



Science and Technology Select Committee

Corrected oral evidence: Ageing: Science, Technology and Healthy Living

Tuesday 22 October 2019

10.25 am

[Watch the meeting](#)

Members present: Lord Patel (The Chair); Lord Borwick; Lord Browne of Ladyton; Lord Hollick; Lord Kakkar; Lord Mair; Baroness Rock; Viscount Ridley; Baroness Sheehan; Baroness Walmsley.

Evidence Session No. 3

Heard in Public

Questions 22 - 27

Witnesses

Dr Jordana Bell, Head of Epigenomics Research Group, King's College London; Professor Avan Aihie Sayer, Professor of Geriatric Medicine, Newcastle University; Professor Richard Faragher, Professor of Biogerontology, Brighton University; Professor David Melzer, Professor of Epidemiology and Public Health, Exeter University.

USE OF THE TRANSCRIPT

1. This is a corrected transcript of evidence taken in public and webcast on www.parliamentlive.tv.

Examination of witnesses

Dr Jordana Bell, Professor Avan Aihie Sayer, Professor Richard Faragher and Professor David Melzer

Q22 The Chair: Good morning, ladies and gentlemen, if I am allowed to use that phrase. We are on live broadcast streaming. This applies to Committee members as much as to our witnesses: if you have a conversation, it might well get picked up and streamed, so try to avoid conversations. Thank you very much for coming today to help us with our inquiry into the signs of ageing and any associated factors.

Before we start, if you do not mind, please introduce yourselves so that we get you on the record. If you want to make any opening comment or statements, please feel free to do so. Once you have done that, we will carry on with the questions.

Professor Avan Aihie Sayer: Good morning. I am a geriatrician—that is, a doctor who specialises in the care of older people—at Newcastle Hospitals. I am a professor of geriatric medicine at Newcastle University. I also direct the National Institute for Health Research Newcastle Biomedical Research Centre, which has a particular focus on ageing and long-term conditions. My area is ageing syndromes such as sarcopenia; the loss of skeletal muscle mass and strength; frailty, particularly physical frailty; and multimorbidity.

In Newcastle we have a particular remit in trying to build translational ageing research capacity—that is, taking findings from ageing science discoveries through into improved diagnosis, treatment and prevention of these ageing conditions in older people.

Dr Jordana Bell: Thank you for inviting me. I am reader in epigenomics at King's College London. In the context of ageing, my research focuses on epigenetic changes with increasing age across human cohorts.

Professor Richard Faragher: I am professor of biological gerontology at the University of Brighton and a past chair of the British Society for Research on Ageing. My research interests are in the fundamental cellular mechanisms that cause ageing in humans and other species, with a particular interest in cellular senescence.

Professor David Melzer: I am a professor of epidemiology at the University of Exeter. I also have an appointment at the University of Connecticut. My group has been involved in genetic studies of longevity and lifespan, and my main focus today is on human genetics.

Q23 The Chair: Thank you. Are you happy if we get on with the questions? You will find that one of us will have a main question on different aspects of the inquiry and then others may well chip in with a supplementary. Feel free to talk about any issues that you think might be appropriate. I always get a silly question to ask, but please do not feel that this is silly, because we need someone to define the issues for us.

My question is: what definition would you use of ageing, particularly about healthy ageing? Geriatric medicine is a good place to start.

Professor Avan Aihie Sayer: It is a difficult thing to define, partly because ageing is such a broad concept. That is something that I have gradually understood over the many years that I have studied it. It extends to everything from changes in molecules and cells to changes in individual body systems, such as the cardiovascular system or the musculoskeletal system, through to whole-person changes such as cognitive and physical function and age-related disease, and then all the way to population structure and ageing populations.

Because it is such a broad field, with many disciplines studying it, it can be difficult to navigate and confusing. As an academic geriatrician I have started with the person and look at how ageing is affecting the whole person, and then work backwards to try to understand the systems that are involved underneath that—for example, skeletal muscles—and link to basic science to understand the cells and molecules that are changing, while looking upstream to how that person functions within an ageing population.

I have a couple of other observations. Ageing is not a disease—it is universal and therefore cannot be—but we know that ageing happens at different rates, and it appears that the rate of ageing is modifiable, so that is a target for change.

The other area that I have thought about a lot over the years is the fact that ageing is a life-course process. It is not just about something that happens, and influences that operate, later in life. To understand where you are in later life, you need to take into account what has happened from gestation through early life, early adulthood and maturity through into later life.

If you had to pin me down for a definition, I think the simple descriptive definition of ageing, such as deteriorative changes occurring with the passage of time that impair the ability of an organism or a person to survive, is a good overarching one. Within that, there are many different aspects.

Professor Richard Faragher: Perhaps in contrast to Professor Sayer, if you are a biologist interested in ageing, ageing is really rather easy to define. It is simply an exponential increase in the chances of dying or getting sick with the passage of time, even in a protected environment, for a population of whatever creature you are studying.

I happen to like humans, so if you take, for example, a 10 year-old boy, that child has about a 0.1% chance of death in the next decade, but his 75 year-old grandfather would have about a 40% chance of dying in the next decade. That is what it is to be a member of a species that experiences ageing.

We call this the Gompertz-Makeham relationship, or the Gompertz curve for short, and really everything that we do in biology is an attempt to understand why and how that happens. We use alterations in the Gompertz curve with laboratory animal populations to determine if we

have slowed the ageing process down. With a certain mathematical inevitability, if we have slowed the ageing process down we have almost invariably done so as a result of improving the organism's health.

You may be interested to know, for completeness, that while most species show a Gompertz relationship, a very few do not; they show what we could perhaps call a Gompertz flatline and have a fixed chance of death each year, and this includes some of the longest-lived animals on earth. There is also some evidence that in species that show ageing the Gompertz curve eventually flattens out, meaning that ageing ceases at extreme ages. There is a light piece of evidence that suggests that this might happen in humans, so if anyone on the Committee is fortunate enough to reach the age of 105 you can tell everyone that you have now officially stopped ageing, although I am afraid that your chance of death at that point will be so high that it may be cold comfort.

The Chair: So what is healthy ageing?

Professor Richard Faragher: I would define healthy ageing in very simple terms: the longest possible period of later life that is free of chronic disease and impairment. Now, "later life" is always slippery, because people tend to define it as "any period of life that is later than mine", but I use the UN definition of 65-plus. It does not really matter to me whether that healthy, chronic-disease-free life is present as a result of interventions throughout the life course, in the middle of the life course or later on; as a biologist, I could quote you examples of interventions at all those stages that would enhance health in later life.

I know that my healthy-ageing definition is considered a bit narrow by some people, because it fails to bring in areas of social well-being and is sometimes considered too optimistic by other people who seem to have the idea that you should step down your expectations of health as your number of birthdays increases, which I am afraid I always think of as the tyranny of low expectations. My definition is the easiest to translate from what we know in experimental animals straight into humans. I am not entirely sure what social well-being would be for a fly.

Viscount Ridley: Professor Faragher has largely answered my supplementary, which was which species do not age, but I have a supplementary to that.

We know that human cell lines can be immortal in the laboratory—Henrietta Lacks died a long time ago, but her cells are still living in laboratories all over the world—but can we learn anything from that about the potential immortality of human beings?

Professor Richard Faragher: Oddly enough, you can learn one of the most profound things for a study of abnormal cells like those of Henrietta Lacks. Cells that grow indefinitely are almost always derived from tumours. It turns out that one of the fundamental mechanisms that makes you age is a tumour-suppression that I work on called cell senescence.

Effectively, in the normal course of your life you lose cells. That loss is balanced by cell division. Cell division is monitored continuously as an anti-cancer mechanism, and, after a while, permanent arrest from the cell cycle is signalled. This means that the cells will never divide again, and that they start to adopt a range of behaviours that are effectively poisonous to the body. They throw out pro-inflammatory molecules and start to degrade tissue.

Why are they misbehaving? It is a cry for help. They want the cells of your immune system to come and kill them, but your immune system is also made of cells and is ageing at the same rate. At the start of your life, every time you make a senescent cell, it is almost always dealt with quickly. By the time you are my age, it is more along the lines of when you call up telephone banking: "Hello, this is your immune system. Your call is important to us, but we are experiencing a high volume. Please stay on this line". Some things do not change.

As a result, you tend to accumulate these cells. We know that this is a major ageing mechanism, because in experimental animals where it has proved possible to delete these cells, those animals show an enormous increase in their health.

The example that I like to quote most of all, because it is the most resonant to me, is voluntary wheel running. If you delete senescent cells in mice, they run about three times as hard and fast as their litter mates that are still full of senescent cells. I did some back-of-the-envelope calculations for what this would mean if you were a human. Effectively, it would be like taking somebody of 80, putting something in their drinking water for a few weeks and then watching them jog like a person of 30. The difference is very big.

The Chair: I volunteer.

Professor Richard Faragher: Please come and see me afterwards, Lord Chairman.

The Chair: Have I understood correctly that only aggressive cancer cells such as HeLa cells—Henrietta Lacks cells—obtained from an aggressive tumour, which, 50 years later, exist in every laboratory, are immortal, while normal cells such as embryonic stem cells—

Professor Richard Faragher: There are two classes of cells that are considered immortal. The first is aggressive tumours, the second is germline sperm and eggs. If one thinks about it, there is a transitional point where sperm and egg fuse, where you have had something that was going to grow indefinitely and now has to go towards making a body, so at some point you will see a decision point where you shift from immortality to mortality.

If you look more deeply into stem-cell populations within the adult, which are sometimes quoted as being immortal, the evidence for this, when you dig down into it and do the audit, is far less compelling than perhaps one would like. I would be surprised to find any population of cells in an intact body, other than the sperm and eggs, that were truly immortal.

Q24 Viscount Ridley: My question is about our current understanding of the biological mechanisms of ageing. We have already trespassed on that territory. What are the biological markers and at what level do they exhibit molecular-cellular tissue? How firm is the evidence that these pertain to humans as well as to other animals? To what extent do we understand the relative contribution of biological processes of ageing—or their absence—to health span as well as lifespan?

Professor Richard Faragher: Colleagues will perhaps feel free to dive in if I misspeak.

I am glad that we are asking this question now, because if we had asked it 30 years ago, there would not have been enough Committee time. It was a running joke in gerontology then that there were more theories about how ageing happened than there were scientists to work on them.

That has changed. We have gone through a period of extraordinarily rapid progress, and it looks now as if, rather than having one mechanism for everybody on this Committee, with a few dozen left over, there are just a few—perhaps 10 or so—with firm evidence that they are relevant to humans as well as experimental animals. We sometimes refer to these as hallmarks.

To qualify as a hallmark, any biological process has to meet three criteria. First, it must be present in an ageing body. If it is not, it cannot cause ageing. Secondly, accelerating it should accelerate ageing. Lastly, slowing it down or getting rid of it should slow ageing down and improve health.

If you are going to make a list, please do not treat it as timeless and unchanging. Science is a progress report. I do not need to tell Viscount Ridley that. I expect that we will see more hallmarks turn up in time. Key hallmarks are stem-cell exhaustion, epigenetic modification—respect to Dr Bell—and nutrient sensing and cell senescence, which I think are the two strongest in the current suit.

I can explain why, if the Committee wishes. Effectively what happened with nutrient sensing was that from the 1980s onwards, with the pioneering work of Michael Klass, the scientific community was able to isolate a series of single-gene mutations in different species. *Caenorhabditis elegans*, the worm; *drosophila*, the flies; and mice. These mutants showed extended lifespan. The problem when you have a new mutant is that it is like owning a piece of alien technology. You know what it does, but not how it does it. The problem then is to try to reverse engineer it and find out.

In essence, these mutants showed extended lifespans, because whatever we had done had made them much healthier. If one looks closely at what those mutants did, they were all involved in nutrient sensing, and that nutrient-sensing network converges on a protein called mTOR—mammalian target of rapamycin. Rapamycin is a drug. In 2009, it was shown that giving it to mice extended their lifespan in much the same way as these mutations did.

The importance of this cannot be understated, because the human race has only about 1,200 drugs. The way it works is tied to a phenomenon

you may have heard of: dietary restriction. This is the observation that if you eat a diet complete in all regards but deficient in calories, two things will happen. You will probably spend the rest of your life hoping for a bacon sandwich, and you will see a significant extension in lifespan. This has been done in a range of species. There are some humans who try, although I would not recommend it.

I think what is going on here is that if you put an organism in a state of dietary restriction, it has no nutrients and is forced to recycle the things that it has, so the longer you live, the better you recycle. The mutant cells are fooled into thinking that they do not have any nutrients, so they recycle.

That is one key mechanism. The other, cellular senescence, we have touched upon. The accumulation of senescent cells appears to drive multiple aspects of the ageing process.

Professor David Melzer: I would add to my list of hallmarks some more difficult ones to deal with in humans.

On DNA damage, a series of recent studies have shown the accumulation of very large numbers of mutations in the somatic cells. These are certainly a big risk factor for cancer, and in future over half of humans will die of cancer rather than cardiovascular disease, which was the main reason in the past. Similarly, there is damage to the mitochondria, the energy plants of the body. That kind of intrinsic damage is probably upstream of the senescent cells. As a public health person, I am very interested in how we prevent that damage, and the sources of damage that we need to think about first include, of course, smoking, which greatly increases the number of DNA mutations and the amount of damage to DNA. That upstream damage is very important.

Being interested in the human part of ageing science, we must bear in mind that a lot of the evidence that you have talked about is from short-lived organisms. Mice share a lot of genetics with us, but of course their lifespan is a tiny fraction of ours. We have already evolved many of the protective mechanisms that some of these laboratory experiments are trying to add to these short-lived organisms. Going from an organism that lives three years to one that lives for 100 or 110 years is a big jump, and I think we need to be more realistic or a bit cautious about simply extrapolating to a long-lived organism.

Professor Richard Faragher: The point is well taken, but it is also clear, with things like cell senescence, that this is an operative mechanism in humans.

The Chair: Could we hear from Dr Bell, with your special interest in epigenetics and genetics?

Dr Jordana Bell: My interest focuses very much on epigenetics, and we can discuss epigenetic changes related to ageing in more detail. Telomere attrition is something else that has not been mentioned; nor has genomic instability. They are all related, so it is important to consider them as well.

We think of epigenetics as molecular information that guides the same piece of DNA sequence to act differently in different types of cells. There are many levels of epigenetic control of gene function, and most of those show age-related changes. Take one of these that is very stable and most commonly studied: DNA methylation, which is the addition of methyl marks to the genome.

Here we see three major types of changes in humans. One is if you compare a centenarian's genome with a newborn's genome, we see a slight loss in the number of methyl marks across most of the genome in the older subject. We think that has to do with genomic instabilities; a lot of our genome is repetitive, and these epigenetic marks maintain stability, so removing them induces instability, which is also seen in cancer.

Another set of changes are very targeted changes, where we see a directional increase—or a decrease, but predominantly an increase—of methylation with increasing age. Many of these happen at the start of the gene, so we think they are regulating and potentially silencing gene expression.

With the third set of changes we see an increase in variability, predominantly. If you take a pool of older subjects, at these targeted marks you see higher or lower levels of epigenetic change, while in a pool of younger subjects you see a more homogeneous level of change, again implying epigenetic dysregulation or variability.

If you look at the genes that the age-related targeted changes either fall in or distantly relate to many of the genes have roles in important cellular processes such as regulating gene expression, DNA repair, the regulation of cell death and so on. A lot of the human age-related epigenetic changes are detected in blood samples, but they occur in other types of tissue as well.

The Chair: To simplify it, you get epigenetic factors that then affect the genome and change it. What are these epigenetic factors, so that the everyday man in the street would understand what those factors are? Is it one exposure to those factors, or an accumulation of exposure to these factors, or indeed a lack of it?

Dr Jordana Bell: There are several types of factors. I have talked about one of them, but there are multiple layers and changes related to age occur across these different layers. They are studied mostly in one of them, which is DNA methylation. Here it is important to say that we do not see changes only related to age; we also see separate changes related to lifespan, so there are different types of change that are coming out.

Why do they occur? When we identify these changes, we try to control for differences in different exposures. Smoking, which we know has a major impact on the epigenome, also impacts on ageing. This is taken into account as much as we can in the identification of these age-related changes. So in a way we are identifying changes that occur naturally with

ageing, controlling for differences in exposure. From my point of view, we are looking at these as a marker of how fast or how slow we age.

Viscount Ridley: Professor Bell, you briefly mentioned telomeres. A few years ago, there was some excitement that telomeres might be the main underlying mechanism. I sense that that has faded, but then, sad person that I am, I woke up early this morning and looked up the latest papers on telomeres, and there was a very interesting paper from Madrid last week saying that they had developed mice with hyper-elongated telomeres as a result of taking embryonic stem cells and turning them into an embryo from internal cell mass, so it is not a genetic modification but simply a question of exposing them to telomerase for a bit longer.

The consequence was that these mice lived 24% longer, had lower tumour rates and more insulin resistance, and had lots of features that you would associate with health span. Is it possible that there is a silver bullet here and that at some point we might suddenly find a cheap, simple drug based on telomeres that could solve ageing?

The Chair: You might start by saying very simply what a telomere is.

Professor Richard Faragher: This falls within my direct area of competence. The telomere is simply the end of a chromosome. It is the thing that stops the end of a chromosome looking like a break in the middle. That is the easiest way to deal with it. If a telomere is absent or severely damaged, the cell senses this and, typically, ceases to divide, and there are certain circumstances in which it may simply die.

Telomeres have attracted a great deal of attention, because it became clear from the 1990s onwards that the shortening of telomeres is the mechanism that controls cell senescence in many human cell types and in many cell types from long-lived organisms. In that sense, a lot of the literature on telomeres is also the literature on cell senescence, which we have covered.

With reference to the paper on the long telomeres, which we have both read, it is possible for a telomere to be damaged but still partially functional, and at that point you can get a senescent-like phenotype. So the lengthening-up of telomeres in that particular species is protective and allows it to soak up a bit more damage.

One analogy that people use for telomeres, although I do not like it, is the plastic caps at the end of your shoelaces that protect them from fraying away. In essence, what has happened with that work is that an extra plastic cap has been stuck on to stop the telomere getting a little bit frayed. There is real potential there, but the whole thing really could be considered a subset of the senescence literature in certain specialisations.

Baroness Walmsley: What is a telomere is made of? Is it a string of proteins or is it some of the four bases that make up DNA?

Professor Richard Faragher: It is a simple repeating sequence of DNA bases. In humans it is TTAGGG.

Baroness Sheehan: I have a quick question on DNA methylation. It is a simple question, really, but it would help me to understand. Where do the methyl groups come from?

Dr Jordana Bell: From the intake of folate in the diet. Folate is the source of methyl groups. Then they are transferred on to the DNA with an enzyme called methyltransferase.

In older subjects we observe a slight global reduction in methylation, and there are at least two potential explanations for this. First, the source of methyl groups is slightly depleted. Secondly, it could be that the action of the enzymes that transfer those methyl groups is somehow impaired, so either there are fewer enzymes or they are not working as well.

Baroness Sheehan: And the folates come from folic acid?

Dr Jordana Bell: Yes, it is the dietary intake of folate.

Q25 **Lord Mair:** My question is about the brain. Do the biological processes underlying ageing also impact cognitive function and mental health? Is our understanding of the influence of these processes as we age as thorough for mental health as it is for physical health?

Professor Avan Aihie Sayer: That is a really good question. The area that I focus on is physical health and function, and the biology of ageing links quite well to that. I think there is also evidence for cognitive functioning but—I do not know the literature very well—a lot less with regard to mental health. That would be my assessment of the situation.

Professor Richard Faragher: It would also be fair to say that it would be very surprising if we found that a Chinese wall separated the ageing of the central nervous system from that of every other system in the body. You can see this if you look at the real human epidemiological data. Individuals who develop cognitive impairment are at significantly reduced risk of certain cancers, whereas individuals who develop cancers in later life show a significantly reduced risk of cognitive impairment. That is after correcting for the kind of mistakes in the data that anyone could quote: people who die young with cancer are unlikely to develop Alzheimer's disease, for example.

The Chair: Heads you lose and tails you lose.

Professor Richard Faragher: Exactly. Now, those epidemiological data are incompatible with the idea that cognitive disorders and, for example, cardiovascular disorders are as separate as athlete's foot and measles. There is good evidence that the mechanisms of ageing—the hallmarks that I mentioned—play important roles in cognitive impairment, and that they may in turn be amenable to treatment.

When we look at ageing, we hope to target multiple impairments and disorders in a single strike. There is evidence that this is achievable within the context of cognitive impairment, which I could explain if the Committee wanted.

Dr Jordana Bell: Briefly, if I may, I will comment in terms of epigenetics. Epigenetic patterns have been looked at in ageing brains

post mortem. In older brains, when compared to younger brains, a de-differentiation starts to be seen. Different areas of the brain usually have very different epigenetic profiles. That seems to be attenuated in older brains. You see a similar finding in certain pathologies, such as Alzheimer's disease. Some epigenetic marks have also been linked to improved cognitive function. I think that one speaker on the next panel has led one of those studies, so that might be worth pursuing.

The Chair: Okay, we will get to that.

Lord Kakkar: To be clear, are you suggesting that single-organ dysfunction can drive systemic ageing?

Professor Richard Faragher: I think that the dysfunction of a single organ, if you consider the cardiovascular system a single organ, could do that. The systemic dysfunction could also drive the ageing of a single organ. It may be a false dichotomy.

Lord Kakkar: Is there good epidemiological evidence for that? Have we studied, for instance, a single-organ dysfunction and a trajectory for ageing? Has that been done?

Professor Richard Faragher: I think the question is too broad to admit a precise answer. An example I might use is that if one looked at diabetes, one could say that it is a change within a single organ affecting glucose. However, you see a range of changes as a result of the disturbed glucose balance. Obviously, if you see disturbances in the cardiovascular system, that will be reflected in the central nervous system. That was the intent of my argument.

The Chair: Diabetes is not, of course, a single-organ disease. It affects lots of organs.

Professor Richard Faragher: Well, I believe that this is the point in discussion. It is about where the nexus of cause and effect lies.

Professor Avan Aihie Sayer: I wanted to say that identifying a single system as the driver for systemic ageing is probably not the right framework. It is more interesting to look at how all the systems age together. Understanding that epidemiologically is probably more fruitful.

Q26 **Lord Borwick:** Regarding the contribution of genetics to healthy ageing, do we really understand which are the key genes? How complete is our understanding of the role of genetics in how we age?

Coupled with those two questions, there was a lot in the papers this morning about prime editing. A new paper has come out in *Nature*, about it apparently being more accurate than CRISPR as a solution to this. Do you agree that that is important, or is it just a small thing that the papers have taken up?

Professor David Melzer: In terms of human genetics, we now have over 1,000 variants proven for various diseases of ageing. If you think of the common diseases—cardiovascular disease, diabetes, osteoarthritis, the common cancers and so on—there are over 1,000 variants, mostly of small effect, which add up to a kind of score for people. Some people end

up with a lot of bad variants; some are lucky and end up with much fewer.

For longevity, the genetic influence is much less. For individual diseases, about 30% of the difference between people is explained by the genetic differences between them. There is also a much bigger environmental effect. The genes that have been implicated by genetic studies in humans are heavily dominated by cardiovascular genes: a lot of the lipids, the cholesterol levels, high blood pressure genes and obesity genes.

There were articles in the newspapers, based on journal papers, claiming that obesity was good for older people.

The genetics clearly shows that that is profoundly wrong: it is a mix-up of cause and effect. The genetic variants that make people slightly heavier result in more cardiovascular damage, more diabetes and shorter lifespans. We see that in the generation being studied and in their parents—in these human studies.

The genetics is also very exciting because it supports the senescence story. We are seeing variants in the key senescence cell gene, p16. Variants in that in humans are implicated in a wide range of diseases, including cardiovascular disease, diabetes and a whole bunch of cancers. That almost certainly suggests that the senescence cell story is very relevant to humans.

Telomeres are a bit more complicated. Six variants are proven: people are walking around with slightly longer telomeres or slightly shorter ones, because of these six variants. If you study these people, those who have genetically longer telomeres have less cardiovascular disease, but unfortunately they more than pay for it with extra cancers. The effects seems to completely balance out. We used UK Biobank and have published on 500,000 people across the UK, and there is no net improvement in everyday functioning in the 60 to 70 year-olds because of that. A lot of that balance—that trade-off—is a feature of some of these ageing pathways. If you intervene in those pathways, you can improve the chronic disease outcomes, but you risk cancer problems.

There are a number of other pathways, including, as I mentioned, the obesity pathways, which play into calorie restriction. We have to remember that, for the future of human ageing, the ONS says that over 30% of older people are obese and another 40% are overweight. The proportion who are of normal weight is actually quite small, which will be a huge driver of senescent cells. Senescent cells are one of the pathways in which these avoidable environmental risks play out. In the human context, we must not forget that there is a lot of potential for public health intervention, weight reduction and so on.

That is the common variation. There are also a whole bunch of less common mutations causing specific diseases that are important in older people, so we see the auto-immune genes—the so-called HLA-type genes—coming up for longevity and ageing. People who have inherited rheumatoid arthritis genes or type 1 diabetes genes obviously age faster.

An interesting example that I have worked on recently is the *HFE* gene, the hemochromatosis gene. This is a northern European mutation that seems to have become common when people moved to farming and intakes of iron became very low. The UK and Ireland have the highest rates of the haemochromatosis gene in the world. Some 0.64% of people—that is, one in 156—are homozygous; they develop very high iron levels and aggressive arthritis, liver disease and diabetes.

We showed this in the *BMJ* in January, reporting doubled rates of chronic pain and muscle loss in older men. In the UK Biobank study, this one mutation accounts for 1.5% of all the frailty in older men. The wonderful thing about this gene is that it is very treatable; all they have to do is give blood. There is so much iron in the blood that you can get that excess iron from the blood. Many of them are not being diagnosed at the moment. This is just one example of these less common genetic conditions, so the ageing of maybe 5% or 10% of the older population is accelerated by less common mutations with major effect specific damage pathways.

I mentioned before that cell sequencing studies are showing the accumulation of lots of acquired damage in cells. These DNA changes that are caused by damage. The numbers are quite small in newborn babies but rise dramatically with age. They seem to be the source of cancers. It is still debated how important they are to the chronic diseases, but it seems very likely that they are.

The Chair: Perhaps you will correct me, but the important point is that you are not born with these gene defects—you acquire them.

Professor David Melzer: The first lot of genes that I talked about, the cardiovascular genes, are the ones that we are born with. Each person is born with a variety of thousands of variants. There are literally millions of variants that are normal in the human population that cause very small changes in risk, so if you are unlucky and get a bad hand with all the bad cards you will get very accelerated outcomes.

In addition to the ones that we are born with, which are very interesting scientifically because they are not biased by whether you smoke later or whatever, there are also the acquired ones, the ones that are due to damage during life. They are different in every cell. So the inherited ones are the same in every cell, but the damage ones are different in every cell and are part of driving the senescent cell story and the shortening of telomeres.

Lord Borwick: Is the thing that I read about prime editing important, or not?

Professor David Melzer: For the less common specific gene disorders such as cystic fibrosis, haemochromatosis and so on, correcting the germline variant in babies would be a fantastic thing to do if you could do it with 100% precision and 100% safety. That is going to be a pretty high

bar. Up to now, the CRISPR mechanisms have had collateral damage. Sometimes they change the DNA—

Lord Borwick: They change something else, yes.

Professor David Melzer: —away from the target as well. Everyone agrees that doing that in humans is very irresponsible at this stage. If this new technique turns out to be much more precise, it will be a fantastic step forward, but only for those rare large-effect genes. When the ageing outcomes for most of us are influenced by hundreds, maybe thousands, of small-effect genes, that is not going to be a feasible way forward.

Lord Borwick: That is very helpful.

Lord Kakkar: To come back to epigenetics, how much do we know about the environmental and behavioural factors that can impact on the epigenome, and how well have we been able to characterise their impact on the epigenetic effects in ageing?

Dr Jordana Bell: There has been a lot of work trying to identify environmental exposures that impact the human epigenome, predominantly in blood. Of those, smoking is by far the one outlier that has major effects. Clearly there are many other factors, and measuring them precisely and correcting for the exact dose of exposure is very difficult to do across different studies.

In terms of ageing, the vast majority of the age-related epigenetic effects that we are discussing, and which we look at as a set, already correct for differences in smoking, so they take that into account. Things like air pollution and diet are very difficult to measure, and some studies try to incorporate them but others do not, so there is a lot of variability in that.

In some cases, one of the changes that I described, the global slight reduction in methylation, has been linked to some environmental exposures, but not necessarily consistently across all studies. From my point of view, on the age-related epigenetic changes that we are talking about, many of them correct already for environmental exposures. Clearly there will be some overlap between age-related and environmentally-induced epigenetic changes, but we are not yet at a stage in the human studies where one can get a very good grasp of the extent of this overlap, or of the impacts of specific doses of exposures from many different environmental factors.

Lord Kakkar: Turning to specific ageing-related genes, which of those have specific epigenetic regulation?

Dr Jordana Bell: We touched on this previously. There are hundreds to thousands of epigenetic changes, and many of those target the start sites of genes or relate to the expression of distal genes. There is not really a striking relationship between age-related methylation changes and age-

related changes in expression. That might be because a lot of the age-related methylation changes are actually silencing gene expressions and we are just not picking that up.

On the question of what genes they are targeting, many of the genes are related to repression of the expression of particular pathways related to growth and cell differentiation, so they are very important to development and cell fate establishment, as well as cell death and DNA repair processes.

In addition to identifying these particular genes, we also see that many epigenetic markers of ageing lie in particular DNA motifs, where regulators bind and impact the expression of a network of other distal genes. That allows us to identify the regulators that are important—by looking at the DNA motifs where the age-related epigenetic change lies and overlaps with the motif that the regulator binds, that has allowed us to identify particular regulators that are important in the ageing process.

Lord Kakkar: How far is that leading us to the capacity to modify these and provide therapeutic options?

Dr Jordana Bell: To expand on David's point, I think that is still quite far in the future. I am not sure, because there are so many changes that we observe, to what extent this will be a viable strategy. Perhaps it will be in five or 10 years' time, but at the moment the research is really focused on using epigenetics as a marker of ageing. It is really focused on that knowledge to develop predictors, such as predictors of age.

So we have an epigenetic-based predictor of chronological age; you can look at the difference between the predicted age and your actual age and say that the person is ageing faster or slower than expected. That difference—the biological ageing, if you like—has then been related to a lot of diseases, cancers and indeed the menopause.

Furthermore, in the past year or so, these predictors have been extended to predict not only age but lifespan or health span by taking into account time to death or lifespan as well as different phenotypes that capture healthy ageing. We would look, for example, at a particular intervention for ageing and see that when you apply it, the ageing epigenome changes and the epigenetic predictor of ageing or lifespan improves.

Lord Kakkar: Can you give me an example of such an intervention?

Dr Jordana Bell: In model organisms, diet restriction has been used. As a result of that restriction, age-related epigenetic changes attenuate and slow down, and in some cases stop. In humans, a very recent study looked at a protocol to regenerate the thymus, which improved the epigenetic predictor of lifespan.

Lord Kakkar: In patients who have had a thymectomy, do we see a change in the epigenetic profile?

Dr Jordana Bell: I do not think that has been done.

Lord Kakkar: Thank you.

Q27 **Lord Hollick:** How realistic is the Government's aim to ensure that people can enjoy at least five extra healthy, independent years by 2035, while at the same time narrowing the gap between the rich and the poor? What steps or policies should the Government take to achieve those objectives?

The Chair: An absolutely definite answer, please.

Professor Avan Aihie Sayer: Right. I think it is an ambitious aim, but there are some near wins that we can think about, certainly coming from a population level and putting interventions in place that we already know do help. As I think you heard in the evidence last week, we know that, for older people, exercise is effective, as is changing diet to avoid malnutrition; and, as David mentioned, obesity, stopping smoking, social connection and avoiding loneliness. We have not mentioned that, because we have talked more about ageing in animals than in people.

There is a suite of interventions that could happen at an individual or a population level. You might say that we all know that, so how could it make a change, but I do not think that for older people we have had a systematic, comprehensive approach to implementing these changes, either to be self-directed, for those who are more advantaged, or with the promotion and delivery of these interventions targeted to the least advantaged. We have not done that specifically for the older population. There is now an opportunity in that area.

Looking a little further out, I mentioned at the beginning my interest in translational ageing research. You have heard of the beautiful science that is going on in animal organisms and in cell lines, but to me there is still a big gulf between what is happening there and what we can do for people. The patients I see filling our hospitals are older people with multiple conditions and functional decline associated with ageing. We are a long way from translating ageing science into improving their lives. Focusing on how we can make the join-up better, now that the scientific advances are coming through, is a really important area.

The third area is what we can do to work with companies and businesses to address some of the deficits associated with ageing. There are probably not so many in this area. Considering our ageing population and the number of people, there is a big market but surprisingly few companies, although I think that is changing.

Anecdotally, I would say that in Newcastle we have had a lot more interest since the National Innovation Centre for Ageing was set up there. This has been expressly set up to bring together companies, the NHS, academia and members of the public to say: "If ageing is resulting in problems, how can businesses solve those problems through technology?" Increasingly, that has become an area of real promise for quick advance.

Lord Hollick: How would technology help? What initiatives would you like to see pursued?

Professor Avan Aihie Sayer: There are lots of opportunities in the area that I am in, physical function and mobility. There is a really nice study across Europe being led by Professor Lynn Rochester in Newcastle, with funding of €50 million, involving 35 partners of industry and academic backgrounds, looking to use wearable technology to monitor and understand gait in order to address the loss of mobility that comes with ageing and a whole range of age-related diseases.

Lord Hollick: One of you made the point earlier that the problem starts earlier in the life course. If you look at people who are now 50 and 60, is there the possibility that they can, let us say, mend their ways, change their lifestyle, in order to recover the lost ground? Or is it too late?

Professor Avan Aihie Sayer: No, absolutely not. That takes me back to that point I made about ageing being a life-course process. It starts very early in life, through to midlife and thereafter. Some of the epidemiological studies that we have done show that influences operating in midlife affect later-life function, so intervening in those middle years is critical.

It comes back to what I was saying about exercise and diet. The most advantaged are often able to change if they are guided as to how, and technology is increasingly able to support that, because people can wear smart sensors, even as a watch, that can monitor levels of activity, give feedback to change activity, and so on. There is a huge opportunity there if the message comes through that not only are you affecting your health here and now in midlife, but that potentially you can maintain your independence for longer into later life.

Professor Richard Faragher: I would echo quite a bit of what Professor Sayer says. I like to think, to steal a phrase from someone else in the room, that I am a rational optimist. However, I look at the way we are going forward and I am compelled to become something of a rational pessimist as well. If we proceed in that way, I am not sure that the industrial strategy will achieve the goals that it seeks.

I will explain why. It is as though the whole swathe of biological research that we have talked about has not been considered to the depth that it should be. I will give two examples, which are happening right now, about closing the gap that Professor Sayer mentioned.

As I am sure all of you are aware, older people are about 150 times more likely to die from influenza than young people, which is why they are prioritised. About a year ago, a group in the US, led by Joan Mannick, carried out a randomised placebo-controlled clinical trial to determine whether a low dose of rapamycin-like drugs would enhance immune function. Two hundred and fifty people were given the drugs for about six weeks, and were then vaccinated against the flu. Individuals who could not make a protective titer made it, there was good evidence that they were protected against multiple strains of flu, the rates of infection in that group significantly decreased at 12 months, and it was safe.

There are clear public health implications there, and again, the first trials of crude drugs that can destroy senescent cells in humans have already

taken place this year. They have been shown to be safe and that there is some sign of improvement. This is an area for industry to be moving into. I am aware of new charitable foundations—for example the Chernajovsky foundation, which launches tomorrow—that support this area, and investment trusts such as World Vision and Juvenescence that are trying to invest in start-ups in this area.

I believe that if the Government lead, funds basic research properly and establishes a full translational pipeline with our clinical and pharmaceutical colleagues, this country could build up a formidable industrial base in this area.

Lord Hollick: Would it be safe for the Government to green-light those interventions now?

Professor Richard Faragher: It is not fully within my competence, but we are at the stage of clinical trials already.

Professor Avan Aihie Sayer: Certainly, the drug that you mentioned has gone through a trial in the US and is now at the phase of going through further trials. In Newcastle, we are leading one of those trials but we are a way off implementation even in the most promising areas.

Lord Hollick: What sort of period of time would you need?

Professor Avan Aihie Sayer: Traditionally, from bench to bedside is a period of 15 years. We are part-way along that journey now.

Professor Richard Faragher: We are talking about a 15-year timescale for the industrial strategy. We are not here saying that we need interventions in five and will be ready in 30. We are on the same order of magnitude. If we push hard, I think it could be achieved. What I fear—and I am not ashamed to say this while conscious that I am being broadcast—is that this country misses the boat and that we push exclusively on technological interventions. That would be akin to when a polio vaccine was on the horizon and the Government deciding that the solution was to ask the British Motor Corporation to build thousands of iron lungs, because there was clearly an immediate market demand. We must balance the portfolio.

Professor Avan Aihie Sayer: I would not disagree with that. There is huge opportunity for the UK, because we not only have the excellent biology of ageing but clinical cohorts and great infrastructure through the National Institute for Health Research. The opportunity for the translational ageing research pathway, and for building the whole pipeline, is major for the UK.

Lord Hollick: What I am hearing is that this is ready to go but industry has not picked it up. So how do you make that link?

Professor Avan Aihie Sayer: I think industry is starting to pick it up, in terms of the pharmaceutical companies and the drugs that you are talking about. Possibly the technological industries are lagging behind, but again, as I said, my experience is that that is starting to move as well. We have probably been talking about it for a long time and things

have not been moving, but there is a sense that they are starting to move now.

Professor Richard Faragher: I am less optimistic. I am sure the research councils will speak to this Committee, but I see no drive at the basic end where there should be, no significant focus, no money and no translation going through as it should do. That is an area that I genuinely believe must be corrected as a matter of urgency.

Lord Hollick: What can the Government do to correct that?

Professor Richard Faragher: First, they could show that they value the biology. Secondly, if the research councils were to develop an effective programme aimed at the biology of ageing, the Government could indicate that they would look favourably upon this subject. The Government must provide leadership on this matter and indicate that the biology is valued and that Britain wants to have it.

Viscount Ridley: On exactly this point, we have had a piece of written evidence from Michael Fossel in the US, who is both a doctor and an entrepreneur, in which he talks about the cell-senescence model. He says: "If the above model of age-related disease is accurate and if implemented, then the costs of treating age-related disease will fall substantially, to perhaps 10% of current annual costs, rather than rising to fiscally unsustainable levels". Is that crazy, or is it possible?

Professor Richard Faragher: No, it is not crazy. I can speak to one piece of evidence, a piece of modelling that says that if the US were able to translate into the clinic the modest benefits in healthy lifespan that we are achieving in the lab—and, as you can see, which are already going into humans in cell senescence—the US, out to 2050, would save, from memory, \$7 trillion gross and \$4 trillion net, and that includes paying the entitlements due to older people. It would save about 1% of global wealth, and that is money that we could use to improve people's lives in other ways. There are vast stakes to be played for, and I think we should play for them.

The Chair: Do the other witnesses agree with that comment?

Professor David Melzer: As always, my reading is a little more cautious. There are tremendous grounds for optimism, but not boundless optimism. Even in the mice, knocking out the senescence cells does not change maximum lifespan. These mice are still getting ill and dying eventually, although it helps many of the ones that would otherwise die early to live longer and in much better shape. The other big problem is how you do these trials and get them regulated through the drug system. At the moment, the drug regulators are looking for very specific indications.

Professor Richard Faragher: I can speak to this, David, if the Committee will allow me; I am conscious of the time.

One thing that is also happening is that the trial methodology known as the TAME trial is in the advanced stages of preparation in the US. It exactly addresses Professor Melzer's comment: if you had a drug that

slowed ageing down, how would you know since we cannot wait 50 years?

The way in which TAME is postulated to work is this: the age at which you develop your first age-related impairment is very variable from one person to another, but the time from first impairment to second impairment is relatively tight, 18 to 24 months. So a compound that improves healthy lifespan would be predicted to lengthen the time from first impairment to second impairment.

That is the rationale of TAME, and underlying it is a large amount of choice of ideas. The goal is to take thousands of older people, each with a single impairment, split them into two groups, one receiving a placebo and the other receiving a drug called Metformin, for reasons that we do not really have time to go into, and to follow them, looking at any first event to any second event.

The FDA is smiling kindly on this, I am given to understand, and funding is almost completely in place. I must confess, although I did not mention it, that I am on the board of directors of the American Federation for Aging Research, the leading charity in the area, which has taken it upon itself to attempt to raise money for this. So there is a methodology that would do that.

The Chair: The last comment, please, as I have overrun the time.

Professor Avan Aihie Sayer: I wanted to follow on from that. There are opportunities, and the approach that we are taking, certainly in Newcastle, is to focus on ageing in one system, which is slightly easier and slightly more tractable, so we are focusing on skeletal muscle as a good model for ageing.

To follow on exactly from Richard's description of that study, one of the nice things in the UK, with the infrastructure for research that we have, is that we can be quite nimble, so we have been thinking about Metformin ourselves and doing pilot intervention work for skeletal muscle ageing. So we may yet steal a march on the US with that.

Professor Richard Faragher: That would be nice.

Baroness Sheehan: Just a quick question. A large number of multidisciplinary sectors need to come together. Is the overarching institutional infrastructure necessary to bring everything together in place in the UK?

Professor Richard Faragher: If you ask me personally, I think we need some version of the American NIA setup here. This area is too big and has been too fragmented for too long. It needs unified leadership and responsibility.