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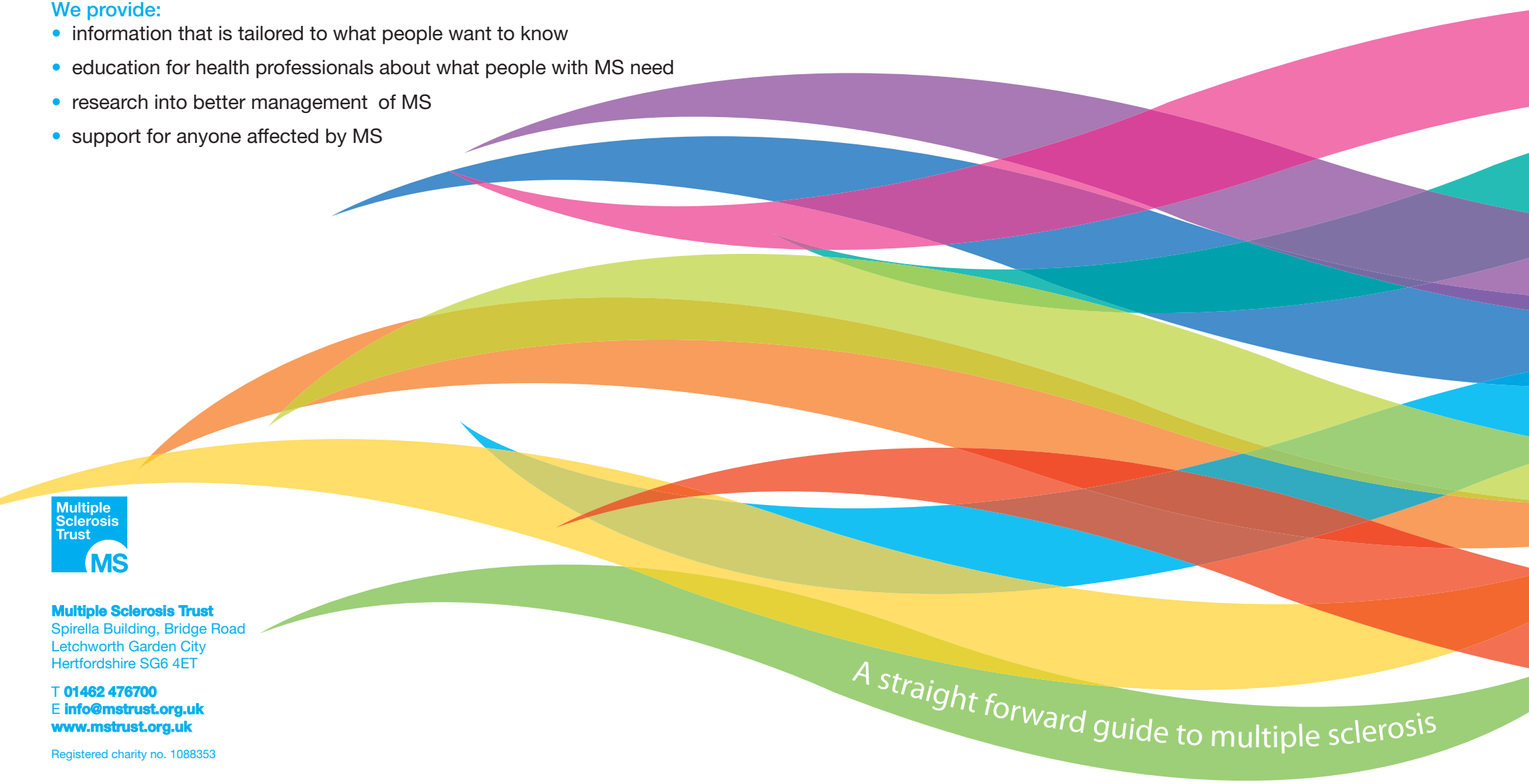
MSExplained

The MS Trust is a charity working with and for the 85,000 people in the UK with multiple sclerosis (MS). Our vision is to enable people with MS to live their lives to the full.

We provide:

- information that is tailored to what people want to know
- education for health professionals about what people with MS need
- research into better management of MS
- support for anyone affected by MS



Multiple Sclerosis Trust
Spirella Building, Bridge Road
Letchworth Garden City
Hertfordshire SG6 4ET

T **01462 476700**
E **info@mstrust.org.uk**
www.mstrust.org.uk

Registered charity no. 1088353

MS Explained

Simon Webster
Information Officer, MS Trust

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Thank you to
All the people with MS and health professionals who helped with the development of this book

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Introduction

In 2004 we published the first edition of 'Multiple Sclerosis Explained' to give a basic introduction to what MS does to the body. Readers could include people with MS; their family and friends; people caring for someone with MS; and those simply interested in this most enigmatic condition.

Prior to producing this second edition, we asked readers for feedback. As a result, there is now an extensive look at current research and areas where advances might occur. There is also a separate glossary.

The book purposely avoids discussing the treatment and management of symptoms. This is covered by other MS Trust publications, details of which are given in relevant sections and on page 62.

Contents

Who gets MS?

How many people have MS?

MS is the most common disease of the central nervous system affecting young adults. An estimated 2,500,000 people in the world have MS.

There is no currently register of people with MS in the UK and so the figure commonly used is an estimate based on a number of studies of local areas. When the prevalence rates from these studies are applied to the national population, it suggests a rate of about 140 cases per 100,000 people. This gives the estimated figure of 85,000 people with MS.

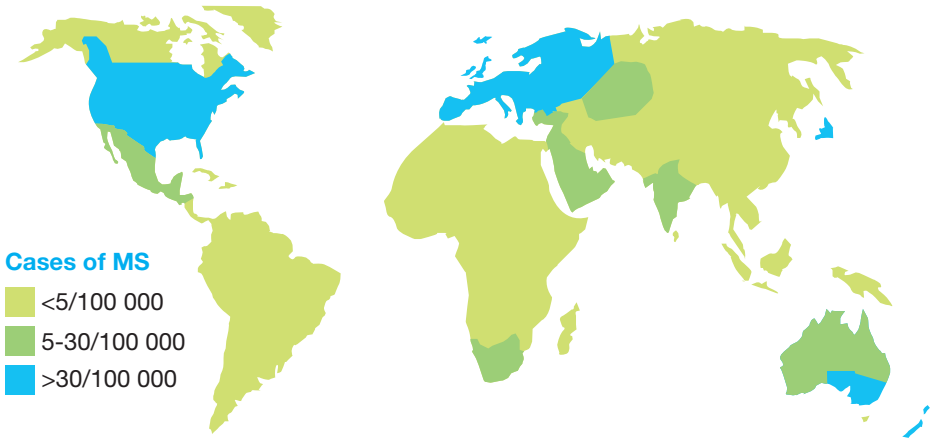
However, there is a growing consensus that the actual number may be higher than this.

Similarly, if the results of local area studies are applied nationwide it suggests that about 2,500 people are diagnosed with MS in the UK each year, or about 50 a week.

Who gets MS?

Age

Most people with MS are diagnosed in their 20s or 30s, although it can appear in people who are older than this, and, less frequently, in children.



Research suggests that one person in 50 with MS is diagnosed in their teens or younger, although precise figures are unknown.

Due to the age at which it is diagnosed, MS is sometimes referred to as a condition affecting younger people. However, as it only has a small effect on life expectancy, most people live with the condition for a long time.

Gender

More women than men are diagnosed with MS. Roughly two women have MS for every man with the condition, although research suggests that the proportion of women with MS may be growing. Recent studies in north America suggest that the figure may be closer to three women to each man diagnosed.

When MS is diagnosed in people in their teens, the proportion of women to men is about 3:1. When MS is diagnosed in older people or in those whose MS is progressive from onset, the numbers of women and men are more equal. (see page 48 or more on types of MS).

The reason for the larger proportion of women with MS is unknown but this pattern occurs in most other autoimmune conditions (see page 8 for more on autoimmune conditions).

Where is MS more common?

The distribution of MS around the world is uneven. As a rough guide, the prevalence increases as you travel further north or south from the equator. Those parts of Asia, Africa and America that lie on the equator have extremely low levels of MS, whilst Canada and Scotland have particularly high rates.

For instance, studies in countries near the equator have shown a prevalence rate in Peru of about 4 cases per 100,000, 8 in Saudi Arabia and just 1 amongst Indians in Mumbai.

In contrast, studies in Australia show a range from 11 in the north to 68 in Tasmania in the south. This increasing prevalence is more marked in the northern hemisphere. Studies in the UK suggest that the rate in England and Wales is between 100 and 120

Who gets MS?

per 100,000, about 160 in Northern Ireland and as high as 190 in Scotland. Individual studies in Orkney have recorded rates of over 200.

Race

A simple geographical spread is not the whole picture. Studies show that some ethnic groups have a markedly lower prevalence of MS, despite living in countries where MS is relatively common. For instance, the Sami (Lapps) of northern Scandinavia and the Inuit in Canada have very low rates of MS. A similar pattern is observed amongst the Maoris of New Zealand.

In contrast, a study in Kuwait showed that the rate for Kuwaitis was half that of the ethnic Palestinian population - many of whom had been born and raised in Kuwait. Similarly, the same studies in India that showed very low rates for Indians found that the rate for Parsis, an ethnic group that originated in Persia, was much higher and equivalent to areas in southern Europe.

Vikings and Scots

The fact that MS is most prevalent in Northern Europe, North America, Australia and New Zealand has led to speculation that it has been carried around the world by European colonists and settlers. It has been suggested that the origins can be traced back to the Vikings who colonised those parts of Northern Europe where MS is now most pronounced and that 'Viking' genes can make people particularly susceptible to MS.

It has also been noted that Scotland has a much higher rate of MS than England or Wales and that areas of high MS prevalence around the world have been settled by Scottish immigrants. In Ireland for instance, the prevalence rate of MS in the Irish Republic - based on an old study from 1971 - is about 66. In Northern Ireland, which was extensively settled by immigrants from Scotland from the 17th century, the rate was recorded in 1996 as 168.

Migration

Research looking at the effect of migration on the risk of developing MS suggests that the age someone moves is important. If someone moves from an area of low risk to an area of high risk as an adult, they retain the risk level of the location from which they originally came. People who move as children and the subsequent children of immigrants have a risk of MS similar to that found locally.

This explains the old fashioned, incorrect idea that MS was a condition that only affected white people and was rare or unknown amongst black or Asian people. Whilst this might have been true for the initial immigrant generations, it is not the case for the people born and brought up in the UK.

The geographic spread of MS suggests the genetic make up of people from different parts of the world has an impact on risk of MS; the migration studies point to there being an environmental element at play as well.

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The possible causes of MS

Almost 150 years after the condition was first described, the cause of MS remains a mystery. There has been a great deal of research looking for the solution to this problem and a number of theories have held sway as to what triggers MS.

During this period, speculation on the cause of the condition has included:

- acute fevers or exposure to damp or cold
- blood clots or poor circulation in the brain
- environmental poisons
- dietary factors such as a food allergy or food intolerance
- mercury leakage from dental amalgam fillings

Research has failed to prove any of these theories and it is now widely believed that MS is an autoimmune disease.

Autoimmune disease

An autoimmune disease is one in which the immune system, which should only target invading germs, turns on the body's own tissues. Other autoimmune conditions include diabetes mellitus type 1, in which the insulin making cells of the pancreas are destroyed, or rheumatoid arthritis, where the immune system attacks the joints and organs such as the lungs and skin. In the case of MS, the immune system attacks myelin, the substance covering and protecting nerves in the central nervous system.

The reason for this reaction is unknown but it is thought that the genetic make up of some people means that MS can be triggered by something in the environment, possibly an infectious agent or agents. In response to the infection, some cells from the immune system come into contact with the central nervous system and attack myelin, mistaking it for the invading agent.

Genetics

It is important to state that MS is not hereditary and the majority of people who develop MS have no previous family history of the condition. However, there is a higher, but still small, risk of developing MS for someone with a relative with the condition.

The risk of developing MS

In the general population in the UK, the risk of developing MS is about 1 in 700. Studies have shown that the risk for first degree relatives (parents, children, siblings) of someone with MS is about 1 in 40. For second degree relatives (cousins, uncles/aunts, nephews/nieces) it is around 1 in 100.

It is worth putting MS in context with other conditions.

- 1 in 9 women will develop breast cancer
- 1 in 14 men will develop prostate cancer
- 1 in 26 people has some form of diabetes
- 1 in 85 people has some form of dementia
- 1 in 240 people live with disabilities caused by stroke
- 1 in 500 people have Parkinson's disease
- 1 in 700 people have multiple sclerosis

The possible causes of MS

Whilst the rate of MS within families indicates that there is a genetic factor involved in developing the condition, studies of identical twins show that genes are not the whole story. Identical twins have exactly the same genetic make up. If MS were solely dependent on genes, it would be expected that if one identical twin developed the condition, so would the other. Studies have shown that rather than this 100% risk, the actual risk of developing MS for the identical twin of someone with MS is about 1 in 4.

Which genes are involved in MS

Genetic research has started to identify conditions such as cystic fibrosis that result from variations in a single gene. This is not the case with MS and it is believed that the interaction of a number of genes determines whether or not an individual is susceptible.

In 2007 two new genes were identified as contributing to the risk of MS, bringing the total known to three. The scale of the problem is shown by the fact that researchers suggest there might be more than a hundred genes that contribute to an individual's risk of MS. On its own, each gene raises the MS risk by a negligible amount. However, if an individual has enough of these genes, the combined effect will make them susceptible to MS.

A major reason why the identification of genes has been so slow is that none of those associated with MS is unique to people with the condition. For instance, one of the recently discovered genes, called IL7R, is carried by nine out of ten people in the general population. However, researchers are confident that new and better tools will mean that further genes will be indentified over the next few years.

External factors

Whilst a specific combination of genes can mean that an individual is at risk of developing MS, this in itself does not cause the condition. There is believed to be some other external or environmental factor. When people with a particular genetic make up are exposed to this, it triggers their body to react in a way that starts the development of MS, although it may be years before any symptoms become apparent. Many people believe that this trigger is probably an infection of some sort.

Infection

From the early days of MS there has been research into the role of an infection or infections in the onset of MS. Initial work looked into the theory that MS was directly caused by an infectious agent, but this work failed to find any positive results.

Subsequent research, which still continues, has worked on the theory that, rather than being an immediate cause, an infection acts as a trigger which sets off a train of events in some people that develops into MS over a period of time.

A number of common infections have been investigated, including chicken pox, measles, mumps, canine distemper and several herpes viruses.

When someone is infected with a virus or bacteria, the immune system creates antibodies to help it fight off the invasion. The antibodies remain in the blood to help fight off further infections. Researchers can identify antibodies in the blood that indicate the infections to which someone has been exposed.

It is also not yet clear if there is a particular virus or combination of viruses that might trigger MS, or if this varies from person to person. A challenge with this type of research is that most adults carry evidence of common infections, even if their immune system managed to prevent any symptoms developing.

For example, a virus that has recently been investigated is the Epstein Barr virus, which causes glandular fever. As children have a lower level of exposure to some infections, researchers in Canada compared exposure to the Epstein Barr virus in a group of children with MS and a control group who did not have the condition. They found that 83% of the MS group had been infected compared to 42% of the controls. Whilst this suggests that the Epstein Barr virus might have a role in the

The possible causes of MS

development of MS for some people, almost one in five of those with MS had no evidence of exposure.

Vitamin D

The role of vitamin D as a protective agent against the development of MS has also been the focus of research.

Vitamin D is manufactured by the skin when it is exposed to sunlight. Studies of the geographical distribution of MS support the link between lack of sunlight exposure, consequent lack of vitamin D production, and the development of MS.

A review of blood samples taken from US military personnel found that levels of vitamin D in people who subsequently developed MS were lower than levels in people without the condition. This effect only seemed to occur in samples from white people, and was not demonstrated in the smaller set of samples from black or Hispanic people.

Another study found that amongst sets of identical twins, where only one of the twins had MS, the twin who had engaged in less outdoor activity as a child and had been less exposed to sunlight was the twin more likely to have developed MS.

Although these results suggest a protective effect for people without the condition, there is currently no evidence of the effect of vitamin D in people who already have MS.

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The central nervous system

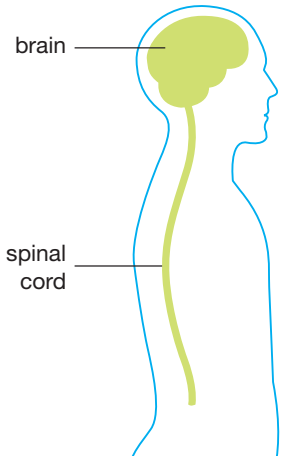
MS is a condition in which damage occurs within the central nervous system.

The nervous system

The nervous system is the means by which the body communicates messages to and from muscles and organs and maintains awareness of the outside world through the senses.

The nervous system is divided into two areas

- the central nervous system (CNS) consists of the brain and spinal cord and is enclosed within the skull and backbone
- the peripheral nervous system (PNS) comprises all other nerves.



The peripheral nervous system

The peripheral nervous system is the cabling that transmits information to and from the central nervous system from the rest of the body.

There are two main types of nerve in the peripheral nervous system:

- Sensory nerves - these collect information from the body's sense organs - responding to touch, temperature, pain, position, smell, sound and sight.
- Motor nerves - these pass messages from the central nervous system. When information has been processed centrally, these nerves carry instructions for action to the muscles controlling movements, speech, internal organs, and to the various glands, such as the sweat glands in the skin.

The central nervous system

The central nervous system receives, processes and stores information and initiates instructions for bodily activities.

The central nervous system is divided into two major parts:

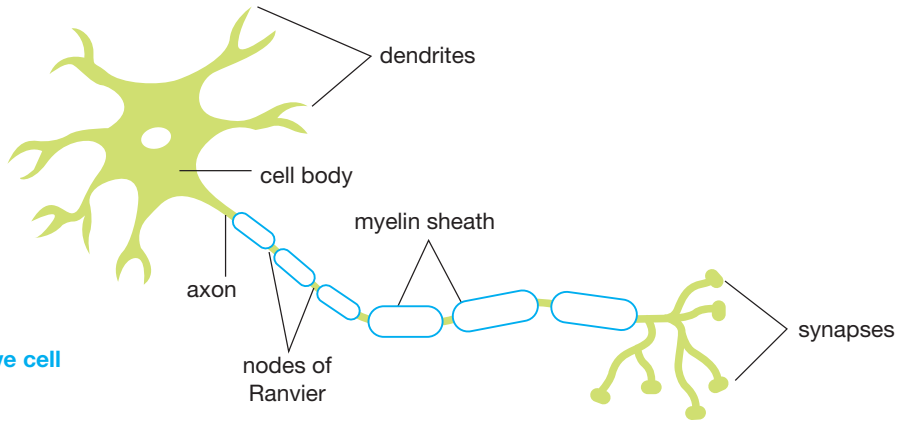
- the brain analyses and stores information and directs the action of the body
- the spinal cord passes information to and from the brain and is responsible for reflex reactions. Reflex reactions are automatic responses to stimuli, such as pulling the hand away if it touches something hot. By responding immediately to stimulation before a signal has travelled to the brain for processing, we can react to situations that need instant actions without wasting time waiting for the brain to analyse the problem.

The central nervous system is made up of two types of cells - nerve cells and support cells.

Nerve cells

Nerve cells are called neurons. The human brain and central nervous system contain about 100 billion neurons.

The brain develops rapidly in the unborn child and in the first years of life. By the age of two, a person has most of the neurons that they will have during their lifetime. Although other cells die and are replaced, many neurons are never replaced when they die. As a result, damage caused by MS that leads to the damage or destruction of neurons can cause permanent disabilities.



Nerve cell

The central nervous system

Neurons have specialised extensions called dendrites and axons. A neuron usually has a number of dendrites but only one axon.

Information enters the neuron via the dendrites, passes through the cell body and then along the axon. At the end of the axon, chemicals called neurotransmitters carry the message over a small gap called a synapse to a dendrite of another neuron.

The axon can be as long as a metre, making neurons some of the longest cells in the body. It is surrounded by a sheath of fatty protein called myelin, which acts as insulation. The myelin sheath has short gaps about one micrometre apart known as nodes of Ranvier, which assist fast conduction of messages. Nerve messages pass along the axon from node to node. The thickness of the myelin sheath and the size of the gap between nodes determine the speed of messages, which can travel as fast as 120 metres/second (268mph).

Support cells

About 40 per cent of the total volume of the brain and spinal cord is made up of cells that support neurons in various ways but which do not carry information themselves.

The collective name for these support cells is glial cells. Glia comes from the Greek word for glue and one of the roles of these cells is to hold the nerve cells in place. Other functions include transporting nutrients to neurons, cleaning up debris and digesting parts of dead neurons.

Glial cells also provide the insulation to neurons through the production of myelin. The specific glial cells that produce myelin in the central nervous system are called oligodendrocytes. Each oligodendrocyte can supply myelin for several axons and each axon can be supplied by several oligodendrocytes. The myelin produced by oligodendrocytes wraps around the axons in thin sheets like a Swiss roll.

Damage to myelin, and the interruption or delay to nerve messages along the axon that this causes, leads to the symptoms of MS. If the protection of myelin is lost, the axon itself will be destroyed, which can cause permanent problems.

Cerebrospinal fluid and the blood brain barrier

The entire surface of the central nervous system is surrounded by a clear, colourless liquid called cerebrospinal fluid (CSF). This acts to cushion the brain and spinal cord within the bony casing of the skull and backbone and helps support the weight of the brain.

The cerebrospinal fluid and the central nervous system are surrounded by a layer of cells called the blood brain barrier. This prevents larger molecules circulating in the blood from reaching the central nervous system. In MS, the blood-brain barrier is breached, allowing immune cells to move across from the blood stream and into the central nervous system.

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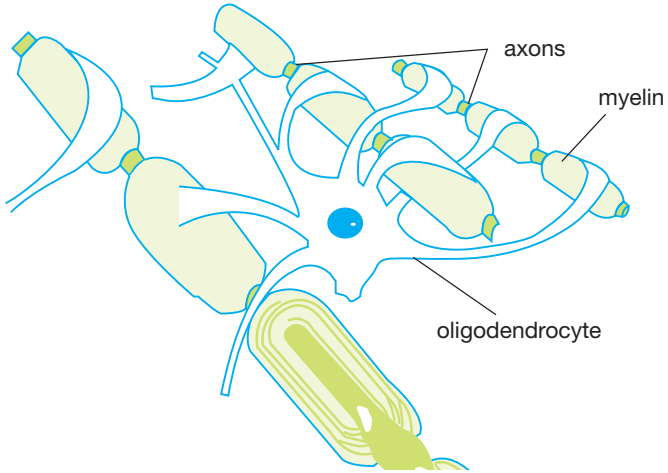
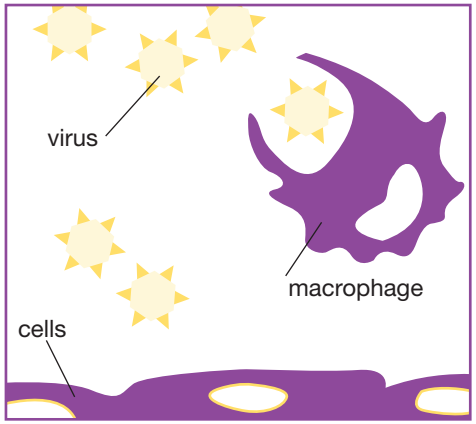


The immune system

How does the immune process work?

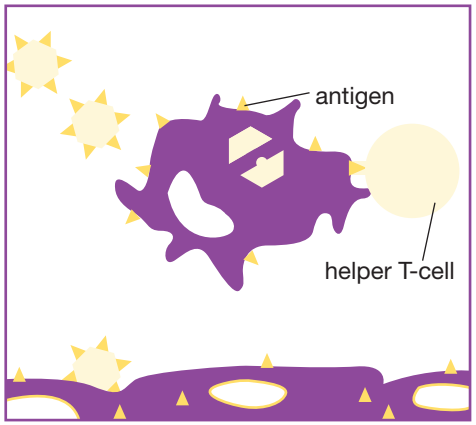
The immune system is the body's main defence system against infection. It consists of a complex collection of special cells and chemicals that patrol the body, identifying and fighting off material that it identifies as foreign, such as bacteria and viruses.

When a cell is attacked by a virus or other invader, it sends out a chemical as a warning signal. This alerts a type of white blood cell called macrophages which mount the initial immune response. When macrophages encounter foreign matter they encircle and digest it. [1]



1. When macrophages encounter foreign matter they encircle and digest it

Once some of the invading germs have been destroyed, macrophages use particles of the debris, called antigens, to tell other immune system cells which cells to attack and to encourage a greater response to the invasion. When this happens, macrophages are known as antigen presenting cells. [2]



2. Macrophages use particles of the debris, called antigens, to tell T-cells which cells to attack

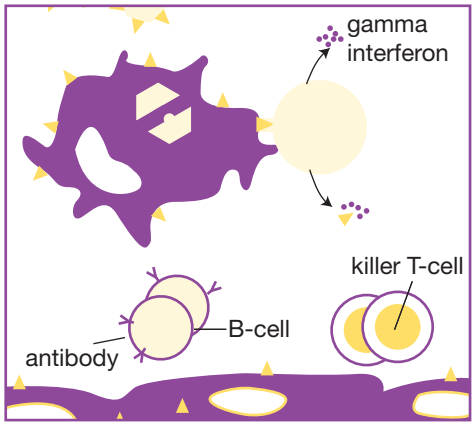
The cells that are prompted to respond are another type of white blood cell called lymphocytes. There are two main groups of lymphocytes, named after the part of the body where they are produced

- T-lymphocytes or T-cells, which develop in the thymus, respond to the antigen presenting cells
- B-lymphocytes or B-cells, which develop in bone marrow, are programmed to attack a specific virus or bacterium

There are different types of T-cells - helper T-cells help to influence how the immune system responds whilst killer T-cells attack and destroy cells

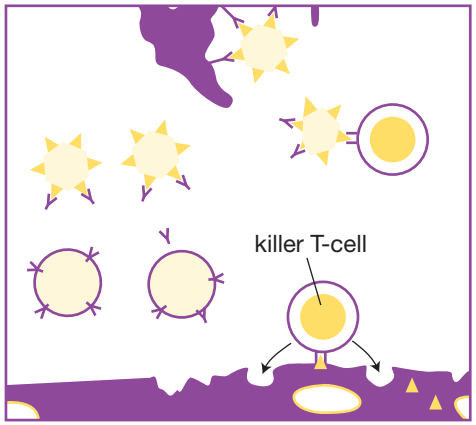
Prompted by the antigen presenting cells, helper T-cells activate and direct other immune system cells by producing 'messenger' molecules called interferons. These molecules tell other elements in the immune system how to act.

At the start of an immune response, a molecule called gamma interferon is produced that stimulates B-cells and killer T-cells to attack. [3]



3. Helper T-cells produce gamma interferon to stimulate B-cells and killer T-cells

Killer T-cells attack and destroy cells containing the antigen - both the invading cell and the body's own cells that have been infected, preventing the germ from reproducing and then infecting other cells.



4. B-cells produces millions of antibodies, which lock onto an invader, helping the body to destroy it

B-cells are tuned to specific germs. When the germ is found in the body, the B-cell clones itself and produces millions of antibodies. Antibodies are proteins that lock onto the surface of the specific invading germ helping the body to kill it off. [4]

The immune response causes inflammation of damaged or infected tissue. Inflammation causes local blood vessels to dilate, increasing blood flow to the injured site and allowing more white blood cells to attack invaders in the affected area.

Once the infection is under control, helper T-cells release different messenger molecules called beta interferon that help to calm down the immune response.
Once an infection is over, some of the antibodies developed to fight it remain in the immune system. This creates the 'immune memory', which means that should the same organism invade again, the body is already prepared to combat it. This is why many infectious diseases such as mumps or chicken pox usually only occur once.
Vaccination uses this principle to forewarn the immune memory. A small amount of matter from a weakened version of an infection is injected into the body. Whilst this is not strong enough to cause illness, it allows the immune system to recognise the disease and to fight it off should it appear again.

Why does a white blood cell not attack every cell in the body?

The antigen presenting cells are controlled by genes called the Major Histocompatibility Complex (MHC) or the Human Leukocyte Antigen (HLA). These genes, which are different in each person, allow the immune system to indentify which cells belong to the body and which are 'foreign'.

It is these genes that create the problems with rejection in organ transplantation. Unless the genes of the donor and the recipient are closely matched, the immune system will treat the new organ as an invader and start to attack it.

In some conditions, for reasons that are not known, this protective mechanism fails to work. The immune system turns on the body's own tissue and attacks it as if it were an invader. These conditions are called autoimmune diseases. How this causes the symptoms of MS will be explored in the next sections.

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What happens in MS?

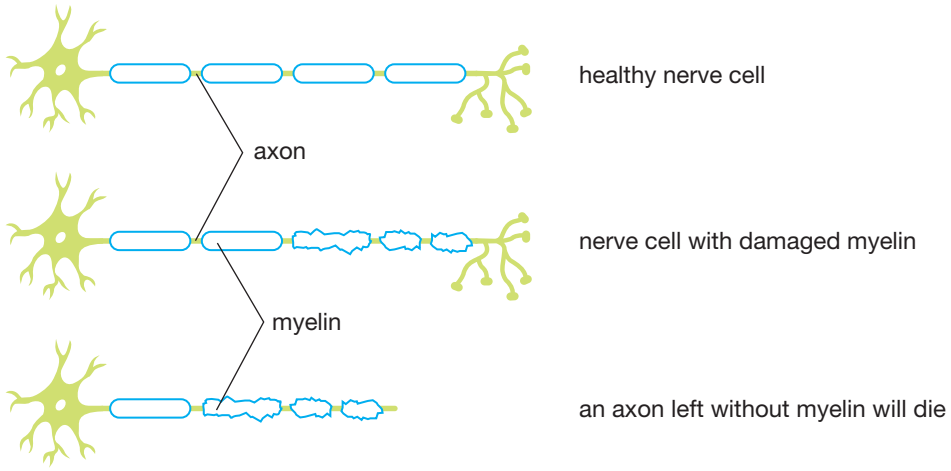
It is thought that MS is an autoimmune condition. For some reason - possibly following exposure to an as yet unidentified infection - the body's immune system starts to attack cells within the central nervous system. T-cells manage to pass through the blood-brain barrier where they mistake the myelin sheath for a foreign body and start to destroy it.

The process of damaging or stripping away myelin from an axon is called demyelination. Messages that pass along a demyelinated nerve become delayed or blocked. As the central nervous system controls processes throughout the body, a wide range of symptoms can occur, depending on where the damage has happened.

For reasons that are not yet understood, the attack by the immune system tends to stop after an indefinite period and scar tissue develops on the damaged nerve. The forming of scar tissue over an area of damaged myelin is what forms the plaques, lesions or scarring ('sclerosis') that show up as white blotches on MRI scans. The name multiple sclerosis comes from the fact that it causes areas of sclerosis at different places in the central nervous system.

Once the inflammation caused by the immune attack is over, it is possible for damaged myelin to be replaced, a process known as remyelination. Whether this happens or not depends on damage to the surrounding oligodendrocytes, the supporting cells that produce myelin and which are also attacked by this process. Although the new myelin can work effectively, it tends to be thinner than unaffected myelin and so messages through the affected nerves may not be as fast as before the attack. If there are several periods of damage, the amount of remyelination is reduced.

Remyelination tends to occur in the earlier stages of MS. Over time, with repeated attacks, oligodendrocytes are damaged and destroyed and myelin is not as easily replaced. If an axon is left without the nourishment and protection of myelin it will be more vulnerable to damage.



It has been found that the central nervous system is able to overcome small areas of axon loss by finding ways to reroute messages around an area of damage through undamaged nerve cells. This ability to adapt to areas of damage is called plasticity. Should the area of damage become too large, this rerouting process is no longer able to compensate and messages to or from that part of the central nervous system are permanently blocked, resulting in symptoms that do not improve.

Remyelination and rerouting occur in the stage of MS where an attack of worsening symptoms, or relapse, is followed by a period of remission when some or all of the function returns.

Remyelination, rerouting and the loss of axons can happen at the same time in different parts of the central nervous system.

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The cause of symptoms

In MS, only nerves in the brain or spinal cord are damaged. However, as these nerves control the functions of the whole body, symptoms can affect many different areas, although an individual with MS will only experience some of these. As well as the variety of symptoms, the severity and duration will also vary from person to person.

How MS affects an individual depends on where damage occurs and which nerve messages are interrupted or blocked.

Some people can have MRI scans that show a number of areas of scarring but in areas that have not caused them to experience noticeable symptoms. Conversely, a single scar that damages an area controlling bladder function, for instance, can have a serious impact on someone's life.

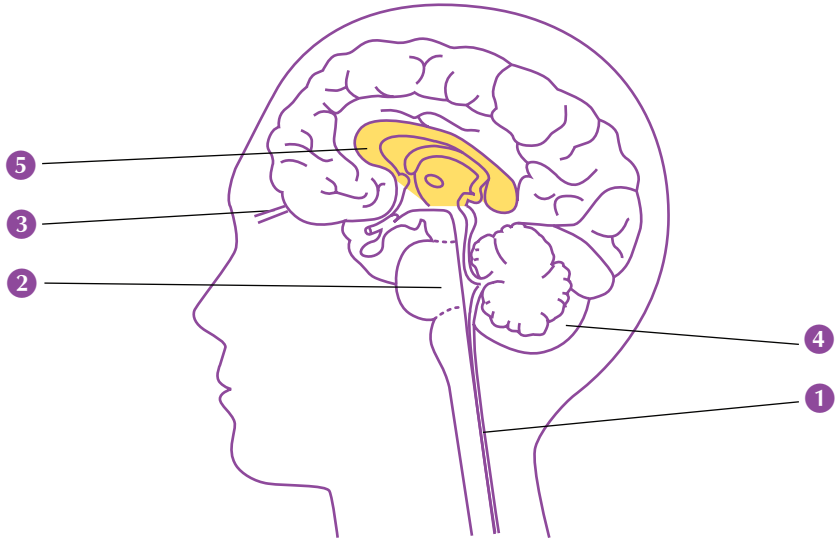
Similarly, the actual level of disease activity can remain constant with a consistent number of areas of scarring. However, if a new scar interrupts an important function, such as walking, it can seem to the individual as though the MS has accelerated.

Whilst the complexity of the brain and how it handles information are still far from fully understood, certain areas are associated with specific functions. This section gives a very broad overview of how damage caused by MS to these areas can lead to certain symptoms being experienced.

The following pages cover a range of symptoms that MS can cause, but it is important to stress that most people only experience a small number of these. Although there are no drugs to cure MS, there are treatments for many of the symptoms. Information on treatments can be found in other MS Trust publications or by contacting the MS Trust Information Service.

MS Trust Information Service

Spirella Building, Bridge Road,
Letchworth Garden City,
SG6 4ET
T: 01462 476760
e: infoteam@mstrust.org.uk
www.mstrust.org.uk/publications



Site of Damage	Symptom
1 Spinal cord	Spasticity Bladder problems Bowel problems Weakness
2 Brainstem	Double vision and nystagmus
3 Optic nerve	Optic neuritis
4 Cerebellum	Balance and dizziness Tremor
5 Areas involved with thought and emotion	Cognition Depression
Symptoms not associated with a single area	Fatigue Speech and swallowing Pain

The cause of symptoms

1 Spinal cord

Most nerves in the peripheral nervous system are not connected directly to the brain but to the spinal cord, which acts as the main route for nerve messages to and from the brain.

The spinal cord also controls reflex reactions. Reflex reactions are automatic responses to stimuli, such as pulling the hand away if it touches something hot.

Spasticity

Spasticity is a condition in which muscle tone becomes greatly increased. Muscle tone refers to the level of tension or resistance to movement in a muscle and is what enables people to move limbs or hold a position. For instance, to bend your arm, you must shorten or contract the biceps muscle at the front of the arm (increasing the tone) and at the same time lengthen or relax the triceps muscle at the back of the arm (reducing the tone).

When someone has spasticity in a limb, the signals from the brain are interrupted and the muscle remains in its shortened, contracted state. This causes the affected limb to feel stiff or tight and often to be difficult to move.

The instruction to contract a muscle can be triggered by sensory signals from peripheral nerves in a muscle. When the signal reaches the spinal cord, it responds with an automatic, reflex response and also by passing the message to the brain. The brain assesses the situation and sends a message back down the spinal cord telling the muscle how to respond. The whole process is normally almost instantaneous.

In MS, spasticity occurs if there is an area of scarring between the brain and the point where the nerve from the muscle joins the spinal cord. The reflex action takes place but the message to or from the brain is interrupted. Thus no message to relax the muscle is received or is delayed and the muscle remains contracted and stiff.

Depending on the area of damage in the process, spasticity can occur in any muscle in the body. This can lead to a number of problems including the walking, speech or swallowing and bladder control.

The degree of spasticity can vary from mild muscle stiffness to severe, painful muscle spasms.

More information from the MS Trust:

- Spasticity factsheet

Bladder problems

Types of bladder problem

Frequency - an increase in the number of times someone needs to urinate in a day

Urgency - the feeling of having to empty the bladder immediately, an inability to 'hold on'

Hesitancy - the difficulty in starting to urinate

Incontinence - the inability to hold urine in the bladder until an appropriate time

The wall of the bladder consists of muscle called the detrusor muscle, which stretches to store urine. At the base of the bladder is a valve called the urethral sphincter, which opens to let urine out.

The average capacity of the bladder is between 300 and 500ml (about three quarters of a pint). On average, an individual produces about 1ml of urine every minute.

The urge to empty the bladder usually occurs when it contains about 200ml. At this point the bladder is expanded enough to stimulate nerve endings in the detrusor muscle. This triggers a message to an area of the spinal cord that controls the reflex action that causes the bladder to contract. A message is also sent to the brain, signalling the need to urinate. When the brain assesses that it is appropriate to do so it passes simultaneous messages back through the spinal cord telling the valve to open and the detrusor muscle to contract, and urine is passed. Normally this occurs four to six times a day.

The cause of symptoms

Damage to areas of the spinal cord or brain that control phases of this process can cause different types of problem.

Failure to store

In this situation, damage occurs to the spinal cord between the area controlling the bladder reflex and the brain. When this happens, the controlling message from the brain is interrupted and the reflex action means the bladder will empty automatically. For the individual this means they will need to go to the toilet often (frequency), but usually with little or no notice (urgency), resulting in incontinence.

Failure to empty

This happens when the scarring occurs in the reflex area of the spinal cord interrupting the instruction to empty the bladder. This means that even when someone goes to the toilet, they find it difficult to pass urine (hesitancy). The bladder does not empty properly and keeps filling beyond its normal level until it overflows. This leads to frequent, urgent needs to go to the toilet, often accompanied by overflow incontinence.

Combination of failure to store and failure to empty

This occurs when scarring causes a loss of coordination between the contracting of the bladder and the opening of the valve. Depending on where the damage occurs this can either mean:

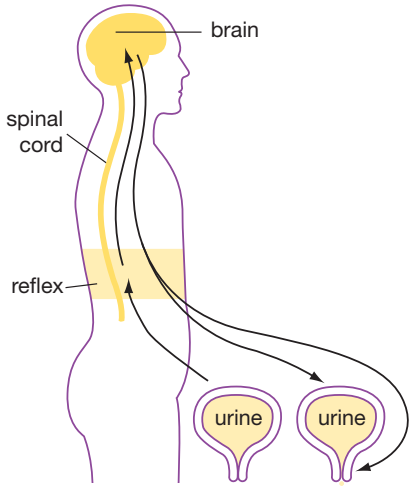
- the bladder contracts but the valve remains closed, so that urine can not be released - the individual feels a strong urge to go to the toilet (urgency) but is unable to properly empty their bladder (hesitancy)
- the bladder relaxes and the valve opens resulting in an inability to store any urine - which causes incontinence.

Rather than helping the problem, reducing fluid intake can in fact make bladder symptoms worse. If the body does not have sufficient fluid, urine becomes concentrated and flow slows down. This allows painful crystals to form and bacteria to grow, which can lead to infections developing.

Difficulty with bladder control and with walking often go together in MS. The wiring of the nervous system means that the connections to the bladder from the spinal cord come below those to the legs. If there is damage to the nerves further up the spinal cord, both functions can be affected.

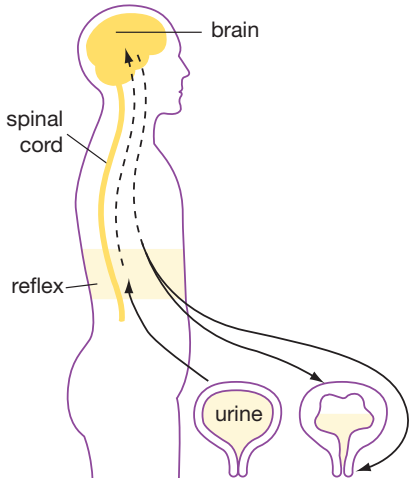
More information from the MS Trust:

- Bladder problems factsheet



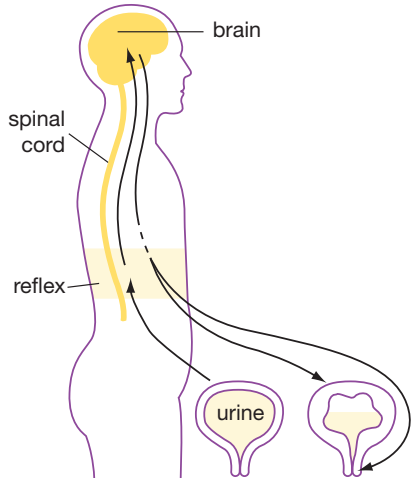
Normal function

The bladder triggers a message to the reflex area of the spinal cord and a message is also sent to the brain. The brain passes instructions to the bladder.



Failure to store

Damage occurs between area controlling the bladder reflex and the brain



Failure to empty

Scarring occurs in the reflex area of the spinal cord interrupting the instruction to empty the bladder

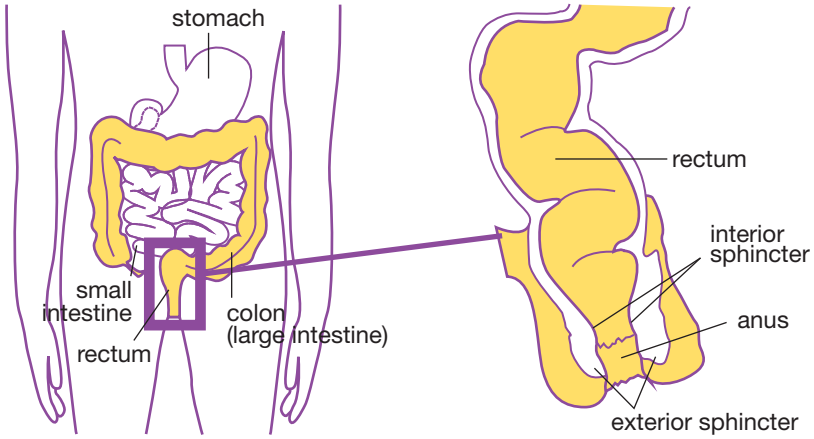
The cause of symptoms

Bowel problems

In the healthy bowel, once food has passed through the digestive system, waste material is collected in the colon where it forms into stools. When the colon is stretched to a certain size, nerve responses trigger a reflex process that causes a bowel movement. The stool is passed into the rectum - the area occupying the last six inches of the digestive system. As the rectum fills, it triggers another reflex action that causes the stool to pass to the anal canal.

The anal canal is about an inch long with a valve, or sphincter, at each end. The internal sphincter, which separates the anal canal from the rectum, is opened by an involuntary reflex action under the control of the spinal cord. The external sphincter can be controlled to prevent inappropriate defecation. When someone wishes to defecate, the external sphincter is relaxed and they 'bear down' - increasing the pressure in their abdomen to help push the stool out.

Although the causes of bowel disorders in MS are not fully known, it is thought that damage to nerves controlling different parts of this process can lead to different bowel problems.



Constipation

Constipation can be caused by interruptions to the sensory messages from the colon or rectum that signal fullness. The body does not realise that there is a need to move the stool on to the next stage in the process.

Constipation can also be due to the slowing down of the digestive process that can occur in people who do not undertake much physical activity or who can not bear down with sufficient pressure due to weakness.

Not drinking enough can also cause constipation. As food passes through the body, water is extracted. If there is not enough fluid in the diet, by the time food reaches the end of the process, it has become a dry, hard stool which does not move as easily through the system.

Faecal incontinence

Faecal incontinence is the inability to control defecation. This happens when damage to nerves occurs between the reflex area in the spinal cord and the areas of the brain that give voluntary control to bowel movements. This does not necessarily mean that the individual experiences diarrhoea, but if this lack of coordination affects the parts of the process where stools are formed, it can result in ill formed and runny stools.

Faecal incontinence can also be caused by constipation. A build up of constipated matter can sometimes mean that the sphincters in the anus and the rectum do not close properly, allowing runny stools to escape around the blockage.

More information from the MS Trust:

- Bowel problems factsheet

Weakness

One of the causes of weakness in muscles in MS is the poor transmission of messages by damaged nerves, mainly within the spinal cord. It is often associated with fatigue. As the nerve damage makes muscles less responsive, it requires more energy to carry out actions. Feeling weak can cause

an individual to become less active in an attempt to conserve energy, but this can cause weakness to increase. An already weak muscle that is not used will become weakened further, a process known as atrophy.

However, as muscle weakness in MS is primarily due to problems with nerves rather than within muscles, expending a great deal of energy by exercising to the point of exhaustion can also make weakness worse.

For many years people with MS were advised to avoid exercise due to the impact it could have on weakness and fatigue. It is now felt that exercise is beneficial if it works on gently building up endurance and strength in muscles without increasing weakness and fatigue.

More information from the MS Trust:

- Move It For MS DVD
- Exercises For People With MS

2 Brainstem

The brainstem is the area at the base of the brain that connects to the spinal cord. It contains areas responsible for basic functions such as breathing, heart rate, blood pressure and control of the bladder. Many of the processes handled by the brainstem are outside conscious control. The peripheral nerves that maintain processes such as breathing and digestion are referred to as the autonomic nervous system.

The midbrain area of the brainstem controls vision, hearing, body movement and the movement of the eyes.

Visual problems

Visual problems are common in MS and are often one of the first symptoms people experience.

Double vision

Visual disturbances in MS can be caused by damage to the nerve pathways that connect to the 12 muscles that control the movement of the eyes. A reduction of coordination in the eyeballs leads to double vision (diplopia).

Nystagmus

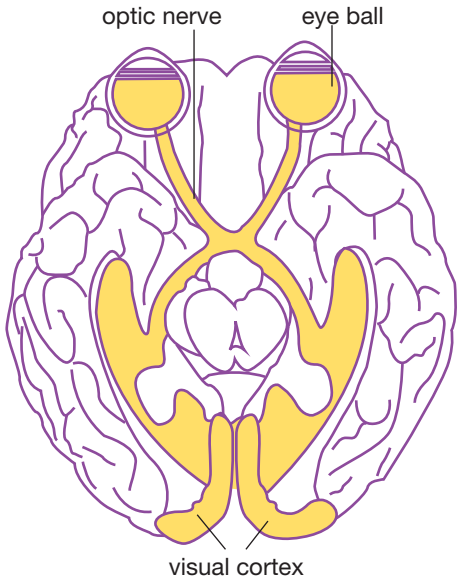
Sometimes nerve damage results in a flickering or jerking motion of the eyeballs, often when moving the eyes to a certain position. This disorder is called nystagmus.

Uthoff's phenomenon

Some people find that an increase in temperature affects their vision in some way. This effect is known as Uthoff's phenomenon or Uthoff's sign. These symptoms lessen or disappear when the individual cools down again.

3 Optic Nerve

Another common visual problem experienced by people with MS is due to damage to the optic nerves, which carry information from the back of the eyes to the brain.



Optic neuritis

Inflammation of the optic nerve is called optic neuritis. Optic neuritis can cause a sudden, usually temporary, loss of vision. An attack usually occurs on one side only and is often accompanied by pain behind the affected eye. The

effects of an attack of optic neuritis can include complete loss of sight, partial blind spots (called scotomas), blurred or foggy vision, or the loss or worsening of colour vision.

More information from the MS Trust:
- A to Z of MS www.mstrust.org.uk/atoz/

4 Cerebellum

The cerebellum controls movement, balance and posture

Balance problems and dizziness

The body uses the complex interaction of a variety of sources to maintain an idea of how it fits in with its environment, such as whether it is upright or maintaining balance. This requires the coordination of information from vision, from the balance systems in the inner ear and information from movement, touch and joint sensors throughout the body.

For instance, when someone turns their head, their eyes, neck muscle sensors and two inner ears all give matching information to the brain. If something causes a mismatch in the information, it affects the sense of orientation and causes feelings of dizziness, vertigo or loss of balance. These outgoing and incoming messages are coordinated in the cerebellum. If MS causes damage to the nerves in this part of the brain, balance can be affected.

More information from the MS Trust:
- A to Z of MS www.mstrust.org.uk/atoz/

Tremor and ataxia

Disruption to the coordination of movements is called ataxia. In its mildest forms this can be apparent as clumsiness. If damage to the cerebellum is more severe, the disruption to coordination can lead to shaking or tremor.

Tremor in MS usually does not happen in completely relaxed limbs but is triggered by a mismatching of messages when trying to perform a function. This makes tremor in MS distinct from that found in Parkinson's Disease, where shaking occurs in muscles at rest.

There are two main types of tremor that can affect people with MS.

Intention tremor occurs when someone tries to carry out a task. For instance, an arm can start to shake as it moves to pick up a teacup or the telephone, with the shaking worsening as the hand approaches the object.

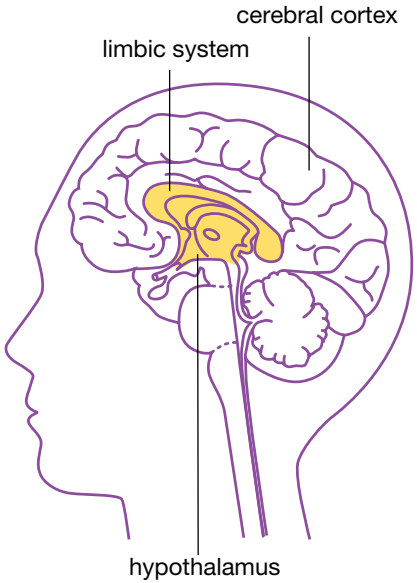
Postural tremor occurs when the body has been held in a particular position for a period of time. It usually affects the head, neck and trunk.

More information from the MS Trust:
- A to Z of MS www.mstrust.org.uk/atoz/

5 Areas of the brain involved with thought and emotion

Cerebral Cortex

The cerebrum makes up nearly 70 per cent of the brain. This is the outer layer that has the familiar walnut like bumps and grooves (called gyri and sulci). The cerebral cortex controls thought, voluntary movement, language, reasoning and perception.



The cause of symptoms

Hypothalamus
The hypothalamus is a small structure at the base of the brain that controls body temperature, emotions, hunger, thirst and the circadian rhythms - the natural variations in the body's activities throughout the day.

Limbic System
The limbic system (or the limbic area) is important for controlling the emotional response to situations. It includes the hippocampus, which is important for memory.

Cognition
As well as affecting the control of muscles and actions in different parts of the body, damage to the brain caused by MS can also affect mental processes. These disorders are called cognitive or cognition problems. Generally, cognition problems in MS affect the speed or ease with which someone can process information, and do not indicate a loss of underlying intelligence.

Memory difficulties
Memory difficulties are primarily related to the recall of recent events or information and forgetting to carry out planned actions.

Information processing problems
Difficulty following complicated instructions or a series of instructions, especially if the information is given rapidly.

Problem solving difficulties
An inability to hold a number of pieces of information in the head at once and being unable to mentally structure thoughts to carry out a series of separate actions.

Word finding
The inability to find the right word when speaking, also called the 'tip of the tongue' phenomenon, is a short-term recall problem rather than the loss of memory for that word.

Concentration and attention span problems
This tends to occur when a lot of information is being delivered to a person at once, for example where several people are talking or in a noisy, bustling environment.

Cognitive problems can fluctuate from day to day and can worsen during relapse or periods of fatigue. Some medications, including those used to counteract pain, fatigue and depression, may also have an impact on these problems.

Although research suggests that these symptoms can affect almost half of all people with MS, many people may not recognise them as symptoms of MS or may find ways to compensate for the problems without seeking treatment. Problems can arise early in the course of someone's MS, although the greater the disease duration and severity the more likely problems are to occur.

More information from the MS Trust:
- Cognition factsheet

Depression
Many people with MS experience depression. Depression involves persistent sadness lasting more than two weeks, accompanied by other symptoms such as an altered sleep pattern, feelings of hopelessness, guilt and low self esteem, thoughts of death, reduced energy and the inability to concentrate and to take pleasure in anything.

Depression can be caused by a reaction to living with a long-term condition or as a side effect of some medications for other symptoms. It can also be caused directly by MS damage to the nerves in the brain.

Recognition of these disorders as symptoms of MS has only occurred relatively recently and the precise causes are poorly understood.

More information from the MS Trust:
- A to Z of MS
  www.mstrust.org.uk/atoz/

The cause of symptoms

Mood swings

The effects of MS can cause alterations in an individual's mood. As with depression, alteration to mood can be due to a number of factors. The uncertainty and frustrations of living with the condition can have a negative effect on mood and the side effects of some medication, such as steroids, can also affect emotional responses. Episodes of fatigue are particularly associated with affected mood, with an individual becoming short tempered or more withdrawn.

MS can also directly affect responses and cause episodes of uncontrolled laughter or crying. Referred to as 'emotional lability' or 'pathological laughter and crying', the exaggerated response will have little or no relationship to actual events or the individual's feelings.

More information from the MS Trust:

- A to Z of MS
  www.mstrust.org.uk/atoz/

Symptoms not associated with a single area of damage

For some symptoms it is not possible to identify a single area of the central nervous system that is the chief area of damage.

Fatigue

Fatigue is one of the commonest symptoms of MS and one that can often cause major problems to people's lives.

The cause of fatigue in MS is not well understood. It is thought to result from a combination of factors, partly caused by MS itself (known as primary fatigue) and partly by other factors (secondary fatigue) that affect the person with MS more significantly than those without the condition.

Primary fatigue is thought to be a combination of slowed nerve messages from the brain and spinal cord and a build up of weakness in muscles due to lack of stimulation. The level of fatigue does not reflect the severity of someone's MS and people can experience fatigue that prevents them from working or which interrupts their daily life whilst having no other symptoms.

MS fatigue or 'lassitude' is very different from the tiredness or exhaustion that people without MS experience following strenuous exercise or a busy day at work. Fatigue is described as interfering with normal activity and being out of all proportion to any activity undertaken. It is characterised by the sudden loss of energy and the inability to continue an activity.

MS can also cause 'short-circuiting' or neuromuscular fatigue. This happens if nerve messages to muscles become confused when someone is performing repeated movements. Messages start to 'leak' into other nerve cells and it becomes harder for the brain to get instructions through. For example, the legs may become increasingly heavy and difficult to move when walking, or the arms may be affected when writing for a period of time.

Secondary fatigue is fatigue that results from another symptom or cause, rather than being caused by the condition directly. Factors that can add to fatigue include lack of sleep, low mood or depression, stress, inadequate diet, lack of exercise, infections or side effects of medication.

Heat can increase fatigue in MS and some people with MS find that symptoms get worse during spells of hot weather. This was first observed in the late nineteenth century, and for a time, one of the diagnostic tests for MS was to put the patient into a hot bath and observe if this made symptoms worse.

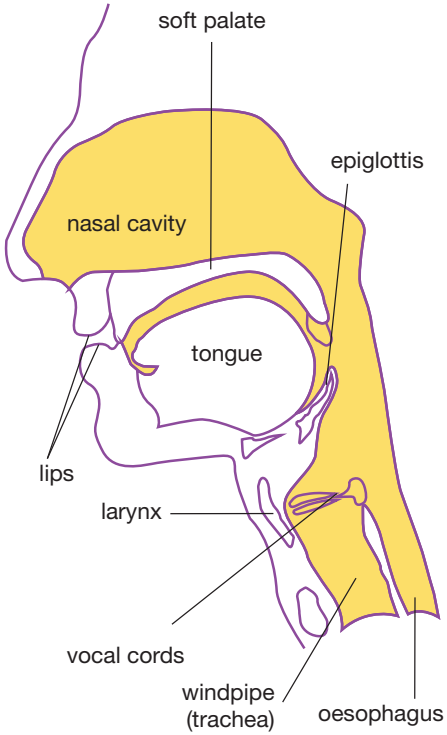
More information from the MS Trust:

- Living With Fatigue
- Fatigue factsheet

Speech and swallowing

There are a number of different speech and swallowing problems that can affect people with MS.

Damage to the various parts of the brain that control thought, memory, verbal fluency or attention can lead to difficulty in finding words or forming sentences. This disorder is called dysphasia.



Speech requires the complicated interaction and coordination of several parts of the body including the lungs, diaphragm, vocal cords, lips, tongue and nasal cavity. Damage to the areas of the central nervous system that control any of these elements can have an effect on speech. Similarly, fatigue or weakness can affect any part of the process. When a speech disorder is due to damage affecting the muscles used in speech, it is called dysarthria. This can lead to slurred speech or difficulty in controlling volume, articulation or intonation.

Many of the muscles used in speech also have a role in swallowing and a lack of coordination can cause difficulties when a person is eating or drinking. This is known as dysphagia.

If the various processes involved in holding food in the mouth, chewing and swallowing are not synchronised, a number of different problems can occur. Food may get stuck in the throat, which causes choking; may move too slowly in the oesophagus (the tube connecting the mouth to the stomach), which causes coughing and spluttering; or may go into the windpipe (which should be closed during swallowing) or the lungs, which is known as aspiration.

More information from the MS Trust:

- A to Z of MS
  www.mstrust.org.uk/atoz/

Pain

For many years, the medical world considered MS to be a pain free condition. This idea has now been completely overturned and studies suggest that the majority of people with MS experience some form of pain as a symptom at some stage.

There are two main types of pain in MS.

Muscle pain

Muscle pain (called nociceptive pain or musculoskeletal pain) is generated by damage to the muscles, tendons, ligaments and soft tissue of the body.

This is the sort of pain that is felt when someone falls over or cuts themselves. In MS, this pain is not caused directly by damage to the nerves but develops as a result of other symptoms. For instance, spasticity in a leg can cause someone to alter the way they walk or alter their posture, which can result in added strain on the back or legs or arms.

Nerve pain

Pain that results from damage to nerves is known as neurogenic or nerve pain. With this type of pain, nerve messages are interrupted or blocked and the brain interprets the incomplete information it is receiving as pain. Whilst the pain experienced can be severe or long lasting, unlike muscle pain, there is no physical cause of the symptom.

Examples of nerve pain include:

Paraesthesia or dysaesthesia

Persistent, uncomfortable, abnormal sensations. The pins and needles effect is an example of paraesthesia, but other sensations can include burning and crawling feelings, numbness and tightness.

The cause of symptoms

Lhermitte's Sign

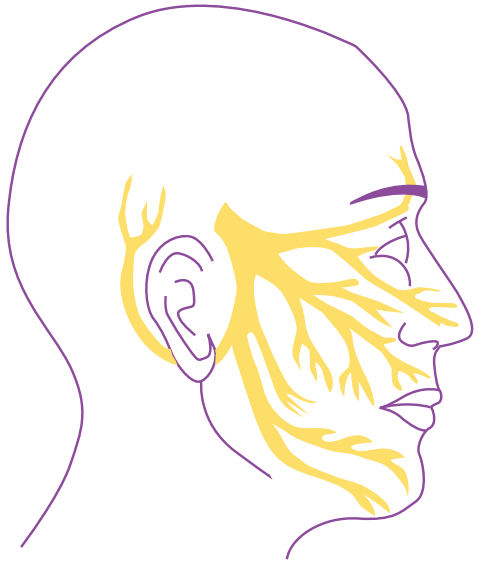
Sometimes referred to as the Barber Chair phenomenon, this is caused by damage to the spinal cord in the neck. Movements of the neck cause a short lasting but sharp, painful, buzzing, electric shock feeling running down the spine and into the legs.

Trigeminal neuralgia

The trigeminal nerve controls movements and sensation in the face and mouth. Damage to this nerve at the point where it meets the central nervous system at the base of the brain can lead to episodes of sharp pain in the face triggered by actions such as talking, chewing, smiling or brushing teeth.

More information from the MS Trust:

- Pain factsheet



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Diagnosis

There is no one test that will conclusively show that someone has MS and diagnosis usually involves a combination of investigations. Similarly, none of the individual symptoms people can experience are unique to the condition. This means that in order to reach a diagnosis, a range of other possible explanations has to be ruled out and so the process can be difficult and take some time.

The diagnosis of MS is made by a neurologist. To show that someone has MS, the neurologist is usually looking for evidence of two or more areas of scarring in different parts of the central nervous system that have occurred at different points of time.

Brain imaging or scanning is becoming more powerful and it is now technically possible to make a diagnosis based on information from one attack of symptoms and evidence of further disease activity from scans. However, it is still unusual to diagnose MS from just a single attack of symptoms.

A number of tests are used to try and find information to help a neurologist decide if someone has MS.

Patient history

As the neurologist needs to establish that different symptoms have occurred at different times, a discussion of someone's previous symptoms and health is important in establishing a diagnosis of MS. Sometimes a previous episode of numbness or double vision, for instance, that might have passed of its own accord or been treated without thought of MS at the time can prove significant.

Neurological examination

There are a number of simple tests that a neurologist can carry out that may suggest whether or not MS is a cause of symptoms. These include checks on movement, coordination, vision, balance, reflexes and other functions of the five senses. Information from these tests may also give an indication as to where in the central nervous system damage has occurred and which further tests might be useful.

Blood may be taken for testing. There is no blood test that can determine whether someone has MS, but if there are abnormalities, it is an indication that another condition may be present and might be causing symptoms.

Although the patient history and neurological examinations might suggest the diagnosis of MS, the process usually involves one or more tests to look for evidence of MS within the body.

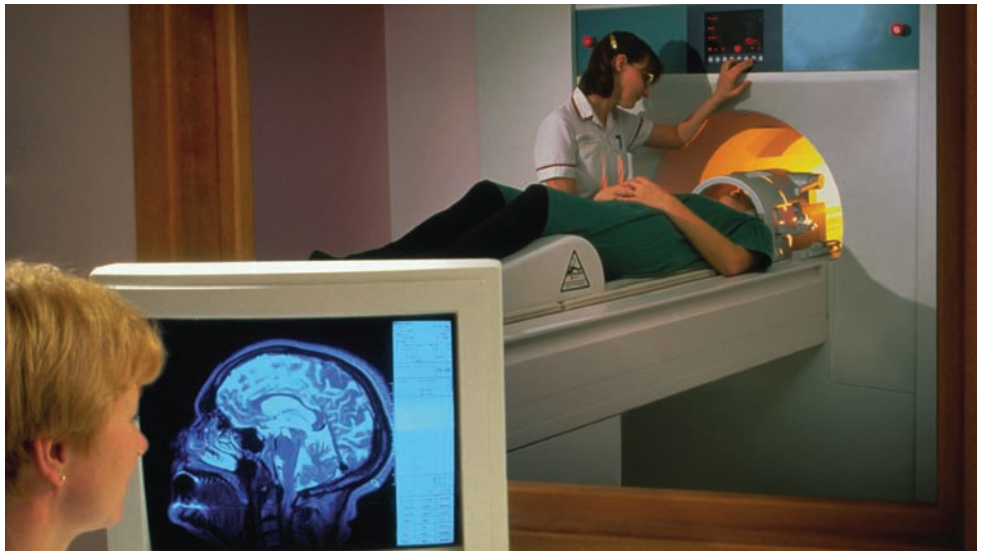
Magnetic resonance imaging (MRI)

First used in MS in the early 1980s, MRI has become a key diagnostic test.

An MRI machine is essentially a large magnet, shaped as a tube, within which the person being scanned lies. The procedure is painless, although the machines can be noisy.

Images are created by using magnetic fields and radio waves to monitor the behaviour of hydrogen atoms in the body.

The nucleus at the centre of an atom spins like a top. The powerful magnetic field in an MRI machine (more than 10,000 times stronger than gravity) makes the atoms line



up in the direction of the magnetic field.

The machine then fires a pulse of radio waves that causes the atoms to spin in a different direction (causing 'resonance'). When the pulse is turned off, the atoms return to their natural alignment within the magnetic field and release energy. The machine picks up this signal and sends it to a computer, which converts it into an image of a slice through the body.

Scars caused by MS show up as white patches on MRI images, giving a very clear picture of the effects of MS on the brain and spinal cord.

Depending on what the scan is looking for, some people may be injected with a contrast enhancing agent called gadolinium before a scan. This allows the MRI to show damage to the blood brain barrier, which indicates areas of active MS.

Lumbar puncture

A lumbar puncture involves inserting a hollow needle into the base of the spine and drawing off a quantity of cerebrospinal fluid (CSF), the fluid that surrounds the brain and spinal cord within the skull and backbone.

In the diagnosis of MS analysis of cerebrospinal fluid is looking for:

White blood cells

Generally the number of cells from the immune system in the cerebrospinal fluid is low. For many people with MS the count of white cells in cerebrospinal fluid is up to seven times higher than normal. A count that is even higher than this is probably due to an infection of some sort, such as Lyme's Disease, and not MS.

Oligoclonal bands

In MS, cells from the immune system cross the blood-brain barrier and attack the myelin that surrounds nerves. As a result, the level of proteins from the immune system in the cerebrospinal fluid of someone with MS is higher than it should be and is higher than the level in the blood, a sample of which is also analysed.

The test that shows the presence of immune system proteins in cerebrospinal fluid is called electrophoresis. A sample of fluid is placed on a gel and voltage is applied. This causes proteins of the same size to bunch together, forming visible 'bands'.

One band (monoclonal) in the cerebrospinal fluid is normal. The term oligoclonal bands refers to the presence of two or more bands and shows the presence of disease activity. Whilst this does not necessarily mean that someone has MS, more than 80% of people with MS do have oligoclonal banding in their cerebrospinal fluid.

Evoked Potentials

Evoked potentials are tests that measure the speed of nerve messages along sensory nerves to the brain.

The most commonly used test is called visual evoked potentials (VEP). Electrodes placed on the skin measure messages sent from the eyes in response to being shown a flashing chessboard pattern on a computer screen. Less frequently, tests of sensations from the skin (somatosensory evoked potentials), which involve tiny electric impulses, and of hearing (auditory evoked potentials), using clicks, can also be carried out.

Visual evoked potentials work on the basis that it is possible to measure how long it takes for input from the eye to get to the visual cortex at the back of the brain where this information is processed. As damage to the optic nerve in MS can slow messages down, evoked potentials tests can indicate the presence of an area of scarring that is not causing any obvious symptoms (described as clinically silent). Delays of as little as 10 milliseconds can indicate that there is damage to the nerve pathway.

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Types of MS

Typically MS is a condition in which there is a period of relapses - also called attacks, episodes or exacerbations - which initially get better but are then followed by episodes where recovery is not complete, and eventually a period of slow progression with more persistent symptoms. However, this is a broad generalisation of a wide spectrum of experiences of MS.

The range of possible symptoms and the levels of severity of those symptoms mean the way MS affects one person may vary widely from someone else. Some people will live with the condition for many years with few or very minor symptoms. Others may experience no relapses at all but find that their symptoms and level of disability increase gradually from the onset of MS.

There are a number of 'types' of MS that are used to try to broadly group individuals in accordance with how the condition has developed. However, each type encompasses a wide range of experiences of MS and it is sometimes difficult to ascertain what type an individual has. It is also impossible to predict how an individual's MS will develop over time.

Relapsing/remitting MS

The majority of people with MS are diagnosed with the relapsing/remitting form. This means they will have periods when symptoms flare up - a relapse - followed by periods of good or complete recovery - a remission.

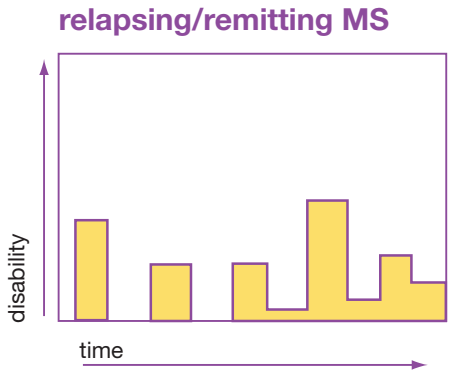
A relapse is the appearance of a new symptom or the reappearance of old symptoms that lasts more than 24 hours. A relapse often lasts for considerably longer than that and may persist for weeks or months. Many people also find that some of their symptoms will vary from day to day, being worse one day and better the next. This fluctuation is not classed as a relapse.

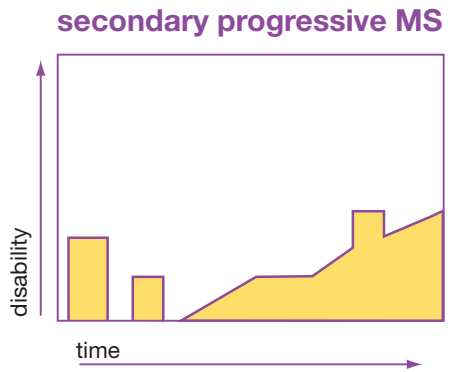
As a very broad average, people with relapsing/remitting MS have one or two attacks a year, although for the individual, the number and frequency of relapses and the nature and severity of symptoms experienced are unpredictable.

Secondary progressive MS

Many people who are initially diagnosed with relapsing/remitting MS find that over time the frequency of relapses decreases but disability increases. As this progressive phase follows a period of relapsing/remitting MS it is known as secondary progressive MS.

As with relapsing/remitting MS, people's experience of secondary progressive MS can vary widely.





Types of MS

Some people find that the increase or progression of disability is very gradual, whilst for others it can occur more quickly.

Studies that have monitored people with MS over a long period of time suggest that after ten years, half those people who were diagnosed with relapsing/remitting MS will have developed secondary progressive MS.

Primary progressive MS

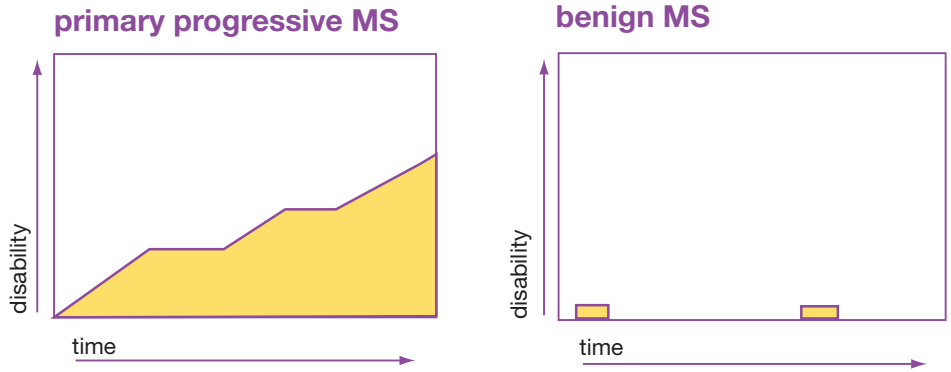
About 10% of people with MS are diagnosed with a form in which disability increases from the outset, usually with the absence of distinct relapses. As this type is progressive from onset it is known as primary progressive MS.

Unlike the relapsing and secondary progressive types where there is a proportion of two or three women for each man with MS, primary progressive MS is evenly distributed between the sexes.

Again, there is a variety of experience of primary progressive MS. Some people can have a persistent increase in disability whilst others may experience plateaux or a more gradual worsening of symptoms.

Benign MS

People with benign MS have very mild attacks separated by long periods with no symptoms. It is estimated that about 10% of people with MS have this form of the condition.



As the defining characteristic of benign MS is the long-term absence of symptoms, it can only be diagnosed retrospectively after ten or more years. The phrase is sometimes used inaccurately to describe a period of mild symptoms following diagnosis.

Rather than being a static form of MS, benign MS is probably a slower version of relapsing/remitting MS in which the disease activity is not apparent. Over a long period of time, some people may find that their MS has started to display a clearer relapsing/remitting pattern.

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Future research

Where will we find an answer?

Almost 150 years after it was first described, MS is still a condition with many mysteries: no known cause, no means of prevention, and no cure - but there have been significant advances.

Until the 1990s there were no drugs that had any effect on the underlying disease activity of MS. Treatment was focussed on medication and management of the various symptoms that people experienced. Whilst symptomatic treatment remains at the core of the medical management of MS, the last few decades have seen breakthroughs that have shown the possibility of developing therapies that may effectively tackle MS itself.

Very broadly, there are three main focuses of research for altering the course of MS:

- Immune system - altering the processes that cause damage to nerves
- Neuroprotection - protecting nerves to prevent any further damage
- Repair - repairing or replacing damaged cells to reverse disabilities

Immune system

Initial experimental therapies for modifying the course of MS were based on attempts to control the activity of the immune system.

The first drug to be licensed was beta interferon - a commercially produced version of a substance that occurs naturally in the immune system. The role of beta interferon is to calm down the immune system once an infection has been dealt with. As a drug it was hoped that this would limit the effect of the immune cells that mistakenly attack the myelin surrounding nerves. Several different beta interferon drugs are now available.

Another drug called glatiramer acetate was developed at the same time as beta interferon. This is a synthetic combination of four molecules that resembles the myelin protein surrounding nerve fibres.

Studies showed that on average both the beta interferon drugs and glatiramer acetate helped to slow the relapse rate of someone with MS by a third and to reduce the severity of those relapses that did still occur.

Attempts to produce more powerful drugs that reduce the immune response further have come up against the problem that this approach is not focussed on any specific part of the system. As a result these drugs can attack aspects of the immune system needed to fight infections as well as the elements that might be involved in MS.

Targeting antibodies

Research has also looked at ways of targeting specific elements within the immune system that play a role in MS, while leaving the remaining immune system intact.

This approach has led to the development of a new class of drugs called monoclonal antibodies. Antibodies are proteins in the immune system that bind onto an invading cell and help to destroy it. Although the body will make millions of copies of an antibody during the immune response, each antibody is

targeted at a single type of cell. This means that if antibodies can be identified that bind to cells involved in attacking nerve cells and causing disease activity in MS, maybe drugs can be developed that will only affect those cells.

Monoclonal antibodies are created by cloning a single antibody and this has led to the creation of several new drugs that may be used to treat MS. Examples of monoclonal antibodies include:

- natalizumab (Tysabri), which binds to and disables the area of white blood cells that allows them to cross the blood brain barrier, effectively keeping cells that might attack myelin from coming into contact with the brain or spinal cord
- alemtuzumab (Campath), which binds to proteins on the surface of the white blood cells associated with attacking the myelin on nerves (this drug is still at an experimental stage)

The World Health Organisation's standards for naming drugs means that all monoclonal antibodies end with -mab.

Research into these drugs suggest that they will be more effective than existing treatments at reducing the number of relapses. The research has however shown that there are also more serious side effects and any treatment with these drugs will need to include monitoring for and treatment of these effects.

Future drug development

All of the drugs available so far have to be injected or given intravenously. If taken as tablets, the active ingredients would be digested before they could work. A number of drugs are currently being researched that may be able to provide a disease modifying effect in tablet form.

All of the current drugs treat the relapsing type of MS. Increasingly, research suggests that early, aggressive treatment of MS, effectively before someone is showing any signs of disability, may prevent or greatly reduce subsequent damage from occurring. If treatment is carried out once MS has started to attack and destroy nerve cells, then drugs are much less effective in controlling progression.

The disease modifying drugs work by altering some of the processes within the body that cause MS relapses to happen and thus protect nerves from damage. Unfortunately, the processes that cause MS to become progressive, once nerves have been damaged or destroyed, are less well understood. As yet there are not the same opportunities for drugs to alter or prevent this. A number of different drugs have been, and continue to be, studied as treatments for progressive MS, but any positive results so far have been very modest. Alternative approaches will probably be needed to protect existing nerves and to repair or replace those that have been lost.

For more information:

- Disease Modifying Drug Therapy
- Natalizumab (Tysabri) factsheet
- Alemtuzumab (Campath) factsheet

Neuroprotection

Neuroprotection is a relatively new area of research in MS. The permanent symptoms of the progressive types of MS seem to develop when nerve cells are destroyed. This is thought to occur when nerve fibres are exposed to chemicals produced by the inflammation of tissue that MS causes. The theory of neuroprotection is that, if the nerve cells can be protected from these chemicals, destruction - and thus further permanent problems - can be lessened or prevented.

Different aspects of neuroprotection are being examined, concentrating on different elements that lead to loss of nerve cells. Inflammation leads to the increase in levels of nitric oxide, calcium and sodium. Contact with high levels of these chemicals can damage nerve cells. Research is underway to examine the effect of blocking these chemicals.

Another approach is looking at a type of drug called glutamate receptor blockers. Glutamate is

one of the chemicals involved in transmitting messages from nerve cell to nerve cell. Excessive glutamate can also damage nerves.

Drugs that have been investigated as neuroprotectors include riluzole, eliprodil (both work by reducing levels of glutamate) and lamotrigine (which limits the level of sodium). A study of the neuroprotective effects of cannabis is also underway.

Research in this area is at a relatively early stage and these studies are exploring the potential of neuroprotection as a strategy rather than the possibility of bringing a particular drug to market in the short-term.

Neuroprotective drugs will not be able to reverse progression or restore function that has already been lost. However, if suitable drugs can be developed, it is hoped that this will mean that the progression of MS can be significantly slowed down.

Repairing and replacing myelin

Whilst drugs that alter the action of the immune system or that protect nerves may help to limit the accumulation of damage, neither will reverse the progressive effects of MS. Exploration of processes that might repair areas of damage and thus allow people to recover function that has been lost is another important area of MS research.

From observing areas of the central nervous system that have been damaged by MS it is known that in the earlier stages of the condition the body can to some degree replace lost myelin. If the affected area is no longer being attacked by the immune system, new myelin can be formed, which will repair damage to nerve cells and reverse, at least to a degree, some of the disability caused.

Various strategies for repairing and replacing myelin have been investigated. For instance, chemicals within the immune system have been identified that can accelerate the growth of myelin. Myelin-making cells from the peripheral nervous system (Schwann Cells) have also been transplanted into the central nervous system to see if they will stimulate regrowth. Results have suggested a small effect at best.

Stem cells

Interest has also focussed on the possibility of using stem cells to repair damaged areas in the central nervous system.

Stem cells are unspecialised cells that can develop, or differentiate, into any of the specialised cells of the body, such as those in heart muscle or the insulin-producing cells of the pancreas. Stem cells are the first cells to develop in embryos and allow the foetus to develop the specialised functions and mechanisms that occur in the human body. Stem cells derived from an embryo are capable of developing into all the cell types that make up the tissues and organs, such as the heart, skin and brain.

The use of stem cells from embryos is the cause of much ethical debate. This has also affected the issue of 'hybrid' embryos in which human genetic material is implanted into animal cells that have had most of their own genetic material removed. After six days, stem cells can be extracted for research and the hybrid is destroyed.

Not all stem cell research involves the use of embryos. Stem cells also occur in adults and are used by the body to replace areas of damage. For instance, stem cells in bone marrow produce the different types of blood cells. Although more limited in the types of cells into which they can differentiate, research is now looking at how adult stem cells can be stimulated to turn into oligodendrocyte cells that produce myelin or into nerve cells in sufficient quantity to be used in treatment.

Work is also looking at how best to deliver stem cells so that they go to the appropriate places to carry out repair, and also at ways to ensure that transplanted stem cells do not harm the recipient or grow into unwanted tissue.

Stem cell treatment has been demonstrated for experimental

forms of MS and pilot studies in humans - focused principally on safety rather than effectiveness - have started in the UK. If processes can be developed, it opens the possibility that cells destroyed by MS might be replaced and disabilities caused by the loss of nerve pathways reversed.

For more information:
- Stem cells factsheet

Genetics

As we have seen earlier, it is thought that there is a genetic element to MS and that people with MS have a particular genetic make up that can be triggered by an as yet unidentified virus or toxin in the environment.

Advances in biotechnology mean that genes are now far better understood. Although any treatments may be some way off, greater understanding of the genetic basis of MS means researchers will be able to identify how the condition develops and theoretically create the opportunity to target genes that are malfunctioning. It will also allow for the potential evolution of treatments that may prevent those with a genetic risk from developing the condition.

For more information:
- MS Trust website - Research section www.mstrust.org.uk/research/

Summary

Although the nature of MS remains unclear, new areas of research offer the chance to increase understanding of the condition. Increasing levels of research over the last twenty years have seen some major advances. This period has witnessed the arrival of the first drugs to have some effect on the underlying disease activity of MS and new ones in the pipeline; continuing discoveries about the nature of the immune system and how it can be manipulated; knowledge of the involvement of genes in the development of disease; and breakthroughs in stem cell technology. This momentum offers the hope that multiple sclerosis will eventually be controlled.

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Glossary

Aetiology (or etiology in American English) - the study of the causes of a disease

Antibody - chemicals in the immune system that help target the attack on invaders

Antigen - chemicals in the immune system that prompt the generation of antibodies and can cause an immune response

Autoimmune disease - a condition in which the immune system attacks the body's own tissue

Axon - a long extention of a nerve cell along which the nerve message is passed

Blood-brain barrier - the line of cells that keeps cells in the blood from coming into contact with the central nervous system

Central nervous system - the brain and spinal cord

Cerebrospinal fluid - the fluid that surrounds the brain and the spinal cord

Demyelination - the destruction of myelin

Dendrite - extentions of a nerve cell through which incoming messages are received

Epidemiology - the study of the geographical distribution of a condition and patterns of disease as it affects groups of people

Glial cells - support cells in the central nervous system

Incidence - the number of new cases of a condition within a set period of time, usually a year

Interferon - a chemical generated by the immune system to alter the response to an invasion

Lymphocyte - type of white blood cell in the immune system

Macrophage - immune system cell that attacks foreign particles in the body

Myelin - the substance covering nerves in the central nervous system

Neuron - nerve cell

Neurotransmitter - chemicals that pass messages from one nerve cell to the next

Oligodendrocyte - cells in the central nervous system that make myelin

Peripheral nervous system - nerves other than the brain and spinal cord

Prevalence - the number of people with a condition, usually measured in cases per 100,000

Progression - a period of gradual increase in disability unrelated to relapses

Reflex reaction - physical response automatically generated by the spinal cord with no involvement from the brain

Relapse - an episode of new or worsened symptoms

Remission - a period of partial or complete recovery from symptoms

Remyelination - the replacement of myelin

Synapse - the gap between nerve cells across which nerve messages are passed from one cell to the next

More information
from the MS Trust

MS Trust publications
All publications are free unless indicated

Books
- Disease Modifying Drug Therapy
- Exercises For People With MS
- Living With Fatigue
- MS: What Does It Mean for Me?
  for people recently diagnosed

DVD
- Move It For MS
  a DVD of exercises for people with MS. Led by Mr Motivator. £1
- MS Together
  features contributions from a range of health professionals and interviews with people with MS, sharing personal reflections and experience of living with MS

Factsheets
- Alemtuzumab (Campath)
- Bladder problems
- Bowel problems
- Cognition
- Fatigue
- Natalizumab (Tysabri)
- Pain
- Spasticity
- Stem cells

Website
The MS Trust website includes:

- a comprehensive A-Z of MS covering a wide range of information about symptoms, treatments and more
- a complete list of MS Trust publications, which can also be downloaded or read online
- a section discussing ongoing research and developments

MS Trust Information Service
Our team of information professionals is on hand for anyone with a question about MS. Using our collection of medical papers, textbooks and other resources, we will find practical, evidence based information to match your particular needs. If we can't provide answers directly, we will do our best to direct you to organisations that can.

MS Trust Information Service
Spirella Building, Bridge Road, Letchworth Garden City, Hertfordshire SG6 4ET

T **01462 476760** E **infoteam@mstrust.org.uk** **www.mstrust.org.uk**

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