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Webcast Transcript

The Next Frontier, Understanding and Treating Progressive MS

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MODERATOR

Dr. Timothy Coetzee - National Multiple Sclerosis Society - Chief Research Officer

PANELISTS

Dr. Peter Calabresi - Professor of Neurology at the Johns Hopkins School of Medicine and the Director of the Johns Hopkins MS Center

Dr. John DeLuca - Vice President for Research at the Kessler Foundation Research Center and Professor of Physical Medicine and Rehabilitation and Professor of Neurology and Neurosciences at the University of Medicine and Dentistry of New Jersey

Dr. Daniel Reich - Chief of Translational Neuroradiology Unit at the Neuroimmunology Branch at the National Institute of Neurological Disorders and Stroke and Adjunct Assistant Professor at the Departments of Radiology, Neurology and Biostatistics at Johns Hopkins University

PRESENTATION

Timothy Coetzee: Hello and thank you for joining the National Multiple Sclerosis Society's live webcast, 'The Next Frontier, Understanding and Treating Progressive MS', coming to you live from New York. I'm Dr. Timothy Coetzee, Chief Research Officer of the National MS Society and the moderator of today's program.

Progressive MS is an important focus for the National MS Society. We take a comprehensive research strategy in funding projects around the world to stop MS, restore function and end MS forever for all forms of the disease, including progressive MS.

MS progression can be slow or it can be fast, but it occurs in many people who have MS, even in people successfully treated for relapses. Addressing the challenges of progressive MS is an urgent unmet need.

People with progressive MS often tell me that they feel like they're being ignored. While we understand their frustration, I wonder how many in our audience know that virtually every therapy available today for relapsing MS has also been tested in progressive forms of MS. Unfortunately, the treatments just didn't work in progressive MS. We're still not sure why they failed, but we're working harder than ever to overcome this hurdle.

During this webcast we'll address issues that we know matter to our viewers, such as why aren't there more therapies for people with progressive MS? Why is it so hard to understand progressive MS? And what's on the horizon for repairing the nervous system?

To help us better understand and explore these issues, I'm pleased to be joined by three panelists who not only recognize this important work, but who have played a significant part in advancing research, knowledge and clinical care. Let me introduce them.

Dr. Peter Calabresi is a Professor of Neurology at the Johns Hopkins School of Medicine and the Director of the Johns Hopkins MS Center. Dr. Calabresi is also the recipient of a five-year Collaborative MS Research Center award focusing on nervous system repair in MS. Welcome Peter.

Peter Calabresi: Thank you.

Timothy Coetzee: Next, we have Dr. John DeLuca. Dr. DeLuca is Vice President for Research at the Kessler Foundation Research Center. He is also Professor of Physical Medicine and Rehabilitation and Professor of Neurology and Neurosciences at the University of Medicine and Dentistry of New Jersey.

As an expert in MS cognition, Dr. DeLuca is training the next generation of experts in this field with the help of a National MS Society mentor-based fellowship in rehabilitation research. Thanks for being here, John.

John DeLuca: Happy to be here, thank you.

Timothy Coetzee: In addition, we have Dr. Daniel Reich. Dr. Reich is Chief of Translational Neuroradiology Unit at the Neuroimmunology Branch at the National

Institute of Neurological Disorders and Stroke. He is also Adjunct Assistant Professor at the Departments of Radiology, Neurology and Biostatistics at Johns Hopkins University. Welcome Danny.

Daniel Reich: Thank you.

Timothy Coetzee: So before we kickoff our discussion, let's talk a bit about what progressive MS is, which in short is any form of worsening MS. Currently we know there are four types of MS. There's relapsing and remitting MS, primary progressive MS, secondary progressive MS and progressively relapsing MS. For more information on these different types of MS, I invite you to go to our website, nationalmssociety.org.

Now, let's talk specifically with our panelists about progressive MS. And just as a reminder to our viewers, if you have a question that you would like answered, please use the "Submit a Question" box at the bottom of your screen.

So Peter, you've conducted clinical trials in MS and have been treating people with MS for many years. Can you explain why there aren't more treatments for progressive MS?

Peter Calabresi: Well, Tim, as you said, it's not for a lack of trying. We've used all of the FDA-approved drugs that are indicated for relapsing MS in progressive MS and so far they haven't worked, although some of those trials are still ongoing.

But I think the real issue is the underlying mechanism of progressive MS may be different than relapsing MS, and by that I mean that in relapsing MS we understand that there's inflammation, and we know how to target inflammation. The drugs that we have are good at modulating the immune cells.

But in progressive MS there's a different process going on. The nerves themselves become unhappy from the loss of myelin, and we need to figure out how to rescue those nerves and keep them happier and target remyelination, as we'll talk about later in rescuing the nerves.

And so I think the key to progressive MS is getting a better understanding of what's happening in the brain and spinal cord, targeting that more specifically in addition to the anti-inflammatories that we have right now.

Timothy Coetzee: Interesting. So what you're saying is that we have to take a different approach to treating progressive MS. So Danny, do you think that part of

the problem is that pharmaceutical companies aren't interested in doing trials in progressive MS?

Daniel Reich: Oh, I don't think that's really the problem here. I think the problem is that it's very hard to do a trial in progressive MS. As Peter was saying, unlike in relapsing MS where we have good medicines because we know that a lot of the problem is inflammation, in progressive MS we don't really know exactly what the problem is and how to target it.

There are a lot of new drugs, new ideas for new therapies that are coming out, but what we don't yet have is a really great way of testing them. Currently there are -- to do a trial in progressive MS takes several years and lots and lots and lots of patients. And we need to come up with new and better ways of doing that.

And there are trials that are going on that drug companies are running, that investigators at universities all over the world are also running. And from these trials we are learning better ways of targeting and doing the trials.

Timothy Coetzee: Okay. So finding ways to measure progression so that you don't have to wait years to see whether or not a therapy works is important. Danny, I know that at NIH your teams are also conducting clinical trials in progressive MS. Can you tell us a bit about the trial that you're running?

Daniel Reich: Sure. Sure, I'd be happy to. We have two trials that are going on right now. One of them is for primary progressive MS, and what we're testing is a drug that we think will improve the brain's ability to make energy.

And nerve cells in the brain need energy in order to do their work, and so we need to find ways. And this is a real problem in progressive MS so we need to find ways of improving the brain's ability to make energy. And so that's one of the drugs we're testing.

We're also doing a trial in secondary progressive MS, and in that trial what we're testing is whether we can reduce any inflammation that's left over in progressive MS by giving medicine both through the blood and also through a spinal tap directly into the spinal fluid, using a powerful anti-inflammatory medication. And if people are interested in these trials we are still recruiting for them, and they can call our clinical office.

Timothy Coetzee: Okay.

Daniel Reich: And I can give you the number for that.

Timothy Coetzee: Great. And we have the number on our screen, so --

Daniel Reich: Great.

Timothy Coetzee: -- I certainly would encourage people to visit our website where they can learn more information on that.

I'm sure that our viewers are interested that there is progress. I know, John, that you've done work with a rehab technique called self-generation to improve memory. Can you tell us what that is and how might a person who lives with progressive MS use that at home?

John DeLuca: Well, yes, Tim, actually there are a number of behavioral techniques that we've been able to study to improve learning and memory in persons with MS. And they're all based on the idea that persons with MS have problems primarily in the learning of information, not in retrieving that information from the brain when it's stored.

And if the problem is difficulty in learning, then the behavioral techniques have to be focused on making sure they learn. And once they learn the information they'll be able to recall it pretty much like all of us.

And so self-generation is an interesting technique. It's been known for decades. It's used with individuals with learning disabilities, for example, and it's a simple idea. And that is to learn new information you will remember it better if you generate the answer yourself than if someone tells you the answer.

It sounds like a very simple concept, and it's very powerful. The amount of information that can be retained through self-generation is about 50% better than if someone just provides the information. So it's trying to learn the information by generating it itself. It causes a stronger code in the brain that can be retrieved.

Another example, for example, that we've looked at is something called reminding yourself. It's called spaced retrieval. And the idea is, if you want to learn something you can study it or you can -- and you can study it again, but if you're sort of quizzing yourself on it, that quizzing actually increases the strength of the information in the brain, and it makes it a lot easier to retrieve.

So if you put together things like, self-generate something that you need to learn and remind yourself of that and come up with a system of how you use that, we can show about 50% improvement in learning and memory in individuals. So it's best to try to work with a rehabilitation team to do that because it sounds like an easy concept but how you do it in your real life can be somewhat of a challenge.

Timothy Coetzee: So it sounds like there are things that people can do right now to help with their cognition, and that's really important to know. But I know that people want to know what can be done to stop MS progression. So Peter, I know you've been researching ways to protect the nervous system from damage in MS. What have you and others found on this so far?

Peter Calabresi: Well, Tim, we're looking at a lot of different things. It's a challenging problem, as we've talked about, but we're looking at how nerve cells survive and the signals that are required to keep them alive.

And so we're screening drugs, compounds that may be already available. A lot of people are talking about repurposing drugs. So a drug that's already indicated by the FDA for one disease maybe we could find that it has neuroprotective effects in our model. So we're doing high-throughput screens there.

We're also trying to find out how we can repair the tissue, of course, and so remyelination is very important. And we're just starting to get ideas about how to do that. We actually know that within all of our brains there are cells that have the capacity to turn into myelin-making cells. We call these oligodendrocyte precursor cells.

The oligodendrocyte makes myelin and is a precursor cell, kind of like a stem cell, but different because stem cells can become any different kind of cell. And this precursor cell seems to be more selectively geared towards becoming a myelin-making cell. And if we can figure out how to turn these cells on and get them to turn into myelin-making cells, we could actually repair tissue.

And as Danny said, the next big issue is okay, so suppose we have a drug that seems to work in the laboratory. How are we going to take it to the clinic and test it? And so we focused a lot and put a lot of effort into imaging biomarkers of remyelination and neuroprotection, trying to get at issues separate from the inflammation that we talked about, which is so prominent in relapsing MS.

And so it turns out that there's some new MRI techniques and a new eye imaging technique called optical coherence tomography that gives us almost a microscopic

picture of the nerves in the back of the eye. And I think this could be very promising as a way of directly imaging the health of the nerves and may give us that rapid feedback that we're looking for to test some of these compounds as we transition into the clinic.

Timothy Coetzee: So it sounds like MS is -- the research in this area is going really fast and lots of tools that you're developing.

Peter Calabresi: Exactly. Exactly. It's an exciting time.

Timothy Coetzee: Excellent. Well, I know that you -- part of this is that the Society recently awarded you with a Collaborative MS Research Center award to find ways to repair damage. Tell us a bit about that collaboration, and tell us why is nervous system repair so hard?

Peter Calabresi: Well, first of all, I think nervous system repair is so hard because there are a lot of different things that may be happening. In some patients it may be microscopic inflammation. We know that there are immune cells that are what we call resident immune cells, the glial cells that are hard to understand because we don't always have access to the tissue. We can take blood and spinal fluid, but we're only indirectly looking at what's happening in the brain.

And then some patients have demyelination. Other patients have more neurodegeneration where their axons are damaged, so it may be playing out differently in different people.

But the Collaborative Center award approach, I think, is really exciting. We had one before and the idea here is that we tap into expertise in other areas. And so two established MS investigators collaborate with people from different fields, and so we're working with a myelin biologist, a PhD scientist, Dr. Dwight Bergles, who specialized in understanding how myelination happens in the first place.

And using the tools that he's developed in his lab, we can now better understand how we can maybe recapitulate this in older people and get the myelin to come back, almost to dial back the clock and make our bodies think that we're children again and we need to myelinate. And through understanding how it happens normally, we can use Mother Nature's expertise and perhaps trigger that to happen in patients with MS.

And then we have another investigator, Dr. Jeff Rothstein, who's working on another disease called ALS where there's degeneration. And I think it's very important that there be cross talk so that we can understand lessons that have been learned from that

disease and apply them to MS. And so it's an exciting time, and I think this kind of collaboration is really critical to making progress and move forward quickly.

Timothy Coetzee: That's terrific. It's really inspiring. It's exciting to see that much progress. John, let me ask you, can the brain rewire itself and create new paths inside the brain?

John DeLuca: Oh, absolutely. It's really based on the concept of neuroplasticity. And the brain has a number of natural responses to damage. And one of those responses is areas that are around the part of damage in the brain sort of take on -- take up the slack, if you will. They sort of take up some of the neural tissue that's required to do that task. And that's actually one of the best ways that the brain shows a way to reorganize.

Another way that the brain does that is that it takes tissue or areas on the other side of the brain, so there's two sides of the brain, and so on the other side it will recruit areas from the other side, sort of as if to help with the damaged area to see if we can actually improve behavior or whatever it might be.

And the third way the brain tries to repair itself is by taking tissue around the areas of the brain, maybe not necessarily around the damage or the other hemisphere, but other resources. To take collectively those resources that try to make it so the symptoms of MS can be overcome. So the brain has a very nice way of reorganizing, and we're learning a lot more about how the environment can actually change the brain. And I think that's very exciting for MS.

Timothy Coetzee: You know, I'm going to pause here. Danny, your reaction? You've heard Peter and John, and why is it so hard and why are we so excited?

Daniel Reich: Well, I think there's a lot of good research going on. I think we're getting at really basic mechanisms of how the progression happens. There's a lot that's not known and that kind of work is really, really hard to do. But it is an exciting time, as everybody said.

Timothy Coetzee: Sounds like it's holistic -- we need a holistic approach and research across the board. Let me follow up with John by asking whether behavioral treatments that can result in changes in brain organization, and tell us a little bit about the kinds of treatments that can be used to do that?

John DeLuca: It's really, Tim, very exciting. Like I say, we know that for example if you're learning to play the piano that you start off really slow with your hands and

your fingers. And then after a while you start getting faster. That's because the brain is reorganizing, and the brain is taking other areas to help out.

Well, you do the same thing with behavior. We just completed a clinical trial of a behavioral intervention. And we had a group that got the significant intervention to improve learning and a placebo group. And it was the people who had the intervention that showed significantly more activation in a variety of regions around the brain.

So with the brain we can mold it in such a way that it can increase its capacity to learn. And that's what's very exciting for the areas of cognition.

Timothy Coetzee: Can you tell us a bit about that intervention that you're describing?

John DeLuca: Sure. Well, the intervention was based on two concepts that we've known for decades that improve the learning of information. One is imagery, so we teach our patients how to use imagery to improve the learning of information.

And the second is context. So when people tell you a story or they're telling you something about what happened or that happened yesterday that's important to them, we train people to learn the context. Put that into a context rather than memorizing words.

And we've known that if you train yourself in imagery and context that that will significantly improve the strength of that code in your brain. And if it's stronger in your brain it's easier for you to find it when you need it. And our intervention showed pre and post-fMRI imaging that the people who got the training showed significantly more activation, as well as did better behaviorally.

Timothy Coetzee: Wow, so it sounds like there's great implications of this research for people with MS today. Let me shift gears a bit and come back to Danny, and ask you, we've heard that silent progression and tissue injury can be detected using MRI even when a person isn't feeling worse. What does that tell us about progression and what's happening to the brain in progression?

Daniel Reich: Yes, unfortunately that's true. It's definitely the case that the disease may even be progressing, and we can see that on MRI even if people are in remission. And there's a few ways that this can happen. One way it happens is something we've known for a long time is that people can get new plaques even when they don't develop symptoms and that can be seen on MRI.

Another way that that can happen is that some of the damage that has occurred due to the inflammation, that there can actually be some loss of the brain cells and the brain tissues and what we can see is that the size of the brain is actually getting a little bit smaller in this disease. And we think that's related also to the progression. It happens on average about twice as fast in multiple sclerosis as it does in the rest of us.

And the third way that it can happen, and this is probably really important, is that there's low grade sort of quiet inflammation that is occurring throughout the brain, and that process may be getting more and more significant as the disease goes on. And that may also be contributing to the progression that we see.

Timothy Coetzee: I see. So I've heard that lesions can disappear or shrink as seen on MRI. Does that mean that when they disappear that they've been repaired or are actively being repaired?

Daniel Reich: That's a great question, and it certainly can mean that, and that's of course the goal. And the treatments to improve the myelination that Peter was talking about certainly are targeted to try to do that. It's not the only thing that can make a plaque get smaller.

We know there's a lot of swelling in plaques. There's water just, as if you were to get an injury on your arm and there's some swelling. That can go down as well, just part of the normal course of repairing.

And as I mentioned also, sometimes they get smaller because there's been some loss of brain cells and the brain is just sort of cleaning that up.

But one of the challenges for us, those of us who are interested in imaging and trying to look inside people at the processes that are going on in this disease, is to figure out how to see the repair that's happening that we know is going on. And that's something we're working really hard on.

Timothy Coetzee: Peter, your -- tell me your reaction and this repair that happens, do you see that in patients that it can have benefit?

Peter Calabresi: Oh, we do. I think that's an important point. Some people don't appreciate that with the drugs that we have right now a not unsubstantial proportion of patients actually improve. And this has been seen in all of the Phase III trials from the first line drugs interferon and glatiramer acetate and perhaps much more so with natalizumab. But some of the patients actually get better.

Now, these drugs are not designed to remyelinate by themselves, but what I think is happening is if one successfully dampens the inflammation to the point where there's very little inflammation that some of these natural reparative pathways can start to kick in, what I call Mother Nature's healing. And so that we do see a substantial number of patients have remyelination and some patients get better when they go on therapy, which is very encouraging.

Now, of course, there are other people who do not and start to progress, and we need to target that. But I feel as if it is happening, that the drugs that we're getting in there are better and stronger and we're making a lot of progress there.

Timothy Coetzee: Wow, so being able to harness the natural repair mechanisms in the brain sounds like a really exciting area.

Peter Calabresi: Yes.

Timothy Coetzee: So this sounds so promising. Let's take some questions from our audience. Here's one for Danny again. We're picking on you today. Kevin would like to know how many participants have been chosen for the NIH studies that you're recruiting for?

Daniel Reich: We've enrolled about 30 people so far.

Timothy Coetzee: Yes.

Daniel Reich: Both the trials that I mentioned, the one for primary progressive MS, the other for secondary progressive MS still have openings for them. As you mentioned, you can go to the MS Society website and find out how to enroll. The NIH where I work, National Institutes of Health, has put a large emphasis on these trials, and as a result we are recruiting nationwide for them.

Timothy Coetzee: Great. Well, so another question for Danny, actually, Jutta has asked here if an MRI is unchanged for many years, is there any reason for her continuing to have her annual MRI?

Daniel Reich: That's another great question, and it's a hard one to answer. I think I might even turn to Peter for his opinion. Peter also sees a lot of patients. But I would say that if things are really stable and their MRI is really not changing and there aren't new clinical symptoms and things really are going well, then it's reasonable to drop back on the frequency.

Timothy Coetzee: Great. Peter?

Peter Calabresi: Well, I agree with Danny. In the beginning, as Danny said, there can be a lot of silent disease so we tend to do it once a year. But as time goes on, if someone is extremely stable for several years I'll back off to every other year.

And then there's some patients who really you haven't seen any new activity for five or 10 years and so we can back off a little bit as time goes on. But in the beginning during the relapsing stage I think it is important to get MRIs more frequently.

Timothy Coetzee: Okay, thank you. So Peter, a couple more questions for you. Beth is wondering how she knows if her MS is becoming more progressive? And Steve also asks why do so many people turn -- become progressive?

Peter Calabresi: Well, these are great questions, and the issue of MI becoming progressive is really such a challenging one that the National MS Society has convened a panel to address this because clinically it's a little bit hard to say from just talking to a patient or even following them over many years. And I urge some caution before calling someone progressive for a variety of reasons.

First, I've had the experience that some patients actually have lots of little exacerbations. And when you're seeing them every six months or every 12 months, and you think that they have progressed over that period of time, what you don't know is whether there have been lots of little attacks and it's been mediated by chronic inflammation, which is responsive to the therapies that we have.

Second, there can be medical problems. So I've seen patients who have untreated iron deficiency or B12 deficiency or thyroid problems or even depression that can mask as slow worsening of their disease. So it's important to take a holistic approach. Talk to your patients. Find out what's going on in their lives. Is there something else that's making them worse?

But ultimately after a year or two and you can't identify any other cause then we start to become more comfortable. And for me it's really a diagnosis that I make retrospectively. We've kind of looked back and say, well, I think you may have become progressive. And of course that's very different from the proactive approach that we take in relapsing disease where identifying the inflammation and being aggressive up front is important.

And part of that's because we have less that we can offer for progressive disease, but we always offer people rehabilitation, which is really important. I think we should talk about exercise because more and more it appears that exercise can not only help the brain but improve function. And one should never ignore the power of rehabilitation.

Timothy Coetzee: It sounds also like you're saying that we need more research to really help us define and understand progressive MS even better than we do today.

Peter Calabresi: Well, that's exactly right because some of the processes, as Danny was talking about, are happening in the brain. And we just don't have access to the brain in a microscopic way yet to fully understand what's going on.

But I think that as we start to understand the complex interplay between demyelination, the dying of the nerves and this inflammation that comes from the glial cells, the immune cells that live in the brain, we will get better at targeting that specifically.

Why have so many people become progressive? Well, I think it has to do with not treating the early stages of the disease effectively in some cases. But in other people it may be that they predominantly have problems with, for example, the mitochondria, the energy packs of the cells that Danny was talking about.

And we're finding that in other diseases like Parkinson's disease what these mitochondria and the lack of energy may be a problem. And of course this is -- we recognize this clinically in MS, but we haven't fully explored whether maybe we can target mitochondrial dysfunction more effectively using cocktails of drugs, not just one approach.

So I think we're going to enter into an era where we have patients on anti-inflammatory and then we try to understand better what's driving that progression. And if it's an energy demand problem go one direction. If it's a myelin problem go in a different direction and try different combination approaches.

Timothy Coetzee: That's really remarkable. So let's ask John a question. Deborah says that she has progressive MS, is no longer able to walk. Can a drug like Ampyra help her?

John DeLuca: Well, Deborah, if you really are unable to walk it's unclear if Ampyra would help, and primarily because the clinical trials for Ampyra were based on some ability to walk. It did include some people who were in a wheelchair, but you had to

have some ability to walk because what Ampyra is designed to do is to improve walking speed.

So if you really are unable to walk, then it's unclear. If there is some ability to walk then it is possible. I think it's promising. I think if there's -- it probably wouldn't hurt, but it would be something certainly to try with your healthcare professional.

Timothy Coetzee: Yes, I want to pause here and just talk a little more about this with Peter and Danny. Part of -- drugs like Ampyra are managing symptoms and are you seeing more and more of that as part of treating people with MS, particularly progressive forms of MS?

Peter Calabresi: Absolutely, and I think the conversations with my patients covers many different aspects. First we confirm the diagnosis, make sure we have that correct. Second, we rule out confounding illnesses like the medical problems that can happen to people with MS or any other disease.

And then we talk about the immune modulating therapies and the symptomatic therapies, and there's a lot to do for progressive MS with respect to managing symptoms that can improve quality of life. Relieving pain, properly treating the depression, treating the bladder dysfunction, and the rehabilitation approaches with stretching and exercise can all really have a great impact on quality of life.

Timothy Coetzee: Okay. Danny, anything to add?

Daniel Reich: I think I would just echo one thing Peter said earlier, which is that I think in the end what we'll be doing is trying to target what we think is going on in progressive MS very, very early on in the disease. And not everybody gets progressive and we'd like nobody to get progressive, and in order to prevent that I think in the end that we're going to be treating people very, very early, even before they get that way.

Timothy Coetzee: Great. Peter, Marcia asks when will there be a treatment to reverse damage?

Peter Calabresi: Well, as I said, actually I had the experience that many of my patients get better with some of the treatments that they're on, so that's quieting the inflammation and letting Mother Nature repair and harnessing that is partially effective in some people.

But the real issue is when will we have a therapy that directly targets that process? So we're actually entering the era of remyelinating therapies, so these cells that I talked about the oligodendrocyte precursor cells that have the capacity to turn into a myelin-making cell exist in our brain and there is one trial that's already under way with a compound called anti-LINGO that seems to target these cells. And the idea is to wake them up and get them to turn into myelin-making cells.

Now all the preclinical data look very promising. It induces remyelination in the tissue culture dish. It improves myelination function in models of MS, but as we move into the clinic we have to have the right outcome measures so that the Phase I was completed. It seems to be safe. It gets into the brain. It's not toxic because the target is only on these cells, so that's all good.

But the Phase II trials will be, I think, very informative about how we can measure the remyelination. One will be predominantly using MRI and our conventional outcome measures at the time of a relapse to see if we can get better recovery from the relapse.

And probably a second trial design would be using the eye imaging and seeing if at the time of an eye attack with optic neuritis can we get remyelination in the optic nerve? And we know how to measure that much better now with a variety of these new modern technologies. And I think if this trial is successful it will really open up a whole pathway by which new drugs can be tested. And we'll see more and more happen.

Timothy Coetzee: All right. Setting the stage for the future, that's --

Peter Calabresi: Exactly. Exactly.

Timothy Coetzee: -- remarkable. All right, another question for you, Peter, from Meredith, who's wondering are there any treatments that can manage pain?

Peter Calabresi: Well, pain is very tough, as you know. And I think the first thing is to identify what kind of pain it is. So sometimes patients have pain from spasticity and muscle cramping, and in addition to some of the drugs that we have out there now there are clinical trials going on with new drugs to target spasticity.

However, there's also central pain, and this is less well understood. There are pain relay centers in the deep part of the brain called the thalamus and the National MS Society is now sponsoring research, as you know, to try to better understand pain so that we can target it.

But one of the drugs that was just approved for mood disorders is out now actually being tested for pain. We talked about repurposing drugs, and sometimes in a clinical trial with a drug that's targeting mood you find that pain actually gets better.

Timothy Coetzee: Right.

Peter Calabresi: And so this will be formally tested, and I understand that they are looking for patients for that trial.

Timothy Coetzee: All right. It is important, an important area, and the National MS Society's goals are -- for progressive MS -- are to find out what drives it, to discover new therapies to stop progression, restore function, and find better ways to manage symptoms and improve quality of life.

John, what are some of the frontiers in rehabilitation that you and others are doing to improve the quality of life for people living with MS?

John DeLuca: Well, Tim, one of the more exciting things that are going on right now in rehabilitation and particularly in cognition is realizing and discovering that environmental factors can actually decrease symptoms, particularly cognition.

So we've done a series of studies where we've looked at individuals who have achieved -- who've had higher lifetime intellectual achievement that is people who did a lot of reading, who had -- who were more involved in educational activities.

And when we look at individuals who have higher educational intellectual attainment and compare them to individuals with lower intellectual attainment, people who didn't go to school or don't read a lot, then what we find is that people with higher intellectual attainment have fewer cognitive problems than the other group.

And in fact what's important about that is that they have less cognitive problems, but they had the same degree of atrophy. So the impact of the disease was the same, but individuals who were involved throughout their lives in a lot of intellectual activity sort of built a brain that was more resistant to the expression of the disease. They didn't show the cognitive effects. It's really exciting to show that environmental factors can have that kind of an effect.

We also -- and Peter had mentioned exercise. We did a study where we asked patients 20 years ago tell us about your cognitive lifestyle and your physical lifestyle. And what we found was people who were self-reported doing a lot more aerobic activity as opposed to did not, they had better cognitive problems.

They had fewer and they had less gray matter loss and less white matter loss. So there was less brain loss, actually, and less cognitive problems if they were involved in a lot of aerobic activity throughout their lives.

Same thing with cognition. If they were involved in a lot of cognitive activity, you see greater cognitive activity and less loss. That's really exciting to me, and it really begs the question then well, can we build a cognitive reserve?

So let's say a patient with MS is 25 years old. Can we as part of our rehabilitation then say to that patient, well, we need to prescribe for you an exercise regimen. If you read one book a month, start reading two or three. We need to build this reserve so that when you're older, while the disease might progress, the expression of the disease may not.

I think it's really exciting to think about how the environmental factors like this can sort of mediate this impact of the disease on the brain in everyday life.

Timothy Coetzee: So would it be accurate to say that people with MS should consider investigating rehab programs and other exercise therapy strategies to help them improve how they feel?

John DeLuca: Oh, absolutely. I absolutely agree with that. I think that rehabilitation is going to be the key. It's not just medication. Medication is going to have an effect on the disease, but rehabilitation can have an effect on the expression of the disease.

So I would go to rehabilitation centers, work with therapists, cognitive and physical, to see how you can come up with prescribed cognitive and exercise activities. Be active in that.

Timothy Coetzee: So really take a comprehensive approach to managing your care?

John DeLuca: I think we have to. I think the medication approach is an incredibly important one to manage the disease. I think the patient then takes an approach to manage how their symptoms can be expressed by the environment.

Timothy Coetzee: It sounds like a real partnership between an individual and their healthcare provider.

John DeLuca: Absolutely.

Timothy Coetzee: Peter, I want to come back to you and talk a bit more about laboratory research. So tell us a bit more about the approaches that you and other researchers are taking to stimulate nervous system repair in MS?

Peter Calabresi: Well, I think one of the most exciting areas right now is remyelination, and of course, people know about stem cells and they're in a way the Holy Grail. The idea that we can put in a cell that could repair tissue of any type. One of the areas that seems to be really accelerating moving forward right now is these endogenous stem cells, so ones that are sort of in our brain and we are learning the cues to turn them into myelin-making cells.

So we talked about anti-LINGO, our laboratory is screening compounds in a tissue culture dish that enhanced the differentiation or the change from a precursor cell into a myelin-making cell and we have a high throughput system where these cells change color. They're red when they're precursor cells and they turn green when they become myelin-making cells and we can screen many compounds in a tissue culture dish and find which ones turn on those cells. So that's exciting.

We're also doing the same with nervous system tissue trying to figure out why the neurons die or become unhappy and how we can rescue them. Now of course once the cell's dead we can't rescue it, but the idea here is that there are probably many cells that are in a state where they're damaged but not dead and we can rescue them.

And I like to think -- I think when I talk to my patients and ask them you probably have good days and bad days. And they all say, yes, you know, some days actually when I'm feeling well I can do much more than other days. And to me that tells me that enough of the wiring is still intact that there's something there to rescue.

And so I'm really optimistic that through some of these approaches of learning how to rescue the dying cells and get them to turn on and function better, that we'll actually be able to translate that into the clinic.

Then one of the final areas of research that I think is much more practical is the exercise approach. So we're using bicycles called FES bicycles for functional electrical stimulation. And the idea here is that a lot of patients tell me, well, I hear you, I'd like to exercise, doctor, but I can't. I'm too tired. I just can't get going.

And so they get into this downward spiral where they can't exercise because they're too tired. They become deconditioned and then it's harder to exercise. So the idea

behind the FES bicycle is that it provides electrical stimulation to the muscles and helps them to contract. So it actually assists the patient in doing the exercise.

And after several weeks of this a funny thing happens. The patients actually --- the muscles may feel tired but they become conditioned. They get the benefits of the aerobic conditioning, the well-being that happens after we exercise and release endorphins that make us feel good. And then they break that cycle, and they start to have a little more energy and they can start participating in the exercise.

So I think this is a very practical approach, and we're starting a trial right now for secondary progressive MS where we're putting people on these bicycles three times a week and seeing how much exercise they have to do to get better.

Timothy Coetzee: That's remarkable. John?

John DeLuca: It's interesting because it's kind of in some ways counterintuitive. People think that if you do exercise is you're going to get more fatigued. And many years ago the approach to fatigue was not exercise.

But what we're learning is actually doing some mild exercise can reduce fatigue. So it might seem counterintuitive to the patient, but that's really something that can be reduced with exercise, let alone some of the other things you were talking about, Peter.

Timothy Coetzee: Terrific. Well, Danny, what are some of the things that we don't know about progression that imaging can help us with?

Daniel Reich: There's unfortunately a lot we don't know about progression, but a lot we have learned. And a lot of the ways we have learned it is through imaging. So I go to meetings with colleagues who are working also on imaging just like we are in our lab, and here's a couple of things they're talking about and that I think we're making great progress on.

One is what Peter mentioned, is the ability to look directly at the myelin in the brain, in the optic nerve and even in the spinal cord. There are some new technologies that are being developed to do that, various ones that are in various stages of testing. But I think as new drugs are being tested that can help improvement the myelination we'll be able soon, in the near future, to be able to look specifically at whether those drugs are working. And so I think that's one great area of promise.

Another area that's I think pretty important and that's gotten a lot of attention in the last few years is the gray matter. What is the gray matter? The gray matter is the part of the brain where the bodies of the nerve cells live. We talk a lot about the nerve wires which are surrounded by the myelin, but the nerve cells also have bodies and they live in the gray matter. And you may hear about structures like the cortex or the thalamus.

And for a long time it was thought that most of the disease is happening among the wires and with the myelin, but we know a lot of it is also happening in the gray matter with the cell bodies. And that turns out to be a lot harder of a job to take good pictures of with imaging.

And yet there are new techniques for seeing directly the damage that's occurring in the gray matter both as it's happening and down the road as some of these cells are being lost. And there are more and more reports that even some of the existing drugs that have been approved can slow down the rate at which the gray matter is damaged.

Timothy Coetzee: Okay.

Daniel Reich: And the third thing that I think we are working hard at is being able to use imaging to make predictions for individual patients. Now, I think we're a long way off from being able to do that well, but it's something a lot of people are really interested in being able to do, to say -- and we don't even know how long it'll take, but to be able to say based on even a few years of imaging somebody what their prognosis is. That's a goal that we have and that people are working on.

Timothy Coetzee: So if I understand you correctly, what you're saying is that at some point in the future someone could see -- come and see you or Peter, and on the basis of their MRI images you'd be able to help them get a better prognosis of what's going to happen with the disease and what treatment may or may not be effective for them?

Daniel Reich: It's certainly one of our goals. There's a big push from the director of the National Institute of Health towards something called personalized medicine where we know that people have a disease but the disease expresses itself differently in each person. How do we understand that? That has something to do with genes. It has something to do with medicines and all sorts of things.

And imaging is certainly one of the tools we can use to understand how the disease impacts each person. There are other tools as well, and we need to be able to integrate that in order to understand each specific person's disease.

Timothy Coetzee: So Peter, what would that mean for you as a physician who sees a lot of people with MS? How would that change your practice?

Peter Calabresi: Well, of course, it would be great if we had better tools, but I think it's happening though. We already use the MRI of the brain and the spinal cord and we know people have a lot of spinal cord involvement that they might be more likely to become progressive and so we weight that a little bit more.

And now we're using the eye imaging device to look at neurons right in the back of the eye and see if they have damage directly to the neurons. That's a location where there's no myelin so that's starting to teach us that maybe not the whole response is directed against areas of demyelination but there may be other things going on where the immune system directly attacks nerves.

And I think that we're going to have blood tests and imaging devices that really guide what specific type of MS the patient has.

Timothy Coetzee: All right. And Danny, is the imaging of the spinal cord something that's going to become more common in MS? I know that people typically have an image of their brain, but what about the spinal cord?

Daniel Reich: Yes, well, I think now people get imaging of the spinal cord if they have an attack that the doctor thinks is coming from the spinal cord, but not routinely. Why is that? That's because the spinal cord is really small. It's sort of about the size of my thumb. And it's very hard as a result to take really good pictures of it.

So I would say the state of spinal cord imaging is probably 10 or 20 years behind the state of imaging of the brain, and yet there are a lot of good studies that have been done recently showing a much better depiction of the plaques in the spinal cord, much better pictures than we had before. We're also learning about how the spinal cord can atrophy just as the brain can, and we're developing ways of measuring that.

And I think people are finding with those techniques, with other techniques, such as diffusion MRI, which is something we've been working on in our group to look at the spinal cord, that we can understand much better, though not perfectly yet, how an individual's disease relates to the damage that's occurred.

Peter Calabresi: I'm going to interrupt just for a second. Danny's being modest here. And when he was at Hopkins he helped develop a diffusion tensor imaging

protocol in the spinal cord that has really changed how we think about imaging the spinal cord. And we're starting to find that it's not just the plaques but underlying the plaques in the normal appearing part of the cord that this DTI technique picks up abnormalities that someday we're going to be using in the clinic.

Daniel Reich: That's something we did together.

Timothy Coetzee: He's turning red. This is great. John, your institution helps people with many different types of rehabilitation needs. Are there things that you're learning from people who experience a stroke or spinal cord injury that can be applied to help improve function of people who live with MS?

John DeLuca: Oh, yes, absolutely, Tim. The rehabilitation approach is the approach to treat the whole person, and we don't necessarily treat singular populations, but we treat function disabilities and we look at abilities.

So for example in the area of the spinal cord we've had -- we do a technique that's been around for a few years now called locomotor training where we do this intensive training of the legs and doing this over 70 sessions. I've taken people who haven't walked in years out of the wheelchair and walking for the first time.

It's really phenomenal to see that. I'm not sure how that would work with MS, but certainly if you deal with mobility you're not necessarily dealing with a clinical population, so it's there as a possibility with that.

Another area in our organization, for example we do a lot of research on medical adherence -- I'm sorry, adherence to medication regimens. And it's particularly important in stroke, and if you don't adhere to your medication regimens, helping with these parameters to help the disease may not work. And we know that's a problem in MS as well.

For instance, people who feel like their medicines are not having an effect will tend to start to slack off in taking their medications. They're not adhering to their regimens. And some of these things you don't see that can take a long period of time. And so medication adherence is something we study which is a really important thing.

And the cognitive work that we do is not just in MS. We do a lot of work in stroke and in TBI and learning how these various cognitive techniques can significantly improve learning and memory, but not just that. Using things like DTI there are actual changes structurally in the brain and functionally with these behavioral

interventions that we're applying, not in just MS but working with our colleagues in TBI as well. So it's a really exciting time.

Timothy Coetzee: All right. So Peter, I'll let you know, another question that asks is how -- the question is how would repair therapies help if a person has underlying MS? Wouldn't the disease process that's causing the damage just come back again and actually reverse the repair and just cause new damage on top of that?

Peter Calabresi: Well, it's a great point, and as Danny talked about there are several things happening at once. So there's the inflammation and then very early on in the disease we can see in some people the beginnings of the nerve damage happening.

And so even if we were to develop a way to remyelinate, we are still going to have to stop the inflammation and the attacks. So this is why I think we're really going to be looking at combination approaches where we are always trying to optimize the anti-inflammatory, reduce the relapses, stop the inflammation and at the same time enhance the recovery process.

Timothy Coetzee: Okay. And Danny, how can imaging be applied to efforts to actually repair, to see the repair that's happening in MS?

Daniel Reich: Well, we've talked a little about myelin. To expand on that a little bit, it turns out that there's water that's inside the layers of myelin that we can see with the MRI and that kind of water is something we can detect to see if myelin is getting better.

We didn't talk as much about looking directly at the nerve wires. I mentioned that we see that they can be damaged and lost, but the challenge for us is really to be able to detect nerve wires and nerve cell bodies that are sick but not yet gone. And there are a variety of new technologies that are being developed to look just at that.

One of the most promising of those is a technique that Peter mentioned called optical coherence tomography which gives us really detailed pictures of the back of the eye that doesn't use an MRI at all that just uses light inside the eye. And Peter could talk a little bit more about that.

Timothy Coetzee: I have one question that comes to mind often that people ask me and that's some patients with primary progressive MS get worse at a slower rate over many years, and other people get worse at a much faster rate. Do we know what causes this different course for different people?

Peter Calabresi: I personally think that when people are getting worse quickly that it probably means that there's inflammation going on. And so I look very carefully, and even if I can't find it by imaging sometimes will try to ramp up on their anti-inflammatory treatment or give them a course of steroids because usually neurodegeneration plays out over many years to decades. And so if someone's getting worse over months then that might be a red flag that there's more of an inflammatory process going on.

Timothy Coetzee: And any --

Daniel Reich: Oh, I would agree with that completely.

Timothy Coetzee: Well, let me ask both of you also another question is what else do you think needs to be done to find treatments for progressive MS? Is there something out there that we're missing?

Peter Calabresi: Well a variety of things. So I think we need to collaborate with people in other fields because there are a lot of bright scientists who work on other diseases that have ideas that they may be ahead of us in. We need to think about repurposing drugs, like we talked about, FDA drugs that carry an indication for another disease and screen them with high throughput screens for neuroprotection or remyelination and take those to the clinic.

We need better imaging outcome measures to open up the block in the pipeline between target discovery in the laboratory and the phase II proof of concept clinical trial. I think that's a real area where things slow down and right now for remyelination there's only one drug because I think a lot of people are nervous that we don't quite know how to do it yet. And so we need to put a lot of emphasis on these early phase trials.

And we need to keep an open mind. I think that we need to look for the breakthroughs, the paradigm shifting experiments and modern technologies have provided us with new tools to really look at the brain and spinal cord in a different way. And so I'm hopeful that in addition to the slow incremental progress that we're making that we'll have some breakthroughs along the way that will really change how we think about this disease.

Timothy Coetzee: Okay, great. Let me ask John quickly, your thoughts on what we might be missing or what we need to look at?

John DeLuca: I think we need to I would say from my perspective look at environmental ways to improve the progression of the disease. I think that there are a lot of things we can do with that, and I think a lot of work is going to come from imaging. How does the brain change with these kinds of interventions? And I think that's going to be really promising.

Timothy Coetzee: And I guess the other question is, are there worldwide efforts going on in progressive MS, Danny? Your thoughts -- or do you have collaborators outside of the US?

Daniel Reich: I do. I have collaborators in Holland, collaborators in Israel and we're thinking about the same problems on both sides of the Atlantic, both sides of the Pacific related to progressive MS.

I would echo what Peter said about collaboration as being a critical component of how we can approach this. We just last week had an initial meeting of a group of imaging scientists with the goal of trying to get together to work on some problems together and ultimately we hope to develop new ways of testing drugs quickly with imaging.

The Europeans are way ahead of us on this. We have a little bit of catch up to do, but I think it's a pretty promising development that hopefully will move things along at a faster clip.

Timothy Coetzee: Great. Well, before we wrap up I'd like to ask each of you your final thoughts on understanding and treating progressive MS. John, why don't we start with you?

John DeLuca: Well, I'd say for the patients with MS is to take some more control. Take some more control over their treatment. Work with their physicians and with their team, but also do what they can and be open to a number of these other kinds of new interventions, exercise and cognitive stimulation. I think that's going to be a big step. And with these new treatments and these new ways of looking at the brain I think that we're going to be able to see that taking active control is going to have a benefit.

Timothy Coetzee: Great. Danny?

Daniel Reich: Well, we don't yet have a cure. We don't even have really great treatments, but despite all that I think there's been no better or more hopeful time for

people with the disease. And even with the progressive disease because of all of the things we've been talking about here.

We need more research. The MS Society and the NIH recognize this. We need to think outside the box. We need to pursue promising leads. But there's still a lot of work to be done.

Timothy Coetzee: So Peter, some final thoughts?

Peter Calabresi: Well, I'd like to emphasize that we really are making a lot of progress and so 20 years ago when I started in this disease we didn't have any FDA-approved treatments, and so it was a very frustrating time. And now we have eight or nine, depending on how you count them.

And so I think we are making progress. But the real message for people with progressive MS is that the progress is happening at the preclinical level. And by that I mean that the treatments that we have right now for relapsing MS came out of scientific projects, many funded by the National MS Society in the 70s and 80s, and that led to those treatments coming on the market in the 90s.

The treatments that we will have for progressive MS, the groundwork is already being laid. So for the last decade the MS Society has been funding researchers to better understand remyelination, neuroprotection, how this all happens, how we can target it. And the targets have been identified. Many of the drugs have been made or identified and are starting to go into clinical trials. So I think that we are going to start reaping the benefits of all this research in the next decade.

Timothy Coetzee: And that's -- well, thank you. These are really inspiring prospects. So we've heard today that to develop better treatments for every type of progressive MS we have to gain a better understanding of the underlying mechanisms that drive progression. Our scientific advisors are helping us map out a course of action to move this work forward quickly.

We're also working to design new ways to conduct clinical trials and to develop better outcome measures of the kind that Peter talked about to speed up the testing of promising therapies and promising repair strategies.

But in the meantime, we've heard today that there are clinical trials going on right now in progressive MS and there are rehabilitation techniques that can help people take charge of their many symptoms.

Additionally, we're working with a global consortium to propel specific elements of this work that will go faster through international collaboration. There is a lot of work to do in progressive MS, but there are also unprecedented opportunities to achieve advancements that will make a big difference in people's lives.

We will be continuing our conversation on progressive MS in a live community chat on June 18th on our [MSconnection.org](https://www.msconnection.org) website. Check it out for more information on how you can participate.

I also want to thank our panelists, Danny, John and Peter for being here today and sharing your expertise with us.

I also want to thank our viewers for joining us, and let everyone know that if your question wasn't answered please speak directly with your healthcare provider or visit the Society's website at [nationalmssociety.org](https://www.nationalmssociety.org), or contact our information resource center and speak with one of our MS navigators at 1-800-344-4867.

Thank you all and good night from New York.