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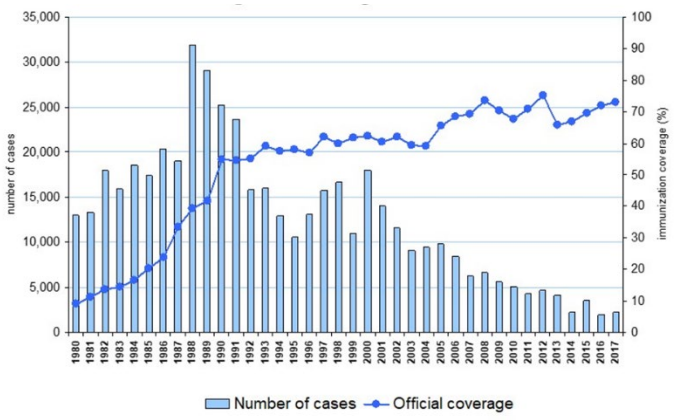
INFECTIONS AND THE NERVES

PROFESSOR CHRISTOPHER WHITTY

The brain thinks but the peripheral nervous system is needed for the body sense, and to act. Infections can damage all parts of the peripheral nervous system. For the purposes of this talk on infections, the peripheral nervous system can be divided into four areas: the motor system which controls muscles and movement; sensory system which senses touch, pain, movement, vision, hearing, taste, smell; the autonomic nervous system which controls basic functions and the ability to respond to flight and fight; the spinal cord. An infection can cause disease in one, some combination or all of these.

Infections can damage nerve function by many routes. The main ones are: producing toxins which interfere with nerve function; direct infection of nerves; activating the immune system in a way which damages the nervous system; physical pressure which damages nerves directly. Our ability to prevent nerve damage is greater than our ability to treat it so prevention is almost always better then cure.

Let us start with toxins produced by bacteria which affect the nervous system. The most important of these in terms of numbers affected is the toxin produced by tetanus. The bacteria which causes this lives in the soil and dung and causes small and often unnoticed infections from puncture wounds, dirty wounds and after childbirth where sterile procedures had not been followed. Although the infection is trivial the bacteria produce a toxin which enters the motor nerves and then travels back to the central nervous system in the spinal cord. Here it disrupts the reflex system which prevents muscles from spasming and the result is uncontrollable spasms. Tetanus the disease is almost entirely preventable by vaccination, not against the bacteria but against the toxin they produce. There have been rapid reductions in tetanus in adults and in newborn children as a result of widespread vaccination and better birthing practices



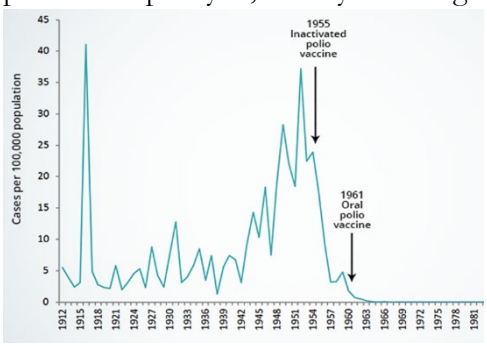
(Fig1- WHO data on number of neonatal tetanus cases globally and vaccine coverage).

Whilst the toxin of tetanus causes uncontrollable muscle contraction, toxins produced by *C. botulinum* can prevent muscles from contracting at all. A rare infection associated with home canning, intravenous drug use and some infant foods, botulinum toxin is now most well-known for the massively diluted drug Botox, used in medical procedures and for cosmetic reasons. Botulinum toxin is however probably the most potent toxin known to man and in more than minimal doses can be lethal.

A third toxin producing bacteria which affects the nerves is diphtheria. As with tetanus botulinum the actual bacterial infection is often relatively trivial in the absence of toxin. The toxin produced causes nerve inflammation

and can lead to localised paralysis. Generally in the modern era most patients make a full recovery historically diphtheria was a very serious cause of mortality in the UK and globally. Like tetanus vaccine is to produce immunity to the toxin rather than to the infection.

Tetanus, diphtheria and botulinum are bacteria which produce their effect on the motor nerves by toxins. Polio by contrast is a virus which causes its damage to motor nerves by direct infection. Polio is passed on faeco-orally and in most people produces no lasting effect. However, in a small proportion go on to get a temporary or permanent paralysis, usually affecting one or more limbs but in severe cases this can go on to cause paralysis of respiration. The World Health Organisation estimates there are more than 10 million polio survivors worldwide. From the 1950s we have had extremely effective vaccines, both injected and oral. The result of these, as well as better sanitation, is that polio rates have dropped rapidly: Fig. 2 shows polio cases in the USA. There were over 350,000 new wild polio cases in 1988, and less than 30 in 2018. There are now more circulating vaccine derived polio cases (102) than wild ones. Polio is close to eradication, and the reasons there are still problems are related more to political issues than technical ones.



Although polio is the principal virus globally which causes acute flaccid paralysis, rarely other viruses can as well. There was for example a small UK spike of 28 cases in 2018 probably caused by an enterovirus.

Infection of the nerves is not the only way they can damage motor nerve function. Following infections, which can be bacterial or viral, an immunological effect can occur damaging nerves or the myelin nerve sheaths. This group of processes goes under the name Guillain-Barré syndrome. Typically it causes an ascending weakness starting in the legs. In many cases this resolves rapidly, but in severe cases can cause paralysis of respiration or residual weakness.

Infections we have considered so far predominantly affect the motor nervous system. There are however infections which are mainly an issue for the sensory system. The most common of these are the herpesviruses; herpes zoster which causes chickenpox and herpes simplex. These viruses after an initial infection lie dormant in the motor nerve roots but reactivate periodically. In the case of chickenpox (zoster) this can cause the very painful condition shingles. During attack of shingles there is burning pain along the distribution of a sensory nerve, and it can leave pain for months or years afterwards. Modern vaccines substantially reduce the risk of shingles occurring, and are now being rolled out in older age groups in the UK and globally. There is currently no vaccine for herpes simplex.

More destructive of the sensory nervous system is the ancient and highly feared disease leprosy. Once common around the world, as the 'leper window' in many mediaeval churches show, it is now only occurring in significant numbers in a few countries, including India and Brazil. Leprosy damages sensory nerves, and can lead to their virtual non-functioning. The result of this is repeated damage as people do not notice injuries. The pattern of leprosy varies depending on the immune response; in some people leprosy is highly localised with discrete anaesthetic patches of the skin whilst in others it is spread throughout the skin and especially the peripheries (particularly hands and feet). Most people who come into contact with leprosy are naturally immune to it, and immunity is boosted by having the BCG vaccination. We now have highly effective drug treatments for leprosy which will kill the infection, but the damage the sensory nerves is usually permanent.

An important disease which can cause a peripheral neuropathy causing altered sensation in a glove-and-stocking distribution is HIV. Mild peripheral neuropathy is common (and can also be caused by some of the older HIV drugs); more severe symptoms can occur in advanced HIV disease. A different form of peripheral neuropathy seen with HIV but also rarely in a number of other infections including leprosy, Lyme, and Hepatitis C is

mononeuritis multiplex where isolated nerve trunks can cease functioning normally giving rise to localised weakness or changed sensation.

The autonomic nervous system makes up the third broad category of peripheral nerves. Many of the infections we have talked about so far can damage it including tetanus, diphtheria, leprosy and other infections including HIV and rabies. In general however in these infections autonomic nerve damage is a relatively minor part of the disease process. One parasitic infection may exert a lot of its damage through the effects on the autonomic system and that is Chagas disease in Latin America. This parasite is passed on by biting reduviid bugs and damages heart function. Global prevalence dropped from 18m in 1991 to <6m today.

So far we have considered peripheral nerves. A major area where infections can cause significant neurological damage is the spinal cord. The spinal cord has multiple functions, but major ones include sending sensory impulses up to the brain, motor commands down from the brain, and some basic processing functions including reflex arcs. If the spinal-cord is damaged effects will be felt at the level of that damage and below it. Depending on the pattern of damage it may predominantly affect one side of the body, or particular parts of the motor and sensory systems.

Several infections by different mechanisms can cause damage to the spinal cord by physical pressure on it. Infections of the bone and discs of the spinal column are one major group of these and the earliest known cause of this was Pott's disease of the spine caused by tuberculosis. This can cause substantial spinal deformities. Other bacterial diseases can also cause damage or abscesses from the spinal column that press on the spinal cord and nerve roots. Treatment for these is by antibiotics and in some cases surgery. One parasite can cause substantial disruption of the spine are and that is the sheep to dog tapeworm hydatid disease. Abscesses or other infections which are in the soft tissues between the spine and the spinal-cord pressing on the spinal cord or nerves but without significant damage to the bones can also occur.

One infectious disease which historically caused significant damage to the dorsal sensory columns of the spinal cord was tertiary syphilis (tabes dorsalis). This particularly damaged sensation and proprioception (ability to locate the body in space). This leads to significant problems with normal gait. Tabes has now almost disappeared in most parts of the world due to the impact of antibiotics.

A few infections can occur within the spinal-cord, and cause direct damage. Tuberculosis, cysticercosis and the common parasitic disease in Africa schistosomiasis are examples of these.

An important, although rare, group of diseases can cause inflammation of a section of the spinal cord- transverse myelitis. These include several bacterial infections. The immunological reaction to a variety of viral diseases can also cause a transverse myelitis. Some people with this will make a full recovery, whilst others will be left with profound long-term disabilities below the level of the spinal cord the myelitis has occurred.

Infectious diseases affecting the nerves are some of the most debilitating and feared. Most of the worst historically are substantially reduced in scale and impact, including tetanus, polio, leprosy, diphtheria, neurological syphilis. Risks from others like shingles are reducing, if more slowly. A smaller but important group remain and still cause serious and persisting disability.