Introduction to Longevity and Upstream Medicine

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Now I said it's important to find heart disease and cancer, because if you're that individual that has it, it's very important. But on average, if you cured all heart disease, you would extend lifespan by less than 5% for the population.

If you did both of them, it would be around six to seven years. But if you could slow aging, now, so why is that? I'll just go back there. Why does it only extend lifespan by such a short period when I said it's what kills everybody?

It's because aging is the biggest risk factor for chronic disease. So if you don't die of heart disease, you're gonna die of cancer. If you don't die of cancer, you're gonna die of another chronic disease.

But if you slow the whole process of aging, you can extend lifespan and healthy lifespan very significantly. So that's what we're gonna talk about now.

This is Doctor Talks, real talk from real doctors on the issues that matter to you most. Welcome to the Longevity Leaders podcast. I'm Dr. Isaac Jones.

And what you're about to hear is part of a special series recorded at the Disrupt Clinical Event, where the world's top health medicine and longevity experts gather to share their latest breakthrough strategies and real world results.

Let's dive in to the conversation. Such a pleasure to be here with you all. My job is to kind of educate you and set the stage on what's coming next. So we're going to talk a lot about the hallmarks of aging.

So I call it the upstream medicine, right? Upstream medicine is really, let's look at the root cause. Let's look at what's upstream. Let's not wait for symptoms at the end and just control those symptoms.

We want to look at what's happening before that, ultimately to reverse any disease that's there, but to prevent it. So that's what I mean by upstream medicine.

And now in the field of longevity, this is Jean Calment. Jean Calment was the oldest person to ever live that's recorded. And I think part of it has to do with her attitude.

She said, I had to wait 110 years to become famous and I intend to enjoy it as long as possible. So it's that attitude, right? She lived to 122. That's what we want to emulate.

So how do you guys want to age? Does everyone want to be like the person on the left? No offense. How about the right? That's where we want to get to, right?

We want to age with vibrancy, vitality, a lot of what Isaac was telling us already. But you know, as we get older, things start to happen. Have you guys noticed any of this?

Maybe your skin changes, nail changes, some wrinkles, aches and pains. You're kind of more forgetful. Where'd you put those car keys? You know, maybe you just can't handle things anymore, like alcohol.

Hallmarks of Aging and the Big Chronic Diseases

You're not as good at detoxifying. Maybe a little bit of weakness. Can't get that heavy bag up in the overhead bin anymore. Or just insomnia. These are all things that happen as we get older, right?

But they're not inevitable. So let's take a step back and look at what exactly is aging in the first place. Well, aging is characterized by this gradual loss of physiological integrity.

And then that results in impaired biological function, happens in our skin with wrinkles, our liver, our heart, our blood vessels. And then that leads to increased vulnerability and death.

And now aging is the biggest risk factor for chronic disease, right? As we get older, every chronic disease that we know of goes up. Heart disease, cancer, dementia, osteoarthritis, all of that increases as we get older.

And that's because of aging. So this is, has everyone heard of the hallmarks of aging? Put your hand up if you've heard of this. Okay, good. So we've got good.

We're starting with a good base. So the hallmarks of aging is a paper that was originally published in 2013. There were nine hallmarks. It's been updated again in 2023 with 12 hallmarks.

and more keep getting added all the time. But the hallmarks of aging are these underlying biological processes that cause damage to ourselves and that contribute to aging and then all of those age-related diseases I was just talking about.

So these hallmarks then, these changes that happen at the cellular level are now driving that chronic disease that I talked about. That's why aging is the biggest risk factor.

So what are the big top chronic diseases that drive most morbidity and mortality. You know, Peter Tia likes to call them the four horsemen. I talk about five because there's MSK, heart disease, cardiovascular, cancer, neurodegenerative disease, metabolic disease like diabetes, fatty liver, and then breakdown of joints and MSK diseases.

Those are driven by those hallmarks of aging, but we can't ignore them, right? Because step one in longevity is make sure you don't die of one of these diseases.

So we have to look at them. We have to find them early. And you heard Tom Blue talk earlier today about some of the clinics and centers that are doing this advanced testing.

This is multimodal testing. And what do I mean by that? It means looking at the same thing with overlapping but different technologies. That allows you, so if you look at say a blood-based test for cancer, along with a full body MRI.

That allows you to be much more comprehensive. You're not going to miss anything, more accurate, right? Less risk of those incidental lomas or those false positives, false negatives that we're all worried about.

So again, what we want to do is don't die of something stupid. And at Fountain Life, Peter Diamandis is one of our co-founders and he likes to say this all the time.

So that's step one in longevity. And so when is the best time to do this? When is the best time to detect disease? Yeah, as early as possible, right? So let's just take one example of cardiovascular disease, heart disease.

70% of people who die from a heart attack have zero symptoms before they die, right? Every 34 seconds, so just imagine, just in the time I've been up here, someone dies of a heart attack.

Half of you in this, actually probably more than that if we look at our data, have heart disease. And 50% of those people who have a heart attack, it's gonna be their first one because it will kill them.

So this is the biggest cause of death in men and women across the board. We know so much about it and we still haven't solved it. So longevity is don't die of something like this.

So, you know, we need to do a cardiovascular assessments. Have anyone, you've done this or sent patients for this treadmill test? Yeah, helpful. By the time it becomes back positive, you have at least a 70% blockage.

In my view, that's way too late to find things. We have to be looking way further upstream. That's the upstream medicine I'm talking about. So you can start to do some of these advanced cardiovascular assessments.

You can use a CT scan. Has anyone had a CT calcium scan? Great. That's good. That's good. That's a much better step. But did you know that the majority is missed with a calcium scan?

Now, if you now can do the CCTA, you add in some AI technology, that's what you're seeing here on the right is this blue right there. I don't know if the pointer works, but the blue is actually the calcified plaque.

But look at how much plaque there is. Look at the yellow and the red. That's non-calcified plaque in the yellow, in the red. That's non-calcified in that soft, mushy plaque.

That's the stuff that breaks open and causes heart attacks, right? So if you just did the calcium scan, you would think you're doing pretty good, but you would miss most of it.

So it's so important to look deeper and further upstream. Now at Fountain Life, we've been collecting, we have data from about 5,000 people. This is just a summary of some of that data.

And if you look at stage, the green is stage zero plaque, no plaque at all. Stage one is yellow, two is red, and the dark red is the severe plaque. All comers, only 10% of people didn't have any plaque of everybody that came through.

Now, of course, Men have more than women. That's the middle graph. You can see that, but women do too. If you're a medical doctor, nurse practitioner, chiropractor, or other health expert that's stuck in a broken system, there's a better way.

Cardiovascular Screening Beyond Basic Tests

The Freedom Webinar shows you a proven five-step system to build a seven-figure virtual health practice or how to modernize your current brick and mortar practice without the burnout.

Learn to create high ticket programs, automated income, residual revenue, and attract clients ready to work with you. Book your million dollar strategy session today by clicking the link in the description.

We see a lot of plaque in women. So just because you think female, you're not, it still kills women. But here's what's really interesting on the right.

People under 30 years old, So under 30, you think, no, there shouldn't be have any heart disease at all. 70, over 70% of people under 30 had plaque. And now of course it gets bigger as you get older.

Here's the hope, the good news. There was 1.3% of people that were over 70 that had zero plaque. So it's not inevitable. And that's the point. happens early, kitsch it early, but it doesn't have to happen.

Now this is the soft versus the calcified plaque. The blue is calcified. You can see the vast majority of plaque we're finding is that non-calcified plaque.

So just doing the calcium scan is gonna miss it. So it's really important. Now if you think you can find this by looking at biomarkers like cholesterol, okay, let's measure everyone's cholesterol and let's see if they have plaque.

This is what we looked at. We looked to see if we can use a machine learning model to predict the presence of plaque by using their biomarkers, no correlation whatsoever.

You could not predict plaque by looking at cholesterol. Now you got about 40% prediction with one marker here. That's the pink one at the top. It's kind of small.

Hemoglobin A1C, that's your average sugar in your body. That's more predictive of whether you have heart disease than cholesterol does because cholesterol is down there in the light green.

So that's not very predictive of whether you have plaque. Now, when you do have plaque, you may want to consider treating cholesterol. So don't get me wrong, still an important factor, but you have to look at, you look at all those things.

So these are some of the tests we do. We look at, you know, the CT, the fancy MRIs and imaging, but also some of the things that lead to disease in the first place.

So just we'll, we'll. can answer questions of that. And just to look at some of those things that can lead to disease in the first place, this is an example.

Has anyone here heard of the endothelial glycocalyx? Yeah, if you're next door and talking in the boutique, yeah, this is the inner lining of all of our blood vessels.

Every single blood vessel in our body has this little shaggy coat. It's made of these very complicated proteoglycans and glycosaminoglycans. And when those get degraded, that's what allows the cholesterol to get into the wall of the artery in the first place to cause the plaque.

One of the things that breaks that down is high blood sugar. So that's one of the reasons why we see the blood sugar so related to the plaque. So this can be regenerated as well.

And you can check out Cal right next door. So this is where we want to get to, right? You know, we spend, we're born, we get to our peak maturity. And then, you know, somewhere in our mid or about 40, mid thirties, forties, there's this long, slow decline.

Now prevention, we push that decline out a little bit. We want that. But ultimately, we want to get to that top green line there, right? That intervention line.

Now, this is kind of some of the concept of longevity escape velocity. We're not quite there yet, but we want to start to think about what could we do to get there?

And you heard Dr. Attala give an amazing talk on what we can potentially, some of the technology that's available to get us there. Now, I don't know if any of you have seen this, but if you cured all cancer in the world, How long would that extend the average lifespan?

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So back to these hallmarks of aging, fundamental cellular things that happen, but the key is they provide targets for us. Now we can start to use our knowledge of these to understand what can we do to actually impact it and make a difference.

So these are the hallmarks and we're going to go over these. So the first one is epigenetic modification. As we get older, epigenetic, the modification, epigenetics change.

So what is epigenetics? It's just the way that our genes are expressed. It's what controls the expressions of our genes. As we get older, those marks on our DNA change.

So we have a number of different kinds of modifications. You can see little methyl groups can get added to the DNA. When methyl groups get added to the DNA, that kind of turns it off, keeps that gene from being read in most cases.

We also have histones. In order to pack that very long piece of DNA into a tiny little cell, you have to wrap it around really tightly. And we wrap it around these proteins called histones.

But when you want to read the DNA, you got to open that DNA. So how you wrap it and how it opens can change whether it's red or not. So we can add all of these modifications to the histones.

You've probably heard of histone deacetylase. So we had methyl groups and acetyl groups and other groups to those histones to also control how DNA is expressed.

So the way I like to kind of explain this to patients is it's kind of like a highlighter. You have your DNA, and now is your DNA being red or not? If it's being read, if you have the epigenetic marks to read it, it's like putting a yellow highlighter through it.

But you can also add marks like a black marker through it. Don't read this gene, read this gene. So that's what epigenetics do. It doesn't change the sequence of the DNA.

It just changes whether we can read that gene or not. And so we've used this. As we get older, there is a very pretty much in everybody, change in those marks on our DNA that are very predictive.

They're so predictive that we can create biological clocks around them, right? So as we get older, you can see those marks on our DNA change. And so we can have, that's what, one of the most common things we use for measuring biological age now is measuring those methylation tags and marks on our DNA.

And so we have clocks like the Grimage clock that can actually predict your time of death. But the good news is those clocks can be modified a little bit.

And I'm going to show you that. The first trial that really showed that you can impact that rate of epigenetic change was the TRIM trial. They actually used growth hormone DHEA and metformin to control for the insulin resistance you cause with the growth hormone.

Epigenetics and Biological Age

And they showed that it could slow down the progression of those methylation marks, and it slowed down the biological aging. Now they're doing a trim trial too right now, so there's more to be said about that.

So think of your DNA as the hardware of your cell, and think of epigenetics as the software. It's the program that runs how it's read. So we all have the exact same DNA in every single cell of our body, But our liver cell doesn't look like our eye cell, because different genes are read in your liver versus in your eye.

So that software program, it's modifiable. It results in differentiation of the cells. It's reversible, and that's really important. It's adaptable, because we can reverse it when we make stem cells.

And we'll talk a little bit about that. It's inheritable, but it's also prone to errors and bugs, just like software programs can be. Therapeutics is how you can modify that program, the epigenetic program.

Now is this even possible to actually make a big difference in aging? Like if we do modify that epigenetic program, what does that really do? Well, we do that every single time we make a new baby, right?

We actually have very old, you know, you get old sperm, old egg, you combine that, you get a complete reset of the whole program. Whole program goes back to zero.

You reboot it and now you start with all of those new methylation tags again. So we know this is possible because we do this all the time. We just don't know how to exactly the details of it.

So we're working on that. Now, these two mice are exactly the same age, and they're exactly identical genetically. But one looks a lot older than the other.

And that's because they've shown that you can actually accelerate. By changing those tags on the DNA, you can accelerate aging. So we know we can accelerate aging.

Question is, do we know how to reverse that? Well, we've done this, and you heard Dr. Attala talk about this a little bit. These iPSC cells, these are cells that like a mature skin cell can be taken.

Four factors, you heard him talk about SOX, OCT, KLF, and CMIC. Those are four transcription factors. Those are proteins that bind to DNA that help return on and read that DNA or not.

When you just take four of those and add them to a mature cell, you can reset the whole program. It's like pushing the reboot button and make a stem cell.

And you just heard it, that that's a pluripotent stem cell. That's a stem cell that can turn into any other cell in your body. And so we can do this very consistently and effectively.

And so this is now, of course, being used in regenerative medicine. And you heard a lot about that. So we know that it's possible. And we're using these induced pluripotent stem cell technology to create immune cells, for example.

And then you can actually genetically engineer them to recognize and eliminate cancer cells. So there's a lot of research being done around this. And it's very, very exciting.

It's been done in mice when they, this is David Sinclair's lab, where they actually completely wreck the optic nerve. And we know nerve regeneration is very difficult, but with just three of those factors, they were able to restore a site and completely regenerate that optic nerve in a mouse.

So this is really exciting time. Now, what can we do today? Cause it's not available in humans just yet. Well, we know that those methyl groups come from what we eat, right?

The methyl factors from the food we eat. It comes from that food, and that's what helps get added to the DNA, those tags. And that comes from the methylation cycle.

Everyone knows what the methylation cycle is? I want to make sure. Put your hand up. You've heard of it? You work with it? OK, good. So that SAM, right there, the SAM up there, SAMe, that is our methyl donor.

We have to make SAMe in order to provide those methyl groups. Then you get the DNA methyl transferases and all the other enzymes that grab that methyl group.

They add it to the DNA. They add it to a lot of other molecules in our body. And then we end up with S-adenosyl homocysteine and homocysteine. So if you see high homocysteine, a lot of times you think B12 folate.

It's also probably because you're using a lot of methyl groups, right? So you can regenerate that with B12 and folate, but sometimes it doesn't work. And that's, so you have to think what might be using up all those methyl groups, okay?

So you wanna give that. Now this is a classic experiment done by Randy Jertle where they had this strain of mice called the agouti mice. Now they have a gene called the agouti gene.

When that gene is turned off, means methyl groups are added to it. These mice are small little brown mice, they're healthy, they're sort of what they should be.

But if that gene is turned on, These mice are obese, they're prone to diabetes, and they die early. And what they did, and this is the exciting thing, and this is what really started the whole field of epigenetics in the first place, is that the mothers of these mice were fed bisphenol A.

Uh-oh, toxins turned on that agouti gene. That's a bad thing. But the mouse on the left, That mother was just fed the basic mouse chow, and the mouse on the right, the mouse's mother was fed all of these extra methyl groups, given betaine that we would get from green leafy vegetables, methyl B12, all of those things, and that turned off the agouti gene and resulted in a healthy mouse.

So really exciting. This was done in humans. This was Dr. Fitzgerald, a friend of mine, who did this by feeding people A diet rich in these methyl groups could turn back their biological clock, looking at the methylation biological clock.

We know that stress changes that. We know that acute stress, like things with surgery, COVID-19, it increases the biological age, changes the methyl groups, but the good news is it can recover and you can reverse that age.

So there are a lot of things that we have absolute control over right now that can change our methylation and our epigenetic modification. And you can see them all here, things that make us older, like toxins and things like exercise that can actually reverse that age.

Things like food, we talked about that. Not only can food provide methyl groups that act as that substrate, food can actually go in there and change how DNA is actually read.

So sulforaphane and broccoli, it's a whole field called nutrigenomics, it can go in and it turns on the expression of genes that make glutathione and all of these different antioxidants.

So we can use food to actually change how DNA is expressed. we can use things like meditation. Now this is on the left, the non-meditating control. In the red are genes that are lower, and in the green genes that are expressed that are higher.

And on the right here, you can see people that meditated for 30 minutes, just 30 minutes of meditation changed over 200 genes, the expression of 200 genes.

DNA Repair, Telomeres, and Mitochondrial Health

So there's a lot of things we can do right now, and it's really exciting. So think of the same DNA, what environment you put it in is going to change a lot.

So that's the first hallmark, and I always love this one, right? If they ask you anything you don't know, just say it's due to epigenetics, because you're still learning a lot.

All right, the second hallmark that we're going to talk about is genomic instability. And we know we could

accumulate damage in our genes, right? As we get exposed to ultraviolet light, as we get exposed to toxins, it can cause breaks in our DNA.

That's a bad thing because if we get breaks in our DNA leads to mutations, can lead to cancer. It can lead to senescent cells. We'll talk about that, but we have repair enzymes.

So we have repair enzymes. Some of the big ones are called PARPs. So those are poly ADP ribose polymerases. They go in there and they fix the breaks in our DNA.

Okay, that's really important. Now why you've probably people heard of PARPs. Yeah, what's the substrate that PARPs use to fix the DNA? NAD, right? So one of the reasons we talk a lot about NAD and longevity, that's one of the reasons, many reasons, but it's a substrate for these enzymes.

Other enzymes that can repair double-stranded DNA breaks specifically are sirtuins. Now, sirtuins are proteins. They do a lot of things in the body, growth and repair.

But one of the things that certain sirtuin proteins do is repair DNA. Sirtuins also need NAD as a cofactor for them to work. So what we want to do with this is we want to avoid substances that damage our DNA.

Overeating, alcohol smoking, exercise can help. And there's a number of supplements that can help. Now, I'm going to quickly skip over most of the supplements.

You're going to hear from Dr. Rudy Mueller a little later today. And he's going to go into more of the specifics of supplements that can actually address all these hallmarks.

But they're here for you if you want to, you know, grab them. But there are supplements that can really help with repairing DNA like NAD that I mentioned to you.

Vitamin D is really important. Vitamin C, magnesium, zinc. Telomere attrition, another hallmark. Telomeres are those little protective ends on the ends of our chromosome.

Think of them like the caps on the end of shoelaces. When that cap comes off a shoelace, what happens? The shoelace starts to fray and it rips all the way down.

That can happen when that telomere gets too short on the end of our chromosome. The DNA starts fraying. That's bad. So the cell will shut down and the cell will become senescent because you don't want to keep dividing when you have that damaged DNA.

Okay. So the Hayflick limit, so every single time a cell divides, that telomere gets a little bit shorter and a little bit shorter with every division.

So the Hayflick limit, Hayflick was a guy that sort of discovered this, said that a human cell can undergo only so many divisions before it will stop, before those telomeres get too short for it to keep dividing, okay?

So over time, of course, as we get older, you can imagine those telomeres keep getting shorter and shorter. So that's why that's a hallmark of aging. Now there's a lot of different things that affect telomere aging or telomere length.

Some people are born with longer telomeres than others. Now it's interesting that there's a study that showed that children who had older fathers had longer telomeres at birth.

That was kind of interesting, but other things that happen lifestyle, gender, age, right? If you smoke, you shorten your telomeres. Obesity, men tend to have shorter telomeres than women do.

We also know that women live longer and older people, of course. So there's a lot of things though that can affect

these telomeres. Some of them I just went over, but we have an enzyme called telomerase.

Telomerase can actually lengthen some of those telomeres. So there are things that we can take in supplements and other things that can help lengthen those telomeres.

One of the things, and I showed you in the epigenetics as well, that lengthens our telomeres. I want to just shout it out. It's meditation. Meditation lengthens our telomeres.

Okay, so we started the day with a meditation. I think that's great. We all have a little bit longer telomeres now. But there's a lot of things that will shorten them and other things that will lengthen them.

So reducing stress is a huge one. for lengthening and keeping our telomeres long. Inflammation can damage them and shorten them. Toxins, of course, can shorten them.

Exercise, you're going to see sleep, exercise, nutrition. They pretty much affect all of these hallmarks. And then there's other types of supplements we can use as well that will affect these telomere length.

Okay, another hallmark are the mitochondria. I know, I'm not going to ask because I know you all know what the mitochondria are. But the power plants of our cell, right, they take the food we eat, they turn it into energy, which is ATP.

But in the process of making that energy, just like power plants, they produce a lot of exhaust, they produce a lot of free radicals. And those free radicals can damage the power plants again, that exhaust can damage both us and the power plants that make them.

And so one of the things that happens, again, as we get older, is those mitochondria get more and more damaged. We collect more and more damage around them.

And then, of course, when we don't have good functioning power plants, that can lead to cell death and, of course, all of the things that happen with aging.

Now, what's really interesting, as you can see here, is that mitochondrial dysfunction actually affects almost all of the other hallmarks. So you can see when you have an increase in reactive oxygen species, that can cause shorter telomeres.

It can lead to DNA damage and genomic instability. It can cause epigenetic alterations and deplete our stem cells and cellular senescence and impair our protein folding.

So mitochondrial dysfunction is really important to address. And that's why, of course, a lot of people focus on it. because when you have dysfunctional mitochondria, it underlines almost all the other chronic diseases that we've been talking about.

Cancer is actually, I talked about getting cancer from genomic mutations, but if you think, if you look at some of the literature, cancer is actually a metabolic disease.

It's a mitochondrial disease and we know that that's actually a hallmark of cancer. If you take a normal cell and a cancer cell and you take the nucleus from that normal cell and you put it into the cancer cell, it stays normal.

So it's not the DNA. But if you take the nucleus from the normal cell and put it into the cancer cell, it's cancerous. So it's what's in the cytoplasm that keeps the cell cancerous or not, which is the mitochondria.

So we know that in cancer, mitochondria change. They can't use oxygen. They just use sugar and glycolysis to make energy. So the thing about these mitochondria is they're exquisitely sensitive to everything.

They're very sensitive to the reactive oxygen species that they actually make, but all other toxins damage these

mitochondria. We all have probably heard that mitochondria are probably early bacteria that came into our cell, right?

They look like little bacteria. Well, what do we use to kill bacteria? We use antibiotics. Antibiotics really damage our mitochondria, because they're so similar.

So those are things to think about. And then NRF2, you saw this on Dr. Atala's slide as well. This is another one that gets turned on by broccoli. It's one of my favorite foods.

So the sulforaphane in broccoli can actually go in and turn on NRF2, which is a transcription factor. It's normally kept in the cytoplasm, but when it gets triggered and turned on by things like sulforaphane, it goes into the nucleus, and it turns on the expression of a whole host of antioxidant genes.

Because if we depended on the antioxidants just from our diet to protect our mitochondria, we would probably all just die very quickly.

Stem Cells, Inflammation, and the Microbiome

So we have to make our own antioxidants and things like Nrf2 that help us do that. Okay? So avoid all these things. These are drugs that all damage your mitochondria.

Oh yeah, good. No antibiotics should be on there as well. Smoking, toxins, alcohol, all damage our mitochondria. But one of the things we can do that we, you know, talk, you've probably heard a little bit about this, is zone two training.

People know a zone two training is one of the best ways you can support your mitochondrial function. Because zone two training is right at that point.

So when you're not working too hard, when you're at rest, you guys sitting here right now, your mitochondria are burning fat and they're using oxygen to make energy.

But if you now start working really hard, jumping up and down, going for a run, your mitochondria aren't gonna be able to keep up and give you all the ATP you need to keep up with that work that you're demanding.

And they're gonna switch over to using sugar and glycolysis. So they're gonna make energy without oxygen and without the fat. So at that point where they switch from using fat to burning sugar, that's your zone two.

Okay. When you do that, you're actually, you're not working so hard that you're going to damage your mitochondria. You're working just hard enough that you're sending a signal to your mitochondria that, hey, I can't quite keep up.

I need a few more. And that triggers your mitochondria start dividing and making more. So zone two training is a really great way to do that. I want to get about four hours a week of zone two.

These are all supplements that I think you guys are aware of that can also support mitochondrial function. Urolithin A is another supplement you've probably heard a lot about.

It's actually made from the illagic acid found in pomegranates that when we eat the pomegranates, the bacteria in our GI tract turn it into urolithin A.

And that actually helps clean up the damaged mitochondria or stimulate what we call mitophagy. Glutathione, I mentioned that already, right? Anacetocysteine is one of the rate-limiting precursors to glutathione.

But what I like to tell my patients is, look, this is your cell's garbage truck, right? When you have enough glutathione, you're protecting your mitochondria from a lot of that reactive oxygen damage, right?

Goes around, collects all of those reactive oxygen species. So it's kind of a vicious cycle though, right? When you get damage, Reactive oxygen, you use up your glutathione and then you get more damage without the ATP because as your mitochondria get damaged, you can't make enough glutathione and then it becomes a vicious circle.

So supporting and taking either NAC or glutathione can be very helpful. Alright, you've heard a lot about stem cells already from Dr. Atala, but stem cell exhaustion is another one of the hallmarks of aging.

Now, stem cells are important because if we damage ourselves, if we cut ourselves, if we have any kind of tissue damage, we need those stem cells to come in and regenerate that, right?

We always have a supply of stem cells in our body, but as we get older, the number of stem cells and their ability to regenerate gets less and less. And that's why there's so much research right now in the whole field of aging of using stem cells, because we get fewer and fewer of them.

So a stem cell is defined as a cell that can actually make more of itself. So it can replicate and make more stem cells, but it can also differentiate into different types of cells in the body.

And you actually, Dr. Atala set that up really nicely for me. A totipotent stem cell is a cell that can turn into a new human being. That's what happens when an egg and a sperm combine.

You get a totipotent stem cell. As that divides, it turns into a pluripotent stem cell. The pluripotent stem cells are ones that can turn into any other tissue in the body.

You heard the ectoderm, the mesoderm, the endoderm. But then it starts differentiating a little bit more, and now you've got more tissue-specific stem cells, like a muscle stem cell, a bone, a nerve, others.

stem cells or blood stem cells. So there's different types of stem cells. And you heard that embryonic and those induced pluripotent stem cells are the only ones that are pluripotent that can turn into all the different kinds.

And as we get older, of course, the number of stem cells in our body tends to decrease. Now, the placenta is really nature's stem cell biorefinery, right?

That's why a lot of people And you heard about the amniotic stem cells, which are really exciting, but using cord blood, other things for stem cells is also being done.

And there's a lot more to it, but that's kind of what I'm going to say for booing exogenous stem cells. But there's a lot you can do to keep your own stem cells healthy.

You can do intermittent fasting. That can really help your stem cells. It increases the number. Reducing your triglycerides. So high triglycerides can actually inhibit stem cells.

Don't like growing in that fatty environment. So things like omega-3s, exercise, boost your stem cells. Sugar is bad for your stem cells. Inflammation is bad for your stem cells.

Vitamin D is good for them. Resveratrol is good. Curcumin is good. And alcohol is bad for your stem cells. So things kind of no brainers, but they also work on You know, so these things like exercise work on a lot of the hallmarks, as I said.

And now NAD, again, can also support your stem cells. I put nicotinamide riboside, because taking just straight NAD doesn't seem to work very well, but taking a precursor to NAD, and we can get that into that.

And if anyone has questions about that, I'm happy to jump into it. Those can all help. All right. Chronic inflammation is another hallmark of aging because we know inflammation is really important, right?

If we didn't have inflammation in our body, again, we'd all die. We need inflammation to heal wounds. We need inflammation to fight infections. Inflammation is critical.

But when that inflammation doesn't turn off, that's when we have a problem. So acute inflammation is great. We need it. Chronic inflammation, not so much.

Chronic inflammation, the inflammation that just doesn't turn off, that's what causes all of the chronic diseases. So these are a lot of reasons for inflammation.

And I know you guys probably know all of these already, but diet and food sensitivities, your gut microbiome and leaky gut are big reasons for inflammation.

Infections that just never go away that we can't clear. Toxins can drive inflammation. I'm going to show you about blood sugar in a second, the next slide.

Stress is a huge driver of inflammation. If we don't have enough antioxidants to clean up all of those reactive oxygen species, not enough nutrients, just 30 minutes less of sleep a night.

They did this study in young college students. totally increase their CRP levels or inflammatory levels with just 30 minutes less sleep. So not sleeping absolutely increases your inflammation.

That visceral abdominal fat, that's very inflammatory. Now blood sugar, you've probably heard of AGES. So AGES stand for Advanced Glycation End Products.

When we have high blood sugar in our body floating around in our bloodstream, that sugar binds to the proteins. Does anyone know what the biggest age we measure all the time is?

I showed it to you on a way earlier slide. Just make sure you guys are awake. Hemoglobin A1c is an age, right? Hemoglobin A1c is sugar binding to the red blood cell, okay?

So that's an age. But sugar also binds all sorts of other proteins in our body. Why is that bad? Because our immune system has receptors for these ages.

These ages, it doesn't like to see them. And those receptors is perfectly named rages, right? Receptors for these advanced glycation end products. When that age binds the rage, it triggers huge inflammation.

Okay? That's one of the reasons that sugar drives inflammation. One of the reasons we see it's so associated with cardiovascular disease as well. And those ages can drive wrinkling and all of the other things.

So we know a lot of the things you can do to really address inflammation. And these are just some of them there. All right, gut microbiome dysbiosis. That's one of the newer hallmarks.

It wasn't in the original nine. but it's in the newer 12, we know that our microbiome, those trillions of organisms that live in our GI tract, they change as we get older, okay?

And we know that when they change, they can get inflammatory, they can lead to leaky gut. When you have leaky gut, they leak across that gut membrane and that LPS, the coating on these bacteria, again, can drive inflammation.

So this imbalance or dysbiosis happens as we get older and it can drive inflammation. Now, microbiome metabolism is so important, and you guys know how important a healthy gut microbiome is just for overall health.

It turns out that at least 10% or more, if you just do metabolomics and measure all of the metabolites in a human's blood, 10% of them are exclusively derived from the microbiome.

They're not even human. So we have a lot of microbial metabolites circulating around in our body. And we know that, you know, we all know about the gut brain axis, but there's the gut skin axis, the gut lung axis, the gut liver axis.

This microbiome impacts every single part of our body.

Protein Cleanup, Autophagy, and Nutrient Sensing

So keeping it healthy is really important. And like I mentioned already, as we get older, our microbiome tends to change in a very predictable way. You can actually measure microbiome and also predict someone's age.

So you guys know what to do. You probably, if you're functional medicine trained, you've probably heard of the 5R program. I like to simplify it and call it the 4P program, right?

The prebiotics, the probiotics where you give the bacteria, the prebiotics where you feed those bacteria. So fiber, fiber, fiber, fiber, fiber. And then the polyphenols, all of the fruits and vegetable, the coloring in those fruits and vegetables, they create an environment in our gut that actually is conducive to all of the beneficial microbes growing.

And then parasympathetic is that rest and digest nervous system, right? It's very important in order to. just digest our food. We need that rest and digest as we call it that in the first place.

And we also know that with lower stress, we get lower pathogenic bacteria. It turns out, I mentioned, we know that cortisol stress lowers our immune system, right?

We all get vulnerable to infections when we're under stress. What turns out that the bacteria in our GI tract They have signals waiting for that cortisol.

And when they sense that cortisol, they're going, ah, now's a good time to start attacking, right? The host is vulnerable. And so they start growing when we're under stress.

So just being under stress can cause a huge dysbiosis with that alone, right? Another hallmark is loss of proteostasis. Okay, what does that mean? That's really the decline in the ability of the proteins to fold properly.

When we get improper protein folding, that can cause damaged proteins and that of course leads to aging because it disrupts all of the cellular processes that we need those proteins for.

So protein folding is very complex. We have these long strings of amino acids, and we have to fold them in very precise ways in order to make the protein, because proteins only work when they're in a 3D configuration.

And so we have alpha helices and beta folds. We now have the ability, it's called alpha fold, it's an AI that can predict how every protein in our body is folded.

Now, it used to take a grad student an entire thesis, five years to figure out the folding of one protein using x-ray crystallography. We now do this all with AI.

It's really exciting. But what happens when these proteins get damaged, right? So we get oxidative stress, other things that can damage our cells, those proteins get damaged.

So we have to deal with those damaged proteins. And we have all sorts of systems in our body to deal with them. We've got autophagy, right? So we can take those proteins, we can gobble them up and get rid of them so they don't cause any more damage.

We can actually degrade them using these proteasomes. we can actually try to refold the protein. So that's what heat shock proteins do. They're little chaperones that bind and try to refold the protein back to where it should be.

Or we might not be successful and we might get an aggregation of these misfolded proteins resulting in aging. What's the one that everybody knows about the misfolded protein?

Beta amyloid is a misfolded protein driving Alzheimer's disease. Okay, whether you say it drives or consequence of it, it is associated with Alzheimer's disease.

That's a misfolded protein. Again, why dementia and other things are a big part happen as we get older. So what can we do for these proteins? Well, we want to support those pathways that clean them up, the damaged pathways.

So calorie restriction, we turn on the pathways that clean up the misfolded proteins. We want to activate AMPK because that helps clean them up and inhibit mTOR.

Now, I put sleep in here in yellow because all of that cleaning up of everything in our brain, all those misfolded proteins happen only when we sleep.

So if you're not sleeping, you're not cleaning that beta amyloid out of your brain. That whole glymphatic system that washes your brain happens when you sleep.

Okay, we've got 15 minutes and like five hallmarks. I think we can do this. Okay. So cellular senescence happens when the cell just stops dividing. So there's damage to the cell.

The cell does not want to turn into a cancer cell. So it stops dividing and becomes senescent. Okay. So we call them zombie cells. They're the undead cells.

They're still sort of semi-alive, but they're not dividing or doing what they're supposed to do anymore. Now, cellular senescence is not all bad. We need some cellular senescence to heal wounds.

We need some cellular senescence to fight cancer cells. So these ideas of using senescence or senolytics to get rid of all senescent cells is not a good idea.

But as we get older, we do tend to accumulate senescent cells. So different types of stress can cause different types of cell damage. this lethal, intense stress, the cell's just going to kind of shrivel up and die.

It's just necrosis. It can't do anything. Kind of a large stress, it will trigger that whole programmed cell death or what we call apoptosis. But a moderate stress tends to turn that cell senescent and keep it still semi-alive.

But what's the problem with senescent cells? The problem with senescent cells is they secrete what we call SASP, or the senescent-associated secretory phenotype.

That is a whole bunch of inflammatory molecules. It's cytokines and other things that drive chronic inflammation. So cellular senescence is a big driver of inflammation.

And that's why they are bad. And that's why I showed you inflammation is associated with a lot of these chronic diseases. So are senescent cells. Senescent cells can drive a lot of these chronic diseases.

Now, there have been interventions. This was the first trial that showed a drug desatinib, which is a leukemia chemotherapy drug, plus quercetin, or in this case, bisetin, actually decreased all the senescent cells in mice.

So it shows that you can actually use certain things to decrease senescent cells. Now, there's a lot of work being done now on quercetin and other compounds that are similar to phycetin, apigenin as well, that can actually decrease senescent cells.

So the thing in our body that actually gets rid of senescent cells are natural killer cells. There's also a lot of work being done right now of using natural killer cells to go in there and get rid of senescent cells.

Another hallmark is decline in autophagy. I've talked about this one already with the proteins. So we, we, every day, just the fact of living, we cause damage.

We need to go in there and clean up that damage. Again, happens when we're sleeping at night and it gets rid of all the cellular debris, right? Autophagy is just self eating.

We just clean up and use lysosomes and other things to chomp up all of that junk. Okay. And as we get older, their ability to clean up that junk goes down.

So what can we do to actually make a difference? We know exercise can help. Intermittent fasting. When we're fasting, we're turning on all the pathways to clean up the cellular junk.

Stress is bad. Don't eat two to three hours before bedtime. A circadian rhythm, really following a very healthy circadian rhythm is the best thing you can do for autophagy and cleaning up all that damage.

Social connection, cold therapy can also really help. And then there's different supplements. I mentioned quercetin and fisetin already, but there's other supplements that can also really support that whole process of autophagy and cleaning up.

Now this is sort of related. Another hallmark is called deregulated nutrient sensing. So it's really important for ourselves, for our body, to understand Is there food around or isn't there food around?

Because when there's food around, it has to do all the things to use the food, right? It stimulates insulin and IGF and growth hormone. It makes new muscle cells.

It makes new bone cells. It's all of this anabolic activity when there's food around. When there's no food around, when we're in a fasting state, then it turns on all of the pathways that gobble up all the junk, right?

So we need both. You can't live in one and not the other. There has to be a rhythm to it. You need catabolism and breaking it all down, but you need to also build it up again.

Now, in this age of everybody eating a ton of protein, I have to start thinking about that, because I'm going to show you this in a second. mTOR, everyone's heard of mTOR?

Yeah, nod. Okay, cool. Yeah, so mTOR is a regulator of lifespan and aging. Why is that? Because mTOR is a sensor for, do we have food around or not? So when there's a lot of protein and amino acids, that triggers mTOR.

mTOR then goes and triggers all of this anabolic activity. Let's make new muscle, let's make new bone. So is mTOR bad? I'd say no, right? But in longevity, we always talk about inhibit mTOR.

That's the best thing you can do is inhibit mTOR. No, no, we need mTOR. We just don't need mTOR all the time because we need to actually clean up. So now we've got the opposite of that called AMPK.

Now when we don't have, when they're in a fasting state, when there's no protein, no food around, now we turn on AMPK. AMPK goes in there, turns on all the pathways for cleaning up the junk.

But mitophagy, autophagy, you know, it increases our making glucose and decreases gluconeogenesis and increases glycolysis.

Cell Communication and Plasma Exchange

All of those things happen when there's not enough food around because it has to keep us alive when we're going through starvation, right? Or not eating when we're calorie restricted.

So the two work in tandem. They work side by side. When mTOR is up, AMPK is down, that means there's lots of

food, you're building things. When mTOR is down, AMPK is up, that means you're cleaning up all the junk.

Okay, so we need both of them. And so what are things that can change this balance? Well, we know that metformin actually increases AMPK. So one of the reasons metformin is really being looked at right now is a longevity drug, because it helps with cellular cleanup.

We know that rapamycin, everyone's heard of rapamycin, right? Rapamycin is the mammalian target of mTOR, right? And it was found on the, sorry, mTOR is the mammalian target of rapamycin.

So rapamycin was found on the island of Rapa Nui, and that is how mTOR was actually discovered. But rapamycin decreases mTOR. So now if you take rapamycin every single day, what are you doing?

You're inhibiting your immune system from working, right? We use it in organ transplants. But if you take rapamycin periodically, every now and then, what you can do is actually keep this little teeter totter balance going.

Okay. Now, when you do that, is anyone taking rapamycin? One person, two people, three, okay, four, five. All right. Some people are taking it. When you're taking it, the idea is like, don't eat, when you're inhibiting your mTOR, don't eat a bunch of protein that day.

Right? Because you're working against it. So you want to really use it in cycles. And there's a lot of, there's a big research study being done on dogs right now about rapamycin to see if it will extend lifespan.

I think this is our last hallmark is intracellular communication. Now, the cells have to talk to each other, right? We need to know what one cell is doing.

They have to talk. And so they send a lot of signals back and forth. And again, as we get older, those signals start to get interrupted. Now there's a lot of ways to talk to each other.

Cells can actually touch each other. They can make little nanotubules between each other. And these direct ways of connecting to each other signal from one cell to the other, but they can also signal each other when they don't touch directly.

They can signal each other by releasing these soluble factors, these autocrines that go back and talk to each other, but these extracellular factors. Now, little vesicles that blub off the side of a cell that are filled with all kinds of messaging molecules, we call those exosomes.

Exosomes are these little packages that blub off the side of a cell that are filled with communication. So when one cell wants to talk to another, it might send an exosome out.

Okay, so now exosomes are just signaling molecules. They're not good or bad. A signal might be, danger, danger, be careful, it could be a bad signal, or it could be a beneficial signal.

So when you talk about the world of exosomes, and I know this is a really big thing in longevity right now, if you have beneficial exosomes, beneficial signaling molecules, that's a great thing.

But some of these exosomes might not be beneficial and they might be sending signals that can damage cells. So those are things you just have to be aware of.

Now, in general, exosomes that come from things like stem cells tend to be more healing versus other types of exosomes. But how cells are grown before exosomes are harvested from them matters a lot, right?

The conditions of the incubator, the The media that the cells are grown on before you collect the exosomes can change whether those are good or bad exosomes.

So just something to keep in mind. And then synapses as well. Now, parabiosis is the sharing of all of these

intercellular communication factors. Probably heard of the mice that were stitched together, an old mouse circulatory system stitched together with the young mouse.

Turns out when they shared all of these factors, the young mouse got old and the old mouse got young. Okay, so there's something in our blood, these communication factors that can drive aging or youthfulness or both.

So it turns out that we can start to mimic that. There's me sitting in the chair. Therapeutic plasma exchange or plasmapheresis is a way that we can actually take some of the aging factors out of our blood.

We actually like filtrating our blood, getting rid of the plasma, replacing it with fresh saline and albumin, and so really trying to dilute these pro-aging factors.

But when we do this research, we're now finding these pro-youth factors as well. We find factors circulating in the blood like GDF11, or TIMP2 that seem to actually be only in young plasma.

So we're learning more and more. So it's just such an exciting time with all the discoveries. There's going to be so much more available soon. And they're even starting to develop synthetic plasma as well.

2-HOBA and the Call to Take Action

OK, we did it. We made it through the hallmarks of aging. So I just want to end with talking about a compound that's pretty new to you. that has an effect on almost all of the hallmarks of aging.

So this is a compound called 2-Hoba or 2-Hydroxybenzoymine. Now, it's found in marine organisms, it's found in fermented food, but it was really discovered in Himalayan Tartary buckwheat.

So when plants grow in the Himalayas, it's a really stressful environment, right? There's not a lot of water. The temperature is extreme. And so plants start to make these beneficial compounds to help keep them alive.

Turns out that those compounds that the plant makes to keep it alive in extreme conditions can be really beneficial to humans as well. And that's why things like the polyphenols in plants are compounds that the plants make to help them stay alive in stressful conditions.

So another reason you want to eat plants that are organic, that are stressed, if you eat plants that are kept in a nice, safe, cozy little environment, they're not going to have all of those beneficial factors.

So Himalayan tarty rebukeweed is one of those extreme plants, and tuhoba is one of those compounds that they make. And we also see it in human blood plasma, might be one of those youthful factors that I just talked about.

But it turns out that it impacts a lot of different longevity pathways. It's a very small molecule. It's highly bioavailable, and it can cross right into your brain.

It crosses the blood-brain barrier, and it's a very powerful antioxidant. So that's the chemical structure of it there. It actually binds to a receptor, a family of these G protein-coupled receptors, and it signals a whole cascade of actions.

It triggers and activates the AMP pathway that I just talked about to help with autophagy. It actually increases NAD, which can improve the sirtuins and DNA repair that we talked about, and it upregulates that NRF2, right?

That's the transcription factor that goes into the cell and turns on all of these antioxidant elements. And so, of course, it's going to have a lot of beneficial downstream effects of optimizing metabolism and improving stress response and inflammation and maintaining stem cells.

Another word for it is hobamine. And these are all of the different hallmarks of aging that hobamine can act on. It reduces senescent cells. It helps with your mitochondria.

It activates those DNA repair mechanisms and maintains that epigenetic modification of the histones. And it helps with cleaning up all the cellular junk.

So the last step I'm going to end there, and I think we're right on time, is the most important step in longevity, and that's do something. Take action now.

Don't wait for all of these great technologies that are coming. They're coming. It's awesome. But you need to act now to stay alive so you're there to get them.

So maintain yourself, right? We maintain our cars, but we don't think about maintaining ourselves, probably talking to the wrong audience here, I think you probably do, but it's important to really stress that with our patients as well.

So if you want to learn a little bit more about what we do at Fountain Life, you can get that QR code and I'm happy to send the presentation as well. Thank you for tuning into Doctor Talks.

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