How Fasting Resets Your Biology and Helps You Live Longer – Valter Longo, Ph.D., with Dave Asprey – #812

Announcer:

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Dave Asprey:

You're listening to Bulletproof Radio with Dave Asprey. Today, we've got our live audience from the Upgrade Collective in the house. We got lots of people in because this is going to be a really powerful episode. If you'd like to be in the live audience, be able to ask questions, go to ourupgradecollective.com and join my private membership group, where I'm teaching all of my books and all of my knowledge with a team of coaches, super-structured to answer all your questions and teach you how to be Bulletproof. Today is an episode that I've wanted to do for a long time, and it's hard to get this guy on as a guest.

Dave:

He's a director of the Longevity Institute at USC, the Leonard Davis School of Gerontology, director of the Longevity and Cancer Program at the IFOM, the Italian Foundation for cancer research. And he was named by Time in 2018 as one of the 50 most influential people in healthcare for his research on fasting mimicking diets, as a way to improve health and prevent disease. He wrote a famous book called the Longevity Diet, I'm talking about none other than Professor Valter Longo. Valter, welcome to the show.

Valter Longo:

Thanks, Dave. Good to be on it.

Dave:

I've called you multiple times when I'm talking about fasting and answering questions about the godfather of fasting. One of the reasons I say that is that, you've spent so many years looking at fasting way ahead of the curve. Why did fasting come into your lens so early compared to almost everyone else alive? Where did the original inspiration come from?

Valter:

Yeah, I think two things mostly. So I went to UCLA because Roy Walford was there. Roy Walford back in the days in the early `90s, he was in biosphere too, and he was basically doing the first human calorie restriction experiment, and he was a pathologist, a medical doctor at UCLA. And at the time he was the most famous person in the world for, let's say nutrition and longevity, and aging. And so certainly, Roy was a big influence. And then the other part was, the other lab that I worked on at UCLA which was, first Steve Clark and then John Valentine, and with Steve Clark, I worked on starving bacteria. And with John Valentine, I worked on starving yeast. I don't know, I was interested in that maybe because of the role for the influencer.

Valter:

And so every time I got an opportunity, I was really infatuated by the starvation and the effects of course, that I was observing early on. So the bacteria, you starve them, they become long lived or much longer lived and they become very resistant. And the yeast you starve them, same thing, long lived and

very resistant to all kinds of toxins. And so when I saw bacteria and yeast responding the same way, and then connecting with Roy Walford, he was not working on fasting, he was working on calorie restriction, but I think I made the connection, and I knew this was a very powerful three billion years old function that was poorly understood. And keep in mind, everybody was making fun of this at the time, they thought it was a joke. "Why would you possibly work on starving bacteria and yeast? It's just the most boring thing ever." So that was the attitude back in those days.

Dave:

Do you like to be seen more as a longevity researcher or as a fasting researcher?

Valter:

Yeah. I think longevity, and not just longevity, but what I call youth span and juventology. How do you stay young? And then once you can not stay young anymore, once a youth span period is over, how do you stay healthy? And that's the health span program. Fasting really in my mind is, probably the most powerful way to reset and help regenerate, but also help clear junk and damage that is accumulated.

Dave:

How often do you fast?

Valter:

I mean, first of all, I always start by saying fasting doesn't mean anything, fasting is like saying, eating. How often do you eat? So I think the answer is every day. So every day I do about 12 hours of fasting and 12 hours of feeding. And then maybe once a year, I would do a five day fasting mimicking diet. Sometimes I may do it twice a year depending on the need. But mostly, I follow my diet, what I discovered in the book, the Longevity Diet. And so I think we've seen a lot of evidence in the lab that, for the very few that follow this very precise type of diet, the fasting mimicking diet doesn't have to be done as much. So the average person may do it three or four times a year, but I think for somebody that has an ideal diet, maybe once or twice a year is efficient.

Dave:

Okay. So if you eat the right stuff, then once or twice a year you do a longer fast. And it's permissible to have something during the fast, as long as you're getting your macros right?

Valter:

Yeah. It's-

Dave:

Because you're still maintaining autophagy.

Valter:

Yeah. It's not just eating the right stuff, I think it's the timing, it's the frequency, it's whatever else you do, the exercise, et cetera, et cetera. So I think it's lifestyle, mostly nutrition, but not only nutrition. If you do all the right things, then probably that's sufficient. Yeah.

Dave:

A lot of the research I've seen says that 12 hours is the very minimum effective length of a fast for increasing ketosis over time. Dr. (Miriam) Merad has done some studies on alternate day, 12 hour intermittent fasting and seen slight increases in ketones. But a lot of the research I've seen lately is looking more at 16 hours without food. That seems to be where a lot of people end up and occasionally going longer. Okay. For me, it's been 24 hours since I ate anything and I'm not hungry, and I guess I'm going to force myself to you because I don't want to do a two day fast, but why 12, not 14? Is there a specific reason for that?

Valter:

Yes, there is. I always say I could never find a negative study under 12. But I found many negative studies in the 16 hour, and also multiple of them are having to do with gallstone formation, people that fast for 16, 18 hours a day tend to have twice as much bladder operations than people that fast for 10 or 12 hours. And also I'm concerned about the, now four or five studies showing that people that skip breakfast live shorter, and have more cardiovascular disease. And now a new study showing more, cancer.

Valter:

Of course these are epidemiological studies that are associations. Most people that skip breakfast will say, "Fast for 14, 16, 18 hours." If that was so beneficial, why isn't it counter balancing whatever negative these people may be doing? So maybe they're not leaving shorter because of the fasting, but why is the fasting, if it's positive, not making them live normal? And that's a concern.

Dave:

It's always a question, are people skipping breakfast because they're too tweaked, or too busy, or going to work, or they're having a cigarette? And I think the account for cigarette smoking usually mentioned in most of these, but is it an unhealthy lifestyle choice because the people aren't caring for themselves or is it conscious fasting?

Valter:

Yeah. So my point is-

Dave:

And that's hard to tell.

Valter:

... why is the fasting not helping them against whatever other bad lifestyle they might have? That's my point. So you figure that if it was so powerful to do 16 hours a day, then it should take care of, and they'll live at least a normal life, they won't have a shorter life. The concern is when you see shorter. Yeah, that's when you say, "That's very surprising. If it was so good for you, why don't we see them at least living normal?"

Dave:

Got it. And it could be that if they ate breakfast, they'd be even worse off, but we don't really know because of epidemiology. It's a tough one.

Valter:

Right. Exactly. Yeah, we don't know. But the question is-

Dave:

It's a fair question.

Valter:

... how much you want to risk considering the studies, considering the gallbladder operation, considering also that most centenarians don't do 16, 18 hours. So this is why in my book, I always talk about a five pillar approach and try to get the common denominator, what do they all support? So if you look at centenarians, 12 hours is very common.

Dave:

Is there a difference in the length of fast that's appropriate based on your age?

Valter:

Well, again, it depends on what fasting you're talking about. I think the five day fasting mimicking diet as we're testing clinically, we think it's appropriate until age 65 to 70, then it does not mean it's not appropriate anymore let's say, to do it three times a year, we now have an ongoing clinical trial in Alzheimer's patients, and so they're fine. So far, they're doing okay, they're doing fine. They're much older than 65, some of them are in their 80s. So it doesn't mean they cannot do it, but right now we just don't have enough data to do this long fast in the 70 and older, let's say. Then if you're talking about intermittent fasting, again, if you do 12 hours, it's perfectly fine. There is really no reason to stop at any age. In fact, that maybe very healthy even for 100 year old person.

Valter:

If you looking at other forms of fasting, I would put it under the same category, let's say that somebody does two days a week or one day a week, I would put it under the same category as the fasting mimicking diet, meaning that, to do one day a week of, lets say a 24 hour fast, I will not recommend that to somebody who's 75 years old. Yeah.

Dave:

I agree with that assessment. I found one person who's 81, who's been doing about a 14 to 16 hour fast every day for 59 years. She does not look like she's 81, her brain is totally sharp, her name is Margaret Paul, she was just on the show, does a lot of work more around emotional and psychological trauma. But when you look at the few people we can find who've practiced it, it seems that there's something going on that's really beneficial.

Valter:

Right. I mean, we're starting to think of an FDA like standard. And then if you have an FDA like standard, if you think about that, it's like saying, if you give a vaccine to a few people they've done pretty well, can we give it to the whole world? No. Well, we need 70,000 people. Right?

Dave:

Yeah. We do.

Valter:

Yeah. The same is true here, and unfortunately, the epidemiological studies, when you do 70,000 people or 700,000 people, they show a shorter lifespan. So for the biggest group that we can find doing 16 hours, that's why you have to say, "Wait a minute. Even though it could be beneficial to a lot of people, what if it's detrimental to even more people than it is beneficial to..." And this is very typical for most of the traditional things. If you look at something that is very old, it usually tend to do lots of good in one sense and lots of bad. And that's why they never quite stick around. Yeah. Then you have to find, how do you get... And this is calorie restriction, for example, say, calorie restriction that Roy Walford used to study has been around for 100 years. And they used to do say, fantastic things about calorie restriction back in the `70s. How many people do calorie restriction right now? Almost nobody.

Dave:

120.

Valter:

Almost nobody. But why? Well, because even the monkey studies after Richard Weindruch, somebody else who was in Roy Walford's lab. He did the 25 year long study, he realized that, there is lots of positive and lots of negative. So if you look at cholesterol, blood pressure, fasting, glucose, amazing results. And then the monkey may drop dead after anesthesia. And you're thinking, "Wow, how is it possible?" What happened in calorie restriction that makes somebody so sensitive to anesthesia? Yeah. So the age related disease cause of death were much affected by the lifelong calorie restriction, but then the overall survival was not that much improved. And when they did the same study at the NIA, the National Institute on Aging, it wasn't improved at all. There was no difference in survival. Yeah. That's the type of thinking that we try to put together to then come up with, what's very safe for people? And at the same time can make them live to 110 healthy.

Dave:

Do you think we're going to get to the point where, you look at your genes or you look at your gut bacteria, or some mix of markers from the blood and go, "Oh, for you, you should do X amount of fasting, or this is your ideal eating window." Is that even conceivable?

Valter:

Oh, it's very much conceivable, and I think no more than five years ahead of us. Yeah, absolutely. That's already done for, should you eat this or that? And so I will imagine soon enough we'll have enough data associating or correlating a certain profile of microbiota with the response or lack thereof to fasting. So we're already collecting this, for example, for multiple sclerosis trial, we're collecting microbiota, the cancer trial, we're collecting microbiota, the Alzheimer trial, we're collecting microbiota. Yeah, the IBD trial, I'm sure we're also doing that. So I think it's just a matter of time before we have enough data that we can say, the non-responders happen to have this profile. And at some point I think artificial intelligence is going to have to help us do it because it's just going to be lots of data that is extremely difficult to analyze the classical way.

Dave:

Are there private companies that you've seen that are working on that problem? Or is this all university and government funded?

Valter:

I know. I don't want to mention the name of the company because I don't know if they wanted me to mention it, but I know even years ago we were approached by a private company looking for the data. So I will assume there are many already that are looking at intermittent fasting, periodic fasting, et cetera, et cetera. And they're starting to collect data that eventually they will analyze to distinguish the responders from the non-responders.

Dave:

Well, I'm looking forward to that day. I would love to be able to sit down and look at someone's stack of hormones and thyroid and everything else, plug it into an AI engine and say, "Eat for X amount this day." And maybe even what to eat. And I know there's a bunch of people working on it, so I was hoping you'd tell us the coolest ones. But I understand there's NDAs in place and all.

Valter:

Yeah, no. I don't think they have it as a service yet. So I don't think they're at the point that they can give it to the public. Yeah. So that's the main reason why I don't want to mention it. If I knew it was publicly available, I would mention it, but I'm not sure. I don't think it is actually.

Dave:

I get it. Yeah. Don't throw a company in hot water with thousands of people calling them all at once when you can't buy what they have. But when you know, send me a note and I'll definitely talk with them. What did you learn from yeast that translated best into human aging in your labs?

Valter:

Oh, everything we do is based on yeasts research. Yeah. So I think we forget that this is as old as we are. Meaning, we all come from the same organisms and we've evolved in parallel with the yeast. And so we obey the same rules they obey, we have the same, what's it called? Force of natural selection. And so for example, all our work that we do on cancer started in yeast, when they discovery that, if you starve a yeast, the same genes that are proto-oncogene, so the ones that are involved in cancer are the one that prevent the protection. Remember earlier I said, the yeast you starve it becomes very protected of all kinds of toxins. Well, if you have an oncogene, which most cancers have in them, that oncogene prevents the protection.

Valter:

So that's the first observation was, well, if now, by having this type of gene like RAS, if you have RAS that is always armed, and if that prevents the cancer cell from becoming resistant, then this is a way to distinguish all cancer cells from all normal cells. So all normal cells including bacteria, by the way, will respond to starvation in a coordinated manner, and they'll go into the starvation response mode. The only disobedient cells are going to be the cancer cells. Yeah. Then it will all the way to clinical trials and now even successful clinical trials. I think everything. So we discovered the TORs kinase pathway with yeast, and now everybody talks about rapamycin and TOR in aging. Well, we discovered that thanks to yeast. It was a screen, meaning that, where we basically mutated all the genes in the DNA of the yeast, I'll say most of the 6,000.

Valter:

And then we asked a question, which mutations make the yeast live longer? And one thing kept coming up, and it was something called Sch9, and Sch9 is what TOR regulates. That's what the drug rapamycin that is now so famous for aging research is blocking. So that was not something that we even thought about, it was the yeast that told us, "Focus on this, because this is the most important thing that you can block to extend life." And in fact, once we combine the mutation in that gene and in the, so I call that, the protein pathway. The amino acid pathway, and there's a sugar pathway, which is pKa. So once we have two mutations in these two genes in yeast, and then we also starve them, we extend the lifespan by tenfold. So we make the organism 10 times longer lived than the normal ones. Yeah. Again, yeast pointed to all the right direction.

Dave:

And today, like you said, mTOR and rapamycin are all the rage. And certainly that original discovery that you had led, long time listeners have heard me talk about tripling down things that suppress them, TORs that can come back up later, very well fasting, and coffee, and exercise suppress them TOR. So just thanks for doing that work, I think it's led to all kinds of innovations, and understanding, and nutrition, and anti-aging, and exercise. And it's really foundational work, which is really cool.

Valter:

Thanks.

Dave:

Now I have some more questions in my book on aging, I had seven pillars of aging. Things that we know, pathways we want to maintain, so we can be youthful. And in your book, you had this concept of pillars as well, we had five pillars of longevity. Can you walk me through those five pillars? So people hear at the show can get a sense of how you're looking at aging because you studied it for 30 years. I want to know.

Valter:

Yeah. I mean, one is for sure, the genetics of aging and the basic research, like what I just mentioned. So what controls the lifespan of all organisms and is there a longevity program? And can you switch that program? Because now, you take advantage of what I call three billion years of research and development, and you basically say, the organism already have something, an alternative program that they can go to that can already extend the lifespan. So the question is, how do you get in there? Is there a hibernation state for humans that you can switch to and how do you get in there? Or is there a regenerative mode in humans that you can get to and how do you get there? So the basic organisms in the research on longevity, what we call model organisms, is very essential. The other one is of course, epidemiology.

Valter:

So studies a large population what I was mentioning earlier. What happens to people that fast for a certain number of hours? A few years ago we published on protein, what happens to the Americans that eat low protein versus those that eat high protein? And is there an age specific effect? We published that. Yeah, the low protein was better up to a certain age, but not after 65, then after 65, the moderate protein intake was better.

Dave:

Thank you for that study, by the way, that was part of the recommendations in my anti-aging book was based on. And I did reference your study in the book.

Valter:

Oh, great.

Dave:

So well done. Good finding.

Valter:

Thanks, yeah. So the epidemiology large population, because then you bring in the math. The ability to do statistics and use math to make conclusion. Then randomized clinical trial, I always site the one by Asterisk and colleagues in Spain. You take 7,000 people, you put them in either a low fat diet, and there's always been this fight. Low fat versus high fat. And so there's 7,000 people either on a low fat diet or on a high olive oil and nuts diet, and you wait five years, and then you say, "In that case, they showed that the olive oil and nut consuming people had less heart attacks and live longer." Yeah, so that's a very good study to publish in the New England Journal of Medicine by the way, that tells you maybe a very low fat diet, if it is olive oil is not such a good idea for people that have cardiovascular disease or a high risk for cardiovascular disease.

Valter:

And another pillar is the centenarians. So what if you go to Okinawa, or southern regions of Southern Italy, whether it's Sardinia, Calabria, or Loma Linda, or lots of other places? What do they do? What do they eat that makes them get to 100 so frequently? So I think that's probably one of the most important pillars just because it brings in, I think, a major safety factor. If all of this population had this in common, so if most of them or all of them have vegan plus fish or vegan plus a little bit of meat diet, it probably is not bad for you. At least we can say that now, did it make them live to 100? Well, it's more complicated than that, regardless of the stories we hear, most of them seem to have a genetic component. So they have the right diet, but they also genetically predisposed to get to a very long lifespan.

Dave:

Yeah, the guy who's been on this show, James Clements flew around and collected genetic data from 100 and something people, all over 100 to get the genetics into a lab, to be able to figure out what are some common genetic markers there that's been influential. I forget who he worked with on that. But there's definitely a genetic component. Have you seen the studies that say the other component is a poor record keeping and high taxes in some of those areas that there's some amount of fraud?

Valter:

Yeah. Most areas actually. I have a larger amount for I always remember the Vilcabamba. Everybody used to ask me, "What about Vilcabamba in Ecuador?" And then finally a sense from journalists. And this was world famous for the centenarians, but then I was talking to my colleagues because we do research in Ecuador and they say, "This is all made up." And so the people that will tell the journalists whatever they want to hear, so that the journalists keep coming. So I sent some people from an Italian television to check, and there was not a single centenarian in Vilcabamba. So this is very common that people exaggerate, they may take the identity of their father or uncle for whatever reasons and maybe to get their pension and-

Dave:

Yeah. Inheritance, taxes and all that.

Valter:

Whatever. Yeah. So I think it's very, very common.

Dave:

And it still doesn't say we shouldn't study people who're actually older. And there's some pretty well validated ones where my perspective is that, there's at least one person that we are pretty darn sure is 120 years old. So that's our current basically top level. How do we beat that over the next 100 years so that, that becomes more of a mid-level? If you put on your hat 100 years from now, how old do you think the oldest person on earth will be?

Valter:

That's a tough question. I think that fortunately, or unfortunately, I think technology is going to take over in the next 50 years and I think bionics is going to take over in the next 50 years, and I think it's going to be a very different world. I don't even think that, and I could be wrong, usually it takes us longer to get there. So maybe 200 years and not 100. But I don't even think right now whatever we're doing is going to be that relevant for 200 years from now. I think it's going to be a very different approach, and it's going to be an approach that it has to do much more with memory and memory transfer, and all kinds of crazy things.

Valter:

Yeah, I imagine that's the world of one to 200 years from now. It's not going to be modifying TOP, or pKa, it could be that one of us identifies a way to reprogram. I always say, can you reprogram a mouse to make it live as long as a naked mole rat. I say-

Dave:

My favorite spirit animal. Yeah.

Valter:

So you go from two to three years to 30 years. Yeah, that's possible. That's possible that we can turn some of the programs on and this programs could revolutionize a lifespan, but I think it'd be in parallel with some of the more crazy science fiction things that are unavoidably going to happen.

Dave:

You're thinking the oldest living person 100 plus years from now will be a cyborg?

Valter:

I think that I would be shocked if in 30 or 40 years where most people before we die are not going to be part human and in part something else. And we already have that. So the pancreas and all kinds of artificial hearts. So we already have a lot of that. And I'm not endorsing it, but I think it's hard to imagine that we're not going to use that more, and more, and more. It's much easier to build things. Now, of course, when you get to a brain or a liver, it's much more complicated, but for sure, even in the next 50 years, I think that we're going to see a lot of bionics and a lot of parts being introduced. And rightfully

so, I mean, somebody is waiting for a kidney transplant why not use an artificial kidney? And I imagine that technology every year is going to get better and better. Yeah. Now [crosstalk 00:29:13]-

Dave:

You seem concerned though. For better or worse, I hear a lot of trepidation in your voice. What's scary about that to you?

Valter:

Well, I think it's the abandoning who we are. That's got to be a scary thing to anybody. As we are investing in technology, we have to ask the question, is all these technology, I mean, atomic bomb? But the atomic bomb in a very small example compared to what this could be. This would be much, much worse. So that's what I'm worried about. Our inability for the first time in history to control where it goes. Not so much what we can do with it, but are we going to be in control of it? And that's the scary part.

Dave:

Personally, I hope Facebook's in control of it so that my ocular implants can get malware. Wouldn't that be great?

Valter:

Yeah. If it was Facebook maybe, but as systems are starting to self-learn, you can only control that up to a certain point. And then at some point that self-learning process is going to take into something that can decide for itself. It's exactly the-

Dave:

So you're worried about skynet?

Valter:

Yes. I'm worried about human beings losing control of the technology and the technology being in charge of the technology. So that's my big concern. Yeah.

Dave:

Coming out of Silicon Valley as an actual computer hacker, one of the reasons that I named it biohacking is that generally hackers are the people who try to take back control from the big companies. And we have Linux an open source operating systems, which run most of the internet now, not closed source big companies. And I'm hopeful the future of biohacking is relatively transparent because we have a community of people who are paying attention to these things. And I'm still hopeful about a positive future, but yeah, it could go dark. I'm 100% with you Valter.

Valter:

Yeah, [crosstalk 00:31:30]. Great. I mean, that's exactly what we need. We need a lot more of that. So who is regulating this? And what is going to be our plan to fight this? To make sure it doesn't go that way, or it goes in a positive way and not in a, we lost control away.

Dave:

Yeah. We've got to define our humanity so that we can maintain it, and it's such a mushy concept right now, being able to decide what that means and what we want it to mean. And these are huge philosophical questions that go beyond just life extension. I love it that you're thinking about this in the context of longevity, in fact, it's really refreshing to hear where your mind is on it.

Valter:

Well, I mean, I come as a 18 year old, that wanted to live forever. I mean, that's how I got started. And then I always say I heard the story, I never heard it from Roy Walford, but I heard he was going to freeze himself, and then I heard he also took himself off the list to be frozen. So at some point, Walford like myself went from, I want to live forever to, I'm not sure anymore. Yeah, so I don't know why, and if that's a correct story, but that's what I was told. And so I wouldn't be surprised if it's true. That he went from that state of mind to a very different state of mind as he was getting in his 60s and 70s.

Dave:

I have often said that I'm going to live to at least 180, but the reality is, I'd like to die at a time and by a method of my choosing. If I'm done, I'm done, I have the freedom to do that.

Valter:

Right. Sure. I mean, and I'm the same way, of course. Yeah, I would definitely like to have that option, but I think that it can get more complicated than we appreciate but certainly, yeah, 180, I think it would be something that most people will say, yes. I always remember I asked my mother, maybe 20 years ago. She's very religious, and I said, "Well, would you want to live to..." I forget what it was. 200 or something like that. And I was sure that she was going to say, "No way, because of the religion."

Valter:

And she said, "Of course." And then she said, "Because I'll be able to see your kids grow up." It was very interesting from such a religious person to hear that she will want to live to 200 because of feeling like she's leaving now when maybe she's got four or five generations that she can watch and then she's ready to go.

Dave:

I'm really hopeful Valter that the longevity movement, and you've played a major role in it, but it's going to enable us to have an epidemic of wisdom. We have people who've been around long enough to have figured out a lot of the stuff in life, like you're saying Roy did as he aged, where we attain some wisdom, we learn some things, and we have enough energy to share it so that we can maybe steer the ship a little bit better than we have before. Because if people started losing their faculties in their late 60s. When you probably figured life out when you were 16, and then you don't have much time to pass that on, so we end up doing these waves of change that doesn't always go in the right direction.

Dave:

But if we have people who are, "Hey we've seen this three times before, it's all right, here's how we're going to navigate it." It feels like we could actually do a better job as a species. I mean, do you look at longevity as maybe something that's going to support the planet versus put a further burden on it?

Valter:

Yeah, I think that there is no doubt. I always talk about 110 healthy. Roy used to talk about 120 healthy. So I think it's a very good goal, if we could get. And I always say, I don't think we're going to get the planet to be 110 healthy. I think we're going to get the people that follow all the things they should follow to get to 110 on average healthy. So that's the goal. A lot of people are going to keep smoking and doing whatever they want, and they're just going to probably keep about what they got already right now. But then I think that for the group that wants to get there, there's going to be ways to do it. And of course some people are going to die earlier, some people are going to die later, but that is reasonable to start thinking about 110 average lifespan with most of it lived healthy as a goal.

Dave:

Do you ever get life insurance companies who call you and say, I want the data so that we can actually figure out who we should or shouldn't sell life insurance to?

Valter:

They don't call me, but they are certainly working with us, I think now at least some of the biggest ones are starting to work with us, getting aligned with the patient's health. More the health insurance company, then the life insurance company. Yeah, the life insurance companies are also aligned with the health insurance companies, I would say. Yeah, so we're starting to work with the health insurance companies in looking at, instead of reimbursing whatever problem disease cost somebody has, can we avoid that? Can we think about getting to 100 healthy or 110 healthy? And in the past surprisingly, it wasn't like that.

Valter:

So the health insurance companies were just reimbursing whatever it cost and charging people for it. So now I think that's moving and soon enough, we'll move more into, here's what we've reimbursed, and if you can keep everybody healthy, then you can be wealthier as a clinic, or as a doctor and keep more of the funds. Yeah.

Dave:

I love that. I'm really hopeful that we start getting a more normal and science-based situation there. I bought some life insurance a few years ago and they're like, "We're not going to say a life insurance." I'm like, "Why not?" They said, "Well, you had this really advanced cardiac risk profile done." I said, "Yeah, but it showed that I was healthy." And like, "Yeah, but you must be worried about something because you got the lab data." I'm not worried about a thing, I'm tracking my progress. So we were coming from very different worlds and they finally did give me a policy. But it took a lot of banging around and aggressive maneuvering so they would do it. I feel like in the future, maybe they'll look at the actual data versus some mythical tables from the 50s, which is [crosstalk 00:38:26].

Valter:

Yeah. I mean, of course a lot of people are resistant to that. So a lot of people don't want them to look at the data, especially in the United States, they're not going to have an easy time in doing that. But I think they certainly want to do that. In both health insurance and life insurance company.

Dave:

I guess the trick is for some health insurance or some life insurance company based in Mauritius or somewhere where there's no regulation to just sell out of country policies based on real data to people.

I like that idea. Somebody start that company and so many good life insurance that's actually going to be there. There we go. We'll just get around the regulation. Now-

Valter:

Certainly it could be going the other way around. It could be that the very healthy people now decide to release the data, because that's the biggest problem. Once they're very healthy people, so let's say the ones that invest in all the longevity intervention, they could say, "Can we find that or form even an insurance company that just treats us because we're okay releasing the data?" So if the group was okay releasing the data, then I think most insurance companies will probably go for it because to them, it's just numbers. If they know you have a much lower risk, then they don't mind lowering the premium.

Dave:

That's a good point. I'm hoping that the data from your lab eventually makes its way into our decision making in a broader way. Right now individually, we can use it but to use it for the systems of society is one of the things I hope is of benefit for the future. So something else you've said in your book that made me really happy was, you said without understanding how nutrients such as proteins and sugars affect cellular function, aging and aging damage, and regeneration, it's difficult to determine the type and quantity of nutrients for optimal longevity. What have you learned about the type and quantity of nutrients that are important in different types of fats, different types of proteins, different types of carbs? What has come out of your science that tells us different carbs do different things and things like that?

Valter:

Yeah, so we learned a lot. So we can now usually go down to, let's say a specific amino acid or for example, in our cancer studies, we define what the level of sugar needs to be lowered to for the cancer to start suffering. And we're also starting to distinguish between different types of cells and what cell needs what. Yeah, so the mechanisms before you can get something approved by the FDA, you have to have mechanisms and here is no different. So if you don't understand the mechanisms, you're really walking in the dark. Because we know that, let's say proteins control growth hormone, releasing hormone, which controls growth hormone, controls IGF-1. But the protein also control the levels of insulin and they control insulin sensitivity.

Valter:

But then within the protein, it's not just about protein it's about the amino acid profile. [crosstalk 00:41:37] amino acid profile, it can have completely different effect. So you can have 100 grams of protein that are bio similar to 20 grams of protein depending on the source, and depending on what you're going after. Yeah, so the same is true for fats. What type of fats? And not just in a simple way, because again, you have 100 different types of cells, let's say they can respond 100 different ways. So a liver cell can respond to something the opposite way as a muscle cell responds. So now if you're using the liver cell, it means producing IGF-1 in insulin and the muscle cell is responding to IGF-1 in insulin. So of course they have to have a very different role.

Valter:

Yeah, so this systems biology approach is really fundamental. If we don't use it, then we're just going to be lost. And I think soon enough, this is why I really am a promoter of the team of doctors together with molecular biologists. My foundation has a clinic here in Los Angeles, we have one in Italy, and I think our

approach has been like that. You have a molecular biologist, you have a physician, you have a dietician, and the rest of the medical team. And they work together because now I think the systems biology is so complex that the doctor couldn't possibly try to handle all of this, including let's say microbiota, metabolomics. But just strategizing based on, if you just look at the blood tests from a regular doctor, that already has an immense level of information about that patient, that if you really bring it into systems biology understanding, you can come up with the opposite treatment for that person than a doctor would come up with.

Valter:

So for example, lots of doctors will say, "Put somebody on Metformin." Metformin, sulfonylurea, and then eventually insulin. So of course in our clinic, the doctor tries to do the opposite, if you are on Metformin, is there a way working with the endocrinologist, we can get you back to not needing Metformin and is there something that we can do to unlock that insulin resistance that was generated? And is it because of the fat in the liver? Is it because of the fat in the visceral area? How do we eliminate, not necessarily make you lose a lot of weight, but make you lose whatever is responsible for the generation of insulin resistance? Yeah. So I think that systems biology and mechanisms have to be in the next five years. I'm not talking about 50 years, in the next five years, they have to be at the center of decision-making in the doctor's office.

Dave:

I love your view, and I share it. We're right on the cusp. When it comes to Metformin, many of my anti-aging friends go back to when the first studies came out that said Metformin causes some genetic or epigenetic changes similar to what a calorie restriction diet does. I think in 2003, a biomarker pharmaceuticals was out talking about this. I met with those guys and I took Metformin for three years because I thought it was going to make me live a long time. And then I saw some other studies and felt some effects around mitochondrial suppression. What's your take on Metformin occasional use or regular use as an anti-aging substance? Are you for it or against it, or?

Valter:

Yeah, first of all, I'm very scared of Nir Barzilai because if I ever say anything negative on Metformin, I get a call. Dr. Nir is a friend of mine at the Albert Einstein College of Medicine, and he's the person leading the big trial on the team study Metformin. Yeah. So I think if I had to pick two drugs, one would be rapamycin black mTOR and one would be Metformin black both TOR by the way, and the pKa pathway. The sugar pathway and the protein amino acid pathway. I think there's a lot of potential, we just have to wait and see. And I think Nir is doing it the right way, basically saying, there's enough data suggesting that this could be benefiting people. Let's do the Asterisk study, thousands of people, the danger is very low. For the vaccines and everything else, we should be able to get a pretty good idea hopefully of, not only does it benefit people overall, but is there a sub group of people that shouldn't take it.

Valter:

Because it may not benefit them at all, it might actually hurt them. Yeah. So like you say, it's an inhibitor of mitochondria respiration, it's an inhibitor of gluconeogenesis when the liver makes its own glucose because the brain needs it. So what happens for example, if you're doing intermittent fasting or periodic fasting and you're taking Metformin, well, you could be in a lot of trouble. And we've seen lots of mice dying like that. The combination of fasting and Metformin. This is why in the clinical trials, I'm always

very, very scared of combining the two, whether it's cancer trial or diabetes trial that we're running. And we usually stop the Metformin for the days that somebody is fasting. Yeah, as it goes out there, how many combinations are there or Metformin plus that are negative or very negative as the one I just described?

Valter:

I think there's 50 different things that you could do, and maybe they're not very common things to do. Fasting is not necessarily very common, but it is becoming very common. And so now, if for 50 or 100 times you combine Metformin with fasting, you end up in the hospital, if not worse.

Dave:

Wow.

Valter:

Yeah, that's the thing that we have to think about but hey, I think it's a good idea to do the research. And I think at some point I'd love to see maybe a form of rapamycin that does not cause hyperglycemia because rapamycin unfortunately, cause the blood glucose level to go up. So hopefully some studies will be done trying to avoid this side effect of rapamycin.

Dave:

It's interesting. I think that for people who want to use Metformin, the likely lowest risk path is use it once or twice a week on days where you're not doing heavy exercise because it inhibits your ability to benefit from exercise and don't do it on a day during a fast, and if you want to do that, and then get some benefits, there might be some in there. And that seems safe. I think taking all the time for anti-aging is... I did do it for awhile, but I don't think it's necessarily something we know enough about yet, but I think I'm in the minority of anti-aging extremists.

Valter:

Yeah. Also you have to think of something else. Whether it's rapamycin targeting our own pathway or Metformin. I always was very scared about intervention at the core of life. So if you look at the TOR pathway, and you look at the pKa pathway, and the RAS pathway, I mean, they are the center of everything. And so the question is, I always think about, I have these car analogies, I love car analogy. So if you take a car and you say, "Why don't I just poke holes through it until I just randomly block things. Until I get something that gives me a benefit." But then the question would be okay, you're probably going to find something like that. The question is, would you want to, let's say block some electrical wire in the car for the life of the car and what are the consequences of that?

Valter:

Or, take a pipe in the car and you block it. Well I say, you want to make a car better, you have to be better than the engineers that made it in the first place. So you want to take a car that is already sophisticated, you just don't block things. You go in and say, "Okay, I'm going to take 20 years to understand how this car was built and then I'm going to improve it." And I may get this effect that you will get by blocking the pipe, but also I will avoid the long-term consequence that the car is going to overheat two years from now and then blow up, or you damage the engine. Yeah. I mean, pharmacology is extremely sophisticated and extremely unsophisticated.

Valter:

It's extremely sophisticated because it's very hard to be able to find a drug that targets, let's say TOR pathway, or pKa or whatever, but it's very unsophisticated because it just goes in there and it just blocks it all, every cell type. Yeah, so I think yours is a good suggestion. If you're going to have to go that way, don't block this pipe all the time, try to let it work most of the time, and then once a while you can block it. But even then, what you and I are saying, it's very unsophisticated, at some point you want to know, why exactly is Metformin doing what it is doing? And how can you replace the Metformin with something that does not have those types of side-effects and dangerous?

Valter:

Yeah. So that's the question. And I will argue that at least periodic fasting and some other forms of fasting are starting to get in that category. They don't need to be done all the time, they can be done periodically, and they can achieve all of it or a lot of it so far, without any side effects that we see. Eventually, we could sink, but I think by being very, very careful in the way we approach it. So for example, if you look at our fasting mimicking diet, people will say, "Why don't you have less carbohydrates in there? Why don't you have less sugars?" And I say, "I don't want to have less sugars in there." I mean, there's very little sugar, but, should we go even lower? I don't want to do that because I want to make sure that we don't have this back and forth extremes. Which even though I don't have any evidence now that they may hurt people in the long run, I'm afraid that one day we'll find that out.

Valter:

So I want to avoid the possibility. I don't want to put anybody out of 1000, not even one in 1000 in the situation where I say, "I should have thought about this." I should have thought about the fact that one person in 1000 as you know, if it's, let's say 10 million people, one in 1000, it's a lot of people. So that's how we're thinking that we should be sophisticated enough in the approach that nobody gets the side effects. And I think some of the side effects you see from these drugs are not going to be one in 1000, I think we're going to be much, much higher.

Dave:

The car analogy is really fitting. If you look back at the history of hacking, some of the first modern day hackers were people who would build hot rods. And they did this to get away from the cops during prohibition in the US. So they would take a car, and that was relatively simple back then, and they would study it and they'd figure out, how do I make it go faster? And then you fast forward. I used to, years ago, I had a BMW and I had it serviced at the Dine-In Garage. Dine-In makes racing cars. So you take your car into a racing car mechanic, and it is noticeably faster and better when they're done. These are the people who did the work right. But when you do that, you also have to be on an aggressive maintenance schedule for the car, because otherwise the car falls apart because you're running it hotter.

Dave:

And it feels like when we're doing more longevity work, that it does take more maintenance. If you're going to be tweaking with pathways, but the returns are, all the time, you have more energy in a car that stops better and accelerates faster and all that. But if you don't do the right maintenance stuff, we don't get there. And I feel like to your point systems biology is what's going to give us the maintenance schedule for our race car, whether it's a Honda or not. Does that seem accurate?

Valter:

Yeah. It seems very accurate. But the problem I think is, the sophistication. If you look at a car is extremely, extremely simple. Even the face travel it's extremely simple compared to a human body. So when you got to go in and fix millions of components if you think about it, then you have to say, right now, I better use something that has been around. So I always use the example of, if you cut yourself, can you imagine if we had to repair a cat with technology, then you have to bring in stem cells and you have to bring in epithelial cells, et cetera, et cetera. Instead of letting the body fix its cell. And two weeks later, you let the body do its job and the wound is fixed. Yeah, so I think in the short term, and it is where so much fasting, we let the programs develop and in history, do their job. We just have to learn how they work, so that we can point them in the right direction.

Valter:

So that's why we could take out a mouse and damage the pancreas and they become type one diabetic, and then we start the fasting mimicking diet refeeding and we see that there is an embryonic like program that starts, and these cells in the pancreas turn into the same type of cells that were there when the mouse was first born, and they start regenerating the pancreas. And it's really an incredible program, but imagine if we had to do that with technology just by inserting all the cells. You're looking at a 50 year project just to get what we were able to do with the fasting mimicking diet and refeeding,

Dave:

I love that analogy. Yeah. It would be so challenging to re-engineer that, but we're going to get there. It's just a question of when. Let's go into a couple of audience questions. The Upgrade Collective is a group of people who're really interested in biohacking and they've studied my books, or they are studying my books, and it's a vibrant community. So I'm really stoked on these questions. What we'll do is, you and I will be quiet while Diane ask her questions, so we don't get any echoes. And then once she's done, we'll put her on mute and then we'll answer it. Diane, you're ready to go?

Diane:

I'm ready. Can you hear me? Are you okay? Can you both hear me? Okay, great. So first of all, thanks for all your work, Dr. Longo, you're amazing. Here's a question, why can't humans use anti appetite prescriptions like phentermine to help with our fasts? Especially if somebody is really obese and this is something that they're having a hard time handling, does it maybe interfere with the pathways that lead to autophagy or mTOR, or is there a molecular issue that makes it harder and it doesn't work?

Valter:

Yeah. I can tell you, we just finished two trials, one on hypertension subjects, and one on diabetic subjects. Most of the subjects were overweight or obese. We had very high compliance and this was done both in Europe and the United States. In fact one of the studies were done in Tennessee. Yeah, I will say we're going back to what we just discussed with David about the poking a hole through a car. Some of these drugs are probably to be avoided. But I understand, in some cases, there may be no options. And so if there are no options, then drugs are okay. The right type of drugs. So I don't know enough about this appetite suppressing drugs to tell you, can they interfere with the fasting? I think they just are probably to be avoided at all costs unless you really need them. So unless that's the only way that you're going to achieve the effects. Yeah, I will say that's probably a safe way to go.

Dave:

I really like that answer. Thank you. [Cas 00:58:08], are you up for asking a question on the air?

Speaker 5:

Okay. I wondered Mr. Longo, or Dr. Longo, with regard to the COVID-19 vaccine that so many people are getting shots for currently, do you agree that this is the proper way to go? Are you going to get the vaccine, or do you already have it? If so, why? If not, why not? Thank you.

Valter:

Yes. So I'm vaccinated, I got two of the Pfizer vaccines, and the answer is obviously yes. Why? Because COVID-19 is a very scary virus and whatever minimal danger there is from the vaccine, there's a very big danger from the virus, even for younger people, but especially for those that are older. If you look at the numbers, that is really no doubt about it. The sooner people get the vaccine, the quicker we be out of this very historical moment. Yeah.

Dave:

Do you have any concerns about the poking holes in the system sort of thing? Where we haven't done this vaccine before? But I agree with your thinking. There's definitely risks from the virus that are known and relatively large, not as large as Ebola by a long shot, but there's real risks and longterm mass cell activation and things like that. There's less data about the vaccine, but the data we have says it's lower risk than the virus itself. But are you worried about the long-term aging effects of vaccines or anything like that? And this is not a pro or an anti-vax show, it doesn't have to be polarized. It's a science show where we're curious.

Valter:

No, no, I understand.

Dave:

Okay.

Valter:

Yeah. I'm very worried about any intervention, especially intervention that is going after the immune system now. Especially in an era where auto immunities are everywhere, and they're going up very, very rapidly, not just auto immunities, but also inflammatory diseases. Yes. So that's very unfortunate that we don't have an extra body or control that says, even if I give you a vaccine, and this could be, let's say the flu vaccine. Let's forget about COVID. But say, who's watching to make sure that whatever we get injected all the time are truly optimizing our health span? That's what I think the clinic in Los Angeles that we have, we call it Outspan Medicine. So our goal, whether a dietician, or nutritionist, or a physician is, I'm not treating you for what you have today, I'm treating you to make sure I optimize your chances to make it to 110 healthy.

Valter:

And of course with COVID, I have to also worry about, "Are you going to make it to tomorrow?" Yeah, so I can take more risks because this is really putting you in such a dangerous position that having had three or four FDA approvals related to this really minimize the acute risk. But we still have an uncertainty on longterm risk, and that's just very unfortunate that the CDC, et cetera, are not looking at,

what are the lifelong consequences of, let's say the flu vaccine every year? Maybe they are, and if they are that's good, but we would like to hear more about it because if they are, nobody's ever heard that, I never heard a comment about this. Yeah.

Dave:

Very well put rational response, and I want everyone listening to the show, it's okay to choose to get vaccinated because you look at risk profit. There is no good or bad, we're all doing our best here. And so don't be judgy of people who choose to do something different than you. We're all working through it and we're all making our best decisions, and this should not be a political thing. It is simply a question on the science thing. So I don't do polarization about that stuff.

Valter:

Yeah. And again, particularly my purpose is to get people to 110 healthy. So without worrying about the ideology behind it.

Dave:

There you go. And we need a lot more thinking like yours in the world today. Another question is coming through, but I can't tell who it's from, in the Upgrade Collective because of our interface here. Have you looked at using alpha keto-glutarate AKG with vitamin C, with yeast longevity? Is that a part of what you're doing? I've been seeing a lot of anti-aging about that as well. I actually prefer OKG to AKG, but have you looked at those pathways at all?

Valter:

We are certainly looking at the pathways. We never supplement alpha-ketoglutarate or anything like that. Again, we try to be much more upstream. Because if you interfere with the cells at the level of some of these molecules, you may not get the full reprogramming effect. So this is why we really like the growth hormone receptor, growth hormone level signaling, because it's what I call the master regulator. Well, of course we now have people that we follow down in Ecuador, they have mutation in the growth hormone receptor. So it means they're almost as if they had very low growth hormone activity as adults. And we show they have much less cancer, rarely develop diabetes, cognitively they're younger or much younger than you expect them to be.

Valter:

And now we're about to publish a new study on cardiovascular disease. And then let's say that that's also not negative. Yeah, I really like looking at this master regulators rather than looking down almost say, again, alpha-ketoglutarate is really almost at the end of that pathway. So again, it could be very good for one cell type, it could be very bad for another one, and sometimes it could be, let's say feeding some cancer type cells and could be killing some other cancer cells. Yeah again, the focus on the pathways that have evolved for the purpose of changing longevity is probably the best one.

Dave:

Really good answers. It sounds like more research is needed on that one. And a new study just came out in the last two weeks that showed arginine supplementation was actually causing more harm than good. So I'm going through that and writing it up. I don't know if you came across that yet, but I'll share that with the Upgrade Collective and I'll put it on my blog. So it also has some good sides with nitric oxide and things like that. But again, the same with systems biology, pros and cons, and maybe you should do

it once a week, not every day. And it seems like for a lot of these things, it might be occasional interventions, just like with fasting, you don't have to do it every day. And you're-

Valter:

Yeah. I haven't looked at your pillars yet, but that's what the multipolar approach comes in. So you want to say, arginine supplementation for example, is it extending the lifespan of a mouse? Is it extending the lifespan of a rat? Is it epidemiologically, people that have a lot of arginine in their diet live longer? What about arginine rich foods? What about the centenarians? They consume a lot of arginine rich food. That's what I think is a good way to put it together and say, "Do I do it or not?" Well if four out of the five pillars are negative, you definitely don't want to do it. If let's say one is negative and three or four are positive, yeah, that's probably a much safer direction to follow.

Valter:

So I would assume if you do look at arginine, there'll be no data for most of these pillars. So it'd be in conclusive that arginine consumption in the food is associated, let's say with a longer lifespan or less disease. I would be surprised if you see pillar after pillar showing positive correlation with mortality, or let's say negative correlation with mortality.

Dave:

What are the top five supplements that you take or that you think are most helpful?

Valter:

I mean I take two supplements. And one is a multivitamin, and I take it every, maybe three days or so. And the idea is to plug holes. So let's say that I'm becoming vitamin D deficient, and if you get this every three days or calcium deficient, it's probably going to plug that hole and make sure that I never develop a severe deficiency. And the other one I take if I don't eat a lot of fatty fish instead of omega-3 fish oil. Those are the two that I feel pretty confident about. Yeah.

Dave:

So you're taking Vitamin D without vitamin K2. It's interesting. Any reason you don't add K2 to it?

Valter:

Well, I don't take vitamin D alone.

Dave:

Oh, it's in your multivitamin.

Valter:

Yeah. I think they're already in there.

Dave:

It's okay.

Valter:

I assume they're already in there. But-

Dave:

Yeah. Make sure, because vitamin D without K2 tends to drive tissue calcification, which is not the direction we want to go, but when you have it with K2, it tends to keep the calcium in the bones, at least according to all the research I've done. I bet it's in there, I'm assuming you're taking a high end multivitamins, so you should be fine. Beautiful. Valter, thanks so much for your work in the world, and academia, and working on cracking the code of aging here. I think you're one of the greats in the field. I'm grateful you were on Bulletproof Radio, grateful you shared those answers with the Upgrade Collective and just keep doing what you're doing.

Valter:

Yeah. Thanks for having me and great questions. Yeah. Great discussion.

Dave:

If you guys liked today's episode, you know what to do. We'll try intermittent fasting at least some of the times, seems there's some pretty good evidence for that. Don't have to do it all the time, and join the mission to live way longer than you're supposed to. I think we can all do that. And it's a lot of fun working on it. Think about being a part of the Upgrade Collective because we're doing that together, ourupgradecollective.com, and you can find everything about Valter Longo's work by going to valterlongo.com. V-A-L-T-E-R, Longo, L-O-N-G-O .com. See you on the next episode.