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## Editorial

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# Limiting and repairing the damage in multiple sclerosis

Much has been learned from clinical, neuropathological and imaging studies about the nature of multiple sclerosis since the disease was first depicted and described in the nineteenth century; and it is now possible to define what has to be achieved if structural and functional repair of the central nervous system is to become a reality for patients with demyelinating disease. It is self evident, both with respect to patients and plaques, that the requirements for repair can be reduced if treatment is given early in the course. Clinicians have been reluctant to use potentially hazardous therapies, even if these have proved useful in related disorders, since up to 30% of patients with multiple sclerosis remain free from disability even after several decades of intermittent disease activity. Disability correlates with onset of the progressive phase and this eventually occurs in about 65% of patients. The dilemma is that the disease relapses from onset in almost 90% of patients and the clinical phenotype is not a reliable guide to whether and when the switch to disease progression will occur.<sup>1</sup> The application of MRI has not resolved this problem for, apart from the minority of patients in whom the disease progresses from onset, it is not possible to differentiate reliably benign from more disabled individuals or relapsing cases from those with secondary progression.<sup>2</sup> One factor which may influence the impact of individual plaques is their strategic placement within the nervous system but a more interesting explanation is that some lesions do not develop to the stage of demyelination and others spontaneously recover.

It is against this background that the sequence of events involved in the development of a typical plaque should be considered.<sup>3</sup> Initially there is increased permeability of the blood-brain barrier which accounts for perivascular inflammatory cell infiltration; this is followed by acute changes in oligodendrocytes and active myelin breakdown with macrophage or microglial degradation of the lamellae;<sup>4,5</sup> significant remyelination occurs in the acute stage<sup>6</sup> but with resolution of the inflammatory component, the lesions show astrogliosis, chronic oligodendrocyte depletion and axonal loss—and this may be the main determinant of persistent disability.

### The blood-brain barrier

The blood-brain barrier is made up anatomically by endothelial cells, surrounded by a basement membrane and a layer of astrocytes whose foot processes form the tight junctions.<sup>7</sup> The available evidence suggests that cell surface adhesion molecule expression alters when circulating T lymphocytes and macrophages are activated, increasing

their endothelial cell attachment;<sup>8</sup> the secretion of cytokines and locally active enzymes leads to transendothelial passage, opening the barrier and bringing an array of potentially pathogenic inflammatory cells and mediators to the abluminal surface of blood vessels. The possibility arises that activated T lymphocytes are themselves directly cytotoxic to some component of the oligodendrocyte-myelin unit but it seems more likely that infiltrating T cells play no direct role in myelin injury and only influence demyelination either by the production of gamma interferon, which activates macrophages and microglia, or by providing local help for B lymphocytes. According to this model, therapies targetted at T lymphocytes primarily influence vascular penetration of the nervous system and their effect on demyelination is indirect; however, blood-brain barrier penetration can be regarded as the primary disease process without which none of the events directly responsible for myelin injury would occur.<sup>9</sup> The development of reshaped humanised monoclonal antibodies directed against molecules involved in lymphocyte activation and cellular adhesion, in which mouse anti-man peptide sequences responsible for antigen binding are inserted onto a human immunoglobulin molecule promises to bring improved precision to the immunological treatment of multiple sclerosis; these antibodies retain immunological specificity but anti-idiotypic responses that might limit the efficacy of long term therapy, are minimised.<sup>10</sup> Selective and therefore safe functional blockade, and the depletion of individual inflammatory cell populations, can be achieved without exposing patients to the risk of non-specific immune suppression.

### Limiting oligodendrocyte injury

Where blood-brain permeability is not contained, an entirely different approach may need to be taken in seeking to limit the consequences of inflammatory cell infiltration of the nervous system; this will depend on manipulating the biological and pharmacological responses to injury of oligodendrocytes, their cell processes and myelin membranes. The underlying principle is that a sequence similar to the physiological binding of excitatory amino acids to surface receptors, ion channel opening, signal transduction in the cell membrane and activation of intracellular second messengers occurs when cells are injured by inflammatory mediators. Irreversible injury ensues when cells cross the threshold for recovery. Oligodendrocytes are uniquely susceptible amongst glia to contact with the membrane attack complex of complement, T cell derived perforins, arachidonic acid, the ionophore A23187, and tumour

necrosis factor—many of which act by selectively forming pores in the cell membrane and function initially as calcium ionophores. Oligodendrocytes express on their surface an unidentified ligand that binds and activates complement through the classic pathway but in the absence of antibody. Cells exposed to serum as a source of complement swell and their cytoplasm becomes cloudy as the membrane permeabilises to the nuclear dye propidium iodide.<sup>11</sup> This sequence may be associated with a transient rise in intracellular calcium which activates a repair mechanism involving vesicular shedding of membrane lesions from the cell surface.<sup>12,13</sup> Vesicular repair is not exclusively a property of recovery from membrane injury by complement membrane attack complexes. It is also seen with exposure to perforins and calcium ionophores.<sup>14,15</sup>

Vesicular repair, however, may not compensate for overwhelming membrane injury; high concentrations of complement or perforin result in an uncontrolled rise in intracellular calcium and cell lysis. The role of calcium in injury and repair is further emphasised by the effects of inhibiting the calcium activated intracellular binding protein calmodulin, which normally limits the consequences of transmembrane calcium flux or release from intracellular stores.<sup>15</sup> The pivotal role of calcium in regulating the responses to inflammation or immunological attack potentially provides an opportunity for limiting the consequences of damage to the oligodendrocyte-myelin unit: this approach has also attracted attention in the treatment of ischaemic and excitotoxic neuronal injury. Alterations in ion flux, similar to those occurring across oligodendrocyte and myelin membranes with changes in intracellular calcium, are known directly to disturb conduction through myelinated peripheral nerve fibres and cause vesicular disruption of the myelin lamellae.<sup>16</sup>

### Limiting macrophage activity

Cell biological techniques can also be used to investigate interactions between macrophages or microglia and oligodendrocytes, thus providing an *in vitro* reconstruction of the sequence of events that underlies the degradation of myelin lamellae and oligodendrocyte depletion *in vivo*. Macrophages and microglia adhere to targets either through constitutively expressed C3b receptors, which are activated following exposure to gamma interferon, or through Fc receptor binding of antibody coated target cells.<sup>17</sup> It may be the case that local availability of gamma interferon is sufficient to activate locally infiltrating macrophages and resident microglia, enhancing their adherence to oligodendrocytes following complement activation and the presence of C3b.

Another possibility is that complement induced vesicular repair of the cell membrane releases potentially immunogenic vesicles that stimulate the local production of antibody directed against components of the oligodendrocyte surface. *In vitro* studies have confirmed that opsonisation of the cell surface by any one of a number of anti-oligodendrocyte antibodies in sub-lytic concentrations stimulates macrophages and microglia to contact and digest the oligodendrocyte and its processes, mimicking the core pathological features of active demyelination.<sup>18</sup> Several pharmacological agents are available that inhibit macrophage function and they could be used to limit oligodendrocyte and myelin injury occurring in areas of perivascular infiltration. Methylprednisolone, given intravenously and in high dose, inhibits the release of eicosanoids and other mediators of macrophage activity, reduces tissue oedema in the white matter of patients with multiple sclerosis, and is associated with rapid reduction in the MRI appearances of individual T2 weighted lesions.<sup>19</sup> Biologically active molecules that block the release or

activity of macrophage mediators are being evaluated and important pharmaceutical developments can be expected in this therapeutic area.

### Increasing spontaneous remyelination

Modern neurobiology has provided the means for addressing the problem of how fixed deficits might be repaired by exploiting the developmental properties of glial organisation in the central nervous system. Much original work has been carried out using the optic nerve and this epitomises how other parts of the nervous system are organised. The first cell type to populate the developing optic nerve is the type 1 astrocyte; this produces platelet derived growth factor which binds to receptors on oligodendrocyte-type 2 astrocyte (0-2A) progenitors, influencing their migration from the brain and proliferation in the optic nerve.

At about the time of birth, the intrinsic capacity of these progenitors to divide expires and type 1 astrocytes cease to produce platelet derived growth factor with the result that 0-2A progenitors differentiate down their constitutive pathway into oligodendrocytes.<sup>20-23</sup> These interdigitate themselves, in an array whereby the 10-15 myelin sheaths that each cell produces line up in parallel with axons traversing the optic nerve from the retinal ganglion cells to their synapses in the lateral geniculate bodies.<sup>24</sup> Those 0-2A progenitors that retain proliferative and migratory potential in early neonatal life, now find themselves exposed to ciliary neurotrophic growth factor, also produced by type 1 astrocytes; this stimulates the differentiation of 0-2A progenitors into type 2 astrocytes (a cell that has yet to be identified *in vivo* but is thought to contact the node of Ranvier) thus completing the glial arrangements that ensure saltatory conduction through myelinated nerves and ion buffering at the axo-glial junction.<sup>25</sup> It is now clear that progenitors survive into adult life retaining the potential for repopulating oligodendroglia-paenic areas of persistent demyelination.<sup>26</sup>

All the evidence suggests that these cells or their oligodendrocyte progeny repair areas of focal macrophage mediated inflammation but lasting remyelination does not seem to be achieved. Two explanations can be offered. First, adult 0-2A progenitors are the only cell type other than mature oligodendrocytes that fix and activate complement so they will be vulnerable to pathological processes involved in tissue injury recurring at the same site,<sup>9,27</sup> as has been demonstrated using MRI.<sup>28</sup>

Second, the availability of adult 0-2A progenitors might not achieve oligodendrocyte repopulation if local availability of growth factors was to divert any progenitors that did repopulate demyelinated plaques down the type 2 astrocyte lineage; chronic lesions are characterised by intense astrocytic overgrowth and these may then act as a physical barrier to the inward migration of other cells and to the regeneration of axons.<sup>29</sup> Although restructuring the growth factor environment in areas of demyelination has theoretical attractions as a means of exploiting and stabilising the potential for remyelination by progenitors and their oligodendrocyte progeny, complex interactions between glia and growth factors may offset these advantages when the requirements for axonal regeneration are also considered.

### Enhancing axonal regeneration

The mature central nervous system needs to safeguard the complexity of its anatomical arrangements; stability is imposed by determinants on the surface of contiguous cells that direct growth during development and inhibit subsequent rearrangements. One such inhibitory molecule, expressed on the surface of mature oligodendrocytes,

inhibits neurite outgrowth and limits axonal regeneration.<sup>30</sup> In vitro studies indicate that neurites will grow across a matrix of astrocytes, even though axons will not necessarily penetrate the glial cell layer, but they skirt around oligodendrocytes and their growth cones collapse through contact inhibition if they should meet the surface of an oligodendrocyte or its processes.<sup>31</sup> In vitro, this phenomenon can be prevented by the use of antibodies that disinhibit the inhibitory molecule,<sup>32</sup> and in vivo, axonal regeneration through an area of spinal cord injury can be much enhanced by the local availability of this anti-oligodendrocyte antibody, neurites then advancing a substantial distance beyond the area of cord injury.<sup>33</sup> This molecule is not found on Schwann cells; these provide a permissive environment for regeneration of peripheral nerve fibres—a property that has been exploited by attempting to encourage regeneration of the central nervous system through transplanted peripheral nerve bridges.<sup>34</sup> These considerations are bound to complicate strategies for the restoration of glial arrangements within the central nervous system if the main source of neurological disability is axonal loss and not merely the physiological consequences of altered conduction through demyelinated but otherwise intact axons. Nevertheless, measures aimed at altering the growth factor environment of demyelinated plaques to reproduce the conditions that favour migration and proliferation of adult progenitors, and their differentiation into oligodendrocytes, offer a prospect for the repair of critically placed lesions.

### Glial repair by transplantation

It is reasonable to speculate on how these complex issues might be solved by the use of transplantation as a means for restoring structure and function in the central nervous system. Although neural transplantation has been used in humans to treat the neurochemical deficits of Parkinson's disease, it is apparent that a great deal has yet to be learned before this can be considered a viable therapeutic option in neuro-degenerative disease.<sup>35,36</sup> Experience with neuronal grafting has demonstrated that replacing neurotransmitters is not sufficient to restore complex functions. Extensive connectivity also needs to be established between grafted neurons and their targets in the appropriate receptor zone. This is best achieved by placing grafts at the site from which degenerate neurons originate, that is, homotopically. But under these circumstances grafted neurons must grow through the hostile environment of the adult brain if connectivity is to be restored. Ectopic grafting partially overcomes the requirement for growth but limits the extent to which grafted tissue can explore the target area and connect appropriately. Peripheral nerve bridges, combinations of growth factors and cells may all be required to ensure sophisticated structural and functional recovery.

These principles of transplantation neurobiology are also important when considering the possibility that areas of demyelination and axonal loss—particularly those that are strategically placed in the spinal cord so as to cause significant disability—could be repaired by glial grafts used in conjunction with measures designed to enhance regeneration and limit on-going damage.

Blakemore *et al* have used a model in which ethidium bromide is injected into the spinal cord resulting in focal glial loss with resulting demyelination.<sup>37-39</sup> Limited spontaneous remyelination is achieved in these lesions by Schwann cells migrating from neighbouring parts of the peripheral nervous system but this is partial and prevents extensive repair. In a more complex model involving injection of ethidium bromide and local X irradiation, all glial cells are destroyed and no spontaneous Schwann cell

remyelination occurs. These persistently demyelinated lesions are therefore suitable for grafting with suspensions enriched for cells of the glial lineage. Remyelination is achieved by mixed glial grafts if these contain large numbers of oligodendrocytes; this may reflect the need for an adequate supply of progenitors.

Subsequent experiments show that a continually dividing population of adult 0-2A progenitors, stimulated by a combination of platelet derived and fibroblast growth factors, will also successfully remyelinate X irradiated, ethidium bromide treated lesions (W Blakemore and M Noble: personal communication). However, the requirements and interactions of different glial cell types are best revealed using mixed cells grafted into non-irradiated lesions. Here, the activity of contaminating or resident Schwann cells derived from adjacent tissue can be inhibited, and more extensive oligodendrocyte repair achieved, only when there is an adequate source of type 1 astrocytes; presumably the grafted cells are acting as a source of growth factors required for satisfactory oligodendrocyte differentiation even in the face of Schwann cell competition for naked axons. Purified type 1 astrocytes grafted into demyelinated areas will simultaneously inhibit the local invasion by Schwann cells and attract migratory adult host progenitors capable of remyelinating naked axons.<sup>40</sup>

It is not unreasonable to speculate on the long term possibility for engineering the expression of cell surface receptors and the proliferative potential of grafted cells, to maximise their capacity for accomplishing the biologically and metabolically complex tasks of contact, adhesion and myelination of naked axons whilst at the same time permitting axonal regeneration.

### Conclusions

The difficulty of restoring structure and function in the adult nervous system and solving the problems of demyelinating disease, increases with the extent and distribution of the lesions. The long term aim is to prevent the disease and this might be achieved by the application of advances in epidemiological genetics and the identification of viral triggers; in the absence of prevention, limiting the consequences of multifocal myelin injury is likely to require the exclusion of inflammatory mediators from the central nervous system, manipulation of the intracellular consequences of oligodendrocyte membrane permeability, inhibition of macrophage activity, enhancement of 0-2A or oligodendrocyte regeneration, and reconstitution of defective cell populations in critically placed lesions. This is work that requires the commitment of a research community comprising individuals working in molecular, cellular, systems and behavioural neuroscience integrated with the disciplines of clinical neurology and brain imaging.

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## Neurological stamp

### Aureolus Philippus Theophrastus Bombastus Von Hohenheim or Paracelsus 1493-1541

Paracelsus, one time professor of medicine in Basel, and "father of pharmacology" had a bombastic, impetuous personality but managed to rouse people against existing dogmatism. High self esteem led to his adopting the name Paracelsus, to indicate his authority was equal or superior to that of Celsus. A pioneer in chemical therapeutics he was the first to promote chemical substances in treatment. Paracelsus attacked all medical authorities except Hippocrates. He incurred displeasure by lecturing in German, rather than Latin. Academic colleagues excluded him from university halls, but he continued to give lectures based on his own experiences, many obtained from extensive travels in Europe and the Middle East. He expressed his antagonism for traditional medicine by publicly burning the books of Avicenna, Galen and others. Paracelsus was the first to write on the occupational diseases of miners and to note geographical differences of diseases. His contempt for anatomy was combined with a failure to see how knowledge could be gained from a dead body.

He established the correlation between cretinism and endemic goitre and described the congenital transmission, and mercurial treatment of syphilis. He introduced tincture of opium—labdanum or laudanum—with which he effected miraculous cures probably learnt during his travels in the East. Paracelsus warned against stress and advised avoiding strongly flavoured wines, rich food, anger and women, made observations on epilepsy, took the view that St Vitus' dance was a disease and knew of paralysis and disturbance of speech after head injuries. Ironically his



death followed a tavern brawl. Germany honoured him on a stamp issued in 1949. (Stanley Gibbons 1040, Scott 8311).

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