1 AN INTRODUCTION TO MS

1. What Are the Worst Symptoms for Newly Diagnosed Patients?

There is no question in my mind that the worst symptoms for almost all newly diagnosed patients are anxiety and fear. Most MS patients are young, healthy people at the time they are diagnosed. Many have not seen a doctor for many years when the symptoms of MS begin to hit them out of nowhere. Naturally, questions arise about the future: Will I be able to continue to walk, to work, to have a family? For many newly diagnosed patients, the anxiety far outweighs whatever symptoms they may have experienced that lead to the diagnosis. In thinking about this, I am reminded of a patient of mine who suffered a spinal cord injury many years ago. He will never walk again, but from a psychiatric standpoint, he long ago adjusted to his illness and is doing well. Many of my patients will never suffer this level of disability. However, they are faced with uncertainty and live in fear of an unpredictable disease.

Although MS is obviously a significant disease for many people, I hope that with newer and more powerful treatments we are able to continually prevent disability and relieve the symptoms many patients feel. I do not want patients to think that they are made of glass or that they are a different species. As much as possible, I want them to try to lead the same life they led the day before they were diagnosed.

2. What Is MS?

MS is a disorder of the central nervous system, which is composed of the brain and spinal cord. It affects about 1 in 750 people in the United States, which means there are approximately 400,000 Americans currently living with the illness. Around the world, there are about 2.5 million people with the disease. More recent research suggests that these numbers are a vast underestimate, and that nearly 1 million people have MS in the United States alone.

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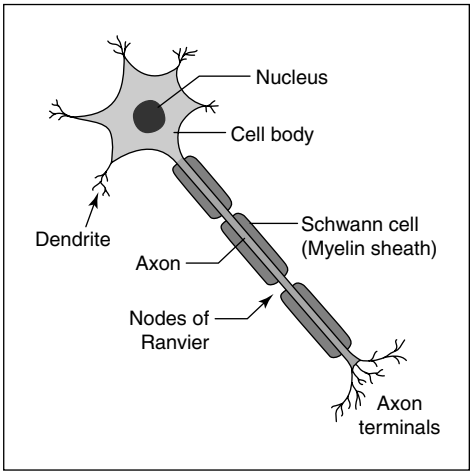
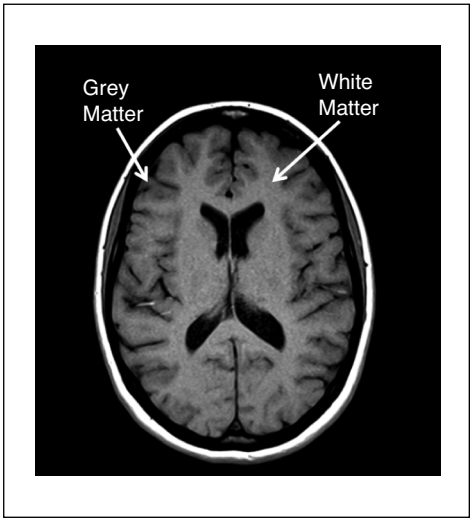
MS typically affects people between the ages of 15 and 40, though occasionally people are diagnosed outside of this age range. Aside from trauma, it is the major cause of neurological disability in young people. Once MS has been diagnosed, it is not possible to provide anything other than a very general prognosis, though there are certain risk factors associated with an aggressive disease course. It is a mysterious illness. No one knows what causes it, though certain risk factors have been identified.

3. Neuroscience Basics



Anatomy of a neuron.



Grey and white matter seen in a normal MRI.

To get a general understanding of what happens in MS, it is important to review some basic neuroscience. Neurons, the main cells in the brain, are composed of a cell body, called the soma, and a tail, called the axon. Axons are the means by which neurons communicate with each other and their structure can be compared to a telephone cord. The axon is the wire at the center of the cord. Each axon has a protective coating composed of fats and lipids, termed the myelin sheath. Myelin is made by cells called oligodendrocytes. Myelin allows electricity to conduct much faster along axons, permitting rapid communication between cells. More specifically, myelin allows an electrical signal to "jump" along an axon (at spaces called nodes of Ranvier), in a process called saltatory conduction.

The soma, or cell body, of neurons of neurons are in the outer part of the brain, called the cortex or grey matter, while the axons and myelin are in the inner part of the brain, called the white matter.

4. What Happens in MS?

MS is considered an immune-mediated disorder, meaning that the immune system attacks healthy parts of the body. In MS, the primary target is the myelin sheath, though with advanced disease the axons can also be damaged. When this happens, conduction within the nervous system slows down or stops entirely, and patients develop neurological symptoms. Unlike many autoimmune diseases, no pathological antibody has ever been discovered. There are also no blood tests to diagnose MS. Although MS has traditionally been considered a disease of the white matter, abnormalities of the grey matter have become recognized as playing an important role as well. MS only affects the central nervous system; the peripheral nerves in the arms and legs are completely spared.

5. What Causes MS?

One of the most common questions is what causes MS. The short answer is that no one knows for sure, and there is no single cause. It's like asking why someone is rich; unless that person won the lottery, there is likely no single answer. There are some known risk factors, however.

GENETICS: Genes play a role in MS, though they are not the determining factor as to whether a person will develop the disease or not. Most people are the first in their families to have the disease. If a first-degree relative, such as a sibling or a parent, has MS, the odds that a person will have the illness are about 3% to 5%. If both parents have the disease, there is about a 12% chance that their child will have it. Even in identical twins who share the same DNA, the odds of one twin developing MS if the other has it are only 34% for women and 5% for men. For fraternal (non-identical twins) the risk is only about 5%.

A common fear among people with MS is that it could be passed on to their children. In the United States, the overall risk of developing MS is about 1 in 750 people. So, while the rate of MS for people with affected family members is substantially higher than that of the general population, the vast majority of people with MS have children who do not develop the disease.

The most common genes linked to MS are involved in the human leukocyte antigen system, which plays a role in the immune system. Presently, over 200 genetic loci have been linked to MS. Most of these genes were discovered in the last 4 years.

The advances in the genetics of MS has recently expanded significantly and will serve to further our understanding of the disease. There are many

diseases, both neurological and otherwise, where the genetics are almost entirely understood but there is no cure.

For MS and many other immune-mediated diseases, the finding of over 200 genes linked to the illness makes understanding and putting these discoveries to practical use much more difficult. Clearly genes play a role in MS, but they are not the major determinant in disease development. As stated previously, if one identical twin has the illness, the chances that the twin will have the illness are less than 50%. Since identical twins share the exact same DNA, some unknown factor must influence who develops MS and who does not. Moreover, these genes do not provide a prognosis about the severity level of MS.

I suspect that, in the future, genetic testing will play a powerful role in determining who is at risk for developing MS and which treatments will be best for that person. Unfortunately, the science just isn't there today.

SEX: As with most autoimmune illnesses, MS is more than twice as common in women than in men. A report from Canada shows that this imbalance has become even more pronounced in recent years for unclear reasons.

RACE: MS has traditionally been thought to not occur equally in all ethnic groups. Caucasians tend to have the highest rate of the illness, while other races have a lower rate. However, recent research suggests that there is not a large difference among races in incidence of MS, at least in the United States. In black people from Africa, the disease is rare, though not unheard of.

ENVIRONMENTAL FACTORS: The risk of getting MS depends on where a person spends the first 15 years of life. People who live near the Equator have very low rates of MS, but the rate increases the farther one travels away from the Equator. The rate of MS in Ohio is almost double the rate in Texas. There are several theories as to why this might be, but the most popular one is that people who live near the Equator have higher rates of exposure to ultraviolent light, which the body requires to make vitamin D. Low vitamin D levels have been linked to MS. For example, in one study of 800,000 women from Finland, the women with the lowest vitamin D levels had double the MS risk, while those with the highest levels had the lowest risk. Another study found that women exposed to more sunlight during childhood had a lower risk of MS. Currently, vitamin D is being explored as a possible preventive treatment in those people with a strong family history of MS.

EXPOSURE TO INFECTIOUS AGENTS: Infectious agents have long been suspected to be a cause of MS, though no pathogen has been definitively

shown to cause the disease. Certain "outbreaks" of MS have occurred, most notably in the Faroe Islands, a small group of islands in the North Atlantic Ocean. Multiple cases of MS occurred there after British soldiers occupied the islands during World War II.

The strongest evidence that an infection predisposes people to MS exists for the Epstein-Barr virus (EBV), which causes mononucleosis. Although the majority of the population has evidence of exposure to EBV, the rate is almost 100% in patients with MS. Exposure to the varicella zoster virus, which causes chickenpox and shingles, has also been implicated in causing MS. More recently, in 2013, researchers identified a bacterium, *Clostridium perfringens* type B, which seems to be related to MS.

Other research indicates that certain infections may help prevent MS, a theory known as the hygiene hypothesis. While it is wonderful that children no longer die of infectious diseases at high rates (at least in wealthy countries), growing up in a relatively sterile environment may lead to more autoimmune diseases. Indeed, one of the more adventurous treatments for MS and other autoimmune disorders is infecting people with parasitic worms in the hope that this will help dampen down the immune response.

OBESITY: In 2013, a study found that obese girls are at greater risk of developing MS. According to the study, the risk was more than one and one-half times higher for overweight girls, almost two times higher in moderately obese girls, and almost four times higher in extremely obese girls. Several other studies have found similar findings. This is likely related to hormonal changes that occur as a result of obesity. The finding that obesity is linked to MS is not as strong in boys.

SODIUM INTAKE: In 2013, a study found that a high sodium diet was linked to the onset of MS. However, another study in 2017 found that there was no such risk.

CONCUSSION: One study from 2017 found that concussions in adolescence, particularly repeated concussions, were associated with an increased risk of MS

SMOKING: The main behavioral factor that leads to MS is that old demon—cigarette smoking—which nearly doubles the risk of developing MS.

In summary, there is no single cause of MS. Rather, it is an illness that occurs in genetically vulnerable individuals exposed to certain environmental conditions. Patients should know that they did not cause their MS. Many MS patients led the healthiest lifestyles imaginable prior to their

diagnosis—some professional athletes and dancers have been diagnosed. In contrast, people who smoke, use drugs, eat only junk food, and never exercise are certainly not leading healthy lifestyles. They have much higher rates of cancer and cardiovascular disease, but they do not necessarily have a higher risk of MS. Put another way, if I were an evil doctor who set out to purposefully give someone MS, I would fail. More work remains to be done to illuminate the causes of MS and more discoveries are on the horizon.

Finally, it is important to know what does *not* cause MS. There is no compelling evidence that stress, "toxins," or an unhealthy diet can cause MS. Vaccinations have also been definitively ruled out as a cause of MS.

6. How Is MS Diagnosed?

In medical school, every doctor is taught that the key to a correct diagnosis is obtaining a comprehensive history and performing a thorough physical examination, with radiographic and laboratory tests serving as invaluable aids. The diagnosis of MS is no different. The key to diagnosing MS is to identify two separate episodes of neurological dysfunction that have lasted at least 24 hours and occurred at different points in time (at least 30 days apart) in different parts of the central nervous system. This is technically referred to as dissemination in space and dissemination in time.

In patients who provide a history of two separate neurological relapses with evidence on physical exam of two or more lesions, no further evidence is required to diagnosis MS. However, many patients will come to the neurologist after having had a single episode of neurological dysfunction. Once a patient presents with a neurological symptom suggestive of MS, most neurologists will order a magnetic resonance image (MRI) of the brain and spinal cord. If this reveals lesions typical of MS, further tests are usually unnecessary. However, if the MRI is not typical for MS, a lumbar puncture might be necessary to look for a marker of inflammation known as oligoclonal bands (discussed in the following) in the central nervous system. Only if certain abnormalities are present on these tests can the diagnosis of MS be made. For example, if an MRI shows evidence of both old and new lesions (MRIs are discussed more in the following), this satisfies the criteria for separation in space and time, and a diagnosis of MS can be made in a patient who has had a single clinical event. If such lesions are not present, then patients with only one event are deemed to have clinically isolated syndrome. Only time will tell if a patient with clinically isolated syndrome will develop MS.

The formal criteria for diagnosing MS are known as the McDonald Criteria, and they were most recently updated in 2017. It is important to

SUMMARY OF 2017 MCDONALD CRITERIA FOR THE DIAGNOSIS OF MS

✔ *Requires elimination of more likely diagnoses*
✔ *Requires demonstration of dissemination of lesions in the central nervous system in space and time*

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
…in a person who has experienced a typical attack/CIS at onset	
● 2 or more attacks and clinical evidence of 2 or more lesions; OR ● 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None. DIS and DIT have been met.
● 2 or more attacks and clinical evidence of 1 lesion	DIS shown by one of these criteria: – additional clinical attack implicating different CNS site – 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxta cortical, infratentorial or spinal cord
● 1 attack and clinical evidence of 2 or more lesions	DIT shown by one of these criteria: – Additional clinical attack – Simultaneous presence of bothenhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – CSF oligoclonal bands
● 1 attack and clinical evidence of 1: lesion	DIS shown by one of these criteria: – Additional attack implicating different CNS site – I or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxta cortical, infratentorial or spinal cord **AND** DIT shown by one of these criteria: – additional clinical attack – Simultaneous presence of bothenhancing and non-enhancing MS-typical MRI-lesions, or new T2 or enhancing MRI-lesion compared to baseline scan (without regard to timing of baseline scan) – CSF oligoclonal bands
…in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least two of these criteria: – 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) – 2 or more T2 spinal cord lesions – CSF oligoclonal bands

DIT = Dissemination In time **DIS** = Dissemination in space **CNS** = Central nervous system
CSF = Cerebrospinal fluid **T2 lesion** = Hyperintense lesion on T2-weighted MRI

The 2017 McDonald Criteria. (Used with permission of the National Multiple Sclerosis Society.)

remember that these criteria were not delivered to neurologists on stone tablets. Rather, experts in the field meet periodically and decide on these criteria. At some point in the future, they will be tweaked again.

7. Do I Need a Lumbar Puncture?

If an evil doctor wanted to instill fear and horror in the heart of patients everywhere, the doctor would come up with the lumbar puncture. Yet, this is a test that I find myself frequently recommending for some terrified souls. As stated previously, the diagnosis of MS is primarily a clinical one, made by talking to and examining patients. All patients with suspected MS will also have MRIs of their brain and spine. In those patients for whom the history, physical, and MRI are highly suggestive of MS, there is not much of a role for a lumbar puncture.

Approximately 90% of MS patients have a marker of inflammation in the central nervous system called oligoclonal bands. In patients with a single relapse and clinical or MRI demonstration of dissemination in space, the presence of oligoclonal bands allows for a formal diagnosis of MS. Given that most neurologists would suggest treatment to such patients, a lumbar puncture is not always necessary for them either.

However, in ambiguous situations, a lumbar puncture can help determine whether or not the patient has MS. There are some patients for whom the diagnosis of MS is unclear, as many other diseases can mimic MS, both clinically and on the MRI. A lumbar puncture to look for oligoclonal bands is most useful when the history, neurological exam, or MRI are in any way atypical for MS. Examples of atypical presentations include:

- Patients with symptoms not usually seen initially in MS, such as depression, language impairment, or significant cognitive impairment.
- Patients with symptoms that are characteristic of MS, yet with a relatively normal MRI or an MRI that shows abnormalities that are atypical for MS.
- Patients with another illness that can mimic MS.
- Patients outside of the normal age range for MS.
- Patients with symptoms outside of the central nervous system, such as a fever, rash, or weight loss.

If oligoclonal bands are absent in these patients, an alternative diagnosis to MS should be considered. Also, the lumbar puncture should not show too many other abnormalities, such as numerous white blood cells or a very elevated protein level. If these are found, an alternative diagnosis

should be sought. Occasionally, some patients request a lumbar puncture, as they want to be as certain as possible about the diagnosis.

The presence or absence of oligoclonal bands may also provide a small clue about the prognosis of MS. One study that investigated the spinal fluid of patients who had a single episode suggestive of MS found that patients with oligoclonal bands had twice the risk for having a second attack, regardless of the initial MRI. The presence of these bands, however, did not seem to influence the development of disability. Another study found that patients with MS, but without oligoclonal bands, "were significantly more likely to exhibit neurological or systemic clinical features atypical of MS (headaches, neuropsychiatric features, and skin changes)." However, other studies have not identified a difference between MS patients with and without oligoclonal bands.

Lastly, oligoclonal bands are not specific for MS, and they can be found in a wide range of other neuro-inflammatory diseases.

8. What Should I Expect With a Lumbar Puncture?

WILL IT HURT? It might. Lumbar punctures require placing a needle into the back. A local anesthetic will be applied to numb the area, but most people can expect some degree of pain. In my hospital, we are spoiled in having radiologists perform the lumbar punctures. They are able to use imaging to guide the needle right where it needs to go. In most cases, however, the lumbar puncture is performed at the bedside by a neurologist who guides the needle by feeling alone. Naturally, the ease of this procedure depends on the experience of the neurologist and the size of the person undergoing the lumbar puncture.

In my experience, patients vary widely in their tolerance of lumbar punctures. I had one patient fall asleep during what is usually the most painful part, while others have screamed in pain when I washed their back. If someone is terrified, a mild sedative may help.

Some patients develop a headache a day or two after a lumbar puncture. This headache, while not serious, can be very painful. It is a positional headache that lessens when people lie down but returns with a vengeance when they stand up. Fortunately, there is a simple cure for this called a blood patch. In a blood patch, a doctor will inject the patient's own blood at the same location as the original lumbar puncture. This procedure is highly effective in instantly and permanently eliminating the headache.

IS IT DANGEROUS? Not really. When done properly, there is very little risk for any serious complication, such as paralysis or infection. The procedure

does have to be done in a sterile fashion to minimize the risk of infection. This does not mean that it has to be done in a sterile operating room, however. To minimize the risk of bleeding, a lumbar puncture should not be performed on someone with a bleeding disorder.

Fortunately, a lumbar puncture is a procedure that someone with a possible diagnosis of MS needs only experience once. It usually takes about 30 minutes, and patients can leave as soon as it is over, though they are advised to relax for the rest of the day. So, while it can be painful and scary, it should not be viewed as a "major procedure" or something that carries a significant risk of permanent damage.

In summary, a lumbar puncture is most useful in patients for whom the clinical diagnosis of MS is a possibility, but not a certainty. Although it is unpleasant to undergo a lumbar puncture, it is worth doing in some patients, given that it might make the difference between a diagnosis of MS or not.

9. What Are the Initial Symptoms of MS?

Since MS can affect the entire brain and spinal cord, the initial symptoms of MS can include almost any symptom in neurology. However, some symptoms are more common than others. Weakness and sensory disturbances are the two most common initial symptoms in MS, simply because these axons span the length of the central nervous system, from the surface of the brain to the end of the spinal cord. Any MS lesion is, therefore, very likely to affect one or both of these pathways. Visual symptoms—a painful, partial loss of vision in one eye (termed optic neuritis), or double vision—are also very common initial symptoms. The symptoms usually do not develop suddenly, like a stroke, but come on over the course of several hours or days.

The most common initial symptoms in MS are:

- Sensory abnormalities (occurs in 34% of people with MS), which is a numbness and tingling in the feet, hands, torso, or one side of the face
- Weakness (22%)
- Visual loss or double vision (21%)
- Clumsiness (11%)
- Vertigo (4%)

Other characteristic symptoms include Lhermitte's sign, which is a brief shock-like sensation that some patients have when they flex their neck due to a lesion in the cervical spine. Other patients may have an unpleasant squeezing sensation on their torso, which is informally termed the "MS hug."

It is often easy for people to ignore a little numbness or weakness, especially as these symptoms often go away without any treatment. It is also common for doctors to misattribute the initial symptoms of MS to something more benign, such as a "pinched nerve" or muscle strain. Occasionally, a patient will have MS for many years before they seek medical attention or receive the correct diagnosis. In contrast, symptoms such as visual loss, double vision, imbalance, and vertigo are less likely to be ignored or misdiagnosed. Other neurological symptoms, such as cognitive deficits, psychiatric symptoms, and language difficulties, may be the initial symptom of MS, but this is extremely rare.

10. What Is a Relapse?

Relapses, which are also called flares, attacks, or exacerbations, are a hallmark feature of MS. This characteristic defines the disease for most people, at least in the early stages, and most of the medicines for MS have been approved based on their ability to prevent relapses. Despite this, some patients are confused about what a relapse actually is and what it means for their prognosis.

Let me clarify some important points in the definition of a relapse based on conversations I have had with patients who are confused by this admittedly confusing topic.

First of all, relapses have to last at least 24 hours, although usually they last at least several days or weeks. I have met many worried patients who believe they have had numerous relapses after experiencing a transient neurological symptom lasting for only a few minutes. With rare exceptions

What Is a Relapse?

- Neurological disturbance of kind seen in MS.
- Subjective report or objective observation.
- At least 24 hours duration in absence of fever or infection.
- Excludes pseudoattacks, single paroxysmal symptoms (multiple episodes of paroxysmal symptoms occurring over 24 hours or more are acceptable as evidence.)
- Some historical events with symptoms and pattern typical for MS can provide reasonable evidence of previous demyelinating event(s), even without objective findings.

Determining Time Between Attacks

- At least 30 days between onset of event 1 and 2

(such as pain on one side of the face), these transient events are not considered relapses. Persistent symptoms of fatigue or "brain fog" are also not considered relapses, though they can be quite disabling.

Also, to be considered a relapse, the symptom almost always has to be something brand new. Many patients recover well from relapses, though sometimes the recovery is not complete. Symptoms such as tingling, weakness, stiffness, visual loss, or double vision may come and go for reasons that are not entirely clear. These fluctuations of existing symptoms are not considered to be relapses. Admittedly, it is often difficult to tell if a patient is having a new relapse or a recurrence of an old symptom.

Moreover, a relapse cannot occur in the setting of a fever or infection. When the symptoms of a relapse occur in these circumstances, it is termed a *pseudorelapse*. During a pseudorelapse, patients can feel worse, but this usually is due to the re-emergence of old, partially healed symptoms when the body is stressed. This most commonly occurs in the setting of a urinary tract infection. Fatigue or stress may also bring out old symptoms.

To understand why pseudorelapses may occur, consider the scenario of a broken bone. Though a bone may heal, it will probably not return to its full strength. If it is stressed again, it is more likely to break in the same location. The same is true in MS and for the nervous system; fevers, infections, or metabolic derangements can cause old, previously healed, symptoms to temporarily return. This is why many neurologists will inquire about symptoms of an infection and check for a urinary tract infection prior to treating patients for a relapse. It is important that patients tell their neurologist about any symptoms of an infection if they feel they are experiencing a relapse.

11. What Are the Stages and Different Types of MS?

MS presents in very different ways in different patients, and several different categories have been defined. The most common way to categorize MS, however, is to track its course over time. At present, there are four categories of MS:

CATEGORY 1: CLINICALLY ISOLATED SYNDROME (CIS): Patients who have had one clinical event are said to have clinically isolated syndrome or CIS. If certain findings are present on either the MRI or in the cerebrospinal fluid, patients with one clinical event can be diagnosed with MS. Otherwise, a diagnosis of MS can be made only if the patient develops lesions not previously seen on the MRI or experiences a second clinical event. The distinction between MS and CIS is somewhat artificial. CIS is usually a precursor to MS, not a different disease. Because the evidence suggests

that MS is best treated in its early stages, most neurologists recommend initiating treatment after the first event indicative of MS.

CATEGORY 2: RELAPSING-REMITTING MS (RRMS): About 90 percent of patients are diagnosed with relapsing-remitting MS (RRMS). This term refers to the tendency of an MS symptom to develop rather abruptly (a relapse) and to then gradually abate over the next few days or weeks (a remission). Usually patients recover well, but it is common to be left with some residual symptoms. There can be a high degree of variability in the specific symptoms, the frequency, the severity, and the degree of recovery from relapses. But as long as patients are experiencing relapses without progression of their symptoms in between, they are considered to have RRMS.

RRMS is further subdivided as follows:

- **Active**: The patient is experiencing a relapse and/or new MRI activity.
- **Not active**: No disease activity is occurring.
- **Not active but worsening:** Disability becomes worse as symptoms persist.
- **Active but not worsening**: There is new MRI activity, but no worsening of disability or new clinical symptoms.

Almost all of the treatments available for MS have been studied and approved for RRMS. Therefore, it is very important that neurologists spend time talking with their patients to understand not only their current symptoms, but how these symptoms began and progressed over time.

CATEGORY 3: SECONDARY PROGRESSIVE MS (SPMS): After 15 to 20, years most patients with RRMS enter what is called the secondary-progressive phase (SPMS). In SPMS, relapses either disappear completely or are very infrequent. Yet there is a slow but steady increase in disability. Patients in this stage of the illness may tell you that 1 year ago they could walk 10 blocks before needing a rest, but now they can walk only eight. Patients with SPMS develop symptoms similar to the way my hair is going gray, slowly but surely.

There is no formal transition between RRMS and SPMS, nor are there laboratory tests or radiographic tests to distinguish between these two stages of the illness. Again, the SPMS stage of the illness can only be determined by talking with patients to understand their current symptoms and examining them. Patients who are diagnosed at a younger age tend to remain in the RRMS phase longer than those who are diagnosed at a later age.

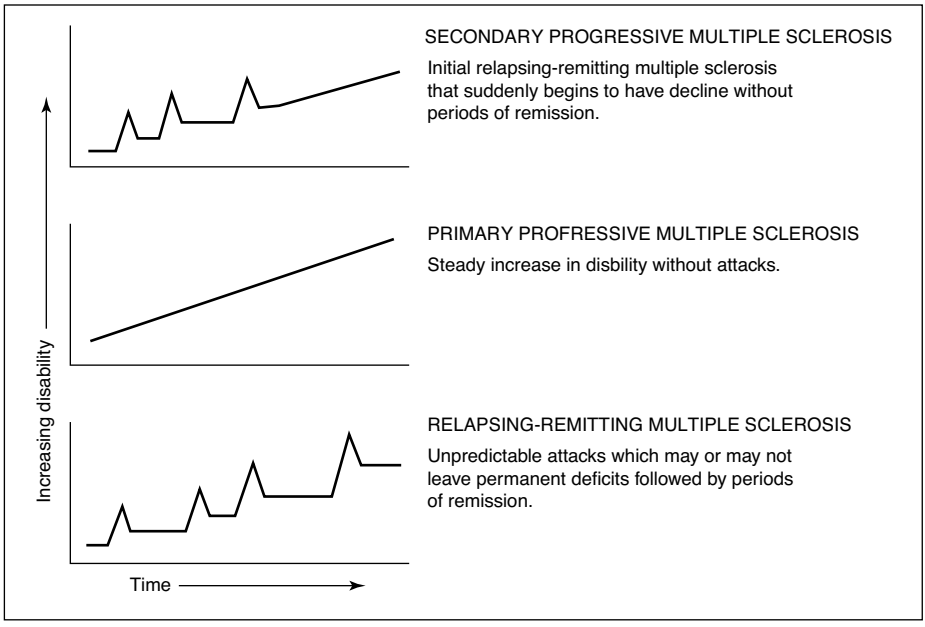
Unfortunately, most disability accumulates in the SPMS phase, and this is where treatments are currently lacking. As with RRMS, however, there

is a large range of disability experienced by patients with SPMS. Most patients fear the SPMS stage the most, anticipating a gradual, inevitable decline in their ability to function. However, aside from the inevitable decline associated with aging, a fair number of patients with SPMS experience little or no progression during the later stages of the disease.

CATEGORY 4: PRIMARY PROGRESSIVE MS (PPMS): About 10% of patients present with a progressive form of MS at onset without relapses. This is known as primary progressive MS (PPMS). It is characterized by steadily worsening neurological function or disability from the onset of symptoms. To diagnose PPMS, there must be 1 year of disease progression. Unlike RRMS, PPMS presents equally in men and women, and tends to occur at an older age. It almost always presents with gradual trouble walking. Certain presentations, such as optic neuritis, that are common in RRMS are rare in PPMS. Enhancing MRI lesions indicative of active inflammation are also less common in PPMS than RRMS. PPMS patients usually accumulate disability more rapidly than patients with RRMS.

A diagnosis of PPMS may be further modified at any point in time as:

- **Active**: With new MRI activity and/or relapses and/or new lesions on the MRI.
- **Not active:** Without new MRI activity and/or relapses.



The different types of MS.

In addition, both active and not active PPMS may be further modified as:

- **With progression**: There is objective evidence of increased disability
- **Without progression**: There is no objective evidence of increased disability

Lastly, some patients may be diagnosed with an entity called radiographically isolated syndrome (RIS). RIS occurs when a patient gets an MRI because of a non-MS symptom (such as a headache), but the MRI reveals lesions that are characteristic for MS. One of my patients got an MRI after getting into a car crash, and it looked utterly classic for MS. Although there is some disagreement, most neurologists would suggest treating such patients with medications to hopefully prevent symptoms and disability in the future.

12. How Can I Tell What Stage of MS I'm in?

A natural question is whether patients are in the relapsing remitting phase (RRMS), secondary progressive phase (SPMS), or progressive phase (PPMS). Let's again review what these terms mean. About 90% of patients start with RRMS. This means that they develop a neurological symptom, usually over the course of hours to days, which then spontaneously improves over days to weeks. The recovery from relapses is usually quite good, though this is not always the case. Patients may then go months to years before they have another relapse, and there is no or minimal development of disability in between relapses. After 15 to 20 years, patients will then enter the SPMS. Relapses are very rare or absent in SPMS. However, patients may accumulate gradual disability from year to year.

Often it is quite clear when patients are in the RRMS or the SPMS phase of the illness, but there is no formal transition between the two stages. In this way, it can be compared to asking "when does someone become old?" A person who lives to 100 is old by any definition, but no one can tell you the exact moment they became "old."

Though it is not always easy, it is important to determine the stage of a patient's MS to the best of our abilities. The treatments are most effective with RRMS and are of minimal benefit in SPMS. One of the challenges faced by neurologists and patients alike is to be bold enough to stop using medications for MS in patients who are clearly in the PPMS phase and for whom relapses are no longer a concern.

Finally, the divisions of MS into RRMS and SPMS say nothing about the disease severity or what symptoms are present. Some patients have very mild progressive MS, while others have severe RRMS. In this sense, one stage of the illness is not "better" than another.

13. What Is the Prognosis of MS?

MS is a disease that causes a very wide spectrum of symptoms and disability. A natural question asked by a newly diagnosed patient is, "What is going to happen to me?" For some patients, MS will be little more than a mild nuisance. Many patients will live full, complete lives. There are some people who, unfortunately, will suffer life-altering disability at an early age. Generally speaking, about one third of patients will have minimal disease that impairs only the most vigorous activities; one third will have moderate disease; and one third will have more severe disease that prevents them from working or living independently. It is my hope that we are able to improve these numbers with new, effective treatments.

The wide range of symptoms and disability among MS patients makes it challenging to provide more than a general prognosis, especially early in the course of the disease. However, some prognostic factors have been discovered. Following an MS diagnosis, favorable prognostic factors include:

- Caucasian race
- Female sex
- Younger age at disease onset
- Sensory symptoms at onset
- Full recovery from the initial relapse
- Fewer relapses in the years after diagnosis
- Fewer lesions on the baseline MRI

Keep in mind these are generalizations and can only give a rough estimate of disease severity over time. Each individual case follows its own unique course. As with all generalizations, they will not apply to all individuals. For example, men are usually taller than women, but this is certainly not always the case.

The same is true with MS. I know young, White females who have had a very difficult time. I also know older African American males who have little clinical evidence of the disease. Additionally, the prognostic factors can sometimes be misleading. Even though younger patients generally have slower progression of their symptoms, they are going to live longer and will have more time to develop additional or worsening symptoms.

If I could add any tool to my treatment arsenal for patients with MS (other than a cure), it would be a crystal ball. Some patients are destined to have mild disease even without treatment. My aunt, for example, had a very clear episode suggestive of MS when she was 30 years old. She is now 80, still working, and outlasted me during a recent hike. At present, we cannot predict early on who those relatively fortunate patients are. As a result, most neurologists suggest the initiation of early treatment, even in those patients who do not meet the formal criteria for MS. When these patients do well, we can never know for certain if it is because the medication is working or because they were destined to have mild disease.

Unfortunately, there are also young patients who are going to have a severe disease, and we often cannot predict who these patients will be early in the disease course. Several years ago, when there were fewer treatments available to patients, predicting a patient's clinical course would have limited value. However, with the approval of powerful medicines to treat MS, the issue of prognosis has grown in importance. Hopefully, future research will provide better tools to give more accurate prognoses for MS. The hope is that we will be able to recognize which patients should be started on aggressive therapy and which patients might never need treatment at all.

14. What Is the Life Expectancy for People With MS?

Several studies have examined the life expectancy of people with MS. One review found that people with MS live 7 to 14 years less compared to people without MS. Another study of over 30,000 patients found that people with MS live an average of 6 years less. While this may seem discouraging, the majority of patients will lead full, long lives. Unfortunately, a small number of patients will become bedbound. These patients are at risk for complications that shorten life expectancy, bringing down the average for the entire group of MS patients. To consider how extremes can affect an average value, consider Bill Gates going to a homeless shelter. By averaging, his wealth would make it appear as if every person there was a millionaire. It should also be noted that MS itself is almost never directly fatal. I have never seen a patient die from an MS relapse.

15. Will I Wake up One Day and Not Be Able to Walk?

The short answer to this question, is almost always “NO!” Many patients naturally wonder if they are likely to be significantly and permanently disabled from a relapse. They are understandably fearful that they will wake up one morning unable to walk or suffer some other severe disability.

MS patients should know that a single relapse is unlikely to be a permanently devastating event. On the other hand, just because a patient is not experiencing relapses, this does not mean that they are disease free. The current thinking about MS is that it is both an *inflammatory* disorder, where the inflammation manifests as relapses, and a *neurodegenerative* disorder (like Alzheimer's or Parkinson's disease), where there is a slow, steady progression of symptoms over years and decades. The inflammatory part of MS predominates early on, while the degenerative process is a later feature. Unfortunately, much of the disability from MS occurs in the progressive phase, and our ability to slow down progression is limited at present.

16. Do Relapses Matter?

If most of the disability occurs in the progressive phase, does this mean that relapses don't matter? Since the main MS medications are used to prevent relapses, are we tricking ourselves into thinking that we are having an impact on the course of the disease? Several well-respected neurologists have written that relapses really don't significantly impact long-term disability. After all, about 10% of patients have primary progressive MS (PPMS). These patients do not have relapses yet they generally accumulate disability at a faster rate than patients with relapsing remitting MS (RRMS).

Despite this, I believe that relapses matter, even though they are not likely to be permanently devastating events and much of disability increases during the progressive phase. Firstly, even if relapses have minimal effect on patients' long-term physical disability, they can cause significant emotional distress. I have seen many patients who are having what might appear to be a "minor" relapse pay a significant emotional price, knowing that their disease is not under control.

Secondly, the studies I discussed used the Expanded Disability Status Scale (EDSS) to measure disability, as do most studies in MS. I will discuss it more later, but briefly, the EDSS is a scale that is heavily dependent on a patient's ability to walk. However, I have seen patients suffer relapses characterized by pain, visual difficulties, and cognitive disturbances. Who can argue that these symptoms do not matter? Yet, based on the EDSS, these patients might not be considered as having significant disability, as long as their ability to walk was not affected.

Finally, while the prevention of long-term disability is what most neurologists and patients care about, the short-term should not be undervalued. It is very common for patients who have relapses to be left with

abnormal sensations, weakness, visual disturbances, and other symptoms. While these symptoms may not make a difference in how someone is doing 20 years after a relapse, they can make a huge difference in how someone is doing 20 days after a relapse. Why should this not matter?

What does this mean in terms of treating MS? If a medication were invented tomorrow that completely eliminated relapses, it is doubtful that MS would be cured. Yet, there is evidence that, over periods lasting several years, patients who take medicines for MS have less disability than those given placebo in the clinical trials, indicating to me that relapse prevention in MS is no trivial matter. I prescribe medications for MS patients with confidence that they have a positive influence on the course of the illness, while at the same time recognizing there is much work to be done before the disease can be conquered.

17. What About Pediatric MS?

MS typically affects young and middle-aged adults, but about 3% of patients develop symptoms during childhood or adolescence. Pediatric MS is defined as MS occurring in children under 18 years of age. Most patients with pediatric MS are adolescents. Only very rarely do symptoms present before age 10 years.

Pediatric MS is the same condition as adult MS. Usually the symptoms and laboratory and MRI findings are similar to adults with MS. Like adults, children present with several days or weeks of vision loss, sensory disturbances, weakness, or balance problems that tend to improve, usually back to normal.

There are some differences, however. Relapses tend to occur more frequently in children than adults, but children recover more quickly and more fully from relapses than adults. Importantly, children always present with RRMS. PPMS does not occur in children. So, children who experience years of struggling in school and notice that their problems are getting worse do not have MS.

Increasingly, MS centers are gaining experience helping children. A number of centers have been specifically established for pediatric MS in the United States and around the world. They are working together to help ensure that children get the best possible care.