Why We Die: The New Science of Ageing and the Quest for Immortality

Transcript

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Hello and welcome to this year's Simoni Lecture of the Oxford Playhouse. My name is Marks de Sotoy. I'm the Simoni Professor for the Public Understanding of Science and this is kind of the university's premier event for communicating science to the public.

And this year we're very lucky to have Venki Ramakrishnan, who's going to give this year's lecture on a topic that I think unfortunately affects us all, which is why do we die? Or maybe not, because this is about the science of aging and the quest for immortality.

So please give a big Oxford welcome to Venki Ramakrishnan.

Venki Ramakrishnan

Thank you very much. It's a real pleasure to be back here in Oxford and also to give this lecture in Simone's name. So I'm going to talk a little bit about the biology of aging and how we understand aging and it's leading to death. And then I'll talk about some of the attempts to try to slow it down and then talk a little bit about what that might mean for us. So the first thing I want to say is that awareness of mortality has driven us since we were humans. In fact, if you look at all of religions, you can think of a major aspect of them is a denial of death. For example, Abrahamic religions believe that your body will be resurrected corporeally, and that's why they insisted on burial. And Eastern religions said, well, the body might decay, but you would have an immortal soul that could occupy other bodies and be reincarnated and eventually escape the cycle. And then there are other ways people want to avoid death, which is For example, you can live on through your offspring, but you can also live on through your works and monuments. And the Egyptians actually combined all of that. So they did build monuments, these huge pyramids with their fancy tombs. This is the tomb of Tutankhamen when it was discovered just over 100 years ago. by Howard Carter, it was amazing that there was all these beautiful artifacts in a tomb that was locked up and no human was supposed to enter. So what was the purpose of it? Well, the purpose was that they believed that eventually the pharaoh would be resurrected and he'd want to see some nice things

around him. And then if he was a good fellow, he would go off to some immortal paradise. Now, yet we know that the end, we're all sort of destined to an end. In fact, we may be the only species that's aware of our mortality. Animals are aware of death, but there's no evidence that they're aware that they have a fixed lifespan. And this leads to the question of whether aging is programmed. Is it something that is just simply programmed as part of our genetic makeup and our biology. And one reason that many people naively thought that was that if you look at the lifespan of various species, they vary enormously from a mayfly, which can last for a day, to these very long-lived animals like this Galapagos tortoise There could be a tortoise around today that might actually have encountered Darwin. And that's rather an interesting thought. And then you can have things like the bowhead whale and the Greenland shark, which can live for several 100 years. So this might lead to the idea that while each species has a program, a kind of biological clock that's ticking away that makes it that's programming it to die. there is a genetic component to aging, but it doesn't work the way that you might think of as a programmed kind of death. Instead, it's really evolution at work. And if you look at the lifespan of mammals versus size, you can see it's roughly correlated with size. And this means that the larger the mammal, typically, the longer it lives. Now there are some outliers. We humans actually live much longer than we should, given our size. And there are some historical reasons for that, evolutionary reasons, but also some modern reasons. But look at all these outliers over here. These are mostly bats and they live much longer than a mouse. So there's a bat called Brandt's bat that lives 40 times as long as a mouse, which is about the same size. So what's going on there? Well, evolution doesn't select for longevity. it only selects for reproductive success. It selects for the survival of the genes because that's what, I mean, as you know from the first Simoni professor who wrote The Selfish Gene, it's really acting on genes. And so if you're a mouse, does it pay for a mouse to live very long? Because it costs resources to maintain and repair the body And those resources could be put into other things like rapid growth and reproduction. And so if a mouse were to live very long, if it, let's say, had intrinsically high longevity, it would not lead to increased reproductive success because a mouse like that would be killed by a predator or be starved to death or die of other causes long before it got old. typically in the wild. So it doesn't pay for a mouse to put its resources into growth and into longevity. Instead, the mouse has been selected to grow very rapidly and reproduce prolifically early on. Now bats, though, have an advantage. They can fly around and and avoid predation. Even when they're roosting, they're roosting on the ceilings of caves typically. And so they're relatively protected. And so, you know, there it does pay. If a bat lives longer, it will tend to reproduce more. And so that's roughly speaking, you know, how evolution works. But there's A twist to that. And that is that evolution will select for traits that help you early on in life and ensure reproductive success, even if those very traits contribute to aging later on. And this is called the antagonistic pleiotropy theory of aging. Pleiotropy means it has effects other than the original trait that was selected for. And antagonistic means that it's

opposing the original benefit. And there are many examples to that. For example, many things that reduce the risk of cancer early in life eventually cause senescence and aging later in life. Things that accelerate growth early in life, later in life are the cause of various kinds of aging. And so this is an idea that's more or less accepted. It's not universally accepted, but I would say it's the consensus among biologists. There are some animals which appear not to age at all. For example, two famous examples are the freshwater hydra and the species called the immortal jellyfish, which can actually, you can think of it as aging backwards because when it's stressed or faces injury, it reverts to an earlier stage of development, almost like a butterfly turning into a caterpillar, in that sort of sense. And so what's going on here? Well, these species have what are called stem cells, which I'll come to later, which essentially can regenerate tissue. And so they have these stem cells distributed throughout their body. So they appear to age very slowly because they're constantly replenishing their older age tissue. But if you were to follow a single animal of these species, you'd find that they do age. It's just that they don't age as fast. It was the same with Galapagos tortoises. People thought that they didn't age biologically. But then these 150-year-old Galapagos tortoises, they are old. I mean, they move more slowly. They have wrinkled skin, they have poor eyesight, and all of the problems that we all experience. So the main thing about programming is you can compare genetics of aging versus genetics of, say, development, where a cell grows from a single fertilized egg to an entire body. In development, the genes are selected for those specific functions. Now, aging has a genetic component, but those genes were selected for something else, and aging is an unintended consequence that evolution simply doesn't care about because presumably you've reproduced by that time. So that leads to the question of, you know, well, This is all fine. Evolution has acted on every species, including us. So what is our natural lifespan? And the limit for humans, the world record holder so far is this woman, Jeanne Calmont, shown in a typical pose. And she holds a record at 122 years. And if you As you see from the picture, she had a cigarette and a glass of port every day after lunch. It's not something any doctor would recommend as an anti-aging mechanism. She was just extraordinarily lucky and probably had the luck of good genes as well. But she also ate 2 1/2 pounds of chocolate, and I can't help wondering whether that was the secret. That's something I could really get behind. Anyway, nobody else, she died 30 years ago and no one else has lived past 120. So it looks like somewhere between 110 and 120 is our natural biological limit. That means if everything goes well, you've been extraordinarily lucky, you didn't get infectious disease or get run over by a bus or whatever. and didn't get cancer early on, and you had great genes, you still can only expect to live between 110 and 120. That's only the survivors. And by the way, the number of centenarians is growing. It was growing exponentially in the sort of early part of Queen Elizabeth's reign. And the queen used to send out telegrams or letters to everybody who turned 100. And then it got very tiresome because the number of centenarians kept growing. But the number of super centenarians, that is people who

have lived to be 110, has not grown. Okay, that is really remain constant. And the reason the centenarians are growing, and that also is plateauing, is because of health advances and medical advances. More and more people are reaching 80. So statistically, more of them are surviving to live past 100. So that's what's happening there. But then they start hitting a wall, a biological wall, at about 110 to 120. So I've talked a lot about aging without actually saying what aging is. And so there are two ways of describing aging. One is the macroscopic way, the external manifestations such as loss of muscle strength and balance, which are all related, cognitive decline, which many of us are all too aware of. And then there's also chronic conditions. So things like diabetes, high cholesterol, all of these things increase with age. Susceptibility to infection increases with age. Our immune system is less functional as we get older. An 80-year-old had many times the odds of dying of COVID compared to somebody who was, say, 15. And then a decreased ability to do everyday activities because of frailty and all of the combination of things. Some people had, very old people have trouble even getting out of bed by themselves or taking care of themselves. So those are the external manifestations. But those external manifestations are the result of underlying changes. And the underlying changes are at the molecular level. And what they are, the accumulation of changes and damage. Not everything is technically damaged. Some things like modification of your DNA by so-called methyl groups, you wouldn't call that actually damage. In fact, that methylation of DNA has a purpose. But the accumulation results in a gradual loss of function and results in increased dysfunction over time. And biologists like to think of, because aging is so complex and multifactorial, they like to think about what are some of the major things that cause aging. And they've defined them, grouped them as sort of hallmarks. The idea being that a hallmark is something that's present in the condition, whether it's aging or cancer or whatever. And the more severe this condition, the more the hallmark is present. And if you reduce the hallmark, you ameliorate. the condition. So that's sort of roughly the idea. And I won't go into this because it'll take, essentially most of my book is about this one slide. But I'll just point out that it goes from the very molecular level, that is our DNA, which contains our genome, to the way that the DNA is packaged as chromatin or chromosomes whose ends are what are called telomeres, which keep getting shorter. And when they get to a point, then the cells go into a particular state called senescence. And then I mentioned how DNA can be modified. And then DNA, of course, our genes code for proteins of all the proteins that we, the thousands of proteins that allow us to live. But the genes not only specify what proteins to make, how to make them, but also when to make them and how much to make them and when to degrade them. So there's a very sophisticated orchestration to preserve what is called the proteome, the collection of proteins, which have to work like an orchestra working together in the cell. And when that coordination goes awry, then the cell becomes dysfunctional. And some of that is controlled by external things called, this is called nutrient sensing. So the cell can sense whether there are nutrients outside, and that in turn affects its metabolism and

its rate at which it grows, the rate at which makes proteins, and so on. And that too, loss of that ability to control that can lead to aging. And these are mitochondria. These are organelles in our cell that are essentially descended from bacteria that an ancestral cell swallowed about 2 billion years ago. This event might have happened millions of times. But that particular time, the two somehow got along and survived and kept evolving together. And today, mitochondria are the place where the energy metabolism of the cell occurs and a lot of other metabolic activity including metabolism of fats. And so when mitochondria, which have their own small genome and live in a highly oxidizing environment, when they get damaged, then the rest of the cell also suffers. And then it goes all the way to interaction between cells and like the immune system and so on. So The main takeaway is that aging occurs at every level of complexity, from molecules to the cells in which the molecules reside in their organelles, to the interaction between cells that form a tissue, and then to the entire organism. Now I want to switch now to why people are interested in aging and why more people are interested in aging and why governments and societies and corporations are interested in aging. And that is that we have today a combination of two factors. We have increased longevity due to medical advances, but at the same time we have lower fertility whose causes are debated. But at least part of the reason is the emancipation of women and the economic independence of women. And so you have this lower fertility combined with increased longevity, and that means you have aging populations. And just to give you an example, Italy Is in the vanguard of Europe it's not the vanguard of the world, which is South Korea and Japan and East Asian countries, but... This was a population distribution in Italy in 1950. So this is age, this is a number of people in that age group. And what you can see is most of Italy is young, and then when they start reaching about 40 or 50, they start gradually dying off, okay, because of disease or whatever. Now, because of medical advances, what's happened here is in 2022, first of all, fewer people are being born. So fertility rates have gone down, birth rates are low. And then there's a cohort that was, where lots of people were born, say, 50 years ago. but they've not died. And so you've got the slight inversion of the pyramid. This reduction shows falling birth rate, and this reduction shows that cohort has survived and hasn't died off. And then the death rate is also slower. And then the prediction is, and this is before the recent data on birth rates falling. So it may be out of date. And what you see here is that there's a complete inversion of the pyramid. And so the prediction is that fewer and fewer young people of working age will be around to support an increasing aging population. So this has led to governments funding a lot of aging research. Aging research used to be kind of the backwater of molecular biology about 50 years ago, but today it's a rather trendy area. And part of that is that governments are very concerned. They would like older people to remain healthy and independent for as long as possible. And that's led to both real advances and some dubious claims. So for example, there have been about 300,000 papers on longevity or some aspect of it published in the last 10 years alone, and not just in what scientists call the Holy Trinity, which is nature, science, and cell, but there's

a whole fusion of journals that are specifically devoted to longevity or aging. And so this has led to a huge explosion of literature. Of course, like any other area of science, only a small fraction of it will actually stand the test of time, but that's just the nature of science. But that's also resulted in over 700 startups with 10s of billions of dollars invested. And I'd like to point out that Calico, for example, was a spin-off of Google. So Google was the company Alphabet funded and founded Calico in San Francisco. And then a big splash was made a few years ago when Altos Labs opened up three campuses, two in California, not surprisingly, but one in Cambridge, England, which was a bit of a surprise. And that was funded by tech billionaires like Jeff Bezos, and it was the brainchild of another tech billionaire, Yuri Milner. And it offered such great resources and salary that they essentially ended up persuading a lot of top longevity researchers to leave their very prestigious university posts and join Aaltos Labs. So along with that, there's also some pretty dubious stuff going on. So this was a slide provided to me by Tom Check. I remember I said that one of the things that's related to aging is the shortening of the ends of our chromosomes. Each time the cell divides, those ends get a little shorter until they become so short that there's a trigger and the cell changes its state to a senescent state. So the idea was, well, maybe you can have an enzyme that lengthens those telomeres again. And we all have telomerase, but it's inactive except in certain cells and also including cancer cells. So it's not a good thing to have around in all your cells, by the way. So whether it's a good thing or not, you can go to amazon.com and you can look at lots of things that claim to lengthen your telomeres. Now, first of all, we don't even know if that's a good thing. Secondly, we have no idea if they actually do lengthen our telomeres because there have been no randomized clinical trials, no FDA approval. They're sold as food supplements. So another, when you tackle aging, the question often arises, would you consider aging a disease? Now clearly there's a whole strain, and I think a lot of longevity researchers like to consider aging a disease. And certainly, tech billionaires think of aging as a problem to be solved. So definitely a sort of disease. And I'm more skeptical, but I'll tell you the arguments. One is that the pro side is that people say that, look, all of these diseases of old age, for example, the four big ones are cancer, diabetes, heart disease, and neurodegenerative diseases. If you look at all these four diseases, the biggest risk factor is age. The older you are, the more likely you are to come down with one of these things. So the idea is that, well, actually aging is the primary driver that is making these other diseases more likely. So if you solve aging, then you will also postpone or delay the onset of these other diseases. and maybe you'll hit your biological wall before that and die of sort of natural frailty. And so that's the rationale behind it. But I should point out that WHO, and with one notable exception, the FDA does not consider aging a disease. And the reason is you can get diabetes when you're very young. You can get cancer when you're young. You can even get early Alzheimer's, and heart disease. young people have heart attacks. And not every old person has any of these either. So it's not like aging, which happens to every single person. It's inevitable and it's

ubiquitous. And so something that is absolutely sort of normal, how would you consider that a disease? So I think that's the argument against considering it a disease. And the reason people want to consider a disease is if you want to test any compounds that are going to be anti-aging, then it's convenient to say, well, aging is a disease and that's the thing I'm tackling. But the way people are getting around it is they target diseases of aging. So for example, one anti-aging thing is actually on trials for things like osteoarthritis or fibrosis. Now another problem with anti-aging therapeutics is that there's a very high threshold for long-term safety and efficacy, and clinical trials are very difficult. The reason is that if you have serious cancer and you're going to die within a year, you'd be willing to take very highly toxic compounds that have terrible side effects or subject to radiation, all this stuff. Because the alternative is that you're going to die. But with aging, you have to persuade someone that, look, take this pill for the next 20 years and it'll give you an extra 10 years of healthy life at the end of it. And that's, so then you have to put up with all of those potential side effects over a very long term for some benefit later in life. So the bar is higher for anti-aging therapeutics. unless you're targeting particular diseases of aging, which as I mentioned. The other is that if you, in a trial, say of an antibiotic or even an anti-cancer agent, you divide up your groups and you'd give the cancer patients, half the cancer patients this drug and the other half not, and see if they improve and if they die. And a trial might take a few months or a year. With antibiotics, it could be even faster. But with aging, you have to wait until the person dies, typically, and that could take a long time. So who's going to be enrolled in a clinical trial for 20 years? it's just not realistic. So people have tried to segue into using markers of aging as proxies. So there are biological markers. I mentioned, for example, your DNA gets tagged. That tagging has a certain pattern that increases with age. And so from the distribution of those marks on your DNA, frequent can calculate what your biological age is. Why they call it the biological age is because That pattern is more correlated with your mortality than counting the days since your birthday, your date of birth. So it's better correlated than chronological age with your mortality. So they think it's a better indication of how old you really are. And there are other markers, for example, sugar groups that get added to your proteins as you age. In normal biology, these sugar groups get added in a very specific way, but they become added in aberrant ways as we get older. And then your distribution of enzymes in your blood changes and so on. And then there are also things called the frailty index, which measures all these external traits like grip strength and how fast you can walk 50 yards. things like that, cognitive ability and so on. So all of these are markers for age. And people sell you kits, they'll charge you a few 100 pounds to tell you your biological age. Now the problem is they're using one criteria and other criteria may not agree and each kit seller will tell you that their kit is the most reliable one. And the second problem is that different parts of our body age at different rates. So the same person may have a liver that's a different age from their lungs, which is a different age from their kidney or brain and so on. So the idea that you have a single biological age is not very useful. And the final thing is, even if

you knew your biological age, what are you going to do about it? There's nothing you would do that you shouldn't be doing anyway. We want to live healthily. You should live healthily without spending a few 100 pounds to get a number. So anyway, so that's another aspect. But aging, as I said, is a huge market and it has brought all sorts of players into it. Now, there are some promising approaches, and I may have mentioned that the cell senses nutrients and that sensing nutrients induces metabolic changes. And this is related to the fact that if you deprive many species from flies to worms to mice, even yeast, if you deprive them of calories, they live longer. And these old mice that are restricted of calories tend to have markers that resemble younger animals rather than other animals of their own age. And so this turns out to be something promising. But caloric restriction is extremely hard to practice in humans because Even these mice, the moment you take them off that diet, they start gorging on food because they're hungry all the time. You're hungry, you're cold, you're more prone to infections. If you get wounds, they're slower to heal. You have loss of libido, et cetera. All of which reminds me of the doctor who recommended caloric restriction to a patient. And the patient said, really, if I do all this stuff, I live an extra 10 years. And the doctor said, I'm not sure, but it'll feel like it. So anyway, but then, people are always looking for cheats. And so one of them is to look for compounds that inhibit the same pathways or affect the same pathways that are affected by caloric restriction. So if caloric restriction turns down a pathway, then you could have a drug that turns down that same pathway. And so some of these more touted ones are things like rapamycin, which was originally discovered as an antifungal agent, then it was thought to have anti-tumor properties. Eventually, it was approved as a drug for immunosuppression. So it was given to organ transplant recipients to prevent graft rejection. But of course, it's an immunosuppressive drug. So if you give it in the dose that it would give to an organ transplant patient, then you're more prone to infections and you're more prone to all these side effects that come about as a result of suppressing protein synthesis. But nevertheless, it's a kind of darling of some elements of the longevity community, I should say. And one of the things is that they say, well, maybe you can give rapamycin at lower doses and maintain the good effects without some of the bad effects. And there's some early indications, but really that sort of thing needs to be done on a large scale over a longer period with proper random trials. And anecdotally, two of the biggest public advocates of rapamycin both tried reducing their dose and they kept getting skin lesions and other infections and they eventually stopped. So that's, I think it's still very much up in the air. But another aspect is that people are trying to chemically modify rapamycin to ask, can the modified rapamycin have beneficial effects without some of these side effects? But the problem is the side effects may be really part of the exact way that it works. So it may not be possible to be so selective in that. Similarly, metformin was touted, there was a lot of excitement because people, there was an initial report saying that diabetics on metformin actually lived longer and healthier lives than even non-diabetics, which was very surprising because diabetes

itself is a high risk factor for aging and and for death. And so that led to a study. But then other studies found no relationship. And then people asked, a big advocate of metformin in New York who started funding a trial, started a trial called the TAME trial. This is to test metformin in healthy individuals. But that trial has not had any luck getting off the ground. you need funding and you need people enrolled in the trial and so on. And it's been years and the data has not really even begin to come out. And recently, there's been a lot of excitement about these GLP-1 agonists. Originally, these are appetite suppressants that were given to extremely overweight people and especially if they also had diabetes. So I think here you have to have a BMI over a certain amount and you preferably also should have diabetes before the NHS will prescribe it to you. But it turns out that these GLP-1s have some unexpected effects. For example, they seem to have beneficial effects on other organs, including, I believe, the heart, but also the central nervous system. And so there is this idea that maybe GLP-1 drugs really have a broad benefit and not just for people with diabetes who are overweight. And of course, they're finding out many different types of GLP-1 agonists and related agonists. And so this is a very active area. But as with all these other cases, GLP-1 drugs also have side effects. You have, many people have nausea. A typical symptom is muscle loss. And frailty is a problem with aging. The last thing you want is muscle loss. So I think the problem is that there's no such thing as a free lunch. And so it is going to be hard, I think, for something that is effective for the general population. Now, another quite promising area is targeting senescent cells. I pointed out that senescent cells can happen when cells are stressed out, when they're infected or suffer DNA damage or loss of chromosome length, which the cell interprets as DNA damage and triggers the same kind of response. And the cell goes into a weird state called senescence, where it stops dividing, it doesn't function normally, but importantly, it also sends signals inflammatory molecules, which are a signal to the immune system to come there and repair the damage, maybe the original cause of the damage, but also clear the senescent cell. And early, this is an example of that evolutionary trade-off that I was talking about. Early life, senescent cells play an extremely important role. They're even present in the fetus. So they're not just present in young individuals, they're present right from the beginning. And there's indications that they're important in development. But later in life, what happens is, because there's so much dysfunction and stress in our cells, that we have an increased amount of senescent cells. At the same time, our immune system is also not as functioning as well. So the clearance mechanism isn't as great. So you have an accumulation of senescent cells, and then you have more inflammation, systemic inflammation, which then causes more damage and creates more senescent cells. So this is a kind of vicious cycle. So people have asked, can you target senescent cells? Because senescent cells have certain pathways turned on and you could inhibit those pathways selectively and kill those cells off. And there's been success with that in mice. And so there are now several what are called senolytic drugs in clinical trials And you remember I said that you can't target aging as a disease, but

what they've done is said, we're going to use these senolytic drugs to target things like fibrosis or osteoarthritis, which are also caused by senescent cells and are inflammatory diseases. So that could be another promising area. here's a slightly bizarre experiment. This was done several decades ago where two mice, or rats in this case, were essentially stitched together and their circulatory systems were joined. So the idea is that these rats would sort of have to move around together and they'd be sharing their blood. And this part of it was to ask, could we do something in cases where blood vessels had been injured. And another aspect, a later aspect, was to ask whether factors in blood were different with age. And it was kind of gruesome in the early days because they didn't socialize the rats and the rats didn't like being attached to each other and would sort of attack each other while they were together. But now they sort of socialize the rats, but still not as a vegetarian, I'm not sure I would want to take part in an experiment like this. But anyway, what they did find was that the old rat benefited from the young blood and the young rat actually suffered from the old blood. And so this leads to the idea that there are factors in blood that change with age And so if you were to identify those factors, you could find out what they're doing, and then you could maybe develop a therapeutic that conferred the same benefits or prevented the same harm. Either way, you'd be better off. And that's a large and very legitimate area of research. There's some top scientists working on that. But this didn't stop companies right from, by the way, right from the time these guys in Stanford published this report, they got creepy phone calls from very rich people wondering where they could get young blood. And of course, this being California, there were companies that sprouted up overnight, taking blood from young donors and extracting the plasma and infusing it into rich people willing to pay for young blood. Now there's a guy, a tech billionaire named Brian Johnson, who is this guy in the middle there. And he made a lot of money and now his big sort of goal in life is not to age. He has a t-shirt which says, don't die. And he tweets every year. Last year, I only aged 0.6 years or something like that. So anyway, he spends $2 million a year on his own longevity. He does all kinds of testing because as a techie, he's very into data and tries almost everything. And he says, look, I'm doing this for science. I'm willing to use my own body to test out these things. And in the case of blood transfusion, though, he decided to keep it all in the family. So he took blood from his teenage son, who was about 17, I think, at the time. And then he donated blood to his dad, who's on the left. So it was like this three-generational blood transfusion experiment with an N of 1. And so he tried this for a while. And then, of course, he's also measuring these markers and seeing if these markers improve or not. And he abandoned it after a while. He said the principle is still sound, which probably he's right. But it's not a question of just taking transfusions from a young person and thinking, suddenly you're going to be invigorated, like in some vampire movie or something. So that's where it is. And by the way, this is also a guy who was very big on rapamycin and then tried it at different doses and eventually stopped because of these skin lesions. Now, another area that's also very popular, you could go to any number of

health food stores or even boots in Oxford, and you can find all kinds of supplements which are supposed to help you with aging. And there is a legitimate idea behind it, which is that as you get older, you stop being able to make certain metabolites, certain important biochemicals And maybe as the level goes down, the cells are not able to function, they can't do their metabolism. And so if you then supplement them, then you might increase that level and restore sort of normal health. And so one of the guys who sort of pioneered this was Bruce Ames. Bruce Ames is very famous in the cancer biology world because he developed something called the Ames test, which is a test to see if any new chemical has to go through the Ames test to see if it's a carcinogen or not, a potential carcinogen. But later in life, as we do, he became interested in aging. And remember I mentioned mitochondria, those organelles that are so important. And he found a couple of compounds that restored the health of mitochondria with age. And that was sort of the beginning. And then he went on to propose all kinds of supplements. And then recently, the big buzz has been in these things called NAD precursors. So NAD is a very important biochemical that's involved in all kinds of chemical reactions. including energy metabolism. And NAD levels decline by 30 to 40%. That's known. What's not clear is whether that declining, that decline is actually somehow causative of aging. Maybe it doesn't matter. The body can do fine with 60 or 70%. But nevertheless, it's resulted, there have been experiments done where they've supplemented NAD precursors. These are chemicals from which the body can easily make NAD. And they've shown that it slows down the loss of these stem cells, which are involved in regenerating tissues, but not in lifespan. There's been no evidence that it affects lifespan. But that's okay if it improves health. And as with many other things, the supplement market is not, they don't bother waiting for clinical trials. And in fact, the sales of NAD precursors are expected to be about a billion dollars quite soon. Now, the last and most exciting area of aging research is this idea of reprogramming cells. And let me tell you what I mean by that. So a cell has a genetic program that drives it forward in development. So you start with a fertilized egg, Then it keeps dividing and then forms a blastocyst and then eventually becomes a fetus, which keeps growing until it reaches a full-grown baby. What is happening here at the cellular level is that you start with the fertilized egg and then it reaches this blastocyst stage. Now at the blastocyst stage, each of those cells is capable of forming any of the tissues in that final body. So it has the information and the ability to make any of the tissues in the final body. But as it develops further, as you go further in development in the early fetal stages and so on, it starts specializing into what are called more specialized stem cells. So certain stem cells can only form cells of the blood system. That's still a large number of cells, all the white blood cells and your red blood cells and so on, which are all the cells of the immune system as well. Or skin and hair or others from bone and cartilage, others form the nervous system. But this thing never goes backwards. You only go, the direction is only normal, one directional. However, John Gurdon, while he was at Oxford, I should add, took a skin cell from a frog, implanted it into the egg of another frog, and grew a

whole new frog that was actually a clone of the original frog that had the skin cell. So that means even these final tissue cells have the capability, if tinkered with, to go back to this early stage and go all over again. Now, of course, we don't want to clone ourselves. We want to rejuvenate ourselves. And so the question is, can you do this inside the body? And a guy named Yamanaka, who was born the same year that Gurdon did his experiment, by the way, and although they shared the Nobel Prize together, so one was 50 years older than the other. So they, I mean, sorry, they were 50 years apart, their experiment. So Yamanaka showed that if you introduced 4 genes into a cell, you would somehow change its program so you would start making it go backwards and it could go all the way back to the so-called pluripotent state where it could then be driven forward and make any other kind of cell. Now if you do that in an organism, the system doesn't work completely in a controlled way. It often forms tumors called teratoma. It's a cancer risk because you're taking a cell and saying, you know, you can do, you know, divide as you like and you have to It's not quite the same as during embryonic development. But the idea that some people had, especially a guy named Belmonte at the Salk Institute, who now works for Aaltos Labs, by the way, was that what if you gave Yamanaka factors just briefly and you made these cells sort of go backwards just a little bit and then what would happen. And mice treated that way tended to appear rejuvenated. Now, they don't like the word rejuvenated, but I think that's a good common description. And anyway, they seem to have improved many of their markers of aging. But again, doing it like this in mice it was done in ways that you would never be able to do to a human. For example, some of the mice were transgenic and you could turn on those genes by giving it a chemical. You could create transgenic humans. And also when they looked at it, they found that in the tissues, only certain cells had reverted, other cells were the same. So it was highly heterogeneous and you couldn't target organs in a very controlled way. So I would say this is at the beginning of something, but I'm not convinced that this is going to lead to some miraculous anti-aging thing two years down the road or even five years down the road. But we'll see. People have been wrong before. I couldn't have predicted that AI would solve complicated mathematical theorems. So one never knows. So all of this anti-aging is predicated on an idea called compression of morbidity. The idea is you prevent aging so that people stay healthy all their lives and then suddenly hit that biological wall and then die. So now what happens is you're healthy, then you start acquiring various morbidities and you're feeling worse and worse and worse and you decline. And so you have this long period of morbidity. And the idea is you want to compress that period of morbidity. And that idea was formed by this guy, James Freeze, who's one of the founders of the healthy aging movement, which by the way, the entire longevity community, the premise is healthy aging. If you ask them, are you trying to extend lives? They'll say, no, we're trying to increase health span. And they will point out to evidence of life expectancy has increased, but our maximum, that wall has not increased. So they'll say, well, we have done that. However, it's not quite true. And I'll I'll point that out

in a second. So the goal is to die young after a long time. That's what this guy who was the head of Altos Labs said. Now, I had the question, I was at that launch of the Cambridge Lab. My question in my mind was, if you were young, why would you die? What would suddenly cause you to collapse? And James Fries himself realized the paradox in what he was trying to suggest. because he quoted a poem by Oliver Wendell Holmes, which is called The Wonderful One-Horse Shea. Now, shea is a term for a carriage for one or two people. And this particular shea was constructed in such a way that all its parts were designed to wear out at the same rate, so nothing would break down. And so the farmer was riding along in this 100-year-old shade and then suddenly found himself on the ground surrounded by a heap of debris because the entire shade suddenly collapsed under him, disintegrated under him. So that's what we're asking. We're asking to remain healthy and then suddenly decline. And the question is, it possible It is true that we're living longer, but that doesn't mean that our period of morbidity is shorter. Yes, we're approaching the wall, but each individual may be going through a long morbid period. And if you look at the UK, the number of years spent with four or more morbidities has actually increased as a fraction of our lives, which means we're actually spending more years unhealthy. And of course, some of it is not bad. Medicine is keeping us alive even though we're not 100%. Whereas in the old days, if you were Beethoven and you got pneumonia, you would just die very quickly. You had very high compression or morbidity in the old days. And if you read Brave New World, you had perfect compression or morbidity. You lived up to a certain time and then you went to these euthanasia chambers. That's 100% compression. But that's not what we want, right? And so, and by the way, the British statistics are borne out worldwide. And so we're spending more years and possibly a greater fraction of our lives in poor health, except there's one odd statistic, and that is, remember those 110-year-olds? Those people have had extremely healthy lives all their lives. Some of them have never visited a doctor until they were well over 100. And then they suddenly decline and die somewhere between 110 and 120. So maybe it's theoretically possible, but we don't know if these supercentenarians are simply a matter of selection bias. That is to say, we're simply statistically selecting the survivors. And it's not, there's nothing, they were just lucky. They had lucky genes, lucky life history. They dodged all the things that could bring about various things. And then eventually the frailty caught up with them. So I think we just need more data. Now, the question is whether health span can be improved. And there is some evidence that things can improve. For example, by the way, 0 is 60. So this is, oh, sorry, 65. So this is years post 65. And dark means you're not doing so well. You have poor health or morbidities. Now if you look at Britain, if you look at Britain and Sweden, the overall life expectancy is not that different. So this is women and this is men. And women live longer, but you can see in Britain, women spend more of their lives in poor health, even though they live longer. What you see in Sweden is that the fraction of lives that they live in poor health has been shortened. It doesn't mean that compression morbidity is indefinitely possible. It just means there are things that

public health can do, governments can do. For example, Sweden has less socioeconomic inequalities. It might have better population health measures. It might have just generally other health factors that make Sweden show better statistics. But it also shows that it's not universally true, it doesn't have to be true, that women have to spend more of their lives poor health. But it's not clear that when you improve aging, that you're not just going to extend the morbidity period, because you may simply be postponing the onset of morbidities and then you still have a long, prolonged period of morbidity. The other thing is that mortality is easy to define because it's when you die. But morbidity is not easy to define. And it's not, I don't know how the Swedes defined it and how the UK defined it for this sort of complex. I didn't look into that. And I have high cholesterol and high blood pressure, and I'm A pre-diabetic. And yet, I was able to cycle to the railway station and take the train and walk here from the Oxford station. And I'm doing, generally leading a reasonable life. So measuring healthy life is not very straightforward. And that's a problem. Another final thing is that, the difference in longevity is very pronounced between the rich and the poor. The richest 10% live 10 years longer in the UK compared to the poorest 10 years. And that's despite having a national health service. In the US, which doesn't have it, it's 15 years. But the difference in health years is almost twice as long as the difference in overall life, which means that the poor not only live shorter lives, but they spend more of it in poor health. And that has to do with a lot of socioeconomic factors. For example, poor people will smoke more. Many of them will also drink more. These are things that are socioeconomic factors. And also poor nutrition. If you're poor, you often don't have the resources or the time to eat healthily. And there's the joke that the best way to live long is to be rich. There's a question of whether we should actually try to live longer lives. And people are trying to do all these things about aging and it's going to increase life expectancy, as previous efforts have done. And there's a lot of question about intergenerational fairness. So the old, as you get older, you accumulate wealth you accumulate power and influence. The 3 are very highly correlated. And you can see how politics is influenced a lot by the older segment of the population. You can see in many countries led by relatively old people, news media led by, controlled by someone who's over 90. So, and this leads to increased disparity because the older people, richer people are going to live longer. They're going to live, possibly reproduce more, who knows. But whatever it is, you're going to increase disparity as this goes on. There's also a general problem, which is that people are most creative when they're young. And I know those people in my generation will call that ageist, but I'm old, so I can say that. And I mean, I'm nowhere near as sharp as I was when I was in my 20s. And I used to think this was just a thing in science and mathematics, especially physics and mathematics, but it's actually true across the sciences. If you look at big discoveries that were made by people in their 20s, 30s, and 40s, very rarely did somebody over 60 make a big groundbreaking discovery. And Kazuo Shiguro mentioned that it's also true in literature. If you look at great works of literature, yes, people can continue to write and be read

and be well thought of, well into old age. But when they die, the thing that they're remembered for is some book that they wrote when they were quite young, War and Peace. late 30s for Tolstoy. You wouldn't think that a work of that breadth and maturity would be written by a young person. And even Kazuo Ishiguro, he's written very good novels, but I suspect he's going to be remembered for Remains of the Day again when he was in his 30s. And so there is that issue. And then There's a question of general renewal. If you look at, if you think of an aging society where birth rates are low, the same people are just hanging on forever, clinging on to power. Imagine 100 years from now and we still have Trump and Putin and Xi Jinping controlling much of the world. So whereas if you have turnover and new ideas and new ways of thinking. And this creativity is not about biological age. Partly it has to do with the fact that when you're young, you're seeing things for the first time. You're fresh and less opinionated and more open to new ideas and less sort of dogmatic about things. So I want to leave by saying that we've understood a lot about aging. And as I said, there are a lot of things in the offing that maybe in 10, 20 years, probably too late for me, but certainly if you're young today, you can expect amazing things to happen as a result of this research. But today we can take matters into our own hands in a way that makes sense in terms of all of the biology we know. And this trio of diet, exercise, and sleep affects all of those biological pathways we're talking about. So diet is related to those caloric restriction pathways. Exercise is involved in regeneration of many things, including mitochondria and muscle. And sleep is when a lot of repair is done, both molecular and cellular repair is done. And they're synergistic. If you exercise, you'll also sleep well. And by the way, you'll also reduce stress, which is another driver of aging. And then apart from these three things, which I think are synergistic and so act well in concert, There are things that every person should do as they approach middle age. Luckily, I think the NHS will essentially do this for you in Britain, which is to make sure your blood pressure, your cholesterol, and your sort of diabetes markers are normal because these are things that are eminently treatable if they're detected early. And there are also certain kinds of cancer that are well worth screening for. And 2 curious things are that social isolation has been known to be bad for you. It accelerates your decline. And so it's important to have a network of friends and family and so on. And perhaps related to that, but not quite the same as having a sense of purpose in life. is important. And I retired a year ago and that is something that is very important and somewhat hard to do because when you have a job, you have a purpose. It's sort of defined for you. But then suddenly when you're retired, you have to find your own sense of purpose and that's quite important. Thank you very much.