The diagnosis of “secondary progressive MS” has long been thought to mark a shift in the course of the disease from a primarily inflammatory process to a neurodegenerative one. Although the majority of people with MS are initially diagnosed as “relapsing-remitting,” about half of them, after ten years, will transition to a secondary progressive disease course. This progressive phase is characterized by gradual loss of function and thought by some to herald a shift.

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IT’S JUST THE TIP OF THE ICEBERG
A New Paradigm For MS

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Welcome Dr. Miravalle

We are thrilled to welcome Dr. Augusto Miravalle, the newest member of our team at the Rocky Mountain MS Center at Anschutz Medical Campus. Dr. Miravalle joins us from Harvard University, where he spent the last year as an MS and Neuroimmunology Fellow. Born and raised in Argentina – he is fluent in both English and Spanish – Dr. Miravalle is an accomplished MS-specialty physician and has been consistently praised for his excellence in patient care. Interestingly, he is also a gifted concert pianist and has competed in a number of international piano competitions.

Changing Healthcare from the Ground Up

Reforming healthcare is headline news these days. It’s a highly contentious topic – probably the only place where there is agreement is that it’s a huge problem that will take time to fix.

We would like to propose a more immediate place to start.

A personal health record is simply a collection of the important information about you and your health concerns, compiled by the person who knows the most about it—you. It contains the information you need to verify accuracy, avoid duplication, ensure continuity of care, and provide easy and portable access to the data you need to make informed healthcare decisions and put you and your healthcare provider on the same page.

At the MS Center, we encourage people to participate fully in the management of their healthcare journey. To that end, we created a user-friendly planner to help people map their travels through the often confusing jungle of the healthcare system. We have mined 30 years of MS experience to organize and identify the types of resources and information that can strengthen the partnership between medical providers and those who live with MS. The Healthcare Navigator is a contact book, a journal, a resource guide, and a snapshot of current health challenges.

Join us on October 8th for a two-hour class that will provide the information you need to be an informed healthcare consumer. Participants will also receive the Healthcare Navigator.

To register call: 303-788-4030 ext. 100
Cost: $40
in MS pathology--from inflammation to some other process that causes neurons to die in the absence of inflammation. The nature of this “neurodegenerative process” has never been well understood.

An important study, published in March of this year, in the journal *Brain*, has provided some surprising new information on this topic. A group of researchers examined brain tissue from 67 people who had MS. What they discovered was evidence of “pronounced inflammation” not only in the brain tissue of people with acute and relapsing MS, but also in the brains of people with secondary and primary progressive disease. Evidence of demyelination and axonal degeneration was only found when there was also evidence of acute inflammation. These data strongly suggest that there is not a transition to a secondary disease process and challenge the notion that, in MS, the inflammation stops and then the neurodegenerative process takes over. When neurodegeneration was found in the absence of acute inflammation, the levels were similar to those of healthy, age-matched controls which suggests the degeneration was a consequence of the aging process.

This study challenges the increasingly prevalent notion that MS is partially or even primarily a neurodegenerative disease. It is also significant because, if the inflammation is indeed the primary culprit in the MS disease process, it has implications for how we treat the disease. What follows is a conversation with Dr. Timothy Vollmer, neurologist, MS researcher and Medical Director of The Rocky Mountain MS Center.

Q: It would be helpful to begin our conversation by establishing a few definitions. For the purpose of this discussion, what is inflammation?

**Dr. Vollmer:** Inflammation is certainly an imprecise term. For what we’re talking about here, inflammation

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Vollmer

should be understood to mean "an immune attack on the brain." When we look at patients as they go through the life-stages of MS, the majority of them seem to have an inflammatory process that is very brisk at first, and then it decreases over time until, for reasons we don't understand, it generally shuts off when patients reach their late 50s or early 60s.

Q: What is neurodegeneration?

Dr. Vollmer: Neurodegeneration means "death of nerve cells." There are two fundamental ways that can happen. In primary neurodegeneration there is a process going on inside the neuron that leads ultimately to its death and destruction. Any inflammation is thought to be a reaction to this primary process because treating that is very brisk at first, and then it decreases over time until, for reasons we don't understand, it generally shuts off when patients reach their late 50s or early 60s.

There is another type of neurodegeneration that is secondary to the inflammation—that is, it only occurs as a consequence of inflammation. In this case, the inflammation causes the cell death. It can do this in a number of different ways—by a direct attack with antibodies or T cells; or by creating an environment that is ultimately toxic to nerve cells; or by transecting fibers and preventing interneurons from firing, which deletes them from the system, because the brain doesn't keep non-functioning neurons around.

What the article in Brain suggests is a shift in thinking about this process in multiple sclerosis from this first type of neurodegeneration to the second.

Q: How has your thinking about MS evolved over the past 20 years?

Dr. Vollmer: I believe there have been four really important advances in our understanding of MS.

The first is that the majority of disease activity is sub-clinical. Our understanding of the tempo of the disease has been changed by what we have learned from the MRI. Twenty-five years ago, we thought MS was a disease that caused inflammation to occur in the brain but we didn’t think this inflammation was occurring all that often. We also thought we could see the disease activity pretty well, that by looking at a patient in clinic, we could tell how much damage they had and where they were headed in terms of the disease course. People were having relapses maybe once a year and we thought those relapses were due to these new local areas of inflammation. But, when the MRI came on board, we found people were actually having 10-20 inflammatory events per year but only one clinical relapse.

So, today we know that the clinical activity we see, at least in the relapsing stage of the disease, is just the tip of the iceberg. Most of the disease that occurs in MS is sub-clinical. When you are using standard MRI approaches, most gadolinium-enhancing lesions (90-95%) are clinically silent and are not associated with relapse. The patient doesn’t know they are going on and the physician doesn’t know they are going on, unless they do an MRI. That’s why we use MRI as a primary outcome measure in Phase I and Phase II studies because we see 10 to 20 times as much clinical activity as we would if we only counted clinically evident relapses.

The brain does a remarkable job of repairing and rewiring itself to overcome this ongoing, sub-clinical damage. But, all the time the brain is compensating, the brain is losing its substance—it is losing nerve cells, it is losing oligodendrocytes and incurring injury that, for a while, it can get around.

Another important advance in our understanding is that the current classification system we use (relapsing-remitting MS, secondary-progressive MS, primary-progressive MS) isn’t very useful and doesn’t predict whether a patient will respond to therapy. When you look at all the clinical trial and imaging data, the things that determine whether a patient responds to immunological therapy is not which MS classification they are in—it’s their age and whether they are having active inflammation. If patients are having active inflammation—by virtue of the fact that they are having relapses, or they are developing new T2 lesions, or they are having gad-enhancing lesions—then they respond to the therapies more or less.

The third advance in our thinking about MS is that we now believe the major target of the immune attack on the brain is not myelin—it’s the central nervous system—it’s neurons. In most patients neurons are included but in some patients they are the dominant targets. So, MS doesn’t just attack white matter in the brain—it attacks gray matter as well. It is not the number of white spots (lesions) patients have—it is the decrease in the population of neurons, that is, decrease in the cortical gray matter and deep gray matter—that ultimately determines disability and probably the onset of secondary progressive disease.

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Finally, the term “remission” is quite inaccurate. The disease is actually very active during this phase but it’s clinically invisible, and because it is invisible, we are missing the damage that is occurring. What we think of as remission (that time when symptoms improve) is actually cortical remodeling and rewiring, when functions are being shifted around and the brain is compensating for the injury caused by the immune attacks. The most likely explanation for the clinical onset of progressive disease is the inability of those compensatory mechanisms to continue to mask the disease activity that’s been going on all along. The onset of progressive disease may not represent a fundamental change in the biology of MS. It isn’t the onset of neurodegeneration, but rather, the brain has used up its reserve capacity and can no longer compensate for the sub-clinical disease activity.

Q: Why are 90% of all lesions clinically silent?

Dr. Vollmer: We probably overestimate our ability to understand this. It is probably a combination of factors. As previously mentioned, the ability of the brain to accommodate and repair itself is critical.

Location is also important. Most lesions on brain MRI are in the deep cerebral white matter where there are a large number of fibers from different systems. A lesion in that area might affect a small number of fibers from a large number of systems. Most of those systems have a large enough reserve capacity that, unless we are working at peak performance, (and very few of us are) we wouldn’t notice a change in them, and in fact, we don’t. A lesion occurring in the brain stem or spinal cord is much more likely to be symptomatic but — even in the spinal cord, where we thought any damage would be evident — we still don’t see clinical evidence of about half to two-thirds of the disease occurring there.
An inflammatory event can have a variable impact on the ability of nerve signals to get through an affected area. Demyelination can transiently affect the signal in a particular fiber and axonal transection can terminate it, but remember, nerve fibers aren’t unitary structures. They work as a sum total of all the firing that’s going on and they work in sequence with other pathways. So, some pathways may be more symptomatic because they are more sensitive and some may be less so because they are part of redundant systems.

It’s not just the location. The probability that a lesion will be clinically apparent also depends on whether it occurs in an eloquent pathway and has the kind of immune attack that actually destroys nerve fibers, so that it has a big effect. If it’s just destroying myelin, it may not have that effect—when we measure myelin destruction specifically, there is a pretty low correlation with disability.

And finally, you have to look at what the patient is doing that day. If someone is sitting at a desk and not moving much, they may not notice that something isn’t working 100% because they aren’t pushing 100%.

Q: Why is it, in MS, that two patients have the same disease but one ends up with disability and the other with mild disease?

Dr. Vollmer: You would predict that patients who have more inflammation would have a worse outcome. In general that’s true, but it turns out not to be the only factor. If you follow patients with MRI and you measure the amount of injury that’s occurring in the brain (by using T2 or FLAIR), you can compare patients who have the same amount of white spot damage in the brain stem, spinal cord and cerebral hemispheres. What you find is that one of them is very disabled and the other is not. We used to think that the variable outcomes were because the nervous system was being hit in a random sort of way—it was a matter of luck that your spots resulted in more disability because they occurred in a critical pathway. That’s probably not true.

The thing that seems to correlate better on the MRI with whether or not you are disabled is whether those white spots are associated with T1 black holes and whether they are associated with marked loss of gray matter in the brain—loss of neurons. So, the more important factor is not simply the amount of inflammation, but how damaging it is to the neural component—not to the myelin component but to the nerve component. In some patients the immune attack on the brain is much more destructive to the neurons and axons: those are the patients who will have the higher level of disability.

Q: You have several times referred to the “different kinds of immune attacks in MS.” What do you mean?

Dr. Vollmer: The immune attack on the brain in one MS patient 

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**MRI: Making MS Visible**

The MRI is an important tool in the diagnosis and treatment of multiple sclerosis. Different MRI sequences offer different ways to look at what’s going on in the brain and spinal cord. MRIs are commonly done of the brain both to diagnosis the disease and to follow its course. Spinal MRIs are not routinely repeated after diagnosis.

The most common sequences used in MS are T1, T2 and FLAIR. An injected dye, gadolinium, can be used to “enhance” a T1 sequence. These different sequences provide different information about the impact of MS on the brain.

T2 sequences show demyelination, glial scarring and axonal loss. Lesions (MS plaques) will appear as white spots, hence the phrase “counting white spots.” This sequence shows “old lesions” and provides a measure of how active the MS inflammatory process has been over time.

The FLAIR sequence is a modification of the T2 sequence. It provides essentially the same information as the T2 sequence but it is more sensitive for disease.

In the T1 sequence the lesions in the brain will appear to be black if the nerve axons have been destroyed—hence the name “black holes.” Where the axons have been transected we see “T1 black holes” which show there has been a loss of structure.

A gadolinium-enhanced T1 sequence is used to detect active inflammation and new disease activity. What you see, however, can vary, depending on variables such as how much gadolinium is used and how long you wait before doing the MRI after the gadolinium is infused.
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Vollmer

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is not necessarily the same as that in another MS patient. The immune system has a number of different ways that it can damage the brain and those different mechanisms may or may not be employed in a given patient. For example, T cells can move in and recruit other T cells that can directly kill neurons, or oligodendrocytes or other cells in the brain. Or, they can release toxic molecules that can just sort of damage everything in the area. Or they can recruit macrophages, monocytes, and dendritic cells that can move in and begin to strip myelin.

Differences in the type of immune attack can be determined by genetics, or by the type of brain antigens targeted in your immune attack or by your environment and what kinds of things you’ve been exposed to. There is an interaction between your environment and your genetics: how that works is not clear. What influences this variation in the clinical expression of MS is an area of research that is not receiving as much attention as it should given that the immune response is usually pretty similar in patients.

Q: Sometimes, although patients report that their MS is getting worse, the neurologist will tell them that the MRI has not changed. Do MRIs always detect disease activity?

Dr. Vollmer:

For reasons that are not fully clear, when an area of the brain is injured once, it becomes a preferred target of subsequent attacks and has a higher rate of repeat inflammation. So, any lesion we see in a patient may be the sum of multiple inflammatory attacks in the same spot that have accumulated over time. When you look at an MRI, and it looks the same as the last MRI, it may be over-interpreting the data to say that there is no change. New lesions may appear in the bed of old lesions, and may be buried under old disease where you can’t see them. MRIs are insensitive and can’t see the gradual progression of that lesion over time. There is no perfect MRI sequence that can detect all disease activity.

Q: You talk about “patients who are at a high risk for disability.” Can you only identify them from MRI or are there indications in their clinical presentation as well?

Dr. Vollmer: You do get hints. Patients who have serious attacks, with a high level of disability and poor recovery at the onset of the disease are at a higher risk to have major disability down the road. However, that’s only a minority of patients. Initially, patients often have serious attacks, but then they have pretty much have full recovery.

There are broadly three factors that determine your outcome: one is the amount of inflammation you are having, the second is how destructive

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It is not surprising that MS disability (impairment) is related to the amount of damage that the brain and spinal cord (central nervous system or CNS) have sustained as the result of the MS-related inflammatory process. What may be surprising, however, is that the amount of damage that the CNS has sustained is only one factor in determining disability. Two people with similar lesions in similar locations in their brains may have very different functional abilities. Or, stated differently, all people with MS have some degree of brain damage, but not all have cognitive problems. Why?

One answer is that people have different levels of brain and cognitive reserve. These two related terms refer to the brain’s resilience to injury. Brain reserve refers to such characteristics as brain size and surviving neuron (nerve cell) count. Indeed, different people have different size brains and different numbers of neurons and this may allow one person to have more resilience in the face of MS damage than another.

Cognitive reserve is more complex and probably more important. It refers to the efficiency with which people use their existing brain circuits as well as their ability to compensate for injury by developing new neuronal pathways. Cognitive reserve is the concept used to explain the fact that one person can function better than another despite similar injury—even though they have the same brain reserve.

Cognitive reserve has been much discussed as an important factor in many neurological diseases, especially Alzheimer Disease. But until recently, the concept of brain reserve has been little discussed and little researched in relationship to MS. A recent paper has shown that cognitive reserve can indeed protect against MS-related cognitive decline. Researchers used a verbal intelligence test to estimate

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that inflammation is, and the third is how much reparative capacity your brain inherently has. These three factors all interact and the common final denominator is the loss of gray matter. However these three factors interact, you can see their consequence in terms of how fast the gray matter is disappearing from the brain.

Q: How does this recent study, which suggests the disease process in MS is primarily inflammatory, change how you think about treating MS patients?

Dr. Vollmer: It's an important issue when we think about long-term management of MS. Given that the only process that we can identify right now is an inflammatory process—if we want to change the outcome, we need to shut off that inflammatory process early. And that's not what we do—we only suppress it slightly, and over the long term that has not resulted in a major change in outcomes for patients. Clinicians are treating patients in the clinic based on what they look like right now. They only use aggressive treatment when patients are clearly failing with the first-line therapies and accumulating more disability.

The model we are trying to promote now says: don't wait for them to develop disability. Use the MRI to determine how active they are and be willing to take the risks upfront, before they get disability, by selecting patients based on what's happening to their brains, particularly in terms of TI black holes and ventricular size.

If we wait until patients have fixed disability, we have waited too long. They have lost so much neural tissue that we can't restore function. What I think is critical for everyone to understand is this: it's not where patients are now that is important. It's where they may be when they are 55 or 65 years of age.

What we are trying to do is protect their brains for their futures. That's a different paradigm.
cognitive reserve in a group of people with MS. Those with higher pre-MS verbal abilities and lower pre-MS verbal abilities were compared to people without MS. MS patients with lower pre-MS verbal intelligence scores didn’t perform as well as healthy controls with equal cognitive reserve whereas MS patients with higher cognitive reserve did perform as well as healthy controls with equal cognitive reserve on tests measuring complex processing as well as verbal learning and memory. This finding fits with another study showing that higher education may protect MS patients from cognitive impairments.

These studies are important not only because they show a protective effect from education and verbal intelligence, but because they suggest that those factors that support cognitive reserve in general may protect MS patients from cognitive decline. This is good news. Borrowing from the Alzheimer disease literature, there are a number of factors, some of which are within our control as adults, that contribute to cognitive reserve. These factors include:

- Increased physical exercise;
- Greater social interaction;
- Greater participation in leisure activities;
- Higher education;
- Higher occupational attainment
- Greater participation in intellectual activities.

Broadly speaking, there are two ways to prevent MS-related disability. One obvious and critical strategy is to protect the brain from MS-related inflammation. Increasingly, medications are able to accomplish this goal. The other emerging strategy is to pursue a lifestyle that is likely to increase cognitive reserve. The brain is a remarkably adaptable organ and the choices we make can help all of us — whether we have MS or not — mitigate the effects of inevitable CNS injuries.

"My dad was diagnosed with MS in 1974, and he couldn’t accept that there were no treatments for this disease. He founded the Rocky Mountain MS Center in 1978, with the help of his friends in the Denver business community. His legacy lives on through the continuing work of the Rocky Mountain MS Center." — Adam Writer

Naming the Rocky Mountain MS Center as a recipient of a bequest in your estate is an act of great meaning, and one that makes a difference for those living with MS. Donors of planned gifts are recognized as members of the N. Daren Writer Society. Your generosity will help us realize our vision of a world in which MS is no longer the most commonly diagnosed neurological illness of young adults.

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Brain Drain
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We need your support now more than ever! Join us Saturday, September 12, 2009. Festivities begin at 6 p.m at Infinity Park Event Center in Glendale, CO.

For more information, please visit www.mscenter.org and see the ad on page 7.
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MS 101 for the Newly Diagnosed
Mondays, Aug. 17, Sept. 14,
Oct. 5, Oct. 19

Join Pat Kennedy, Nurse Practitioner and Pat Daily, Director of Support Services for an informal discussion of issues important to people newly diagnosed with multiple sclerosis. Family members and friends are also welcome to join this small group seminar. There is no charge, but registration is required and class size is limited. Call 303-788-4030 X 102 or email alinstrom@mscenter.org.

MS 201 Living with MS
Thursday, Sept. 24th from 5-7

Join Tom Stewart, M.S, PA-C, and Pat Daily, LCSW for a conversation about wellness and the range of treatment options for MS and its symptoms. Call 303-788-4030 ext. 100 to register.

Having Trouble Accessing Healthcare?

Metro Communities Providers Network, working with the Rocky Mountain MS Center and its affiliated expert health care providers, is now providing a new service to meet the special needs of people with MS who have difficulty accessing healthcare services. This clinic is staffed by Mr. Thomas Stewart, a physician assistant. Mr. Stewart works in consultation with primary-care physician Filip Amadore, physiatrist Karen Theriot, M.D., neurologist Timothy Vollmer, M.D., and our expert rehabilitation team.

If you do not have insurance or have inadequate insurance and would like to learn more about this clinic, please call Corinne Carrigan at MCPN 303-360-3712.

Registration is required for all seminars. Register online at www.mscenter.org, or by calling Amber at 303-788-4030 x102.