

[Transcript] Huberman Lab / Dr. Satchin Panda: Intermittent Fasting to Improve Health, Cognition & Longevity

Welcome to the Huberman Lab Podcast,
where we discuss science and science-based tools
for everyday life.
I'm Andrew Huberman,
and I'm a professor of neurobiology and ophthalmology
at Stanford School of Medicine.
Today, my guest is Dr. Sachin Panda.
Dr. Sachin Panda is a professor and director
of the Regulatory Biology Laboratory
at the Salk Institute of Biological Studies.
His laboratory has made numerous important contributions
to the impact mental health, physical health,
and human performance.
For instance, his laboratory discovered
the neurons in the eye and neurons within the brain
that regulate our so-called circadian rhythms.
Circadian rhythms are 24-hour rhythms
in everything from gene expression
to the overall functioning of tissues,
our levels of mood and alertness,
our ability to sleep, appetite, and much, much more.
In addition, over the last decade,
Dr. Panda's laboratory has made critical discoveries
in terms of how our patterns of eating over time
impact our biology and our health.
In particular, his laboratory pioneered discoveries
related to so-called intermittent fasting
also sometimes referred to as time-restricted feeding.
Today, Dr. Panda and I discuss how our circadian behaviors,
everything from when we wake up to when we view light,
to when we avoid viewing light,
to when we eat and what we eat,
and when we socialize and how we socialize
impacts our biology and our psychology
and how all of that has a strong impact on our health.
During today's discussion,
you will learn how restricting your feeding
to specific periods within each 24-hour cycle
or perhaps even exploring longer patterns of fasting
and eating cycles can impact everything
from the health of your liver to your gut to your brain
and how all of that impacts things like mood
and your ability to perform cognitive work.

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Indeed, today's discussion goes deep into all aspects of intermittent fasting, aka time-restricted feeding. We talk about the basic science as well as the recent clinical trials that have explored time-restricted feeding in a diverse range of people, including men, women, children, people with diabetes, people who are otherwise healthy and much, much more. I'm quite aware that intermittent fasting is a topic of much debate these days. We go deep into that debate and by the end of today's discussion, you can be certain that you will have learned all the latest and all the details, all made very clear to you thanks to the incredible expertise, discovery, and clear communication of Dr. Panda. As some of you may already know, Dr. Panda has authored several important books on the topic of intermittent fasting and how it can benefit various aspects of health. Those books include The Circadian Code and a more recent book, The Circadian Diabetes Code, both of which we've provided links to in the show note captions. In addition, if any of you are interested in learning more about Dr. Panda's work, including seeing his publications and reading those publications, or supporting his laboratory, you can do that by going to his laboratory website, which we have also linked in the show note captions. 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 HVMN ketone IQ. HVMN ketone IQ is a supplement that increases blood ketones. I want to be clear that I am not following

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a ketogenic diet.

Most people fall into this category.

They are not following a ketogenic diet.

They are omnivores and they do eat carbohydrates.

So their standard fuel source for the brain and body is not ketones.

However, I found that by taking ketone IQ,

which we know increases blood ketones,

I can achieve much better focus for longer periods of time

for any kind of cognitive work

and much greater energy levels for exercise,

especially if I'm going into that exercise fasted

and find myself a little bit hungry

when I start that exercise.

And this is no surprise.

We know that ketones are the brains and bodies preferred

fuel source, even if you're not following a ketogenic diet.

So in other words, I and many other people are now starting

to leverage endogenous ketones as a fuel source

for the brain and body,

and yet we are not following a ketogenic diet.

And of course, if you are following a ketogenic diet,

ketone IQ will further allow you to increase your blood

ketones as a source of brain and body fuel.

If you'd like to try ketone IQ,

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to save 20% off your order.

Again, that's hvmn.com slash Huberman.

Today's episode is also brought to us by 8Sleep.

8Sleep makes smart mattress covers with cooling, heating,

and sleep tracking capacity.

As I've talked about before on the Huberman Lab podcast,

there is a critical relationship between sleep

and body temperature.

That is, in order to fall asleep and stay deeply asleep,

your body temperature needs to drop by about one

to three degrees.

And in order to wake up in the morning and feel alert,

your body temperature needs to increase

by about one to three degrees.

The problem with most people's sleeping environment

is that even if you make the room cool,

the actual environment that you sleep on,

that is your mattress and underneath your covers,
is hard to regulate in terms of temperature.
With 8Sleep, regulating the temperature
of that sleeping environment becomes incredibly easy.
In fact, you can change the temperature of that environment
across the night, making it a little bit cool
at the beginning of the night,
even cooler still a few hours into your sleep,
which really helps getting into very deep sleep,
and then warming it as you approach morning
so that you wake up feeling most alert.
I've been sleeping on an 8Sleep mattress cover
for over a year now,
and it has completely transformed my sleep.
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to save up to \$150 off their Pod 3 cover.
8Sleep currently ships in the USA, Canada, UK,
select countries in the EU and Australia.
Again, that's 8Sleep.com slash Huberman.
Today's episode is also brought to us by Thesis.
Thesis makes custom new tropics.
Now, I am not a fan of the word new tropics
because it translates to smart drugs.
And as a neuroscientist, what I can tell you
is that you have circuits in your brain
that allow you to focus.
You have circuits in your brain
that allow you to be creative.
You have circuits in your brain
that allow you to task switch and on and on.
In other words, there is no specific brain circuit
or even circuits for being quote unquote smart.
Thesis understands this and has developed new tropics
that are customized to different types of mental operations.
What do I mean by that?
Well, they have formulas that can put your brain
into a state of increased clarity or focus or creativity,
or that can give you more overall energy
for things like physical exercise.
I often take the thesis clarity formula
prior to long bouts of cognitive work
and I'll use their energy formula

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prior to doing any kind of really intense physical exercise.

If you'd like to try your own personalized new tropic starter kit, go online to takethesis.com slash huberman.

You'll take a brief three minute quiz and thesis will send you four different formulas to try in your first month.

Again, that's takethesis.com slash huberman.

And if you use the code huberman at checkout, you'll get 10% off your order.

The huberman lab podcast is now partnered with momentous supplements.

To find the supplements we discussed on the huberman lab podcast, you can go to [livemomentous](https://livemomentous.com) spelled O-U-S livemomentous.com slash huberman.

And I should just mention that the library of those supplements is constantly expanding.

Again, that's livemomentous.com slash huberman.

And now for my discussion with Dr. Sachin Panda.

Sachin, Dr. Panda, so good to see you again.

Yeah, good to see you.

We are colleagues still,

but we used to be right across the street from one another.

Yeah, I remember those days.

Yeah, so I'm delighted that you're here.

I think we're going to talk about a number of things, mainly intermittent fasting,

time-restricted feeding and health,

but also the many other things that you're doing.

Just before we started recording,

we were discussing your recent paper in Nature that involved recordings from postmortem human retina.

So maybe if there's time at the end, we can get back to.

Your lab has shown that it can essentially maintain or resurrect neurons from dead people

in order to potentially and eventually

provide transplants to rescue vision in the blind.

So that's extremely exciting.

But of course, not the main focus of today's discussion.

So we'll have to split it up.

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The first question I have is,
how am I supposed to define
fasting and time-restricted feeding?
In meaning, when I go to sleep every night,
I'm not eating.
So in some sense, everybody
is doing time-restricted feeding to some degree or another.
At what point can we start thinking about
the pattern of eating as time-restricted feeding,
so-called intermittent fasting?
Does it have to do with how regular one is
about the start and stop times?
How do you think about defining intermittent fasting,
time-restricted feeding,
and maybe just to simplify the conversation,
is one term more correct than the other
in terms of describing this incredible pattern of feeding?
Well, you know that intermittent fasting
covers many types of fasting.
Actually, it started a long time ago,
and it's embedded into the history of caloric restriction.
Almost 100 years ago, people showed that
if you reduce calorie intake in a rat,
then that rat can live for a long time.
And in those experiments,
the calories were reduced every single day.
And that led to the idea that if we cut down our calories
by 20% say,
then we can potentially live longer by doing two things.
One is preventing is-related disease,
or even if we fall sick,
maybe we can accelerate cure
and keep the repair mechanism going
so that we can live longer.
But it was very difficult to count calories every day
and reduce, maintain that.
I must say that it's not that caloric restriction is impossible,
or we are not doing it.
In fact, a lot of us, we do count calories
in our subconscious mind.
And so every time we take out a soda bottle or something,
I'm looking at 160 kilo-calorie, 30 kilo-calorie, 0 kilo-calorie.
We are doing that.

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So the point is we are doing subconsciously some kind of calorie intake.
And subconsciously some kind of calorie counting, but reducing calorie by 20%, 30% every single day is not possible for many people.
So then the idea came in mouse and rat experiment whether they can eat every other day.
And in fact, this every other day feeding also led to very similar, almost equivalent health improvement as continuous calorie restriction.
So then the idea was, well, every other day is a little bit hard for humans, but just imagine I would just get to eat only one day and then another day.
Then the idea came, well, for humans, can they eat less for one or two days in a week?
So that led to this 5-2 diet where people can eat for five days and then two days they have to reduce calories.
Also, intermittently people are fasting.
Then as you know, Walter Longo also came with this idea that periodic fasting, maybe four or five days in every month or two months, three months, you can fast or reduce calorie.
And he also found many benefits of calorie restriction was there.
Were those studies on humans?
Many of the studies started in mice, but alternate day fasting, 5-2, and Walter's periodic fasting, all of them have now been done in humans, not for longevity, of course, because you cannot do those for a long time, but for weight maintenance, for reducing some signs of aging or reversing, those things have been done.
So all of them have been done in humans, mostly healthy humans, and in some cases people with pre-divities or some aspects of metabolic disease.
So that led to the idea that all these forms of fasting in which the total calorie can take on any given day is reduced for one or more days in a week or month,

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that umbrella term became intermittent fasting.
So if you look up the scientific literature,
most intermittent fasting involves
intentionally reducing calories
for at least one or two days in a week
or few days in a month.
So when we publish time-restricted feeding,
the initial mouse experiments,
and even now most of the mouse experiments,
we want to test what is the impact of time restriction
versus calorie restriction.
So in these experiments we don't reduce calorie
on any day of mouse life.
So the mice eat the same number of calories
as the ad libitum-fed mice,
but still they see health benefit.
So that's why we call it time-restricted feeding.
But since it involves living without food for several hours,
for some people, which can be very difficult,
the initial experiments were done for eight hours of feeding
and 16 hours of fasting.
That kind of became popular.
And so that's why people use the same term
as intermittent fasting.
And now if you say intermittent fasting
in popular literature or popular media,
then people usually refer to time-restricted feeding.
So now coming back to how do you define time-restricted feeding?
So the way we have been trying to define experimentally
and also in literature is trying to confine
all your energy intake from solid and liquid food combined
within a consistent window of eight to 12 hours.
Because that's something that doable.
Of course, people have done time-restricted feeding
with four hours, six hours,
and some people even try to eat everything
within two hours, one meal a day.
But the point is those are not feasible
to maintain for a very long time for a lot of people.
One question about the six-hour versus eight-hour
versus 12-hour feeding window.
Is it important that the feeding window
begin and end at the same time more or less?

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Yeah, more or less.

And if so, how much flexibility is there?

So for instance, I'm somebody that I am not terribly hungry in the morning, I like to drink water, usually some caffeine and electrolytes in the period before my first meal.

And my first meal always lands sometime between 11 a.m. and 12 noon.

There are exceptions.

Occasionally, I'll have a breakfast, a proper breakfast as it's called.

I guess it would be improper if you're intermittent fasting for me.

But typically, 11 a.m. or noon is when I first eat.

My last bite of food is typically around 39 p.m.

That's what works for me.

Is that consistency affording me any benefit?

Let's just leave aside total caloric number, macronutrients, plant-based meat, et cetera.

But is there any benefit to shortening that feeding window that we are aware of or extending that feeding window or being even more rigid about the start and end of that feeding window?

Yeah, so the start of the feeding window, that's interesting because the concept of time-restraint feeding,

when I describe animal studies, it's feeding for humans, it's eating.

So the concept actually came from the science of circadian rhythm.

So that means our body has an internal timetable that's present in every cell, in every organ, that pre-programs many molecular aspects of the cells that leads to physiology and all that stuff.

So that essentially, there is a predetermined timetable for every cell, every organ to do certain things at certain time.

And the circadian clocks, as you and I know, are more sensitive to light.

Light is the most dominant time-giver.

So for example, when daylight's having time changes or when we travel from one time zone to another time zone,

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we feel kind of crappy because our daily activities are out of sync from our internal clock. So that was known for a very long time, but then around the year 2000-2002, there was a famous experiment by Uli Sibler from Switzerland. What he did, he just fed the mice at the wrong time. Mice are knocked on all their night feeders. And when he fed the mice during daytime, the liver clock, instead of following its own routine, liver clock actually started following food. So that means by changing our feeding time, we can tune our liver clock. And subsequently, the same experiment has been repeated many times, and we repeated that in 2009. And we figured out, yes, actually, outside this brain center called suprachiasmatic nucleus, or SCN, which is considered the master circadian clock, almost the rest of the brain even follows when we eat. And that came out from Peer Shambon's lab in Europe, where they systematically looked at even places that are very close to the SCN. For those who know, there's some medial hypothalamus, paraventricular nucleus, all of this, within a couple of four or five millimeters of the SCN, but they were following food queue. So then, now if we think about it, so for example, when the daylight seven time changes, just one hour change, one hour change in alignment between our internal time and external time leads to kind of feeling groggy and feeling not at a peak for four months for one or two days. So the rule of thumb is when the time giver changes by one hour, then our internal clock takes at least a day to catch up. So that means if you're flying from LA to New York, you're moving through three time zones, then on an average it will take three days to catch up with the New York time. For some people it can be even slower, and for some people it can be two days, but the bottom line is yes, there is a de-synchronous. So then what does it mean for the body? So one of the functions of clock is to anticipate when you're going to wake up, for example, so the blood pressure slightly goes up,

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or heart rate goes up, or breathing goes up.
Similarly for food, almost every organ that is involved in feeding or eating digestion, all of them have clocks.
So even from saliva production,
that is the first phase of digestion,
to secretion of all the digestive juice and the stomach
and then absorption of nutrient and liver metabolism,
everything the whole village expects when you're supposed to eat,
and they're getting ready for you to eat their first meal
after fasting for a long time.
So that's why it's breaking the fast or breakfast.
And when that time changes,
when you change it by two or three hours from one day to another,
then sometimes they're like, oh, food didn't come.
Maybe we'll come at a wrong time.
We were at the wrong time,
and then they'll track the new eating times.
So suppose one day you have been eating every day at 8am,
I ate at 8am.
Is that when you start your feeding window?
When does your feeding window shut?
6pm. So I eat for around 10 hours.
Okay.
And then one day if I switch to 10am,
then what happens is a clock is thinking,
well, the food didn't arrive at 8, but it arrived at 10.
Maybe tomorrow the food will arrive somewhere between 8 and 10,
so we'll be ready around 9.
So then the next day if I come back and eat at 8 o'clock,
then I may eat, but my clock is not ready to digest that food.
So that's why this idea is you have to be consistent
to take advantage of this anticipatory activity of our clock
in different systems to get the best out of it.
Is there evidence that those anticipatory systems
as they relate to digestion help us better assimilate our food?
I would imagine so.
I mean, if you have the gastric juices that are going to help digest
the proteins, fats and carbohydrates
and already deployed at the time when you eat,
I could imagine that food will be better utilized than if you don't.
So in other words, what is the advantage of having these anticipatory signals
in terms of potential health benefits?
The anticipatory signal is really important even from working up.

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The reason why many people feel not ready completely when they wake up to an alarm clock, because the alarm clock wakes you up, but your body is not prepared, so that sleepiness after waking up to an alarm clock is due to our body is not prepared for that.

And then the best example is when the daylight saving time changes, particularly when we have to wake up one hour early, what happens?

People who have underlying heart condition, when they are waking up, when the body is not ready or heart is not ready and all of a sudden the heart has to start pumping a little bit harder, then there is chance of heart attack.

And in fact, people have looked at hospital records and they find that on those days there is a sharp rise in heart attacks. In car accidents, right?

In car accidents too, because your brain is not coordinated, so you cannot make those fine decisions.

So that's a great example of anticipatory activity.

But coming back to digestion, one thing is, and this is something that many people might have experienced, there are many rhythms in our digestive system and one of the rhythms is our intestine has this peristaltic function. It kind of contracts and expands and that moves food.

Food doesn't move due to gravity, so it goes back and forth.

And that peristaltic action actually slows down at night, a few hours after our last meal.

And so that's why when people eat late at night, for example, then that food doesn't get digested because there is not enough digestive juice, first thing. And second, even if it gets digested in the stomach, it doesn't move properly.

So then the next morning people get up and think, of course, people consume some alcohol very often and then they think that this is hangover, but those who don't consume alcohol then they have the food hangover because it doesn't digest.

So that's one extreme example where food at the wrong time can, so healthy food at the wrong time can be crap or junk.

Yeah, I've experienced that where if I've worked late or I couldn't eat dinner or something and then I get home, I always debate whether or not to try and sleep. But if I'm too hungry, oftentimes it's challenging. And so for me, sometimes consuming something

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that at least seems easily digestible like yogurt
or something in a liquid form is better for me than if I eat a meal.
I've made the mistake of going to the refrigerator,
being super hungry and eating a bunch of food at 10 or 11 p.m.
and then falling asleep.
And indeed the sleep, if I'm tired enough, can be quite deep.
But the next morning I feel just completely physically
and cognitively weighed down.
So I think what you just described makes a lot of sense.
So if someone were to select a feeding window,
regardless of whether or not it falls into classic intermittent fasting,
time-restricted feeding,
sounds like eating your first bite of food and eating your last bite of food
at more or less the same time each day has benefits.
I have this question, you mentioned feeding versus eating.
And I think it's actually not just a grammatical semantic issue.
And here's why.
We tend to think about when you take your first bite of food
and then when you take your last bite of food.
Of course, foods digest at different rates, more fat in there is going to digest,
make carbohydrates digest slower, et cetera.
I mean, there's all these adjustments to the glycemic index and so forth
with foods in combination.
Is it better to think about not eating but your fed state and blood sugar?
So for instance, I often get asked on social media, does blank break a fast?
And so I like to think about it scientifically like,
okay, does plain water break a fast?
No.
Does air break a fast?
No.
Does one grain of sugar of sucrose break a fast?
Well, probably not.
But does one teaspoon of sugar break a fast?
Well, you could say yes, but transiently.
Like so, I mean, when we're talking about breaking a fast,
are we talking about a rise in blood glucose?
Or are there molecular signals downstream of a rise in blood glucose
that cannot be reversed?
So I'm going to eat my first meal every day at noon,
and I'm going to eat my last bite of food at 8 p.m.
And at 9 a.m., for whatever reason, I have coffee with one teaspoon of sugar in it.
I suppose in the strictest sense, I've broken my fast.
But maybe if I went for a hard run that morning,

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maybe by 9.30 a.m., I'm back in a quote-unquote fasted state.
So what is the fasted state really?
Because when I'm eating at 8 p.m., just to give another example,
I'm start fasting at 8.01, perhaps.
But I have my blood glucose is elevated, so I'm not really fasted.
I'm fed.
It's just that I'm not eating the verb, right?
So again, I don't want to get overly detailed just for sake of getting detailed,
but I think a lot of the confusion out there about what breaks a fast
is related specifically to this issue,
which is if I eat a whole pizza after sitting around all day,
it's very different than if I eat a whole pizza after having run a 26-mile marathon that day.
Very different, metabolically speaking.
So how should people think about fasted versus fed?
Can we be mildly fasted versus severe fasted?
Can we be fed-ish versus very fed?
Anyway, I'll stop asking questions now because they all relate to the same theme.
Yeah, now these are very interesting questions, and then unfortunately,
as you might have seen in life, the most obvious questions are often unanswered
because it's so hard to do these damn experiments
because if you really want to address this in humans,
you have to bring humans, put them in isolation.
Just like you said, I can now imagine planning five or six different experiments.
Each experiment should involve eight or ten volunteers, each gender, sex,
and then do it, so it's difficult.
So now let's go back to see how do we, let's dissect it in terms of, say, indirect calorimetry.
So for example, indirect calorimetry is based on this principle
that whatever oxygen we breathe in and carbon dioxide we breathe out,
if we can measure these two, then we can figure out whether our body, in total,
we are not saying whether it's the liver, gut, fat, or muscle,
in total whether it's consuming glucose or fat as energy source.
The idea is when we, when we are without food for several hours,
then ideally our body will tap onto glycogen first and then do a little bit of fat,
and then when the body is mostly running on fat, then that ratio of CO₂ to oxygen will come to 0.7.
But what is interesting is we can do these experiments in mice.
So we can go to mice and ask, okay, so what happens in mice?
So in mice, mice are a little bit very different because mice are not simply little people.
They are, the metabolism is different.
They store relatively less glycogen than humans do in terms of total metabolism.
So they overnight within 12 to 14 hours, the RER, respiratory exchange ratio,
this ratio will go from one when they're consuming mostly glucose or carbohydrate as energy
source.
It will slow down, slowly go to 0.7, 0.75.

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So after 12 to 14 hours, they're kind of mostly running on fat.
So now as we give them food within 10 or 15 minutes,
they're not actually consuming couple of grams of food.
They might have consumed say 100 or 200 milligram of that food,
so which is less than say 5% of the food.
And then the RER will immediately begin to rise as if that small amount of food,
stopped that fat burning process and cranked up the carbohydrate burning process.
When you say fat burning process, you mean body fat stores being burned, right?
Not dietary fat, correct?
Yeah, so it's all body fat.
That's why I said we don't know where that fat is being burned
because we are just measuring how much mice is bidding in and out.
So for example, it can be from the skin, so subcutaneous fat or belly fat.
But not dietary fat.
No, by that time the dietary fat is already observed and digested
and hopefully it's sitting in the liver or adipose tissue somewhere,
but it's the fat that's body fat.
Yes, thank you.
Yeah, the reason I ask is that nowadays I think more than half of the battles
about nutrition that I see online relate to this issue where I won't name names,
but someone will come along and say low carbohydrate diet allows you to burn more fat.
And the more nuanced people out there will say,
well, that's true, but you're also talking about dietary fat.
You know, the word fat can confuse people.
I realize you're not doing that.
You are certainly not one of the people guilty of doing this,
but indeed you eat more fat, you'll burn more fat,
but that doesn't mean you'll burn more body fat.
In fact, I think the data say that under conditions of caloric restriction
you'll actually burn less.
I'll probably get pitchforks sent through the mail toward me on that one,
but I think that's true, whereas people who consume carbohydrate can still burn body fat,
even though the majority of the fuel they're burning is from carbohydrates.
So here in this case, for example, from mice, we know that as soon as they start eating,
the RER goes up.
Coming back to your question, what would be ideal for us to do the experiment would be,
okay, so we'll go back to that and then give the mouse maybe 100 milligram of food,
and mouse runs around in the cage, and then we'll continue to measure to see how long it takes
for the mouse to come back and then.
So that's one aspect.
So now let's see, let's stay on this, and then I'll come back and talk about non-caloric food
and how whether that is considered.
I'd like to take a quick break and acknowledge one of our sponsors, Athletic Greens.

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Athletic Greens, now called AG1, is a vitamin mineral probiotic drink that covers all of your foundational nutritional needs.

I've been taking Athletic Greens since 2012, so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and the reason I still take Athletic Greens once or usually twice a day

is that it gets to be the probiotics that I need for gut health.

Our gut is very important.

It's populated by gut microbiota that communicate with the brain, the immune system, and basically all the biological systems of our body to strongly impact our immediate and long-term health.

And those probiotics in Athletic Greens are optimal and vital for microbiotic health.

In addition, Athletic Greens contains a number of adaptogens, vitamins, and minerals that make sure that all of my foundational nutritional needs are met.

And it tastes great.

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And they'll give you a year's supply of Vitamin D3K2.

Again, that's athleticgreens.com slash Huberman to get the five free travel packs and the year's supply of Vitamin D3K2.

So there is a famous experiment that was published last year by Jota Kahasi Slav.

And it came out in science.

And that relates to calorie restriction.

And we kind of started with this idea, we started discussing that the rat experiments were done with calorie restriction

and researchers gave reduced calorie consumption by 20% or 30% and gave that food.

The rats and then subsequently mice and they all lived longer.

What is interesting is in all those experiments, the researchers came and gave this bolus of food at one time.

Whereas the ad libitum-fed mice or rats, they had access to food all the time.

So they were eating all the time.

And then these rats were given 20% less.

And what happens is these mice or rats, they're not going to take that less food, which is less now, and just eat a little bit of lunch and then snack after three hours or snack after three hours.

They gobble up all that food.

Within two to three hours, maximum four hours, food is gone.

So they're sort of on the OMAD diet, the one meal a day.

Yeah, they're almost like one meal a day, three to four hours, food is gone.

Or you can say they're on four hours eating or feeding and 20 hours fasting.

And the question became, well, the benefit of calorie restriction, as we know, is it due to reduced calorie or time restricted feeding or timing?

There is a timing component to it that they're eating all of that within three to four hours.

And then there is a long fasting.

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And this is a difficult question to answer because now you have to ask these poor grad students or technicians to come and split that food into eight or 10 or 15 different small portions and then give them to mice in every two hours.

So Joe Takahashi, who actually published the first paper in 2017, showing that most calorie restriction, I mean, he used the protocol that was used by calorie restriction field.

It actually creates a condition of time restriction.

So he showed that and then he went back and worked with engineers to come up with smart kids where he could actually tell,

he could program how much food is given to mice at what time of the day or night, completely programmed.

So then he took this, for example, suppose say the ad libitum fed mice eats five grams of chow in a day.

And if you want to reduce calories by 20%, then the CR mouse would get four grams of food.

And he divided this into nine or 10 meals and then gave them in every 90 minutes.

So in this case, they're eating small meals throughout the night.

So there is no fasting.

So you can say that, well, this mouse actually is not getting into fasting because in every few hours is getting some food.

And then he measured how long the mouse is going to live.

And he used account, means this is a very standard protocol.

People count how many mice are dying on which day and then examine them to see whether they died because there was an accident or they actually, there was a natural cause.

And then they calculate at the end what is the half life.

So 50% survival because that's on an average, that's a good indicator because if there is an outlier that will live for a long time, then that can skew.

So what was interesting was the ad libitum fed mice, of course, they live certain number of days and then this caloric restricted mice that never got into super fasting,

but kind of eating snacking throughout the night, that also lived 10% extra, 10% longer.

So that means caloric restriction extended lifespan by 10%.

I've wondered about this because recently, you know, there's been, there were a bunch of news headlines about intermittent fasting.

And frankly, I was frustrated if you looked at one major news outlet, they would say time restricted feeding affords,

no additional benefit beyond caloric restriction for weight loss.

Then another popular press venue, let's call it that, same study described as time restricted feeding doesn't work.

And then another one, maybe someplace even more extreme, you know, time restricted feeding only beneficial because of caloric restriction or something like that.

So what you've essentially got are three different interpretations of the same data, all of which are, well, two of which are true.

One of which is false in my opinion.

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But what I think people take away from that is, oh, time restricted feeding isn't valuable, which is not the case.

I think for many people, it's a convenient way to eat because at least for people like me, it's simpler to designate between portions of my day when I'm eating and portions of my day when I'm not eating as opposed to portion control.

For other people, portion control can work.

But all of that is related to either maintenance or loss of weight.

None of it deals with the potential health benefits independent of weight loss.

And so I think that if we can segment those out, obviously in humans, it's hard to know if a given treatment or experiment is extending life because you don't really know how long people would live anyway.

Whereas with mice, you have some sense of when the mortality was likely to occur.

So what can we say about time restricted feeding and longevity in terms of biomarkers or in terms of any other indication that people who start and stop their feeding window at a consistent time somewhere between 8 and 12 hours per 24 hour cycle are tilting the scales towards living longer as opposed to living shorter.

This example of this news article that you mentioned is really interesting because that relates to Joe Takaz's study because I described that if you split calories and eat throughout the day, throughout day and night, then the mice lived 10% extra.

But if you now give mouse the same calorie restricted diet and feed them during daytime, whether within 12 hours or two hours, then the mice lived 10% extra.

Beyond that. So 20% longer.

So let me make sure I understand so that I make sure I understand.

If you take a certain number of calories and you distribute them throughout the 24 hour cycle, it's caloric restriction, the mice will live 10% longer.

If you, however, restrict that to the active cycle, so for humans, the daytime, then they live 20% longer.

So it's not just total caloric intake.

Yeah.

Meaning it's not just important to be sub maintenance and calories for sake of longevity.

It also is important as to when in the 24 hour cycle, you eat those calories. Do I have that right?

So now that's still the story is not over because this mice were fed during daytime and they're not supposed to eat.

That's right.

So for us, it would be the equivalent of being on the night shift and only eating at night but a sub caloric sub maintenance calorie diet.

I guess is the right way to say it.

But when he fed mice during nighttime when they're supposed to eat and they're seeing this getting the same number of calories within 12 hours or two hours, then the mice lived 35% longer than they control.

35% longer.

So scale to human lifespan, which, you know, we don't know, but, but a 35% longer would mean that.

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And again, no one knows, but humans now what is the average mortality in the United States somewhere around life?

Yeah.

So it's around 80.

It used to be 80 now.

Slow reduced a little bit because of COVID, but let's take 80.

Okay.

So people are then now living somewhere between 25 and 35 years longer.

I'm putting some error bars on.

Yeah.

Yeah.

So that was really profound.

But now you pointed out biomarker and other stuff.

So now if you look at any given time within that experiment and actually Joe went back and had a separate cohort of mice, very similar.

And so that he could take tissue samples.

And of course, in this case, you have to sacrifice the mouse.

And he looked for, he did a lot of molecular analysis with known markers.

For example, hemoglobin A1c equivalent or glucose control cholesterol, all this stuff.

He could not find anything that predicted the benefit of caloric restriction.

So that means in this experiment, whatever we know so far, the predictor of longevity, none of them could predict whether this CR only mouse which it throughout the night.

That mouse is going to live less than the night fed mouse that was going to live 35, 25% extra.

Does that mean that there are biomarkers related to longevity that we just haven't discovered yet?

Yeah.

So that's exactly.

So that means whatever we know so far about biomarkers, those he could not use to predict.

Maybe there was a lot of noise.

Maybe he wanted, he had to use more number of mice to get that because biomarkers are not going to predict in every instance.

So there is some error.

What is also very interesting is if you look at the body weight and body composition of all these mice, there is no difference in body weight and body composition.

Across all these different groups.

Across all these groups.

So it doesn't matter when they ate, provided they were sub maintenance calorie intake.

So fewer calories than is required to maintain their weight.

It didn't matter what pattern of eating, they were the same weight.

So that in many ways seems to mimic the human studies where they say, look, it doesn't really matter whether or not you use caloric restriction or you start your feeding window in the morning or start your feeding window in the evening or you portion control for sake of weight loss.

Because you're taking a snap sort of that.

And then another thing with the human study that we are referring to here.

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That in that human study, people are actually already eating within 10 hours window habitually when they selected these people to have them enroll in the study.

So they were already eating for 10 hours and fasting for 14 hours.

All participants had to reduce their calorie intake and they reduced by almost 25%.

The CR group continued with 10 hours eating window and the CR plus time restricted group had to eat the same number of calories within eight hours.

So it's just a two hour difference.

It's just a two hours difference.

Okay, so that people, I just want to make sure people can understand.

So in this human study, which is the one that I felt that the popular press venues all except one venue got either semi wrong or badly wrong in terms of their conclusion.

That was my interpretation anyway, was that either people came into the study eating basically in a 10 hour feeding window, which goes back to my first question, which is that most people are not eating in the middle of the night.

Or if they're on shift work and they are, then they're sleeping during the day anyway.

So they're eating in a 10 to 12 hour feeding window anyway.

So you're saying they either did caloric restriction portion control within a 10 hour window or another group within the study.

A sub maintenance calories to caloric restriction CR as we're calling it the acronym CR, but restricted that to an eight hour feeding window and they didn't see any difference in terms of weight loss.

Yeah, but that's not all that surprising, right?

I mean, if it's just a two hour difference.

Yeah, exactly.

So we have done that experiment in mice and we don't see difference in not only weight loss, many other markers.

And I was telling you about this Jota Kahasi's paper where I told you that he allowed these mice to eat within two hours or 12 hours.

Subcaloric diet.

Two or 12.

Two or 12.

Yeah, that's dramatic.

But still he did not see change in longevity even within those two.

So that means when you do caloric restriction and then at least for months and you are within 12 hours window.

That is giving the mice the best benefit, the optimum benefit.

And two, three or five or 12 for a mouse doesn't matter, at least for longevity.

Can we conclude for humans that whether or not a feeding window is four hours, six hours, eight hours or 12 doesn't matter provided the calories are similar or same?

Well, I won't go to that extent because we don't know many of these.

Particularly, we don't know how this sort of eating window will affect both sexes because we always think many of these mouse experiments even that I told you about those are done only in male mice.

But that should be changing, right?

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Because the NIH, I know this because I'm on study section, which is just a bunch of people who review grants, is that every grant now has to include sex as a biological variable.

It's hard to get away with, or rather I should say it the way it should be stated, which is people are required and should want to look at these phenomena in male and female mice, especially if there are differences.

So in this case, there are many, I mean, there was also another paper in time-restricted feeding that also came out, a big paper showing that the thermogenesis was accounting for loss in fat mass and time-restricted fat mice.

That was also done only in male mice.

So this is, we are paying attention to it.

So we are now doing all of our studies in male and female, and we do see big differences between male and female coming back to humans.

What typically happens is when you're trying to do four hours or six hours of time-restricted eating, people will inadvertently reduce their calorie intake.

Just because of gut volume.

I tried one meal per day, and I felt like I was eating so much at that one sitting that it led to a lot of gastric distress and I got tired after the meal.

And part of the reason I like to do time-restricted feeding is I have more energy.

And certainly in the fasted state, I feel more energized, especially if I'm ingesting a little caffeine or something like that.

So people will reduce energy intake, and then some people who are more active, they can actually unconsciously, they may be spending more energy in their physical activity and basal metabolic rate, all of this combined than how much they're eating.

And that can have a very adverse effect in the long term, because we know that this energy deficit, and in fact, there is a scientific term for that.

It's called Red S, Relative Energy Deficit in Sports.

Relative energy deficit in sports, okay.

Yeah, it's because nearly 40% of athletes, not the NFL guys, but a lot of people who do track and field, and nearly 40% of athletes actually experience this Red S without knowing.

Can male and female athletes both experience Reds?

So it's Reds, R-E-D-S, Relative Energy Deficit in Sports.

Interesting, as a first I've heard this acronym, we have a new acronym folks, this is good to add to it, a list of other acronyms.

So males and females can experience it.

So in females, I've heard that Reds can lead to amenorrhea, so loss of the menstrual cycle.

Yeah, so that's so common, so prevalent that in fact many female athletes, they take it for granted that yes, if they are more active than they will lose their menstrual cycle, which may be common, but it's not normal or optimal for health.

Even if they don't want to get pregnant.

Yeah, we had an expert on female hormones come on and say the very same thing, that regular cycling is very important.

Obulatory menstrual cycle is important to try and maintain.

Yeah, so that's one, but then what is really concerning is it does affect bone health.

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And in this state, people actually over a long period of time, they lose bone mass and the bone also becomes more prone to injury, micro fracture and fractures.

So again, it's a risk, means if some people are trying to eat within very short time and they're physically active, that happens.

And it also has impact on, means the reason why these women are losing menstrual cycle is their HPG axis is disrupted.

Hypothalamus pituitary gonadal axis and it starts, it may start even upstream at hypothalamus pituitary.

So that means that HPA axis, hypothalamus pituitary and adrenal axis may also get disrupted.

One of the symptoms of red is also depression, anxiety, bipolar-like symptoms and we know that many athletes experience that.

Well, this may be just peer pressure that always trying to compete and we know that unfortunately there are few athletes who just can't cope it.

And there are many attempted suicide or suicide.

So this is a serious issue and there's also another new topic in the lab to come up with a mouse model of reds and then study it.

But this is one risk why we should not reduce our eating interval to one meal or very short time because it can have adverse side effect that we don't know now.

Maybe in future we'll figure out when we systematically study them.

There are studies that are published showing four hours and six hours time restricted eating has benefits on weight loss.

But those are on healthy individuals and they were in the study.

So the study team were already monitoring.

They made sure that there was no sudden weight loss or weight loss below some safety level.

So those are very different from regular people who may be even normal weight or even within the healthy range.

If they do, then they can potentially.

So that's why what we think is 8 to 10 hours maybe the ideal spot to begin with.

And once you are physically active and you are also spending a lot of energy in physical activity or sports, you can even go up to 12 hours because in mice we have done that experiment.

Up to 12 hours they do get a lot of benefits not all but.

So this is 12 hours of feeding 12 hours of fasting in humans.

Again, nobody has done systematically 12 hours.

But there was one study in Europe from Tin High Collet Lab and Tin High and I we collaborate.

So they used our Mycichadian Clock app.

This is a research app we developed just to this is mostly used in time restricted eating studies.

And he had nearly I think he started with 200 Swiss participants but then at the end he selected and took very small number of people who are very meticulous about recording all their food and divided them into usual feeding whatever they wanted to eat whenever they wanted to eat.

And they were given the advice of Swiss nutrition advice that's given to improve health and reduce blood glucose almost like diabetes prevention program in the US.

And then the other group was given advice to eat within 12 hours.

This was very early on in time restricted eating and we thought that the mice were getting some

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benefit.

Let's try whether 12 hours has any benefit.

The bottom line is at the end of three months and six months what he reported is both groups lost same amount of body weight.

And then there was not too much significant difference between groups, but both groups actually improved their health.

So the bottom line is the Swiss nutritional advice that he was giving, which is the standard of care there.

It achieved the same amount of weight loss as just giving people this advice that eat within 12 hours.

So one way to look at it, look at the result is like this.

And then he went to more extent and actually looked at every single meal these people consume.

So they're close to, I think close to 60 or 70,000 meal records and pictures he went through and then classified them to say whether these are good quality food.

So they call it the Nova classification.

One, two, three, four.

One is the food that you can almost eat raw fruits, vegetables, yogurt, dairy products that you can almost without any preparation.

And then second, Nova 2 is kind of home cooked food that most people will prepare in a few minutes and then three and then fourth one is the food that you can never prepare at home.

So for example, biscuit or cookies that we usually purchase and few other things.

And usually the Nova 4 are unhealthy ultra processed foods, so which we should not be eating.

So the advice is to reduce Nova 4.

And what he found was people who got all this advice to improve their nutrition quality, they actually improve their nutrition quality.

They reduce their Nova 4 food.

And people who were in time restricting, they ate within 12 hours.

They did not change their nutrition quality.

But what is interesting is they both got the same modest weight loss.

So that begs the question that maybe Chin Hai will do this experiment again to combine nutrition advice with time restriction and maybe reduce the time to 10 hours.

And that might help.

So 12 hours is something that I say anyone from five year old to 100 year old can do.

And if you are trying to maintain weight, that might be a good way and combine that with exercise. It will be great.

And people can more easily avoid reds in that way.

And for non athletes or recreational exercises, it sounds like women, if they distribute their calories across 12 hours are less likely to lose their menstrual cycle.

Yeah, so again, this is something that we have to look carefully.

Because we do have the My Security and Clock app that many people download and self monitor and they share the data for researchers.

We will provide a link to that by the way.

It's a great tool.

But once in a while, we do get this input from some women saying, oh, I started doing your time

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negotiating and I am seeing all these problems.

And then I asked them, okay, so what else are you doing?

They typically improve the nutrition quality so that eating only salad and few and they're trying to increase the fiber intake.

And it's really hard to eat so much of uncooked food because cooking helps to absorb more nutrient and then at the same time they're running five miles every day.

And of course, all of this combined can lead to reds like symptom.

So that's why 12 I think is a good point if you're combining physical exercise and better nutrition quality.

Because in mice also, we have seen that if mice are eating healthy food and they're eating within 10 to 12 hours, then they also live longer than mice that are eating healthy food but distributing that calorie over a long period of time.

This is Rafa DiKabah's finding from NIH.

He has systematically done this study with two different types of diet and in mice.

And he finds the same thing that even mice that are eating within 12 hours, they do live longer than mice that eat randomly, even healthy food.

I recall a recent study, I think it was either published in Cell Reports or Cell Reports Medicine, forgive me for not remembering which, but both of course Cell Press journals, excellent journals, which explored time restricted feeding in the context of low carbohydrate or non-low carbohydrate diet.

So it was low carbohydrate versus low carbohydrate and time restricted.

So these are all caloric matched between groups and then non-low carbohydrate diet. So it's a more standard, I think it was somewhere in the neighborhood of 60% of calories from complex carbohydrates.

And as I recall, the greatest weight loss, remember same calories across groups, was achieved with low carbohydrate plus caloric restriction.

And I wondered why all the popular news venues didn't cover that study, but that's why I'm bringing it up now. I thought this is really interesting.

And I'm somebody who's cycled low carbohydrate diet before.

I find it hard to sleep after about three or four days of being on a low starch diet just personally. So I like to eat some starches, especially if exercising intensely or working intensely.

That's just a little editorial there. But look, I know many people who do just feel better on a low carbohydrate diet.

But what do you think of those data? Because it speaks to the idea that, okay, it's not just the total number of calories. It's not just the quality of those calories.

It's the timing of those calories and maybe carbohydrate restriction in conjunction with time restricted feeding might be the best path for people who are looking to lose weight.

No, I totally agree that when it comes to nutrition, quality, quantity and timing, all these three matter.

Nearly 40% of people who maintain healthy body weight, because 60% are overweight and obese, 40% are maintaining healthy body weight.

And out of those 40%, I would say nearly majority of them are very aware about how much dieting and what quality of food dieting.

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So you're really an optimist. You're looking at the 40% of the glass that's, oh, should we say not full? That was pun intended.

But no, it's a very interesting way of looking at rather than saying, you know, why are 60% of Americans obese, saying why are 40% not obese?

That's a very interesting way to look at it.

I mean, subconsciously, we're always making that decision. I mean, I'm sure that you're not going and eating cheeseburger every day because you want to improve.

Yeah, exactly. I wouldn't feel good. I enjoy cheeseburger now and again, but no, certainly not at this stage or any stage of my life.

I think that I think people actually think the pandemic had a lot to do with this. I think that people started to take a look at what they were doing to support or not support their health generally.

I know people gained a lot of weight during the pandemic. Other people got really into fitness. I've seen some colleagues, but you've always maintained, you've always been in good shape.

Actually, it's the first time I've seen you in a while and you've seemed to have aged backwards. So you are a poster for your own ideas and hypotheses about time or street defeating.

But I noticed that during the pandemic, a number of people emerged from the pandemic in better shape. Other people in much worse shape. It seemed like it was a bimodal distribution there.

So yeah, I get the sense that starting and stopping eating at more or less the same time each day, even if caloric restriction is not the main focus, has additional benefits.

Can we talk about some of those benefits as they relate to the other things that impact health? So for instance, if you're starting and stopping eating at more or less the same times each day, are you sleeping better?

Are you getting more predictable shifts in alertness and sleepiness? Can you predict when you'll feel good enough to exercise?

Maybe we could talk about that because you of course are well known for time restricted feeding and the science around that, but also other things as well, not the least of which is circadian biology generally.

So I always think of the main timekeepers for our system being feeding, light, activity and social connection. And temperature.

So how do these combine with one another? And using timing that we begin and stop feeding is kind of an anchor point. Can we explore that a little bit?

Yeah, so we got into this beginning and end and then you asked for the calorie, how much calorie will break the fast. One thing that I want the listeners and viewers to bring back to this timing of when we're breaking the fast because we equate health with weight, body weight.

And that's why we are talking about nutrition quality and quantity because both of them have impact.

So now let's think about mental health because a lot of people do struggle with mental health. They have anxiety or depression and also, so gut health because there are a lot of people who also have acid reflux or heartburn.

And we know that acid reflux or heartburn can be exacerbated by caffeine intake and empty stomach.

Those who have acid reflux or heartburn, they're prone to that than having black coffee in the morning before any food can upset their stomach.

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So that's why in those cases, it's very clearly that caffeine for them becomes the trigger that something, the food is supposed to come and then the stomach is not seeing the food.

So it's overreacting, producing excess acid and that comes up to the esophagus and that's what their experience is.

So if people have that kind of condition, then maybe they should consider when they drink their first coffee is breaking their overall fast or putting their health at risk for acid reflux.

The other thing is people who have anxiety, panic attack, we know that caffeine can judge you off. Especially on an empty stomach.

So for them, again, caffeine can be a trigger.

So that's why I want to kind of differentiate that there is this mental health and other aspects of health.

And these are two clear examples where anxiety, panic attack related to brain health or acid reflux related to our gut health.

In those cases, when we consume that caffeine in the morning can affect.

Do you avoid caffeine in the morning?

No, actually, here is the interesting history about caffeine.

And this is something I did not know.

And I was once invited to this history of nighttime activity.

And maybe we can take a little bit of detour and talk about nighttime activity because that fascinates me as a circadian biologist.

Because over the last 200,000 years means we assume that humans homo sapiens evolved 200,000 years ago.

So we have been as a species, we have been living on this planet for 200,000 years.

And only in the last, you can say, couple of thousand or 5,000 years when we came to control fire, or maybe you can even go back to 100,000 years.

There is some debate.

So then the question is, well, when you control fire and we lighted up the fire and we could light up whenever we wanted, we can add fuel and we can stop the fire when we don't want it.

That's the key ability in humans that differentiates them from all the other species.

No other species.

We can always say, yes, there are signs of this intelligent decision making.

For example, we know many crows can make decisions.

Many animals, they kind of figure out, strategize how to get food, but controlled use of fire is something very specific to humans.

And when we started controlling fire, fire did not essentially extend the day because fire created an evening that was very different from what people did during the day and what people used to do during the day.

They worked a lot, means gathering food was almost everything that we did.

And so in the evening after we brought food, mostly tubers or maybe lentils to cook or once in a while animals so that we could barbecue, all of these things happened around fire.

And fire was so expensive that it was mostly communal fire.

So if you go back to, for example, Maasai and all these populations that have no access to electricity and are still living kind of that historical life, fire is a communal event.

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And they sat around the cooked food.
And then what happened?
They did not talk about work.
They talked about culture.
They sang.
They danced.
They strategized.
That's how politics started.
Philosophy started.
Science started.
All of these things that are very unique to human civilization started around fireside chat.
So in that way, if you think about it, we are still doing fireside chat.
The only thing is we have the microwave and the television or social media.
So now we chat with our thumbs, right?
So it's still, so we are hooked to that evening activity because that's when we are completely free from the pressure of the work.
And we want to express ourselves.
That's our independent time.
So that's why most people find it very difficult to do time restraining and stop eating at six o'clock because it's ingrained in our even DNA that we want to eat and socialize in the evening.
So now let's fast forward and see what is the role of coffee in this.
If you look at coffee conjobs and particularly cafe where people can come and have a little bit of coffee and socialize, it also started as an evening activity.
And this is in, now we can go back to Istanbul because that's one place where coffee cafes started in mid 16th century.
So we are talking about 1540 to 1570.
And that's when, I'm sorry, I'm forgetting the name of historians who actually invited me.
Okay, his name is Cemal Kefferdahl and I must be butchering the name, but I'll try.
We will provide the spelling and the wonderful thing about social media is somebody will tell us on YouTube the proper pronunciation.
So this is a great opportunity.
If you know the proper pronunciation, please put it in the comments on YouTube.
Actually, I'm even checking right now in my end note library.
It's not picking up that.
That's right.
We'll provide a link.
So what happened was so coffee was introduced and people came and drank coffee and talked about politics at night at night at evening.
And it actually started with with Sufi branch of Islam because they are the ones who consumed coffee in the evening.
And this is the branch of Islam where they actually sing and dance and all that happened in the evening.
So singing, dancing by the Sufi and then here in Istanbul, people started congregating and having

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talk about politics.

But then around the same time, some, you know, in Turkey, there was a good sizable number of Muslims who have to do five prayers a day, number of prayers at set time.

The first prayer is very early in the morning.

And then they figured out that if they wake up and immediately have coffee, then they can stay awake for the first prayer.

And in that way, they felt pretty good when they woke up.

So that's how it started as a morning drink to stay awake and kind of get on with the day.

But what happened was, I don't know whether you have ever tried Turkish coffee.

It's very thick.

Yeah, a few years ago, right before the pandemic, 2019, I traveled to Turkey is first of all, the food is amazing.

The coffee is indeed very, very thick.

Yeah.

And I have a pretty high caffeine tolerance from drinking so much coffee in Yerba mate over the years and still do.

I really enjoy it.

But yeah, it's very intense.

And so what you're saying is that coffee intake started as a way to extend into the night.

The ability to extend into the night at all was because of the ability to harness fire.

And then coffee's stimulatory properties were leveraged toward morning, which is essentially like the way I think about it.

We did an episode on caffeine and someone else, Michael Paul and Nadai described it this way that you're sort of taking a loan out on your energy bank account with coffee.

You're suppressing the adenosine system.

Adenosine makes you sleepy.

But that adenosine system will kick in later.

So it's a credit card of sorts with an interest.

Right.

And the interest being an energetic lag that you're going to experience in the afternoon.

But what happened was with the strong coffee, that gave heartburn and acid reflux to a lot of people.

So then they started eating something with coffee.

And that's how the culture of breakfast started in Turkey.

So coffee actually led to the development of breakfast, not the other way around.

And that, yeah.

So that's very heartening.

Again, no pun intended for the caffeine lovers among us, which I count myself one of those.

So essentially the food before coffee became breakfast.

So you kind of give something to your stomach, so it's busy digesting that.

And then when the coffee comes in, it's not reacting to coffee and creating acid reflux.

So it wasn't as fascinating.

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So it wasn't that breakfast is necessary on its own.

It was essentially a buffer against the gastric distress caused by caffeine intake.

At least in that culture, in that context.

We cannot say that whether the same thing happened and all over the world where coffee is not consumed,

but still people eat something in the morning.

You said you start your first meal of the day at around 8.

What time do you wake up?

I wake up around 6.

What time do you have your first caffeine?

No, actually I have.

So that's why I brought up this story because I have coffee after my breakfast.

Fantastic.

I'm a big proponent of delaying caffeine intake for a few hours after waking for other reasons that my listeners have heard me talk about endlessly, so I won't bother with that now.

But I think just suffice to say that allowing some of the natural waking up signals to occur and using light to kind of clear away and adenosine to further extend and activity is better than using a stimulant until a few hours later.

This is fascinating because I've never thought about the link between extension into the night, socialization, or socializing rather, feeding and caffeine.

I'd like to take a brief break and thank our sponsor, Inside Tracker.

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Actually, I'm kind of speaking what many other researchers have found, and this particularly, this fireside chat, I'm forgetting again the name of the scientist.

I think she's from University of Washington, Seattle.

She went to Africa and kind of recorded what people are talking.

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Of course, she could not understand what they were talking.

Twitter and whether or not Tesla's stock is going up, of course.

Just kidding, folks.

Then came back and tried to translate and then figured out what they were talking during daytime and in the evening were very different.

What are they talking about at night?

Exactly. They're talking about matchmaking and talking about politics and strategizing to gather food or even singing and dancing.

This is, if we think about it, how we manage sunset to our bedtime.

What we do between sunset and bedtime affects most of our health.

I'm going to think about that for a moment.

I totally agree.

By the way, I'm a huge believer and I'm living in great hope for the idea that right now I do think that scientists understand a lot more about the different stages of sleep, slow wave sleep, REM sleep, et cetera, than we do active waking states.

We talk about being focused or being alert, but those aren't scientific terms as we know.

I do believe and I've noticed a distinct difference between the first eight hours of the day in terms of cognition and we know that the catecholamines are at much higher levels plus cortisol, dopamine, cortisol, epinephrine.

That is really at much higher levels than in the later evening.

This evening time, it's certainly in the context of mental health.

We know that morning and evening, we are basically different creatures.

Yeah.

Completely.

Yeah.

That's why I think in the evening, if you think about it, again, this is, again, another set of research from my good friend Horacio.

Dear Glacius.

Yeah.

Oh, yeah.

I'm a big fan of Horacio.

He's a fellow Argentine, so occasionally we riff about things related to that, but he's a wonderful biologist.

Are you guys collaborating?

Yeah.

He's kind of, I say, he's very humble and keeps a low profile, but he does amazing, amazing research.

Totally agree.

He does research that we want to know, but nobody is ready to do it because field research is very difficult to go to the wilderness or go to the places where there is no electricity and then record when these people are eating, sleeping, or in this case, activity, exposure to light, that's what Horacio has done.

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And he puts this active watch, which is kind of a modern activity tracker, but it's a little bit more refined because it also collects light information. What he found was most of these Argentinian toas who have no access to electricity, they consistently go to bed somewhere between three to three and a half hours after sunset. So this is very important because we always think that our ancestors, when they didn't have electricity, as soon as the sun went down, they just went to sleep. No.

The fire extended their evening, so they were staying awake for three to four hours, kind of decompressing themselves, that we say, and then doing all these activities, cooking, sharing meals, and then they would go to sleep.

And if you look at the sleep onset variability, it was very small. They are going to bed almost within 15 to 30 minutes standard deviation.

So no night owls versus morning people.

Exactly.

So we'll get to that.

I get attacked for many reasons.

It just goes with the business I'm in of being public facing these days.

But every time I talk about viewing sunrise or low angle sunlight,

getting some sunlight early, someone says,

well, I'm a night owl and it's almost like a protest of trying to protect identity.

It's become this ideological identity related thing.

I'm a night owl.

I'm a morning person and I'm not.

You're telling me that in these cultures where there isn't electricity,

but there is fire, people are going to sleep within all of them

within about 15 minutes of one another.

Yeah.

So there is no such thing as a night owl or a morning person in the context.

Yeah.

So Horacio actually asked him pointedly because,

and then he said, no, he has not seen.

And he has dragged hundreds of people.

And if we ask, there are many sleep researchers,

at least the public facing sleep physicians or experts, they will say,

yeah, we can say one third of people are night owl,

one third are morning and one third are in between.

Yeah, they call them like bearers, wolves.

And I'm not being disparaging of that idea.

I think people really do feel as if they orient towards one pattern or another.

When I was an undergrad student, I never went to bed before midnight.

And actually midnight was my going to bed time.

Exactly like 11.45. I'll try to get ready to hit bed.

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And then by 12, I'm in bed and I used to get up at 6, 6, 15.
That's a pretty short sleep.
With an alarm, of course.
But then daytime, I used to take 45 minutes to one hour nap.
And that was regular.
Like even if whenever I got time, of course in college, you know, you don't have the whole day.
Unlike in high school, you don't have opportunity to nap, but in college, you can.
I might have been one of those kids with his hoodie on napping on the desk, but they come around and they wake you up.
Yeah, but in this case, just come back to the dorm.
And after lunch, usually I used to take nap.
So then in grad school, I remember I rarely went to bed before 2 a.m.
And I could have clearly said that I'm a night owl.
And actually I was a night owl.
I was very comfortable staying off so late.
I was very productive doing experiments, writing all these manuscripts mostly.
But then afterwards, when I look back in postdoc, when we had our daughter, then things started changing because you have to put the baby to sleep.
And then after the baby's slaves, it's almost when you have a baby, your life revolves around the baby.
So then we had to dim down the light.
There is no caffeine and alcohol drinking or any other things after the baby's slaves because we cannot do too much noise.
So then I realized that no, I'm actually not a night owl.
And I became kind of more normal because I could go to sleep between 10 and 11.
And that's how I thought, well, maybe this was very unique to me.
But what is interesting is I have another colleague, good friend, Ken Wright, Jr.
At Colorado.
At Colorado.
And he also had grad students and postdocs like me who strongly believed that they were night owls, just like everybody else.
And Ken took the whole lab for camping.
And when they were camping, of course, there is less light and a lot of physical activity, hiking during the day,
and they all went to bed between 9 and 10.30 p.m.
I love that study.
Yeah.
What Sachin just described was a study.
I think there were two studies.
And there are two.
Yeah.
And what's interesting, as I recall, is that after going camping for a weekend where people wake

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more or less with the sunrise
and go to sleep a few hours after sunset, their melatonin rhythms and cortisol rhythms and sleep wake rhythms persisted on that schedule
for several weeks, despite returning to environments where there was a lot of artificial lighting, which I find amazing that just a weekend of consistent rising and going to bed with the sunrise and sunset more or less
allowed a reset that was very long lasting.

Yeah.

So actually, even in Horacio's study, he found that almost all the Tobas, they wake up around sunrise time.

And it's amazing when I look at the standard deviation.

It's like so tight.

So take that night owl, so-called night owls.

I also, in graduate school, I would work until 2 a.m.

I loved it.

I'd blast music in the lab.

Everyone was at home pretty much.

Not everyone, but there were the night crew.

And then I'd get in sometime around, get up sometime around 9.30, 10, and then get in around 11.

And it was no problem because I was going to stay so very late.

And then over time, I noticed I'd become more locked to a standard schedule.

So I think what we're saying is that the clock can, our internal clocks can shift.

Yeah.

But this idea that we are genetically biased toward one schedule or another may need revisiting.

That's the conclusion I'm taking from this.

A couple of aspects. One is, you know, some people are genetically so pre-programmed because the other flip side is what is called technically familial advanced sleep phase syndrome.

So these people, you can give them caffeine or whatever, but they will fall asleep at 8 o'clock.

They cannot stay awake till 9 or 10.

And since it's a very strong phenotype in sleep and circadian rhythm field, they are very well studied.

So in fact, Louis Petacock and Ingwi Fu, they were the first one to track one family like this.

And then they figured out there was a mutation in one of the clock genes, period two, that clock gene.

And that mutation allowed the clock to run in a way that these people went to bed very early.

So I guess historically, given these fireside chats, those people were probably not contributing much to the political discussion.

Whatever they decided after they went to sleep is what they woke up into.

That reminds me because as you were describing the difference between nighttime discussions versus morning discussions,

is there any theme to what is discussed in the morning versus in the nighttime,

where people just sipping their eating and sipping their caffeine and just waking up?

But are there any ideas about what morning discussions really consist of?

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Morning discussions or daytime discussions are mostly about work and like hunting, gathering, farming, all that stuff.

And even these days, that's what we do.

I go to work and it's mostly one meeting after another and we're talking about how, means if you're in different committees and you're solving problems or your students come with questions, you have your TA or the office hours.

All these things work related.

We're not talking serious philosophy, unless you're in the philosophy department and you're talking of political science.

And also we are not singing and dancing.

So that's why the evening activity, even these days, are very different.

And typically the evening activities are where we express ourselves.

We express who we are.

We feel like we are free.

And you know, you and I, we have this academic intellectual freedom.

We can talk about our work just like we are talking now.

There are a lot of people who work for, even in tech industry, they may be working for Google and all these big tech companies.

They cannot talk about their work to anybody else.

It's all secret.

It's all secret.

So just imagine they're spending more than half of their wake up time at work, thinking and doing work, but they cannot talk about that work, even sometimes to their own family members.

So then what happens for them?

A lot of people also do the same thing, like the person who is going and baking in a restaurant or cooking or the person who is taking drugs and driving.

Or nurses and doctors can't talk about their patients.

There's confidentiality.

And some people just don't want to talk about it.

It's so stressful.

They don't want to bring that stress home.

So that's why I always say that from sunset until we go to bed, during that time, we try to find time for ourselves.

People say this is me time.

The me time is essentially we want to truly express who we are or we want to entertain ourselves because on the fireside chat, it's not that everybody was a performer.

There are also some audience.

So we always switch our roles.

Sometimes we are performing and sometimes we are observing.

So that's what happens with me time.

I love this.

So maybe social media time should be restricted to just maybe a small portion of that evening time because I would hope that people would also interact socially in the real sense.

Or maybe in a constructive way or maybe you use that for connect with your family members whom you love or you can have some productive discussion or something.

So it's kind of interesting.

I think it's extremely interesting because I think again this conversation about time restricted feeding is really a conversation about security and sleep wake activity and human evolution.

So that's why let's go back to this night out because we kind of made a comment that maybe it's not genetic, but this is where I'm still wrapping my head around because these days there's some GWAS studies where they're trying to look at night

owls to see whether there are some genetic linkins.

And you know, sometimes we always think, yeah, if you take half a million people, of course you'll find some loci that.

But going back to this idea that are some people more sensitive to light so that it's likely that the same level of light even in the same household may make some people stay awake late into the night.

Whereas other people are more resistant to light so that they can go to bed early.

And since light has become so prevalent these days, and the store bus story that we're talking about or people going on camping days, we have removed that light.

So there is some evidence that people's light sensitivity, particularly the IPRGC of this intrinsically photosensitive retinal ganglion cell or the simple speakers, the blue light sensors in our eyes.

There seems to be even one log unit change in sensitivity as measured by pupil constriction.

So for some people, a small amount of artificial light at night could really shift their circadian clock and wake them up essentially.

And then for some it may not.

Yeah, I'm very sensitive to light at night.

Yeah, exquisitely sensitive to it.

Oh, so then you are like a teenager.

Yes, in many ways.

I've been told this. Thank you.

I think I have actually switched to using a red nightlight, but I should be clear, not a fancy high cost red light for sake of any kind of infrared simulation, but a red party light type light.

And I find that was based on reading one study that we covered in an episode on jet lag and shift work, which was that it seems to reduce the cortisol releasing properties of light at night to use red shifted light.

So I just use a red light bulb actually travel with one if I go to an Airbnb or hotel and I switch to red light.

And I find that I fall asleep and stay asleep throughout the night much more consistently, especially when I'm in new environments where it always makes it disruptive to sleep.

It's made an enormous difference in the depth and duration of my sleep.

And because oftentimes hotel lights, you know, in the bathroom, you'll turn them on and just you're just getting being and you're right.

Some people don't seem to be bothered by that.

I really struggle with that.

Yeah.

And in fact, in teenagers, right after puberty, there seems to be, I think that's when the teenagers become more sensitive, sensitive to light.

And it's very, it's well known that the teenage boys and girls, they tend to stay awake late into the night and they can stay up to 12 past midnight.

Although they can stay up that late, that doesn't mean that their sleep schedule is reduced.

Their body still needs the same amount of sleep as other teenagers.

So that's why they are more likely not to wake up at six, 30 or seven when we expect them to wake up and go to school.

I have a question and I ask every circadian related biologist that I can come into contact with this and no one has been able to give me an answer one way or the other.

But I grew up hearing that every hour of sleep before midnight was of more value or potency than the hours after midnight.

And indeed, I find that if I go to sleep at 930 or 10pm, I can wake up at three or four am feeling pretty fantastic and ready to lean into the day.

But if I get the equivalent number of hours of sleep starting at midnight, I feel like complete garbage when I wake up after five, six hours.

So is there any truth to the idea that going to sleep within three hours of sunset is somehow better for our circadian timing mechanisms?

Well, there are a few things. One, you said that you are very sensitive to light.

So I assume that you also avoid bright light in the evening.

As best I can.

As best as you could.

And then what is happening is with absence of that bright light, your melatonin levels begin to rise.

So you are prepared for sleep.

Of course, this is something that we cannot measure because measuring melatonin in every one hour or 30 minutes is very difficult and there is no consumer facing product yet.

So it's likely that your body is preparing very well under this dim light to fall asleep. And when you are trying to stay awake and go sleep at midnight, then maybe from midnight for the first three or four hours, you are sleeping well.

But then after that, your melatonin level might be beginning to fall and it's not only melatonin, your core body temperature and then your heart rate and everything is changing to make you awake.

But the sleep debt that you have accumulated is pushing you to be in bed. So there is this tension between the circadian aspect and your sleep debt.

And unfortunately, you cannot have good night of restorative sleep for the second half of the sleep because of the tension.

That makes good sense.

So that's why you are not the only one. There are many people who experience that. And in fact, a lot of people think that, well, this may be the way I sleep.

Maybe I am not designed to sleep restoratively until I sleep one day just like the camping trip.

And then they realize what it feels like to be happy.

Absolutely. I want to make sure that we talk about the other aspect of fire, which is you had a paper that came out recently, very interesting paper, studying firefighters and time-restricted feeding and firefighters.

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Would you share with us the general contour, maybe even some of the specifics of that study? Because I think it's very interesting for the sake of shift workers, but for everybody really to understand these results.

Yeah. So let's go back to shift workers because this also relates to all of us because I always say that each of us is a shift worker or has lived the life of a shift worker.

And we have experienced how terrible difficult it is.

And now let's start with what is the definition of a shift worker or shift work like lifestyle.

There is no universal definition, unfortunately, but there are many European countries and particularly if you go to international labor organization, then you'll find some references.

Different European countries have slightly different definition, which essentially points to if you stay awake for two or more hours during your habitual sleep time.

And when they say habitual sleep time, they assume that we have, just like you said, we are kind of programmed to sleep somewhere between, say, 10 p.m. and then stay in bed and kind of wake up after 5 a.m.

So the idea is if you stay, if you're staying awake for two or more hours between 10 p.m. and 5 a.m. and you are engaged in some activity, whether it's physical activity or intellectual activity, you are not lying in bed and wondering, worrying about something, but actually working.

So that defines, that's defined as shift work and you don't have to do it every single day.

Even if you do it once a week for 50 weeks, then that itself is enough to disrupt your physiology and metabolism behavior, brain function, like a shift worker.

The reason is, as you discussed, when you change our external timing queue, so in this case, when you travel jet lag or traveling across three days, three hours of jet lag will take three days to reset. Similarly, if you're staying awake for two hours extra or if you're waking up two hours before your habitual wake-up time, then we just don't get wake-up and then be engaged in some activity in the dark.

Most of us, unless you are wearing infrared goggles, we turn on light and light research our clock. So in that way, every time we stay up for two or more hours, even for one night, then for the next two nights, our clock is kind of trying to catch up.

So in that way, for three days, the day of the disruption and then two days following the disruption, our clock is trying to catch up with the outside time.

Our clock, our body is not on time with our clock. So that means almost for half of the week or half of the year, our clock is trying to catch up.

So that's the definition of shift work.

So now let's come back to Department of Labor Statistics, US government.

They have not been tracking what percent of people are doing shift work accurately because there are many difficulties in tracking too.

But it's generally accepted that one in five working adults is a card-carrying shift worker.

Card-carrying shift workers means they are nurses, doctors, firefighters, and bakers, truck drivers, and many in the service industry.

So that's one in five. So 20% of working adults.

Then if we think about all the college students, just like I was doing and you must have done, there are also...

Granted deadlines.

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Granted deadlines.

Granted deadlines.

Then we are also experiencing the lifestyle of a shift worker because we're delaying sleep.

Even if you're delaying sleep by two hours for most of the college students for five days and then the weekend you're trying to catch up.

That's kind of a circadian disruption going on.

Then you take 1.5 or 1.6 million new moms in the US every year.

So when the child is born, then that mother is a shift worker.

And actually that mother is worse than a shift worker because, you know, you don't know what time of the night the baby will wake up and how many times.

And there is no weekend in motherhood.

So they're also living the life of a shift worker.

We don't count many food delivery and Uber drivers, Lyft drivers as shift workers, but many of them we know that they live.

So in that way, we think the actual number of people who are experiencing the life of a shift worker is somewhere around 50% of the adult population at any given time.

So that's why it's also another point that you might have heard from people that will say, oh, I cannot do time restricting because my schedule is messed up.

Or I work in a different way and that comes into play.

So that's why we thought, okay, so we should try something on shift worker.

Another point is although one in five people are shift workers, they carry disproportionately heavier burden of disease because almost all is related disease that we can think of whether it's high blood pressure.

Usually high blood pressure starts in 40s or 50s.

High cholesterol, gastrointestinal problem, indigestion, chronic inflammation of the colon, and then even colon cancer in many cases.

And then of course, diabetes, all of these are disproportionately more prevalent among shift workers.

But then when you think about clinical trials, whether it's a drug or a lifestyle, often one of the top 10 exclusion factor criteria is shift work.

So people who are doing shift work, we exclude them from many of these trials.

One thing is most physicians and most scientists, even people who do shift work, they know that their body and mind is so messed up that often time even medications may not help them.

And so that's why we don't try new medication, why to take the risk when we know it may not help them.

And then when it comes to lifestyle intervention, whether it's sleep extension, for example, we cannot do because they are supposed to stay awake and do their job.

We cannot ask them to stay asleep at night.

And then physical activity and exercise, some people can do, but some people are so tired after all night that they don't have the energy to do physical activity.

And then nutrition, again, most nutrition studies involve the participants to come to the clinic and get one-on-one or one or attend group sessions and they cannot come.

And they cannot even sometimes come to the clinic visit when people have to take, draw blood.

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And in fact, there is another caveat that just if suppose I'm healthy, I have perfectly normal blood pressure, blood glucose, cholesterol, everything is normal.

And I live the life of a shift worker just for five nights.

That means I'm sleeping less, maybe four or five hours.

And even if I don't eat at nighttime, of course, many shift workers also feel hungry and just to keep their work, they eat.

Just after five days, my blood glucose level will read almost like I'm pre-diabetic.

Wow.

I actually saw a study in published in Proceedings of the National Academy that showed that even 100 lux dim light present in the room while people are sleeping with eyes closed can lead to disruptions in morning blood glucose levels and directions that are not good.

Yeah.

One night.

So the faint clock in the corner or even a nightlight that's too bright, yeah, could be problematic.

By the way, folks, these effects are reversible.

So whenever I say these things, we get a lot of comments about, oh my goodness, what have I been doing for years?

But kids with nightlights, this is an issue.

But what I'm hearing is that one in five people are truly shift workers in the classic sense.

Their jobs require they work at night or into the night and sleep into the day.

But far more people are shift workers by virtue of the fact that they're tweeting or working or watching movies at night, even though it's not work in that they're not being paid for that time.

They are essentially operating like shift workers.

If we add those two groups together, would we say it's what, a third of Americans?

I would say half of Americans.

Yeah, if you take teenagers because high school students and college students, because again, going back to Horacio's study, because Horacio also collected activity data from high school students and college students.

And we have replicated that with high school students and college students in San Diego.

So that's Seattle and San Diego.

And this study, now there are many sleep researchers that have been collecting this data.

And what we find is typically the high school students, they are going to beds around midnight and college students, at least the UCSD students, we found maybe one out of 100 who went to bed before midnight.

That reminds me that Horacio Iglesias just published this really nice paper showing that counter to what we believe students.

Now there's the University of Washington in Seattle, I should mention, where it's very dark in the winter.

Young people, these are people in their 20s, are staying up later in the winter months compared to the summer months, which is totally counterintuitive.

You think, hey, everyone stays up late in the summer and goes to bed early in the winter, but because of artificial lighting, it's the exact opposite.

Yeah, so another, I don't know whether Horacio monitored it, but my other suspicion, I'm not saying

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whether it's true.

In winter, we are more likely to consume more coffee, hot chocolate in the evening, and that might also be delaying sleep onset.

Makes sense.

So in that way, again, here is another thing which can be related to policy or practice at Educational Institute.

So what happened during COVID was everybody went to remote learning, the assignments became digital and assignment submission became digital.

And there are many systems, online systems that came into play.

And by default, the assignment submission deadline became midnight.

So then now what is happening is, I don't know about Stanford, maybe when you are giving assignment, what is the deadline?

Midnight, typically.

So then most of us, most students, they will try to cram as much as possible, try to solve as much as possible and submit at midnight.

And it'll be really cool to go back to your system administrator to see, is there so many frequency plot of frequency distribution of what time people are submitting their assignment.

Because we know, means when we submit our grant.

Yeah, so I mean, you know, you hear about the obesity crisis, the crisis of metabolic disorders, not just in the US, but everywhere in the world.

I mean, it's really striking.

I remember going to a Keystone meeting, scientific meeting in the early 2000s, and there was a map of the United States and it showed where the obesity rates were over 30% in adults and the entire country basically was lighting up like crazy.

Now it would be the entire country, but there were these kind of zones in the middle that were almost devoid of obesity, Colorado, namely Idaho at that time.

Those are now also fallen under the umbrella of rampant obesity.

And you and everyone is speculating, okay, is it, you know, is it seed oils?

Is it, is it this, is it that, is it highly processed foods?

I mean, I'm guessing it's all of those things, including lack of activity.

But one has to wonder, given everything we're talking about in terms of metabolic dysfunction, late shifted eating, all these issues with late shifted eating and staying up late with artificial lighting, whether or not that could be one of the major factors in the so-called obesity crisis.

It's likely, you know, we always say freshman 15.

That's right.

Because these kids are gaining 15 pounds in their freshman year in college. And this is where I think as educator or professors, it'll be interesting to go back and see what can we do, because another thing that's also becoming more and more common.

For example, I give a circadian rhythm class, means I just give two lectures.

And I remember when I started 15, 17 years ago, that lecture used to be around 1.30pm or 2pm in the afternoon, and it's a two and a half hour lecture.

So it's done by five.

And for the last, before the pandemic, I realized that they changed the timing.

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Now the lecture was starting at 7pm.

So I was finishing by 9, 9.30pm.

And these kids, they had to go and eat after 9.30.

Study, socialize.

Study, socialize.

Fireside chat.

Fireside chat.

And then to express themselves, like to feel free from assignments.

What are they going to do that?

After they submit the assignment, then they're going to do that.

So that's why we had to go back and revisit this issue.

Say, okay, so for adults, for most of us who are working a day job, our deadline is 5pm in most cases.

At least in the university system, the person who is submitting the grant or who is taking care of my IRB or IRC,

they are all living at 5 o'clock.

So for me, everything has to end by 5.

I think for most people out there, so this raises a kind of macroscopic question,

which is maybe it's not so much about restricting the feeding window,

but maybe it's about feeding mostly and being active mostly in the early part of the day.

I mean, I could imagine a time three, four years from now when waking up early

and going to bed within three hours of sunset is the protocol which harnesses all other protocols.

You're going to exercise, you're going to do it in that time.

You're going to eat, you're going to do it in that time.

You're going to socialize, you're going to do it in that time.

And in doing so, you're also avoiding a lot of the issues related to disrupted sleep.

So that's why all these things, as you said,

time-restricted feeding is just one aspect of the circadian health and these are all interconnected.

And going back to the comment about within three hours of sunset, yes, that's good.

But then what happens in, say, Toronto or Vancouver in wintertime?

I guess they're going to bed very, very early, but also waking up very, very early.

You know, one of the things that I hear all the time,

because I'm always beating on the drum of getting morning sunlight,

even if through cloud cover, as people say, there's no sun here this time of year.

And I forgive me, but there is sun unless you live in a cave,

there sun is just coming through cloud cover.

No matter where you live in the world, there's sun unless you live in a cave, of course.

So I want to make sure that we didn't overlook,

what was the major conclusion of the firefighter study?

Okay, so we'll go back to the firefighter study.

So the reason why we did this study was, as I said,

there are a lot of us who are living the lifestyle of firefighters or shift workers.

And shift workers are excluded from studies.

So that means whatever we are learning about, lifestyle or even medications,

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that may be beneficial for people who actually have a normal schedule, but not for people who have a disrupted schedule.

And if you look up clinicaltrials.gov, there are more than 400,000 studies listed.

And if you search, how many studies are on shift workers?

It's less than a thousand.

And then if you ask, most of them are to see what is wrong with shift workers.

Like that's how we know that shift work increases our risk for metabolic disease, cancer, and even some aspects of dementia.

But if you ask how many studies are done to improve the health of shift worker alone, that's less than 50.

It means I have to go back and check the actual number, but it's less than 50.

So that's why we got super excited.

We thought from circadian rhythm perspective, that's something to address.

So this study, again, this kind of study is only possible because I'm at Salk and we are affiliated with UCSD and I can work with UCSD physicians to do this study.

So I collaborate with Dr. Pam Taub, who is the director of cardiac rehab center in UCSD.

And Pam has many firefighters as her patients.

And we both know that the number one cause for death and disability on work for firefighters is not fighting fire, but just getting heart attack and stroke.

So they have a very high incidence of heart attack and stroke.

And they're also highly prone to different kinds of cancer.

And it may be difficult to ascribe cancer to disruption, circadian disruption, because they're also exposed to a lot of toxins.

Anytime fire burns, that smell of fire is essentially smell of carcinogens.

And they're breathing, even if they have the hood on and respirator, they're still good.

So the idea was very simple.

We know that firefighters, nearly 70% of firefighters in the US, full-time firefighters, because there are volunteer firefighters and then full-time firefighters.

The full-time firefighters, 70% of them work 24 hours shift.

So, for example, in San Diego, they come in at, their shift is from 8 a.m. to 8 a.m. the next day.

And they do, at least in San Diego, they do one day on, one day off, on, off four cycles, and then four days off.

But in some fire departments, they actually do 48 hours shift.

So they come for two days, two days off, two days, two days off, and then four or five days off.

Brutal. Thank you, firefighters.

Yeah. I mean, so then the idea was, okay, so we'll screen firefighters and then find firefighters who are metabolically unhealthy.

And then we'll see whether they can actually follow 10 hours time-restricted eating, because the point is, if firefighters can follow it, then everybody else will be.

With all that stress, if they can.

And this is, again, where I should also acknowledge the San Diego Fire and Rescue Department, because without their help, we could not have even submitted the grant.

And at that time, David Picon, who is the Health and Wellness Battalion Chief,

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he's the one who actually approached us because he's very careful.

He knew that the job that they do makes them weaker in the long term and can kill them in the long term.

So he was always looking for new solutions.

So he approached us and then we said, this is the idea.

He said, well, I love this idea because we are not asking them to sleep more

or we are not going to cut down their overtime or shift or change the work schedule.

The only thing we'll be doing is ask them to eat within 10 hours.

And hopefully we can do this.

Consistently between the days that they're working and not working.

Yes.

So that means if they're from 8am to 8am working, then they go home,

then they're going to eat on the same schedule they did when they were at the firehouse.

Yeah.

But while at home.

So they're not allowing themselves to deviate from that.

Yeah.

So we thought whether they can do it or not because the number one goal or the primary outcome in this clinical trial was feasibility.

Can they do it?

And then second was if they do it, then what happens to their blood sugar and weight and all this other stuff.

And then we started the study and we hit the next hurdle.

And that is, you know, firefighters are very, very tight knit community.

And they want to make sure that you understand their culture.

And the best way to understand their culture is to live the life of a firefighter.

So Emily Manugian, who is the first author C and then we had Adina Jadurian, who is now in med school.

She was a research coordinator at that time.

They volunteered.

They said, okay, we'll go to the busiest fire station in San Diego and we'll live the life of a firefighter.

And the San Diego Fire and Rescue and the city, they all agreed they reported for duty at 7.30 in the morning.

They were assigned a bed in the station because all fire stations do have some beds for firefighters to rest and they have assigned beds.

So they were assigned a bed.

Yeah, so every time a 911 call came and if that fire station, in that fire station, that fire engine was called, then just like other firefighters,

they had to run, get into the gears, just the shoes and a jacket and a helmet and get into the seat and attend the call.

Of course, they won't go to the side.

They just get out of the truck, wait there and come back.

So in that 24 hours, Emily got 10 calls at night that she had to run to, but there are more than 10

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times.

They got the 911, every time the 911 call came, then there is a beep that goes out.

All firefighters who are sleeping or resting, they'll get up or if they're doing something, they'll look up to see which engine is called.

Interesting.

So it's not just the ones that go out, it's everyone gets woken up.

Everyone gets woken up.

So that means in a night, typical night, they're waking up 10, 15, 20 times sometimes.

So they're almost like, you know, new moms are like firefighters because they don't have any idea what time the baby will cry and for what reason.

Also, they don't know.

So similarly, that's what Emily did.

And then next morning, once he came back, she was like, no.

It seems easy. So then we did the study and we essentially assigned all the firefighters.

We recruited 150 firefighters.

We assigned half of them to Mediterranean diet because you cannot do any harm.

You have to give them something good.

So that's another thing.

They said, no, we want something that we know works for firefighters.

And there was a Mediterranean diet study.

So everybody was supposed to follow Mediterranean diet and then half nearly 75 of them were supposed to eat within 10 hours.

We did not fix the 10 hours because we said you pick your own 10 hours that you can stick to.

But it has to be consistent from day to day.

So if you start eating at 9am, you finish it at, you know, at 7pm.

And then try to be consistent because we said, yes, we understand that there will be some things.

And you can take maybe half an hour here and there.

And we'll see how many times you can do it.

And what is interesting was, although they were all doing 24-hour shift, they more or less chose to begin eating somewhere between 8am and 11am.

And they did not skip any meal.

They had their first meal or what we call breakfast.

But it was several hours after waking up because they are waking up at 5 or 6.

And they're driving to come to work at 7.30 or 8.

And they're eating the first meal, say between 8 and 11.

And then they finished meal 10 hours later.

And what we found is more or less most of them could stick to doing this at least 5 days out of 7 days.

And then at the end of the study, when we look at their health parameters, one thing is, as I said, we recruited everybody who came.

So that means nearly 1 in 3 firefighters were completely healthy.

They had no sign of any illness, no high blood pressure, high blood sugar, high cholesterol, depression or anything.

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So since we have one third of the population who are already healthy, and then everybody has slightly different conditions, some have high blood pressure, but they don't have high blood glucose. Somebody has high blood glucose but not high blood pressure.

So it was kind of heterogeneous.

So we did not see big difference in weight loss or any weight change between these two groups. Another thing is firefighters actually run almost 8 to 9 miles when they're at the job, because that's part of their exercise routine.

But then one thing that changed significantly in the time-restricted eating group was what we call VLDL particle size and particle number, because this is something that we know is very low density lipoprotein.

These are atherogenic, and if we can manage them much better, then we reduce the risk for atherosclerosis.

So that's one parameter that changed in the time-restricted eating group, even when you combine all healthy, unhealthy, everybody.

Now if we take firefighters who were beginning with high blood pressure, then we saw significant reduction in their systolic as well as diastolic blood pressure.

And the change in blood pressure, of course, we don't claim that in the manuscript, but when we talk about it, some physician would get up and say, wow, that looks like almost there on a blood pressure lowering drug.

So the extent of blood pressure lowering is equivalent to somebody taking an antihypertensive drug. Amazing.

And then those who started with high blood sugar, of course, we didn't have too many type 2 diabetes,

but there were a few pre-diabetic, and they could better manage their blood glucose.

And this is interesting because once shift workers become pre-diabetic or diabetic, they have more difficulty managing their blood sugar than non-shift workers because the work schedule itself will mess them up too much.

Even if they're on many medications, they have difficulty.

That's fascinating.

And I'm really glad that you explained the study in such detail because I would have thought, you know, from reading the abstract, and I did look at the data, but if someone were to look at the abstract, they'd say, oh, firefighters, so they're waking up in the middle of the night and they're, you know, throwing on their gear and going out to calls and do it.

But if I understand correctly, all firefighters are being woken up by the signal, which makes the firefighter population a bit more similar to the more standard population who's waking up in the middle of the night to use the bathroom, getting on social media for a couple of minutes or flipping on the lights.

I mean, it's maybe not as severe as what firefighters are doing.

But we know there are blood sugar regulation issues related to those multiple middle of the night wakings,

especially if people are then staring at screens.

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So I think it's really important that people were able to hear about the deeper contours of the study. I mean, this result of regulating blood sugar better is really powerful. I get asked all the time, you know, I've got a new kid or I'm a shift worker. How can I do this morning sunlight viewing? What I'm hearing is that keeping a regular meal schedule every day. At least five out of seven. Five out of seven or as close to every day. Like sleep, I always say, try and get a really great night's sleep 80% or more of the nights of your life. And on the other 20%, hopefully it's for fun reasons. A great party or something like that or a celebration of some sort. That seems to me a great anchor point when one can't reliably control their sleep wake cycle. Does that mean that if somebody is coming off of shift work and they're very, very tired, that they would be better off staying awake and eating than sleeping? Well, it's, yeah, so this is where we get into nuances. So here the firefighters are 24 hour shift workers. So that means, and they have been working the shift for very long time. So they have figured out. And one thing is, yes, firefighters are different from nurses and healthcare workers who have to work throughout the night. And they're staying awake throughout the night. Whereas firefighters, they get opportunity to sleep. Even with their 10 calls, they actually have opportunity to come back and go to sleep. And in fact, when Emily and Adina, they were in the fire station, what they observed was firefighters after attending a call, they're not coming back and playing cards or trying to watch the news or get the score. They know they will just go back and lie in the bed and switch off the light. So whenever they got any opportunity to sleep, they would try to sleep. So in that way, their sleep debt and sleep pressure during daytime is not as strong as a night shift nurse or a truck driver who is driving all night because they are staying awake throughout the night. So when people say, yes, you found this and can you extend it to other shift workers? My answer is no, we have to go back and figure out. That's why we went to the station and figured out what would work for them. If I have to go and do this for nurses, maybe even I will go or our staff will go and figure out what is their work schedule? What happens? Do they have opportunity to eat? Do they have opportunity to even take five minutes break? What do they do during break? And all of these things come into play. But here, another thing is, I always said that in other time-restricted feeding paper, we see change in nutrition quality and quantity.

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But here, we also saw that somehow both groups inadvertently improved their nutrition quality because everybody was told to eat Mediterranean diet.

They increased their fruits and vegetables and olive oil in text slightly.

And when they had to stop eating early, they also reduced their alcohol intake.

And this is very significant because many shift workers, just to cope with the shift work, they tend to depend on alcohol at night and caffeine in the morning.

So they begin their day with caffeine and end with alcohol.

And now we can relate that many normal people who are not doing shift work, we also more or less begin our day with caffeine and many of us end with alcohol.

And then when they reduce that eating to 10 hours, and then we saw a significant reduction in alcohol intake in the time-restricted eating group, but not in the standard of care or Mediterranean diet group.

I certainly support that.

We did an episode on alcohol and I was shocked when I researched that to learn that zero to two drinks per week is essentially the threshold beyond which you start seeing health deficits, in particular cancers and metabolic disruption, sleep disruption, and increased anxiety when people aren't under the influence of alcohol.

I mean, it's pretty incredible how alcohol has kind of escaped as the opposite of caffeine and therefore not a health hazard.

And here, I'm somebody, I have a drink every once in a while, no big deal for me.

I can have it or not have it.

But it's just striking how alcohol, despite extensive data that it can really disrupt health, even at three drinks per week, is just avidly consumed as if it was kind of like food or caffeine.

It's really incredible.

I want to make sure that I circle back to something you mentioned earlier because I know there are going to be a number of people that ask this.

If I recall, you said that provided that the feeding window is not shorter than eight hours, that men, women, and children can use time-restricted feeding.

Well, what I say is 12 hours.

Excuse me, 12 hours.

Thank you for that clarification.

Because we did a study that was published in 2015.

And again, behind many of our studies, there is a story.

So we are publishing all these mouse stories and then I would go to conferences and then, of course, some people would give me a look saying, well, you must be doing something wrong.

This just breaks the X law of thermodynamics because how come they're eating the same number of calories and not getting wet?

Of course, by that time, we figured out that at least in mouse, time-restricted feeding also changes the gut microbiome in a way that the mice may be pooping out a little bit more fat and sugar than absorbing them.

So one thing that happens in time-restricted feeding, at least in mice, is the liver cholesterol metabolism to bile acid and bile acid excretion in the gut changes because the gut microbiome changes.

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So this is a very nice study.

When Amir Jareenpah was in the lab now, he has his own lab in UCSD and he meticulously did that and we even did bomb calorimetry from the poop and metabolomics from the poop.

And then we figured out that they excrete some calories and then their brown fat activity goes up.

So they may be burning some of these extra calories.

So they're more thermogenic.

More thermogenic.

But anyway, so one nice thing, awesome thing about Salk is if they see that your science is going well, then they will find ways to help you.

And this is when Bill Brody was our president.

He was the president of Hopkins for 12 years and then he was president.

And that time he had started this innovation grant program, which was funded by Arwin Jacob.

Arwin is the founder of Qualcomm and was also a faculty at UCSD.

So he understands there are very few tech leaders who actually spend some time in academia.

So he understood the pain of getting grant money when you have some interesting idea or test some idea.

No knock on the NIH, but I'll do it anyway because I sit on study section for the NIH.

I mean, the NIH wants to see proposals for things that are so certain to work that they're mostly done.

And so really groundbreaking work can happen and does happen with NIH funding.

But more often than not, it is the generosity of philanthropists like Arwin Jacobs and other people that allow the really pioneering the new stuff, the cool stuff, the groundbreaking stuff.

The stuff that really, no, I'm not going to say really matters. It all matters. It's all important.

It matters, but you know, it's high risk and NIH means NIH is not just government is not making money from thin air when it's taxpayers money.

So there is a little bit responsibility or conservative that, okay, so we should not waste taxpayers money on buying this guy kind of project too much.

To be clear, we're not talking about politically conservative. We're talking about scientifically conservative.

They'd be so careful with language nowadays. Pretty soon, we're just going to sit and stare at one another at the microphones to stay safe.

So that's interesting.

So then we started this and then what we did was we, I had an awesome grad student and we got this funding from Arwin and also there are some, any philanthropy matters.

So actually the way we say is yes, if you give me 50 bucks, then that 50 bucks towards goes towards buying the gloves and effing of tubes for one postdoc for maybe seven days.

So true. I think a lot of people don't realize that 99% of laboratory scientists just they don't make them any money off their discoveries.

And even if there is a patentable discovery, typically the divide between the institution and the company that will eventually put that to market is so slim in favor of the others involved that scientists really do this as work of passion, labor love.

So we came up with this app My Security and Clock at that time and we took some lessons from tech leaders, particularly from Amazon, one click checkout.

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Because we thought most nutrition apps actually ask people to detail describe what they ate, go to their food library and then portion size.

So we'll just shortcut all of that.

We just ask people to take a picture of the food, open the app one click, take a picture, second click and press save, third click.

And when they save, the picture actually came to our server, did not stay on their phone.

And we asked 156 people who are not shift workers, just regular worker or homemakers to be part of the study.

No student was allowed to be part of the study because we know that there's lifestyle is like shift workers.

And we monitor for three weeks.

And so here is some nuances and I want people to understand.

So suppose when somebody is starting to eat at say 7am and since the recording everything, we caught every single thing.

Even if they ate half a cookie, they had to take a picture and they actually took picture because it's not, it becomes second nature after three or four days that every time they ate something.

Even if there was a glass of water, they actually took a picture because we asked them, take picture of everything, we'll figure out what it is.

What is surprising was we found the median, so the median number of times people eat within a day 24 hours a day is actually seven.

So it's not, it's not that we are eating three times a day.

We actually snack a little bit.

Seven times per day.

Seven times.

And there are 10% of people, the top decile was eating 12 times a day.

Wow.

And it makes sense in retrospect sometimes maybe I'll fall into that seven or eight before I did this study.

Because you know, getting up having coffee with cream and sugar is one and then I ate my breakfast.

That's two.

Then I came to the lab and I found that cookie.

That's three.

I went to a meeting and there was some cookie and something else.

That's another one and lunch and then afternoon somebody asked me to go out and have a meeting and so if you think about it, it's very normal that we can go seven to eight times 10 times.

But then if we look at what time say I start breakfast and as I said, we see that in many people they'll start at seven o'clock and one day than 730 another day than 815 another day.

They go back to 6am because they had to get up early and go to work.

So we took all these food data from three weeks and then ask what is the time when your body's system is expecting it to eat because it's kind of averages out.

It's kind of thinking, okay, maybe for you if you're eating breakfast at say somewhere between 6am, 730, 745, 8.

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Maybe you are expecting food around seven o'clock.

Let's forget about 6.15.

That's an outlier.

And then similarly at the end of the day, if somebody is eating, finishing the last bite or the nightcap, whatever you call it, say one day at 9pm, 9.30pm, 10, 11, 12.30 or one.

Let's ignore that one and 12.30.

But still we got somewhere between 7 to 11.30 for that person over three weeks time.

So this is how we kind of figure out what is the likelihood that your body will encounter food.

So when we do that, what we found was nearly 50% of adults in our study ate for 14 hours, 45 minutes, that window when your body is expecting food.

So it's easy to say that 50% of adults are eating within 15 hours or longer.

Wow.

And quite frequently throughout that.

Quite frequently too.

And then if we ask what fraction of our adults were actually eating the conventional within 12 hours, three meals a day or something like that, that's 10%.

So snacking has gone up dramatically.

However you wanted to find snacking, the frequency of food intake throughout the day.

And outside this breakfast, lunch and dinner, there are all these small snacks here and there.

And also for a lot of people, the dinner is delayed.

And we went back and looked at, okay, so what kind of food people are eating later at night and all that stuff.

And what came out interesting, which is very counterintuitive is people who prepared their own dinner.

They're more likely to eat later at night because they're coming home and then they're taking some time to prepare dinner and then they're sitting down and eating or maybe they're eating next to the computer, whatever it is.

So that's kind of interesting that came out. But coming back to your point, that's why I say that nearly 90% of adults are eating for more than 12 hours.

So that means a lot of people can, there is scope or there is enough headspace to reduce and eat within.

So as I said, all of this are interrelated.

So when you think about children, most sleep researchers agree that children and teenagers should sleep somewhere between 9 to 10 or 11 hours because young children, even 5 to 10 year old, they should sleep 9 to 10 hours.

They're just pumping out growth hormone and growing, growing, growing.

And then the teenagers, actually the recommendation is they should be sleeping 9 hours because if you take teenagers, take out all the stimulatory inputs to them and then remove homework assignment and everything and then let them kind of equilibrate to their homeostasis.

What they're likely, how many hours they're likely to sleep, that turns out to be somewhere between 8 and half to 9 and a half hours, which also means that going back to sleep, nearly 90% of high school students in this country are chronically sleep deprived because most high school students don't get 9 hours of sleep on a regular basis, maybe in the weekend.

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Probably because of devices.

And also, as I said, this new idea that midnight is your assignment submission time.

I'll come back to that again and again.

I'm hearing that again against a teacher's take note.

It's a very interesting idea as a way to kind of anchor behavior earlier in the day.

I mean, public health is complicated because people are incentivized by fear, but you get more bees with honey, as they say, right?

There's incentivizing people to wake earlier, not necessarily with the sunrise, but wake earlier and go to sleep earlier and eat within an 8 to 12 hour window.

If it's children, it sounds to me like all these health benefits are what I think are going to incentivize people more than, for instance, this idea that, well, if you don't do this, you're going to get dementia or something like that.

Like every day, people will feel more healthy and more productive.

And so that's why I said that even if children are supposed to sleep for 9 hours, of course, they're not eating during those 9 hours.

And we're not feeding children and putting them down to sleep because their core body temperature will be high.

They cannot fall asleep.

So at least they should have their last meal one or two hours before going to bed because typically parents feed them and maybe give them a shower or a bath.

And then they read the bedtime stories.

So it's one to two hours before bedtime.

They're finishing food.

Similarly, on the other hand, after they wake up, it's not that we're waking them up and then feeding them.

So hopefully we're not doing that.

So that's at 12 hours.

Seems to be optimum.

And it's not only I'm saying that if we put all the health recommendations together from pediatricians, then it makes sense.

Fascinating.

I have a question about structuring meal intake or food intake during the eating window.

I have a good friend.

Actually, he's he's the neurosurgeon at Neuralink now, but he came up through Stanford and and he has a habit of eating of skipping one meal per day within a feeding window.

So it might be breakfast lunch, skip dinner one day, then it might be breakfast, dinner the next day, lunch and dinner the next one.

So it's not in keeping with the same start time always, but the end time is either going to be earlier or there's a gate.

It's never later.

Yeah, it's never later.

What do you think about that as a strategy?

You know, in many ways, it feels like that fits with the way that a lot of people's lives run.

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So sometimes, for instance, if I'm in a podcast, I don't tend to eat much during the middle of the day because it makes me a little bit groggy, the post perennal dip in energy.

So I'll do breakfast.

Well, again, at 11.

That's the first that's when I break my fast 11 ish and then dinner, maybe a snack in the middle of the day.

But other days, it's three meals.

Does it matter overall as long as one isn't allowing the start time and the ending time to drift out?

Is it okay if you go from 12 hours to 10 to 8, 8, 10, 4, 12, as long as you don't exceed that, the brackets, are you okay?

So this is where the circadian aspect come in because if you're going, if you're moving that breakfast time or dinner time, three, four hours,

we are essentially causing maybe a metabolic jet lag.

You know, in short term, in weeks, months, or maybe even a few years, you may not see any change.

By the same time, we don't know what is the long-term consequences.

One thing is we always think, I'll come back to this point again and again, we think that our body weight is a marker of health.

Our body composition is a marker of health.

It's not always true because, as I said, it should reflux, feeling, you know, having some pang of depression or anxiety.

We're LDL, like high LDL.

High LDL.

A lot of thin people or low body fat people have very high LDL.

Yeah.

So those are the things that we don't connect with our habit.

And since circadian rhythm and meal timing, meal structure now is a very new field,

I think good studies will come out only in a few years because right now people are just going back and retrospectively looking at some diet record,

one day of diet record and trying to glean too much out of it.

But I think hopefully things will improve where people will become, it will become standard to at least look for one week of diet record.

Meal time and what they're eating, all that stuff because now mouse studies also showing whether front-loading carbohydrate or front-loading fat or protein has benefited.

So I think these studies are starting.

So I should not comment whether that's good or bad.

I think it's great to hold off until then we have you back on to discuss.

I have a question about fasting on the longer term.

And there it's a near infinite space we could explore of two days of fasting.

I know people that every once in a while they just decide, I'm fasting.

They've either been eating too much at parties or they're not feeling well or whatever.

They just decide, I'm fasting for 24 hours and they'll still consume water and caffeine, but they'll just fast.

Is there any health benefit or detriment?

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You mentioned the circadian clock shifting effects, but if somebody wakes up on Sunday and they ate too much or they feel they ate too much or they don't like the food they ate on Saturday, they're not really feeling it.

And they're just going to fast into Monday.

Is there any known benefit or health detriment to doing that kind of thing?

There is actually a rich literature on this complete fast and in fact in many religion people practiced complete fast as a way to cleanse their body and people have seen that there are benefits to that. So in fact, every other day eating in mouse model or even in humans that are also initially some studies were done, there are many health benefits.

And right now there are even fasting clinics in Germany where people check in and they're under strict supervision and then they do complete fast or maybe a small bowl of soup which has 100, 200 kilo cal.

And that's all they get to eat.

Sometimes two, three days, four days, five days, even they have gone up to three or four weeks.

For sake of weight loss, is that why?

There are so many different things and they come out pretty well healthy.

Of course, they're under supervision, make sure that they're getting micro, micronutrients, vitamins and electrolytes.

So those studies are pretty solid.

People have observed that.

In fact, there are even idea that fasting, this kind of fasting can have huge impact on brain and people may come out of treatment, resistant depression or something.

So those studies are very difficult to do.

There are only case of one here and there that we hear once in a while.

But hopefully in future we'll see whether the depression, anxiety, the mental health aspect will benefit from fasting.

Because now as there is more and more evidence that there's this gut brain axis and whether the presence of food or the microbiome changes in the gut,

if they can affect brain, then maybe long term fasting, periodic fasting or a few days of low calorie diet back to back,

will be interesting to see how it impacts brain health.

Very interesting.

What are your thoughts on fat fasting where people try and limit their blood glucose by only eating mainly fats,

mainly healthy, typically they'll eat healthier fats of avocados, olive oils and nuts and some animal fats perhaps.

But as a way to keep blood glucose low and also time restrict, this goes back to the kind of low carbohydrate thing.

What are your thoughts on that as a general strategy for health?

I mean it combines sort of two general themes that are out there.

I think both of which are data are still incoming that restricting the feeding times it can be beneficial as well as keeping overall blood glucose lower can be beneficial.

Yeah, I think there is too much emphasis now on blood sugar spiking or we don't know this kind of

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eating pattern for example.

It means we are essentially telling pancreas that okay, these are the islet cells that produce insulin. That is okay, you can take a break, go on vacation for a month or two or three months.

My question is it will be interesting to see what happens to those islets because for example we know that if we disuse or unused our muscles, there is muscle atrophy, muscles will become weaker.

We don't know whether long term consequences of this very low carbohydrate diet where you are not essentially engaging the islet cells periodically.

What is its impact?

So if there is no impact, maybe it's okay because as you know, many people who actually work on ketogenic diet, the researchers themselves, they find it very difficult to stay in true ketogenic diet because the true ketogenic diet is consuming less than 10% of calories from carbohydrate.

And not very many from protein.

A lot of people think ketogenic diet allows them to eat massive amounts of meat and that's not necessarily the case.

Just one clarification for people, Sachin was referring to islet cells of the pancreas which are the ones that manufacture insulin.

So the question is whether or not taking in low levels of glucose by way of a low carbohydrate diet, those islet cells are going to shut off their production.

Very interesting.

I mean, the liver is a very plastic tissue.

I mean, it tends to react very dramatically to lifestyle changes.

Yeah, so that's why it will be interesting to see what happens.

We know that even muscle disuse, for example, people who become bedridden, they lose some muscle mass, but when they come back and exercise, they gain it back.

So it will be interesting to see what happens in these people who are going through long-term ketogenic diet.

And of course, once in a while, because of social pressure or something else, if they don't have access to food or something happens, they may consume some sugar, some blood glucose will spike. But it's not that every spike is bad.

I mean, the reason why we have insulin is for good reason.

To buffer that spike.

To buffer that spike and also, you know, people always say that, well, if you have insulin produced or insulin-like growth factor, those are really bad and you should avoid that.

And I think that's a little bit extreme.

I mean, insulin growth factor is involved in muscle protein synthesis, tissue repair, maybe even cognition.

And it also goes back to, as I say, mTOR activation and all that stuff, people get really excited about how to reduce mTOR activation, rapamycin and all that stuff.

So this is where, again, from circadian point of view, I ask people to think.

So two very popular drug-like molecules or drugs that people think will increase longevity of metformin, which many people agree not all will come to a consensus that it activates ampicinase or

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the sensor and the cells that sense that your cells are fasting.

So metformin kind of activates it so that it kind of, you can say, although it may not be scientifically accurate, the fasting and appeal.

So sort of mimics fasting.

And the thing I'd lump in there with metformin is that berberine is kind of the poor man's metformin.

It's a tree bark extract that also dramatically lowers blood glucose.

It mimics kind of that fasting.

And then rapamycin also kind of reduces mTOR activation.

And people have shown that rapamycin and metformin can extend mouse lifespan and improve health.

So now let's go back to the calorie restriction study that I mentioned.

In calorie restriction, people are giving food as a lump sum and they were essentially doing time restriction.

The mice were doing time restriction.

If we think about it, during daytime, when experimenters are coming to the bivarium, the mice should be sleeping and fasting.

And they should naturally have high level of ampicinase if they're truly fasting and they should also have low level of mTOR activity because mTOR responds to insulin and that should go off at night.

So my suspicion is in many of these experiments where the mice were allowed to eat ad libitum, even normal standard chow.

Now we know that as mice get older, they actually consume a little bit more food during daytime.

Which is the equivalent of human nighttime.

Human nighttime eating.

This is like nighttime eating we know is an issue.

I didn't realize that was more of an issue as people age.

Yeah, so we don't know.

But at least in mice because we can put the mice in calorimetry, look at every single bite they're eating, how much they're eating.

So I guess it was natural to see that researchers found that there is some mTOR activity during daytime when the mice were not supposed to have mTOR activity because they should be fasting.

And since they ate a little bit, they were snacking during daytime, ampicinase activity was not at its peak.

So giving metformin kind of mimic their fasting state and reducing mTOR activity by drug like rapamycin also kind of mimic some aspect of the fasting state.

So my suspicion is since these studies were done always in mice who are supposed to be in the fasting state and both mTOR, sorry, rapamycin and ampicinase activity or metformin kind of are mimicking that fasting state.

That's why we have seen those benefits.

And it will be interesting to see if that experiment will be done in humans in long term because many people are very excited about, you know, there is mTOR long term metformin study and then a lot of people are actually consuming good amount of rapamycin off level.

They can get their own.

So that's my curiosity.

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I'm not saying whether it's good or bad or whether there is science or not.
That's something that will be interesting to control for and see because recently I saw one of my again close friend and colleague at Scripps Katya Lamya suited a very simple elegant study.
People should have done in metformin field.
So it took mice and then measured their blood glucose at different time of the day.
And in fact, just like human blood glucose, our blood glucose fluctuates a little bit.
She saw that rhythm and then in every two hours or three hours on different days, of course, she gave the same dose of metformin to mice.
And what she found was at different time of the day, metformin had very dramatic change in glucose reducing ability.
So which means that even if you take metformin and give a different time of the day for the mouse or even for humans in very long term, of course, in these mice, these mice were not diabetic or anything.
They were healthy mice to begin with.
So in long term, we might see benefits that are very different.
So this brings to this idea that, well, maybe metformin, say, at the end of the day, evening metformin may trigger that fasting state much earlier than end of digestion.
Whereas metformin in the beginning of the day may not, at least from longevity perspective, I'm not talking about diabetes type 2 to diabetes here.
So the same thing with mTOR. Is mTOR going to have much better impact if taken during evening, morning, before meal?
So these are my thoughts that go along with all this fat story that we talked about.
Do you take metformin or blueberry?
No, I haven't taken. Although, you know, I have close friend and colleague, Ruben Shaw, who is now the director of cancer center at Salk.
He extensively works on ampicinase and its mechanisms and so it's always fun to talk to him.
He's a fan. Yeah, I've taken berberine before and I have had two very distinct experiences with them.
First of all, berberine, when ingested with carbohydrates and particular carbohydrates to have a lot of simple sugars,
definitely, I know this because I measured my blood glucose, I did the experiment, allows you to flatten out your blood glucose response.
So, you know, in some sense, if you're, you know, there is this idea if you're going to eat a particularly big meal or sugary meal and you don't want to get a massive blood glucose rise, you take berberine or metformin. Metformin is prescription. I went with berberine because as far as I know, it works as well.
At least for healthy people.
Yeah, for healthy people. That's right.
When I took berberine and did not ingest large amounts of simple sugars or carbohydrates along with it, I experienced profound hypoglycemia.
I felt like complete garbage for about eight hours and I had one of the worst headaches of my life.
Which makes sense. You just got a blood sugar crash. So, if you lower your blood sugar when you already have fairly low blood sugar and you're not ingesting carbohydrates,
you can really bottom out your blood glucose. So, I say that for two reasons. One is kind of a

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cautionary note.

And the other one, when you think about the biology of these compounds, it makes perfect sense.

And I did not pay attention to circadian effects.

Yeah, yeah. I mean, it's a, you know, when I joined Salk, we know Ron Avanthu is the kind of the big leader in metabolism.

And he works on nuclear hormone receptors. These are the master regulator of metabolism in normal cells, cancer cells and many other.

And what was interesting was in the first few years, Ron did a very simple experiment.

He just looked at what time of the day this nuclear hormone receptors are turned on at gene expression level and some at protein level.

And he found that almost all of them have a circadian pattern, at least in some tissue.

So, he went to that length to say even that circadian is metabolism and metabolism is circadian.

The reason why we have a circadian rhythm is to have a daily rhythms in food seeking behavior and eating and also go through a period of time when we should be fasting.

And then on the other hand, all the metabolic regulators also have to follow that rule and almost all metabolic regulators, everything that we can think of connected to metabolizing macronutrient protein, carb and fat, they should also have a circadian rhythm or diurnal cycle to align or misalign.

So, for example, fat oxidation should be in the opposite phase with feeding.

And, you know, in retrospect, at that time, it was kind of amazing to see Ron could foresee, of course, he's smart enough to foresee and predict that this is going to happen to circadian period.

Because at that time, we're thinking of the supra-chiasmatic nucleus, sleep, wake, cycle, and we are not thinking too much about metabolism.

So, that's the awesome thing about SOG, being at SOG, because we have 50 PIs, really crammed into two awesome buildings and with open lab structure, so you bump into each other and talk to yourself.

And with an ocean view.

With an ocean view.

Yes.

It's an amazing place.

I was lucky enough to have an adjunct position there when my lab was at UCSD and it is an amazing place doing incredible ground-breaking work, which of course includes yours.

Listen, Sachin, I'm clear now that we have to have you back on for another series of discussions, seriously speaking, if you'd be so kind and willing to do that.

I want to thank you for several things. First of all, for your taking the time today to sit down and discuss these incredibly interesting ideas in detail.

You know, much of what we talk about on the podcast is obviously grounded in science and often, but not always, is actionable.

And so much of what we talked about today is actionable in the sense that many people are already doing certain dimensions of these things.

Some are not.

Some are hearing about it and considering it.

You've given dozens, I've listed some out dozens of tools and considerations based on whether or not

people are engaging in shift work or not.

I think a lot of people are going to realize that they are shift workers, even though they didn't think they were because of the nature of their habits now to light and to activity and so forth.

I absolutely love the firefighter study because of its relevance to the general population.

Also, another nod to fighter fighters and shift workers everywhere. Thank you.

And, you know, I think among the colleagues I've known for several decades now, you really are one of a very small few who've managed to do both animal studies and human studies, but also animal studies with a very clear eye and a pointer toward human health.

And that's such a vital and rare thing, especially in this day of extremely competitive funding.

So I want to thank you for your time today, for the knowledge you share, the actionable aspects to that knowledge, the science that you're doing in your laboratory.

We will provide links for people to learn more about you and, of course, to go to the app so people can engage in some of the science directly.

And of course, you have several wonderful books now that we will also link to both of which I've read and are wonderful.

In particular, the book, the first book, but also a book related to diabetes and so for diabetics and people interested in metabolic and blood sugar regulation there.

So, you know, on behalf of myself and my team here at the Heberman Lab Podcast and all the listeners, I just want to say thank you so much.

Your time is valuable and the fact that you share it with us and educate so many people is really a gift.

Yeah, thank you. And actually, likewise, there are very few scientists who have taken this leadership role that you have taken to come and communicate science to the public.

It's not easy because sometimes you have to distill it down to a simple sound bite to the point where the scientists and they'll say, oh, that may not be right.

But we always have to keep in mind that we are always living in the dark is of science because the reason why I say that this is not my quote.

Actually, this is from one of my scientific hero Paul Simmel from Scripps.

He always says, think about it. 10 years ago, what you thought was right and the best has already changed.

But one thing is the circadian rhythm and aligning it to our internal clock to our habit is very important.

And as you mentioned, we have our my circadian clock up, which is research facing.

But we have also distilled all of this down to five or six timing component and we have a new app called on time health or get on time health.

Can people access that through the standard app stores?

Yeah, so now it's available in an app store, sorry, Apple app store.

And we want to see how because people always think about fasting.

But as we discussed today, feeding fasting or eating fasting and activity and sleep kind of interlinked.

And we have to kind of balance both of these.

So that's that was the idea behind this on time health program.

And thank you, Andy, because what you're doing is immensely necessary.

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Particularly these days when science is moving at a very fast pace, there are a lot of results coming out.

Sometimes something can be very confusing and you spending your time to communicate science is exceptional.

So thank you, Andy.

You're most welcome. It's days like today where I get to sit down and talk to brilliant colleagues like you who are doing the important work that that really matters so much.

And so as you mentioned a moment ago that there's a lot of darkness and confusion out there.

But thank you for being one of those who's shining light.

Thank you.

Thank you for joining me for today's discussion with Dr. Sachin Panda all about circadian biology and time restricted feeding.

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Again, that's Huberman Lab dot com.

Thank you once again for joining me for today's discussion with Dr. Sachin Panda.

I hope you found the conversation to be as informative and actionable as I did.

And last but certainly not least, thank you for your interest in science.