Wellcome Film Project

Demyelination and Remyelination in the Central Nervous System

The Scientific Basis of Medicine

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Black-and-white

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<**Opening titles**>

<**Dr W Ian McDonald to camera**>

Demyelination is one of the two types of pathological process which affect central nerve fibres. It occurs under a variety of circumstances and is, of course, the hallmark of multiple sclerosis. One of the outstanding clinical characteristics of demyelinating disease is the tendency for recovery to occur after single episodes. But as everyone familiar with multiple sclerosis knows, repeated episodes of demyelination leave an ever-increasing neurological deficit. In this talk I want to describe the disordered physiology which leads to neurological symptoms and signs in demyelinating disease and to discuss what is known of the mechanism of recovery. To provide a background to this discussion we must first answer two questions: what is demyelination and in what circumstances does it occur? After dealing with these questions I shall go on to consider how demyelination interferes with conduction. Finally, I shall consider two questions in relation to recovery: does

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remyelination occur in the central nervous system, and if remyelination does occur, does it play a part in recovery.

Let us begin with the background. What is demyelination? First we must recall the structures of central nerve fibres.

<McDonald narrates whilst standing next to large slide projection showing various images of nerve fibres, uses indication stick>

All central axons are surrounded by satellite cells, the oligodendrocytes, which in this respect perform the function of the Schwann cells in the peripheral nervous system. On all but the smallest fibres, the oligodendrocyte reduplicates its surface membrane to form a spiral membrane which becomes compacted to form the myelin sheath. The myelin sheath is interrupted by gaps, the nodes, and the nodes occur at regular intervals along the length of the fibre. Here you see a fibre in which the nodes have been indicated by arrows. It's a single fibre, teased from the spinal cord and, for the convenience of illustrating it, I've mounted one portion below the other but it is, in fact, one continuous fibre.

In demyelination, the myelin is destroyed, leaving the central axon in continuity. Demyelination begins at the nodes and spreads along the fibre to involve part, or the whole of a myelin segment, or sometimes several consecutive segments.

<McDonald to camera, then is shown again standing next to large slide projection showing images comparing demyelination with Wallerian degeneration, uses indication stick>

Now, demyelination contrasts with the other common type of abnormality which affects central nerve fibres, the Wallerian type of degeneration, in which both axons and the myelin are destroyed. The contrast between these two fundamentally different processes is best seen using a combination of using the two classical methods for staining axons and myelin in the same preparation.

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Here you see a longitudinal section through the posterior columns. Most of the fibres are normal, but at the top, in the middle and towards the bottom there are fibres undergoing the Wallerian type of degeneration. You can see that the continuity of the axons is broken up. Let us contrast this now with demyelination again, using the same method of staining. You can see that the axons here are running in continuity through the regions of myelin debris, right through the section.

<**McDonald to camera, then over slide showing optic nerve, then back to camera**>

The next piece of background information that we need concerns the circumstances in which demyelination occurs. The commonest condition in which demyelination occurs is multiple sclerosis and optic neuritis. Here we see a longitudinal section through the eye and optic nerve of a patient who had died from multiple sclerosis and who had had attacks of optic neuritis. You will notice that the black myelin staining, instead of extending right up to the globe, is first seen about a centimetre and a half behind it. The next section was stained for axons and you will see that they are running in continuity through the whole of the section of the nerve.

Demyelination also occurs in the allergic type of encephalomyelitis which sometimes follows the acute exanthemata and various types of inoculation. It occurs at sites of compression, for example, in the spinal cord. And it occurs as a response to a number of toxins, a fact which is of considerable importance experimentally. Finally, there are a host of rare diseases, both of childhood and adult life in which demyelination occurs. At this point it is worth stressing that the term demyelination is often used loosely to refer to any lesion in which the myelin stains poorly, irrespective of the state of the axons. This usage is confusing and should be avoided. In this talk I use demyelination only in its strict sense, to refer to destruction of myelin with preservation of axon continuity.

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Against this background, I should like to consider the effects of demyelination on conduction in the central nervous system.

Professor Sears and I studied this question in a focal experimental demyelinating lesion produced by the direct microinjection of diphtheria toxin into the spinal cord of the cat. Two to four weeks after inducing demyelination we studied conduction through the lesion.

<**McDonald over series of animated diagrams detailing changes in conduction due to demyelination**>

Here are the experimental arrangements. At the terminal experiment, the spinal cord was exposed and the posterior columns isolated functionally by cutting away all the rest of the cord in a small region. Thus the posterior columns were left as the only bridge connecting the rostral and cordal portions of the spinal cord. A pair of stimulating electrodes was placed rostral to the bridge. A mobile recording electrode was then used to take records from successive sites going more cordally from the edge of the bridge. Here you see a set of records from a normal animal, the increasing conduction distances are given in millimetres at the side. You will notice the normal triphasic configuration of the action potentials with a small initial positive, that is downward wave, a large negative upward wave, and finally a small positive wave.

Now let us look at a comparable set of records from an animal with a large bilateral lesion in the posterior columns, which is indicated by the black square. In the histologically normal portion of the cord, the configuration of the action potentials is normal even though the amplitude is reduced. The changes at the margin of the lesion are better seen at higher gain. At 40 and 41mm conduction distance, the configuration of the action potentials is normal. But at 42mm there is an abrupt change, the upward going negative deflection is abolished and the initial positivity is exaggerated. These are the electrical signs of conduction block. From this we conclude that large demyelinating lesions give rise to complete conduction block.

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<**McDonald to camera**>

You will notice that this experiment also establishes that conduction persists in the histologically normal portion of the blocked fibres, a fact which has important implications for recovery.

We next studied smaller lesions and found that conduction persisted through the lesion in many fibres but was abnormal in several respects. We analysed these conduction defects in single fibres, using a technique of Professor Sears which allowed us to record from individual, undissected fibres, and to compare conduction in the demyelinated and normal portions of the same single fibres.

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An important property of nerve fibres is the ability to transmit faithfully long trains of impulses.

<**McDonald over animated illustration showing how nerve fibres transmit impulses**>

In this experiment, we are recording from a single fibre. When the fibre is stimulated at 1000Hz cordal to the lesion, every impulse is transmitted to the distant recording electrodes. The taller lines represent the stimulus artefacts and the shorter lines, the single nerve fibre action potentials. When the same fibre is stimulated at less than half this frequency rostral to the lesion, so that the impulses have to pass through the demyelinated region before reaching the recording electrodes, each of the first four shocks is followed by a transmitted impulse, but thereafter alternate impulses fail. Subsequent experiments have shown that intermittent failure can occur at the much lower frequencies commonly encountered in human nerve fibres during natural activity, and that continued stimulation results in increasingly severe block.

<**McDonald to camera, then over graph showing conduction velocity in demyelinated parts of single fibres**>

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Another property we examined was the speed of conduction through the lesion. We compared conduction velocity in the histologically normal and demyelinated parts of the same single fibres, and we found that the velocity was locally reduced at the site of demyelination.

Here is an example from our experiments. Along the bottom a single fibre is shown diagrammatically. The velocity in each portion of the fibre, that is S_1 to S_2, and S_2 to r, is represented by a symbol placed above its midpoint. Normally there is no significant difference between the conduction velocities of adjacent portions of the particular fibre type we were studying. This is illustrated by a fibre from a normal animal. The velocity of conduction through a demyelinated region, indicated in the diagram by the cross-hatching, on another fibre was, however, reduced by 50% compared with the velocity in the normal portion in the same fibre.

<**McDonald to camera**>

To summarise, large experimental demyelinating lesions give rise to complete conduction block. Smaller lesions allow conduction to continue but at a reduced velocity.

We must now consider whether these conduction abnormalities occur in human demyelinating disease.

Dr Martin Halliday, Joan Mushin and I have recently been examining this question in one of the commonest manifestations of demyelination in man – acute optic neuritis. The histology of this lesion I showed you earlier. The only method we have at present of regularly obtaining information about conduction in central nerve fibres in man is the rather indirect one of studying cerebral evoked potentials. Dr Halliday has long been interested in this field and has recently been working on visual responses.

<**McDonald over illustration of optic system, then film showing a man having his optic nerve patterns recorded onto an averaging computer**>

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When light falls on the retina, a volley of impulses is set up, which is transmitted through the optic nerves, tracts and radiations to the occipital cortex. The arrival of the impulses in the cortex evokes a response which can be detected with scalp electrodes.

Here you see the electrodes in place and being connected to an averaging computer. The most useful stimulus from our point of view is a chequerboard pattern of black and white squares. The subject sits in a chair and fixates on the centre of a screen. The pattern of squares is reversed at a frequency of 2 per second so that each black square becomes white and each white square, black. The potential evoked by each reversal is recorded by the computer.

Here you see the potential growing as each successive response is added to the previous one. There is a dominant initial positive wave, that is downgoing at approximately 110 milliseconds. There is a very narrow range of latency amongst different normal subjects and in any individual subject the latency from the two eyes is almost identical.

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<**McDonald to camera, then over diagrams showing optic conduction in patients with optic nerve defects, to camera in between**>

We have now studied several hundred patients with demyelinating disease and I want to describe two features which are important to our present discussion. First, demyelination produces a delay in the evoked response from the affected eye in more than 90% of patients.

Here are a pair of records from a patient with unilateral optic neuritis. The upper record is from the normal eye and closely resembles the normal response you have just seen being recorded. The lower record is from the abnormal eye and the first positive wave is substantially delayed. Although the mechanism of the very long

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delays is not yet altogether clear, it is obvious from the experimental studies that slowed conduction through the zone of demyelination must play a part.

It is worth noting, in passing, that this delay is permanent; it persists even after apparently full clinical recovery, and thus provides the most sensitive index that we have at present for detecting subclinical optic nerve damage. The second point relates to cases of severe impairment of vision in the acute phase.

Here is a series of records taken from a patient with severe unilateral optic neuritis over several weeks. At the bottom you see the response from the normal eye showing the dominant initial positive wave. At the top you see the record taken from the affected eye in the early stage of the illness; at this time the visual acuity in the affected eye was down to counting fingers and you can see that there is no detected response. Later, however, the visual acuity improved rapidly and the second record, the middle record that is, shows the response when the vision had returned to 6 over 6. The absence of a response in the early record and the presence of a delayed response in the later record implies that conduction was completely blocked in the majority of fibres in the early stage but returned, with a delay, as recovery occurred. From the evoked potential studies in man, therefore, we may conclude that both conduction block and slowing may occur in demyelinating lesions of central nerve fibres in man.

<**McDonald to camera**>

Now let us turn to the question of recovery. Very little is known about the mechanism of recovery from damage to the central nervous system. In the context of this talk I want to consider whether demyelinated nerve fibres in the brain or spinal cord can be remyelinated and, if so, whether remyelination contributes to the recovery process.

Does remyelination occur in the central nervous system? It is now clear that in certain circumstances, demyelinated central nerve fibres can be remyelinated by oligodendrocytes, the normal myelin-forming cell. This fact was first established by Bunge and his colleagues in the early 1960s, who studied a physically induced

demyelinating lesion in cats. Remyelination has since been demonstrated in toxic, allergic and compressive lesions. We have been interested recently in the characteristics of the newly formed myelin and have studied them in cats following acute compression of the spinal cord.

<McDonald narrates whilst standing next to large slide projection showing remyelination of nerve fibres, uses indication stick, then to camera>

The first characteristic is that the newly formed myelin is abnormally thin. Although the sheath thickens with time, even after 9 months adult thickness is never reached, we don't know whether it ever is. Secondly, Gledhill has demonstrated that the new myelin is organised into segments bounded by node-like gaps. Moreover, these segments are abnormally short. In these two fibres, the nodes are indicated by arrows – the upper fibre is normal, the lower fibre has many short internodes and one of them is very short indeed, only about 16µm. Finally, Harrison has shown that many of the known ultra-structural specialisations which appear to be necessary for conduction are present in these new myelin segments.

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But is conduction, in fact, restored in remyelinated fibres? The questions we've considered so far have all had fairly definite answers, derived from solid experimental and clinical observations. There is, as yet, no answer to this last question. I should like, however, to consider it from two points of view. First, there is the problem of the length and thickness of the new segments of central myelin. Cole's and Rasminksy's computer simulation of conduction in peripheral demyelinated fibres, where conduction is known to be restored by remyelination, suggests that as little as 3% of normal myelin thickness over a whole internodal segment might be sufficient to restore conduction. The new myelin in our compression lesion certainly exceeds this critical value. But there is also the factor of the length of the segments. As Rasminsky and Sears showed, the reason why conduction fails in demyelinated fibres is that so much of the current generated by a node is lost through the low resistance pathways and in charging up the capacitance of the thin, surviving myelin

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that insufficient is left to discharge the next node. It is possible that there is still so much current loss through the chains of very short internodes, such as we have seen, that the critical depolarisation of the next active nodal site cannot be reached. Direct experiment must establish whether conduction is restored remyelination of central fibres. My colleagues, Jacobs and Smith, are tackling this problem now.

The second problem is this: let us assume for the moment that conduction is restored in experimental remyelination – what is the evidence for remyelination in man? The only information we have at present relates to multiple sclerosis and this is scanty. Thin myelin has been seen around normal axons but such appearances can be produced by partial demyelination. Suzuki and her colleagues have seen appearances resembling the early stages of developmental myelination in biopsies from multiple sclerosis patients undergoing therapeutic stereotactic thalamotomy. Andrews has reported a single example of a complete short internode in a patient with multiple sclerosis. Thus at present the evidence for remyelination in multiple sclerosis is suggestive but not conclusive. One thing is clear, however, that if it does occur, it is scanty and incomplete.

It might be argued that the mere fact of recovery must imply restoration of conduction by remyelination but this is not so. The dramatic recovery of vision in optic neuritis which can occur in a few days, is far too rapid to be accounted for by remyelination. The earliest remyelination seen in any experimental lesion in vivo is in the third week. In optic neuritis it is much more likely that the very rapid early recovery is related to the dispersal of oedema which has been compressing critically damaged fibres.

Finally, it is clear from the recovery which can follow lesions producing total destruction of nerve fibres, for example, haemorrhagic capsular hemiplegia, that there are other fundamentally different mechanisms contributing to recovery. These mechanisms must involve compensation for the loss of function by surviving parts of the nervous system rather than restoration of the damaged parts themselves.

In this talk I have shown how demyelination interferes with conduction in the central nervous system. Remyelination occurs in the central nervous system and the new

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myelin exhibits many, although not all, of the known morphological prerequisites for conduction. We don't yet know whether remyelination is effective in restoring conduction in demyelinated fibres or whether significant remyelination occurs in multiple sclerosis. The solution of these problems should come from further systematic study of experimental and clinical lesions of the central nervous system, along the lines that I have described.

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