor of mTOR.
Metformin reduces inflammation.
Metformin potentially tamps down on senescent cells and their secretory products.
There are lots of things metformin could be doing that are off target.
And it might be that those things are conferring the advantage.
As many of you know, I've been taking AG1 daily since 2012, so I'm delighted that they're sponsoring the podcast.
AG1 is a vitamin mineral probiotic drink that's designed to meet all of your foundational nutrition needs.
Now, of course, I try to get enough servings of vitamins and minerals through whole food sources that include vegetables and fruits every day.
But oftentimes, I simply can't get enough servings.
But with AG1, I'm sure to get enough vitamins and minerals and the probiotics that I need, and it also contains adaptogens to help buffer stress.
Simply put, I always feel better when I take AG1.
I have more focus and energy and I sleep better and it also happens to taste great.
For all these reasons, whenever I'm asked, if you could take just one supplement, what would it be?
I answer AG1.

If you'd like to try AG1, go to drinkag1.com slash huberman to claim a special offer.
They'll give you five free travel packs plus a year supply of vitamin D3K2.
Again, that's drinkag1.com slash huberman.
So fast forward until a year ago, and I think most people took the banister study as kind of the best evidence we have for the benefits of metformin.
And I'm sure you've had lots of people come up to you and ask you, should I be on metformin?
Should I be on metformin?
I mean, I probably get asked that question almost as much as I'm asked any question outside of due.
I mean, people definitely want to know if you should be consuming due, but after that, it's metformin.
Fresh off the leaves.
So let's kind of fast forward to now the paper that I wanted to spend a few more minutes on.
And thanks for that background.
I'm still dazzled by the insertion of the straw by way of insulin.
I don't think I've ever heard that described.
I need to go get a better textbook.
It's a pretty short straw in fairness.
It's just a little transport.
Just to give people a sense of why I'm so dazzled by, I am always fascinated by how quickly, how efficiently and how specifically biology can create these little protein complexes that do something really important.
I mean, you're talking about an on-demand creation of a little of a portal, right?
I mean, these are cells engineering their own machinery in real time in response to chemical signals.
But remind me.
It's great.
But I'm sort of rusty on my neuroscience, but an action potential works in reverse the same way.
Like you need the ATP gradient to restore the gradient.
But once the action potential fires, it's passive outside, right?
Yeah.
So what Pierre's referring to is the way that neurons become electrically active is by the flow of ions from the outside of the cell to the inside of the cell.
And we have both active conductances being there triggered by electrical changes in the gradients by changes in electrical potential.
And then they're passive gradients where things can just flow back and forth until there's a balance equal inside and outside the cell.
I think what's different is that there's some movement of a lot of stuff inside of neurons when neurotransmitters like dopamine binds to its receptor and then a bunch of, you know, it's like a bucket brigade that gets kicked off internally.
But it's not often that you hear about receptors getting inserted into cells very quickly.

They have to go through a process of transcribing genes and making sure that the specific proteins are made.
And then those are long, slow things that take place over the course of many hours or days.
What you're talking about is a real on-demand insertion of a channel.
And it makes sense as to why that would be required, but it's just, oh, so very cool.
It's cool.
Yeah.
So Keyes and colleagues came along and said, we would like to redo the entire banister analysis.
And I think their motivation for it was the interest in this topic is through the roof.
There is a clinical trial called the TAME trial that is, I think, pretty much funded now and may be getting underway soon.
The TAME trial, which is an important trial, is going to try to ask this question prospectively and through random assignment.
So this is the targeting aging with Metformin trial.
That's correct.
Barzoli is probably the senior PI on that.
And I think in many ways, the banister study, along with some other studies, but of lesser significance, probably provided some of the motivation for the TAME trial.
So they said, OK, look, we're going to do this.
We're going to use a different cohort of people.
So the first study that we just talked about, the banister study used, I believe it was, roughly they sampled like 95,000 subjects from a UK biobank.
Here, they used a larger sample.
They did about half a million people sampled from a Danish health registry.
And they did something pretty elegant.
They created two groups to study.
So the first was just a standard replication of what banister did, which was just a group of people with and without diabetic that they tried to match as perfectly as possible.
But then they did a second analysis in parallel with discordant twins, so same sex twins that only differed in that one had diabetes and one didn't.
I thought this was very elegant because here you have a degree of genetic similarity and you have similar environmental factors during childhood that might allow you to see if there's any sort of difference in signal.
So now turning this back into a little bit of a journal club, virtually any clinical paper you're going to read, table one is the characteristics of the people in the study.
You always want to take a look at that.
So when I look at table one here, you can see it's and by the way, just for people watching this, we're going to make all these papers and figures available.
So if you're, you know, don't, you know, we'll have nice show notes that'll make all this clear.
So table one in the keys paper shows the baseline characteristics.
And again, it's almost always going to be the first table in a paper.
Usually the first figure in the paper is a study design.

It's usually a flow chart that says these are the inclusion criteria.
These are all the people that got excluded.
This is how we randomized, et cetera.
And you can see here that there are four columns.
So the first two are the singletons.
These are people who are not related.
And then the second two are the twins who are matched.
And you can see, remember how I said they sampled about 500,000 people?
You can see the numbers.
So they got, you know, 7,842 singletons on metformin, the same number then they pulled out matched without diabetes.
On the twins, they got 976 on metformin with diabetes.
And then by definition, 976 co-twins without them.
And you look at all these characteristics.
What was their age upon entry?
How many were men?
What was the year of indexing when we got them?
What medications were they on?
What was their highest level of education, marital status, et cetera?
The one thing I want to call out here that really cannot be matched in a study like this, so this is a very important limitation, is the medication.
So look at that column, Andrew.
Notice how pretty much everything else is perfectly matched until you get to the medication list?
Yeah, it's all over the place.
Yeah, it's just, it's not even close.
They're nowhere near matched, right?
In other words, just to give you a couple of examples, right?
On the, and let's just talk about the singletons, because it's basically the same story on the twins.
If you look at what fraction of the people would type two diabetes or on lipid lowering medication, it's 45.6% versus 15.4% in the matched without diabetes.
It's a three X difference.
What about anti-platelet therapy?
That's 30% versus 14%.
Anti-hypertensive, 65% versus 63% versus 31%.
Because people who have one health issue and are taking that form and are likely to have other health issues.
Exactly.
So this is, again, a fundamental flaw of epidemiology.
You can never remove all the confounders.
This is why I became an experimental scientist.
So that we could control variables.
That's right, because without random assignment,

you cannot control every variable.
Now you'll see in a moment when we get into the analysis,
they go through three levels of corrections,
but they can never correct this medication one.
So just keep that in the back of your mind.
Okay, so the two big things that were done in this experiment or in this survey or study to differentiate it from banister was one, the twin trick, which I think is pretty cool.
The second thing that they did was they did a sensitivity analysis with and without informative censoring.
So one of the other things they wanted to know was,
hey, does it really matter if we don't count the metformin patients who progress?
So let's see what transcribed.
So the next table, table two, walks you through the crude mortality rate in each of the groups.
So the most important row, I think, in this table is the one that says crude mortality per 1,000-person years.
Now you recall that in the previous study, in the banister study,
those were on the ballpark of about 15 per.
Okay, so let's look at each of these.
So in the single, the singletons without, so the non-twins who were not diabetic,
it was 16.86.
And could you put a little more contour on what this 1,000-person years?
What would it is?
Are you talking about pooling the lifespans of a bunch of different people until you get to the number 1,000 because you're normalizing not, so it's not who's going to live 1,000 years, because no one's expecting that.
You're essentially taking, so you've got some people that are going to live
76 years, 52 years, 91 years, and you're pooling all of those until you hit 1,000.
And then that becomes kind of a, it's like a normalized division.
You're basically like, so let's say the control group, you're asking if there were 1,000-person years available to live.
How likely is it that this person would live another 15 years?
Yeah, so a couple of ways to think about it.
So taking a step back, we always have to have some way of normalizing.
So when we talk about the mortality from a disease like cancer in the population,
we would, we report it as what's the mortality rate per, and it's typically per 100,000 persons.
Okay, that's a much more intuitive way to express it.
It is, but the reason we can do it that way is because we're literally looking at how many people died this calendar year, and we divide it by the number of people in that age group.
So it's typically what you're doing when you look at aged groups in buckets of like decades.
So that's why we can say the highest mortality is like people 90 and up.
Even though the absolute number of deaths is small, it's because there's not that many people there, right? The majority of deaths in absolute terms probably occur in the seventh decade.
But as you go up, because the denominator is shrinking, you have to normalize to it.

So we just normalize to the number of people.
Here are all the people that started the year.
Here are all the people that ended the year.
What's the death rate?
Why are these done in a slightly more complicated way?
Because we don't follow these people for their whole lives.
We're only following them for a period of observation.
In this case, roughly three years.
So to say something like, you know, we have a crude death rate of five deaths per thousand person years, one way to think about that is if you had a thousand people and you followed them for one year, you'd expect five to die.
If you had 500 people and you followed them for two years, you expect five to die.
If you have a thousand people and you follow them for one year, you expect five to die.
Those would all be considered equivalent mortalities.
Great. Thank you for clarifying that.
No, no. This stuff is, I mean, I find epidemiology when you get in the weeds is way more complicated than following the basics of experimental stuff.
Where you just, you get to push all this stuff into the garbage bin and just say, we're going to take this number of people, we're going to exclude this group, we're going to randomize, we're going to see what happens.
Yeah, that's what, like the paper we'll talk about next.
Yeah. So when you adjust for age, and they don't show it in this table, it's only in the text, when you adjust for age, a very important check to do is what is the crude death rate of the people on Metformin who are not twins versus who are twins?
Now, in this table, they look different because it's 24.93 for the Metformin group and 21.68 for the twin group that's on Metformin.
When you adjust for age, they're almost identical.
It goes from 24.93 to 24.7.
One other point I'll make here for people who are going to be looking at this table is you'll notice there are parentheses after every one of these numbers.
What does that offer in there?
Those parentheses are offering the 95% confidence interval.
So, for example, to take the number 24.93 is the crude death rate of how many people are dying who take Metformin.
What it's telling you is we're 95% confident that the actual number is between 23.23 and 26.64.
If a 95% confidence interval does not cross the number zero, it's statistically significant.
Okay, so the first thing that just jumps out at you, I think when you look at this, is there's clearly a difference here between the people who have diabetes and those who don't.
It complicates the study a little bit because it's basically two studies in one, but you're comparing 24.93 to 16.86, which, by the way, remains after age adjustment.
When you go to the twin group, it's 24.73 to 12.94.
So maybe just to zoom out for that, what you're describing, if I understand correctly, is this crude deaths per 1,000 person years, let's just talk about the singletons, the non-times,

is 16.86. So, 16.86 people die, and some people are probably thinking,
how can 0.86 of a person die?
Well, it's not always whole numbers, but there's a bad joke to be made here.
Yeah, just call it 17 versus 25.
Right, 17 deaths per 1,000 versus 25 deaths.
And the 25 is in the folks that took metformin. Now, that to the naive listener, and to me,
means, oh, metformin basically kills you, not faster, or you're more likely to die.
But we have to remember that these people have another, they have a major health issue that
the other group does not have. Because people weren't assigned drug or not assigned drug.
It wasn't placebo drug. Let's look at people taking this drug for a bad health issue and compare
to everyone else.
That's right. So now you have to go into, and I'll just sort of skip the next figure,
but the next figure is a Kaplan-Meier curve. I think it's actually worth looking at it because
they show up in all sorts of studies. So if you look at figure one, it's a Kaplan-Meier curve,
which is a mortality curve. So you'll see these in any study that is looking at death.
And this can be prospective, randomized, this can be retrospective,
but these are always going to show up. And I think it's really worth understanding
what a Kaplan-Meier curve shows you. So when the x-axis is always time and on the y-axis
is always the cumulative survival. So it's a curve that always goes from 0 to 1,
1 or 100%. And it's always decreasing monotonically, meaning it can only go down or stay flat.
It can never go back up. So that's what a cumulative mortality curve looks like.
Now we're looking at, you're starting at alive and you're looking at how many people die
for every year that passes.
That's right. And in each curve, there's one on the left, which is the matched singletons,
and there's one on the right, which are the discordant twins. You have two lines.
You have those that were on metformin with type 2 diabetes, and you have their matched controls.
And in this figure, the matched controls are the darker lines,
and the people with type 2 diabetes on metformin, that's the lighter line.
You'll also notice, and I like the way they've done it here, they've got shading around each one.
And we should mention for those that are just listening that in both of these graphs,
the downward trending line from the controls, so again, non-diabetic, not taking metformin,
is above the line corresponding to the diabetics who are taking metformin.
Put crudely, the people who are taking metformin that have diabetes are dying at a faster rate
for every single year examined.
The two lines do not overlap except at the beginning when everyone's alive.
It's like a foot race where basically the people with metformin and diabetes
are falling behind and dying as they fall.
That's right, and I'm glad you brought up a good point.
It's not uncommon in treatments to see Kaplan-Meier-Kirbs cross.
It's not a requirement that they never cross.
It's only a requirement that they're monotonically decreasing or staying flat.
So I've seen cancer treatment drugs where they have two drugs going head to head in a cancer
treatment and one starts out looking really, really bad, but then all of a sudden it kind

of flattens while the other one goes bad and then it actually crosses and goes underneath.
But that's not the case here.
So to your point, the people with diabetes taking metformin in both the matched singletons and the discordants are dropping much faster and they always stay below.
I was just going to say that the shading is just showing you a 95% confidence interval.
So you're just putting basically error bars along this.
So if this were experimental data, if you were doing an experiment with a group of mice and you were watching their survival and you'd have error bars on this, which you're actually measuring.
So this is because you have much more data here, you're just showing this in this fashion.
For those that haven't been familiar as to statistics, no problem.
Error bars correspond to like, if you were just going to measure the heights of a room full of tenth graders, there's going to be a range, right?
You'll have the very tall kid and the very shorter kid and the short kid and the medium kid.
And so there's a range.
There's going to be an average, a mean, and then there'll be standard deviations and standard errors.
So these confidence intervals just give a sense of how much range.
Some people die early, some people die late within a given year.
They're going to be different ages.
So these error bars can account for a lot of different forms of variability here.
You're talking about the variability is how many people in each group die.
We're not tracking one diabetic taken metformin versus a control.
I should have asked this earlier, but...
Well, and it's also a mathematical model at this point too that's smoothing it out.
Because notice it's running for the full eight years, even though they're only following people for, you know, typically, I think the median was like three or four years at a time.
So they're using this quite complicated type of mathematics called a Cox proportional hazard, which is what generates hazard ratios.
And basically any model has to have some error in it.
And so they're basically saying, this is the error.
So you could argue when you look at that figure, we don't know exactly where the line is in there, but we know it's in that shaded area.
Am I?
Sorry, one other point.
If those shaded areas overlapped, you couldn't really make the conclusion.
You wouldn't know for sure that one is different from the other.
Yeah, that's actually a good opportunity to raise a common myth, which is a lot of people when they look at a paper, let's say it's a bar graph, you know, and they see these error bars and they will say, people often think, oh, if the error bars overlap, it's not a significant difference.
But if the error bars don't overlap, meaning there's enough separation, then that's a real and meaningful difference.

And that's not always the case.
It depends a lot on the form of the experiment.
I often see some of the more robust Twitter battles over, you know, how people are reading graphs.
And I think it's important to remember that you run the statistics,
hopefully the correct statistics for the sample, but determining significance,
whether or not that the result could be due to something other than chance.
Of course, your confidence in that increases as it becomes typically p-values,
p-less than 0.00001% chance that it's due to chance, right?
So very low, probably less than 0.05 tends to be the kind of gold standard cutoff.
But when you're talking about data like these, which are repeated measures over time,
people are dropping out literally over time, you're saying they've modeled it to make predictions as to what would happen.
We're not necessarily looking at, you know, raw data points here.
Yeah, the raw data was in the previous table.
That's now taken and run through this Cox model, and it's smoothed out.
Got it.
And to your point about the bar graphs, yeah, I think the other thing you always want to understand is just because something doesn't achieve statistical significance,
the only way you can say it's not significant is you have to know what it was powered to detect.
And statistical power is a very important concept that probably doesn't get discussed enough.
But before you do an experiment, you have to have an expectation of what you believe the difference is between the groups.
And you have to determine the number of samples you will need to assess whether or not that difference is there or not.
So you use something, it's called a power table, and you would go to the power table.
So if you're doing treatment A versus treatment B, and you say, well, I think treatment A is going to have a 50% response, and I think treatment B will have a 65% response.
You literally go to a power table that says 50% response, 15% difference.
That gives you a place on the grid.
And I want to be 90% sure that I'm right.
So 90% power, I'm being a little bit...
So there's going to be a statistician listening to this who's going to want to kill me,
but this is directionally the way we would describe it.
And that tells you this is how many animals or people you would need in this study.
You're going to need 147 in each group.
And by the way, if you now do the experiment with 147 and you fail to find significance,
you can comfortably say there is no statistical difference, at least up to that 15%.
There may be a difference at 10%, but you weren't powered to look at 10%.
Yeah, and very important point that you're making.
Another point that's just a more general one about statistics.
In general, the way to reduce variability in a data set is to increase sample size.
And that kind of makes sense, right?
If I just walk into a 10th grade class and I'm going to measure height,

and I look up by the first three kids that I see, and I happen to look over there,
and it's the three that all play on the volleyball team together.
My sample size is small, and I'm likely to get a skewed representation,
in this case, taller than average.
So increasing sample size tends to decrease variation.
That's why when you hear about a study from the UK Biobank or from
half a million Danish citizens, like for instance, in this study,
those are enormous sample sizes.
So even though this is not an experimental study,
it's an epidemiological observational study.
There's tremendous power by way of the enormous number of subjects in this study.
And that's the way that epidemiology will make up for its deficit.
So you could never do a randomized assignment study on half a million people.
So epidemiology makes up for its biggest limitation,
which is it can never compensate for inherent biases
by saying we can do infinite duration if we want.
Like we could survey people over the course of their lives,
and we can have the biggest sample size possible,
because this is relatively cheap.
The cost of actually doing an experiment
where you have tens of thousands of people is prohibitive.
I mean, if you look at the Women's Health Initiative,
which was a five-year study on, I don't know, what was it, 50,000 women,
I mean, that was a billion-dollar study.
So this is the balancing act between epidemiology
and randomized prospective experiments.
And so they both offer something,
but you just have to know the blind spots of each one.
I'd like to take a quick break and acknowledge our sponsor, Inside Tracker.
Inside Tracker is a personalized nutrition platform
that analyzes data from your blood and DNA
to help you better understand your body
and help you meet your health goals.
I'm a big believer in getting regular blood work done,
for the simple reason that many of the factors that impact
your immediate and long-term health
can only be analyzed from a quality blood test.
However, with a lot of blood tests out there,
you get information back about blood lipids,
about hormones, and so on,
but you don't know what to do with that information.
With Inside Tracker, they have a personalized platform
that makes it very easy to understand your data,

that is, to understand what those lipids,
what those hormone levels, et cetera, mean,
and behavioral supplement, nutrition,
and other protocols to adjust those numbers
to bring them into the ranges that are ideal
for your immediate and long-term health.
Inside Tracker's ultimate plan now includes measures
of both ApoB and of insulin,
which are key indicators of cardiovascular health
and energy regulation.
If you'd like to try Inside Tracker,
you can visit insidetracker.com slash Huberman
to get 20% off any of Inside Tracker's plans.
Again, that's insidetracker.com slash Huberman
to get 20% off.
So let's just kind of wrap this up.
I mean, I think, let's just go to table four,
which I think is the most important table in here,
which now lays out the final results
in terms of the hazard ratio.
So this is the way we want to really be thinking about this.
So again, hazard ratios, these are important things
to understand.
A hazard ratio is a number,
and you always subtract one from the hazard ratio,
and that tells you, if it's a positive number,
if it's a number, sorry,
if it's a number greater than one, you subtract one,
and that tells you the relative harm.
So if the hazard ratio is 1.5,
you subtract 1.5 is a 50% increase in risk.
If the number is negative,
you may recall on the banister paper,
the hazard ratio is 0.85.
So if it's nothing,
so that means it's a 15% reduction in relative risk,
and here you can see all the hazard ratios are positive.
So what it's telling you here is,
and I'm going to walk through this
because there's a lot of information packed here,
you've got singletons, you've got twins,
they're showing you three different ways that they do it.
They do an unadjusted model.

If you just look at the singletons
with and without metformin,
and you make no adjustments,
the hazard ratio is 1.48,
meaning that people on metformin had a 48% greater chance
of dying in any given year
than their non-diabetic counterpart.
The only reason I'm smiling,
it's not because I enjoy people dying quite to the contrary,
is that this is novel for me.
And I've read some epidemiological studies before,
but it's not normally where I spend the majority of my time.
But up until now, I was thinking,
okay, people taking metformin are dying more
than those that aren't.
And I'm just relieved to know
that I wasn't looking at all this backwards.
So they're dying more.
But of course, we don't have a group
that's taking metformin who doesn't have diabetes,
and we don't have a group who has diabetes
and is taking metformin plus something else.
So again, we're only dealing with these constrained populations.
Yeah, now there's another arm to this study
that I'm not getting into,
because it adds more complexity,
which is they also have another group
that's got diabetes, takes metformin,
and takes sulfonylureas, which is a bigger drug,
and those people die even more.
Which again, speaks to the point, right?
The more you need these medications,
they're never able to erase the effect of diabetes.
But in this case, it seems that they might be accelerating,
possibly accelerating death due to diabetes, possibly.
We could never know that from this,
because we would need to see diabetics
who don't take metformin, who take nothing,
and I would bet that they would do even worse.
So my intuition is that the metformin is helping,
but not helping nearly as much as we thought before.
So my point is, they make another set of adjustments.
They say, okay, well look,

in the first one in the unadjusted model,
we only matched for age and gender.
Okay, that's pretty crude.
What if we adjust for the medications they're on,
the cardiovascular, psychiatric, pulmonary,
dementia meds, and marital status?
I don't know why they threw marital status in there,
but they did.
I don't know, maybe being married or unmarried.
I'm sure it can, but it just seems like a random thing
to throw in with all their meds.
I would have personally done that adjustment higher up.
But nevertheless, if you do that,
all of a sudden, the hazard ratio drops from 1.48 to 1.32,
which means, yep, you still have a 32% greater chance
of dying in any given year.
All right, what if we also adjust for the highest level
of education along with any of the other covariates?
Well, that doesn't really change it at all.
It ends up at 1.33, or a 33% chance increase in death.
I always knew that more school wasn't going to save me.
It's not doing jack.
So now let's do it for the twins.
If you do the twin study, which you could argue
is a slightly purer study, because you at least
have one genetic and environmental thing that you've attached,
the unadjusted model is brutal, 2.15.
That's 115%.
Think about this.
These are twins who, in theory, are the same in every way,
except one has diabetes and one doesn't,
and the one with diabetes on metformin
still has 115% greater chance of dying
than the non-diabetic co-twin.
When you make that first adjustment of all the meds
and marital status, you bring it down to a 70% increase in risk.
And when you throw education in,
it goes up to an 80% chance of risk.
Now, they did this really cool thing,
which was they did the analysis on with and without censoring.
So everything I just said here was based on no censoring.
Tell me about censoring.
Censoring is when you stop counting the metformin people who have died.

Okay, so in the singleton group, when you unadjust it,
and the reason I'm doing the unadjusted
is that's where they did the sensitivity analysis.
I don't think it really matters that much.
You just have to draw a line in the sand somewhere.
You'll recall that that was a 48% chance of increased mortality,
all-cause mortality, if you stop counting,
pardon me, if you don't censor,
meaning if you include everybody,
including when people on metformin with diabetes die,
if you censor them, it comes down to 1.39.
In other words, this is a very important finding,
it did not undo the benefits that we saw in the banister study.
Banister saw a 15% reduction in mortality when they censored.
When keys censored, it got better, but not that much better.
It went from 48% to 39%.
In the twins, it went from 115% down to only 97%.
So in some ways, this presents a little bit of an enigma,
because it's not entirely clear to me,
having read these papers many times,
exactly why banister found such a different response.
There's another technical detail of this paper,
you can see on the right side of table four,
they did something called the nested case control,
but you'll see, and I was going to go into a long explanation
of what nested case controls are,
it's another pretty elegant way to do case control studies,
where you sample by year and you sort of normalize,
you don't count all the cases at the end,
you count them one by one.
I don't think it's worth getting into, Andrew,
because it doesn't change the answer.
You can see it changes it just slightly,
but it doesn't change the point.
The point here is, the keys paper makes it undeniably clear
that in that population,
there was no advantage offered by Metformin
that undid the disadvantage of having type 2 diabetes.
This does not mean that Metformin wasn't helping them,
because we don't know what these people would have been like
without Metformin.
It could be that this bought them a 50% reduction
in relative mortality to where they'd been.

But what it says is, in a way,
this is what you would have expected.
This is what you would have expected 10 years ago
before the banister paper came out.
Or maybe even before Metformin was used,
because in some ways it's saying,
what is the likelihood that sick people
who are on a lot of medication are going to die
compared to not sick people who aren't on a lot of medication?
It's not quite that simple in the sense that, as you said,
there are ways to try and isolate the Metformin contribution
somewhat, because they're on a bunch of other meds.
And presumably that was done and analyzed in other figures
where they can never attach the results specifically
to Metformin.
But there must be some way of waiting the percentage
that are on psychiatric meds or not on psychiatric meds
is some way to tease out whether or not
there's actually some contribution in Metformin
to this result.
Well, that's what they're doing in the partial adjustment
is they're actually doing their best to say...
Oh, right.
Married or not married.
They're going variable by variable.
They're going drug by drug all the way through.
High blood pressure, non-high blood pressure,
smoking, non-smoking, et cetera.
Right.
And the way they would do that presumably is by saying,
okay, married, not married.
That's a simple one.
Are you on lipid lowering meds?
Yes or no?
Okay.
You are not.
You are not.
They...
And then comparing those groups.
Yeah.
Yeah.
So no differences jumping out that can be purely explained
by these other variables.

Yes.
Although, again, this is a great opportunity
to talk about why no matter how slick you are,
no matter how slick your model is,
you can't control for everything.
There is a reason that, to my knowledge,
virtually every study that compares meat eaters
to non-meat eaters finds an advantage amongst the non-meat eaters.
And we can talk about all the...
Lifespan advantage.
Yes.
And we can...
Or disease, you know, incidence studies.
And yeah, it might be tempting to say,
well, therefore, eating meat is bad
until you realize that it takes a lot of work to not eat meat.
That's a very, very significant decision
that a person, for most people,
that's a very significant decision a person makes.
And for a person to make that decision,
they probably have a very high conviction
about the benefit of that to their health.
And it is probably the case that they're making other changes
with respect to their health as well
that are a little more difficult to measure.
Now, there's a million other problems with that.
I picked a silly example,
because the whole meat discussion then gets into,
well, you know, when we say eating meat, what do we mean?
Like, does that...
Talk to me, it's like deli meat versus grass fed.
Exactly.
Or a deer that you hunted with your ball.
That's right.
So how do we get into all those things?
But my point is it's very difficult
to quantify some of the intangible differences.
And I think that even a study that goes to great lengths,
as this one does epidemiologically
to make these corrections can never make the corrections.
And so for me, the big takeaway of this study is, one,
this makes much more sense to me than the banister paper,
which never really made sense to me.

And again, I was first critical of the banister paper in 2018,
about four years after it came out.
That's about the time I stopped taking Metformin, by the way.
I stopped taking it for a different reason,
which we can talk about in a sec.
But that was the first time I went back and said,
wait a minute, this information,
this informative censoring thing is...
That's a little fishy.
And I think we weren't looking at a true group
of real type 2 diabetics.
Now that said, maybe it doesn't matter.
In other words, maybe...
And even the keys paper doesn't tell us
that Metformin wouldn't be beneficial,
because it could be that those people,
if they were on nothing,
as their matched cohorts were on nothing,
would have been dying at a hazard ratio of 3.
And this brought it down to 1.5,
in which case you would say,
there is some giro protection there.
It is putting the brakes on this process.
All of this is to say,
absent a randomized control trial.
We will never know the answer.
Has there been a randomized control trial
on Metformin?
Not when it comes to a hard outcome.
Now, there has been in the ITP.
So the Interventions Testing Program,
which is kind of the gold standard for animal studies,
which is run out of three labs.
So it's an NIH-funded program that's run out of three labs.
They basically test molecules for giro protection.
The ITP was the first study
that really put rapamycin on the map in 2009.
That was the study that's fortuitously demonstrated
that even when rapamycin was given very, very late in life,
it was given to 60-month-old mice,
it still afforded them a 15% lifespan extension.
Has a similar study been done in humans?
I mean, it's hard to...

No, you can't really control with rapamycin.
No. But when the ITP studied Metformin,
it did not succeed.
So there have not been that many drugs
that have worked in the ITP.
The ITP is very rigorous.
It doesn't use an inbred strain of mice.
It is done concurrently in three labs
with very large sample sizing.
And so when something works in the ITP,
it's pretty exciting.
Rapamycin has been studied several times.
It's always worked.
Another one we should talk about at a subsequent time
is 17-alpha-estradiol.
This continues to work in male mice,
and it produces comparable effects to rapamycin.
Estrogen.
Doesn't work in female mice.
But this is alpha, not beta.
So this is 17-alpha-estradiol, not beta-estradiol,
which is the estradiol that we all...
That is bioavailable in all of us.
And just as a brief aside,
I think you and I basically agree that
unless it's a problem,
males, we're talking post-puberty,
should try and have their estrogen as high as possible
without having negative symptomology
because of the importance of estrogen
for libido, for brain function, tissue...
Bone health.
Bone health.
This idea of crushing estrogen
and raising testosterone is just silly, right?
Let's just leave raising testosterone out of it.
But many of the approaches to raising testosterone
that are pharmacologic in nature also raise estrogen.
A lot of people try and push down on estrogen.
And that is just, again,
unless people are getting hyperestrogenic effects,
like gynecomastia or other issues,
is the exact wrong direction to go.

You want estrogen high.
Estrogen is a very important hormone for men and women.
Yeah, that's good.
Canaga flows in an SGLT2 inhibitor,
also very successful in the ITP.
But again, interestingly,
metformin not.
So metformin has failed in the ITP.
So you no longer take metformin.
I stopped five years ago.
I mean, you're not a diabetic,
so presumably you were taking it to...
I was taking it for a jewellery protection.
To buffer glucose.
Yeah, and ultimately,
potentially live longer.
Yes, exactly.
And the reason I stopped,
and this will be the last thing before we move on...
Well, because you couldn't go to the dairy queen
at the buffet event.
No, finally, the nausea went away
after a few weeks or a month, maybe.
But once I got really into lactate testing,
I noticed how high my lactate was at rest.
So resting fast at lactate
should be in a healthy person,
should be below one.
Like somewhere between 0.3, 0.6 millimole.
And only when you start to exercise
should lactate go up.
And in 2018 was when I started
blood testing for my zone two.
So previously, when I was doing zone two testing,
I was just going off my power meter and heart rate.
But this is after I met Inigo San Milan,
and I started wanting to use the lactate threshold
of 2 millimole as my determinant
of where to put my wattage on the bike.
And I'm like doing finger pricks before I start,
and I'm like 1.6 millimole.
And I'm like, what the hell is going on?
I can't be 1.6.

So you ran the flight of stairs
up the back of the Empire State Building.
Well, no, that would put me a lot higher, right?
But...
I was being generous to your fit.
No, but that's when I started digging a little digging
and realized, oh, you know what?
This totally makes sense.
If you have a weak mitochondrial toxin,
what are you going to do?
You're going to shunt more glucose into pyruvate
and more pyruvate into lactate.
I'm anaerobic at a baseline.
Yeah, you need an alternative fuel source.
That's right.
So...
And then my zone two numbers just seemed off.
My lactate...
Could you feel it?
Sorry to interrupt, but could you feel it in your body?
Because maybe now I'll just briefly describe,
I took berberine during the period of maybe
somewhere in the 2012 to 2015 stretch.
I don't recall exactly.
And what were you taking it for?
Well, I'll tell you, so I was and I still am a big fan
of Tim Ferriss's slow carbohydrate diet
because I like to eat meat and vegetables and starches.
I'm an omnivore.
And I found that it worked very quickly, got me very lean.
I could exercise.
I could think.
I could sleep.
You know, a lot of my rationale
for following one eating regimen or another,
what I eat is to enjoy myself,
but also have mental energy.
I mean, because if I can't sleep at night,
I'm not going to replenish.
I don't replenish.
I'm going to feel like garbage.
I don't care how lean I am or what you know.
So I found the slow carb diet to be,

which was in the four hour body,
to be a very good plan for me.
It's pretty easy.
You drop some things like bread, etc.
You don't drink calories,
except after a resistance training session, etc.
But one day a week, you have this so-called cheat day.
And on the cheat day, anything goes.
And so I would eat, you know,
eight croissants and then I'd alternate to sweet stuff
and then I'd go to a piece.
And by the end of the day,
you don't want to look at an item of food at all.
So the only modification I made to the slow carb diet
for our body thing was the day after the cheat day,
I wouldn't eat.
I would just fast.
And I had no problem doing that
because it was just basically, well, since you said,
what was it, anal?
Anal seepage.
Yeah, gel seepage.
I did not have that.
But since you said that, I won't up the ante here,
but I'll at least match your anal seepage comment by saying,
I had, let's just call it profound gastric distress
after eating like that the next day.
So the last thing you want to do is eat any food out,
just hydrate.
And oftentimes to try and get some exercise.
And what I read was that berberine, poor man's metformin,
could buffer blood glucose and in some ways
make me feel less sick when ingesting all these calories.
And in many cases, spiking my blood sugar and insulin
because you're having ice cream and you know, etc.
And indeed it worked.
So if I took berberine,
and I don't recall the milligram count,
and then I ate, you know, 12 donuts, I felt fine.
It was as if I had eaten one donut.
Wow.
I felt sort of okay in my body and I felt much, much better.
Now, presumably because it's buffering the spikes

and blood sugar, I wasn't crashing in the afternoon nap
and that whole thing.
And do you remember how much you were taking?
I think it was a couple hundred milligrams.
Does that sound about right?
It was a bright yellow capsule.
I forget the source.
But in any case, one thing I noticed was that if I took berberine
and I did not ingest a profound number of carbohydrates
very soon afterwards, I got brutal headaches.
I think I was hypoglycemic.
I didn't measure it, but I just felt I had headaches.
I didn't feel good.
And then I would eat a pizza or two and feel fine.
And so I realized that berberine was putting me on this kind of
lower blood sugar state.
That was the logic anyway.
And it allowed me to eat these cheap foods.
But when I cycled off of the four out,
because I don't follow the slow carb diet anymore,
although I might again at some point,
when I stopped doing those cheat days,
I didn't have any reason to take the berberine.
And I feared that I wasn't ingesting enough carbohydrates
in order to really justify trying to buffer my blood glucose.
Also, my blood glucose tends to be very low.
Did you ever try a carbose?
No, what is that?
So a carbose is another glucose disposal.
Yeah, it's actually a drug that,
but it works more in the gut and it just prevents glucose absorption.
A carbose is another one of those drugs
that actually found a survival benefit in the ITP.
And it was a very interesting finding
because the thesis for testing at the ITP
is a very clever system.
Anybody can nominate a candidate to be tested.
And then the panel over there reviews it
and they decide, yep, this is interesting.
We'll go ahead and study it.
So when I think David Allison nominated a carbose to be studied,
the rationale was it would be a caloric restriction memetic
because you would literally just fail to absorb,

I don't know, make up some number, right?
15 to 20% of your carbohydrates would not be absorbed
and therefore the mice would effectively
be calorically restricted.
They would just pass them out.
That's right.
And what happened was really interesting.
One, the mice lived longer on a carbose.
But two, they didn't weigh any less.
So they lived longer but not through calorie restriction.
That's interesting.
Yes.
And the speculation is they lived longer
because they had lower glucose and lower insulin.
And I don't want to send us down some rabbit holes here,
but there are all sorts of interesting ideas about,
for instance, that some forms of dementia
might be so-called type 3 diabetes or diabetes of the brain
and so things like berberine metformin, lowering blood glucose,
ketogenic diets, et cetera, might be beneficial there.
I mean, there's a lot to explore here
and I know you've explored a lot of that on your podcast.
I've done far less of that.
But, well, at least it seems that we know
the following things for sure.
One, you don't want insulin too high nor too low.
You don't want blood glucose too high nor too low.
If the buffering systems for that are disrupted,
clearly exercise, meaning regular exercise,
is the best way to keep that system in check.
But in the absence of that tool,
or I would say in addition to that tool,
is there any glucose disposal agent,
because that's what we're talking about here,
metformin, berberine, a carboset, et cetera,
that you take on a regular basis
because you have that much confidence in it?
The only one that I take is an SGLT2 inhibitor.
So this is a class of drug that is used by people
with type 2 diabetes, which I don't have,
but because of my faith in the mechanistic studies
of this drug, coupled with its results in the ITP,
coupled with the human trial results

that show profound benefit
and non-diabetics taking it even for heart failure.
I think there's something very special about that drug.
That was another paper I was thinking about presenting this time.
Maybe we'll do that the next time.
But do you believe in caloric restriction
as a way to extend life,
or are you more of the do the right behaviors,
and that's covered in your book Outlive and Elsewhere
on your podcast, and buffer blood glucose?
Do you still, obviously, you believe in buffering blood glucose
in addition to just doing all the right behaviors?
Yeah, I think you can uncouple a little bit
the buffering of blood glucose from the caloric deficit.
So I think you can be in a reasonable energy balance
and buffer glucose with good sleep hygiene,
lots of exercise, and just thoughtful eating
without having to go into a calorie deficit.
So it's not entirely clear if profound caloric restriction
would offer a survival advantage to humans,
even if it were tolerable to most, which it's not.
So for most people, it's just kind of off the table.
If I said, Andrew, you need to eat 30% fewer calories
for the rest of your life.
I'll live 30% fewer years, thank you.
Yeah, there's just not many people
who are willing to sign up for that,
so it's kind of a moot point.
But the question is, do you need to be fasting all the time?
Do you need to be doing all of these other things?
And the answer appears to be outside of using them as tools
to manage energy balance, it's not clear.
And energy balance probably plays a greater role
in glucose homeostasis from a nutrition standpoint
than the individual constituents of the meal.
Now, that's not entirely true.
Like I can imagine a scenario where a person
could be in a negative energy balance
eating Twix bars all day and drinking big gulps.
But I also don't think that's a very sustainable thing to do,
because if by definition,
I'm going to put you in negative energy balance,
consuming that much crap, I'm going to destroy you.

Like you're going to feel so miserable,
you're going to be starving, right?
You're not going to be satiated eating pure garbage
and being in caloric deficit.
You're going to end up having to go into caloric excess.
So that's why it's an interesting thought experiment.
I don't think it's a very practical experiment.
For a person to be generally satiated and in energy balance,
they're probably eating about the right stuff.
But I don't think that the specific macros matter
as much as I used to think.
I'm a believer in getting most of my nutrients
from unprocessed or minimally processed sources,
simply because it allows me to eat foods I like
and more of them.
And I just love to eat.
I so physically enjoy the sensation of chewing
that I'll just eat cucumber slices for fun.
I mean, that's not my only form of fun, unfortunately.
This is an amazing paper for the simple reason
that it provides a wonderful tutorial of the benefits
and drawbacks of this type of work.
And I think it's also wonderful
because we hear a lot about metformin,
rapamycin, and these anti-aging approaches,
but I was not aware that there was any study
of such a large population of people.
So it's pretty interesting.
Yeah, so I think it remains to be seen.
And my patients often ask me,
hey, should I be on metformin?
And I give them a much, much, much, much shorter version
of what we just talked about.
And I say, look, if the TAME study,
which should answer this question more definitively,
this is taking a group of non-diabetics
and randomizing them to placebo versus metformin
and studying for specific disease outcomes.
If the TAME study ends up demonstrating
that there is a geroprotective benefit of metformin,
I'll reconsider everything.
So I think we just have to, I think,
all walk around with an appropriate degree of humility

around what we know and what we don't know.
But I would say right now, the epidemiology,
the animal data, my own personal experience
with its impact on my lactate production
and exercise performance, there's a whole other rabbit hole.
We could go down another time,
which is the impact on hypertrophy and strength,
which appears to be attenuated as well by metformin.
I still prescribe it to patients all the time
if they're insulin resistant, for sure.
It's still a valuable drug,
but I don't think of it as a great tool
for the person who's insulin sensitive
and exercising a lot.
I can't help but ask this question.
Do you think there's any longevity benefit
to short periods of caloric restriction?
So for instance, I decide to,
by the way, I haven't done this,
but let's say I were to decide to fast
and do a one meal a day type thing
where I'm going to be in a slight caloric deficit,
500 to 1,000 calories for a couple of days
and then go back to eating the way that I ate before
that short caloric restriction slash fast.
Is there any benefit to it in terms of cellular health?
Can you reset the system?
Is there any idea that the changes,
the clearing of senescent cells
that we hear about autophagy,
that in the short term, you can glean a lot of benefits
and then go back to your regular pattern of eating
and then periodically, once every couple of weeks
or once a month, just fast for a day or two.
Is there any benefit to that
that's purely in the domain of longevity?
Because there's all discipline function there,
there's a flexibility function,
there's probably an insulin sensitivity function,
but is there any evidence that it can help us live longer?
I think the short answer is no.
For two reasons, one, I don't think that that duration
would be sufficient if one is going to take that approach,

but two, even if you went with something longer,
like what I used to do, right?
I used to do seven days of water only per quarter,
three days per month.
So I was basically always like it would be three day fast,
three day fast, seven day fast.
Just imagine doing that all year,
rotating, rotating, running.
For many years, I did that.
Now, I certainly believed and to this day,
I would say I have no idea if that provided
a benefit, but my thesis was the downside of this
is relatively circumscribed,
which is profound misery for a few days,
and what I didn't appreciate at the time,
which I obviously now look back at and realize
is muscle mass loss.
You're just, it's very difficult to gain back the muscle
cumulatively after all of that loss,
but my thought was exactly as you said,
like there's got to be a resetting of the system here.
This must be sufficiently long enough
to trigger all of those systems,
but you're getting at a bigger problem with gyroscience,
which I'm really hoping the epigenetic field
comes to the rescue on.
It has not come close to it to date,
which is we don't have biomarkers
around true metrics of aging.
Everything we have to date stinks.
So we're really good at using molecules
or interventions for which we have biomarkers,
when you lift weights,
you can look at how much weight you're lifting,
you can look at your dexascan
and see how much muscle mass you're generating,
that those are biomarkers.
Those are giving you outputs that say,
my input is good or my input needs to be modified.
When you take a sleep supplement,
you can look at your eight sleep and go,
oh, my sleep is getting better.
Like there's a biomarker.

When you take metformin,
when you take rapamycin,
when you fast,
we don't have a biomarker
that gives us any insight into whether or not
we're moving in the right direction.
And if we are, are we taking enough?
Just don't know.
So I often get asked,
like what's the single most important topic
you would want to see more research dollars put to
in terms of this space?
And it's unquestionably this,
as unsexy as it is.
Like who cares about biomarkers?
But like without them,
I don't think we're going to get great answers
because you can't do most of the experiments
you and I would dream up.
Got it.
Well, I'm grateful that you're sitting across the table
for me telling me all this
and that everyone can hear this.
But again, we will put a link to the papers plural
that Peter just described.
And for those of you that are listening and not watching,
hopefully you were able to track the general themes
and takeaways.
And it is fun to go to these papers.
You see these big stacks of numbers
and it can be a little bit overwhelming.
But my additional suggestion on parsing papers is
notice that Peter said that he's read it several times.
Unlike a newspaper article or an Instagram post,
with a paper, you're not necessarily going to get it
the first time.
You certainly won't get everything.
So I think spending some time with papers for me
means reading it and then reading it again
a little bit later.
And tell me, I was just about to say,
because I kind of have a way that I do it,
but I'm curious as to how you do it.

Like if you're encountering a paper for the first time,
do you have an order in which you like to go through?
Do you read it sequentially
or do you look at the figures first?
I mean, how do you go through it?
Yeah, unless it's an area that I know very, very well
where I can skip to some things
before reading it the whole way through.
My process is always the same.
And actually, this is fun because I used to teach a class
when I was a professor at UC San Diego,
called Neural Circuits in Health and Disease.
And it was an evening course that grew very quickly
from 50 students to 400 plus students.
And we would do exactly this.
We would parse papers.
And I had everyone ask what I called the four questions.
And it wasn't exactly four questions,
but I have a little three by five card next to me
or a piece of main app by 11 paper, typically.
And when I sit down with a paper,
I want to figure out what is the question they're asking?
What's the general question?
What's the specific question?
And I write down the question.
Then what was the approach?
How did they test that question?
And sometimes I can get a bit detailed.
You can get into immunohistochemistry
and they did a PCR for this.
It's not so important for most people
that they understand every method.
But it is worthwhile that if you encounter a method
like PCR or chromatography or fMRI,
at least look up on the internet what its purpose is.
That will help a lot.
And then it was what they found.
You can usually figure out what they believe they found,
anyway, by reading the figure headers.
Figure one, here's the header.
Typically, if it's an experimental paper,
it will tell you what they want you to think they found.
And then I tend to want to know the conclusion of the study.

And then this is really the key one.
And this is the one that would really distinguish
the high-performing students from the others.
You have to go back at the end and ask whether or not
the conclusions, the major conclusions drawn in the paper,
are really substantiated by what they found and what they did.
And that involves some thinking.
It involves really spending some time
thinking about what they identified.
Now, this isn't something that anyone can do straight off the bat.
It's a skill that you develop over time
and different papers require different formats.
But those four questions really form the cornerstone
of teaching undergraduates.
And I think graduate students as well of how to read a paper.
And again, it's something that can be cultivated.
And it's still how I approach papers.
So what I do typically is I'll read title abstract.
I usually then will skip to the figures
and see how much of it I can digest
without reading the text and then go back and read the text.
But in fairness, journals, great journals like science,
like nature, oftentimes will pack so much information
in the self-pressed journals, too,
into each figure.
And it's coded with no definition of the acronyms
that almost always I'm into the introduction
and results within a couple of minutes
wondering what the hell this acronym is
or that acronym is.
And it's just wild how much nomenclature there really is.
I can't remember.
Was it you or was it our friend, Paul Conti,
when he was here who said that, oh, no, I'm sorry.
It was neither.
It was chair of ophthalmology at Stanford, Dr. Jeffrey Goldberg,
who was a guest on a podcast recently,
who off-camera, I think it was, told us that if you look
at the total number of words and terms
that a physician leaving medical school
owns in their mind and their vocabulary,
it's the equivalent of two additional full languages
of fluency beyond their native language.

So you're trilingual, at least.
And I wanted you to speak a language other than English.
Poorly.
OK, so you're at least trilingual and probably more.
So no one is expected to be able to parse these papers
the first time through without substantial training.
Yeah, no, I think that's a great format.
And you're absolutely right.
I have a different way that I do it
when I'm familiar with the subject matter versus when I'm not.
Well, again, if I'm reading papers that are something
that I know really well, I can basically
glean everything I need to know from the figures.
And then sometimes I'll just do a quick skim on methods.
But I don't need to read the discussion.
I don't need to read the intro.
I don't need to read anything else.
If it's something that I know less about,
then I usually do exactly what you say.
I try to start with the figures.
I usually end up generating more questions.
Like, what do you mean?
What is this?
How did they do that?
And then I got to go back and read methods, typically.
And one of the other things that's probably worth mentioning
is a lot of papers these days have supplemental information
that are not attached to the paper.
So you're amazed at how much stuff gets put
in the supplemental section.
And the reason for that, of course,
is that the journals are very specific
on the format and length of a paper.
So a lot of the times when you're submitting something,
like if you want to put any additional information in there,
it can't go in the main article.
It has to go in the supplemental figure.
So even for this paper, there were a couple of the numbers
I spouted off that I had to pull out of the supplemental paper.
For example, when they did the sensitivity analysis
on the censoring versus non-censoring,
that was in the supplemental figure.
That was actually not even in the paper we presented.

Well, should we pivot to this other paper?
It's a very different sort of paper.
It's an experimental paper where there's a manipulation.
I must say, I love, love, love this paper.
And I don't often say that about papers.
I'm so excited about this paper for so many reasons,
but I want to give a couple of caveats up front.
First of all, the paper is not published yet.
The only reason I was able to get this paper
is because it's on bioarchive.
There's a new trend over the last, I would say,
five, six years of people posting the papers
that they've submitted to journals for peer review online
so that people can look at them prior to those papers being peer reviewed.
So there is a strong possibility that the final version of this paper,
which again, we will provide a link to,
is going to look different, maybe even quite a bit different
than the one that we're going to discuss.
Nonetheless, there are a couple of things that make me confident
in the data that we're about to talk about.
First of all, the group that published this paper
is really playing in their wheelhouse.
This is what they do,
and they publish a lot of really nice papers in this area.
I'm not going to mispronounce her first name,
but I think it's Chao Si Gu who's at the Econ School of Medicine in Mount Sinai,
runs a laboratory there studying addiction in humans.
And the first author of the paper is Ofer Pearl.
This paper is wild.
And I'll just give you a couple of the takeaways first
as a bit of a hook to hopefully entice people into listening further,
because this is an important paper.
This paper basically addresses how our beliefs about the drugs we take
impacts how they affect us at a real level,
not just at a subjective level, but at a biological level.
So just to back up a little bit, a former guest on this podcast,
Dr. Ali Crum, whose name is actually Aliyah Crum,
but she goes by Ali Crum, talked about belief effects.
Belief effects are different than placebo effects.
Placebo effects are really just category effects.
It's, okay, I'm going to give you this pill, Peter,
and I'm going to tell you that this pill is molecule X5952,
and that it's going to make your memory better.

And then I give you a memory test.
And your group performs better than the people in the control group,
who I give a pill to and I say, this is just a placebo.
Or there are other variants on this where people will get a drug
and you tell them it's placebo, they'll get a placebo, you tell them it's drug.
It's a binary thing.
It's an honor and off thing.
You're either in the drug group or the placebo group,
and you're either told that you're getting drug or placebo.
And we know that placebo effects exist.
In fact, one of the crueler ones, I was never the subject of this,
but there was kind of lore in high school that kids would do this mean thing.
It's a form of bullying.
I really don't like it where they get some kid at a party to drink alcohol-free beer,
and then that kid would start acting drunk and then they'd go,
gotcha, it doesn't even have alcohol in it.
Now, that's a mean joke and just reminds me of some of the horrors of high school.
Maybe that's why I didn't go very often, which I also don't suggest.
But no, it's a mean joke, but it speaks to the placebo effect.
And there's also a social context effect.
So placebo effects are real.
We know this.
Belief effects are different.
Belief effects are not A or B, placebo or non-placibo.
Belief effects have a lot of knowledge to enrich one's belief about a certain something
that can shift their psychology and physiology one way or the other.
And I think the best examples of these really,
of these belief effects really do come from Alley Crumb's lab
in the psychology department at Stanford,
although some of this work she did prior to getting to Stanford.
For instance, if people are put into a group where they watch a brief video,
just a few minutes of video about how stress really limits our performance,
let's say at archery or at mathematics or at music or at public speaking,
and then you test them in any of those domains or other domains in a stressful circumstance,
they perform less well.
And we know they perform less well because by virtue of a heightened stress response,
you can measure heart rate, you can measure stroke volume of the heart,
you can measure peripheral blood flow, which goes down when people are stressed,
narrowing a vision, et cetera.
You take a different group of people and randomly assign them to another group
where now they're being told that stress enhances performance.
It mobilizes resources, it narrows your vision such that you can perform tasks better,
et cetera, et cetera, and their performance increases above a control group

that receives just useless information or at least useless as it relates to the task.
In both cases, by the way, the groups are being told the truth.
Stress can be depleting or it can enhance performance.
But this is different than placebo because now it's scaling according to the amount
and the type of information that they're getting.
And can you give me a sense of magnitude, of benefit or detriment
that one could experience in a situation like the one you just described?
Yeah, so it's striking.
They're opposite in direction, so the stress gets us worse, makes you,
let's say, I think that if we were to just put a rough percentage on this,
it would be somewhere between 10% and 30% worse at performance than the control group.
And stress is enhancing as approximately equivalent improvement.
So they're in opposite directions.
Even more striking is the studies that Allie's lab did and others.
Looking at, for instance, you give people a milkshake,
you tell them it's a high-calorie milkshake, has a lot of nutrients,
and then you measure ghrelin secretion in the blood.
And ghrelin is a marker of hunger that increases longer it's been since you've eaten.
And what you notice is that suppresses ghrelin to a great degree and for a long period of time.
You give another group a shake, you tell them it's a low-calorie shake,
that it's got some nutrients in it, but that doesn't have much fat, not much sugar, etc.
They drink the shake, less ghrelin suppression.
And it's the same shake.
And it's the same shake.
And satiety lines up with that also in that study.
And then the third one, which is also pretty striking is they took hotel workers,
they gave them a short tutorial or not informing them that moving around during the day and vacuuming and doing all that kind of thing is great.
It helps you lower your BMI, which is great for your health.
You incentivize them.
And then you let them out into the wild of their everyday job.
You measure their activity levels.
The two groups don't differ.
They're doing roughly the same task,
leaning down, cleaning out trash cans, etc.
Guess what?
The group that was informed about the health benefits of exercise lose 12% more weight compared to the other group.
And no difference in actual movement?
Apparently not.
Now, how could that be?
I mean, literally, this was sparked by, in Allie's words,
this was sparked by her graduate advisor saying,

what if all the effects of exercise are placebo, which is not what anyone really believes,
but it's just such a, I love that anecdote that Allie told us,
because it just really speaks to how really smart people think.
They sit back and they go, yeah, exercise obviously has benefits,
but what if a lot of the benefits are that you tell yourself it's good for you
and the brain can actually activate these mechanisms in the body?
And why wouldn't that be the case?
Because the nervous system extends through both.
So interesting.
So interesting.
Okay, so fast forward to this study, which is really about belief effects, not placebo effects.
And to make a long story short, we know that nicotine, vaped, smoked, dipped,
or snuffed, or these little zinc pouches or taken in capsule form,
does improve cognitive performance.
I'm not suggesting people run out and start doing any of those things.
I did a whole episode on nicotine.
The delivery device often will kill you some other way or is bad for you,
but it causes vasoconstriction, which is also not good for certain people,
but nicotine is cognitive enhancing.
Why?
Well, you have a couple of sites in the brain, namely in the basal forebrain,
nucleus basalis, in the back of the brain structures, like locus ceruleus,
but also what's called, it's got a funny name, the pedunculopontine nucleus,
which is this nucleus in the ponds in the back of the brain, in the brainstem,
that sends those little axon wires into the thalamus.
The thalamus is a gateway for sensory information.
And in the thalamus, the visual information, the auditory information,
it has nicotinic receptors.
And when the pedunculopontine nucleus releases nicotine,
or when you ingest nicotine, what it does is it increases the signal to noise
of information coming in through your senses.
So the fidelity of the signal that gets up to your cortex,
which is your conscious perception of those senses, is increased.
And how much endogenous nicotine do we produce?
Ooh. Well, it's going to be acetylcholine binding to nicotinic receptors.
I see. We're not making nicotine.
We're just binding.
So this is a nicotinic acetylcholine receptor.
Right. Of which there are at least seven and probably like 14 subtypes.
But so, right, they're called nicotinic receptors in an annoying way,
in the same way that cannabinoid receptors are called cannabinoid receptors.
But then everyone thinks, oh, you know, those receptors are there because we're supposed
to smoke pot, or those receptors are there because we're supposed to ingest nicotine.

No. The drugs that we're used to study.
The drug is named after the receptor.
That's right. Exactly.
Receptor is named after the drug.
And so the important thing to know is that whether or not it's basal forebrain,
a pedunculopontine nucleus, or a locus ceruleus, that at least in the brain,
because we're not talking about muscle, where acetylcholine does something else
via nicotinic receptors, in general, it just tends to be
a signal-to-noise enhancer.
And so for the non-engineering types out there, no problem.
Signal-to-noise, just imagine, I'm talking right now and there's a lot static in the background.
There are two ways for you to be able to hear me more clearly.
We can reduce the static, or I can increase the fidelity, the volume and the clarity of what I'm saying. For instance, and that's really what acetylcholine does.
That's why when people smoke a cigarette, they get that boost of nicotine,
and they just feel clearer. It really works.
The other thing that happens is the thalamus sends information to a couple of places.
First of all, it sends information to the reward centers of the brain,
the Mesolympic reward pathway that releases dopamine.
And typically when nicotine is increased in our system, dopamine goes up.
That's one of the reasons why nicotine is reinforcing.
We just like it. We seek it out.
I've done beautiful experiments with honey bees, even, where you put nicotine on certain plants or it comes from certain plants and they'll forage there more.
You get them kind of like buzzed. That was a pun, bad pun.
In any event, there's also an output from this thing, the thalamus,
to the ventromedial prefrontal cortex, which is an area of the forebrain
that really allows us to limit our focus and our attention for sake of learning.
It allows us to pay attention. This is the circuit.
You talked about this in your fantastic podcast on stimulants.
So typically ADHD drugs, so things like Adderall, Vyvance,
methamphetamine for that matter, Ritalin.
Yeah. Why it's counterintuitive that a stimulant would be a treatment for someone with difficulty focusing.
Yeah. In young kids who have difficulty focusing, if you give them something they love, they're like a laser. And the reason is that ventromedial prefrontal cortex circuit can engage is when the kid is interested and engaged.
But kids with ADD, ADHD tend to have a hard time engaging their mind for other types of task and other types of tasks are important for getting through life.
And it turns out that giving those stimulant drugs in many cases can enhance the function of that circuit and it can strengthen so that ideally the kids don't need the drugs in the long run, although that's not often the way that it plays out.
And there are other ways to get at this. There's now a big battle out there.

Is ADHD real? Is it not real? Of course it's real.
Does every kid need ADHD meds? No.
Are there other things like nutrition, more playtime outside, etc.
that can help improve their symptoms without drugs?
Yes. Is the combination of all those things together known to be most beneficial?
Yes. Are the dosages given too high and generally should be titrated down?
Maybe. Some kids need a lot. Some kids need a little.
I probably just gained and lost a few enemies there.
So the point is that these circuits are hardwired circuits.
Sorry. One other question, Andrew.
If my memory serves correctly, doesn't nicotine potentially have a calming effect as well?
And that seems a bit counterintuitive to the focusing one.
Is it a dose effect or a timing effect? How does that work?
Yeah, it's a dosing effect. So the interesting thing about nicotine is that
it can enhance focus in the brain, but in the periphery,
it actually provides some muscle relaxation.
So it's kind of the perfect drug if you think about it.
Again, it was reflecting on this how when we were growing up,
people would smoke on a plane. They had a smoking section on the plane.
People smoked all the time and now hardly anyone smokes for all the obvious reasons.
But yeah, it provides that really ideal balance between being alert,
but being mellow and relaxed in the body. So hence, it's reinforcing properties.
Okay. This study is remarkable because what they did is they had people come into the laboratory.
They gave them a vape pen. These are smokers. So these are experienced smokers.
Typically, there's a washout before they come in, so they're not smoking for a bit,
so they can clear their system of nicotine. And they measure...
How long is that needed? Typically, it's a couple of days.
Oh, okay. Right.
Yeah. Which must be miserable for those people.
That must be interesting to say because they can't have nicorette gum or anything.
No, nothing. They must be dying. And I wonder how many cheat.
But they can measure carbon monoxide, right?
Yeah. They measure carbon monoxide and they're measuring nicotine in the blood as well.
So they do a good job there. So then what they do is they have them vape,
and they're vaping either a low, medium, or high dose of nicotine.
The doses just don't really matter because tolerance varies, et cetera.
And then they are putting them into a functional magnetic resonance imaging machine
so where they can look at... It's really blood flow.
It's a really hemodynamic response.
For those of you who want to know, it's the ratio of the oxygenated to deoxygenated blood
because when blood will flow to neurons that are active to give it oxygen,
and then it's deoxygenated, and then there's a change in what's called the bold signal.
So fMRI, when you see these hot spots in the brain,

is really just looking at blood flow.
And then there's some interesting physics around,
and I'll probably get this wrong, but I'll take an attempt at it
so that I get beat up a little bit by the physicists and engineers.
Do you remember the right hand rule?
Yep.
Right. Okay. So do I have this right? Correct.
The right hand rule, if you put your thumb out with your index finger,
your middle finger, your thumb facing up,
I think that the thumb represents the charge, the direction of the charge, right?
And then isn't the electromagnetic field as the downward facing figure?
And then it's... Do I have that right?
I have to look this up.
I actually don't.
Okay. So someone will look it up.
But what you do is when you put a person's head in this big magnet,
and then you pulse the magnet, what happens is the oxygenated and deoxygenated blood,
it interacts with the magnetic field differently,
and that difference in signal can be detected.
And you can see that in the form of activated brain areas.
Yeah. I mean, MRI all works by proton detection.
So presumably there's a difference in the proton signal
when you have high oxygen versus low oxygen concentration.
Yeah. That's right.
And what they'll do is they'll pulse with the magnet,
because my understanding is that...
And this is definitely getting beyond my expertise,
but that the spin orientation of the protons,
then it's going to relax back at a different rate as well.
So by the relaxation at a different rate,
you can also get not just resting state activation,
like, oh, look at a banana, what areas of the brain light up.
But you can look at connectivity between areas
and how one area is driving the activity of another area.
So very powerful technique.
So what they do is they put people in a scanner,
and then you'll like this.
Because what are the limitations of fMRI in terms of...
I mean, how fine is the resolution?
I mean, where are the blind spots of the technique?
So resolution, you can get down to sub-centimeter.
They talk about it always in these paper as a voxels,
which are these little cubic pixels things.

You know, sub-centimeter,
but you're not going to get down to millimeter.
There are a number of little confounds
that maybe we won't go into now
that have been basically worked out over the last 10 years
by doing the following.
You can't just give somebody a stimulus compared to nothing.
I'll just tell you the experiment.
It was discovered, for instance,
when someone would move their right hand.
Because even when you're in the MRI,
I just went for one of these recently for a clinical,
not a problem, but just for a diagnostics hand,
you're leaning back and you can move your right hand a bit.
And they would see an area in motor cortex lighting up.
But what they noticed was that the area corresponding
to the left hand was also lighting up.
So what you really have to do is you have to look at resting state.
How much are they lighting up just at rest and then subtract that out?
So now you'll always see resting state versus activation state.
Yeah, wasn't there a really funny study done as a spoof maybe a decade ago
that put a dead salmon into an MRI machine
and did an fMRI of a dead salmon
that demonstrated some interesting signal?
No, I didn't know that.
We got to find this one for the show notes.
We should do one of these wild papers ones.
There are papers of people putting, don't do this folks,
putting elephants on LSD that were published in science
and things like crazy experiments.
We should definitely do a crazy experiments journal club.
In any event, you can get a sense of which brain areas are active
and when with fairly high spatial resolution,
fairly high and pretty good temporal resolution
on the order of hundreds of milliseconds.
But it's not ultra, ultra fast
because a lot of neural transmission is happening
on the tens of milliseconds,
especially when you're in talking about auditory processing.
Okay, so they put people into the scanner
and then they give them essentially a task
that's designed to engage the thalamus,
known to engage the thalamus reward centers

and the ventromedial prefrontal cortex.
And it's a very simple game.
You'll like this because you have a background in finance.
You let people watch a market.
You know, okay, here's the stock market
or you could say or the price of peas.
It doesn't really matter.
It goes up, it goes down
and they're looking at a squiggle line then it stops.
And then they have the option, but they have to pick one option.
They're either going to invest
a certain number of the hundred units that you've given them
or they can short it.
They can say, oh, it's going to go down
and try and make money on the prediction.
It's going to go down.
You could explain shorting better than I could for sure.
So depending on whether or not
they get the prediction right or wrong,
they get more points or they lose points
and they're going to be rewarded
in real money at the end of the experiment.
So this is going to engage this type of circuitry.
Now remember, these groups were given a vape pen
prior to this where they've vaped what they were told
is either a low, medium, or high dose of nicotine
and they do this task.
The goal is not to get them to perform better on the task.
The goal is to engage the specific brain areas
that are relevant to this kind of error and reward type circuits.
And we know that this task does that.
So that includes the thalamus,
but that includes the mesolimbic reward pathway and dopamine.
It includes the ventral medial prefrontal cortex.
First of all, they measure nicotine in the blood.
They are measuring how much people vape.
They were very careful about this.
One of the nice things about the vape pen
for the sake of experiment, and not recommending people vape,
but they can measure how much nicotine
is left in the vape pen before,
after they can measure how long they inhaled,
how long they held it in.

There's a lot that you can do that's harder to do with a cigarette.
Okay, they measured people's belief
as to whether or not they got low, medium,
or high amounts of nicotine.
And they were told they got either this is a low amount,
a medium amount, or a high amount.
And then, of course, they looked at brain area activation
during this task.
And what they found was very straightforward.
Sorry, they were all given the same amount.
Yes, this is the sneak.
I was going to offer it as a punchline, but that's okay.
No, I think that the cool thing about this experiment
is that the subjects are unaware
that they all got the exact same amount
of relatively low nicotine-containing vape pen.
So they basically, and they're measuring it from their bloodstream,
so they all have fairly low levels of nicotine,
but one group was told you got a lot,
one group was told you got a medium amount,
and the other was told you got a little bit.
Now, a number of things happen,
but the most interesting things are the following.
First of all, people's subjective feeling of being on the drug
matches what they were told.
So if they were told, hey, this is a high amount of nicotine,
I'm like, yeah, it feels like a high amount of nicotine.
And these are experienced smokers.
If it was a medium amount, I'm like, yeah,
that feels like a medium amount.
If it was a low amount, they think it was a low amount.
Now, that's perhaps not so surprising.
That's your just tricking people.
That's the placebo in that sense.
That's the placebo.
Yeah.
But if you look at the activation of the thalamus
in the exact regions where you would predict acetylcholine transmission
to impact the function of the thalamus,
so these include areas like what's called the centromedian nucleus,
the ventroposterior nucleus, the names that really don't matter,
but these are areas involved in attention.
It scales with what they thought they got in the vape pen,

meaning if you were told that you got a low amount of nicotine,
you got a little bit of activation in these areas.
If you were told that you got a medium amount of nicotine,
and that's what you vaped, then you had medium amounts
or moderate amounts of activation.
And if you were told you got high amounts of nicotine,
you got a high degree of activation.
And the performance on the task,
believe it or not, scales with it somewhat.
So keep in mind, everyone got the exact same amount of nicotine in reality.
So here, the belief effect isn't just changing
what one subjectively experiences.
Oh, this is the effect of high nicotine or low nicotine.
It actually is changing the way that the brain responds to the belief.
And that to me is absolutely wild.
Now, there are a couple of other things that could have confounded this.
First of all, it could have been that if you believe you got a lot of nicotine,
you're just faster, or you're reading the lines better,
or your response time to hit the button is quicker.
I tell you, you have a drug that's going to improve reaction time.
You might believe that about nicotine.
And so you're quicker on the trigger, and you're getting...
They have a... More activation as well.
More activation. They rule that out.
They also rule out the possibility...
How did they rule that out?
By looking at rates of pressing.
And there was no difference.
Nothing. And in sensory areas of the brain that would represent that kind of difference,
they don't see that.
The other thing that is very clear is that the connection between the thalamus
and the ventral medial prefrontal cortex, that pathway scales in the most beautiful way,
such that people that were told they had smoked a low or vaped a low amount of nicotine
got a subtle activation of that pathway.
People that were told that they got a moderate amount of nicotine
got a more robust activation of that pathway.
And the people that were told that they got a high amount of nicotine in the vape pen
saw a very robust activation of the thalamus to this ventral prefrontal cortical pathway.
Now, of course, this is all happening under the hood of the skull,
simply on the basis of what they were told and what they believe.
And technically, the fMRI is showing the activation of those two areas,
and that's how you can infer the strength of that connection.
That's right.

There's a separate method called diffuser tensor imaging, which was developed,
I believe, out of the group in Minnesota.
Minnesota has a very robust group in terms of neuroimaging
that can measure activation in fiber pathways.
This is not that, but you can look at the timing of activation,
and it's a known what we call monosynaptic pathway.
So we haven't talked so much about figures here,
but I guess if we were going to look at any one figure,
and I can just describe it for the audience that doesn't have the figure in front of them,
the most, probably the most important figure is figure two.
Remember, I said I like to read the titles of figures,
which is that the belief about nicotine strength induced a dose-dependent response
in the thalamus.
Basically, if you and figure two B can tell you if they believe that they got more nicotine,
that's essentially the response that they saw.
If you look at the belief rating as a function of the estimate
in the thalamus of how much activation there was,
it's a mess when you look at all the dots at once,
but if you just separate it out by high, medium, and low,
you run the statistics, what you find is that there's a gradual increase,
but a legitimate one from low to medium to high.
In other words, if I tell you this is a high dose of nicotine,
your brain will react as if it's a high dose of nicotine.
Now, what they didn't do was give people zero nicotine.
Yeah, I was about to say there's a control that's missing here, right?
Yeah, so what they didn't do is give people zero nicotine
and then tell them this is a high amount of nicotine,
sort of the equivalent of the cruel high school experiment.
No alcohol, but then the kid acts drunk.
Now, in the high school example, it's unclear whether or not the kid actually felt drunk or not.
It's unclear whether or not they had been drunk previously,
if they even knew what it would be like to feel drunk, et cetera.
And there's the social context.
What I find just outrageous and outrageously interesting about this study is simply that
what we are told about the dose of a drug changes the way that our physiology responds
to the dose of the drug.
And in my understanding, this is the first study
to ever look at dose dependence of belief effects.
To really, and why would that be important?
Well, for almost every study of drugs, you look at a dose dependent curve.
You look at zero, low dose, medium dose, high dose.
And here they clearly are seeing a dose dependent response simply to the understanding
of what they expect the drug ought to do.

In other words, you can bypass pharmacology somewhat, right?
Now, look at Figure 2B.
Am I reading this correctly?
So it's got four bars on there.
You've got the group who were told they got a low dose,
the group who was told they got a medium dose,
the group that was told they had a high dose, and then these healthy controls,
who presumably were non-smokers who were just put in the machine.
That's right.
You mean, yeah.
Yeah, this is measuring parameter estimate.
Is that referring to their ability to play the trading game?
The parameter estimate is the reward-related activities from an independent thalamus mask, right?
So what they're doing is they're just saying,
if we just look at the thalamus, what is the level of activation?
I see.
So this suggests that the only statistical difference was between the low and the high.
That's right.
And nobody else was statistically different.
That's right.
But that's not the whole story?
No, that's not the whole story.
So when you look at the output from the thalamus to the ventromedial prefrontal cortex,
that's where you start to identify the-
Is that figure four?
That is, yes.
So this is where you see, so figure four B, if you look at parameter estimate,
so this is the degree of activation between the thalamus and the ventromedial prefrontal cortex,
and it's called the instructed belief, you can see that there's a low, medium,
and high scatter of dots for each.
And that each one of those is significant.
So isn't it interesting that at the thalamus, which is, and you'll immediately appreciate
my stupidity when it comes to neuroscience, which is more proximate to the nicotinamide,
or nicotinamide, what do you call it, the nicotine acetylcholine receptor,
you have a lower difference of signal strength.
And somehow that got amplified as it made its way forward in the brain?
Yeah.
Does that surprise you?
It is surprising, and it surprised them as well.
The interpretation they give, again, as we were talking about before, important to
match their conclusions against what they actually found, which is what we're doing here.
The interpretation that they give is that it doesn't take much nicotinic receptor occupancy

in the thalamus to activate this pathway, but they too were surprised that they could not detect a raw difference in the activation of the thalamus.
But in terms of its output to the prefrontal cortex, that's when the difference showed up.
Because that figure 4b is more convincing than figure 2, because even figure 2e,
if you read the fine print, the R, the correlation coefficient is 0.27.
That's weak.
It's not that strong.
Yeah, right.
It's weak.
So at the thalamus, it's kind of like, yeah, there might be a signal.
By the way, this goes back to our earlier discussion.
There could be a huge signal here, and we're underpowered.
How many subjects were in this?
You wouldn't have a lot of subjects in this experiment.
Yeah.
And this just speaks to the general challenge of doing this kind of work.
It's hard to get a lot of people in and through the scanner.
Yeah, and it's expensive.
And it's expensive.
We have to, I should know this, but we can go back to the method.
But you can sort of just look at the number of dots on here.
I mean, it's in the low tens, right?
It's like 40, 30, something like that.
So it's possible you do this.
It's not your Dana study.
Yeah, you do this with 1,000 people.
This could all be statistically significant.
Right.
So they talk about this, based on this,
we estimated that an N of 20, N is sample size.
In each belief condition, the final sample
would provide 90% power to detect an effect of this magnitude
at an alpha of 0.5 in a two-tailed test.
OK, so that's them referring to what we just talked about,
which is we believe at 90% confidence to get an alpha of 0.05,
which means we want to be 95% confidence,
we need 60 people, 20 per group.
Right, yeah.
But if the difference is smaller than what they expected,
they'll miss out on some of the significance,
which it looks like they're missing
between the medium and high group.
Right, yep.

And I, too, was surprised that they did not see a difference
in the, between the medium and the high group,
but they did in the output of the thalamus.
I was also surprised that they didn't see a difference.
This is kind of interesting in its own right.
If Figure 3 talks about the belief about nicotine strength,
did not modulate the reward response, the dopamine response.
How was that measured?
Also just in fMRI?
Yeah, exactly.
So if you look at Figure 3B, other people can't see it,
but basically what you'll see is that there's no difference
between these different groups in terms of the amount of activation
in these reward pathways if people got a low, medium,
or high amount of nicotine.
Now that actually could be leveraged, I believe,
if somebody were trying to quit nicotine, for instance,
and they were going to do that by progressively reducing
the amount of nicotine that they were taking,
but you told them that it was the same amount from one day to the next,
you could whittle it down to, presumably, to a low amount
before taking it to zero.
And if they believed it to be a greater amount,
then it might actually not disrupt their reward pathways,
meaning they would feel, presumably,
they'd feel rewarded by whatever nicotine they were bringing in.
What would be your prediction if this experiment were repeated,
but it was done exactly the same way with non-smokers?
Well, one thing that's sort of interesting,
you asked about potential sources of artifact problems with fMRI.
One of the challenges that they know in this study
was you have to stay very still in the machine,
but the subjects were constantly coughing because they're smokers.
Okay, so presumably the data would be higher fidelity,
sorry, chuckling at that one, but I was like,
I had to read that one twice, so that makes sense,
like they're smokers, they're coughing, they can't stay still,
so movement artifact.
But in all seriousness, I think that for people
that are naive to nicotine, even a small amount of nicotine
is likely to get this pathway activated to such a great degree,
sort of like the first time effect of pretty much any drug.
But I wonder if they would be more or less susceptible

to the belief system.
Yeah, that's a really good question.
Right, because they have no prior to compare it to.
They have no pleasant,
they have no experience to compare it to
with respect to the obviously beneficial effects of nicotine
that the smokers are well used to.
So this is the poor kid that got duped into thinking
the non-alcoholic beer was at alcohol,
though they're actually the winner, we know,
because I did an episode on alcohol, alcohol's bad for you.
So in the end, that kid wins and the other ones lose,
poetic justice.
But that kid having never been actually drunk before,
presumably would be more susceptible potentially.
That's my guess as well.
So, you know, my glee for this experiment is not,
or this paper rather,
it's not because I think it's the be all and all,
or it's a perfect experiment.
I just think it's so very cool
that they're starting to explore dose dependence of belief,
because that has all sorts of implications.
I mean, use your imagination, folks,
whether or not we're talking about a drug,
we're talking about a behavioral intervention,
we're talking about a vaccine,
and I'm not referring to any one specific vaccine,
I'm just talking to vaccines generally.
I'm talking about psychoactive drugs,
I'm talking about illicit drugs,
I'm talking about antidepressants,
I'm talking about all the sorts of drugs
we were talking about before,
metformin, et cetera,
just throw our arms around all of it.
What we believe about the effects of a drug,
presumably, in addition to what we believe about
how much we're taking and what those effects ought to be,
clearly are impacting at least the way
that our brain reacts to those drugs.
Yeah, it's very interesting.
I mean, when you consider how many drugs

that have peripheral effects
or peripheral outputs begin with central issues.
So, again, I think the GLP-1 agonists
are such a great example of this, right?
Yeah, I don't think anybody fully understands
exactly how they're working,
but it's hard to argue that they're impacting,
that the GLP-1 analog is having a central impact.
It's doing something in the brain
that is leading to a reduction of appetite.
We believe that.
Yeah.
And I think the mouse data point to different areas
of the hypothalamus that are related to satiety,
that it's at least possible.
Yeah, I mean, there's no quicker way
to make a mouse overeat or under eat
than by lesioning its hypothalamus,
depending on where you do so.
So, presumably, these drugs work there.
But again, it speaks to what do you need to believe
in order for that to be the case?
Have they done placebo trials there
where people get something and they're told?
Oh, they do.
I mean, of course, those drugs have all been tested
via placebo, and the placebo groups
don't do anywhere near as well.
That's how we know that there's activity of the drug.
But again, that's a little bit different
than being told you are absolutely getting it, right?
Because in the RCTs, you're just told you might be getting it,
you might not be getting it.
So it's not quite the same as this experiment.
This experiment is one level up where you're being told,
no, you're absolutely getting it.
You're just getting different doses of it.
Yeah, to take this to maybe the ADHD realm,
let's say a kid has been on ADHD meds for a while
and the parents, for whatever reason,
the physician decide they want to cut back on the dosage.
But if they were to tell the kid it's the same dosage
they've always been taking and it's had a certain positive

effect for them, according to the results,
at least in this paper, which are not definitive,
but are interesting, the lower dose may be as effective
simply on the basis of belief.
And, and this is the part that makes it so cool to me,
is that, and it's not a kid tricking themselves
or the parents tricking the kid so much as the brain
activation is corresponding to the belief, right?
So that's where this, this is why because it's done
in the brain, I think we can, you know,
it gets to these kind of abstract, nearly mystical,
but not quite mystical aspects of belief effects,
which is that, you know, your brain is a prediction
making machine, it's a data interpretation machine,
but it's clear that one of the more important pieces
of data are your beliefs about how these things impact you.
So it's not that this bypasses physiology,
people aren't deluding themselves, the thalamus is behaving
as if it's a high dose when it's the same dose
as the low dose group, wild.
Yeah, I mean, you think, I think of the implications,
for example, with blood pressure, right?
Like we don't really understand essential hypertension,
which is the majority of people walking around
with high blood pressure, it's unclear etiology.
So lots of people being treated, how do we know
that the belief system about it can't be changed?
And yeah, this is, I don't know, this is eye-opening.
Yeah, it's cool stuff.
And Alicrome is onto some other really cool stuff,
like for instance, just to highlight
where these belief effects are starting to show up.
If you tell a group that the side effects of a drug
that they're taking are evidence that the drug really works
for the purpose that they're taking it,
even though those side effects are kind of annoying,
people report the experience is less awful.
And they report more relief from the primary symptoms
that they're trying to target.
So our belief about what side effects are
can really impact how quickly and how compatible we feel about,
how quickly a drug works, excuse me,
and how compatible we feel that drug is with our entire life.

So maybe if we call them something else,
like not side effects, but like additional benefits
or something, it's kind of crazy.
And you don't want to lie to people, obviously,
but you also don't want to send yourself
in the opposite direction,
which is reading the list of side effects of a drug
and then developing all of those side effects
and then maybe later coming to the understanding
that some of those were raised through belief effects.
We definitely see that.
That's the nocebo effect, right?
That's the one we see a lot with all sorts of drugs.
And it's tough because how do you know which is which?
And I think there are some people
who are really impacted by that
and it makes it very difficult for them
to take any sort of pharmacologic agent
because they basically, they can't help
but incur every possible side effect.
Is it true that medical students often will start developing
the symptoms of the different diseases
that they're learning about?
Is that true?
Well, I'll tell you, I do think that in medical school,
you start to think of the zebras more than the horses all the time.
I love racing.
You know what I'm referring to, right?
You see footprints, you see hoof prints,
you should think of horses, but of course medical students,
you only think of the zebras.
There are some really funny things in medical school.
There are certain conditions
that you spend so much time thinking about
that you have a very warped sense of their prevalence.
In medical school, there's this condition called sarcoidosis.
I feel like we never stop talking about sarcoidosis.
I've seen three cases in my life.
It's just not that common.
Does it provide a great teaching tool or something?
I don't know.
Some of these things I don't know.
How much time did we spend talking about cytosine versus?

This is when people embryologically have a reversed rotation
and everything in their body is flipped.
Literally, everything is flipped.
So their heart is on the right side,
their liver is on the left side,
their appendix is on the left side.
And so I'm not making this up.
How common is this?
I've never seen it.
Okay.
I was thinking about boxing in the liver shot.
You could easily be going for the wrong side of the body.
No, I swear to God.
As a medical student,
if you were told someone had left-sided lower quadrant pain,
to which the answer is almost assuredly
that they have diverticulitis,
you'd think they could have appendicitis
in the context of cytosine versus.
The fact that that would even register
in the top 10 things that it could possibly be.
Why?
But yes, you just have a totally warped sense of what's out there.
Oh, man.
Well, this has been pure pleasure for me.
I don't know about you.
Yeah, this is good news.
I don't know about our listeners,
but for me, this is among the things that I just delight in
and even more so,
because you're the one across the table for me
teaching me about these incredible findings.
Yeah, well, light voice.
And the gaps in those findings,
which are equally incredible
because they're equally important to know about.
Yeah.
So let's do this again in Austin.
Absolutely.
Next time on your home court.
Very well.
And bring a little bit of that dew,
if you've got it.

Oh, yeah.
Yeah.
Yeah, I'll bring a low, medium and high.
Low, medium and high.
Thanks, Peter.
You're the best.
Thanks, sir.
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