HOUSE OF LORDS

Select Committee on Science and Technology

Corrected oral evidence: Ageing: science, technology and healthy living

Tuesday 10 March 2020

11.35 am

Watch the meeting

Members present: Lord Patel (The Chair); Lord Borwick; Lord Browne of Ladyton; Baroness Hilton of Eggardon; Lord Kakkar; Lord Hollick; Lord Mair; Baroness Penn; Viscount Ridley; Baroness Rock; Baroness Sheehan; Baroness Walmsley; Lord Winston; Baroness Young of Old Scone.

Evidence Session No. 20 Heard in Public Questions 181 - 187

Witnesses

Dr Fiona Marshall, Fellow, Academy of Medical Sciences, and VP Head of Neuroscience and Head of UK Discovery Research, MSD; Jim Mellon, Co-Founder and Chairman, Juvenescence; Dr Sheuli Porkess, Executive Director, Research, Medical and Innovation, Association of the British Pharmaceutical Industry—ABPI; Dr Lauren Walker, Chair of StR Committee, British Pharmacological Society, and Academic Clinical Lecturer in Clinical Pharmacology and Therapeutics Molecular and Clinical Pharmacology, University of Liverpool.

Examination of witnesses

Dr Fiona Marshall, Jim Mellon, Dr Sheuli Porkess and Dr Lauren Walker.

Q181 **The Chair:** Thank you to all four of you for coming today to help us with this inquiry. Before we start, could you say who you are, so we can get that on the record? If you want to make a comment, feel free to do so, and then we will start the questions.

Dr Lauren Walker: Good morning. I am a clinical pharmacologist and general physician from Liverpool University Hospital. I am here representing the British Pharmacological Society, as a member of the clinical section. I chair a national consortium on polypharmacy, which is a joint venture between clinical pharmacology and clinical pharmacists, to look at strategies for tackling polypharmacy in an integrated care service. I am also a first-in-human clinical trials investigator.

Dr Sheuli Porkess: Good morning. I am the director of research, medicine and innovation at ABPI—the Association of the British Pharmaceutical Industry. We are really pleased to be part of this important inquiry for a couple of reasons. Our members are conducting research into diseases affecting the elderly, so it is really important to be part of this from that perspective, and from the prescribing perspective, to ensure we have the right medicine for the right patient at the right time, and monitoring the outcomes for patients once they are on medicines.

Jim Mellon: Good morning, everyone. I am the co-founder of a company called Juvenescence. The largest establishment of Juvenescence is here in the UK. We started two years ago. We have raised quite a lot money—$180 million so far—to study and advance science in the field of longevity, particularly the diseases of ageing that can be affected by the malleable factors in ageing. We will have our first-in-human trials this year and we will have some products on the market by the end of this year; it does not necessarily take so long to get products to market from pharmaceutical or biotech businesses.

Dr Fiona Marshall: I am here in part on behalf of the Academy of Medical Sciences. I am a fellow of the Academy, but I also head up MSD's neuroscience research globally, and have teams in the UK and the US. I am head of the UK Discovery Centre, and we have chosen to focus on diseases of ageing. In the context of some of your prior discussions around venture capital funding, I was previously an entrepreneur of a biotech company that was spun out of the LMB and worked on a number of diseases of ageing.

Q182 **The Chair:** I will start off. To what extent is research into areas of biomedical science on understanding ageing, developing drugs that affect the ageing process such as senolytics, and repurposing drugs such as metformin that might slow the ageing process down, supported in the United Kingdom?

Dr Fiona Marshall: Perhaps I could start on that. When we started to set up the MSD research centre focused on diseases of ageing, we were very keen to be located in London. We saw London as a very strong location, as a centre of excellence, attracting researchers across the UK, and as a connection through to Europe. We set about setting up collaborations with many academic institutes and universities throughout the UK, including the Francis Crick Institute, Cambridge and Oxford, and made connections with institutes such as the Dementia Research Institute. As an American company, we saw this as an excellent place to be located.

In the two years since we started, we have certainly validated that intention. We have set up some excellent collaborations already in this topic. I feel very positive about the UK's contribution to this area of research.

Jim Mellon: We are at a very early stage in the science. This is like the dial-up stage of the internet. There is everything to play for. The UK has an enormous opportunity. At the moment, most of the science and activity is in the United States, as one might expect, but there is an increasing amount in the UK. Someone mentioned Lynne Cox earlier. Lynne is at my old college, and we are about to announce the first longevity centre at Oxford, which will be headed up by her. That is a start in this field.

As an example, the Longevity Forum, which takes place every November, is trying to educate influencers about the fact that we are going to live much longer. We read the headlines that longevity has stalled in this country and the United States, but that is a temporary thing. The scientific developments we are talking about, and that we are developing ourselves, are not yet in wide circulation, and will not be for the next five or 10 years, but they will make a massive difference. We are the first cohort on the planet for whom bioengineering our bodies is possible, for us to live longer and healthier. As I said, this is a very primitive science. There is everything to play for. It will be the world's biggest industry, because there is no one on the planet who is not interested in living a longer and healthier life and compressing the period of morbidity at the end.

The UK, with its very deep science base, has an enormous opportunity to participate. I urge the House of Lords, the House of Commons and the Government to seize it by the hand and to promote it, because it will be the biggest industry on the planet within 20 years.

The Chair: Your comment about no one on the planet not having a desire to live longer has excited Lady Young.

Baroness Young of Old Scone: It would be useful to get your impression of whether we are sufficiently precise in the way that we talk about this. There is a big difference between extending healthy life and extending life. Personally, I could not care less if I live a lot longer. Three score years and ten was fine for me, and I have done it, and the rest is a bonus, but I would like to be healthy for however long I do live.

Perhaps you could comment on the sort of research you are seeing. Will there be more money in the system for extending how long we live, or, more importantly in my view, for getting healthy life up to the maximum?

Jim Mellon: That is an excellent point. Healthspan is the goal of a company such as Juvenescence or Merck[1], and indeed of the other people on this panel. As a by-product, it is likely that people will live longer, and possibly up to what is currently considered to be the maximal lifespan of human beings, which is 110 to 120. The number of centenarians and super-centenarians is going to explode other the next 30 years, in my opinion.

The most important thing, however, is that those final extra years are conducted in a way that you are not sitting in a nursing home chair, dribbling, and waiting for the end in an undignified fashion; that you are robust until very near the end. At the moment, as I heard earlier, about 15% of people's lives are characterised by one morbidity or more as they get older and older and more decrepit. That is what we are trying to address. The trajectory of things to address that includes: small molecules, which obviously many people are working on; organ regeneration, which is a product that we will have in the clinic this year; stem cells; and ultimately gene therapy. The reason that someone on the planet today will be alive at the age of 150 or beyond is because of gene therapy.

The Chair: Mr Mellon, this is a pipe dream.

Jim Mellon: Lord Patel, I disagree with you. In the last seven years, we have had the development of CRISPR-Cas9, the cure for hepatitis C, and the development of artificial intelligence for the development of novel compounds; and a multiplicity of other things have happened in a very short space of time. The next seven years are going to be even more exciting.

The Chair: Would you agree that, hitherto, we have had no technology whatever—drug or otherwise—that extended life beyond the age of 100?

Jim Mellon: Without putting a specific age on it, the data coming out of the Albert Einstein College of Medicine in the United States on metformin, which has been mentioned already, shows that you can expect probably four to eight years of extra life if you take it.

The Chair: Four to eight.

Jim Mellon: But that is the beginning. I am saying that, in 30 years' time, it will be perfectly possible for people to live to 110 to 120 in robust condition. Governments are not taking account of that, but it will change everything.

The Chair: What about the study that was carried out in a village in Nicaragua, where more than 30 of them are centenarians and more? They have never heard of any drugs or technology?

[1] Mr Mellon was referring to Dr Marshall's company, which is MSD not Merck.

Jim Mellon: Those are called Blue Zones, where people live an ultra-long life. They typically have spartan lives, with very close family ties and so forth. They are not living long lives based on any bioengineering, any drug intervention or any other intervention. They are living long lives based on their local conditions and their family ties. That is not what we are looking at. We are looking at a scientific intervention.

It is possible and it is already in first-in-human trial. This is not science fiction but something that is going to hit us in the face if we do not take account of it. People will live much longer and, to get back to Baroness Young's point, they will live in a much healthier condition.

The Chair: Is the ABPI and its members working on these kinds of areas?

Dr Sheuli Porkess: Our members are primarily focusing on the diseases, rather than on ageing itself, as a general statement. But clearly a better scientific understanding is an absolute foundation that we need to be able to develop those medicines of the future. From an overall ecosystem perspective, it is really important that we have links between the support and the excellent basic science, so that we can translate that into clinical research and getting those medicines to patients.

Certainly one of our main priorities is the life sciences industrial strategy and working to enable that. It was great to see Lord Bethell announced as Life Sciences Minister today; that is a key role for bringing together different parts of the sector, not just for ageing but for research in general, which will have a good effect on the diseases within that.

Viscount Ridley: I want to come back to Mr Mellon's optimism, if that is the right word for it. You say that people might live to be 150 and that the number of super-centenarians is going up. But actually the number of people getting past 110 has hardly shifted in the last 30 years. The oldest man alive today, Mr Robert Weighton, is 111 years and 347 days old—he is British, by the way; we have that record at the moment. The oldest woman is 117. That has hardly shifted, and if we discount Jeanne Calment, the woman who supposedly lived to 123 but turned out to have swapped her birth certificate with her daughter—

Jim Mellon: That is indeed a matter of contention.

Viscount Ridley: If we discount her, there has been no increase in maximum lifespan in 30 or 40 years.

Jim Mellon: I completely agree with that. We are concerned with the idea that people might live to 110 or 120, but it is entirely possible, given that we are just atoms and molecules like other creatures that live apparently immortally, for our atoms and molecules at some stage to be rearranged to enable someone to live to 150. I am not making that claim. I am saying that people will, as a matter of routine, live to 110 to 120, based on technologies that are here today and that are in close development. We should take account of that.

Viscount Ridley: What specific technologies? You mentioned gene therapy and stem cells, but these are both very vague terms. You would

have to have a particular hypothesis about what you are going to do, such as lengthen the telomers or something.

Jim Mellon: Let us say that there are 15 key pathways of ageing. We know from animal models and other organism models that all of them are malleable, to the extent that, for instance, mice can live at least two times longer if they are manipulated in such a way from their natural state. For instance, we know that C. elegans and earthworms can be made to live 20 times longer, if not longer, as can fruit flies, which are the key organisms used in biological research. Those techniques applied to human beings seem to be having some early success, including senolytic drugs, which were mentioned earlier. We also have drugs such as rapamycin, which looks like a golden drug if properly reformulated for humans.

You have the use of hepatocytes in the liver to re-grow the liver. By the end of this year, we will know whether our technique for re-growing a brand-new liver in a human being will work or not; it is about to go into phase 2 studies in the United States, which is amazingly rapid. We know that artificial intelligence is enabling us to develop drugs in a matter of less than a month, whereas in the canonical sense it is three years. Already our AI companies are producing novel compounds which will influence positively those 15 key pathways of ageing.

The Chair: Can you name a drug produced by AI?

Jim Mellon: How about a drug for coronavirus that has recently been produced by AI and is going to go into testing relatively soon?

The Chair: Name the drug.

Jim Mellon: I do not know what the name of it is. It is a compound that has a name; it is being produced.

AI will be a very big contributor to the success of this, but at the moment we have enough in the pipe line and in clinic to keep people alive to 110 or 120 as a matter of routine.

Dr Fiona Marshall: Perhaps I could impart some reality on the discussion.

Lord Winston: I am reminded of: "Glendower: I can call the spirits from the vasty deep. Hotspur: Why, so can I, or so can any man; But will they come".

Perhaps we can come down a little from this massively optimistic view. We have had massively optimistic views about all sorts of issues. I have just been going through some old files in my cupboard of meetings I have been to. In 1991, there was a very full meeting on gene therapy at the Royal Postgraduate Medical School; it was a huge international meeting. The dangers have continued. You mentioned, for example, CRISPR. But when you look through the literature of CRISPR, as I have been for my own work at the moment, you see the risks, such as off-target mutations. It is not that simple: you could cause cancer rather than reduce cancer in an older patient. That is only one example of some of the problems we are yet to see.

I am concerned that perhaps we are being a bit too optimistic. Would you comment on that, because we have to give a realistic report to further what we are trying to achieve in the ageing process?

Jim Mellon: I am a businessman, not a scientist, and so I defer to you on that. But I wrote a book on Juvenescence and I met all the key opinion leaders in this field, who have been in the wilderness for a long time. The elixir of youth has been sought for thousands of years, and nothing has eventuated. However, as I mentioned earlier, it is as though we are now in the dial-up phase of the internet. Some 30 years ago, people would have asked what the point of the internet is, what it can do and whether it will have any validity. Here we are today, and it is completely enmeshed in our lives.

I think it will be the same in the case of the longevity science that we see at the moment. Already for diseases such as osteoarthritis, which is a direct consequence of the build-up of senescent cells in the body, and age-related macular degeneration, senolytic drugs are in human trials to see whether they can influence them. The early results are extremely good. Already you are seeing gene therapies used, in vivo, in human beings for ultra-rare diseases, such as Leber's disease of the eye. The first dosing took place only a few months ago in patients. Yes, we are moving quite quickly.

The Chair: We will get back to reality. Dr Marshall, you wanted to make a comment.

Dr Fiona Marshall: I want us to have a reality check. It is possible that we may be able to extend the total lifespan of people who are healthy, and so we will extend the range of life. But it would be more sensible and prudent to concentrate on the majority of people in the centre who unfortunately do not have a very healthy lifespan. We have heard already about the comorbidities that many people suffer from. You will also be aware of the numerous failures in trying to treat neurodegenerative diseases, even though we have many good fundamental science theories that were taken forward with huge investment from the pharmaceutical industry. None of this is as easy as it may seem.

The Chair: I am glad you got the reality check in.

Lord Kakkar: Would it be possible for you to provide a list? You talked about the 15 biological pathways associated with ageing and said that each of those has target compounds, technologies and innovations, even at a very early phase, that are under development. Could you provide those to us?

Jim Mellon: I can give you a copy of my book, if you like, which has them all in it, and quite a lot of the science.

The Chair: Mr Mellon, we would be grateful if you could let us have that information.

Jim Mellon: I definitely will.

Baroness Sheehan: I have a very similar question. I was looking to see what written evidence we have had. We have not had any written

evidence from yourself, Mr Mellon; is that correct?

Jim Mellon: I was not asked to give any.

Baroness Sheehan: I think it is in the public domain. If you were so inclined to submit written evidence, that would be gratefully received, I am sure.

Jim Mellon: For sure.

Q183 **Lord Winston:** Perhaps I could continue a little. Believe me, those of us sitting on this Committee would be delighted if you found some drugs this year to change us. We are ageing rapidly as we conduct this inquiry.

I wonder whether you might all answer this question. It is about aspects of your work with the Ageing Society Grand Challenge for funding and research into the biomedical and pharmaceutical aspects of ageing. Do you think that this has been sufficiently prioritised?

You mentioned Professor Lynne Cox, who we have taken evidence from. She was very strongly of the view that we should not be content to put up with these things and that we should be developing drugs. I do not doubt that that is right. She says that, for example, the Department of Health and Social Care is perhaps not focused in exactly the right sort of way with regard to therapeutics. On the other hand, we heard fairly compelling evidence from the Physiological Society which refuted that and argued that no major compounds had been useful so far. Could you each give us some view of how you see that conflict in our discussion?

Dr Fiona Marshall: I see the Grand Challenge in part as being a stimulation of everybody who is working in this area, and giving a sense of urgency to people's work. To me, that has been one of the major short-term benefits. As you may have heard, the Academy and the Royal Society held a forum on healthy ageing. Professor Lord was one of the speakers. That brought together a lot of the stakeholders from academia, industry, charities and the funding bodies. Half of the day was focused on basic academic research, but the other half of the day was focused on public health interventions. These were seen as being equally important in contributing to meeting this challenge.

Dr Sheuli Porkess: We have highlighted the Grand Challenge to our members, but as an organisation we have not engaged directly with it. When I was a junior doctor I worked in the care of the elderly, and I absolutely understand why the Grand Challenge has specifically highlighted various aspects such as public health, behavioural aspects and social sciences. Clearly, medicines are just part of that.

The key support for biopharma R&D is through the life sciences industrial strategy and the Life Sciences Council. Our primary engagement has been with the Life Sciences Council, through the innovation, research and data group, and the clinical research working group. Again, that is not specifically about ageing; it is about unmet need in general.

Dr Lauren Walker: I think it is very important that we focus on healthy ageing, not just in terms of new treatments but optimising the use of

existing therapies. For that large proportion of people who are taking eight, 10 or 15 medicines already, that is an area of unmet need. I strongly believe that clinical pharmacologists, working with our colleagues in clinical pharmacy, can really help in that area.

That is the point of developing a consortium, or a network of people. It is not just about clinical pharmacologists who have medicines expertise; our clinical pharmacy colleagues, and people who work within the care of the elderly, and our general practitioner colleagues can look at how you can do that across the UK. We must have a unified strategy for providing support for the optimisation of medicines, such as where we see five or more different drug and disease interactions which have a profound impact on people's lives. Some 6.5% of hospital admissions are related to adverse drug reactions, and that amounts to about 8,000 hospital beds. That is hugely burdensome, and I think we should invest in a workforce that is trained to deal with complications around polypharmacy.

Q184 **Baroness Rock:** I would like to move on to clinical trials. We have heard throughout that it is very difficult to conduct clinical trials into treatments for ageing, in part, because multimorbid older people are often excluded from them. In your view, is the regulatory environment in the UK supportive of biomedical research into ageing and the translation of that research into clinical trials? Also, if you were able to change the regulatory environment, where would you consider that changes need to be made?

Dr Sheuli Porkess: This is a really important point. It is all very well developing medicines, but if we do not know how they are going to work in older people, that is a problem. We have already started to touch on polypharmacy and unwanted side effects. I absolutely recognise the issue.

There are perhaps a couple of aspects to look at here. The first is whether, for trials in general, we are excluding older people for no other reason than their numerical age. There is evidence that that is happening. This is not just a UK phenomenon; it is a global phenomenon. The ICH has produced guidelines to help companies to overcome this and ask how they can get older patients in. The EMA has also identified this as an area of focus and has some guidelines. Given that this is a global issue, we would like to see that global thinking reflected within the UK. We are a global industry and we develop medicines to global standards, so having those global standards as part of how we do medicines is very important.

The other aspect is the specific diseases that occur more in older patients. We have heard quite a lot about multimorbidity already today. That is another area that APBI is working on. With that, it is not just getting patients into the trials; it begins even earlier by asking what the science is that we are trying to address and what we are trying to do here. We know that we cannot do that alone as ABPI, or even the industry. We have two memoranda of understanding. One is with Birmingham Health Partners, and multimorbidity is a key challenge that we have agreed to work on together. The other is with the AHSN

network; multimorbidity has been flagged by its members and we have agreed to work with it on this. Clearly, we will also work with all the other people in the sector, and the people we have heard from already today.

Dr Fiona Marshall: Quite exciting for me in the area of clinical trials is the development of digital technologies such as wearable devices, or devices you could have in your home to allow older people to take part in clinical trials without having to come into clinical trial study centres. We have just started to take part in a collaboration with Oxford University called OxQuip, which is investing in digital technologies for Parkinson's disease. I think this could facilitate more people entering trials, because it is not so onerous for them to do so.

We need the regulators to accept what we would call biomarkers of disease progression, or even biomarkers of ageing. This allows you to see signals from clinical trials, ahead of the more strict end-points of diseases. It is similar to the way in which statins were approved for cardiovascular disease just by lowering cholesterol, rather than seeing an end-point in a cardiovascular mortality trial. That type of thinking can be applied to diseases of ageing as well as to ageing itself, if you move on to there.

Something else we could consider changing is the length of patents for drugs that are developed for diseases of ageing, and ageing itself potentially. But given the length of time it takes to do these trials—and some of these compounds are being reprofiled and repurposed, if they are losing their patent life—extending the length of patents would be a significant incentive to help investment into these types of molecules.

The Chair: We have already alluded to the multiple pharmacological agents which older people with multiple diseases are subjected to, and the interaction of those medicines with each other making matters worse for them. What research is being conducted to understand the interactions in biological and genetic ways to find out which drug is more effective, which is interacting and what you have to do to reduce the damage of interaction?

Dr Fiona Marshall: That is a big area of unmet need. Again, it was identified in the multimorbidity study that there is very little research into the mechanisms of interactions.

The Chair: So there is no research conducted into understanding the effects of multiple pharmacopeia.

Dr Fiona Marshall: Certainly when you do a clinical study, you have to consider drug-drug interactions and do drug interaction studies before you progress into the clinical study, but not at the level of research that you are suggesting.

The Chair: The other question relates to Baroness Rock's question about clinical trials. Is the current methodology for evaluating drugs through the various stages of clinical trial appropriate for new drugs targeted at older people?

Jim Mellon: May I say something on this subject? The problem for us as drug developers is that looking at old age as something to be treated is very difficult, because we cannot hang around long enough commercially to sustain our companies. Every drug that may have a pro-longevity or pro-healthspan effect has to have a specific application beyond those two things. I mentioned age-related macular degeneration as an example of that.

The reason that has been used in trials is because the eye is a closed system, so the drug is non-systemically administered; it is the same with the knee. The idea, as Fiona mentioned, is to look at the hallmarks of ageing. There are nine established hallmarks of ageing. The patients who are treated are typically older patients, and in that sense these trials are useful, to see whether there is a reversal or a slowing of any of the hallmarks of ageing, at the same time as the patients are being treated for a specific disease. That will become much more important. AI is very helpful there. I believe we will find that, for some of these drugs going into trials at the moment, there will be some beneficial effect on the overall hallmarks of ageing that will push public policy in some countries towards using those drugs for longevity effects in the future.

Unfortunately, the repurposing of drugs has no money in it. Some philanthropists, including myself, have supported Nir Barzilai in his quest to see if metformin is a likely candidate to improve longevity. That trial will cost $50 million, and all the money has to be upfront. He now has the money, and is going to look at whether metformin works in elderly patients in a longevity sense, as opposed to just for diabetics at the early stage of their disease. It is very difficult. If Governments could sponsor some of these trials and take note of the hallmarks of ageing as adjuncts to these trials, that would be extremely helpful.

The Chair: I go back to my original question, Dr Porkess. For the drugs that you and your members may produce that are specifically targeted towards an older population, are the current methodologies of doing clinical trials through these different phases appropriate? For instance, is it necessary to do phase 1, 2 and 3?

Dr Sheuli Porkess: There are a number of areas we need to look at and improve. The first recommendation is the involvement of patients and public in the design of clinical trials—PPI, to give one of the acronyms. This is especially true when you think of an older population. It is about getting the perspective of patients, or older people who may be in the trial, on how the trial should be designed; for example, how many times should the patient go to see the doctor as part of the trial and what should be measured. That is one aspect; it means when you have more chance of patients coming into the trial and staying in the trial.

To build on Fiona's point, what you measure in the trial is really important. You have to ask: how can we have an agreement with the regulators, and also the payers, that what we are measuring as the outpoint of the trial is something that could become a licence and allow the payer to be reimbursed and for patients to have access?

The last point is the long-term follow-up. It is not just the trials up to the grant of the licence but what happens beyond that. The point was made earlier about the data system and joining up pieces of data within the NHS so that we know, once a patient is given a medicine and they go out of the pharmacy, what is happening, both from a polypharmacy perspective and to see whether the medicines are working as we anticipated them to.

Q185 **Lord Mair:** I want to come back to the point you made a couple of minutes ago, Mr Mellon, about what needs to be done to strengthen the UK's position in this field. Is the UK well positioned to be the leader in the field of pharmaceuticals for ageing? If that is the case, what should the Government do to promote that leadership?

Jim Mellon: You have an extraordinary person in this country in the form of Sir John Bell. He is a very big advocate of what I have been talking about. I know he has some money to spend on trying to promote this area, so that is a start. I think the UK could be a leader, if not the leader, and certainly in the top three. We have competition from China and Japan, and of course the United States. The United States has the strongest nexus of venture capital. Unfortunately, venture capital in this country was very badly damaged by the antics of Neil Woodford and his company, and it will take some time to recover from that, in my opinion. We apparently have the strongest universities in the world, and we have the science. We have a very strong opportunity here. In my opinion, some of the stuff I said, and Fiona said, about making the trials dual-track trials would be very helpful, especially now that the UK will have its own regulatory system for medicines.

Secondly, it is important to keep an open mind. Everyone is very sceptical about the possibility of our bodies being bioengineered. I would just refer you to Pascal's wager, which is what it is: if this works, it is going to be a huge industry, and it would be a big shame if this country, leader in science as it is, missed out.

Lord Mair: But is it not true that, by and large, venture capitalists in the UK are much more risk averse than in the US?

Jim Mellon: I think they have been badly burned, to be quite honest, by a number of companies here. There is not the pool, or the depth of experience, in venture capital. However, you should track on a chart the trajectory of money coming into longevity science—I would be very happy to send it to you. You will see that it is very similar to the early days of technology research in the 1980s. The money is coming in and it is coming in from all around the world. There will be successes in this area. The problem for us is that we do not know what will be successful, but we know that something will be successful in the relatively short future.

The Chair: To go back to the original question of Lord Mair, what is your view about what more needs to be done to make the UK a leader in pharmaceutical developments?

Jim Mellon: It is all about money. The amount of money I have is trivial compared to what the British Government have, or what big institutions such as Wellcome have.

At the moment, pharmaceutical companies are focused on the diseases that are apparent to us all—our own Biohaven has just released a new drug in the US this week, four years after starting from scratch. They are looking at the five key killers, including Alzheimer's and dementia, which I have my own views on; they are not looking at ageing as a single disease from which all other diseases cascade. That work could be accelerated if more money was given to academia and to research, and there was a smoother path to clinical trials. If the UK is going to invest in anything science wise, I would recommend it invests much more in the science of longevity.

Dr Sheuli Porkess: Could I share some recommendations that we have around improving the overall environment, specifically on clinical research and data? On clinical research, broadly the recommendations are: to increase investment into clinical research through funding of NIHR and other bodies; to simplify the processes for setting up and running clinical trials, which is building on work that is already ongoing; to build a workforce fit for the future, by plugging the skills gap and investing in training for the clinical research workforce; to embed patient involvement in clinical research, which I spoke about a couple of minutes ago; to ensure that we continue the high standards for research transparency that we have in the UK, and make those consistent with other countries; and to secure a UK-EU relationship on medicines and research that enables us to build on existing co-operation.

Our specific recommendations around data are: to reduce the fragmentation in the UK health data landscape; to increase efficiency of data access processes, and we heard about that earlier; to use the data to enable us to do trials better by looking at the design and feasibility of those trials; data transparency; and to use data to demonstrate the value of interventions. Clearly, those five recommendations must be supported by high standards of governance and a skilled workforce which is data-science equipped to attract and develop the right skills in the sector.

Dr Lauren Walker: May I add to Sheuli's point about workforce planning for the future? Much of the research will depend on access to patients through the NHS. Fiona mentioned looking at the populations which will derive the greatest benefit, and how we can recruit those people into clinical trials and access patients who have previously been neglected, such as elderly people within care homes, or people with multimorbidity. How do we think creatively about doing that?

We mentioned some of the problems around the knowledge that we have about polypharmacy in older people and the drug-drug interactions. It is largely because we are developing drugs in a much younger, healthier population, and so we look at safety in young, fit, healthy individuals. We do not have a strategy for how to convert that to somebody who is much older, physiologically frailer, and who takes multiple medications.

We have mentioned that we could incentivise that in a similar way to the paediatric investigation plans that we have, and extend patent protection. We should look at whether we should have elderly investigation plans, or multimorbidity investigation plans, where we ensure that we recruit a cohort of people into trials who are truly representative of the population we are prescribing to. I refer to the people I see in my polypharmacy clinic who have eight different conditions and take 15 different medicines, many of which interact with each other.

We need to look at the research readiness of the workforce. We know that people who are treated in big clinical academic centres have better outcomes, both in patient satisfaction and lower mortality rates. Those centres tend to be linked to universities, where there are lots of clinical academics with lots of research experience and experience as principal investigators. It happens less in the district general hospitals, and there is a feeling that PIs there have less experience of running clinical trials and so are not as research active. Making being an investigator part of a clinician's job plan, and really focusing on that, will help improve retention of the workforce and improve job satisfaction.

Q186 **Baroness Hilton of Eggardon:** The Government have set a target of five more years of healthy life within the next 15 years. At the moment, we have a widening gap between rich and poor, and a diminishing life expectancy among the poorest people in society. That is obviously going to work against the Government's plans. Is this target of five more years of healthy life achievable for the whole community? The technology and drugs you are talking about are expensive, and will therefore probably be more available to the richer parts of the community, and the gap may widen. Do you think the Government's target is achievable?

Dr Lauren Walker: We have to be mindful of the fact that healthy ageing is not just about the newer therapies but about having the expertise to tackle the existing problems that we face. Multimorbidity occurs earlier in people from more deprived backgrounds. We can take the example of the trial in the States around metformin. We recruit people at the age of 65 to see whether we can delay the onset of age-related diseases, but many of the patients I treat develop multimorbidity in their early 50s. We have to be very mindful to ensure that we include the cohort of people who have the most to gain, otherwise we run the risk, in my opinion, of health inequality.

Dr Sheuli Porkess: From a medicines development perspective, an increase of five years within the next 15 is challenging, because it takes 10 to 12 years to develop a medicine, if it does not fail along the way. Clearly, medicines are only part of this. As we have been discussing, it is about social interaction, exercise, diet and many other factors. It is a challenge.

On the gap between richest and poorest, we need to remember that patients are everywhere. Patients do not just live next door to the large research centres; they are everywhere. As part of the clinical research working group, working with different parts of government, the regulators and industry, we are looking at how we can find ways of

connecting patients with the research in a way that works for the patients. That is not the only picture. We then need to be able to get the patients access to the medicines that are right for them, and have ongoing review so that they do not end up with 15 medicines for eight conditions. It is definitely a complex problem and a challenge that needs to be met with a concerted effort.

Dr Fiona Marshall: A significant impact on this could be if we start to see some successes in drugs for neurodegenerative disease, such as Alzheimer's disease. Although there have been many failures, these failures have led us to a better understanding of the underlying mechanisms of the disease, many of which are connected to ageing. Age is, of course, the strongest risk factor for these disease areas. In clinical trials right now, in phase 2, new treatments are coming through for these diseases. We in the UK need to ensure that, if these drugs start to show efficacy and success, their access to patients is accelerated and that we do not delay approval and patient access. In the short term, that could have a very significant benefit on healthspan.

The Chair: What methodology could be used? We have always talked about the short term, but the time period is even shorter when you are talking about medicines that may benefit older people. The methodology we currently use to assess drugs is much more about longer-term benefits. What methodology would you suggest?

Dr Fiona Marshall: The pharmaceutical industry is looking at ways of trying to shorten the time to approval; for example, by combining a phase 2 and a phase 3 trial. That is one of the ways of shortening the trial. You have to then take on more risk, because one reasons you do it in a stepwise fashion is to build your confidence that it will be effective, rather than paying all the money at the start. It can be more costly, but there is increasing collaboration between different pharmaceutical companies now to run these big trials. We have already seen that in the oncology area; for example, MSD is working closely with AstraZeneca in combining drugs. I think combinations of drugs are going to be brought forward by the pharma industry.

The Chair: One side of it is the time it takes for the trials to be completed. That needs to be shorter, and that is the point you are making.

Dr Fiona Marshall: Yes.

The Chair: The second is the assessment of the efficacy of these drugs. The current methodology does not favour the use of drugs sooner. Am I right in saying that?

Dr Fiona Marshall: That is correct. At the moment, for example, in an Alzheimer's trial, you have to look at the baseline decline in cognition against improvement. That in itself takes a significant amount of time. The same would be true for basic measures of ageing. If you are looking at a declining baseline and showing an improvement, you need very large trials over a long period. That is why I referred earlier to some biomarkers that may show you a benefit; for example, in the case of

Alzheimer's, looking at the protein within the brain using a brain scan, you may see a benefit more quickly than you would see benefit on behavioural end-points.

The Chair: Do I take it you are suggesting that the methodology that NICE uses for the benefits of the drug needs to be different?

Dr Fiona Marshall: Ultimately, you need to still show a benefit on symptoms and a benefit in quality of life, but that could be done post approval. That would be one way of doing it. That would mean that people could get wider access to the drug and you could continue to collect data. I think you mentioned that earlier, Sheuli.

Dr Sheuli Porkess: A NICE methodology review is ongoing. We have given a number of comments to that review about how NICE can evolve its methods to reflect the technologies coming through; not just focusing on the traditional end-points, but looking more broadly to see how you can decide whether a medicine is cost-effective or not.

The Chair: Would you let us have that submission?

Dr Sheuli Porkess: Of course.

Baroness Walmsley: I would like to go back to something Dr Walker said a few minutes ago. If we have more multimorbidity at a younger age, we are likely to have more polypharmacy at a younger age. Could you comment on the significance of artificial intelligence as a tool, and whether it could be useful in rooting out some of the problems of polypharmacy without having to deal with actual patients? Can this all be done on computers once you know what the effects are of all these different medicines?

The Chair: Surely you cannot know the answer.

Baroness Walmsley: Is there potential for AI to get involved in this field?

Dr Lauren Walker: It is difficult, because it reflects what we do not know and what we could potentially model using physiologically based pharmacokinetic modelling. Take the example of the development of a new drug. Generally, we develop new drugs in young, fit, healthy people, and the safety part of the drug trial is done generally in young, fit, healthy men. We might then come to the conclusion that the drug we have developed has a wide therapeutic index and is pretty safe across a range of doses. However, when you then put that drug into a much older person, who is physiologically different, with lower muscle mass and declining renal and liver function, it may become what we call a narrow therapeutic index drug, with much more risk across the dose range. Added to that are the cornucopia of diseases and medicines that may be affecting the enzymes which process the drugs themselves. We do not have the information for an AI system to work with, because we do not conduct those kinds of trials at the moment. We do not look specifically at drugs in the old.

The Chair: So first of all we do not understand the mechanisms of the interaction of multiple pharmacology, as was alluded to earlier. Secondly,

we are not talking about artificial intelligence but machine learning, and we do not have the algorithms to put in for the machines to learn and to give us the answer. It has to be in the patient. An understanding of basic biological functions and the changes in the molecular structures that occur will be required before you go to machine learning.

Dr Lauren Walker: That is why I emphasise—as of course I would, because I am a clinical pharmacologist—that you need people who have medicines expertise. I am not a single organ specialist; my job is to look at medicines across all therapeutic areas.

We have some real challenges. We have super-specialisation, and that is fantastic. We have changed the way that we manage many diseases through super-specialising in certain prescribing areas, but the cost of that is that we are less familiar with prescribing in somebody else's specialty, and we end up with five different prescribers all prescribing in their area of expertise but with limited knowledge of how that affects the others.

Baroness Walmsley: So the answer to my question is no.

The Chair: It was always no.

Viscount Ridley: I just want to ask a question related to Baroness Hilton's question and which I asked a panel on a previous occasion. If we succeed in increasing the healthy lifespan of poor people, but we succeed in increasing the healthy lifespan of rich people even more, so that the gap grows, is that a success or a failure?

Jim Mellon: I presume that that would be a success in both categories, but it would not be very good for society.

The great news is that the period of commercial exploitation for drugs is about 10 years post the issuance of the patent. We live long lives, so if someone developed a drug that could keep us all alive in a healthy state, they would have only approximately 10 years—unless there were a lot of patent attorneys and so forth fighting about it—to exploit it. I always use the example of ulcer drugs in the 1980s. Those proton-pump inhibitors were really expensive drugs, as you may remember. My mother used to tell me that I would worry myself into an ulcer. Now no one gets ulcers, and if they do, or if they get acid reflux, they just buy Zantac or Tagamet over the counter for cents at Boots. The same thing will happen with drugs that may have a pro-longevity effect.

The ethics are very complex in this area. I would say, however, that gene therapy and stem cells will remain expensive whatever, and will probably be accessible only to those with money, or with health systems that are prepared to subsidise them

Dr Fiona Marshall: It is the role of government to try and smooth out the inequalities.

Q187 **Lord Browne of Ladyton:** I think my question has just been answered, but I will ask it again to give everybody an opportunity.

The Grand Challenge has a mission to extend healthy living by five years,

but it is also to address the health inequalities that we have. To what extent will biomedical research and development address that aspect of the mission, which in turn defines the challenge, as far as I understand it? To some degree, the last answers dealt with that, but I will give everybody an opportunity to make a contribution.

Dr Fiona Marshall: From a pharmaceutical point of view, the benefit of the NHS is that drugs are available to everybody in this country who is part of the NHS. You could argue that that is one way in which the benefits of research can be provided across the country. Clearly, the other areas are in the area of public health, such as education, food, diet and physical exercise. These are all interrelated with some of the mechanisms that we are looking at from a pharmaceutical intervention point of view.

Dr Sheuli Porkess: It is absolutely about bringing different parts of the sector together. As I mentioned earlier, we have a memorandum of understanding with Birmingham Health Partners. One of the things it has done is to bring together the NHS and the hospitals and the wider population of the West Midlands, so that when they think about research, they think about it from a very inclusive perspective. That kind of collaboration will enable us to do the right research.

Lord Browne of Ladyton: There is a strong thread running through the evidence we have heard, both written and oral, that it is the very opposite, and there is a danger of this sort of longevity research exacerbating inequality because it is likely to bring forward opportunities for the wealthy which the poor will not be able to afford.

Dr Fiona Marshall: I think we have heard exactly that. Many of these interventions could have a significant cost. Unfortunately, that is inevitable. It is like wealth itself: if you increase the wealth of the whole country, you also extend the wealth of the richest, and therefore inequality. This is a moral dilemma, I would say, and it is difficult for us scientists to fix that. All we can do is bring forward the opportunities.

Lord Browne of Ladyton: It does help us. If we want to engage with these moral dilemmas and recommend steps that will make the inequalities worse, we might balk at that.

Jim Mellon: Lord Browne, recently I visited Glasgow University and, as you know, there is a 30-year longevity gap in male life expectancy between those who live in the rich part of Glasgow and those who live in the poor part of Glasgow. The question was asked: why is that? It boiled down mostly to food consumption; to eating processed meat every single day, leading to colon cancer and other morbidities.

The fact of the matter is that, alongside this longevity science, there is a new food science. We will be growing food in labs for food security, and growing food that does not have antibiotics or hormones processes attached to it. That will be a key factor in a healthy lifespan in the next 20 or 30 years. That is another industry that I strongly advocate the United Kingdom should look at, because it plays to all our strengths and weaknesses, given that we import more than half our food.

The Chair: Most of that kind of food comes from the United States.

Jim Mellon: I am not talking about GM food, Chair.

The Chair: No, I am not talking about GM food. I am talking about food that has antibiotics or hormones in it.

Jim Mellon: It does, but I am saying that it is now possible to grow such food in labs without antibiotics, hormones, animal slaughter, intensive farming, emissions and all that sort of stuff.

Lord Browne of Ladyton: Perhaps the next time you go to Glasgow, you could let me know, and I will take you to parts of Glasgow that will show you what the problem is: it is poverty.

Jim Mellon: Which is partly related to food.

Lord Browne of Ladyton: We are getting into a chicken-and-egg situation. If you are poor, you cannot afford the sorts of foods that rich people can.

The Chair: Looking around, I see that we have exhausted everybody. Thank you very much for coming today. We appreciate it very much. You said you would send us a couple of things, please do so.