



Science and Technology Select Committee

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

Tuesday 29 October 2019

10.25 am

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Members present: Lord Patel (The Chair); Lord Borwick; Lord Hollick; Baroness Manningham-Buller; Baroness Penn; Viscount Ridley; Baroness Rock; Baroness Sheehan; Baroness Walmsley; Baroness Young of Old Scone.

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Questions 35 - 42

Witnesses

Professor Sir Michael Ferguson CBE, Regius Professor of Life Sciences at the University of Dundee, Wellcome Trust Board of Governors; Professor Dame Linda Partridge CBE, Managing Director, Max Planck Institute for Biology of Ageing, and Institute of Healthy Ageing, UCL; Professor Sir Munir Pirmohamed, David Weatherall Chair of Medicine, University of Liverpool; Professor Miles Witham, Institute of Neuroscience, Newcastle University.

USE OF THE TRANSCRIPT

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

Examination of witnesses

Professor Sir Michael Ferguson Professor Dame Linda Partridge, Professor Sir Munir Pirmohamed and Professor Miles Witham.

Q35 **The Chair:** Good morning, professors; these days, we are not allowed to say “lady and gentlemen”. We are live-broadcasting this morning on the parliamentary channel, so we are all going to be listened to by millions of people—I wish. If you do not mind, please introduce yourselves from my left first, so that we can get you on the record, and then say what you do—not at any great length, please. After that, we will move on to the questions.

Professor Sir Munir Pirmohamed: I am the David Weatherall chair in medicine at the University of Liverpool and consultant physician at Liverpool University Hospital. I am a clinical pharmacologist by background and have interests in genomics, personalised medicine and trying to understand the problems associated with polypharmacy and new-drug development in the elderly.

Professor Sir Michael Ferguson: I am Regius professor of life sciences at the University of Dundee. I am a biochemist and am particularly interested in translational research, taking fundamental discoveries and translating them through to prototypic drugs.

Professor Dame Linda Partridge: I am a basic scientist working on the mechanisms of ageing. I am the founding director of the Max Planck Institute for Biology of Ageing in Cologne and I have a part-time position at UCL.

Professor Miles Witham: I am professor of trials for older people at Newcastle University and the Newcastle Biomedical Research Centre. I work as a consultant geriatrician, looking after older people in clinical practice. I have also recently been appointed as national lead for ageing at the NIHR clinical research network, which helps to deliver clinical studies across the UK.

Q36 **The Chair:** Thank you. I will start with a question about ageing and diseases. Age is a factor in the diseases that we develop as we get older. Could ageing therefore be regarded, and treated, as one disease? What does the science say about the ageing process and disease development?

Professor Dame Linda Partridge: Ageing starts just after puberty, and I do not think any of us would regard getting slightly less good at tennis as a disease. But as the process proceeds through middle and older age, it is a huge risk factor for disease and, in its very late stages, could be regarded as a disease in its own right.

What has clearly come out of the underlying scientific work on the biology of ageing is that we can intervene to prevent aspects of the ageing process. No single intervention catches everything, but different interventions capture different things that go wrong. If we do that in experimental animals, we can prevent the diseases of ageing and they often have a much less unhealthy period at the end of their lives.

The Chair: So what is it about ageing that leads to all these diseases?

Professor Dame Linda Partridge: It probably kicks off with problems with the way the genetic material is replicated and packaged. Then things go wrong in cells; the powerhouses—the mitochondria—go wrong; the handling of protein and proteostasis goes wrong; stem cells lose their function; cells become senescent and damage tissues; and the whole systemic environment goes down, particularly with inflammation. It is a complex process, and we can target different aspects of it with different interventions.

The Chair: Does anyone else want to say anything?

Professor Sir Michael Ferguson: Linda has done a great job there. I would just say that the time trajectory of these things going wrong is not fixed. The ultimate programme is inevitable, but the trajectory and speed with which an individual progresses through these biochemical and cell biological insults that lead to multimorbidities can be modulated.

Professor Sir Munir Pirmohamed: That trajectory varies between individuals. We are not quite clear about the reasons for that. It may be genetic, but it may also be a lot of environmental and lifestyle factors, which all combine together to change that trajectory in different individuals.

Viscount Ridley: Professor Partridge, is there a hard dividing line between getting old and getting less young, if you see what I mean? Going into puberty as a child is a form of ageing, but getting Alzheimer's later in life is a different form of ageing. Can you draw a hard and fast distinction? Going bald, for example, happens to a lot of people, including me. Is that just maturing or is that a problem of old age?

Professor Dame Linda Partridge: Development and ageing are very different. The developmental process has a very well-orchestrated hierarchy of genetic control to make sure that the right things happen in the right place at the right time. It is a controlled, evolved process.

Ageing is not. It is a side effect. It is a failure of natural selection. We are living way beyond the ages we reached in our evolutionary past, and natural selection has never had a chance to make everything work properly for a 50 or 60 year-old. It is a process of rather random things going wrong that have never been corrected during evolution. They are quite different processes.

Of course, some of the things that happen, like baldness, are trivial; others are health threatening.

Q37 **Baroness Manningham-Buller:** First, I declare an interest in that I am chair of the Wellcome Trust and Professor Ferguson is my deputy, so we see a great deal of each other.

When we heard from the Chief Medical Officer a few weeks ago, he started to help us to think about how we should attack this subject. He made it very clear that one of his priorities was the fact that the NHS was

not geared up to deal with multimorbidity. Do any of our panel have any comments on that? The stage at which these multimorbidities begin to cause the deterioration of people's day-to-day lives is obviously of concern to this Committee. It does not sound as though the NHS is very good at being ready for this.

Professor Miles Witham: I agree. Historically the NHS was designed, or has evolved, to deal with single problems in single-organ systems. It has evolved to deal with episodic care. It is less good and less well designed to deal with chronic care. It is particularly poorly equipped to deal with multiple problems affecting a single person.

Multimorbidity is important and poses a challenge to the national health system. I will give a couple of illustrations of that. If you have six conditions, you will probably take two or three medications for each of them. Those medications are often prescribed with insufficient attention paid to what other specialists have said or what would be appropriate for the other conditions. It is very easy to end up on 15 or 20 medications, each of which has side effects and each of which interacts with the others. That leads to the issue of polypharmacy, which we will touch on a little later.

The other issue that is worth thinking through is the burden of care and the guidelines. Guidelines that are appropriate for the care of one condition may directly contradict the care of another. If you are under half a dozen different specialists, they will all believe that their guideline is the right one and must be followed. That can be very confusing for patients and can lead to harm due to conflicts between the guidelines.

Finally, there is the issue of burden. If you are a patient and you are having to attend appointments in six clinics, take 20 medications a day and undertake multiple, different self-care behaviours that have been recommended by your physicians, the number of hours in a month that that takes is truly enormous. A study in 2015 suggested that if you have six conditions and you adhere to all the guidelines, you will be looking after yourself—self-care appointments—for 80 hours a month. That is not uncommon and is a huge burden. That is, to a certain extent, a side effect of the way we have configured health systems at the moment; they are not well equipped to look after people with multimorbidity.

Baroness Manningham-Buller: Thank you. Going back from that, before we get to the chronic stage, is there evidence that if we were to treat some of the symptoms of ageing at an earlier stage, we could avoid some of these multimorbidity issues?

Professor Sir Michael Ferguson: Yes, there is a plethora of existing evidence from a number of different sources. Linda will be able to talk about the animal model studies in great detail, since she is the world's expert in that. Caloric or nutrient restriction in diets is known to be beneficial for the ageing process. Why? Because it hits a central biochemical pathway in all our cells; it affects a thing called mTOR. We understand some of the central biochemistry; things such as exercise, which activates AMPK, and dietary restriction, which modulates mTOR,

are things we understand. We understand what good things do in our biochemistry, so the question is: Could we also find chemical entities that would modulate those processes if people are not so good at taking exercise or restricting their diet?

Baroness Manningham-Buller: Do you think we might be able to?

Professor Sir Michael Ferguson: I think it is eminently feasible, yes.

Professor Dame Linda Partridge: As Mike says, mTOR is one of the central regulators here, and there are already clinical trials with drugs that tamp down the activity of mTOR. For instance, it has been shown that old people do not respond very well to immunisation against flu. If you give them a treatment of rapamycin—just a short, low-dose course—and then immunise, they show a much better immune response and fewer respiratory infections in the ensuing winter. It is coming in against a particular indication at the moment, but I am sure the trials will broaden to mild cognitive impairment. Periodontitis is another obvious target, because it completely rescues the effect in mice. It is coming with a very broad-spectrum protective effect. It is preventive, not treatment.

Professor Sir Munir Pirmohamed: I come back to multimorbidity and the impact on the NHS. We have done a small study with about 100 patients—larger studies are going on at the moment—looking at patients coming in through acute medical units with multimorbidity. When you evaluate them and look at what happened in the previous 12 months, they will have had three other admissions and at least four secondary-care appointments in the hospital. Every time they come in, the number of drugs increases by one rather than decreasing. That is a major issue, because it is very easy to prescribe drugs but very difficult to stop them.

Because of the multispecialisms we have, doctors, nurses and pharmacists are reluctant to deprescribe a drug when another clinician has started it. We need to change the medical model of care, from the highly specialised medical care model we have at the moment to a much more generalist care model with a multidisciplinary team that includes care of the elderly, people who know about drugs and general practitioners working together to tackle the problems. We need to think about how we develop our model of service for future years.

Q38 **Baroness Walmsley:** As Professor Witham mentioned, we move on now to polypharmacy. Why is it a problem, and does it pose particular problems for older people? In clinical trials, the patient group is often chosen rather narrowly and homogeneously. Is anybody doing a clinical trial with older people with multiple conditions, to identify any potential interactions between different drugs they are taking? How could pharmacogenomics be used to tackle some of the problems of multimorbidity in older people? Does that discipline give us any clues?

Professor Sir Munir Pirmohamed: Polypharmacy is a major problem. Most of the patients I see now are on 10, 15 or 23 drugs—a huge number of drugs to take, let alone to remember to take. Those drugs are used at conventional doses that have been tested in younger populations who

fulfilled exclusion criteria for trials. They have been tested in people who do not have multiple diseases, so when we use a drug at a dose licensed at the moment, we are often poisoning the elderly because of the dosing we use. This is largely because your renal, hepatic and other functions decline as you get older, and you have drug-drug interactions. To treat the elderly for the future, we need to think about how to dose them better. Paracelsus, 500 years ago, said that the dose is either the remedy or a poison. That is still true; we need to think about how we dose our elderly. They may require multiple drugs, which is important for treating their diseases, but we need to treat them with appropriate doses as well, which we do not.

Drug-drug interactions are a major problem in that population. At the moment, most drug-drug interactions are looked at as binary: one drug, a victim, interacting with a perpetrator. Actually, when you have 15 drugs, there are three, four or five-way interactions going on, together with your renal and hepatic functions, which compounds the problem and leads to the adverse drug reactions that are common in this age group and often not picked up in routine clinical care. Then the patients stop taking the drugs, which they really need to prevent their decline, because they are getting side effects. It becomes a vicious cycle, which we need to break somehow by understanding exactly how drugs are handled by the elderly in the face of multimorbidity.

Professor Miles Witham: Perhaps I could add one or two things to that. One of the key challenges for polypharmacy in older people is posed by the concept of frailty—the idea that, as part of the ageing process, you lose the reserve to cope with a stress, problem, injury or insult. If I were to get flu, I would probably feel unwell for a week. I would take a few weeks to recover and come back up to my normal level of function within a few weeks. If an older person with frailty were to get flu, they would likely be bed-bound. It may take them many weeks, maybe months, to recover; they may even have to come into hospital. They may never get back to their previous level of function. That lack of reserve for dealing with problems means that, if a drug causes a side effect or adverse effect, older people are less likely to be able to cope. That is one of the key points here.

That leads us to the points you raise about clinical trials. Historically, older people were explicitly excluded from clinical trials. Until a few years ago, it was very common to find protocols saying, “Nobody above the age of 65”. There were reasons for that. There was a perception that older people were somehow messy and spoiled nice, clean trials, because a lot of stuff happens to older people, especially older people with multimorbidity. They get ill; sometimes they die. They find it difficult to come to clinic appointments. If you are trying to do a trial, particularly if you are a pharmaceutical company for which time is money, that is all terribly inconvenient. So those people were not given the opportunity to take part in research.

Fortunately, explicit exclusion on the criterion of age is less common now, but unfortunately, people are still excluded because of multimorbidity, which means that the overall effect is the same. For example, in the real

world people with heart failure have an average age of 85. In clinical trials, the average age of people with heart failure is 65. That gap is extremely common, whichever disease you look at. The issue is that the evidence we gain from clinical trials—which is absolutely central to the practice of medicine and the delivery of effective, efficient healthcare—is not fit for purpose in many cases, because it does not apply to the people we are giving treatments to and having conversations with to agree on the best course of action. There are ways around this, but we need to be much more aware of this as an issue and work with investigators and industry partners to say, “Bring these people into trials. Accept that there will be some messiness and that you will probably need to bring more people in, and accept that the costs are likely to be higher”.

Clearly, people will not do this without some kind of incentive, and I do think there is a role for regulators here in making sure that the regulatory environment supports bringing older people, people with multimorbidity, into trials. It has been highly effective in the US in making sure that we study men and women in trials; the NIH mandates that, and it mandates that you bring enough men and women in to do sub-group analyses. Similar changes to the regulatory environment in the UK are probably part of the answer to unlocking this issue.

Baroness Young of Old Scone: There was a study—I cannot remember who did it—into prescribing errors and drug errors generally. It was fascinating, because, as well as there being lots of drug errors in the chain of prescription, dispensation and administration, the biggest drug error was that half the drugs were never taken. Presumably the confounding factors of multiple drugs are even more extreme for older people who get confused.

Do we envisage getting a personalised-medicine approach of a single pill tailored to your particular polypharmaceutical needs?

Professor Sir Munir Pirmohamed: It is possible that in the future we will be able to tailor the dose and the different drugs required in a single polypill. Technologies are already developing to enable the formulation and production of those kinds of medicines, even with the person’s name on it. Those technologies are becoming available.

Clearly there are regulatory and pharmaceutical issues that will need to be sorted out, but in the future that kind of technology will become widely available so that you can have that personalised polypill with the dose and type of drug that you require.

Professor Dame Linda Partridge: I just want to make one point about potential repurposed drugs, such as rapamycin, which might be used preventively. They are proving effective at much, much lower doses than are normally used clinically. So for the preventive side, I think the problem of polypharmacy will be much less.

Professor Sir Michael Ferguson: That is really important. If we project to a future where we are targeting some of the fundamental components along the pathway of genome instability, senescence, chronic

inflammation and subsequent tissue damage, we should get to a position where the number of medications needed to be taken is significantly lower. At the moment, we operate on a paradigm of one indication, one drug—or, even worse, one indication, five drugs—which is why people end up on 15 to 20 medications.

If we intervene in the central pathways that lead to these multimorbidities, we should take a much smaller number of chemical entities, so the drug-drug interaction problems will be significantly lower.

Professor Dame Linda Partridge: And the lower doses, at least some of them, are proving effective when taken very intermittently. There are quite strong memory effects for some of these drugs.

Baroness Walmsley: A very simple strategy which some GP practices are using to address the issue of polypharmacy is regular medicine reviews. I think these are normally done by the local pharmacist. Is the local pharmacist the appropriate person to do that? Is further experience or training required for clinical pharmacologists, and do we have enough of them?

Professor Sir Munir Pirmohamed: Pharmacists are very important for medication reviews, and obviously they can help in trying to reduce some polypharmacy issues. But when you have a very complicated patient with seven diseases and on 15 drugs, deciding which one to stop and having that conversation with the patient is quite complicated. That is where the multidisciplinary team, which includes care of the elderly, clinical pharmacology, pharmacy and general practice, is required. We do not have a model of care like that at the moment, but we should develop it for the future so that we can handle issues of polypharmacy at the primary/secondary care interface.

Do we have enough clinical pharmacologists? We do not, unfortunately. We have only 72 clinical pharmacologists in the country. We need many more, and I have been campaigning for that.

The Chair: You are one of them.

Professor Sir Munir Pirmohamed: I am one of the few 72 clinical pharmacologists, yes.

Baroness Sheehan: Professor Pirmohamed just answered this question, but to clarify, we heard evidence from the British Society for Immunology that aspects of pharmacogenomics are ready for implementation. However, the total number of clinical pharmacologists is small, so we cannot implement the testing that will enable clinicians to better identify patients who are most likely to respond. That seems a real shame.

Professor Sir Munir Pirmohamed: The implementation is critical, but it requires different partners to work together to implement it within the NHS. The genomics laboratory hubs that have been developed in England will be a critical part of that implementation. They will provide the laboratories to do the testing, but they do not have enough expertise to

interpret genetic variation in the face of reduced liver function and reduced kidney function. What dose and what drug do you choose for that patient?

That is where clinical pharmacology comes in, working with the genomics laboratories and being able to provide that interpretation and guidance so that we can use genetic testing appropriately. There are genetic tests that are already implemented in this country for pharmacogenomics, preventing serious side effects and trying to identify the correct dose, but it is done in specialist centres at the moment. Genomics England, the genomics laboratory hubs and NHS England are thinking about widespread implementation throughout the NHS so that all patients benefit and have equity of access.

The Chair: Professor Pirmohamed, can you quantify, or say anything about, incidence? If you take 100 patients who are on anything from eight to 16 drugs, how many will suffer what conditions? What will happen to them? Also, how serious will their adverse drug reactions be?

Professor Sir Munir Pirmohamed: Of the general population coming into hospital, 6.5% of patients are admitted because of adverse drug reactions, and 15% of patients develop adverse drug reactions while in hospital. At this very moment, at least 10 800-bed hospitals—8,000 beds—in the NHS are occupied by patients with adverse drug reactions.

That is a huge burden, and a report commissioned by NHS England found the cost to the NHS to be £1.6 billion. If you look at the age profile of those suffering adverse drug reactions, it is mostly the elderly on multiple drugs who are developing them. Here, we come back to the issue of getting the right drugs and the right doses into those patients to prevent that.

Professor Miles Witham: The only thing to add, perhaps, is that we see particular groups of older people—particularly those, as you mentioned earlier, who have cognitive impairment, who have dementia, who fall—who are almost certainly at even higher risk of adverse drug reactions, particularly because traditional ways of capturing adverse drug reactions do not always adequately capture the contribution that medications may make to things such as falls.

Typically, over half the number of people we see in a falls clinic will be on a medication that we know contributes to their risk of falls. Typically half of people in hospital who have delirium, a confusional state, have medications that are contributing to that delirium state. We know that that is a very dangerous state. It makes dementia more likely and means that people are likely to stay longer in hospital.

In the frailest groups—the most vulnerable groups—of older people, adverse drug reactions and side effects are even more of a problem.

Q39 **Baroness Sheehan:** I turn to the new medical treatments and/or repurposed drugs—we have already touched on rapamycin—that target the ageing process as a whole. It would be very useful to know in particular what aspect of the ageing process they target. I then have

another couple of questions that follow on from that.

Professor Dame Linda Partridge: We mentioned the central regulatory nutrient-sensing pathways—TOR, insulin/insulin-like growth factor—against which there are many effective drugs, including rapamycin. In my opinion, that will be the fastest route to tackling aspects of the underlying ageing process to prevent disease. That is the most practical one, and it is coming in already in clinical trials.

Slightly further back, there are senolytics—the treatment of senescent cells that are normally present during development and wound healing to remodel tissues and are removed by cells from the immune system as the wound healing or developmental event resolves but are not removed correctly as people age. They accumulate in tissues at quite low frequency, but they cause a lot of damage because they produce a secretory phenotype—it is called the senescence-associated secretory phenotype—which is damaging to the surrounding tissue. There is a lot of animal evidence that removal of those cells either genetically or by drugs can greatly improve tissue function and keep the mouse—usually—healthy for longer. There is a lot of interest in using those potentially in people.

The Mayo Clinic has just done a small-scale, non-placebo controlled clinical trial looking at idiopathic pulmonary fibrosis, for which there is no current treatment and which is a very dangerous condition. It has managed to reduce the number of senescent cells in skin in that treatment—it has not biopsied the lungs—and there was some indication of improvement in function. That may be on its way. Then things that improve the systemic environment, particularly the inflammatory environment, are certainly going to be protective. In the US, many spin-out companies are looking at those two aspects of ageing.

Professor Sir Michael Ferguson: I would say that we have some low-hanging fruit. The rapalogs, the rapamycin-like molecules, are doing extremely well because they turn out to have quite good properties at very low subclinical doses. One of the problems of repurposing drugs—it is a very popular idea to say, “Well, we’ve already got this drug, so we’ll just repurpose it”—is that the PKPD, the pharmacokinetic and pharmacodynamic, properties of molecules that have been developed for indication X are usually not appropriate for indication Y. That is the rule, rather than the exception. While repurposing can be very good for proof of concept, usually you have to go back and redesign new chemotypes anyway.

As Linda said, we are sitting on a fantastic hotbed of knowledge where we understand much more about senescent cells, the SASP process, proteostasis processes and so on. Within all those biochemical pathways are a whole load of valuable biochemical nodes that we should try to drug. It is just a question of getting on and doing it. When we do that and survey a number of those different biochemical nodes in these key core central pathways to multimorbidity, for sure we will come up with some useful therapeutic agents.

We should look for molecules that are like statins, molecules which are safe enough that you can give them in a preventive manner. We would therefore need to stratify patients and monitor them in some way to decide who needs preventive therapy; you would not give statins to someone without a high cholesterol number, for example. It would be the same thing. We need to develop the biomarkers as to ageing trajectory. If people look like they are ageing badly, that is when you should intervene with the preventive. But it would be one or two preventives.

The Chair: What does “ageing badly” mean?

Professor Sir Michael Ferguson: A lot of people die at the same age, but some live well and die quickly—that is a good trajectory. Others go into a terminal decline of picking up more and more morbidities and have a pretty miserable life. It is that extension of health span that we are trying to target with preventives, rather than lifespan.

Baroness Young of Old Scone: May I ask a question that I asked of one of our previous witnesses? If you are being treated in a way that we hope will become available to tackle the various factors along the pathway, so you end up with a better way of going, how do you go?

Professor Sir Michael Ferguson: Suddenly.

Baroness Young of Old Scone: From what?

Professor Dame Linda Partridge: The animal evidence on that is “don’t know”. For instance, with a dietary-restricted mouse, it is often very hard to say what it died of—it was fine one day and dead the next—whereas with the controls it is much more obvious what is going on.

Baroness Young of Old Scone: Are we not running the risk of some incredibly expensive end of lives being created?

Professor Dame Linda Partridge: Existing evidence suggests not, but, until we try, we do not know.

Baroness Sheehan: Could you address the advantages and disadvantages of repurposing drugs? The Innovative Therapeutics for Ageing Consortium, or iTAC, stated in written evidence: “The low hanging fruit”—an expression which you used, Professor Ferguson—“of repurposing would not deliver acceptable profits”.

Professor Sir Michael Ferguson: This is a complicated one. When you repurpose, the therapeutics are usually off-patent, so the incentive for the development side of it disappears for the pharmaceutical industry. On the other hand, if a new chemical entity is being developed ab initio, it has patent protection and is much more attractive for the pharmaceutical industry to develop it and deliver it into clinical practice. That is what that statement relates to.

The problem of repurposing is, as I said, that the molecules were designed for something else. When you develop a new therapeutic, you

have a target product profile: what should the medicine look like to be useful? If you were developing a therapeutic for a preventive agent for multimorbidities of ageing, your target product profile would be very specific about the pharmacokinetic and pharmacodynamic properties, and its safety profile would have to be exquisitely good. Therefore, you would end up with a different chemotype than if you developed it to a different target product profile. The problem with repurposing is that the molecules were not designed for that purpose and you can tell, because they are not very fit for that purpose.

Repurposing can be extremely powerful for proof of concept in very controlled clinical trials. You can show that it is pushing the biology in the right direction: "If only you could tolerate the long-term toxicity of this compound, it would be fantastic", which is a common outcome in new cancer therapeutics. It treats the cancer well, but it is horribly toxic. Those are the kinds of problems that you have with repurposing.

Professor Sir Munir Pirmohamed: Irrespective of all these difficulties with repurposing, if you found a repurposed drug and there were IP and patent protection issues, there are ways of overcoming them, from developing new formulations to developing combinations of drugs and so on. I guess it needs forward planning.

Professor Dame Linda Partridge: To take the example of rapamycin, which we have been discussing, the main company trying to develop that is called resTORbio in the US. It has used everolimus, which is very similar to rapamycin, but also its own proprietary chemical which targets the complex slightly differently. It has found that the combination is more effective than the off-licence drug, so it now has something that it can take forward and make money from.

Q40 **Viscount Ridley:** I do not think that I have yet declared my interests in this inquiry, so I shall quickly do so—they are pretty tangential. I am a fellow of the Academy of Medical Sciences, president of the Centre for Life in Newcastle—where my wife is a colleague of Professor Witham, albeit in a different institute—and an investor in a medical diagnostic start-up in Newcastle called QuantuMDx.

My question is pretty hypothetical, and Professor Ferguson has already trespassed on it. I want you to cast your minds forward to when we have developed effective senolytics, be it metformin, rapamycin or something different. How would you treat the population? Would it be those who are ageing badly, whom we touched on earlier, or would you imagine a time when we were treating everybody? At what sort of age would we treat people with such drugs? I know this is very hypothetical, but it would be interesting to get a glimpse of how that might look.

Professor Sir Michael Ferguson: I will start, but my colleagues, Munir and Miles, will probably have much more intelligent things to say. At the top level, let us look at the history of how therapeutics are rolled out and then implemented. Obviously, the ideal situation is, when you can, to stratify patients and give people a medicine only if they are going to benefit from it—the hypercholesterolemia/statin model is a good one—so

a lot of what I have been discussing about preventives will be dependent on having good biomarker diagnostics to stratify patients and decide when to put them on those therapies.

However, if we look at other situations such as HIV therapy, we see that people used to be treated only when their CD4 count was at a low level. It became very clear over several years that that was not a good thing to do and that you should test and treat as soon as somebody shows positive. They should be treated right away because you will reduce their subsequent decline very considerably.

I think that one has to wait for the data to come in on whether a therapeutic is sufficiently safe and beneficial to all before deciding whether you want to introduce it, almost like a supplement to normal life. All of us feel very queasy about that. The idea of giving a chemical entity to people who may not benefit from it is anathema to medical treatment. I will let the experts discuss that.

Viscount Ridley: You may feel queasy about that, but what about someone who is starting to go grey in their 40s and just does not want to. They go to a doctor and say, "I have heard about this drug". What is to prevent someone like that getting access to it?

Professor Sir Michael Ferguson: If it is a prescription drug, they will have difficulty accessing it over the counter.

Viscount Ridley: Why? Because we know best, or what?

Professor Sir Munir Pirmohamed: You always need a conversation between the patient and the doctor, looking at the benefits and the risks. I agree that sometimes the earlier you give a medicine the more benefit you will have. However, the down side of that is that you have to take it for decades. Therefore, you need to make sure that the benefit risk of that drug is absolutely positive and the risk side is minimised.

The critical issue will be: do you have a statin-like drug that you can give to almost 30% of the population? We have heard today, and you will have heard in other sessions, that ageing is a complicated process. Multimorbidity is complex and different people have different types of it.

We need to think about our stratification biomarkers which allow us to say that this person has one type of ageing process and that person has another. Then we can personalise the medicine that we give, based on biomarkers, to make sure that we are not giving the same drug to everybody, because that is not going to work: it is going to have a very small effect size. If we can identify the strata, we can personalise the medicines in those strata to get a much better effect in particular populations.

The Chair: Let us simplify it. I heard you say, as others have said to us, that cell senescence is the primary aetiological factor in all diseases because it sets up an inflammatory process, and that those with certain conditions and lifestyles, such as obesity, are more prone to certain

diseases such as diabetes. So why would you not give senolytic drugs as a preventive drug to people at higher risk of disease developing because of senescence?

Professor Dame Linda Partridge: I think you are asking a question about medical policy rather than underlying mechanisms. From the animal studies—

The Chair: Does the science suggest that that would be a good thing to do, in policy terms?

Professor Dame Linda Partridge: Yes, it does.

Viscount Ridley: We are in a sense talking about supply, but what about demand? Is it possible that the medical profession will be overwhelmed with demand for these drugs once they show effectiveness?

Professor Miles Witham: That very much depends on the risk-to-benefit ratio. If these drugs are proven safe over decades, I am sure that the demand will be enormous, depending on cost, of course. If these are drugs that either lack evidence or have significant side-effects, for instance cancer 10 or 20 years on, I do not think there will be the demand for them.

There is a potential issue here about a sweet spot to be targeting, at least in the first instance. These are people who are not well but are not too frail or multimorbid. They are people at higher risk of accelerated decline or ageing, for whom we can potentially demonstrate a net benefit in a relatively short window—within five years, say. They may be the first group we need to look at targeting.

The other advantage of targeting that group is that they have more to gain, because they have already started on that slippery slope, but they are not so frail that they will not be able to tolerate side-effects from these new agents. If you are very frail, you have very little reserve. As we said earlier, if you put an anti-ageing medication that has side effects on top of another 12 medications they are already taking, they are likely to run into problems. If you have only one or two underlying conditions and are relatively well but just starting to decline, you are likely to tolerate it better.

Viscount Ridley: Did one of you not say that one advantage could be that these things would make it less necessary to take lots of specific drugs?

Professor Dame Linda Partridge: Yes, I think that is true. The other thing about senolytics is that you would almost certainly want to use them in a pulsatile, intermittent fashion: clear out the senescent cells then take the person off the drug. You would not want it continuously because the cells are important in wound healing, tissue growth and regeneration. This would be a quick blast and then a gap.

The Chair: Can you measure senescence?

Professor Dame Linda Partridge: Yes, you can measure the presence of the cells. They have a characteristic phenotype that can be monitored, so you can tell what frequency they are at in a person's tissues.

The Chair: And it is quantifiable? So if you are a five you are not too bad; if you are a 10 you are pretty bad?

Professor Dame Linda Partridge: In mice, they go up to a maximum of about 15% of the cells in some tissues.

The Chair: And you can do the same in humans?

Professor Dame Linda Partridge: You are not going to harvest some tissues from humans to monitor their health, but you can, for instance, do a skin biopsy or look in blood.

Baroness Young of Old Scone: Do you think any of the technologies that you are talking about will help the Government meet their big ageing challenge target of 2035?

Professor Sir Michael Ferguson: Only if we get started now, because new therapeutics take about 15 years. We need new therapeutic agents which target these central pathways, such as cell senescence and SASP processes. If we start now, we can have them rolled out, properly clinically trialled and entering clinical practice.

Baroness Young of Old Scone: But it would not give an extra five years of healthy, independent life by 2035, because we would not have had long enough.

Professor Sir Michael Ferguson: No, it would not, but people beyond that date might well benefit from it.

Professor Sir Munir Pirmohamed: But other things can happen at the same time, including changing models of care, which might be able to provide that five years by 2035.

Professor Dame Linda Partridge: An awful lot can be done with lifestyles. An awful lot of the inequality in health during ageing is explained by lifestyle.

The Chair: So you are saying that both things are worth pursuing to meet the target, but that developing a science, with all its nuances, will take longer. Professor Pirmohamed, you are saying that we do have something that could be put into the strategy now that would help.

Professor Sir Munir Pirmohamed: There is no single, simple solution. We need to have a number of different pathways that can be implemented from now. Some will deliver in 2035; some will start delivering earlier. A combination of those will have the most impact.

Q41 **Lord Hollick:** If we are to achieve the target of five additional healthy years by 2035, it is important that the clinical trials go ahead as quickly

as possible. What changes need to be made to achieve that?

Professor Miles Witham: There are a number of things that we probably need. One is funds; there was a supplementary question about why most of the trials were taking place in the United States. There are a number of reasons for that. This is quite a high-risk area; venture capitalists have been active in it and Dame Linda will be able to speak better to that than I can.

We also need to get the right infrastructure and knowhow in place to make these trials happen more quickly. As I said earlier, older people have been neglected in clinical trials in the past. Bringing older people into clinical trials has its own set of challenges, and the old models of doing them will not necessarily suit us well in the future.

We need to get better at finding the right people and recruiting them at scale and pace, and making efficient use of routinely collected clinical data to collect outcomes. That will be particularly important in this field, where we are going to need to do follow up over a very long time. You cannot keep bringing people back every six months for study visits if we are going to do follow up over 10 or 20 years.

We also need to create a regulatory environment¹ that facilitates this work, that allows companies to get marketing authorisations for medicines with multiple benefits. Whether that is specifically as anti-ageing medicines is a slightly different question, but all those things need to come together. The National Institute for Health Research is certainly aware of these issues and has started a series of work streams to accelerate bringing more older people into trials and to reach older people who have been neglected, particularly those who may be housebound or in care homes who do not fit into our current models of delivering clinical trials well. We have been working on that actively in Newcastle recently and we need to accelerate that process.

Lord Hollick: Has anybody put a figure on the amount of money that should be put into research to have a reasonable chance of hitting the 2035 target?

Professor Miles Witham: I am not sure that money alone will be the answer to that. However, if you have some spare money, we would all be delighted to have it. I think money will be necessary but not sufficient to hit that 2035 target.

¹ About 10-15 years ago, we were having similar conversations about the lack of drug development of medicines for children. The situation has improved in the last 10 years through the use of incentives (for example increased patient life) for the pharmaceutical industry. In the EU area now, a new drug coming to market must have a paediatric investigation plan (PIP), unless the manufacturer can justify why it is not appropriate to embark on drug development in children. What if a similar scheme was introduced for the elderly so that every new drug had an elderly investigation plan (EIP)? This would help with new drugs coming onto the market, but of course would not help with drugs already on the market. There will be logistical and legal issues with introducing such a scheme but there is a precedent with what happened with children's medicines.

Lord Hollick: One thing that has come through in this and previous sessions is that lifestyle is obviously important, but preventive therapeutics are very important. What is holding up the deployment of preventive therapeutics?

Professor Dame Linda Partridge: One thing that would make a very big difference would be more co-ordination of the effort so that the contact between basic scientists and people running clinical trials is closer. I have been very struck by the difference from my experience in Cologne and here in London. We have a director of clinical trials in Cologne who is very proactive, going around talking to basic scientists working on ageing, and is very keen to implement trials, specifically preventively, against aspects of the ageing process.

As a result, there are trials starting there that are comparable to what is going on in the US. It has a lot to do with people and contact between people. Structural change in the way that ageing research and ageing translation in clinical trials are organised would make a very big difference.

Lord Hollick: What lies behind the prioritisation of ageing trials in Germany or the United States being more effective than in the UK?

Professor Dame Linda Partridge: It is just down to people and the way that science is funded.

Lord Hollick: Is there any institutional bias at all?

Professor Dame Linda Partridge: I think there has been a recognition by science policy setters in Germany for longer than there has in the UK of the importance of research into the ageing process itself and of translating the findings into health improvements for people. I think that concept has just been there for longer. If I had to name the person who introduced it, it would be Peter Gruss, who was head of the Max Planck organisation and decided that the one new institute he was going to found in his time would be on the biology of ageing.

Lord Hollick: Who is his equivalent in the UK?

Professor Dame Linda Partridge: It is hard to say, but there probably is not one.

Baroness Sheehan: Still on this issue, Professor, you spoke about bringing more older people into trials. Does that include people with multiple morbidities on many drugs?

Professor Miles Witham: Absolutely. There is no point bringing older people into clinical trials unless they have multimorbidity and polypharmacy, otherwise we end up with evidence that is not applicable. We end up with evidence applicable only to a very selective and healthy group of older people and they are not the group who need the services of the NHS and other healthcare systems.

We absolutely need to bring those people in, which is where the challenge is in designing trials appropriately to bring these people in. Getting the structures to deliver these trials for older people is necessary. My post as professor of trials for older people at Newcastle is, I think, the only one of its type in the country at the moment, but it reflects a growing realisation that we need to pay more attention to this issue specifically.

You have heard from Professor Chris Whitty about the importance to the NIHR of multimorbidities. Priorities are beginning to shift, and that process needs to accelerate.

- Q42 **Baroness Rock:** Dame Linda, you just mentioned the need for structural change in how we look at ageing research with better co-ordination. You mentioned that Germany and the US have their own national institutes on ageing. Does the UK need its own national institute on ageing to co-ordinate ageing research and innovation?

Professor Dame Linda Partridge: In short, yes, but a national institute of ageing along the lines you mentioned—the National Institute on Aging in the US, which is a funding and co-ordinating organisation and has been extraordinarily effective in taking the area forward.

I think most of us think that bricks and mortar are not what is required; what is required is much better co-ordination of the existing effort and better funding. I would say that, wouldn't I? But there is a particular thing with ageing: it is very difficult for young people to establish labs in the area for the first time. The research—or progress with it—tends to be rather slow, which does not play well to the career reward system or the funding system that we currently have. There needs to be some recognition of the peculiar requirements of this kind of work and appropriate funding for it, which should be rather more long term than is typical.

The Chair: So it is an institute that co-ordinates; it is a virtual institute rather than a physical one. Can UKRI not do this?

Professor Dame Linda Partridge: It has no particular priority for research into ageing at the moment. Unless there is that priority, things will not get co-ordinated properly; it is all very piecemeal.

The Chair: So who will do other aspects of ageing apart from this science of developing molecules, such as technology development and the social aspects—not social care—of ageing?

Professor Sir Michael Ferguson: The national institute can co-ordinate all these different arms. They are different pieces that need to be joined up: the social science aspect of ageing, the new therapeutics design and delivery for ageing, the assisted living and digital components of ageing—these are all extremely important and all need to go in parallel. Having a central national institute that co-ordinates and looks after that is really what you want, but it must have funding capability to commission and make sure that the right pieces happen—and they all need to happen at the same time.

Professor Sir Munir Pirmohamed: It is also important that our research is conducted in areas where there is the highest degree of deprivation and the highest degree of multimorbidity. That is different in different parts of the country, so it is important that we target the areas where there are population health priorities.

Viscount Ridley: I want to play devil's advocate on this for a moment. One of the things that keeps science honest is Professor A challenging Professor B from a different institution. Is there not some risk that, if you have one national institute of ageing co-ordinating everything, one theory will become dominant and the possibility of a radical idea coming in from someone outside the field might be diminished?

Professor Dame Linda Partridge: All I can say about that is that, looking at the track record of the NIA in the US, I would not describe the scientists working on ageing as a particularly concordant bunch. They are absolutely typical of scientists generally.

Viscount Ridley: So there would still be room for disagreement.

Professor Dame Linda Partridge: There are quarrels and rivalries and all the usual stuff.

Viscount Ridley: Good.

Professor Sir Michael Ferguson: One analogy, an international organisation rather than a national one, is Medicines for Malaria Venture, based in Geneva. It basically oversees the entirety of development of therapeutics for malaria for the whole world. That stretches right from taking basic science all the way through to new therapeutics and having a pipeline there, but also to delivery. It is involved in clinical trial design and the socioeconomics of getting new medicines to people. It does all that on a budget of \$80 million a year; it is pretty good.

Now, ageing is more complex than malaria—malaria is one thing—but the idea that you can have a central co-ordinating body is writ large in that kind of example.

The Chair: May I come back to what you said, Sir Michael, about calorie restriction, which we have heard about in other evidence? We have heard that it is crucial and we have an adviser who does not eat one day a week because he believes in your science. Is fasting for one day a good idea, as opposed to calorie restriction throughout the week? What is the science that says that fasting is a good idea? What does it do?

Professor Sir Michael Ferguson: Again, it all revolves around the central co-ordinating molecule called mTOR, which is the ultimate nutrient sensor of the cell. If you get dysregulated and you do not respond to that and take in too many nutrients, it drives all sorts of syndromes, such as type 2 diabetes, increases in weight and so on.

All caloric or nutritional restriction is doing is playing to that central piece of biology. The truth is that most people find it very difficult to achieve, because the human race, as a hunter-gatherer species, has evolved to go

out and eat what it can when it can. It is very difficult to roll that back—if I may defend all of us who do not do caloric restriction.

Professor Dame Linda Partridge: There may be some very interesting things still to emerge about diet. It is clear that is not just about calorie restriction; specific nutrients are important, especially protein and protein composition, which are beginning to look very important. That is relatively easy to modify. The time of day at which meals are consumed may also be very important. There is a very telling experiment with mice: if you restrict the hours during which they can eat to the hours of night, which is when they are active, they eat no less than mice who can eat whenever they like, but they put on a lot less weight and have a much healthier metabolic profile. There may be relatively simple modifications of food intake that can achieve many of the benefits of dietary restriction.

The Chair: So it is about calories and nutrition. Thank you very much, all of you, for coming today. It has been a most interesting session. I hope you also found it interesting.