DR. VALTER LONGO INTERVIEW
Fasting Mimicking Diet

By Chris Wark

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Hey everyone. Today I'm interviewing the legendary Dr. Valter Longo. Dr. Longo was born and raised in Genoa, Italy and received his undergraduate degree from the University of North Texas, where he majored in biochemistry, with a minor in jazz performance. He received his PhD in biochemistry from UCLA and did his post-doctoral training in neurobiology of aging and Alzheimer's disease at USC.

Dr. Longo studies focus on the fundamental mechanisms of aging. His laboratory's identified several genetic pathways that regulate aging and reduce the incidence of multiple diseases in mice and humans. His laboratory also described both dietary and genetic interventions that could reverse the course of diabetes and Alzheimer's, and protect cells, and improve the treatment of cancer and other diseases. Dr. Longo's most recent studies are on dietary interventions that can affect stem cell-based regeneration to promote longevity.

Dr. Longo is recognized as a global leader in aging and nutrition, with over 100 peer reviewed publications in major top journals like Science, Nature, Cell, Cancer Cell, JAMA, Journal of Translational Medicine, and more. He is recognized by Time magazine as a longevity guru, with three feature articles in less than two years. So, now you know why I'm excited to talk to Dr. Longo.

Chris: So, hey, Dr. Longo. Thank you for taking the time to do this.

Dr. Longo: Hey Chris. You're very welcome.

Chris: So, I'd love to start with how you transitioned from aspiring jazz musician to longevity expert.

Dr. Longo: Well, I'm not sure. I always wanted to be a musician. And then, whenever I encountered some issues, which was they asked me to direct the marching band back in Texas, at the university. And I wasn't going to do that. I was a rock musician.

Chris: *(Laughing.)* Yeah.

Dr. Longo: And then, I thought, "Well, what do I really want to do, in addition to playing?" Of course, I kept playing. And aging came to me immediately. I just loved the scientific challenge, but I also thought, "We'll have so many solutions for diseases, both prevention and treatment." I mean, at the time, I had a very vague idea of what that meant. But yeah, since I was

19 years old, all I've done is study aging and age-related diseases. So, that's my passion, for sure.

Chris: Was there a light bulb moment that got you interested in that?

Dr. Longo: In the book I talk about – and these are cliché things – like my grandfather. But in fact that, I was in the room when my grandfather died. And I never thought much of it. But I think being five years old and seeing somebody die probably sticks in your head. And it's something that becomes like your major issue, all of a sudden. And then I think, at 19 was the first opportunity to say, "You know what, maybe I will just study this. Why do people die?" So, I don't know. But I imagine that's what it was. Because I was so sure that that's what I wanted to do, from a music major to that. It just seems like a little bit of a strange switch.

Chris: Did your grandfather die relatively young? Or did he live to be 90?

Dr. Longo: Well, I mean, relatively young. He just had a hernia actually. And it wasn't treated for years and years and years. And doctors suspected that that was what eventually turned into a tumor. And that's what he died of. So, also, something was in my head, the fact that… And I think the family was fairly aware of the fact that they could have probably avoided this by just a simple surgical procedure, which he didn't do. And so, that stuck in my head too. And that's why in the book I talk about him and his next door neighbor, Salvatore Caruso, who ended up being one of the oldest people in the world. And they probably had the same diet and probably had the same longevity potential. And Salvatore Caruso made it to 110. But just because of that decision of not going to the doctor and getting surgery, that may have cut 30, 40 years of his life.

Chris: I understand. Absolutely. So, will you tell the story of Biosphere 2?

Dr. Longo: Yeah. Biosphere 2, I was lucky enough to eventually work with some of the world's leading figures in aging. And one was Caleb Finch at USC. But the other one was Roy Walford at UCLA. And that's where I started my PhD. And Roy, when I first got to UCLA, was in the Biosphere 2. And Biosphere 2 was this place in the desert of Arizona, and was basically a sealed environment where he and seven other people went into to begin, I think, the first calorie restriction human study. So, they were in there for two years. Most of the time, they were calorically restricted, meaning that they ate the very minimum that you can eat and stay alive, pretty much.

Chris: So, they were basically trapped in this dome for two years together. And they had to grow their own food inside it. Right? Was the main goal of the study calorie restriction? Or were there other things they were trying to ascertain from doing that?

Dr. Longo: No, calorie restriction was not supposed to be part of the study. They were supposed to go in there and do all kinds of studies on humans kept

in a sealed environment. And maybe it was an idea about space stations or something. I think that's probably what it was. But Walford, I think, had an agenda from the beginning. Of course, he was the world leading expert on nutrition and longevity and, particularly, calorie restriction. So, I think he was looking for an opportunity to do that, to do a human calorie restriction study. And sure enough, he succeeded. And if you look at the results, they are amazing. But eventually, we found out that that kind of calorie restriction causes as many incredible solutions as much as it does cause problems.

Chris: And how many calories were they eating per day, roughly?

Dr. Longo: I think the average was 1,800 calories. But if you look… I always show the picture of Walford when he was calorie restricted in Biosphere 2. And he looks emaciated. He looks like a skeleton. So, clearly, on one side you see the effects on blood pressure. I think they had blood pressure of like 85 over 55, and then the cholesterol was extremely low. And the blood glucose was extremely low. So, you look at them and you say, "This group would never get cardiovascular disease, would never get diabetes." And sure enough, the monkey study confirmed that. And they probably got a lot less cancer.

But they were pushed to such an extreme that they probably ended up dying of other problems. And Walford himself died of a motor neuron disease. I mean, nobody if the biosphere was involved in causing this. But certainly a lot of people suspect that being pushed to the limit – he was in these late sixties – could have contributed to eventually developing this motor neuron disease. So, that's tricky. That's what I've been trying to solve for all these decades, since the Walford years. How do you get these incredible benefits of calorie restriction without the problems of calorie restriction?

Chris: Before we move into your research, what were some of the other major findings from that study? Like the big revelations.

Dr. Longo: The Walford study in Biosphere 2?

Chris: Yeah.

Dr. Longo: Yeah. They couldn't do what Richard Weindruch, which was also in the same lab a few years before me, who ended up doing the monkey study at the University of Wisconsin. So, they couldn't do a longevity study. But if you look at the blood markers, it was very obvious that these people were very unlikely to develop any cardiovascular disease or metabolic disease. So, I think those were the major findings. There were only eight people. But I think later on there were larger studies done, and they all confirmed what was shown by Walford in those original studies.

Chris: While we're talking about blood markers, there's a lot of debate about cholesterol. And I would like to hear from you what you think the ideal range of cholesterol is.

Dr. Longo: Well, I mean, I don't know. I mean, I didn't review the literature on cholesterol. But certainly, below 200 is the healthy range. And of course, probably, if you look at Biosphere, I think it was 125 or something like that. So, it was much lower. I think, probably, I wouldn't try to push it too low. As we see for IGF-1, for example, we are finding something like growth factor-one is certainly associated with aging and age-related diseases, particularly cancer.

But we see that people that are in the very low range tend to do worse, probably because that is a marker of frailty. Meaning that if somebody has a cholesterol that is too low, you have to start wondering if something is not working properly. I mean, we make our own cholesterol, and why is the body all of a sudden not making any cholesterol? So, we have to be careful at demonizing things. And eventually, maybe when you get to too low levels – whether it's IGF-1 or cholesterol or triglycerides – then you have to wonder if something is wrong with the system. And this is very common with people that do dietary intervention. They take something good and they make it bad. They push it to such an extreme that then they go from one problem to the other. Let's say proteins, right? We publish on proteins, and I'm assuming we're going to talk about it.

Chris: Yes, definitely. Please do.

Dr. Longo: You can go from high protein, which is a clear problem, to very low protein intake, which is another clear problem. And that's very, very common.

Chris: One of your studies, probably one of your most well-known studies, is related to protein and protein consumption, tripling or quadrupling the increased risk of mortality, before age 65. Is that right?

Dr. Longo: From cancer. The overall mortality, I think, was 75% in the up to age 65.

Chris: And by high protein, you mean eating animal protein three times a day, right?

Dr. Longo: Yeah. This was over 20% of the calories are coming from proteins, in an American population generally had a very high calorie diet, right? So high calorie diet with 20% of the calories coming from protein. So, you're looking at over 600 calories coming from protein. So, very high levels. And this was compared to the people that had less than 10%.

Chris: And those were people eating a plant-based diet, correct?

Dr. Longo: Not necessarily.

Chris: Just very little?

Dr. Longo: Very low protein intake. Now, if people had a relatively high protein intake, but it was from a plant-based source, then you did not see the effect on mortality. You still saw the effect on cancer. But of course, there was nobody that had pure plant-based. Most people had a mix. So, it's very difficult to have a large population that has a high level of protein, all plant-based. So, I don't think that those data are very conclusive. And even when we did the follow-up study with Harvard, it's hard to get a population that has got a mostly plant-based source of proteins. And at the same time, has a high (let's say over 20%) of the calories came from protein. It's almost non-existent. Also because it's so hard to get that much protein from a plant-based diet. If you're on a plant-based diet, eating maybe fish a couple times a week, you don't even have to worry about having too much protein. It's almost impossible. You would need like a kilogram of chickpeas to get into a 100 gram level that might be detrimental.

Chris: So, you feel like 100 grams per day could be detrimental, even of plant-based protein?

Dr. Longo: Yes.

Chris: Okay. Got It.

Dr. Longo: That's what the data suggests. Once you get to very high levels, then you your IGF-1, insulin, and everything else is going to respond to it.

Chris: Talk about what happens in the body when you consume excess protein.

Dr. Longo: Well, basically, we know that fairly rapidly the growth hormone, IGF-1 axis – genes that are involved in growth – are elevated. And also, these intracellular genes – TOR particularly – activities increase. And so, these are recognized as the two major pro-aging pathways. So, a set of genes that accelerate aging – growth hormone IGF-1 and TOR. And so, protein controls both of them. So, if you have very high levels of protein, you're going to have high levels of these genes all the time. And of course, with it (as we've shown in our studies, both in mice and humans) you expect to have a high cancer rate.

Now, the proof of that is our human studies in Ecuador, and John Kopchick and Andrzej Bartke's studies in mice. And so, now in mice there's been many experiments confirming very potent effects of blocking these genes on the cancer. And not just cancer. These mice, that like to grow hormone receptor, which respond to protein, have record longevity extension, right? They live 50-100% longer than normal. And we have shown the people in Ecuador that have the equivalent mutation, rarely

develop cancer. Out of 350 people around the world, there's only been one cancer death in these growth hormone receptor deficient subjects. Which is unbelievable, if you think that the people, their relatives that live in the same houses, develop cancer like everybody else. So, this has nothing to do with Ecuador or the environment.

Chris: Right. Or even the diet. Just because they don't have that growth hormone receptor.

Dr. Longo: Yeah. So, they basically can eat as much protein as they want, and their IGF-1 and insulin levels will be very, very low.

Chris: And this Ecuadorian population, they're very small people, right?

Dr. Longo: Yeah. They're very small people. So are the mice. So are the yeast that have record longevity. But of course, now we know that we can separate at least a part of the longevity effect from the size. But that tells you that there is a very close relationship between these growth factors and cancer, and also longevity.

Chris: So, excessive animal protein drives IGF-1 and TOR.

Dr. Longo: Insulin too. I mean, insulin is also partially regulated by growth hormone signaling.

Chris: But sugar also does the same thing. Correct?

Dr. Longo: Yeah. And this is something that we discovered many years ago, sugar activates the other pathway, which in yeast is called RAS/PKA. And now, recently we've shown at least the PKA component is activated by sugar also in mammals, in mice, and probably humans. So, we call that the other pro-aging pathway, which sugar activates, this protein kinase A. And we think that the high level of protein or high level of sugar together really drives most of the pro-aging and also pro-cancer genes.

Chris: So, the most dangerous meal might be the double cheeseburger with a large coke, right? High protein, high sugar.

Dr. Longo: Well, I will add high saturated fats to make it the, the terrible meal. And this also underlines something that I talk about in the book, the importance of not trying to simplify fat and carbs and proteins, but really understanding that it's much more about the type and the quantity. So, proteins are fine, carbohydrates are fine, and fats are fine. It just depends on how much and what kind. And it's unfortunate that people have to face it. I think in the book I try to make it as straightforward as possible. It's not that hard, but you have to learn it. And it's not enough to say proteins are bad. Proteins are not bad. You have to have a sufficient number probably of plant-based proteins. And same thing for fats and carbohydrates.

Chris: So, let's talk about fasting because I know in your research, starting with observing the calorie restriction and moving on to yeast and mice… The first time I read any of your work, I think, was related to how fasting regenerates the immune system. Can you talk about that process?

Dr. Longo: Yes. I mean, obviously, this started many years ago with bacteria and yeast, and the fact that when I starved them (back in graduate work at UCLA) they would live longer and would be very protected. And eventually, that led to showing protection in mammals. But then, the more surprising part was when we showed that it caused regeneration. And it wasn't so much the fasting that caused regeneration, it was the re-feeding that caused the regeneration. And that that was probably a trick that calorie restriction done chronically… So, if you eat less all the time, you never take advantage of that. So, it turns out that the starvation basically triggers the death of a lot of cell types.

And it seemed like in our work on multiple sclerosis, we showed that it particularly targets damaged cells or cancer cells. Cancer cells, weak immune cells, they're preferentially killed by the starvation conditions. So, starvation is really a destruction of bad component moment. But then the stem cells are turned on and just standing by. They are just few and they're standing by. Then when you re-feed, these stem cells are basically activated, and they can now give rise to new cells to form tissues and organs.

Chris: So, the old and damaged and weak cells, you're saying, basically die-off first, during starvation or fasting. And then, stem cells are switched on. And then, as soon as you start eating again, they ramp up production of brand new young cells, including immune cells. But it's probably system wide, right? They're probably reproducing organ cells and muscle cells and everything, aren't they?

Dr. Longo: Yeah, it's clearly system wide. And it's also both cellularly and intracellularly. So, intracellularly it happens by autophagy. So, the cell eats itself. And cellularly it just happened by clearing and killing itself. I always use the analogy of a steam train. And the steam train burns wood, and running out of fuel and not being able to make it to the next station. And the engineer basically makes a decision, "Let's start burning components of the train to make the next train station." And of course, if you were that engineer, you pick first the damaged part, like damage seats or damaged walls. Anything that is damaged, you burn first. Eventually, then you're going to burn everything else, otherwise you're never going to make it to the next train station.

Now when you get to the train station, then you can rebuild the train. And I think it's a good analogy for what's happening. And it also tells you that this has been around since the very fundamental forms of life, with autophagy in bacteria going on. And basically the bacteria making the decision, "Well there is no food coming in from the outside, let's use the

components that we don't need right now to make it to the next moment where we can feed again."

Chris: Would you say it's a relatively reasonable assumption that because we have such an abundance of food in the US, because we're eating three meals a day every day, that autophagy is not happening very much? Or not as much as it should? In our bodies.

Dr. Longo: We used to eat three meals a day. That's what I'll say. I talk in the book about it. We now eat like five or six meals a day. It's entertaining that in the United States, where 70% of the people are overweight or obese, we still talk about eating five or six times a day. They haven't figured out yet that that's a bad idea. And in the book I talk about how if somebody's overweight or obese, they should go back to two meals a day, plus maybe a 100 calorie snack. Yeah, so there is no doubt that we are now in an eating epidemic, essentially.

So, the human body, like the bacteria, organism, are used to having fasting starvation being a major portion of life. And so, once you remove it completely… And most people get headaches when they fast. I mean, some of it might be due to caffeine withdrawal. But some of it we also suspect is due to the fact that some of these enzymes that are starvation response enzymes, have never been used in their entire life. Let's say most Americans, or Europeans for that matter, have never used a lot of the brain enzymes that are using ketone bodies for fuel. So, the brain usually is fueled by sugar. And when you starve, at a certain point, the brain and other components of the body are now using these ketone bodies – where the word "ketogenesis" comes from, or ketogenic diet. And so, the body now is starting to use these ketone bodies. And for a lot of people, we suspect that some of these enzymes have never even been turned on.

We also suspect that the starvation may have represented a moment… Like sleep. We just didn't use to think much about sleep. Sleep is probably representing a moment where you're regenerating certain things, at least. And starvation was probably the same thing. There's probably represented a moment where you stop ingesting food and use that period to clear up damage components, and turn on good stem cells.

That's another thing. We suspect that we just don't turn on any stem cell. You need to turn on the good ones. There's probably a selection process to say which one is so healthy that should give rise now to a newly regenerated set of cells. And we suspect the selection of that. So, yeah, starvation probably represented a very important moment in somebody's week. So, this probably happened all the time. And now we've completely eliminated it, to the point that people may not encounter it for years and years and years.

Chris: And there's a certain amount of time that has to transpire before you switch on this protection and survival mode in your body. Right? I mean, intermittent fasting is not enough time to trigger this. It needs to be at least three days? Is that right?

Dr. Longo: Yeah. I mean, first of all, I hate the term "intermittent fasting" because it doesn't mean anything. It's like saying either "intermittent eating." What does that mean? Of course, people fast. That's why we have the word "breakfast." Right? I mean, you could go two hours without eating and that's fasting. Is that intermittent fasting, because you had lunch and then you had a snack at five? Is that fasting between? It doesn't mean anything. So, I think it'd be good to stop using it, or to start qualifying. So, are we talking about 16 hours? 12 hours? Are we talking about eating 500 calories every 2 days or whatever?

So, each have very different effects. I mean, I don't really regard any of that as fasting at all. For the purpose of aging and protection and killing of cells that are damaged, etc., like you just pointed out, you need a couple of days. Why? After a couple of days, the glycogen reserves are depleted and the body is starting to break down its own components. And the body's also starting to switch from a glucose-based metabolism to a fat… And mostly, as we've shown in our papers, it's starting to use a visceral fat, right? So, the fat that is so central in insulin resistance and all kinds of other problems.

Chris: Like belly fat.

Dr. Longo: The belly fat, exactly. And that's what you want. You want to start having a preferential effect on the belly fat, and not touching the muscle and even the subcutaneous fat is not really touched very much by the prolonged fasting. So, some forms of what Satchin Panda calls time-restricted eating is very important. But in the book I talk about 12 hours. Why 12 hours? Well, because 12 hours, if you look at the literature, there are really… So, if you eat, say, 8:00 AM / 8:00 PM, or 9:00 AM / 9:00 PM and then stop, that's very good. The centenarians do it and there is not a single study that I could find the shows that to be negative. When you get to eating more than 12 hours, then you start seeing the negative results. But when you get to eating less than 12 hours, you start seeing the negative results. For example, gallstone formation and the need for surgery goes up dramatically for people that consistently fast for more than 13, 14 hours a day.

Chris: So, people that maybe skip breakfast and they just eat lunch and dinner?

Dr. Longo: Well, that's even worse. If you skip breakfast, there are multiple studies and we have our own data supporting that, you increase overall mortality and you increase cardiovascular disease mortality. So, if you go over 12 hours, it's already bad idea of fasting. If you go over 12 hours and you

skip breakfast over and over and over, the epidemiological studies show increased mortality. And it's unbelievable. Even experts that I talk to, almost nobody knows this data.

Chris: I've never heard that either. I'm fascinated by that.

Dr. Longo: Ketogenic and fasting was one of the most searched topics of the year on Google. And nobody knows these facts. It's scary because obviously imagine the consequences of like millions and millions of people now adopting these things without knowing what they're doing.

Chris: Yeah. I'd like for you to talk a little bit more about the ketogenic diet, too, compared to the fasting mimicking diet. But I'd like to talk about the fasting mimicking diet first. So, based on what I've read in your book, I'm going to summarize. So, after doing fasting research, you realized how powerful it was. But I'm assuming that you also felt like it was maybe difficult for a lot of people to embrace. To not eat for three to five days. My community is very motivated and they will do it. Many of them have done three to five days on water.

Dr. Longo: You'd be surprised. This is why we started the fasting mimicking diet, because your community, the cancer community, didn't want to do it. So, we started, 10 years ago, a clinical trial at USC. And the cancer patients basically said, "I'm not doing this." And the doctors, the oncologists said, "I'm not going to ask my patients to do it." So, that was really the motivation to do this. Now, of course, you may have a special crowd that is very motivated.

Chris: I think I do.

Dr. Longo: So, they are they are out there. And they're usually the ones that contact us. But if you grab 100 cancer patients, I would say… Actually we did that. We surveyed that. And I think it was 7 or 8 out of 10 would say, "I'm not going to do it." And the interesting thing was, they felt cheated. They felt that, "Why are you giving me water? This couldn't possibly be good for me." And then, we realized also problems with it. It may get the levels of blood pressure too low, levels of glucose too low, etc.

Chris: Especially if they're taking medications, right?

Dr. Longo: Well, if they're taking medication, that could be even worse. But even without medication, we see people on a water only diet and they may pass out. I mean, again, you have to think about the masses, right? You know, you can get 10 friends and they all can say, "Oh, I didn't have that problem." Especially if people have been doing this for a long time. Sometimes people grow up doing it and they have no problems. But most people, if they're introduced to something like this, they're going to struggle. Water only, I mean, 95% of the people are going to struggle.

Chris: Yeah. I understand that.

Dr. Longo: And a percentage of those are going to have real problems.

Chris: So, you obviously realized that people don't want to do it. It's hard to convince them to do it. And that led you to develop a fasting mimicking diet.

Dr. Longo: Yeah. So, the government, actually, the National Cancer Institute realized that this was very promising. And so, eventually they gave us grants to develop a fasting mimicking diet. And that's what we did. And of course, that changed everything. Now, we have many clinical trials ongoing on the fasting mimicking diet and cancer. And some of them are completed and some of them are ongoing. But hundreds of patients have done it and that's pretty straight forward.

But one thing that we realized with the fasting mimicking diet is something called food aversion. Cancer patients associate the diet with the chemo. And so, now we've realized we have to rotate. So, you cannot give them the same thing twice. And so, that's what we're trying to develop now. Enough of a variety so that they don't associate any particular food with the pain or the suffering of chemotherapy.

Chris: That makes a lot of sense. Can you talk about what the diet looks like?

Dr. Longo: The diet is basically... The version that we now have for cancer patients...

Chris: I know you have two. You've got ProLon and Chemolieve, right?

Dr. Longo: Yeah. ProLon is for people that don't have diseases. I mean, from a scientific point, I can say it's definitely cancer prevention, a cancer prevention intervention. The FDA will not allow that claim. So, it's not a claim because the FDA basically said, "Well, if you want to say it's cancer preventative..." We've shown that in mice, but of course in humans, we haven't demonstrated. "So, you will have to have a formal trial, which will be impossible to do."

Chris: Yeah, you can't follow people for decades.

Dr. Longo: Yeah, exactly. Right. It's an impossible thing to do. So, ProLon is for normal people and people that may be at risk for cancer, at risk for disease, for diabetes, at risk for cardiovascular disease, neurodegenerative disease, etc. But otherwise normal. And Chemolieve is something that we developed specifically for cancer patients. And now, it's undergoing trials in many different hospitals.

Chris: And the ProLon is five days. And the first day is 1,000 calories. And then, days two, three, four, and five are 800 calories, right?

Dr. Longo: Yeah. 1,100 calories on day one. And then I think 750 days two through five.

Chris: Got It. And then, Chemolieve is less. What is it?

Dr. Longo: It is less. I think it's something like 600-`700 calories on day one, and then it drops down to about 300 calories on days two, three, four. It's only four days. And we made it to try to fit more along the different cancer therapy regime.

Chris: And can you talk about what the preliminary, and even the published, results of the human trials you've done on cancer patients following this diet? In terms of chemo working better and it protecting them from side effects?

Dr. Longo: Yeah, we've done multiple studies. Some of them aren't published yet. But so far they're all positive, meaning that they are all showing protection of either the patient or of the cells in the patient. Sometimes it's hard to determine if a patient is doing better. And so, we look at, let's say, DNA damage in the normal cells. And of course that could turn out to be a secondary tumor, if you don't protect the normal cells. And so, so far they're all positive. And now, we have to wait for the final results of the 200 people trials.

Chris: When does that trial finish?

Dr. Longo: Ours at USC is going to be completed, I think, in the next six months. And it is together we Mayo Clinic and MD Anderson Cancer Center. And then the one in Leiden may take another a year or so – University of Leiden. The good news, so far, it has been definitely no issues with the diet. Meaning that people could do it, it was safe, it was feasible. So, that's good news. And there is no evidence of problems caused by it. Now eventually, we have to figure out, like we did in mice, is it making it not just the protection of the patient, but is it making it worse or much worse for the cancer? You know, we suspect that it does. But that part to prove it is much harder because there's so much variability, in the cancer patient. It takes so long to monitor cancer progression. But that's what we're also doing now. And we have to see what the results are.

Chris: So, for the average person who's interested… I've done the ProLon five day fast and my experience with it was very good. I mean, I didn't find it difficult at all. And the food tasted good. And my wife and I did it together, actually. And we just, five days did it. How did you arrive at five days?

Dr. Longo: Well, it was a really a combination of looking at the effects on IGF-1 and something called IGFBP-1, glucose and ketone bodies. So, we wanted to have strong effects on those, and really revolutionize the environment to be like a full fast response. And we also wanted to push the system, the

human body, into a breakdown mode. But we didn't want to push it over the edge. So, we didn't want it to be so long that people started saying, "I'm not going to do that." So, five days we think is a perfect amount of time. So, say you started on Sunday, you finish it by Friday. And also, obtaining all the things that we want to obtain. For example, the beginning of clearing of damaged cells, the turning on the stem cells, and the breakdown of visceral, belly fat, the minimal effects on muscle, which is then reversed during the re-feeding, etc.

I mean, if you look at our clinical trial results from the ProLon, it's truly remarkable how it can have all these positive effects with really, so far, minimal side effects. And now I think over 20,000 people have done it in multiple countries. So, the good news is we really have seen rarely any problems. And we suspect that maybe none of the major problems are caused by the fasting mimicking diet. So, that's very good news.

Chris: So, can you compare the fasting mimicking diet to the ketogenic diet?

Dr. Longo Well, the fasting mimicking diet is a ketogenic diet. Meaning that it's a high fat, low sugar, relatively low protein diet. And so can be the ketogenic diet. The ketogenic diet you have multiple versions now. A lot of the ketogenic diets out there are high protein. And again, we're going back to these words that don't mean anything. There's a lot of ways to promote ketogenesis. I think the fasting mimicking diet promotes a natural ketogenesis. So, it makes the body activate it's own fat breakdown. A lot of the ketogenic diets out there are artificial ones, and they impose an artificial condition. Which is, let's say, high fat – maybe a lot of it is animal fat. And then high protein – and a lot of it is high animal protein.

So, now, you could go very quickly from something very good to something very bad. And now, something very bad doesn't have to appear as very bad, when you first do it. It could be that you do it and you lose weight, and you think, "Oh, well this is great. I feel good. I'm losing weight." And then, eventually, you could start having kidney damage, you could start having effects on IGF-1, and potentially on arteriosclerosis, and blocks formation, etc. I'm not saying that it does this, because there are different ketogenic diets. But I'm saying that a lot of these diets are improvised.

In the book I talk about five pillars, which is epidemiological studies, clinical studies, basic research, studies of centenarians, and studies of complex systems. And I do that for a purpose. Look, when you try to build a space shower, you have all these engineers and you have NASA involved in it, and the top universities in the world. And then, when it comes to telling the world or people what to eat, anybody can have an opinion. And a lot of these ketogenic diets come from nowhere. But they're able to convince, in some cases, hundreds of thousands of people to do it. And it's not clear where they come from. So, I would say, "Let's

stop talking about intermittent fasting or ketogenetic diet. And let's start talking..." I mean, it doesn't have to be necessarily the fasting mimicking diet. But start talking about five pillars.

Where's the data supporting this specific diet? And let's not call it ketogenic. Let's call it something. Let's say this is it. Does it have 60% fat, 30% carbohydrate, and 10% protein? That's a ketogenic diet. That's probably a decent one that you can do for a short period. I wouldn't do that for a long period. In the book I talk about the ideal diet, again, based on the five pillar is 60% carbohydrate – but not sugars or pasta and bread. Carbohydrates coming from fruits and vegetables, mostly vegetable and legumes and some fruit. So, 60, 30, 10, I think, by looking at all these pillars, seems to be the ideal conditions. 60% carbohydrates, 30% fats, and 10% protein (mostly from vegetable sources).

Chris: Well, I'm glad to hear you say that because that's exactly the way I eat. That's my caloric breakdown. And it is from whole food, plant-based sources (for the most part). Isn't it true that the ketogenic diet does not induce the repair and protection mode in the body, because you're eating too much food and your body knows you're not starving?

Dr. Longo: Yeah, I mean, if you think about the train analogy, if you ever allow food, the body after a very short time adapts and says, "Okay, we have energy coming from a different source." And so, you can have minimal effects on sugar levels and everything else, and there is no reason to break anything down because there's plenty of nutrients to keep going as it is now. You know, it depends what ketogenic diet it is. In some cases, you may have a breakdown of fats, etc. We do know that certain high fat diets can promote stem cell activation.

But again, if you look at evolution and you look at where these programs come from, they come from starvation. And you can have a fasting mimicking diet that is very much representing everything that goes under starvation, including a severe restriction of calorie, right? I mean, the FMD is severely restrictive. So, you're fooling the system just a little bit. But other than that, you're just allowing the natural process to occur. You basically don't interfere with the natural process. I mean, that's a key of the fasting mimicking diet.

In the case of the ketogenic diet, instead you're trying to force the system into doing something that has never evolved to do. I mean, if you think about somebody maybe having a high fat, high animal protein diet by hunting 50,000 years ago, that wouldn't necessarily need to lead to the breakdown of anything, or the replacement of anything. There's plenty of nutrients coming in. Let's keep going. This is a moment, in fact, to be very active and keep hunting. If you have that kind of food, keep using that strength and energy to function as a fully as possible.

So, yeah, I suspect that a lot of these things that are interfering with this incredible program. If you look at, for example, our paper recently on diabetes. We destroyed the pancreas of mice and then we started the cycles of the fasting mimicking diet, and we show that it turns on the embryonics, the gene expression profile that you only see during embryonic development. And so, that's extremely powerful. Because imagine having to replace… And we show that we can regenerate the insulin producing better cells. So, we can first destroy them and then regenerate them to normal levels, so they can, they can control glucose level.

So, to reproduce that with an artificial diet or with genetic or stem cell intervention would be almost impossible. This is a very sophisticated program that has always been there. So, it's an evolved program. And that's really what we should explore – the ability of the body to repair itself. And if you start imposing diets that are trying to trick the system in an excessive manner…

Chris: Like taking exogenous ketones, for example.

Dr. Longo: Yeah. I mean, again, if you took some exogenous ketones… Well first of all, let's say you take some exogenous ketones, but you starve otherwise… It may be okay. I wouldn't do it because it's very unknown – using ketones like that, ketone bodies for long periods. But that could work, in terms of allowing these programs to be turned up. If you instead take on ketone bodies and at the same time eat a normal diet or a fairly normal diet, then it's a recipe for disaster because all of a sudden… Not only is it not going to work, but you're pushing the body to have two metabolic strategies at the same time. And that could be problematic.

Chris: Well, that's what's happening. A lot of health influencers are telling their followers to take exogenous ketones and eat tons of bacon, butter, eggs, and avocado. A very high fat diet while supplementing ketones. And yeah, it's just kind of like the Wild West right now.

Dr. Longo: It's very scary, and almost guaranteed failure. And why? Well, because we're not used to that. And even if it was a good thing for one, two, three, four, five years…eventually the body is going to have problems. Because it's never done that. It's not used to that. And when you introduce an environment that has never been seen before, sooner or later, the body starts not being able to function in that environment.

Chris: I'd like to just touch on the results of the human clinical trial that you mentioned earlier. So, you had patients do the fasting mimicking diet for five days per month, for three months in a row, correct?

Dr. Longo: Yes.

Chris: And this was how many patients? 10,000?

Dr. Longo: No, no, no, no, no. This was a 100. In the randomized trial, it was 100 patients.

Chris: So, three months in a row, they did a five-day fasting mimicking diet, and then went back to their normal diets for the rest of the month. And the results are amazing. I mean, they had lower cholesterol, lower blood pressure, they lost weight, lower blood glucose, lower IGF-1. What am I missing?

Dr. Longo: Yeah, lower triglycerides and blood pressure, etc. First of all, if people had very good levels of, let's say, cholesterol or blood glucose, it didn't come down anymore. Right? So, this is also very important, because if you have a fasting glucose of 70, if you do calorie restriction, that's going to come down to 50. And that causes a problem. And we know that. With the fasting mimicking instead, it didn't lower it. It left it where it was. In fact, in some cases even increased it. So, that's very interesting because it basically says if the body is functioning properly, there is no reason to fix anything. But if something is dysfunctional, let's say you're pre-diabetic, you're insulin resistant, you have systemic inflammation, then in the great majority of cases, those problems were eliminated or certainly reduced. And the patients might be better or much better. So, that's also a very interesting component of the fasting mimicking diet. They're not driving everything down, but they're able to, we believe, repair what's not functional.

Chris: That's interesting, in that example you gave. Because what you're saying basically is that that particular example would be someone whose fasting blood glucose was a little too low, and it came up.

Dr. Longo: Yeah. So, some of the people that have very low fasting glucose came up. And that's important, right? Because now, again, you can go from a problem to a worse problem. And you don't want that. You want the body to be healthy. You want the immune system, for example, to be healthy. And when you have too low levels of glucose, of IGF-1, etc., you can start having important components of the human body shutting down or not acting as quickly as possible.

And if you imagine the battle with viruses and bacteria, it's always like an equal battle almost, right? The immune system barely makes it. And a lot of times, we need antibiotics to make it. So, that tells you that even if you take that immune system and you decrease its function by 10%, now you just gave a big advantage to the virus or to the bacteria. And that could kill you. Literally. So, this is why it's so important that levels of many different factors are now going down to too low ranges because that could be almost guaranteed to be detrimental.

Chris: How often do you do a fasting mimicking diet?

Dr. Longo: I follow my own advice. I mean, I have a vegan pescatarian diet. And I follow everything else, low protein, etc. So, I do it twice a year. And that's what I recommend in the book. If you're obese and have high cholesterol, high blood pressure, etc., you need to do once a month until you move to a different range. If you have an ideal diet and you're healthy and none of your markers are out of range, then twice a year is sufficient.

Chris: But do you recommend that almost everyone do that initial three months in a row. And then twice a year beyond that?

Dr. Longo: Not necessarily. I think that if you don't have any problems, you can probably go to once every four months. If you have, let's say, maybe a little bit high cholesterol, you want to drop it a little bit lower, yeah. You could do it once, and then wait four months and do it again. And then if it doesn't work, you can do it more frequently. Or if you feel great and all your markers are great four months later, you can do it every six months. Go to the six months. I think it should be done in a need to do basis. It shouldn't be done just as frequently as possible. Not until we know more about it. I think eventually, when we can do an epidemiological study and say, "The people that are doing FMD once a month are living 10 years longer than everybody else." Okay. Then we'll tell everybody to do it once a month. But until then…

Chris: Keep me in mind. I might sign up for that one.

Dr. Longo: Yeah.

Chris: That's great. Well, Dr. Longo, I really appreciate your time. Thank you so much. This has been really fun. I want to ask you one more question. This is more of a fun question. But if you had to eat the same thing every day – breakfast, lunch, and dinner – for the rest of your life, what would your day look like? And breakfast, lunch, and dinner can be different meals. But what would your ideal, stuck in the biosphere diet?

Dr. Longo: I think probably what I eat for breakfast, which is black tea and green tea together, and I put a whole lemon in the tea. And then, I have a cinnamon raisin toast with blueberry preserve in it, low sugar. And then, for lunch, probably ideal would be a salad, with as many different components as possible. And then, dinner, what I have very often is about 50 grams of pasta and then about 350 grams of wet garbanzo beans. And then another couple 100 grams of mixed vegetables – like corn, carrots. So, it's like a minestrone. And I put a ton of olive oil on it. So, that's something that I do eat all the time.

And if you look around the world at the centenarians, that are so successful at making it to 100, it's unbelievable how much they eat over and over and over. Like you just pointed out, the same every day. Like the Okinawans used to eat sweet potatoes all the time. 70% of their calories came from these purple sweet potatoes. And the southern

Italians from Calabria, where I spent a lot of time growing up, almost every day they ate Pasta e Vaianeia, which was a little bit of pasta and a ton of these green beans. So, I think it's also something important to tell your audience, not necessarily to try to go to too many exotic foods, but maybe pick the 30 healthy foods that your grandparents used to eat. And just stick with those.

Chris: Eat like your ancestors, right?

Dr. Longo: Well, not necessarily. Start with the right list and then go see. Because some people's ancestors ate a very terrible diet.

Chris: Good point.

Dr. Longo: Pick the right foods, and then out of those see which ones your grandparents used to eat.

Chris: That's great. I love it. Okay, well, thank you so much, Dr. Longo. I will provide links below this video so everyone can find out more about Dr. Longo's research, ProLon, fasting mimicking diet, and a whole lot more. Thanks so much for watching. Please share.

Dr. Longo: "The Longevity Diet" and all my royalties go to the Create Cures foundation to continue this type of research. And now we have a lot of trials that are going to be sponsored by the book royalties in Italy, Spain, and elsewhere. And I hope it does very well in the US, so that we can continue to do this.

Chris: Thank you for bringing that up. That's great. So, yeah, all the proceeds go to non-profit Create Cures foundation. And pick up a copy of "The Longevity Diet," Dr. Longo's book. I have it on Kindle, on my phone, and read it this week. And it's awesome. Just a fantastic book, especially if you love this kind of research and you're a fan of "The Blue Zones," you will really enjoy "The Longevity Diet." So, thanks everybody for watching. I'll see you on the next one.

Dr. Longo: Thanks, Chris.