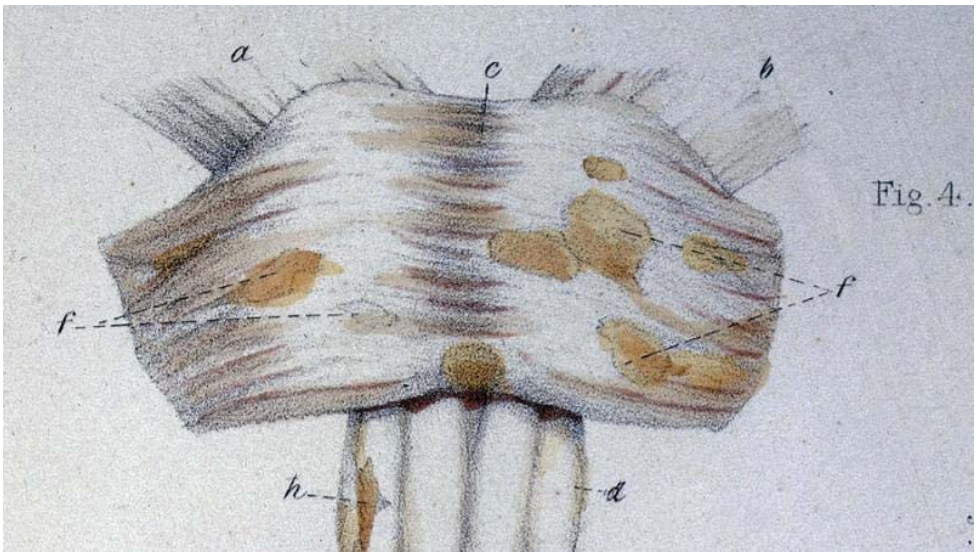
Disease



Part of the illustration from 'Pathological Anatomy' by Sir Robert Carswell. Wellcome Library, London

A "remarkable lesion": the causes and effects of demyelinating diseases

In the early 1800s, a talented Scottish doctor named Robert Carswell attended the autopsy of a patient who had been affected by paralysis. As he examined the spinal cord, he saw that it was covered in "a number of spots, from a quarter of an inch to a half an inch in breadth of an irregular form of a yellowish brown colour, smooth, glossy".

The doctor was puzzled by this "remarkable lesion [damage]". He had not seen the patient in life and did not know the history of his paralysis, so he could not explain the damage. Nevertheless, Carswell meticulously recorded all that he saw in an astonishing watercolour painting. This illustration was published in 1838 as Plate 4, Figure 4 in Carswell's atlas of pathology, 'Pathological Anatomy: Illustrations of the elementary forms of disease'. It was the first illustration ever published of the disease we now call multiple sclerosis (MS).

MS is one of the most common diseases of the central nervous system and affects around 100,000 people in the UK. It is one of a group of diseases called demyelinating diseases. To discover the nature of the "remarkable lesion" in Carswell's illustration, we need to learn more about this group of diseases and their processes.

Demyelinating diseases can have a range of causes and symptoms, but they are grouped together because they all cause damage to the myelin sheaths that surround our neurons, a process called demyelination. When demyelination occurs, the nervous system cannot function properly, resulting in serious, often debilitating symptoms.

Why myelin matters

So why is demyelination so harmful? Myelin has a vital role in the function of the nervous system. In a neuron, the long thread-like part of the cell that carries nerve signals away from the cell body is called the axon. In most neurons within the central nervous system, the axon is surrounded by a white fatty substance called myelin. Myelin insulates the axon, like the plastic coating around an electrical wire. Myelination (i.e., being surrounded by myelin) allows the neuron to conduct electrical signals more quickly.

The speed of transmission is greater in myelinated neurons because the action potential travels differently through myelinated cells. Myelin coats the axon in sections, and the breaks between each section are called the nodes of Ranvier. The insulating effect of the myelin means that depolarisation only occurs at the nodes of Ranvier, causing the action potential to jump from one node to the next. This is called saltatory conduction (the word 'saltatory' means 'to jump'). This means that an action potential can be transmitted up to one hundred times

faster in myelinated cells than in unmyelinated cells. Being able to transmit nerve signals so quickly enables us to maintain an efficient nervous system despite our large body size.

When myelin is damaged, the action potential can no longer be transmitted with such speed and efficiency: nerve signals travel more slowly or may be blocked completely. The effects of demyelination vary depending on the disease, and on what part of the nervous system is damaged, but they may include loss of vision, speech impairment and physical disability. In severe cases demyelination can cause paralysis, as in the case recorded by Carswell.

Different causes

Some demyelinating diseases are hereditary, which means that they are inherited genetic disorders. Others are acquired diseases that can be caused by infection or exposure to certain toxins.

Hereditary demyelinating diseases include Alexander disease and Krabbe disease, which are part of a group of diseases called leukodystrophies. These diseases affect the growth and development of the myelin sheath in infants. They are usually diagnosed in the first few years of a child's life and commonly cause an infant's development to slow or even regress (go backwards). Alexander disease is also associated with an abnormal increase in head size. There are no treatments for leukodystrophy, and most children affected by the condition do not live beyond early infancy. Thankfully, these conditions are rare: Krabbe disease, for instance, affects only about 1 in 100,000 individuals.

MS is an acquired demyelinating disease. Although we don't fully understand the causes and processes of this disease, it is thought to be an autoimmune disorder. An autoimmune disorder is one in which the immune system mistakenly attacks the body's own cells and tissues. In the case of MS, it seems that the individual's immune system may begin to attack the myelin sheath, causing demyelination. Researchers are investigating whether this autoimmune response could be triggered by a viral infection such as measles or herpes.

Relapse and remission

The symptoms and severity of MS vary from person to person. Around 85 per cent of people with MS are diagnosed with 'relapsing-remitting' MS. This is characterised by a fluctuation between periods of 'relapse' in which a person's condition deteriorates and periods of 'remission' in which their condition partially or completely recovers.

During these periods of remission, a special type of glial cell in the neuron (called an oligodendrocyte) generates new myelin to repair the myelin sheath, a process called remyelination. This can reverse the affects of the demyelination that occurred during the relapse.

However, the repaired sheath is often thinner and shorter than it was originally, so the speed of conduction remains reduced. In people living with MS, remyelination is usually inefficient and scars may form in the place of new myelin. These are the 'spots' that are visible in Carswell's illustration. It is these scars, or scleroses, that give the disease its name.

Most people with MS have a normal, or near-normal, life expectancy, but there is no known cure for MS or for demyelination. Instead, treatments for MS focus on managing the disease and reducing its symptoms.

Disease-modifying drugs, such as beta interferon or glatiramer acetate (Copaxone), can reduce the frequency of relapses by around one-third over a period of two years. It is not known exactly how these drugs work to reduce relapses. Glatiramer acetate is a synthetic protein that resembles myelin basic protein, and one theory suggests that it may act as a decoy, diverting the autoimmune response away from the myelin and towards itself. Glatiramer acetate is injected, but other drugs are taken in oral tablets or given as a monthly infusion directly into a vein.

Many people with MS also manage their health by controlling their diet and using exercise to increase their fitness, strength and range of motion.

Research into MS

Research into MS is ongoing, and new treatments are continually being tested and developed. These treatments aim to manage MS using a variety of different approaches. Some new treatments aim to block the action of the immune

cells that are responsible for attacking and destroying myelin. Others focus on anti-inflammatory drugs, which could help prevent the inflammation that is a damaging part of the immune response in people with MS.

Some researchers are investigating how stem cells might be used to treat MS. Stem cells are cells that can reproduce themselves and can develop into many different cell types. There are two different ways that these cells might be used to treat MS: the first would be to use stem cells to stop the immune system attacking myelin, and the second would be to repair the damage caused by MS by using stem cells to regrow lost myelin.

These are exciting possibilities, but developing new treatments takes many years of research and lengthy clinical trials because it is vital to ensure that drugs are safe and effective before they are licensed for general use.

The accuracy of Carswell's illustration has allowed modern medical experts to diagnose the subject of the autopsy he witnessed, even though the patient died almost 200 years ago. The "remarkable lesion" that Carswell observed was the scarring of multiple sclerosis. The patient was paralysed as a result of severe demyelination. Centuries after he died, we have been able to solve the mystery of his condition; perhaps in our lifetime, scientists will be able to unravel the remaining mysteries of this disease.