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"Welcome to 'IFL Science, The Big Questions.' The podcast where we invite the experts to explore the biggest mysteries of Science, with your host, Dr. Alfredo Carpineti."

I: **The dream of immortality is probably as old as humanity itself, and science has helped expand our lifespan. It has many wondering if there is a limit. However, it is not just with death, but also with ageing. There is a cautionary tale in Mythology. The Trojan Prince, Tithonus was granted immortality by his lover, Eus, the Goddess of the Dawn. But not eternal youth. So living longer can not be a goal in itself, if the ravages of age keep up with us.**

Hello and welcome to another episode of 'IFL Science, The Big Questions.' Our query for today is one that many have probably wondered; can humans live forever? And to help us answer this and related questions, we have Dr. Andrew Steele. So Andrew…

R: Hello how are you doing?

I: **Very good, how are you?**

R: I'm very well, thanks.

I: **So, can you tell us a little bit about yourself?**

R: So yeah, as you just said, my name is Andrew Steele, I am a Physicist turned Biologist. So I actually started out by doing a PhD. in Physics, before deciding that ageing was the single most important scientific challenge of our time. So I ended up working as a Biologist for a few years and then during that time, I realised that nobody knows that much about ageing biology, including Biologists, including Doctors. So that's one of the things that really inspired me to write a book about this. So I'm also an Author of a book called, 'Ageless: The New Science of Getting Older Without Getting Old,' which is all about the latest developments in aging Biology, which will hopefully allow us to do just that.

I: **Wonderful! So you are the right person to ask all these questions. Let's start with the big one from the get-go, can humans live for ever?**

R: Well, I think this is one of the biggest misconceptions around aging research, is that as soon as you talk about doing something about aging, people suddenly ask you know, 'Is this about immortality?' Or another popular thing at the moment is, 'Are the Billionaires trying to live forever?' So you've got these investments by people like Jeff Bezos, the founder of Amazon, who's put literally billions of dollars of his own money into this start-up that's trying to develop anti-aging treatments.

But actually, this isn't about living forever and you know, first of all, let's just have a think about what it would mean for humans to live forever. Even young people still occasionally die of infectious disease, which obviously we've all heard far too much about COVID in the last few years and there's other infectious diseases out there too. You can always get hit by a bus. So there are a variety of different things that can kill you, no matter what your age is. And what aging research really wants to do is to change how our risk of death with time changes.

So have a think about what that means. I'm 36, and what that means is, my odds of death this year are somewhere around one in 1,000. I quite like those odds, because if you think about that, you know, if that was to extend for the rest of my life, I'd live another 1,000 years on average, I'd make it into my 1030's. But obviously that isn't what happens. Our risk of death as humans doubles about every eight years. And what that means is, that if you keep on doubling it and doubling it and doubling it, eventually it starts getting very big, very quickly. So if I'm lucky enough to make it to 80 and medical technology hasn't changed in the intervening time, I'll have about a one in 20, so a five percent chance, of not making my eighty-first birthday. And if you're a 90-year-old today, you have about a one in six chance of dying, before you make your next Birthday. That's life and death at the roll of a dice.

And you know, that just staggered me. This is actually the reason that I moved from Physics to Biology, was just you know, understanding the sheer scale of the rise in the risk of death. So that's the case for humans, but the one time I will allow you to use the word 'immortality' is if we're talking about something called 'biological immortality.' And this isn't sort of, true immortality, it's not about living for ever. But if you look at a lot of animals in the animal kingdom – and a really good example of this is the Galapagos Tortoise, the reason there's a Galapagos Tortoise on the front cover of my hardback is because this is one of these animals that is biologically immortal. And what that means, as I say, isn't that it lives for ever, but it just has a risk of death that doesn't change depending on how long ago it was born. So, a Galapagos Tortoise as an adult has about a one or two percent chance of dying every year. And that chance of dying just stays completely flat throughout its adult life. And one consequence of this is they live an incredibly long time. So the longest lived Galapagos Tortoise on record, made it to about 175 years old, we think. And she died of a heart attack, but at 175, rather than 75, like a human might.

But actually, what's more interesting from the point of view of aging biology, isn't that they live an incredibly long time, it's that their risk of death is flat. This biological immortality, this fact that they're, it's actually called 'negligible senescence,' is the more technical term. It's negligible, just mean not much, senescence – meaning the biological word for getting old. And what we can see is, they're not just not dying, they're not getting frail, they're not at increased risk of diseases, because of course it's the things like cancer, the heart disease, all these diseases we know are associated with aging, they're what kills you. So these tortoises literally get older without getting old. And so, you know, it's not against the laws of Physics, it's not against the laws of Biology, because we can see animals out there in the animal kingdom, actually doing it.

The question is, can we squash that change in risk of death with time for humans at least a little bit and try and live a little bit longer in good health, as a result? So that's what really excites me about this aging Biology research, is the idea of trying to live longer and most importantly, do it in good health, without those diseases, without the cancer, without the heart disease, without the Alzheimer's.

I: That is fascinating. Although I keep thinking there is one in 1,000 that I am a similar age of you, so quite high, I prefer one in a million [laughs].

R: [Laughs] Well as long as you're care… so the thing is, a lot of the stuff that kills us at our age; it's accidental causes of death, it is things like road accidents. So if you can dodge some of those accidental causes of death – you know, if you can be careful on the road, if you drive a bit less, that sort of stuff – you can really start to reduce that number down quite a lot. You know, in the next sort of 10 or 20 years, we're going to start getting to the kind of risks that you can't do so much about, which is, you know, the risk of cancer, the risk of heart disease. Obviously you can exercise, you can eat well and try and reduce that risk as well, but inevitably at some point, age does catch up with all of us, no matter how well you live, so yeah, for now, stay safe and stay exercising. But unfortunately aging catches up with all of us, which is another reason I am so excited by these therapies, because they could do something about that seemingly inevitability of life.

I: So, the general idea is to extend the portion of our lives that would be healthy?

R: Aging research has often called this 'The Health Span.'

I: If you want to tell us a little bit more, but do you think there is a limit to how long we can expand this, or are there any indications? Clearly as time has progressed over the last several decades, because of improvement in health and society, our life span has increased and my understanding is also this 'health span' has increased. Do we think there is a limit? Do we think that there is a point after which we can no longer fight Biology or Physics?

R: I think that's a very interesting question and I think the answer looking at the animal kingdom is basically 'no.' You know, these animals they have risks of death that stay completely flat for as long as we watch them. And unfortunately of course, these experiments if you're going to do them thoroughly, take a really, really long time. So let's take an example of another negligible senescence, so a biologically immortal creature, something called a 'Hydra.' And it's a tiny, little centimetre-long pond creature, so it's quite a long way from us, evolutionarily speaking. We perhaps can't go all the way to the achievement the hydra has. But its risk of death, per year, is about 0.2%. Now you'll note that's actually higher than that one in 1,000 that you and me are facing down every year, so it's already a little bit higher than that. But nonetheless, we think that about 10% of hydra, based on that, would still be living after 1,000 years, which is obviously an incredible life span. But the problem being, as I said, you know we haven't yet had time, having made that observation, to do that experiment and watch them for the decades and decades and centuries it would take to finally get to that answer.

I think what's really interesting about human lifespan is that, exactly as you say, the length of time that we live for and the length of time we're healthy for, has been increasing for hundreds of years. Throughout the last 200 years, life expectancy in the top performing country in the world – and that's obviously shifted around, depending on who's winning in any particular year – but that's gone up by about three months per year, every single year. The line is just like, astonishingly straight. As a Physicist, you know, you don't expect to see a straight line in data like that and yet, tick tock, every year we get an additional three months of life expectancy. And this has been caused by this sort of constellation of factors. So back in the 1800's, when this first started out, it was mainly due to the reduction in things like infectious diseases. And that meant that, particularly because they affected young people, they had a really big effect on the life expectancy. And when I say young people, I mean infants and kids.

So if you die – let's go back all the way to the beginning of the Eighteenth Century – you probably only had a bit more than a 50/50 chance of making it out of your teenage years. And actually, if you did make it to 20 or so, then you had a decent chance of making it to 50, or even 60 years old. You know, sort of beginning to be old by modern standards. But their overall life expectancy was really, really dragged down by the massive, massive toll of infant mortality. So at first we started curing a lot of these diseases. We had, first of all it was hygiene and improving sewage and all might sound like quite boring public health stuff, but it had a huge, huge impact on life expectancy.

And then of course, we had vaccines, we had antibiotics, we had the sort of medicine that could deal with infectious disease, at the beginning of the twentieth century. And then, as people's lives started to extend, that's when we really started to move the needle on older life expectancy. So, from the 1950's onwards, most of the advance in life expectancy, at least in the rich countries, has been driven by improvements in cancer care, improvements in heart disease care and that sort of stuff. Also the lifestyle factors, you know, we eat better and we exercise more – although people are getting fatter in general around the world, the general tendency has been for lifestyles to improve.

So it's been this sort of constellation of different things. And I think actually, it is worth stepping back and just looking at the huge achievement this is. It is, I think, arguably humanity's greatest achievement. We've literally doubled what it means to be human, over the course of a couple of centuries, which is incredible. Life expectancy has gone from about 40 to about 80, in the best performing countries in the rich world now. I think it's even 85 in the world leader, Japan. So that's actually a really incredible achievement.

But what's most incredible about this to me, is that we've achieved this entire feat, without a single medicine that targets the aging process. So we've got our medicine for heart disease, we can lower your blood pressure, we can do all kind of things to prevent or, you know, help people who have had heart attacks and that kind of thing. We've got chemotherapy, we've got radiotherapy to treat people who have got cancer. We've got a whole range of different medical interventions. But all of these target not the aging process that causes these diseases, but they target the sort of end point of that process. They target the cancerous cells, they target the build up of plaque in your arteries. And nothing yet has gone after that whole global aging process, which is by far the biggest sort of risk for all of these diseases.

And so, I'm just really excited by the idea; if we can treat aging, what that means is we can reduce the risk, not just of cancer, not just of heart disease, not just of dementia, not just of frailty, not just of wrinkles and grey hair you know, even the cosmetic stuff is caused by the same fundamental, underlying molecular biology, basically. And so given that we've achieved all of that without even trying on the aging process, I'm just really excited about what we will be able to achieve once we actually do target it in earnest.

I: **Wow! So I think my next question is, how are we trying to target the ageing process as a whole? What has been attempted so far? What has been discovered? How far away are to develop an understanding, or the drugs, to actually treat aging?**

R: That's a great question, and actually in the last sort of 10, 20 years, things have really, really come on, in leaps and bounds. And I think one of the things that's most exciting about it is that we've finally got almost a consensus – I'm not going to say a consensus because that's very hard to get amongst Scientists – but there's almost a consensus about what the cause is, the underlying things that change during the aging process, that do increase our risk of disease.

And in the book, I break it down into 10, what I call 'Hallmarks of the Aging Process,' which is named after a 2013 Scientific Paper, with the same name, that actually had nine. A couple of things have happened in the intervening years. I moved some stuff around, but basically that's sort of a relatively comprehensive list of what we think are the kinds of things like damage that happens as you get older; changes in your biology, changes in the signals that your cells send to each other, and all these different kinds of factors that can happen on the very smallest level. It can be damage to your DNA, so the tiny little molecules inside the nucleus of every cell that carry your genetic code, all the way up to the damage of whole systems in the body, so things like the immune system getting weaker as you get older. And the combined effect of all of these things, is the increase in the risk of the diseases that we see.

And so I think actually, the clearest example of what an anti-aging treatment would look like, is targeting a specific hallmark. And the idea is, that by slowing down, or even reversing, that hallmark, you can slow down, or even reverse the aging process and thereby, reduce the risk of all these different things happening. And the clearest example I can think of at the moment and actually, one of the most exciting in terms of near-term drug development as well, is something called 'senescent cells'. This is one of the hallmarks of aging and senescent, we've already come across that word, it's the biological term for getting older. These are cells that are basically, you know, getting old, getting clapped out. They've been around in your body for a long time. They've often divided too many times, maybe they've got a lot of damage to their DNA, a lot of mutations that means your body thinks they might be turning into a sort of cancer.

And so, therefore, what your body does, is it slams on the brakes. It says to this cell, 'You're going to stop dividing, you can't divide any more.' And that's great, because when we're young, those cells reduce our risk of cancer, because maybe that's what they're at risk of becoming. And they send out this cocktail of molecules. And the molecules are basically signals to the immune system that say, 'Hey, over here, I'm this senescent cell, I shouldn't be here, come and clear me up.' And when you're young, you have a really sort of, vibrant, active immune system, it runs over a macrophage gobbles up one of these senescent cells and that sort of keeps the process in this stable equilibrium. But unfortunately, as we get older, a variety of things mean that these cells become more and more common. So for a start, our cells are divided more, just because we've been around for longer, we're getting more and more damage to our DNA and that kind of thing, just because we've had, you know, time for that damage to accumulate and also, our immune systems are getting weaker, so they're getting less good at clearing up these cells.

And it turns out, this cocktail of molecules that the senescent cells omit, it doesn't just attract over the immune system, it also seems to accelerate the whole aging process. So when these chemicals get too high in their concentration, they can increase the risk of a whole range of different age-related diseases. You know, things like heart disease, things like dementia. And ironically, these senescent cells, even though we think evolutionarily, they're an anti-cancer mechanism; when there are too many of them, it can actually increase your risk of cancer as well.

So, that all sounds like a very depressing thing, you know, we're accumulating these cells, there's not much we can do about it you know, they increase our risk of disease and frailty as we get older. The good news is, we have drugs and they're called senolytic drugs, that can kill the senescent cells and leave the rest of the cells of the body in tact. And there was an experiment done in mice, in 2018, where scientists gave mice some of these senolytic drugs and they waited until the mice were quite old, they were about two years old, which is about 60 in human years, because obviously mice have much, much shorter life spans that we do. And they found that by giving the mice this senolytic drug, they removed the senescent cells and they effectively made the mice biologically younger. So what they found was, they lived a little bit longer, which I guess is good, but they weren't dragging out that period of frailty at the end of life. They were increasing their health span, as well as their life span. So, they got less cancer, they got less heart disease. They had better cognitive performance.

So if you put a mouse in a maze, then a young mouse is often very exploratory, it's very excited in its new environment, can it find the food, etc., etc. But an older mouse might be a bit more anxious, maybe it's just a bit more frail and so they don't do so much exploration. But giving the mice these senolytic drugs seemed to increase their, sort of rejuvenate, their youthful curiosity. The mice were also able to run further and faster, on tiny little mouse-sized treadmills they use in these experiments. So they got this little mouse gym they can test out their various muscles in. And they find that mice just do better in all of those, when you remove their senescent cells. And finally, these mice, they just look fantastic. So, when I was a Biologist, I was a Computational Biologist, I barely set foot in the lab, I just sat with a computer all day. And even to my, like wildly untrained eye, it's really worth looking for some pictures of these on the internet, the mice that have had the senolitic drugs, they look great. They've got thicker, plumper skin, they've got less grey fur, they've got thicker fur. You know, all of the cosmetic stuff that a lot of people worry about you know, anti-aging skin creams and that sort of stuff, that also seems to be caused by these same underlying hallmarks of aging.

And so the idea is that we might be able to give these drugs preventatively. So rather than waiting until someone gets cancer and giving them chemotherapy, hopefully at some point, we're going to get to the stage where, as we understand more about these drugs, as they get more effective and most importantly, as they get safer, we're really starting to understand if there are any side effects. We'll hopefully be able to hand them out preventatively, you know, say you're 50, say you're 60 years old, you've accumulated enough of these senescent cells that they're starting to become a problem, then your doctor can give you one of these senolytic drugs, clear out those cells and hopefully, you know, reverse the aging process in your body. And that's going to be a few years away, but actually excitingly, they're already in human trials, these drugs. This isn't just some, you know, wacky experiment in mice; they're currently trialling them for conditions where we know that senescent cells are a problem.

So there's one called Lung Fibrosis, for example, which is an age-related disease, where you basically get scarring in your lung tissue. And we think that senescent cells are implicated. And this is a disease that's got quite a poor prognosis; there aren't really any particularly promising treatments at the moment. So these patients, they've got a bad disease basically, they're willing to take a bit of a punt, on this slightly untested new treatment. But if that drug works, and most importantly if it's safe, we'll start giving it to people with less and less serious conditions and eventually, hopefully, we will be giving it to people who at the moment, the medical system would classify as healthy. And I think that's the real dream of anti-aging medicine, it's to give people drugs that will slow down or reverse these hallmarks, before they get unwell in the first place. And hopefully, sort of push down that risk of death increasing with time.

I: Wow! That is fantastic, yeah and maybe the immediate future is not so great, but the far future looks like very promising!

R: I don't even think it's that far in the future, and I think that's something that's really worth emphasising. So these senolytic drugs that are in trials, they've been in trials for a few years already, we're going to start getting the first results, you know, pretty, pretty soon. And this is the sort of thing where, if it works, there's not really any reason why, in the next 10 years, we could see something that starts to roll these things out preventatively. And there are a load of other drugs in the pipeline as well. So there are things like repurposed existing drugs, there's a drug called Metformin that actually you know, a lot of your listeners might even be taking. It's one of the most commonly prescribed medicines in the world, it's a diabetes drug. And there are some hints that it slows down the aging process. And once a trial is down to that, if that works, it costs literally pence per pill. It's incredibly cheap. It's got very, very low side effect profile, because we've been prescribing it in the UK since the 1950's, so we really, really know about this drug. If it works we could, you know, start handing it out very, very rapidly.

And there are loads of other things in the pipeline, things like gene therapy and stem cell therapy. And these do sound a bit more sci-fi and further into the future, but these are sort of decades into the future, they're not centuries into the future. And so, if you're 36, I don't want to make this all about me, but if you are 36 and you're expecting to live, you know, at least another four or five decades, even with current life expectancy as it stands, then hopefully you can benefit from that first generation of senolytics. Hopefully you can exercise and eat well and you know, not get hit by a bus obviously, there's not much you can do about that, but if you can manage all those things, a lot of these treatments are going to arrive in time for most people alive today. So I'm genuinely, you know, really excited about this in the short term.

I: **Fantastic! I think my final question is, what do you think are going to be the societal impacts of having an older population that might live a bit, or a lot, longer, but with a much healthier lifespan?**

R: That's a great question, I'm really glad you added that last bit on the end, because I think that's the bit a lot of people forget. The fact they're healthier really, really changes the calculation here. So if you were giving people drugs that would like, drag out your period spent in the care home, basically nobody wants to live to 120 and spend their last 40 years in a home. What we want to do is, you know, we want to be vibrant and from a societal point of view, we want to be contributing to the economy, we don't just want to be a burden. And actually, that's the most important thing. And I think the most… the real key takeaway for me from this, and it's something that's sort of almost forgotten sometimes by people who ask about the social consequences, is just how massive the positive consequences would be.

So every single day on planet Earth, 150,000 people die of various things. And this is in all the countries of the world, not just the rich ones. But of those 150,000, over 100,000 are killed by aging. They're killed by the cancer, the heart disease, the dementia. And these aren't diseases that just, you know, you go to bed one night and you don't wake up the next morning, sort of painless disappearance off the face of the earth. They often involve suffering over years, or even decades, there can be very gruelling treatments for things like cancer.

I think aging is arguably the world's largest cause of human suffering. So, on the sort of pros side of the social change, we're going to have, yes we're going to have extended life spans, but most importantly, we're going to have massively reduced suffering from all of these horrible diseases. And so I just think that's by far the biggest societal consequence. And sometimes people forget about it, because they ask, 'Oh you know, aren't Billionaires going to live forever?' Or, 'What are we going to do about global population?' Forgetting that there's this, you know, enormous benefit, that you somehow have to find a disbenefit that counteracts, in order to argue against this kind of research.

Just to give a little example I think, because this is, you know, these are important questions, there are going to be sort of seismic changes to our society in some ways, I think the question I get asked most often is, 'What about the population? What are we going to do if…?' You know, lets imagine people start living to 100, or 120. If they're not dying, they're obviously going to be sticking around for longer, babies are still being born, what are we going to do with all the extra people? Where are they going to live? What food are they going to eat? Isn't that going to be a terrible problem for the climate? And for the rest of the environment?

And I'm really sympathetic to this, I almost became a Climate Physicist at the end of my Physics PhD. and you know, eventually decided an Aging Biology, as we just talked about. And actually, I think the consequences of this for the climate are far smaller than most people really appreciate. So, I try to do, I'm by no means a demographic modeller, but I tried to do a really simple exercise, where I said, 'Let's imagine the most ridiculous 'out there' assumption we can come up with. Let's imagine we cure aging in 2025.' And that means that suddenly, that of those 100,000 people that die every day of aging, they're just not going to die any more, they're going to carry on trucking. And you know, they'll still die of other stuff, but it will just be at a much, much older age and they'll be healthier for much, much longer. What would that do to global population? Now that's obviously ridiculously extreme, not only do we have to complete all the science in the next three years, we also have to roll out these drugs to everyone in the entire world. So this is an absurd sort of, I guess, worst case scenario if you're a population pessimist, but obviously best case scenario if you care about aging.

But even in this crazy, crazy scenario, what you find is that the global population in 2050 is currently projected to be 9.8 billion people. If we literally cancel aging in a couple of years' time, then that goes up 11.6 billion. Now that is more, and it's not nothing, its about 16% more people, but 16% isn't that huge an amount of extra mouths to feed. Isn't that huge extra impact on our carbon emissions and that kind of stuff. I'd happily work 16% harder to reduce my carbon footprint, if it suddenly meant we didn't have any of that suffering, we didn't have the Alzheimer's, we didn't have the cancer, we didn't have the heart disease, we didn't have the frailty, we didn't have… you know, Grandparents unable to play with their grandkids, because they're too unwell. I just think that the benefits massively weigh out the disbenefits and specifically in the case of population. I think it's a smaller increase than most people think.

But what I should say, just as a final comment, is I really think that the societal change, so the thing that I get asked most about when I give talks on this and in a way, it sort of surprises me, because you know, you might think people would be like, 'Oh what can I do to extend my own life span?' or, 'What are the most promising drugs that are coming, are they going to be in time for me?' People are really worried about these ethical issues. And so in order to address that, there's actually a free chapter of my book that you can check out on all the different ethical ramifications, which you can find at ageless.link/ethics. Now that's available in all kinds of different formats to download, so do check that out if you've got any ethical quandaries that I obviously haven't managed to answer in that very, very short answer to the question.

I: No, that was a great answer. And I would like to add that, probably if we all knew that we were going to be around this planet for much longer, a lot of people would take climate change and make this planet liveable for longer, a lot more seriously.

R: Definitely. Because I mean, if you're going to be around in time for that to happen, suddenly it's not just your children or your grandchildren, it's a rather direct concern of yours. [Laughs]

I: Indeed. Well, thank you very much for taking the time and talking to us about all things aging.

R: Thank you very much, that's brilliant, it's been a pleasure.

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