



**National
Multiple Sclerosis
Society**

**MS Learn Online
Feature Presentation
Three Cures: Stop, Repair, Prevent
Part One
John Richert, MD**

Tracey>> Hello, I'm Tracey Kimball

Tom>> And I'm Tom Kimball. Welcome to MS Learn Online.

Tracey>> Can you imagine a world without MS? Well the National MS Society does. It's the largest private sponsor of MS research in the world supporting projects aimed at finding the cause of MS, better treatments and ultimately a cure.

Tom>> This is the first of a two part series focusing on what the National MS Society is doing to find a cure. Kate Milliken spoke with Dr. John Richert, Executive Vice President for Research and Clinical Programs at the Society.

Tracey>> According to Dr. Richert they are actually looking for three cures for MS. What does he mean by that? Let's find out.

>>John Richert: When I speak with people with MS, by far and away the most common question I get is when are we going to find a cure? What might not be so obvious is that if I were to ask everyone

in a room what a cure for them would mean, I would get at least three different answers.

For the people who have relatively early disease or a relatively mild disease, a cure for that person is to stop the destructive process in its tracks. Stop the inflammation, stop the demyelination, stop the axonal destruction, so that even though a person might have MS, we've really prevented the disease from doing damage.

But, on the other hand, if somebody has already sustained a significant amount of disability from their MS, a cure for that person is to repair the nervous system, remyelinate the nervous system, regrow those axons, get me up and out of my wheelchair. So, a totally different cure and requiring a totally different set of experimental approaches to get to that cure.

And for someone who is primarily worried about their children or their grandchildren developing MS, a cure for that person is to prevent the disease in the first place. Learn the cause of MS or the causes -- it may be plural -- and then once we know the causes, learn how to prevent it and just wipe it off the face of the earth.

This idea of three cures is a notion that is not new with us in the MS Society. There are other people who are experts in MS who have been talking about this sort of thing for a number of years. For example, Dr. Howard Weiner in Boston has talked about three cures in a somewhat different form, but very similar. So, it's a concept that really resonates and illustrates how complex our mission is, and how difficult it is, and how expensive it is.

We've got three cures instead of one cure, and each one of those cures is just as important as the next. We can't neglect one or two to go after the third one; we need to go after all three simultaneously, which is one of the reasons why curing MS is so expensive.

>>**Kate:** The first one, stop, is I feel like everybody who has MS goes through the process of having that first stage. So, is there more being done in the world of that cure than the other two?

>>**John Richert:** The first cure, stopping MS, is the form of MS that has had the most therapeutic success, because this is a form of MS that most commonly begins with relapses and remissions, and those remissions are associated with full or partial reversal of those symptoms. And it's the portion of MS that's most inflammatory as opposed to degenerative. So, it leaves us more openings for how to devise therapies to suppress the immune system.

I'm proud to say that the MS Society has played a role in the development of all six of the current FDA-approved therapies for MS. And these have all been therapies that are immunomodulatory. They affect the immune system in some way, so they in various ways block that inflammatory, immune-mediated attack on the nervous system.

>>**Kate:** What about repair, which is kind of the next cure, in terms of the progress you guys have made?

>>**John Richert:** The whole idea of repairing the nervous system seemed like science fiction as recently as six, eight, ten years ago. But I'm happy to say that through the funding of research by both the MS Society and the National Institutes of Health, a cadre of very dedicated researchers have begun to figure out what the basis is for the neurodegeneration that we see, and have begun to devise therapies. And the therapies are generally aimed in one of two directions. One is to learn how to make the nervous system repair itself, and the other is to introduce cells that will do the repairing.

We have learned in just the last five or six years or so that in MS, once somebody has an inflammatory destructive lesion, that sometimes repair occurs in terms of remyelination. But over time, that ability to repair, that ability to remyelinate wanes, becomes less

and less effective. And we've learned in just the last few years that part of the process that leads to that repair involves stem cells that reside in the nervous system that differentiate into mature oligodendrocytes, which are the myelin-producing cells.

But as time goes on, they tend -- this differentiation process stalls at a stage at which what we see are called oligodendrocyte precursor cells. So, it's an intermediate stage between a stem cell and a fully functioning myelin-producing cell. And for some reason they get stalled at that stage and don't, then, remyelinate the nervous system.

And so there is something about that inflammatory milieu in the MS lesion, or the MS plaque, that prevents these oligodendrocyte precursor cells from becoming a fully functional myelin-producing cell.

So, there's a lot of effort now that we are funding of learning what's the impediment to that repair process, that differentiation process and how do we overcome it? What can we do to spur these oligodendrocyte precursor cells to becoming a fully functional, myelin-producing cell? That is aimed at the remyelination part of it.

For the axonal regeneration part of it, that is even a more difficult nut to crack. We've known for centuries, really, that if one damages a nerve in the central nervous system, that is, in the brain and spinal cord, if you cut an axon, for example, it does not regenerate. We also know that if you cut a nerve in the peripheral nervous system, say, in the arm or in the leg, it does have the potential to regenerate.

So, one of the issues has been, what's different about the central nervous system and the peripheral nervous system? And how do we overcome that propensity to not automatically repair and regrow an axon?

Some of our researchers now have identified a reason and maybe the reason, but at least a reason why that occurs, and the reason lies in

the whole issue of growth and development as opposed to repair of the nervous system.

So, it turns out that there are -- and this will sound counterintuitive the first time I say it. It turns out that there are proteins in normal myelin that prevent the regrowth of damaged axons. Now you're saying why would that occur? It seems like it shouldn't be that way. It seems like healthy myelin should promote the growth of damaged axons.

Well, as I said, the reason lies in the phenomenon of growth and development. And the fact that while a child is growing, growing in height, the spinal cord, for example, needs to grow as well. But when the body stops growing in height, you have to have signals that tell the spinal cord stop growing. You can imagine what would happen if the spinal cord tried to continued to elongate when there is no room for it. It would curl up like a pretzel.

So, as it turns out, there are proteins that are produced in mature myelin when the body stops growing that tells the axons, stop growing.

>>**Kate:** Wow, it sounds like there is just so much interesting stuff going on in both of these domains. It's really impressive.

>>**John Richert:** There are now at least two proteins of myelin that have been identified that have this function. One has the interesting name, descriptive name of "Nogo", and the other one is simply called myelin-associated glycoprotein. Now that we know that these two proteins play a role in stopping the regrowth of axons, this now gives us a new set of therapeutic targets that we can zone in on and try to inhibit those inhibitory functions of these proteins, so that we can allow the axons to regrow.

Tom>> There's some amazing work being done in finding 3 cures to MS ... and so far, we've just heard about the first two.

Tracey>> Much of that would not be possible without the help of the millions who are supporting the Society's research efforts.

Tom>> If you want to hear about the third cure, preventing MS, just click on part two on the right of your screen.

Tracey>> Wow, preventing MS! What a concept. That would be amazing!

Tom>> See you then!