

## George Ebers Transcript

### **Intro Comment**

Well thanks very much Elizabeth, this is the third time I've been in Perth. The first time was on my way to Melbourne, as a brief stopover there, the second time was taking my son to a hockey tournament just outside of Ottawa, and this is now the first time I've actually been to this Perth so thanks very much for inviting me to come.

Now this is the second time I've given this particular talk, the first time was in my traditional pre-talk nightmare a couple of nights ago, and my topic on that occasion was... the English summer (laughter). It was a very brief talk!

01:07

Now, what I'm going to try and do is give you some general background of how the Canadian registry got started, what were the key milestones in it, and I'm particularly telling you this story because I know that a registry is being put together here and those of us in the MS community worldwide think that its extremely important for a lot of reasons we'll go into.

So, this is a slide of Canada and all those little yellow dots which don't show up terribly well are all the university sites, there are about sixteen of them, and each one of those developed a clinic. The red arrow on lower right hand corner is just for orientation, Nova Scotia, which is probably the most familiar to people here

01:53

So the original clinic started out in Montreal in the early seventies, and then there was one in London, Ontario, and then, basically motivated by a 'need to' sort of attitude, all the other sites developed. I wish I could say it was all orchestrated and planned with this great grand vision in mind but it wasn't, it actually happened almost initially by chance but then once it got rolling it really got rolling and I'll tell you the reasons why, the first research question was posed in 1981 and involved four sites, and subsequent to that it took a series of good questions to keep it going and it turned out that, as it happened, we were able to come up with questions which required just a slightly larger sample than the previous one.

02:41

So we needed a thousand patients to do a really good study of the natural history of the disease which we carried it over about twenty-five years. When we had five thousand people with MS, we could do a big twin

study which we did. When we had ten thousand we could repeat the twin study on a second five thousand, and we could start to do studies of relative pairs and particular siblings that both had MS. When we had fifteen thousand patients we could do a study of adoption, and I'll show you that in a moment. When we had twenty thousand we could do a study of half brothers and half sisters which turned out to be extremely important, and then we had twenty five thousand to assess the inheritance pattern of the disease which we'll talk about in a moment, and then we had thirty thousand and we could do some other really interesting studies, in this case, the one we've most recently completed, are studies of doubly discordant twins where one has the disease, one doesn't (these are identical twins) and they're discordant for having been exposed to a particular virus. So you might see immediately the strategy here, you've got a pair of identical twins, one has MS one doesn't, one has had viral antibodies or infection with a virus and the other one doesn't and that leads to the question if this is true, then which one has the antibodies to the specific virus? Is it the one who's got MS or the one that doesn't have MS? And it turns out it absolutely kills a few candidate viruses.

So the virologists started hating us with the publication of step 2, and each subsequent study hasn't helped this but there's nothing we can do about it!

04:13

So there have been a lot of key patients that have been incredibly important in all of this and I'm going to list some of them here because I think they might illustrate to you how clinical research actually gets carried out, because I think it's practically meaningful.

So, the first patient who got me interested in MS was a young woman who was in her early twenties. I was a Registrar then in New York City, and she was the same age as me - twenty four. She didn't have much family support, and she evoked a lot of empathy. I felt, well I'd like to be able to solve this problem and that I'd go home this weekend with lots of clues and then maybe by the end of the weekend I'll have it all sorted, and of course that didn't turn out to be the case! However, I subsequently discovered that my Aunt had very severe MS, and I didn't think much of it because I had had no contact with her really, but I'm sure in the back of my mind it must have had some influence.

Now the next pair of twins that had an impact were the ELG twins and they were quite incredible. They came to see me one day, they were obviously very, very different, one was about three hundred pounds and the other was about seventy pounds. And I'd never seen anything like this, they said they were identical and I said 'I don't think so!' (laughter), but they were right, they were

identical and they both had an eating disorder and it just happened they were on the wrong cycle; one was on the bulimic side and the other was on the anorexic side, but at various times they do intercept. It was quite remarkable. One had MS, and then the other one got MS and so I remember thinking at the time, what an extraordinary sample this is and how much we can learn from twins.

05:56

The next pair of twins were from Western Canada, one had MS one didn't, and one was gay and the other one wasn't. It was very obvious they were identical in every way except there were some differences in mannerisms and so on, and I can remember thinking 'Boy this is so incredibly interesting this obviously has to be biological' and we never really pursued that very much except that it was another indication of the power of twin studies.

The next one was a family that came to my attention because the Mother's husband was a scientific colleague of mine. And she came to see me one day and said that she had had an extraordinary experience. She had MS (very mild) and she had recently been contacted by her daughter who she hadn't seen since she had given her up for adoption at birth. She was sixteen, unwed and it wasn't appropriate for her to keep it she thought, so she gave the child up for adoption and hadn't seen the child for thirty years when the child contacted her out of the blue, as is done these days frequently, and it turned out the child had MS too. So here's a pair who were separated at birth and raised apart. So I was thinking 'my, this is unbelievable', so I said 'well, oh gee' (I was trying to do some calculations in my head) 'do we have enough patients to do a study of adoptions?' and I said 'do you have any idea how many people are adopted' and she said 'well as a matter of fact it's 1.2%' and I said 'well gee, how did you know that?' and she said 'well, I'm the president of the Canadian adoption society'. She was incredibly useful as a resource as she allowed us to do a number of other things we wouldn't have been able to do otherwise and we'll talk about that in a moment.

07:40

The next one I call the 'Swooning mom' and she had two daughters with MS and she came to give blood as part of our genetic studies and she asked her daughters to leave the room and told me that she couldn't give blood. I said, 'Oh I'm sorry, are you sure?' and she said 'No, I get a terrible reaction when I give blood' and so on and so forth. So, I said fine and went up to talk to one of the daughters who I had looked after for many years and I said 'listen, it's too bad about your mom not being able to give blood', and she said 'what do you mean?' and I

said 'Well she says she gets a terrible reaction' and she said 'well she gives blood at the red cross every three months!'. So then a little light went on and I went back and talked to her and said well don't worry, this will be discreet so we took the blood and as you might guess one of the daughters was not the child of the husband's so it never went any further. But this gave us an idea and the idea was essentially; what happens when one parent is in common but not two? And it turned out to be extremely useful and you'll see in a moment.

The next one was a family that came from Western Canada and I will show you some slides of them and they are quite extraordinary and have some Scottish interests too and they've allowed us to have some insight into the inheritance of MS.

The next family was a family from Northern Michigan, and this family in four generations has nineteen people with MS. They're the only family in the world like this but there's no question it's MS (even though we thought that it can't be MS as MS never does this). This is the only family that anyone has reported and there are still some very interesting lessons in this family.

09:24

The final pair is a pair of identical twins where one has fifteen different conditions, largely unrelated, and the other has none and is perfectly healthy. So the question is: how can you possibly explain such an extraordinary event? We have an explanation but I don't know if we've got enough time to go into it today.

So, these are the things that one comes across in clinical practice that allow you to ask questions about research.

The final patient I'm going to tell you about is a patient that died recently whose name was Phyllis J. In 1921 aged sixteen she developed Optic Neuritis and her family was quite well off and she had some numbness of her fingers so the family shipped her off to the UK to see the famous neurologist Kinnier Wilson at Queen square. I think it was the Queen Mary she came over on. He said, according to her, 'You've got MS. Tough luck old girl! You'll be in a wheel chair in four years and dead in less than ten, so make the best of things'. Now, I'm doubtful if actually that is what he said, but she was a great performer. I used to bring her every year to the medical students and she would cackle in front of them. In approx. 1985/1990 she would say 'you know he died in 1954!' (laughter). So she left me her brain and spinal cord, dying aged 89. She had a modest limp, having outlived Kinnier Wilson by four decades, and we published her autopsy which showed she had three plaques, that's it! Her whole autopsy is quite remarkable.

11:01

So, this is some geography (we'll get back to these studies in a moment). Here's Australia, and this is where things start. There's a huge difference between the rates of MS in Tasmania versus Queensland (there's a five- or six-fold difference). The people that migrate here are more or less the same. This pattern is true virtually everywhere in the world it's been examined. There's a north-south gradient (or a south-north gradient in the southern hemisphere) and this can't be genes. Obviously it's going to be a big environmental factor. It's much more precisely illustrated in other countries, but before we do that let's look at the question of where this risk might occur. Does it occur within a family, or transmission from one person to another, or is it something more general? So this slide reviews the effect of sharing environment. So let's go through this:

11:58

The general population we encounter is 1 in 1000, so we're going to work back from adulthood in terms of how much environment you share in various types of pairs of relatives. So if you've got MS, the risk to your spouse is not increased at all, it's exactly the same as the general population. So clearly, you can't give it to your wife or to your husband. It doesn't influence your risk at all. That clearly is negative. If you look at the shared environment of being raised together versus being raised apart (half brothers and half sisters we'll come back to) it turns out there's no difference. If you look at birth order (some families in Canada have a lot of children, some have about twenty children. You've got some situations in which one child is born and the first child that was born to the family has already left the household so they've had absolutely no co-habitation) it turns out the risk for all these siblings is exactly the same. It doesn't matter if you're number twenty or number two, if the first one gets MS, it's the same. So again, there's no effect of shared co-habitation in childhood. So, let's go on to the next one. So what happens if you grew up with someone to whom you're not related? This is the standard adoption study which we did. It turns out that if you adopt somebody into a family and they're destined to get MS, your risk of MS doesn't change at all. By the same token, if you look at it the other way around, it's the same essentially; if you're destined to get MS and you adopt somebody into your family, their risk doesn't change. It's very clear that the intrafamilial environment is not playing a role. That's important because that leads us in a completely different direction to that which people have been going. The risk for step brothers and step sisters, again you bring them into a family in a second marriage and their risk doesn't change. So, we can't detect any effect of the shared family environment. So clearly, the environmental part, which is huge, does not operate at

the level of a family, or within a town, or within a small geographical area, it operates at a big macro geographical level.

14:04

So let's go on. We're going to go back to the geography for a moment. This is France and its various regions with the prevalence of MS all the way through the various regions on the right. If we superimpose the map of France, what you see in Red is the highest and pink is the lowest rates. You'll see there is a gradient to this. These people don't move much because this is the French farmers and their families who are looked after by a separate healthcare system, and they're incredibly stable, they just don't move. Why should they? It's nice out there in the French countryside! So, generation after generation they're there and so they're great for this type of study because Australia is the type of Country of migrants, Canada is a country of migrants and so, you need a country which has large North-South extent to do this. Clearly there's this remarkable gradient in France. This allows us to do some things, allows us to ask about things that relate to macro environmental factors that affect a country as a whole, and this is now looking at sunlight in February versus MS prevalence. On the left you've got the high rate which is the darkest, the lowest rate which is yellow. It's not just simple North-South as you can see, it wraps up around the Atlantic coast and we may come back to that. Here is what the ultraviolet radiation, or in this case, sunlight, looks like for France (data taken from Heliosat, which is a satellite that's been put up by the EU and has been up there for quite a long time, which calculated the amount of ultraviolet radiation at any given site very, very precisely). You can see there's a remarkable similarity of these maps. The yellow which is down at the bottom starts to wind up around the Atlantic coast, the green which is in the middle, and the blue which is in the North, North-East. So, the pattern/distribution of MS does parallel the distribution of ultraviolet radiation in terms of intensity. If you look more precisely at ultraviolet radiation with a different way of calculating it you get very similar results.

16:17

So, I think that there's no question that the cause we don't know absolutely, but this is now taking us away from the notion that it is something infectious and taking it towards the notion that of something that is abroad in the environment which operates at a population level. The best candidate for that is sunlight, and the best candidate among the sunlight ray of things is probably going to turn out to be vitamin D.

Now, if you look at Norway, this turns out to be a discrete exception which is particularly informative.

Norway is a very long thin country and has a national health system and it's been possible to calculate out the frequency MS in the various provinces of Norway, and there is not a North-South gradient. Here's Norway, the numbers going from top to bottom just to the right of the map, and surprisingly Finnmark which is the most Northern of the communities is a 86 per 100,000 but the highest rate in Norway is actually down the bottom in the middle in the land-locked Oppland (which is cattle ranching territory if I'm told). They have twice as much MS as up in Finnmark, so this can't be just sunlight.

17:30

Up at the top, there's no sun for two months of the year in the winter, that's how far North that is (I think you're a little South of that here). One of the possible explanations is this, (these chaps are very affectionate with their cod!) there's no question that they are exposed to much more oily fish which is a major source of vitamin D. So vitamin D is still viable as a candidate for an environmental factor in MS.

This is what's been going on in Canada and it's relevant to any kind of registry that's put together here in Scotland. In Canada, MS has tripled in the last three generations and we can show this because the sex ratio has changed. The people that are getting MS now are much more prominently women than men. It's now about 3.5 to 1 females to males, whereas sixty years ago it was almost one to one. It's been steadily increasing just in females, and parallel data is available for other places, and George Mowat-Brown reminded me of a paper that was done in Scotland back in the 1950s which actually showed the sex ratio here was about one to one. I don't know what the ratio is now, and that's one of the things the registry is going to answer, but it's definitely more than one to one. People suggest it's around three to one or more, so probably the same thing has happened here in Scotland.

18:55

Now, what we've been able to do in Canada is look at migrants to Canada and, I think there is no hamlet in Scotland so small that there is not a corresponding town, village, or city in Canada with the same name as far as I can see! When we look at migrants to Canada from Scotland, we get more or less the same pattern. The numbers are small, but people who come from Scotland and migrate to Canada have a sex ratio of about three/ three and a half to one, so I think the registry is going to show that for Scotland as a whole.

Let's look at the various events then that might be important so clearly whatever is going on is probably determined early and I say that because migrants to Canada from Southern Europe, which has a lower sex ratio

of 1.5 to 1, when they come to Canada they tend to maintain some of that lower sex ratio depending on when they migrate. So something happens pretty early and there are a number of things pointing to this, a lot of early life events, migration studies, we'll talk about half-sibs in a moment, there is a slight month of birth effect which you've probably heard about, and fraternal twin rate is higher than sib rate (which we don't have time to discuss).

20:15

So what is the inheritance pattern? Most people with MS don't have a relative with the disease, but in places where MS is really common, then something like 25% I would think in Scotland are likely to have an affected relative. So it's quite substantial. You can ask what the inheritance pattern is. It doesn't follow anything that we know of, it's something different. Yet there are fragments of things that we recognise, it's just that it doesn't hang together in a way that all fits together. It turns out that if you look at the risk for a brother and sister, which in Canada is 3.5%, it's identical to the risk for a parent and child. That's about 3.5%; if one has MS then the other is going to get MS about 3.5% of the time. It's not huge, but it's obviously increased over the general population rate by 35 times. That part looks very familiar, it looks like autosomal dominant inheritance, which means there's a dominant gene and the parent passes it on and half children are going to have that gene and they'll get the disease based on other things like environmental factors and so on.

But what happens? What kills this? The answer is it's totally untenable because if you look at the next generation it typically disappears. So we see very few families who have three generations of MS. Two generations; lots of them, three generations; very few, and four generations; none (except for that family I told you about in Michigan). There are almost no families in the world that have four consecutive generations of having MS. So how can you explain this? This is the family that is of interest to people here. I went to see them one day in February which was a huge mistake! They lived two hours North of Winnipeg, which is cold enough, but getting up to the Pegless Indian reserve in the dead of winter with about 4 feet of snow was extremely dangerous. In fact, I think I was about as close as I've ever come to cashing in my chips. There's nobody out on the road and if you spin out on a snow bank you could easily be there for several hours, before someone picks you up and it was about 40 below which is cold enough!

22:42

These are the two key people here. This is the son of the chief of Pegless Indian reserve. This chap was a legendary athlete and an extraordinary man in many ways,

and this woman was his wife and she was the daughter of the Scottish missionary who was sent to convert this Indian tribe. Her family were Acadian and they had eighteen children, and you can see these children here and they're a remarkable amalgam of the two parents; some look just like the Mum some look just like the Dad, and lots of people in between. I went out to see these people, which was quite a sociological event which left a deep impact on me. We were able to ask the question, does it matter which parent is the parent that expected is to carry the risk? Does it matter that the Mother is the Acadian and the Father is Amer-Indian and not prone to MS? What if it the other way round? What if the mother were Amer-Indian and the father were an Acadian? This gave us the idea of looking at this question in the whole population of Canada where we have lots of matings like this. It's quite skewed, it's a tricky study to do because it's not random by any means. As it happens there are many more cases in which the male comes from the susceptible side and the female comes from an Asian or Oriental side, but nevertheless you can correct for all of that and it turns out that the results were as expected from the half-sibs study (I'm going to show you in a moment).

24:20

But here you have this extraordinary family. They had six children with MS, and all children were seen by me when I went out there, and I was sat there scratching my head and thinking to myself 'this is such an unbelievable experiment of nature it surely must be telling us something important'. This is the next generation (people missing from this slide). One person in the third generation has MS among the 150 people that were present in the third generation, so 149 didn't get MS. So, what's going on here? You go back a generation and there are 6 cases and none of their offspring got MS (it was actually the offspring of one of the other unaffected children that got MS). So how do we explain this? It looks like in that family there was a very high rate but now in the next generation it disappears. This is a paradigm for what happens in MS in general. It disappears in the next generation, the third generation, it's present in the first, it might be present in the second (20% of the time max), and then it disappears.

25:26

Well, we'll come back to that. Now this is looking at a modern American family. These five teenagers were meeting for the first time on this occasion, they'd never met before. How many people think they look alike? They do. They're meeting for the first time because these five children have the same father who's the sperm donor. All had different mothers and that's why they'd never met. So they're all related to each other as half-brothers and half-sisters. This is the kind of family in

the future that will be possible to do such studies. But now we can't obviously do studies like that, but what we can do is take... because the divorce rate has been so high in Canada, approaching 50% (it's not that far from what it is at present in England) it's possible to find lots of people who are related to each other as half-brothers and half-sisters. So what happens if we have one parent in common but not two? You can ask three key questions: 1) does it matter which is the common parent? 2) You can look at the ones who are raised together versus those who are raised apart. Conveniently among half-brothers and half-sisters about half of them are raised together and about half of them are raised apart. The half that are raised apart usually have never seen one another because the parents aren't talking except through lawyers! (Laughter) The third part is you can ask how many genes are involved in determining risk, because the rate at which the risk drops measures that. So what do we find?

27:08

The half-sib rate 'raised together' versus 'raised apart' was identical. The pair of origin effect there is a significant excess of mothers being the common parent, so clearly the mother is contributing whereas the father is not (of course that's certainly true in general!). The third is looking at the full sib rate in half-sib families, and that turns out to be much higher than expected. It was 1.9% which tells you that there are not going to be many other genes, maybe a couple of tiny genes, but there can't be any other genes involved other than the ones that we already know of which are in this area called the major histocompatibility complex. Now, it turns out to be much more complicated than we thought.

27:51

Now, I had a personal interest in what happens when you have an affected aunt. So in Canada we collected all the cases in which we had an affected aunt and an affected niece or nephew, and an affected uncle and an affected niece or nephew, and we managed more than 1000 pairs and it turned out to be very interesting. Here we were able to ask what happens when the parent doesn't have the disease but the parent's brother or sister has the disease. Do we find the same thing with respect to this transmission coming through the maternal side? The answer is we do. This is unfortunately a rather complicated slide, but in essence that's what we found. A re-confirmation of the result found in the half-brothers and the half-sisters that the mother is contributing some special risk that we don't see coming from the father.

Now let's review what happens when we add in genes. So we start out with the general population rate of 1 in 1000. So if you've got MS the risk to your cousin in Canada is about 7 per thousand (even though you've never

seen them – doesn't matter if you've seen them or not!). Paternal half-sibs, or half-brother/ half-sister where the father is shared, is 13 per thousand. Half-brother/ half-sister reared apart is 21 per thousand. Maternal half-brother/ half-sister is 24 per thousand. Full brother/sister is 35 per thousand. So what we're doing here is serially adding in more and more genes that are shared. People are closer and closer in terms of their biological relatedness. Parent-child is 35 per thousand. If the children are HLA identical, which is they have the same gene region in common on chromosome 6 (which is known for thirty years), then it is 80 per thousand. If you look at the risk if the parents are first cousins it's 90 per thousand. If you look at the risk if both parents have MS, we've got about 30 pairs like that in Canada, it's 200 per thousand. If they're identical twins and one gets it, the chances are the other is going to get it is around 270 per thousand. If they're female, identical twins, and both parents have transmitted this gene (the MHC area) it's 450 per thousand. So, what this shows is that in contrast to the environment where we can show no effect of any shared environment, every time you increase the number of genes that are shared you increase your risk. So you could view this as 11 consecutive re-applications of the hypothesis that genes matter.

30:33

There are some other genes, they just have very, very small effects. Several of them have been identified in the last couple of years. This lists them: interleukin 7 receptor, interleukin 2 receptor, EV 15, CV-58, IRFactor, KI, and now the most important of these is an axonal gene which will be coming out on November 9<sup>th</sup>, which is a very important gene in terms of influencing the outcome of the condition. This is showing the dense screen of the genome and the one area that pops up is this one little area where this peak is around the MHC, the area of chromosome 6 called the major histocompatibility complex. It turns out we underestimated how important this gene region was, and the reason why was because we hadn't taken into account how these genes interact that are very close together. You can have the gene that makes you susceptible from one parent, but you can get another gene from the other parent that can block the effects of the first gene. So the presence of the gene isn't sufficient, you've got these interactions that take place and this is called epistasis. This just shows you the magnitude of the epistatic effects. So this is if you've got two copies of this allele 15, and this is if you've got 15 which gives you much risk here, but if you happen to have 10 with it from the other parent it drops your risk down to even less than what it would be if you had neither 15 at all. So this completely blocks the effect of that. This starts to give us some insight as to why this problem has been so hard to crack. Everybody has been looking at just the effects of individual genes, and

what needed to be done was to look at the interactions between them which is where the whole key lies.

32: 40

Let's go back to the family that was from Manitoba with the Pegless Indian Chief's son as the father and the daughter of the Scottish Missionary (Acadian father). We showed you that the risk was very high for the children - 6 of 18 children got the disease, but then it more or less disappeared in a generation of more or less 150 people. How do you explain this? The answer is that it has to do with something called epigenetics. For many, many years... how many people have heard of the term? ...Essentially, it is something that everybody pooh-poohed when I was a student and long afterwards, the idea being that genes can change and that this can be influenced by the environment. The idea was one of the central dogmas of communist theory. Stalin was very hot on this idea. He had a state geneticist, who promulgated this idea. The idea was that if you brought your child up to be a good communist then, whatever happened, that would be transmitted on to his/ her children. He was called Lisenko, and everybody detested Lisenko because he was obviously a puppet of Stalin and was saying things that surely couldn't be true... well, he was right - but, not about communism! Not about bringing up your children to follow it. What he was right about, it galls everybody to admit this, is that genes do change, and the way they change is by chemical modification of the DNA base pairs. So it's not the base pairs that change, it's the chemical modification which changes, which influences the regulation of the genes. This is very big; it's probably the biggest thing that has happened in human genetics in the past 50 years. That's a tall statement because some incredible things have happened! What's been realised now is that a lot of things that were heretofore unexplained are in fact explainable through chemical modifications of genes. Increasingly, a number of these things have been identified and there's very good reason to think that what happens in MS is that there is epigenetic modification, there's a gene environment interaction, the environment influences the changes in the chemistry of the gene and that influences the changes in the gene function. But, nature is clever enough to realise that it shouldn't leave this on because the environmental stress that the parent or grandparent was exposed to is quite possibly transient and therefore they shouldn't make any unrevocable error in the DNA code. This is the way nature does it and it's quite remarkable. You'll be seeing this term pop up in newspapers etc, but it's an important development.

35:38

Now let's look at something completely different. I told you that whatever counts for the environmental factor in MS has to be acting at a broad population level. There

are not many things like that. It's not likely to be, in terms of the Canadian population, diet. Diet is familial. There can be differences in diet as there are in Norway, people in the far North love fish, the people down South don't, but in the Canadian population there aren't those differences. So for the Canadian population there's not much left, there's climate. If it's climate, sunshine is your best candidate and among the sunshine related things the best things in terms of a candidate is Vitamin D for a variety of reasons. One of those is that Vitamin D is represented ubiquitously in your genome. So, we used to think Vitamin D had something to do with bone, but it has a lot more to do than that. You can find stretches of DNA that are responsive to Vitamin D, in terms of regulating genes, in 1000 human genes. That makes it the biggest gene family in the whole human genome, although it is rivalled by odorant receptors for historical reasons. So why is that? It's not although to do with bone and calcium. There are a lot of functions yet to be recognised about Vitamin D and people are just scratching the surface. However, it occurred to us that we could look at this stretch of DNA, which is remarkably consistent in human populations, and ask if there were any Vitamin D response elements (the name of this little stretch of DNA) present in the area that we already know is very important for MS risk. It turns out there is only one in this region, and it's immediately adjacent to the promoter (the regulatory part) of the main locus (region) that's involved with MS risk. This is what it looks like, and here's the actual code and what we see here is the transcription start site which is where the gene starts to be read out, and then immediately prior to that is the Vitamin response element. It would be cruel coincidence if this was just there by chance! There's much more to be said but I will summarise by saying that this is, circumstantial to be sure, but strong evidence that somehow Vitamin D is somehow wrapped up in the story and details need to be worked out.

It turns out that genes also influence how you do. It is in the last several months that this has become apparent. There are three genes that have been identified that are involved in influencing how MS turns out. Finally, some insight in to why some people do poorly and some people do really, really well, and it has to do at least in part with the presence or absence of these genes. The three genes are... the first one is some of the interaction within the MHC (which I talked about), the second is a gene called KIF 5, and the third is one coming out on Monday called KIP 1. So these identify for the first time a key mechanism in outcome. This is to do with axonal transport, which is the transport of little building blocks up and down the long fibres of nerves that are involved in producing disability in MS.

39:32

So this is the last slide... probably more than... Just returning to what Scotland should do. It's not for me to say, Scotland has to decide on its own! Whatever is done, I can tell you it's going to have worldwide implications and be very important. The highest risk of MS is here in Scotland than anywhere in the world. I think a registry is a great place to start and the best way to move forward is to develop some answerable questions that will keep the process going. That's the way it worked in Canada at least. The first question to address is why are women having a steadily increasing rate of MS? Obviously that is hugely important from a public health point of view. There are many other questions that will come to mind and, from the Canadian experience, most of those questions that we have asked that have given us some insight were not things that we would have imagined when we started. They were things that came up as we went along. You can't look forward. I didn't know what genetics was until a few years ago, so there's no way in the world I would ever have conceived of doing anything along the lines of what we're doing now 10 or 15 years ago. So the registry is a tremendous place to start because it really gets a lot of other things going.

That's all I have to say. Thank you!