



**Progressive MS- Treatment & Lifestyle Decisions-
Supplement to 2013 North American Education Program
Featuring: Amit Bar-Or, MD, CM, FRCPC, Montreal Neurological Institute,
McGill University;
Robert Fox , MD, Mellen Center for MS Treatment and Research at the
Cleveland Clinic**

Dr. Fox: In contrast to the excitement over the many treatment options we have for relapsing forms of MS, we don't have any effective therapies to alter the course of progressive MS. This includes primary progressive, and secondary progressive MS. And every day we hear our patients saying, okay, that's great for the relapsing MS patients, but what about us with progressive MS? And it is absolutely true that we do not have effective therapies for progressive MS. That said, it's not that we don't have treatments for progressive MS, it's just that the focus of our treatment is different. We don't have a therapy that alters the ultimate course of progressive MS, but we do have a lot of therapies that can improve the symptoms, improve the function of patients with progressive MS. We can help with weakness, we can help with spasticity, with walking, bladder, bowel, sexual, pain, there's so many different things, mood as well. There's a lot of different symptoms. There, there are very few symptoms of progressive MS that we don't have some treatment, have some modality that we can help improve the quality of life for patients.

Dr. Bar-Or: To date there's been no treatment that has been formally approved for primary progressive MS. And as we know people with primary

progressive MS represent about 10 to 15% of people out there living with MS. This is a situation where there are no obvious relapses and our experience has taught us the treatments that are effective at limiting relapses are not particularly effective at changing the trajectory of progression or the rate of progression that patients experience. So this is certainly one of the greatest unmet needs and one of the most important frontiers, both for the research community to better understand the biology contributing to primary progressive MS as well as to translate that into effective and safe treatments for this group of patients with MS.

Dr. Fox: One of the main challenges for developing a therapy for progressive MS is that we don't really understand what is progressive MS. We don't really know what's going on within the brain and the spinal cord that is causing that gradual, little by little progression of MS. We do know that it's probably not the same thing that is going on in the early stages. There is not active inflammation in the way we see it in early stages of MS. The anti-inflammatory therapies of early MS don't seem to work at all in progressive MS. So all of that points us towards the conclusion that whatever is going on is very different.

Dr. Bar-Or: When it comes to understanding and developing new treatments for multiple sclerosis of course one of the key approaches is to understand the biology that contributes to the injury so that we can then target it most effectively and most specifically. If we knew who the bad guys were, for instance in the immune system, we would choose and figure out how to only target them and leave the rest of the immune system intact and that of course could strike a much better balance between the efficacy and the safety. The other, the other thing to consider is understanding the biology that contributes to injury is what will end up leading to the treatments that in the long run are going to be most effective to change the course of MS. And we now appreciate something that we hadn't appreciated for many years, that in MS there are two different biologies that can contribute to injury.

There is the biology of relapses and we think that this involves immune system activation outside of the central nervous system, trafficking of bad guy cells into the central nervous system where they contribute to local

injury. Treatments that can limit the biology of relapses by changing the way cells respond in the periphery or changing their ability to traffic into the central nervous system can decrease new relapses from happening and thereby limit injury that is associated with relapses.

However, the biology that underlies progression of MS and the progression that is not related to relapses that don't get better but the true progression that primary progressive and secondary progressive MS patients experience independent of relapses, is a biology that we have not fully figured out. But this seems to be a biology that is not related to waves of immune attacks from the outside but rather to something that is happening within the central nervous system of patients.

One possibility is that this is also a type of inflammation, meaning that immune system responses are involved, but then it would not be immune system responses coming from the outside but rather immune responses that have essentially set up shop within the central nervous system and they're percolating and propagating inflammation and damage locally. If that's the case, then immune therapies may still be effective but these need to be therapies that don't just work in the periphery, but also get into the central nervous system so that they can work on what I call the compartmentalized inflammation in MS, meaning the inflammation that is within the central nervous system compartment.

Another possibility is that we're dealing not with inflammation but with another biology of progression that might be more of the degenerative side and for that again we need treatments that will access the central nervous system and be able to work on the neurobiology of MS in tandem with any targeting of the inflammation.

Over the last few years we have seen results from at least two large studies in primary progressive MS populations and unfortunately the primary outcome of the study which is the ability of the medication to decrease the rate of progression was not successfully met. However, very interestingly in both these studies when we looked back at the population of patients treated, there appeared to be a subpopulation of people who looked like they had primary progressive MS in order to qualify for entry to these studies who did

actually benefit and we now understand that probably 20 to 30% of people who have primary progressive MS may actually have under the surface some of the relapsing biology. Now that's very interesting because while they have this biology under the surface, we do not actually appreciate that they have relapses clinically, and yet, treatments that have been effective in limiting relapses may still help limit injury, at least to some extent in these patients and can then change the worsening of neurological dysfunction which may be related to relapses.

That said, while this is a very important appreciation, because when I see patients who have primary progressive MS, I do the best I can to see whether they do have under the surface any evidence of this relapsing biology and then might actually consider one of the standard relapsing remitting MS immune modulators as a reasonable choice for them to consider. That said, we still have to understand what really underlies the progression of MS that is not related to relapses because that really is a different biology and requires a different category of treatments.