What is Brain Damage?
Many forms of trauma and disease affect the nervous system to produce permanent neurological disability. The cells responsible for the functioning of the nervous system are neurones, and various types of glial cell.

What do neurones do?
The neurones are the cells in the nervous system that receive and transmit electrical signals, or nerve impulses. They are connected together by nerve fibres, or axons, which transmit information from one neurone to another at connections, or synapses.

Thus when you contract a limb muscle and move the limb, a neurone in the motor cortex area of the brain becomes electrically active, and sends nerve impulses down its axon which runs into the spinal cord (green on the diagram), connecting to a motor neurone in the spinal cord. The motor neurone, which in turn becomes electrically active, sends nerve impulses down its axon (red in the diagram). The axon of the motor neurone connects directly to muscle cells (red) at a synapse, so when there are nerve impulses in the motor neurone nerve it leads directly to muscle contraction.

The whole function of the nervous system depends on similar processes, with information being transmitted as nervous impulses down axons, and passing to other neurones via synapses.
What happens when the brain or spinal cord are damaged?

Damage to the nervous system can cause functional deficits in three main ways:-

1) Neurones themselves can be killed.
2) Nerve fibres, connecting neurones to other neurones can be cut.
3) Nerve fibre conduction can be stopped, by removing the insulating myelin (see later).

The symptoms, and loss of neurological functions that a patient will experience depend precisely which neurones or axons are affected. Different neurones in particular parts of the brain and spinal cord control particular functions. Thus damage in motor cortex, mentioned above, leads to loss of the ability to control muscles, and paralysis. In the diagram above, a spinal cord injury (yellow) blocks the flow of information from the brain the the spinal cord, leading to paralysis. Damage to other parts of the brain may lead to loss of vision, loss of speech, or other deficits depending on the function of the part of the nervous system that is damaged.

How are neurones killed?

Several processes, rapid and slow, can kill neurones. Rapid death of neurons is usually due to an acute process such an head injury or stroke. In head injury a region of the brain suffers direct trauma, which kills neurons and cuts axons. At present there is no effective way of preventing this form of death. In stroke an area of the brain loses its blood supply because an artery becomes blocked. Neurones need a rich blood supply to provide them with oxygen and nutrients, and die rapidly when the blood supply stops.

In some types of neurological disease neurones die slowly over many years. For instance in Alzheimer's disease neurones throughout the cerebral cortex gradually die, leading eventually to loss of memory and then dementia. In Parkinson's disease a small group of neurones in the substantia nigra region of the brain die over many years. When around 80% or these neurones are lost the symptoms of Parkinson's disease become apparent. The factors that kill neurones slowly in these diseases are not fully understood. However in many chronic neurological diseases the slow accumulation of aggregates of waste proteins in and around the neurones seems to play a central role in the toxic processes.

How are nerve fibres cut?

Cutting of nerve fibres is usually due to trauma, or less commonly due to a growing tumour. In spinal cord injury, trauma to the spine leads to dislocation of the bones of the spine, which crushes the spinal cord, usually at the base of the neck or under the rib cage. This cuts the nerve fibres that carry motor commands from the brain to the motor neurones and therefore to the muscles, and cuts sensory fibres that carry sensory information from the skin to the brain. The result is both paralysis and loss of sensation below the level of the injury.
**How is nerve fibre conduction blocked?**

Many nerve fibres in the brain and spinal cord are insulated by myelin, which is a sheath formed by glial cells called oligodendrocytes. In the diagram, a is the nerve fibre, cy the layers of the insulating myelin sheath, g the cell body of the oligodendrocyte. If this insulating sheath is removed, the nerve fibres cannot conduct nervous impulses. This happens particularly in mutiple sclerosis. In this disease an autoimmune process kills oligodendrocytes in small patches of the brain and spinal cord, leaving the nerve fibres uninsulated and therefore non-conducting. These patches, known as plaques, are usually only a few millimetres in size, but they can occur frequently anywhere in the brain or spinal cord. The plaques do not generally repair themselves. The result is small regions in which the nerve fibres do not conduct. These give symptoms which depend on where they are, and the function of the nerve fibres that are affected.

*Why does the brain need repairing?*

Most types of neurological damage lead to permanent disability. People with spinal injuries never recover from their paralysis and loss of sensation, those suffering from Parkinson's disease will never recover from the condition and always be reliant on medicines, patients with multiple sclerosis never recover fully from their lesions. This is because the brain and spinal cord lack the ability to heal themselves after injury. Above, we stated that the three main causes of loss of function after damage to the nervous systems are loss of neurones, cutting of axons and loss of insulation on axons. None of these deficits heals spontaneously.

1) Lost neurones are not replaced. Neurones are created during embryonic development, but after that time we have almost no ability to make new neurones. Thus when large numbers of neurones are killed they cannot be replaced, and the disability that results from their loss is permanent.
2) Cut nerve fibres cannot regenerate. In order to restore the function of cut nerve fibres, they need to be able to regrow from the site of the cut back to their original connection site. Nerve fibres in the brain and spinal cord are completely unable to regenerate.
Therefore nerve fibres cut in the spinal cord as a result of a cord injury will never regrow, and people with cord injuries will be paralysed for life.

3) Lost insulating myelin is not fully replaced. When the oligodendrocytes that form myelin are lost as a result of multiple sclerosis, the brain and spinal cord have a very limited ability to replace them. Therefore many of the multiple sclerosis plaques never become remyelinated. This means that the nerve fibres that pass through these plaques can never conduct nerve impulses normally, and eventually many of these demyelinated nerve fibres will die.

**What is Brain Repair?**
The objectives of brain repair are:-
1) To prevent or minimise the damage to the brain and spinal cord that results from injury or disease.
2) To repair the structure of the brain and spinal cord so as to return normal neurological function to patients.

**Protecting the brain and spinal cord from damage**

*Preventing chronic neurodegeneration*
The basis of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, prion diseases and Huntington's disease is the steady loss of neurones over several years. A major factor leading to this loss is the toxicity of various proteins that are deposited as insoluble aggregates inside and outside the neurones. Many researchers are looking for ways to prevent these aggregates forming, or to remove them once they have formed. Much of the biology of how aggregates are formed and why they are toxic is starting to be understood. This should lead before long to treatments that will slow the progression of chronic neurodegenerative diseases.

*Minimising the damage after injury or stroke*
When the brain or spinal cord is injured some neurones are killed by the immediate injury, and there is little prospect of rescuing them. Similarly after stroke a blood vessel supplying part of the brain becomes blocked, and this part of the brain dies rapidly due to lack of oxygen. After the initial injury or stroke a secondary process which takes several days is initiated which leads to the injury at least doubling in size. Many of the mechanisms behind this spread of the injury are understood, and several treatments have been identified that are successful in protecting injuries in animal models. However to date none of these treatments have been successful in humans.

**Repairing the structure of the brain and spinal cord**

*Replacing lost neurones*
Where neurones are permanently lost, there are two potential ways of replacing them. The first is to transplant equivalent neurones taken from a donor brain or spinal cord. The second is to persuade primitive stem cells, which are present in the adult brain or
can be transplanted, to turn into new neurones.

1) Neural transplantation. If a group of neurones are lost, an obvious possibility is to transplant new neurones in their place. This is particularly attractive in diseases such as Parkinson's disease, in which the lost neurones are all in a small restricted site. Successful neuronal transplantation has not been achieved using neurones from adult donors. However, if neurones are taken from embryos of just the right age, they will survive transplantation. In addition they will grow nerve fibres into the host brain and make functional synaptic connections. In animal models of Parkinson's disease this cures most of the symptoms of the disease. This has led to several trials of neuronal

![Diagram of brain structures](image)

Normal. The substantia nigra is intact, and its nerve fibres connect to the striatum

Parkinson's disease. Most of the neurones in the substantia nigra have died, and few nerve fibres remain to connect to the striatum

A graft of embryonic substantia nigra has been placed in the striatum. It sends out nerve fibres that innervate the striatum and bring back lost neurological function.
transplantation using embryonic tissue for human patients with Parkinson’s disease. In almost all these trials the patients have had their disease partially corrected, but in no case has there been complete recovery. Methods for improving the results of these operations are ongoing.

2) Replacing lost neurones from stem cells. Stem cells are undifferentiated cells that have the capability to divide and produce many other types of cell. A neural stem cell has the ability to differentiate into any type of cell in the brain. It has recently become clear that the adult brain contains stem cells in some regions, and that these cells can be proliferated in tissue culture. Moreover after some types of brain or spinal cord injury stem cells appear in the injury site. Scientists need to understand how to direct stem cells to differentiate into the types of neurone that are lost after damage. While some of the signals that direct stem cells to differentiate are known, much remains to be worked out. Since stem cells can be grown in tissue culture to produce large numbers of cells, stem cell technology is probably the way forward for neurone replacement in the future. At present the main effort is directed towards understanding how to control their differentiation.

Regeneration of nerve fibres
When nerve fibres are cut in the brain or spinal cord they do not regenerate. There are three reasons for this:-

1) The scar tissue that forms where the brain or spinal cord is injured produces several molecules that inhibit the growth of nerve fibres
2) The oligodendrocytes that insulate nerve fibres produce molecules that inhibit nerve fibre growth
3) The nerve fibres, while capable of regrowing through a helpful environment, mount a very feeble regenerative response.
In recent years great progress has been made in finding methods to promote nerve fibre regeneration. These methods are:

1) Block the inhibitory molecules made by oligodendrocytes
2) Digest the inhibitory molecules produced in the scar tissue surrounding injuries
3) Enhance the vigour with which nerve fibres try to regenerate using growth factors and other treatments
4) Transplant cells into the damaged brain or spinal cord that have the ability to encourage nerve fibre regeneration, and which can form a bridge taking nerve fibres through the scar tissue around an injury

These various methods, illustrated above, have been applied to spinal cord injuries in animals, and have been able to promote nerve fibre regeneration for up to 4cm. This may not sound very far, but 4cm of regeneration in a human with a cord injury would allow some patients to regain the ability to breathe for themselves, and other patients to regain the use of their hands.

**Replacing the insulation around nerve fibres**
The insulating myelin that surrounds nerve fibres is made by the glial cell type called oligodendrocytes. If these cells are damaged, as in multiple sclerosis, they are unable to make new myelin. However there are many specialised stem cells in the brain and spinal cord that can interact with nerve fibres to make new myelin. In some forms of demyelinating diseases these cells are able to divide, and replace the myelin that has been lost. In multiple sclerosis this remyelination usually fails, for reasons that are still not established. There has been much progress in finding out how to make large numbers of oligodendrocyte precursors and other myelin-forming cells in tissue culture
and transplant them into demyelinated regions. However, the processes that prevent these cells replacing lost myelin are still not fully understood, and until then it seems unlikely that simply transplanting cells into multiple sclerosis lesions will be effective in curing the condition.

*Promoting recovery from head injury and stroke*
A severe stroke or head injury kills part of the brain. At present the various transplant methods are not sufficiently advanced that this dead tissue can be replaced. However patients show considerable recovery of function after a brain lesion. After a stroke patients are often paralysed over much of one side of the body, yet a few weeks later much of this paralysis has recovered. The process by which this happens relies on the regions of brain surrounding the injury changing their function to take over some of the functions of the dead tissue. This process is called plasticity. Plasticity relies on the ability of neurones to make new connections with one another after injury, and so reconstitute some of the electrical circuits in the brain that have been lost. At present there are no treatments to control and enhance plasticity, but there are several possible ways to do so, and these are under investigation in the Brain Repair Centre.

*Diseases which Brain Repair will help*

*Spinal Cord Injury*
Injuries to the spinal cord cut the nerve fibres that take motor commands to the body, and that take sensory information to the brain. The body below the level of the injury is therefore paralysed and has no sensation. To cure the disease it is necessary to make nerve fibres regenerate past the injury site and re-form their connections in the spinal cord. Experiments in animal models have been able to promote axon regeneration in the spinal cord for up to 4cm. This is not enough to make a complete repair of a human spinal cord. However most patients are injured in the neck, and for those with very high lesions, such as Christopher Reeve, who are unable to breath for themselves, 4cm of regeneration would bring back their breathing. Many patients are injured rather lower in the neck, and they are able to move their arms, but not their fingers. 4cm of regeneration would bring back finger control, and greatly improve quality of life. Various different treatments, some of them under development in the Brain Repair Centre, have been shown to promote regeneration in animal models. The challenge is now to apply these treatments to human patients. The first trials of various treatments will be beginning in the next few years.

*Head injury and stroke*
Injury to the brain kills neurones, and leads to neurological deficits. Stroke kills areas of the brain when the blood vessel supplying that area gets blocked. In the immediate aftermath of stroke and injury there are prospects for preventing the spread of the injury that leads to an increase in the number of neurones killed, and worsening of the neurological deficit. One active field of research in the Brain Repair Centre is to ensure that the areas of injured brain receive a sufficient blood supply. The spread of injuries
involves changes in the metabolism of neurones and actions at their synapses. Various treatments are under development to counteract these changes. After the acute injury phase of stroke and head injury there is a considerable recovery of neurological function. This a patient who initially is paralysed over one complete side of their body may leave hospital with just weakness in one arm. Much of this recovery is due to the ability of the brain to adjust its connections so as to make new circuits which can take over the functions of circuits that have been damaged. This process is called plasticity. Research in the Brain Repair Centre aims to identify ways to enhance and direct this plasticity.

*Multiple Sclerosis*
Multiple sclerosis is a demyelinating disease. An autoimmune process, possibly triggered by a previous viral infection, attacks the oligodendrocytes of the brain and spinal cord. The pattern of the disease is small patches of demyelination, often less than 1cm in size, which can occur anywhere in the brain or spinal cord. These lesions occur randomly, and tend to recur, with some patients having several new patches of demyelination a month, some hardly ever having a recurrence. The patches of demyelination block the normal conduction of nerve impulses in the nerve fibres that go through the area of demyelination, and eventually the demyelinated nerve fibres may die. The pattern of neurological loss of function depends on the position of the lesions, so a wide variety of symptoms may result. In general patients have acute exacerbations, followed by partial recovery before the next attack. The partial recoveries are partly because some of the demyelination may repair, partly because the brain compensates and makes new circuits by plasticity. Suppressing the immune system can prevent new attacks of demyelination. A treatment with an immunosuppressive antibody treatment is in trials at the Brain Repair Centre. The brain and spinal cord have large numbers of precursor cells which can make new oligodendrocytes, yet in multiple sclerosis these cells for some reason fail to remyelinate. Research in the Brain Repair Centre is working out how these precursor cells can migrate to find demyelinated nerve fibres, how they can proliferate, and how they might be transplanted.

*Parkinson’s Disease*
Parkinson’s disease leads to disability in motor control. Patients find it difficult to initiate and control their movements, and may have periods when they find it almost impossible to move. In addition many patients have a tremor of the arms and other parts of the body. The condition is due to the degeneration over many years of a small group of neurones in the base of the brain called the substantia nigra. This degeneration can be triggered by a variety of factors, including head injury, virus infection and inherited metabolic conditions. Because a common factor in degeneration of these neurones is damage by oxygen free radicals, with accumulation of protein aggregates, various possibilities exist for stopping the progression of the disease. Research into the role of protein aggregates in the disease is in progress in the Brain Repair Centre. Various medical treatments can alleviate the symptoms of the disease, but as the condition progresses they lose their efficacy. Because the lost neurones are in such a small region of the brain, Parkinson’s disease is an obvious candidate for treatment by neural transplantation. In animal models of the disease this type of treatment is extremely
effective. This has led to trials in human patients. To date around 300 patients have received transplants, and almost all have benefitted from the operation, although there has only been a partial cure. Various techniques for improving transplantation of embryonic and stem cells in Parkinson’s disease are under development in the Brain Repair Centre.

**Huntington’s disease**
Huntington’s disease is an inherited disorder, in which there is degeneration of the striatum region of the brain. The disorder usually becomes manifest when those affected are in their teens or twenties. The degeneration of the striatum affects the ability of patients to control their movements, and also affects their cognition. The main treatment is prevention, since diagnosis can now be made at early stages of foetal development. For affected patients neural transplantation is a promising treatment, since the disease kills neurones in a small part of the brain. One of the first trials of transplantation in human patients is in progress in the Brain Repair Centre.