New Standard of Care

MULTIPLE SCLEROSIS

The Healthcare Advancements
You Can't Afford To Ignore

Happy Patients. Abundant Economy.

Volume One | Dr. Charles Mok

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INTRODUCTION

Multiple sclerosis (MS) is a potentially debilitating disease of the brain and spinal cord. It is presumed to be an autoimmune disease, a condition where the body's own immune system, and host defense mechanisms, attack an organ. In the case of multiple sclerosis, white blood cells that are designed to destroy bacteria, for no clear reason, end up destroying some of the white matter in the brain. The diagnosis is made by identifying symptoms that correlate with plaques seen on an MRI of the brain.

The Gut Microbiome

Our intestinal tract not only processes foods and allows for the body to absorb energy and nutrients, but it is also the host to hundreds of trillions of bacteria. These bacteria are of a variety of species and make up our "microbiome." Many foods we eat cannot be digested by our own body, and the bacteria that reside inside of our gut break it down for us to allow absorption. These bacteria have recently been found to be implicated in various states of health and disease. These bacteria not only convert food into absorbable energy, but they can also convert food into beneficial compounds, as well as various toxins. This is largely determined by the relative makeup of the microbiome.

The Microbiome and MS Connection

Recent evidence has shown similarities of the bacterial makeup in the colonies of bacteria that reside in the colon of MS patients. That is, when the type of bacteria in the feces of MS patients are counted, they are similar to other patients' bacterial fecal makeup, but uniquely different from people who do not have

MS. Your gastrointestinal tract is made up of hundreds of trillions of bacteria and we only recently have been able to map out the various species. Major discoveries have shown that various diseases are clearly linked to the types of species of bacteria living in an individual's gastrointestinal tract. Conditions such as obesity, diabetes, hypertension, heart disease, cancers, lupus, Crohn's disease, psoriasis, and numerous others, including MS, have unique bacterial makeups that differ from the general population without those same diseases. What has remained perplexing is the actual cause of autoimmune disease. Why do our cells, which are supposed to protect us, hurt us? It's unknown, but recent discoveries have given us clues to the possible causes of the autoimmune diseases. Once we discover the cause, a cure may follow. To put this in perspective, keep in mind that there are no known cures for autoimmune diseases. There are numerous therapies, treatments and drugs designed to suppress the immune system so that it stops destroying the body. But if the only current treatment for an autoimmune disease is to suppress the immune system with drugs, it's obvious there has to be a better way. All drug therapies do is, either slow down the progression of the disease or lessen its effects. They do not cure it. I want to educate you about the development of multiple sclerosis, and the recent discoveries offering clues to future cures.

Clues for a Cure

Multiple sclerosis is characterized by inflammation of the brain, and the eventual destruction of a protein called myelin, which makes up nerve cells. As reported in the New England Journal of Medicine on January 29, 1998, scientists discovered that MS progresses from inflammation into actual destruction, or

transection (cutting) of nerve fibers. Once this transection of nerve fibers occurs, the damage is likely to become permanent.

Relapsing Remitting MS vs Progressive MS

In relapsing remitting MS, symptoms occur in a cycle. They begin, last for a period of time, and then go away. In progressive MS, the symptoms do not go away.

There is evidence that diagnosing multiple sclerosis early on (when the symptoms are called clinically isolated syndrome) and treating it with drugs that suppress the immune system may be the most effective way to prevent it from becoming progressive and leading to permanent disability.

If there is a key to curing one's MS, it would most likely need to be started early on in the disease, before permanent destruction of the brain occurs. When a cure is discovered, it may help to halt further progression of patients with progressive MS, but actually reversing the disability would be less likely.

"If there is a key to curing MS, it would likely need to be started early on in the disease..."

However, we have helped patients in our practice with progressive MS and long-term permanent disability. These patients have lost the use of their limbs and by treating them with fat-derived mesenchymal stem cells they do get some return of function. That return to function typically lasts nine months to a year and the stem cell treatment can be repeated. We will cover more on the topic of mesenchymal stem cells later in this book, but these are

dormant cells in our body capable of rebuilding tissue.

We have also observed individuals who were treated with stem cell therapy, in conjunction with hundreds of other doctors in our IRB-approved study, that people with milder forms of MS have more benefit than people with severe forms. Our plan in the future is to treat people with more severe forms of MS with higher doses of stem cells, spread out over a longer period of time.

Simultaneous to treating MS patients with their own stem cells, we have been actively seeking other treatments that could potentially cure or reverse MS. There are drug treatments that are effective for reducing MS attacks, as well as, modifying the progression of the disease. They certainly work and patients who seek treatment for MS with stem cells should continue seeing their neurologists for disease-modifying treatments.

What's important to mention here are the additional things that have come to light very recently which may take MS treatments a step further.

Let's go over three potential therapies for MS that have been studied in the literature over the past 10 years, but, outside of research studies, are not typically being practiced by physicians.

1)Treating the gut microbiome.

2)Addressing the hormonal changes observed in MS patients.

3)Realizing that MS may not be an autoimmune disease after all, and treating it as such.

SECTION 1

TREATING THE GUT MICROBIOME

As explained earlier, hundreds of trillions of bacteria live in our body. Organs that we once thought were sterile, or totally devoid of bacteria, such as our bladder or respiratory tract, have recently been found to contain resident bacteria. Until the advent of genetic testing for bacteria, we simply did not know that these bacteria lived throughout our organs, possibly in every organ in our body.

Our immune system is designed to keep bacteria from harming us, while ignoring bacteria that are beneficial or cause us no harm. Our immune system does other things as well, but this is one of its chief activities. We have trillions of bacteria in our bodies, so our immune system needs to differentiate harmful bacteria from bacteria that we can tolerate or may even benefit us. This requires our immune system to sense an enormous number of DNA types to sort out harmful from benign bacteria.

The human gastrointestinal tract is by far the richest

> "...scientists have discovered a relationship between the types of species that reside in our colon and the development of various autoimmune diseases."

source of bacteria; far more bacteria occur in our gut than anywhere else in our body. Recently scientists have discovered a relationship between the types of species that reside in our colon and the development of various autoimmune diseases.

A new study, published in Nature Communications on June 27, 2016, found "multiple sclerosis patients have a distinct gut microbiota compared to healthy controls." [3]

In this study, they did genetic testing of the composition of bacteria present in the feces of patients with relapsing remitting MS and compared them to the genetic makeup of the bacteria from the feces of healthy people matched in terms of gender and age. They found distinct differences between the groups.

Thousands of different strains of bacteria live in human gut, and for the most part healthy people have a strong similarity with MS patients. But there were substantial differences that stood out in the feces of patients with multiple sclerosis. Five specific strains of bacteria were present in the feces of MS patients, and three specific strains of bacteria were notably absent or diminished.

The strains of bacteria in our system can help or harm us. The significance of this difference in the strains of bacteria collected from MS patients is based on food metabolism. When we eat food, we extract energy from the food, but so do our bacteria. And as we recently discovered, the makeup of the bacteria determines not only how much energy we can extract out of food, but also different chemicals that the bacteria produce as a result of eating the food.

The bacteria can give off inflammatory as well as anti-inflammatory chemicals. They can give off chemicals that are toxic to us humans, and they can give off chemicals that benefit us. The bacteria can consume a lot of the calories, as we see with people who eat whatever they want and remain thin.

When the bacteria is very energy efficient and passes on most of the calories to us, obesity can result. In the case of MS, the bacteria in the gastrointestinal tract gives off chemicals that are known to be harmful. These chemicals are released from the gastrointestinal tract, pass through the intestinal blood barrier, and affect the body in both positive and negative ways.

A study published by the Department of Chemistry, University of Nebraska, evaluated the metabolites (chemical byproducts from bacteria digesting our food) from patients with MS versus otherwise healthy patients. They found 27 unique altered chemicals in the patients with MS versus the otherwise healthy patients. [1]

A study published by the Department of Immunology, National Institute of Neuroscience, Tokyo, Japan, also found that the feces from patients with MS differed in the bacterial nature from the feces of healthy controls. They separated out the strains of bacteria further and found 21 different species that differed

"...correcting the unusual makeup of the gastrointestinal bacteria could lead to the prevention and the treatment of MS."

in their abundance between healthy and diseased individuals. The results suggested that correcting the unusual makeup of the gastrointestinal bacteria could lead to the prevention and/or the treatment of MS. [2]

A study from Brigham and Women's Hospital, Department of Neurology, Harvard Medical School, compared the gastrointestinal microbiome of 60 individuals with multiple sclerosis to the microbiome of otherwise healthy controls. They not only found unique bacterial strain signatures present in the MS patients but not in the healthy patients, but also differences between the microbiome makeup of people who were on disease-modifying drug therapy.

They further narrowed down the strains of microbes occurring in the gastrointestinal tract of MS patients that may be the key germs that correlate to the development of neurologic disease. One is called Methanobrevibacter and the other Akkermansia. Methanobrevibacter is a microbe that is known to cause inflammation; it has been implicated in various inflammatory diseases. It is associated with dental disease, asthma and inflammatory bowel disease. It is also more abundant in Crohn's disease and ulcerative colitis, in children who are obese, and in patients with multiple sclerosis.

"Individuals who have MS and a rich colonization of this microbe have more frequent relapses."

Individuals who have MS and a rich colonization of this microbe have more frequent relapses. The significance of Akkermansia is not yet known.

MS patients also have a reduced abundance of the microbe Butyricimonas. This microbe produces a beneficial chemical called butyrate. Butyrate stimulates a healthy immune function and protects the barrier of the intestinal lining. A reduction in butyrate-producing microbes has been linked to autoimmune diseases, inflammatory processes, rheumatoid arthritis, and type 1 diabetes as well as MS. [3]

The link between the gastrointestinal microbiome and MS exists, so the question remains as to whether therapies directed at changing the gastrointestinal microbiological makeup would improve the disease.

A German study published by Immunity, in 2015, studied the impact of modifying the chemicals excreted by microbes on an experimental model of multiple sclerosis.

The food that we eat in our daily diet needs to be broken down into simpler elements in order to be absorbed into our body.

Converting foods that we eat into a digestible compound involves our gut microbes breaking down foods into fatty acids. Even carbohydrates, which are not fat, can be broken down into fatty acids.

There are two main fatty acids that bacteria create from food, and that we as humans absorb for energy. One type is called a short-chain fatty acid, and the other is a long-chain fatty acid. Short-chain fatty acids are broken down by gut microbes from indigestible carbohydrates such as fiber. Long-chain fatty acids are broken down from fatty foods, which are abundant in the

> "German researchers found that the makeup of dietary fatty acids had a significant influence on the progression of MS."

typical American diet.

The German researchers found that the makeup of dietary fatty acids had a significant influence on the progression of MS. Long-chain fatty acids led to the worsening of the experimental MS, while short-chain fatty acids were protective against MS. The fatty acids had a direct effect on the immune system. [4]

As far back as 2008, a study evaluating the effects of probiotics on an experimental model of MS showed that various probiotic drinks were able to suppress MS. This was an animal model experiment so it could not be directly inferred that probiotics would help humans. [5]

There are ongoing clinical trials evaluating the use of various probiotics and their influence on multiple sclerosis. Probiotics are microbes that are beneficial to the host. A study was published by the Multiple Sclerosis Journal in 2011, evaluating the use of a nonpathogenic parasite for MS. This microbe had previously been shown to improve other inflammatory conditions. They gave five individuals with relapsing remitting MS the probiotic every two weeks for three months.

The patients were evaluated with an MRI. They had an average of 6.6 lesions in their brain at the initiation of the study. At the end of the treatment the number of lesions dropped to two. After being off of the probiotic for two months, the number of lesions

rose again to about six. In this case the probiotic was a parasite, actually a parasite ova. While we might think of parasites as being diseases, there are many that live in humans and cause no actual harm. While a probiotic refers to microbes that are beneficial to the host, a parasite is an organism that benefits from the host while giving no benefit. I referred to this parasite as a probiotic because it has been shown to benefit humans with inflammatory disease and does not cause harm. [6]

While research is ongoing in the use of altering the gastrointestinal microbiome for MS patients, a reasonable and healthy approach would be to alter the diet toward one that typically breeds healthier microbiome.

In addition, consuming probiotics would be a logical step. Prebiotics refer to non-digestible fibers that stimulate the growth of probiotics. The one I recommend is galactooligosaccharide, as it has been shown to have a beneficial effect on the gastrointestinal microbiome and inflammation.

"The patients were evaluated with an MRI. They had an average of 6.6 lesions in their brain at the initiation of the study. At the end of the treatment the number of lesions dropped to two."

Eating a diet rich in green plant fiber is also likely to benefit multiple sclerosis patients. We recommend people make "green smoothies," which are basically blended-up greens added to water. It is very easy to drink your vegetables daily. There is also

> "Eating a diet rich in green plant fiber is also likely to benefit multiple sclerosis patients."

a supplement from freeze dried spinach called Thylakoids that are beneficial to restoring healthy bacterial makeup in our gut.

As far as probiotics, there is no good evidence to suggest which ones will be the most beneficial. Studies evaluating the use of probiotics for other conditions have shown us that the most effective probiotics are related to the number of strains and the number of colonies, as well as the duration of use. So, I recommend taking at least 50 billion a day (which can be in one pill) with the ingredients listing at least eight different strains, and consuming them for several months.

SECTION 2

HORMONAL CHANGES OBSERVED IN MS PATIENTS

The link between hormone alterations and MS has been known for some time. Yet very little has been done in terms of addressing this in clinical practice, despite the significant evidence.

A study was performed on 60 patients with relapsing remitting MS, 35 women and 25 men with an average age of 32 years and an average length of disease of six years. MRIs were done of the brain and levels were evaluated of estrogen, testosterone and other sex hormones. They found a significant correlation between low testosterone in women and worsened disease. In men, there is a correlation between elevated estrogen and worsened disease. [7]

Let's take a closer look at how hormones affect males and females.

Men: Sex hormones & MS

The importance of low testosterone has been overlooked by many physicians despite the fact that untreated low testosterone leads to a doubled risk of premature disease and death versus men treated with testosterone. A Harvard study published in February 2014

"They found a significant correlation between low testosterone in women and worsened disease."

evaluated 96 men with an average age of 40 who had relapsing remitting MS for an average of five years. In this group, 40 percent of the men were found to have severely low testosterone. The average testosterone level for men in this age group should be between 600 and 700 ng/dl. However, in men with MS, 40 percent had a testosterone level of 280 ng/dL or less. Symptoms of low testosterone generally appear below 500 ng/ dL, so this is very low. [8]

"Testosterone is known to be neuroprotective and anti-inflammatory."

In 2007, a study from UCLA evaluated the effect of treating men with MS with testosterone replacement. Prior to that time, there was evidence that low testosterone was linked to MS, and there were experimental models of MS that benefited from testosterone replacement.

Testosterone is known to be neuroprotective and anti-inflammatory.

This study evaluated 10 men with relapsing remitting MS. They examined their neurologic exams, as well as MRI changes. They found that one year of testosterone replacement therapy in men led to an improvement of clinical findings. The men with MS functionally improved. They also had better cognitive performance, or better thinking ability. They also found a substantial slowing of the damage to the brain. [9]

Another study published 7 years later in 2014, also from UCLA, evaluated the use of testosterone replacement therapy in men with MS. They found that testosterone not only improved the men's functional outcomes, but also reversed some of the damage to the

brain. It not only protected the brain from damage associated from MS, but there was also an increase in the gray matter of the brain as a result of testosterone replacement.

This has substantial implications. Testosterone replacement therapy in other studies has shown a reduction in obesity, cardiovascular disease and diabetes. This UCLA study showed a significant improvement in multiple sclerosis, and an actual reversing of some of the damage in the brain in MS patients. [10]

Women: Sex Hormones & MS

There are two hormones that appear to play a role in the development or prevention of multiple sclerosis.

Testosterone: Young women are more susceptible than young men to multiple sclerosis and women have far lower levels of testosterone than men. Additionally, low testosterone is found to occur more often in both men and women with MS compared to healthy controls.

Estriol: A type of estrogen that is abundant during pregnancy, seems to be protective against MS as well as other inflammatory and autoimmune conditions. Estriol is one of three estrogens that all women have.

In a non-pregnancy environment, the dominant estrogen is called estradiol. In pregnancy, estriol, which is considered a protective estrogen, significantly increases.

A study observing the relapse rate of MS before, during and after pregnancy of more than 200 women showed that relapse

decreased significantly during pregnancy. [11]

A study was done on non-pregnant women with both relapsing remitting MS and secondary progressive MS. They were followed for six months with MRIs and clinical evaluations. Then they were treated for six months with oral estriol (8 mg per day) for six months. Next, the estriol was stopped and they were followed for another six months.

"After the estriol was stopped, the lesions came back to the baseline."

The MRIs of the relapsing remitting group improved by 80 percent within three months of initiating estriol. After the estriol was stopped, the lesions came back to the baseline. The patients with secondary progressive MS did not receive as much benefit.

Clinically the patients tended to improve, more so in the relapsing remitting group. It left the question unanswered as to whether the progressive patients would have eventually benefited if the treatment went on beyond six months. [12] Scientists further evaluated the use of estriol beyond six months – they studied its use for 24 months. But because of the prior study done on the 12 women (half of them with relapsing remitting and the other half with progressive MS), they only studied women with relapsing remitting in the response to estriol.

This was a two-year study with 164 patients. Half were given estriol and half placebo. They were both on conventional treatment for MS, so this was to determine if estriol gives an additional benefit. At the end of the trial they found that estriol reduced relapse rate by 32 percent versus those taking conventional treatment alone. [13]

SECTION 3

WHAT IF MS IS NOT AN AUTOIMMUNE DISEASE?

What if we just got it wrong? For years scientists have assumed, based on extensive evidence, that multiple sclerosis is caused by the body's immune system attacking itself for no reason. The immune system, among other things, is supposed to protect us from harmful bacteria. White blood cells, and the immune system would detect that a bacterium (or cancerous cell) as a foreign invader, and potentially harmful, and it would destroy the bacterium (or abnormal cell). If the bacterium was left unchecked, and the white blood cells cannot handle the job, an infection would develop.

We talked about the relationship to the bacteria makeup of our gastrointestinal tract and the development of autoimmune disease. This has been the subject of extensive research, particularly over the past 5 to 10 years. Advances in detection of various bacteria because of genetic testing has led us to a far greater understanding into the world of microscopic organisms than ever before. Some organisms are so tiny that they cannot even be seen with the microscope, and some organisms grow so slowly that we cannot detect them with standard laboratory tests.

What if MS is not the result of the immune system going haywire, but the result of a previously unknown type of infection? If we think of this possibility, and there is evidence that it could be true, then new therapeutic strategies could be developed.

> "What if MS is not the result of the immune system going haywire, but the result of a previously unknown type of infection?"

There has long been a known association between the development of MS and the relapsing rates of MS in the face of viral or bacterial infections. But the link is not clear. And we have talked about the unique bacteria strains that occur in the gastrointestinal tract of MS patients. What we didn't talk about was how alterations in the gastrointestinal bacteria lead to an impaired barrier of the wall of the intestines and the bloodstream.

Leaky Gut

There is a condition loosely called "leaky gut" where the barrier between the gastrointestinal tract and the blood system is disrupted. This is known to cause gastrointestinal disturbance and symptoms as well as to increase the absorption of toxins from our colon. In an extreme case, this can lead to significant inflammatory bowel disease, while milder cases may be associated with irritable bowel syndrome.

But, is it possible that these alterations in the gastrointestinal microbes, and the increased permeability of the gastrointestinal barrier, could lead to brain-disrupting germs entering the blood system and then entering the brain? Scientists have discovered antibodies to various viruses and germs in the cerebral spinal fluid, the fluid that surrounds the brain and spinal cord. But they have not discovered a link to brain infection and multiple sclerosis.[14]

Study identifies remnants of bacteria in the brain lesions of MS cadavers. Previous studies done on autopsies of brains of both humans and animals with MS found peptidoglycan, a component normally found in the cell wall of the bacteria.

The Canadian researchers found peptidoglycan in the lesions that cause multiple sclerosis. Until this time, there had been no direct evidence of the presence of bacteria in the brains of MS patients lesions.

These peptidoglycans were found in the white blood cells that were attacking, or at least seemingly attacking, the brain matter. To determine if scientists in the past had missed the presence of bacteria, they used a technique of amplifying the DNA and RNA. The assumption was that perhaps, unlike traditional infections, MS could be a result of unfriendly bacteria colonizing the brain — but not a great number of them.

Thus, perhaps the reason the white blood cells are eating the brain matter is because they are actually attacking the bacteria that are not supposed to be there.

We see conditions like this in other parts of the body. A foreign substance or bacteria is detected and the body sends in white blood cells to eat it and destroy it, then the white blood cells just stay there leaving lesions.

"...perhaps the reason the white blood cells are eating the brain matter is because they are actually attacking the bacteria..."

In this study, they found the bacteria that had been hiding from scientists.

The dominant one was called Proteobacteria, although there were others. As this Canadian study was essentially the first of its kind, scientists will no doubt launch into further investigations based on these results, identifying the presence of bacteria uniquely present in the brain and in the brain lesions of patients who have MS and have died. [15]

Bacteria and other microbes do reside in our body in abundance. Occasionally they will get into the bloodstream, but something called the "blood-brain barrier" is supposed to protect the brain from attack of harmful organisms. When a harmful organism gets into the brain and grows unchecked it is called meningitis. But the previous study showed us that there is likely another disease that is associated with microorganisms that does not reach the acute level of meningitis. There are other brain infections caused by smaller particles of viruses and even particles smaller than viruses that are outside the scope of this discussion. We know it does occur.

There have been numerous clinical studies demonstrating the gastrointestinal microbiota and their influence on the brain through various hormonal and molecular signals.

"This appears to be pretty direct evidence that the bacteria entered our body..."

A study done on animals showed that the gastrointestinal microbiota not only affected the barrier

between the intestinal lining in the blood system, but it also had an effect directly on the blood-brain barrier. The bacteria in your gut can actually open up the barrier that separates your brain from your blood system. [16]

"...if MS is in fact caused by germs as opposed to an autoimmune disease, could we use antibiotics to treat it?"

The gut microbiota is altered in MS patients, and we know that there are actually bacterial remnants in the lesions of multiple sclerosis. This appears to be pretty direct evidence that the bacteria entered our body from the outside world and eventually got into the brain. Since the brain is supposed to be germ-free, the white blood cells consumed the bacteria but in doing so also consumed some of the brain matter as well. Unlike other organs of the body, our neurological system does not respond well to damage; it does not heal itself as well as, say, your skin. So, if MS is in fact caused by germs as opposed to an autoimmune disease, could we use antibiotics to treat it?

The Potential Role of Antibiotics

Long before the discovery of bacteria in the brain lesions of MS patients, scientists were evaluating the use of antibiotics in the treatment of MS. There is a safe antibiotic that can be tolerated for long periods of time called minocycline. Its common use currently is for the suppression of facial acne. Unlike most antibiotics, minocycline can be taken for a long period of time without causing harm. Additionally, minocycline is one of the few antibiotics that freely crosses the blood-brain barrier.

As a follow-up to the preliminary minocycline study, in 2009, the University of Calgary evaluated the addition of minocycline to standard MS drugs versus placebo.

> "Perhaps it is not an autoimmune disease, but actually the immune system's response to foreign bacteria in the brain..."

The patients were given a standard treatment plus either 100 mg minocycline or placebo twice a day. Their initial MRI scans showed an average of eight MS lesions. At six months, the individuals receiving standard treatment plus minocycline had about an 80 percent decrease in the number of lesions. The group on standard treatment and placebo only had a slight decrease in the number of lesions. They assumed that the minocycline worked by decreasing inflammation, but we now know that there is evidence of the presence of unique bacteria in the brains of MS lesions, and minocycline is an antibiotic. [20]

In the studies out of Canada, the authors in their discussion noted that MS treatments cost approximately $22,000 a year — and that minocycline is more than 95 percent less expensive. They discussed how it would be effective if government funding would allow the studies of generic drugs that are inexpensive, safe and readily available.

Currently much of drug research funding comes from large pharmaceutical companies attempting to bring a new drug to market. But in order to get FDA approval for a new drug, they do not have to prove that the drug is superior than standard therapies. They just have to prove that it works and has a certain

amount of safety. Minocycline is generic, and there's no chance of a drug manufacturer getting a patent on it and making a lot of money if they prove that minocycline is superior to current therapies. Therefore, research into potential minocycline use for MS is almost nonexistent anymore.

Studies have sought to determine the reason that the minocycline has a beneficial effect on MS, and various theories have been formed. It might be just a straight anti-inflammatory effect, or it might be the fact that we could have missed the cause of multiple sclerosis in the first place. Perhaps it is not an autoimmune disease, but actually the immune systems response to foreign bacteria in the brain as evidenced by autopsy studies and the response to antibiotics that enter the brain.

Of note, and of great concern to me, is that the studies were done on patients with relapsing remitting MS. Virtually all the patients I treat have either primary progressive or secondary progressive MS and it is not known if minocycline would help them because it hasn't been studied enough.

Because of the extreme long-term safe track record of minocycline, and the fact that it has fairly profound effects on relapsing remitting MS, I am recommending that my patients, even those with progressive MS, take minocycline along with other complementary therapies.

In summary, I want you to know that there may be more options available for treating MS then what we are currently using. I absolutely agree with conventional therapies for MS. In some cases, they are quite adequate. However, in my practice I am

dealing with patients who seek out treatment with stem cells because conventional treatment has failed them. For these people with MS, who have progressed to a point of having some degree of disability, it is appropriate to seek out alternative therapies.

Alternative therapies are commonly discounted by medical providers. There is an inherent bias, particularly among physicians and neurologists, that if something is not manufactured under a brand name by a drug company, and isn't brand-new, it's not worth using.

This totally flies in the face of our obligation as physicians to our patients. The Hippocratic Oath for physicians says "do no harm." This certainly refers to using therapies that may be beneficial but not approved by the FDA. Failing to offer patients complementary treatments to standard modern drug therapy, particularly when they have been proven to be beneficial and have no adverse events, is doing harm.

For patients with multiple sclerosis with an inadequate response to conventional drug therapy, I recommend the following:

Change Your Diet

There is evidence that the gastrointestinal microbiome is affiliated with multiple sclerosis. Altering the diet from a typical American diet to a healthy, largely vegetable-based diet has a favorable effect on the gastrointestinal microbes. This means reducing meat consumption and eating less processed foods.

> "There is no reason, medically or otherwise, to avoid hormone replacement therapy when your hormones decline."

The so-called Mediterranean diet increases diversity, which means that there will be more species of bacteria and they will keep each other in check. This leaves a reduced likelihood of harmful microbes ever growing.

Add Prebiotics & Probiotics

The prebiotic I recommend is called galactooligosaccharide. This form of fiber is very well tolerated, unlike some of the other prebiotics, which cause an upset stomach. As for probiotics, it is "the more the better" -- the more strains of bacteria, and the higher the count, the more potential benefit.

Evaluate Your Hormones

There is overwhelming evidence that hormone replacement in individuals who have declining hormone levels leads to significant health benefits. Long-term studies have shown that women in menopause who have correction of their hormone levels in the specific way that we perform it now -- not with drugs but with hormones -- have about a 70 percent reduction in the development of breast cancer and a substantial reduction in the risk of heart attacks. Left untreated, men with low testosterone will have double the incidence of premature death or heart attacks. They will also gain weight if not treated, and men who are overweight or obese who go on testosterone replacement therapy will consistently lose weight. There is no reason, medically

or otherwise, to avoid hormone replacement therapy when your hormones decline. And there is a clear link to improved multiple sclerosis parameters with hormone replacement. Yet doctors rarely consider this.

Consider Antibiotics

While antibiotics in general can cause negative effects on the gastrointestinal microbiome, minocycline uniquely has beneficial effects on the gastrointestinal microbiome. It also has a substantial role in improving the symptoms of relapsing remitting MS, and improving the brain damage that occurs as a result of MS. Dr Mok currently recommends 100mg twice daily of minocycline for an average of 6 months.

SECTION 4

STEM CELLS SHOW PROMISE

Stem cells have shown promise in the treatment of autoimmune and inflammatory diseases, including multiple sclerosis. The source of stem cells that we use currently are from the body's own fat. Other sources of stem cells include bone marrow, but the fat is much more accessible, has 500 times higher yield, and is much less painful to obtain.

The type of stem cell we harvest is called the mesenchymal stem cell. Other anti-inflammatory cells are also collected at the same time. Here, we will talk about experience with stem cells in the treatment of progressive MS. While relapsing remitting MS comes and goes, progressive MS can be secondary (where a person with relapsing remitting MS goes on to develop permanent disabilities) or primary, (where the MS starts out and progressively worsens), and the disabilities are permanent.

While the goal of therapy in relapsing remitting MS is to reduce the relapses and reduce the chance of them becoming progressive, the goal of treating progressive MS is to slow down progression. As noted earlier, medical therapy generally does not reverse or cure multiple sclerosis. A study from the Department of Clinical Neurosciences, University of Cambridge, (Cambridge,

> "...medical therapy generally does not reverse or cure multiple sclerosis."

UK) evaluated the effect of stem cells in the eyes of patients with secondary progressive MS.

"There have been major advances in management of multiple sclerosis by altering the immune system with drugs. But there are no available therapies or treatments to slow, stop, or reverse the accumulation of a fixed disability and secondary progressive multiple sclerosis," the researchers noted.

"I had debilitating acute facial pain... after my stem cell therapy I am sleeping through the night, and the constant nerve pain in my face is gone."

Sarah Ries, diagnosed with MS & NMO

So they set out to perform a pilot study to determine if stem cells may be able to reverse some of the fixed disability associated with progressive MS. They enrolled 10 patients between November 2007 and August 2010. They evaluated the degree of optic nerve involvement via MRI testing. They harvested some stem cells from the patient's own body and then infused them intravenously. They then followed the patients for 10 months.

After treatment with stem cells, the individuals had improvements in visual acuity and contrast sensitivity. There were also improved responses from the optic nerve. [21]

A study from the Department of Neurology, Military Institute of Medicine in Warsaw, Poland, published late in 2016, evaluated the application of stem cells in patients with more advanced MS.

They enrolled 13 patients with relapsing remitting MS and seven patients with secondary progressive MS. The patients with relapsing remitting MS were in their relapsing phase.

They were followed for 24 months. The average patient had contracted MS about 10 to 15 years earlier and had a severe form. All patients had clinically deteriorated in the year prior to the study. All patients had failed treatment with conventional first-, second- and third-line drug therapies.

In the subsequent follow-up, 18 of the 20 patients did not exhibit any worsening in their disability scores. Only two patients had a relapse, as opposed to the rapidly worsening condition that occurred before the stem cell therapy.

This study demonstrated that patients with a worsened form of MS had a benefit in their functional disability and relapse rates with stem cells alone, when conventional medical therapy had failed them in the past. [22]

Studies are ongoing. Some are adding stem cells to conventional therapy, while others are using stem cells where conventional

> "...scientists question whether or not they could use mesenchymal stem cells as a drug delivery system to target minocycline directly to the lesions of MS."

therapy have failed. There are animal studies attempting to determine which combination of treatments may be effective.

We previously reviewed the substantial positive effect that the antibiotic minocycline has on the improvement of relapsing remitting MS. Stem cells by their nature are attracted to areas of inflammation; this is how we understand that they work. They travel through the blood until they reach chemical signals of inflammation and they attach there. Therefore, scientists question whether or not they could use mesenchymal stem cells as a drug delivery system to target minocycline directly to the lesions of MS.

In an animal study, they treated mesenchymal stem cells with minocycline. In other words, researchers mixed the minocycline with the stem cells. In an animal model of Multiple Sclerosis they compared stem cells to minocycline-enriched stem cells. The combination therapy had a more significant reduction in clinical scores and improvement of inflammation and neurodegeneration. Adding minocycline to the stem cells was more effective at combating the damage to the brain of animals with the simulated MS.

Our experience with stem cells has shown us that stem cells offer a promising treatment for people suffering from MS. We are typically seeing about nine to 12 months improvement of disability scores, and a substantial if not complete abolition of relapses.

Stem cell therapy does not replace conventional treatment, nor does it replace the complementary therapies we also talk about here. Multiple sclerosis affected both my grandmother and my aunt and left them with severe disability years ago, and this has been a topic of personal interest to me. The topics covered in this book are to help people who have or treat MS understand the current emerging complementary treatments that are being researched.

SECTION 5

ECONOMIC IMPACT

The National Multiple Sclerosis Society has estimated that about 400,000 people in the United States have multiple sclerosis. Hundreds of new cases are diagnosed every week. Multiple sclerosis tends to attack people in northern climates more than southern, and also occurs more often in people with lighter skin types.

Women are about twice as likely as men to have multiple sclerosis. There appears to be a slight genetic susceptibility, and there is an apparent, at least a casual, link to other autoimmune diseases.

According to the National Multiple Sclerosis Society, about 2.3 million people worldwide have multiple sclerosis.

The Multiple Sclerosis International Federation has sought to evaluate the global economic impact of multiple sclerosis. Since MS tends to occur at a young age, it is a chronic and potentially debilitating condition, and there is currently no known cure. It is one of the most expensive medical diseases on a case-by-case basis to affect humankind. They noted that the average annual costs, in 2007, internationally was about $40,000 per year in both direct medical and indirect costs related to multiple sclerosis.

In 2015, The American Academy of Neurology's journal of Neurology published an evaluation of the costs and pricing trajectories of multiple sclerosis drugs over the past 20 years.

What they found was startling. The cost for multiple sclerosis drugs has been rising at 5 to 7 times higher than inflation associated with ordinary prescription drugs. Drugs that were introduced at the cost of less than $10,000 per year have inflated so fast that there are no multiple sclerosis drugs on the market that cost less than $50,000 per year.

There are 12 FDA approved disease-modifying therapies for MS. The term disease-modifying therapy means that these are drugs designed to alter the course of MS but do not cure it. And drugs that have been on the market over 20 years, still cost over $50,000 per person per year. This is not to mention the cost of medical care associated with the debilitation of multiple sclerosis; this is just drug costs alone.

About $10 billion annually is spent in the United States on multiple sclerosis drugs. There are no drugs that are known to cure or permanently reverse multiple sclerosis. There are tens of millions of dollars of annual funding for multiple sclerosis research. The National MS Society has spent over three-quarters of $1 billion since its inception in 1947 which is led to many new FDA approved therapies for MS.

According to the American Academy of Neurology paper, it cost about $80,000 to prevent a single multiple sclerosis relapse in a single patient. All of the 12 FDA approved disease-modifying drugs cost over $50,000 per year. Also, it costs more than $900,000 per quality-adjusted life year (QALY). QALY is an index referring to the economic impact to create one year of perfect health. To put this in perspective, treatment of high blood pressure cost about $38,000 per QALY. Treating cardiac risk factors cost about $42,000

per QALY, and screening for diabetes cost about $50,000 per QALY.

The economic impact of MS is enormous. There are 12,000 new cases diagnosed in the United States annually, and the cost of treatment has risen exponentially when compared to the overall economy or the inflation of other medical therapies. Drug companies have some degree of government protection for the exorbitant prices for their medications. The trend of increasing medical costs does not seem to be ending.

"According to the American Academy of Neurology paper, it cost about $80,000 to prevent a single multiple sclerosis relapse in the single patient. Over $900,000 is spent for each disease-free year on FDA approved drugs alone..."

Managing disease is a huge business for drug companies. There is an enormous economic impact on large pharmaceutical companies to preserve the status quo. Major drug companies spend over $20 billion a year marketing directly to healthcare professionals. Nine of the top 10 drug manufacturers spend more annually on marketing drugs, than on research and development.

There is a role for conventional disease-modifying drugs for MS. I want you to understand the additional research that is going on, is not sponsored by major pharmaceutical companies, and the breakthroughs that have occurred, that most doctors are

not aware of because of lack of pharmaceutical company promotion.

In this booklet we reviewed treatments that have been studied by various scientists and concepts that have been researched for the management, and perhaps even evidence towards an ultimate cure for multiple sclerosis. The vast majority of research has been towards finding new disease-modifying drugs, while the answer may be sitting right in front of us.

While the evidence presented here does not suggest that we need to abandon discovering new drugs for modification of multiple sclerosis, it does suggest that inexpensive, generic or natural therapies at least may complement traditional medical treatment of multiple sclerosis.

According to the American Academy of Neurology paper, it cost about $80,000 to prevent a single multiple sclerosis relapse in the single patient. Over $900,000 is spent for each disease-free year on FDA approved drugs alone.

Patients with multiple sclerosis have an altered intestinal microbiota, and there is evidence that there is a direct link between these altered microbiota and the development of multiple sclerosis. There is also evidence that repairing the intestinal microbiota may lead to regression or remission of multiple sclerosis. This is extremely safe and inexpensive to undertake.

Patients with multiple sclerosis have been found to have low testosterone levels, and testosterone replacement in both men

and women has been shown to potentially benefit multiple sclerosis symptoms and disease. Estriol additionally has been shown to improve multiple sclerosis in women. There is extensive evidence supporting the safety of hormone replacement in men and women with altered hormone patterns. This is also very inexpensive and has potential to substantially impact people's lives positively.

Minocycline, and inexpensive, generic, commonly used antibiotic has been shown to alter the course of multiple sclerosis. Even though the exact mechanism has not been well understood, current evidence suggests that it has a direct effect on the actual cause of multiple sclerosis. This again is very safe and inexpensive.

Stem cell therapy, using your own naturally occurring healing cells has been shown to alter the course of multiple sclerosis. It appears to work by modulating the immune system and allowing the body to attempt to heal itself. Stem cells are very easy to obtain, safe and inexpensive compared to multiple sclerosis drugs.

The combination of these factors offers promise for those suffering from multiple sclerosis. The economic impact of the direction that we as a society are going is not sustainable. As noted it cost about $900,000 per additional healthy year of life for those suffering from multiple sclerosis using current conventional disease-modifying drugs.

The potential therapeutics covered in this book are safe, inexpensive, and have an ability to significantly impact the quality of life of individuals suffering from multiple sclerosis with virtually no negative economic impact.

SECTION 6

SUMMARY

1. Conventional drug therapy acts by turning down the thermostat on the immune system.

2. Hormone replacement modifies the disease, improves disability and slows down relapses.

3. Improving the gut microbiome is promising to perhaps prevent individuals from going from relapsing remitting into a secondary progressive phase of MS.

4. The use of minocycline as both an anti-inflammatory and brain antibiotic has shown promise as well.

5. Stem cells are reserved for patients who have the progressive MS. This has been the only therapy that has shown some reversal of the degree of disability. While it does not cure MS, stem cell therapy can improve the patient's quality of life, at least temporarily. This gives us the opportunity to enlist other therapies to get continuous improvement, or at least improved ability.

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