



Webcast Transcript
Finding Answers for Progressive MS
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Webcast Moderator: Kate Milliken

Panelists:

Dr. Alan Thompson, Dean, University College London Faculty of Brain Sciences

Dr. Robert J. Fox, Staff Neurologist, Mellen Center for MS; Vice-Chair for Research, Neurological Institute, Cleveland Clinic

Dr. Riley Bove, Associate Neurologist, Brigham and Women's Hospital; Instructor in Neurology, Harvard Medical School

Dr. Bruce Bebo, Executive Vice President of Research, National MS Society

Presentation

Kate Milliken: Hello, and thank you for joining the National MS Society's live webcast titled Finding Answers for Progressive MS. I'm Kate Milliken, your moderator and I have been living with MS since 2006.

This week more than 100 scientists and researchers around the world came together here in Boston for the International Progressive MS Alliance Meeting, where they spent the last few days talking about finding solutions for progressive MS and discussing ways to collaborate globally to find the answers.

I was on-site and I found it utterly inspiring to see so many people committed to this work. Over the next hour, we'll hear more about the progress being made in the research and treatment of progressive MS from some of the top researchers in the field.

Throughout the live webcast, our panelists will address questions received in advance from participants online, as well as those received in real time during the webcast itself. Check your webcast screen now for information on how to ask questions during the panel discussion. We'll cover as many questions as we can. However, please note that we cannot answer specific individual medical questions.

Let's get started by introducing today's panelists. First, we have Dr. Alan Thompson. Dr. Thompson is based in the UK where he is the Dean at the University College Faculty of Brain Sciences. Dr. Thompson's research focuses on understanding what goes wrong in the body to cause MS, and is finding ways to measure the effective therapies being tested in clinical trials. He also focuses on rehabilitation research to manage and improve function. Thank you so much for joining us, Dr. Thompson.

Dr. Thompson: Thank you.

Kate Milliken: Next, we have Dr. Bob Fox. Dr. Fox is a Staff Neurologist at the Mellen Center for MS and Vice Chair for Research at the Neurological Institute at the Cleveland Clinic. Dr. Fox's current research focuses on clinical trials and innovative MRI techniques to evaluate tissue recovery after injury, and the effects of MS treatments, as well as MS patient decision-making and tolerance to risk. He is leading an innovative clinical trial at the potential nerve protection agent called ibudilast in people who have progressive MS. Thanks for being with us today, Dr. Fox.

Dr. Fox: It's great to be here.

Kate Milliken: Next, we have Dr. Riley Bove. Dr. Bove is an Associate Neurologist of Brigham and Women's Hospital, as well as an instructor in Neurology at Harvard Medical School. Her research is focused on the impact of sex hormones on the course of MS in women and in men, and the effects of aging, menopause and other factors on MS. Thanks for being here, Dr. Bove.

Dr. Bove: Thank you, Kate.

Kate Milliken: Last but not the least, we have Dr. Bruce Bebo. Dr. Bebo is the Executive Vice President of Research for the National MS Society and he oversees mission delivery efforts. Dr. Bebo leads the Society's global investment in MS research. He helped drive the creation of the International Progress MS Alliance and created critical collaborations worldwide to move research and treatment towards faster for people -- to move treatment faster for people affected by all forms of MS. Great to see you, Dr. Bebo.

Dr. Bebo: Thanks Kate. .

Kate Milliken: So, we're going to actually start with first name basis because it's better that way. And I want to start with you Alan because I think people really need to know what the International Progressive MS Alliance is. So, can you talk a little bit about what it is?

Dr. Thompson: Yes, certainly. I think I should set the context first of all. If you look at multiple sclerosis, it's a condition in which, over the last 10 years, we've seen the most extraordinary advances in treatment. Ten, 12, new treatments are available for people with MS, but there's a caveat that this is for people with relapsing-remitting – the early form of MS. If you look at people with progressive MS, and that's over 50 percent of the population, there are essentially no treatments available. And this has been one of the greatest challenges – and has been really for the last 10, 20 years.

So, the Progressive MS Alliance, as you mentioned earlier, is really to focus our attention on developing treatments for progression. And to do that – because this is the biggest challenge, probably the biggest challenge facing the MS world – to do that, we need to bring together everybody: all the key academics worldwide. The MS Societies have really driven this and focused on identifying what the blocks are to treatments and then actually getting rid of those blocks.

Kate Milliken: One of the things, when I had discussion about what it was with some of the researchers, they talked about not only the MS Societies driving it, but also that in different countries, there were patients that were pushing their countries to say, “Come on, we really need to get attention for this.”

Dr. Thompson: Well, yes, absolutely. Because ironically, every time there's a new treatment licensed for relapsing-remitting MS, people with progressive MS feel they're being left out, they're not being thought about. That's not the case. There's a lot of research going on worldwide, but until that research translates into a treatment, it says nothing. People want treatment. So, this is very much – if you do assessments across the world – this is very much what people with MS want us to be doing. So, there's unanimity of this, no doubt.

Kate Milliken: So, the conference was two days and what I felt was, it was like 100 researchers together – and the level of conversations and the people talking – I mean, you couldn't break them apart. So, what were some of the takeaways Bob that you found from what you saw?

Dr. Fox: Yes, there certainly was a lot of excitement and there was a lot of discussion not just during the sessions, but overflowing into the breaks and meals. There were four things that really struck me that came out of this meeting. One was a clarification about the active inflammation in early MS being very different and separate from the degeneration that we see in progressive MS, and clarification that they are separate although maybe overlapping in time.

Secondly, we identified about six or eight different mechanisms or explanations for what may be driving progressive MS - different cells that may be going awry or different pathways within the cells that may be going awry and are driving progressive MS.

Thirdly, we heard from people outside of the progressive MS field to learn lessons from other diseases and other methods that have been utilized to help understand the pathology in those other diseases that we hope to translate into progressive MS.

And fourthly, we heard from our industry partners who are actively engaged in progressive MS trials, trying new therapies and some of the scientific underpinnings for the treatment approaches that they are utilizing right now in progressive MS trials.

Kate Milliken: So there's really a breakdown of the kind of ways people could go, and that researchers could move on.

Dr. Fox: Exactly.

Kate Milliken: So, Riley, let's talk a little bit about the kinds of things that impact a person's disease. I know that some of your studies are based in hormones, let's talk a little bit about that.

Dr. Bove: I'm really glad to be able to talk about hormones because I think that observations relating hormones to MS course might actually hold some important clues as to what's going on with MS, and also how to treat MS. By far the best studied hormone in MS is vitamin D, and there are ongoing trials trying to establish really what the ideal level of supplementation--

Kate Milliken: There's been tons of press about that.

Dr. Bove: Right. Exactly. And, in terms of reproductive hormones, which is my area of research, this sort of started with the observation that women during pregnancy have a decreased risk of relapses, and then after delivery have an increased risk of relapses. And there are ongoing studies trying to establish what affect childbearing has, if any, on long-

term MS progression. And even more specifically, my research focuses on the bookends of a woman's childbearing years, so puberty and menopause.

With puberty comes an increased risk of MS for girls and then after the age of 50 or so – if you look at men and women – the sex differences between men and women's MS courses seem to kind of decrease a little bit, and it suggests that may be something about turning 50 in women might be removing some of the protection that they seem to experience earlier on in the disease.

Kate Milliken: Well, that seems quite interesting in light of watching women who actually have, let's say, started with relapsing-remitting then go into secondary progressive or progressive – that usually, or often, happens at an older age. Is there a correlation between menopause and progressive MS?

Dr. Bove: I think that's a really important distinction because if you're looking at longitudinal course, you're trying to disentangle the effects of age and the effects of the hormones. So, what we know is that around the age of 45, people with relapsing-remitting MS tend to transition to a more progressive phase.

If you look at menopause, which is when women's periods stop and that is associated with the decrease in the ovaries production of reproductive hormones, a lot is going on in menopause for women. So, you have sometimes an overlap of the menopausal symptoms and the MS symptoms, such as changes in bladder function. Is it the menopause or is it the MS? You also have some menopausal symptoms that can make MS symptoms temporarily worse. So, are your hot flashes keeping you up at night or hot flashes keep you up at night and the next day -- is the fatigue from those hot flashes or from worsening MS?

And finally, you have a lot of life changes that happen around the age of menopause. People may become empty nesters, or they may be grappling with mid-life crisis. And so for all these reasons, it's really hard to figure out what affect, if any, menopause itself has on MS course and that's what I'm working on currently.

Kate Milliken: Bruce, something else that's come up in the news, and people talk a lot about are stem cells. So, can you give us kind of the 411 on where we are now.

Dr. Bebo: Sure. First, I think it would make sense to define what a stem cell is. So, first, stem cells are unspecialized cells that live inside various, many tissues in your body and they're kind of an internal repair system that's there to help replace tissues and cells that are lost from various injury or age and they can, under certain conditions, become specialized. They can turn into, for example, a heart muscle cell or a skin cell or even a

nerve cell. And so this is a potential for the cells to promote repair, and we're leveraging this knowledge and this understanding of stem cells to use them in transplantation to try to promote repair in MS.

So, I'd like to talk about that specific study that just was published a year or so ago – and we talked some about at the meeting this week – about a certain type of stem cell that you can derive from the skin – from your own skin. This would have a benefit of being derived from your own body so upon transplant, it wouldn't be rejected, so there's a huge benefit there. Those cells were derived from the skin of a human at the University of Rochester and transplanted into a genetically mutant mouse that lacks myelin. This mouse is called a shiver mouse because the lack of myelin and the unprotected nerve fibers, these poor animals are shivering and they have a lot of problems.

So, this shiver condition was partially reversed by transplantation of these human myelin-producing cells derived from the skin, these stem cells and beautiful human myelin was made on these mouse nerve fibers in this -- in this model. So, it demonstrates a sort of proof of concept, proof of principle that you can transplant these stem cells and they can go in and they can wrap around nerve fibers and produce myelin and it was beautiful to a scientist, to see that beautiful looking myelin.

Kate Milliken: I love that you get excited about it -

Dr. Bebo: I do get excited.

(Laughter)

Kate Milliken: -- But I have to believe the audience is getting really excited, too. So, talk about that in the bigger picture of Progressive MS.

Dr. Bebo: Yes, so I think there are still roadblocks for translating that work into humans still, but--

Kate Milliken: Tell us what it could mean?

Dr. Bebo: So, what it could mean for people with MS – or progressive forms of MS – is that the loss of myelin around the nerve fibers contributes to the loss of the nerve fiber and the nerve cells, resulting in neuro-degeneration, which is what we think is driving progressive MS. So we think if you can either save that myelin or prevent it from being destroyed in the first place, or you can replace it with stem cells or in some other

fashion, that you could protect the nerve fiber and prevent or slow down that neurodegeneration and progression.

Kate Milliken: Because I know that myelin repair has been something that's come up a lot, is there anything, any of you want to comment on in terms of the progress and what you've seen in that domain?

Dr. Thompson: Well, I think there's been a lot of progress and there's work going on in many countries. We mentioned the States, and in Europe we've got a lot of work going on in the UK and in Italy, but it's very challenging. I think it's actually quite difficult to specifically get to myelin where you want to get to it in the human. Humans are a bit more complicated than mice and so the challenges are little greater. But, what we're trying to do is to bring together all the smaller trials and get a more meaningful read out – I think is the word you'd use – of the results so we can have a clear idea about just how useful it could be.

So, you know, repair alongside protection – neuro-protection – are the two key areas we're focusing on and I think there is progress, definitely, but it takes time.

Kate Milliken: I think that's so important, too, for people to hear because people are already debilitated and have the damage, really recognizing that as researchers.

Dr. Fox: The one thing that I think is really exciting is recently we've come to recognize that the cells that put the myelin sheath on, the oligodendrocytes, they are there within the brain even in very later stages of progressive MS, and seem to be trying to reach out and put the myelin sheath on the nerves but are somehow being inhibited. And to me, that's very encouraging that it's not that the cells aren't there and how would we get them in there, but that they are there and they seem to be trying to, but are being blocked by something. If we could figure out what is blocking them to sort of unleash them, to go do what it looks like they want to do, that may be a pathway for treatment.

Kate Milliken: So, Bob, another thing you're doing is a clinical trial with this drug, right?

Dr. Fox: Yes, ibudilast.

Kate Milliken: Ibudilast, thank you very much. And what I'm excited about when I heard this is I think that when people think about progressive MS, one of the common questions and the frustrations I have is, why haven't you found a drug to treat me? So, tell us a little bit about this one and what you're trying to do.

Dr. Fox: Sure, one of the challenges we have with progressive MS is to have a sensitive marker of promise for a therapy. In relapsing MS, we have new lesions on the MRI and it's a very sensitive and strong predictor of success in the later trials that are looking at relapses and disability. And so MRI is very powerful in relapsing MS, but new lesions aren't developed in progressive MS. And so we need to have a different metric, a different measurement stick of what therapy looks potentially promising. And so the trial that we're involved in, the SPRINT MS trial, being run by the NeuroNEXT network – and people can find more information at NeuroNEXT.org about this trial – is not just trying a drug, which I think is important, ibudilast, and we hope it works. If it does, we'll be excited but even more importantly, we are comparing five different imaging metrics, five different outcome measurement sticks to see which one is the best measurement stick in progressive MS. If we can figure that out, then I think we can make conducting Phase II trials in progressive MS better. In the sense that if we catch a fish that will be good, but if we learn how to fish better, that will be an even more important contribution to accelerate the development of treatments.

Kate Milliken: Alan, do you want to add to that about metrics?

Dr. Thompson: Well, I mean, I'd make two points. While I think the imaging metrics that Bob talks about are really important – and there's another group of metrics which measure what the patient thinks, what they feel, patient related outcome measures – and we've developed a number of these over the years, and they complement the imaging and so they're another integral part of the trial. But I was also going to mention that, alongside Bob's trial, there's another -- in the UK, which is looking at three drugs that are neuroprotective but, again, it's a new -- different trial design. It's – MS Smart, it's called – and it's trying to get a clear idea early on in trial which of these three. So, these three drugs are compared to that--

Kate Milliken: These are existing drugs?

Dr. Thompson: -- these are existing drugs, yes, and -- but it's comparing those three with placebo, but after one year seeing which of the three is the best and then moving that one on to the next stage. So, basically, it's looking at adaptive or new kinds of trial design that will get us answers more quickly. So that's, again, part of the -- it fits in very well with the Alliance, with the five pillars that we're working towards within the MS Alliance.

Dr. Bebo: And I think it's interesting to point out too, I mean, we heard about two different progressive, or trials in progressive MS, but they are two of about 40 or so trials testing different approaches. Neuroprotection is a major approach but there are other approaches and so there are over 40 clinical trials right now that are on record that

we know about and there are likely more that we don't know about at the moment. But there's a lot of activity in clinical trials for progressive MS.

Kate Milliken: That's awesome. Alan, I happen to know that you are involved with rehabilitation. What can people with MS do right now to try to make themselves better?

Dr. Thompson: Right. That's a good question. The first thing I'd say is that rehabilitation is absolutely central to our management of MS and it's one of, again, another key area with the Alliance's portfolio. And it's almost as important as medication. In fact, they complement each other. So, what we've seen in recent years is the importance of good quality of living, good diet, exercise. So, the old adage that exercise could be bad for you is gone. Exercise is very good for you in moderation, appropriately. And I think building that in your lifestyle is really important.

But there are also quite innovative and exciting areas of research around trying to harness the brain's plasticity – the brain's response to damage – to see if we could actually accelerate that; make more of it so that we lessen the impact of MS and that's all part of that rehabilitation approach. So, to me, it's the core. It's really no more than optimal management of your MS.

Kate Milliken: And this is a form certainly of wellness, of being better and feeling better. So, speaking of wellness, Bruce, can you tell our audience about the wellness initiative that's happening at the MS Society?

Dr. Bebo: Sure, I'd be happy to. So, you know, there are a number of environmental lifestyle factors that can influence the risk of developing MS or the course of disease. We know what some of these are, and we know that smoking can increase your risk for developing MS. We have evidence that childhood obesity can increase your risk for MS, and we talked about vitamin D a little bit. We know low vitamin D can increase a person's risk. And there's a reasonable amount of scientific evidence for those lifestyle or environmental factors.

We also know that a lot of people are trying diets and they're trying supplements and complementary and alternative therapies, and there just isn't much, as much, evidence for those as there are for some other therapies and environmental factors. And that is a tremendously huge gap in our knowledge of understanding, and that's a gap we have to bridge and we have to fix. And so that's the inspiration for the Society's effort to develop a strategy for research in wellness and lifestyle, and this effort launched a meeting that was held in November along with our leadership conference. We brought in about 60 thought leaders from around the world to discuss what do we know, what

we don't know, where were our big gaps, where were the opportunities we can make a difference in gaining knowledge about some of these ways of managing MS.

So, not only where these thought leaders and scientific experts and smart guys like we have in the room here, but they were also people living with MS and people that have experience trying some of these therapies that were part of this group. So, this is a group that's developing a strategy that the Society would be using to start making investments in research so that we can gain that knowledge that we need to bridge that gap. So, what it means to you and what it means to other people living with MS is that we're working on it. We're going to have more knowledge to inform people about making smart choices around wellness.

Kate Milliken: Yes, it's an interesting kind of juxtaposition of having somebody living with MS, including me, wanting to be proactive and wanting to do something now and then respecting the scientific world who doesn't want to give a bad piece of advice if something's not clinically proven. So, how do you find that balance? So, I think it's interesting that -- because I was at that wellness initiative -- hearing scientists understand that this is something opening their eyes and being open to it, but understanding of wanting to be sure that they proceed with caution. Or making sure that it's right, or that it works, and it won't hurt anybody, and everybody is an individual anyway just to add more complication to your pretty complicated lives. Riley, you spoke about age with your research but I'm curious about gender. So, talk to me a little bit about the men from what you've learned.

Dr. Bove: Yes. Thanks for bringing up the men--

Kate Milliken: Wait, they exist? (laughter)

Dr. Bove: -- about one quarter of patients who develop MS are men, but men tend to have more progressive disease and more aggressive disease and the question is why? Are there chromosomal factors? Is it different response to the environment? Is it difference in repair? I don't think we know enough about that. One sort of big question is, could testosterone actually have a protective role in MS course? And so we actually looked at men with early onset MS -- sorry, men with recent onset MS and in young men and we found that low testosterone levels in those patients was associated with worse disability.

And so the next step is really to figure out, is this an association or can testosterone actually play a role in protection in some way? There's a very small trial looking into this but a larger one is needed to really assess what the risks and benefits of testosterone treatment in MS men might be.

Kate Milliken: Anyone who wants to add to that?

Dr. Bebo: The only thing I would add is -- actually when I was still in the lab, I was studying this -- and this is in mice, so that's the caveat here -- but we saw that testosterone levels went really down during the acute phase of this mouse model of MS. So, that would sort of add, or be consistent with, what Riley's talking about, that inflammation leads to low levels of testosterone, and if testosterone is protective in some way, it would explain why men have more progressive disease perhaps than women would -- it's in mice and--

Dr. Fox: This is a critically important area because there is an imbalance of women getting MS more than men and why, and hormone status during pregnancy, the MS tends to get quieter and then rebounds after pregnancy, and the differences you cite between men and women. So, there must be something in there and I think the studies you're doing, Riley, are critical for us to understand that and to help perhaps develop some treatment strategies that can take advantage of those differences -- and find some new treatment that that we don't know about.

Dr. Thompson: I think the other point is that actually, that difference, is it is increasing? So, we're seeing increased incidence in women, so it's all the more important to try and understand what's behind it.

Kate Milliken: So, we have a question that has come in here and this is for Alan. There are number of questions coming in about the difference between primary and secondary progressive MS. Can we explain the difference?

Dr. Thompson: Well, so I think this can cause a lot of confusion and we haven't necessarily helped because we've used different labels and I think the first key thing is progression. So that's really what we are focusing on, and progression is a gradual deterioration over time that is unrelated to attacks. OK. So, that's progression and we recognize this can occur in two different situations. The first situation is after somebody has had a relapsing-remitting period of MS for maybe 10, 15, 20 years and then they notice this gradual change and that's what we call secondary progression. So, that's secondary because they've had the other phase before it.

And then a small proportion of people -- maybe about 15 percent -- have progression right from the very beginning, and they're often older, we say that equal gender -- there's no gender imbalance -- and that's what we call primary progressive because it is primary. Now, that's the distinction.

Probably the other important point to make is that we don't think that there's a fundamental difference between the progression in these two groups. We think the difference is more relative. So, if we find and understand progression and understand and learn how to treat it, it will apply to both primary and secondary progression then.

Kate Milliken: Awesome definition. Thank you. So, Bob, for you, where do people go for more information and to participate in clinical trials?

Dr. Fox: So, clinical trials are vitally important for us to learn new therapies and learn whether they are effective or not. So, there are several good places to learn about more trials. The National MS Society's website has a great clinical trial listing of MS trials. Also, there is a website that's run by the U.S. government called ClinicalTrials.gov that has a fantastic listing of clinical trials, and in fact, now investigators are required to post the trial on that listing in order to publish it later.

But it's important to recognize that there is more to MS research than just clinical trials. So, clinical trials are important but there are many patients who don't qualify for clinical trials or may not want to be part of the therapeutic trials. There are many other types of research that patients can participate in that aren't treatment trials. For example, many MS registries like the NARCOMS registry – which are opportunities for patients to report how their MS is and how they've done with different treatments, and how it's affected different facets of their life, which allows them to take part in research from the comfort of their living room, or their study, or their kitchen without having to go to a medical center or a university. So, there are many different ways to take part in research beyond just clinical trials.

Kate Milliken: So, I have one more question for you guys and we'll see if some other people put them in, but this person has put you on the spot: How close are we to an actual treatment for primary progressive MS? I feel like this is -- you probably get this question a lot.

Dr. Thompson: Yes, we do. And it's a really important question because as I've said people with progressive MS, primary and secondary, have been waiting for decades. There is a sense that we're in a place now where we haven't been before. We know much more with what -- we've gotten 40 odd trials. There are many others on the way.

Well, one is always careful about giving time, but this decade should see some real change and I would be amazed if at the end of that we didn't have two or three treatments. Some may well be drugs we already have that we now find are useful in progressive MS, and can be used for progressive MS, and perhaps one or two might be new agents that are coming through.

Kate Milliken: You know, I think as scientist, and I'll throw this to you Riley, the whole idea of when you're in the lab, doing what you're doing, how often are the people dealing with primary progressive MS on your mind?

Dr. Bove: It's a really great question. I think too often studies focus on patients with relapsing-remitting MS and up to now, the answers have been too hard in a sense for patients with progressive MS. I think that we're focused on treatments, or we're focused on hormonal interventions or hormonal observations. This can all actually apply very well to patients with progressive MS and so more and more we can actually involve them directly in our research.

Kate Milliken: Bruce spoke about the many clinical trials, which is such a great number. Alan, I'd like to ask you as the scientific lead of the Alliance, talk about some of the things that you guys are actually funding.

Dr. Thompson: Right, well I mean the aim was to identify the blocks. So, the blocks are around understanding basic mechanisms, designing early trials, identifying markers that we can use to get answers more quickly, moving on then into the larger trials and also sweeping up symptomatic management and rehabilitation.

So, what we've done – and we've only been around for a couple of years – what we've done is we've had a call for applications for awards that stimulate research, challenge awards, and we've made 22 of those last September at the ACTRIMS-ECTRIMS meeting.

Kate Milliken: Twenty-two grants were given.

Dr. Thompson: Twenty-two grants were given, and if you look at the range, those grants cover everything from models of disease and mechanisms, to looking at the trial design and biomarkers and rehabilitation. So, it's a very, very good range of the areas we want to target.

Now we've moved on from that to a second call, a much, much larger one, which is really collaborative networks. It's back to this feeling that if we're going to solve this, we've got to bring everybody together. It's critical, and that's how many other conditions have been solved in the past. So, these are big awards and we put out the call before Christmas. We were hoping we might get 15 or 20; we got 52. Huge applications involving about 480 investigators around the world, I think 24 countries around the world.

So you know, what's extraordinary about this and I'm slightly off the point, I'm getting overexcited but what's extraordinary, is the level of interest and commitment of the research community to this area. So basically, to go back to your question, we're really focusing on those key blocks and that's where the research is happening and these networks will then drive that forward.

Kate Milliken: I think it's awesome to hear the excitement because it sounds like in years past it was actually hard to kind of fill those grants, so that's great. Talking more about the holistic way of treating your MS, Riley, do you know whether or not what we eat can make a difference with MS?

Dr. Bove: That's a great question; it's a question that patients ask us all the time. And on a very, sort of intuitive level, it makes sense that what we eat would affect the immune cells that are lining our gut and would trigger an immune response and affect our MS. And it's sort of along that vein, that researchers are looking at the gut microbiome or the composition of bacteria in the gut and what role that may play in MS.

We also found that obesity, particularly during adolescence, may also be a risk factor for MS, but from there to say what specific nutrients or exposures might be that might impact our MS course, we don't know. So recent studies have talked about caffeine intake, salt intake, alcohol intake, sugared beverages, animal fats, we just don't know enough at this point.

Kate Milliken: Whether they're good or bad, right?

Dr. Bove: Right.

Kate Milliken: There was a recent study about coffee, is that correct Bob, can you fill us on that one?

Dr. Fox: Yes, so our Academy of Neurology meeting will have a report coming out from investigators at Johns Hopkins who looked at two different groups of patients. One, from an HMO in Southern California and another from Europe and looked at their coffee consumption in the 5 to 10 years before they developed symptoms of MS. And it found that drinking 4 to 6 cups of coffee a day was protective in the development of MS.

And it raises some questions about, OK, well then how might that be working and what might coffee be doing to exert a protective effect on the development of MS. Now, that's not to say, everyone should go out and start drinking 6 cups of coffee a day, and

some people will just be too jittery for that. But it does point us toward some potential mechanisms of what is leading to MS and then might uncover some potential treatments too.

Dr. Bove: I think that's actually really important because for the patients that we have in front of us, these are patients with diagnosed MS. And so, it's hard to make recommendations to them about what they should do moving forward. And so at least for now, in our center, we try to encourage generally a healthful diet, so lots of nuts, grains, vegetables, fruits and fish, and that's just for general health until we know more about whether specific nutrients will actually help patients long term.

Dr. Thompson: We can tell them and we must tell them not to smoke.

Kate Milliken: That has been proven.

Dr. Thompson: So, that has been proven beyond all doubt. I mean we know smoking isn't good for you anyway but apparently some people still do smoke.

Dr. Fox: And not only is smoking associated with developing MS, but it's also associated with its accelerated progression among those who have MS, which goes back to your point of, well for the people who already have MS, what do we tell them? And we do know for sure smoking accelerates the course of MS in those who already have it.

Dr. Bebo: And I was going to add, related to all of that, is the issue of comorbidities in MS and comorbidities being other health conditions that you're living with in addition to MS.

Kate Milliken: Give an example.

Dr. Bebo: So for example, type 2 diabetes, or cardiovascular disease or hypertension. So, these are other health conditions that we're learning can also accelerate the progression of MS. So, something like diet, a healthy weight could prevent, for example, type 2 diabetes or hypertension or cardiovascular disease, that could indirectly be a benefit to, you know, to slowing down progression that you might otherwise experience living with these comorbidities at the same time.

Kate Milliken: I felt like at the conference, that there was a conversation too about stopping progression and being preventative, right? On where do you put your strategy. Does anyone have a thought on that?

Dr. Thompson: Well, I think, and this goes back to when progression – when we think progression starts. And if actually when you – I mean leaving aside the clinical situation – if you look at what’s happening underneath the skin, so to speak, there’s a suggestion that there is an element of progression almost from the beginning, which doesn’t surface until a number of years into the MS – 10 or 15, maybe more.

So ideally, if you had something that you thought was going to influence progression, you would start it as early as possible and you would, by that means, prevent progression occurring. So, it’s a complicated business, but actually, if you have an effective treatment, you wouldn’t wait until progression starts.

Kate Milliken: Right.

Dr. Thompson: You’d do it earlier.

Dr. Fox: The challenge is studying that, because then you have to do clinical trials that are 5 or 10 years in length, which are very, very difficult.

Dr. Thompson: They are.

Dr. Fox: They are expensive and cumbersome to do, so it makes it tricky if the progressive part of progressive MS starts years before a patient manifests the symptoms. It makes it even harder to study this.

Kate Milliken: So on the subject of the clinical trials, I kind of wanted to go back to myelin repair. We covered it, but are there clinical trials, Bruce, that are happening with myelin repair now?

Dr. Bebo: Yes, Bob alluded to it to earlier. I mean, I think the promise that, for repair in addition to the stem cells is this promotion of what I like to call – I’m trying to spread this word of calling it – natural repair, the repair that is already going on in our nervous system. And a few years ago this was science fiction; this idea that you could regenerate any cells in your nervous system, and it turns out there are a fair number of cells in our nervous systems that have the potential to promote myelin repair. They’re called oligodendrocyte precursor cells, and I know it’s a mouthful. We just generally called them OPCs, so it’s not so hard to say or remember.

They’re plentiful, and as Bob mentioned earlier, they do migrate to sites of damage and early on in relapsing-remitting MS during those remission phases, those cells can actually repair myelin. And as time goes on, as you age and as you experience more and more relapses, the ability of the cells to repair myelin slows down and ultimately stops, but

again, what Bob mentioned was the good news is, those cells are still there. They still migrate; it's not a problem of migration.

They're still alive and viable, and they are there in the lesion but something is blocking them from remyelinating. And we're starting to learn what some of those blocks are, and I think of it as a balance between factors that exist in this lesion that promote repair and factors that inhibit repair, and as we've gone down the road, that balance has shifted towards the factors that inhibit repair.

So, the way we could fix that is we could either add some pro-repair agents on one side of the balance and tip it in that direction, or we could take away some of the factors on the inhibition side and tip the balance towards the pro-repair side. So, there is a clinical trial that just reported – actually a press release, not an official report – of an agent anti-LINGO, which is, LINGO is a factor that's been identified that's an inhibitor of the cells ability to remyelinate.

So, this is an inhibitor of an inhibitor, so it's a little bit like 'the enemy of my enemy is my friend.' And they reported a modest affect in optic neuritis, which is an early symptom of relapsing MS, but also a signal. Well, it remains to be seen when they report on it, on the scientific meeting and we can see more of the data but it's early -- there's a clinical trial of an agent that promotes repair. There's an ongoing clinical trial in relapsing MS with this anti-LINGO and a couple more trials are ongoing right now testing other strategies to promote natural repair.

Kate Milliken: So when somebody reports in a clinical trial, is that a phase III?

Dr. Bebo: So this would be when you're looking at efficacy and something in a population of patients that have the condition. That would be by definition a phase II study. And phase I, by definition, would be exploring the safety and the relationship between the dose and the levels in the blood or tissue in healthy individuals would be phase I.

Kate Milliken: So just to give people perspective, when you get a report of the anti-LINGO at the end of a phase II trial, and let's pretend it goes well, how much longer until it becomes something that might help the actual people?

Dr. Bebo: So then it would enter the phase III stage of drug development, which is testing in a large population of people living with the condition, looking still at safety but more looking at efficacy over a longer period of time to give us the best evidence we could possibly have for how it's going to behave when and if it gets approved.

Dr. Fox: It still takes many years unfortunately.

Dr. Bebo: Yes.

Dr. Fox: Particularly given that the progression of MS takes many years, and so to see an altering of that course of the disease, you have to follow patients for many years. The other thing I wanted to point out is that there's not just excitement about remyelination – that's one potential pathway – but there are other mechanisms in the brain that might be contributing, or perhaps even driving, progressive MS.

There is another type of cell called astrocytes that is the scaffolding of the brain, and there are some thoughts that might be causing problems in progressive MS. Another source of problems may be the organelles that are within the cells, called the mitochondria, which are the energy factories within the cell. That might be what is driving progressive MS. There is some inflammation at lower levels in the brain; particularly from B cells and that might be driving progressive MS.

So we're not just – we, meaning the researchers who are working on this – are not just looking at remyelination, although that's an important target, but are looking at many, many other potential avenues for helping progressive MS.

Kate Milliken: And that's what came out of this meeting also is the whole idea of really getting those set

Dr. Fox: Yes.

Kate Milliken: I called them pathways – I forget what you called them, but really thinking it through. Question from audience member. Cognition is a huge challenge for me, is there any new research in this area?

Dr. Thompson: Cognition is a huge issue in MS and, again, it's one that perhaps did not get much airtime until fairly recently. And in fact, some people didn't really think it was an issue because it can be often be so well covered up, but it is a huge problem and there's a lot of work going on both in trying to understand it, to understand the mechanisms, and a lot of imaging work trying to understand what causes it.

But also some trials – and there have been recently some very good trials – of rehabilitation in cognition that have shown, again, early small, early trials that had been quite encouraging, and the kind of strategies that you might be able to take to address some of this. Of course, this is not necessarily a very helpful thing to say, we really would want treatments to prevent this occurring, rather than slow it, delay it occurring.

Dr. Bebo: Alan can you talk about cognitive reserve because I think that's sort of underlying to what you said.

Dr. Thompson: Yes, I think that's one of the big developments as well, identifying the fact that we have a reserve and that, particularly if we've had a reasonable level of education, that reserve is built up and it gives you a flexibility. It gives you something to fall back on particularly, in relapsing-remitting MS. It tends to become less, you have less reserve over time and as your condition gets worse, but it is something you can work on particularly earlier stages of MS. So, yes, that's a concept, which you wouldn't have heard anybody talking about 5 years ago.

Dr. Bove: I think also it gets back to the importance of early multidisciplinary care and rehabilitative care for patients with progressive MS. Everybody, I think, over time has sort of a 'use-it-or-lose-it' component to all of their cognitive physical functions, and I think that I try to encourage patients – even every year, even if they haven't had a relapse, even if they have progressive MS – to reassess the potential for occupational therapy, physical therapy, cognitive therapy. Look for any obstacles in terms of their sleep, in terms of their mood, their family, their employment to really try to help our patients be at this very moment the best that they can be and to maintain that function.

Dr. Fox: So I get asked a lot about these games, like these video games and puzzles --

Kate Milliken: Any excuse to play Wii for some people... (laughter)

Dr. Bebo: So, I mean, was that something like some of these companies I guess that have some of these mind games and things, would that -- would that be something you would recommend do you think for people?

Dr. Thompson: I'd like -- I mean back to the point you made earlier, I'd like to see some of the evidence. So there is evidence for some approaches, which is quite convincing, but it doesn't mean all games.

Dr. Bebo: Yes, OK, fair enough.

Dr. Thompson: So, I think I'd be a little more specific about that and there is a good literature now.

Dr. Bebo: Yes.

Dr. Fox: Well, in figuring out what's causing the injury and stopping it, we have come to appreciate more in recent years the direct damage that MS has on the cortex, which is the outer covering of the brain. And that cortical demyelination is probably driving a significant proportion of the cognitive difficulties in our patients, and identifying how to measure that and finding therapies that prevent that cortical demyelination, I think, will be just as important.

Kate Milliken: I have another question in the queue for clinicians here. What is the question you get most from your patients with progressive MS and how do you respond?

Dr. Thompson: That's very easy for me. They ask why we don't have a treatment, that's the question that they always ask. And as I said right at the outset, each time we have a major new announcement of a new drug – and we've had, every couple of months there's an announcement – they come in and say, "is there any possibility that this could be useful for me?" And if not why, why are there no treatments for progressive MS?

My response is often quite a lengthy one. If you don't know the answer, you often have a lengthy response, but it's partly because it's very challenging as we mentioned, which is really why the Alliance is there and partly because it hasn't had the focus in the past that should have. There's been a huge focus on relapsing-remitting, but now the focus is completely, not completely, but to a large extent on progressive MS. So, people in the clinic in London where I do mine are hugely excited by that because it gives them hope, which they didn't have before.

Kate Milliken: Right, Robert?

Dr. Fox: So, I have some patients I think most commonly will ask me, "where are the treatments for progressive MS?" And I say, well there are treatments for progressive MS – not in the way they're thinking about it, in that I take this pill and my progressive MS stops – but there are some very clearly defined things that patients can do, including stopping smoking, routine exercise, managing their other medical illnesses, diabetes, obesity, hypertension.

Many of these things have been shown to accelerate the progression of MS. I had a patient just last week who said, "well should I go on this diet, would that help me?" I said if you really want to help yourself, stop smoking and get serious about that. He said, "well I don't want to do that, I would rather..." So there are some things that patients can do that I think they often are not realizing and reaching out and utilizing as well as they could.

Dr. Bove: I think on the topic of comorbidities, what several studies have shown actually is that people with more disability tend to be more behind on their other routine health maintenance. So, are they getting their mammograms, their Pap smears, their blood pressure monitored carefully and clinicians certainly play a role in that and patients also have to play a role in sort of advocating for themselves beyond just the obvious MS problems.

Kate Milliken: It seems --

Dr. Bove: We could be doing a lot better.

Kate Milliken: Yes, well I mean I currently do not have progressive MS, but I think there's a feeling of helplessness, right, that comes with, well I'm too far along, it's not worth it, whatever. And for me, having spent a couple of years doing these types of webcasts I think it is very clear that there is a shift and people are working on it.

You know, Bruce I'll ask you, do you think there is true hope and a possibility that there will be a cure in the next decade?

Dr. Bebo: I think my vision, rather than using the word cure, is that MS is going to look more like type 1 diabetes, where you take your insulin shot and you wouldn't know that somebody was walking around had that diabetes. And I think that's where we're getting. I would be willing to somewhat commit that in 10 years we'll have a treatment for not only relapsing disease but hopefully for progressive disease. We will have advanced to the point where we'll be taking a pill or a few or a shot or whatever might be and really be managing the disease.

There's this measurement that's getting used more and more often in clinical trials called disease-activity-free, which means no clinical signs of MS and no imaging signs of MS. And more often in clinical trials, there's a growing population of people in those trials that are responding to therapies in this disease-activity-free state. So, I think my vision is that we would be expanding, as time goes on, the numbers of people we can get into this disease activity-free state, and hopefully you wouldn't know somebody has MS just like you don't know from looking at somebody that has type 1 diabetes.

Dr. Fox: Well, right now when I see a patient who's just been diagnosed with early relapsing-remitting MS, say a 25-year-old patient, I will look them straight in the eye and say I am very confident, not 100 percent confident, but very confident that I can fully control your MS. It may take a couple of therapies for me to find the right one that works for you but I'm very confident that in short order I can get your MS fully

controlled. And I think in the next 5 to 10 years we will be able to do the same with progressive MS where we can say, yes, we have progressive MS but we do have treatments that can fully control the progression and I think that's on the horizon.

Kate Milliken: I'd like to have each one of you give a closing thought that you can tell our audience about where your mind is in light of what you heard today and also in this past week.

Dr. Thompson: So, if I'm to begin...

Kate Milliken: You are.

Dr. Thompson: I think that -- I just can't emphasize enough how things have changed and how progressive MS is now center stage, and I just keep reinforcing that. And as a result of that, we are going to see treatments, we're going to see drugs that are used for other conditions being used for progressive MS and we're on a totally different trajectory.

Kate Milliken: Great. Bob?

Dr. Fox: I think we -- the error we made in the past was we took what we found successful in relapsing MS and just slapped it on progressive MS. And what we realized is that was wrong, and we now have clarity. We have clarity as to the complete categorical difference of progressive MS from relapsing MS and we're getting better focus about what is driving progressive MS.

So as important as doing the right thing, it's also learning not to do the wrong thing and I think we're learning not to repeat the errors that we did in applying relapsing MS therapy to progressive MS and we have just much better clarity about our pathway forward now.

Kate Milliken: Riley?

Dr. Bove: I think that in addition to the really exciting developments in terms of treatments for progressive MS, the focus on the patient as a whole person and helping them be everything they can be at this very moment I think is really inspiring and sort of helps guide our clinical care.

Dr. Bebo: And I would just add to all these excellent comments that what I saw this week, and what I've been seeing over, I don't know how many years, is this breaking down of silos that there used to be a lot of competition and a lot of silos and a lot of

lack of communication between researchers and – clinical researchers and basic science researchers or even researchers in their own institutions – and that’s breaking down and we saw that today, this week at the meeting: this group of about 100 people really trying to work through this problem collaboratively. And I think I see a lot more collaboration than when I first began in the laboratory, and I think the Alliance is promoting that collaboration because that is one of the keys that’s going to get us down the road faster, it’s collaborating and talking and interacting with each other.

Kate Milliken: You guys have been awesome and, again, as somebody living with MS who also gets to be in the field and get to see it, I can’t express to you enough how much I feel it, and it’s really powerful. So, thank you.

I want to thank our panelists, Doctors Thompson, Fox, Bove and Bebo for being here today and for sharing your experience with us. I also want to thank you, our viewers, for joining us. If your question wasn’t answered, please speak directly to your healthcare provider or visit the Society Web site at nationalmssociety.org. You can also contact the Society’s Information Resource Center and speak with one of our MS navigators at 1-800-344-4867.

Please note that today’s webcast will be archived and available for viewing at nationalmssociety.org. Thank you all and goodbye from snowy Boston.