Brain repair

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Significant improvements in the treatment of common neurological diseases can be expected over the next few years from the application of advances now occurring in the basic neurosciences. In many disorders of the central nervous system, disability accumulates as a result of the degenerative process and its failure to repair. In part, this is because with differentiation, cells in the adult nervous system lose the ability to proliferate and migrate. A family of growth factors orchestrates proliferation, migration, differentiation and survival of neurones and glia: because certain of these growth factors also protect from injury cells which they support during development, there should soon be opportunities for limiting damage following a variety of insults and for rescuing degenerating neurones and glia. The discovery that axon regeneration is actively inhibited, perhaps in order to maintain stability in the complex systems and circuits that are established during development, suggests new strategies for enhancing axonal regeneration in spinal and head injury. Recruiting cells that are capable of restoring glial-neuronal interactions into areas of damage will be an important part of the brain repair strategy but it may prove possible to restore complex cellular arrangements through cell implantation only. Grafted neurones survive, produce appropriate neurotransmitters, form connections and restore some behaviours, but their relative inability to grow limits the degree of structural and functional repair that can be achieved; nevertheless, nerve cell implantation is now being used in the management of certain neurodegenerative diseases of the human central nervous system. There are also prospects for increasing the remyelination which occurs following acute inflammatory disease of the central nervous system, through the combination of immunological treatments that limit the disease process, growth factors that recruit oligodendrocytes and implantation of glial progenitors into demyelinated areas.

Keywords: development, growth factors, injury, multiple sclerosis, neurodegeneration.

Introduction
The last quarter of the 20th century has seen unprecedented advances in the basic neurosciences, some of which have already had important clinical applications: but too little is still being done to influence recovery from injuries of the nervous system or from stroke, and progress has been slow in influencing the course of the neurodegenerative disorders described by James Parkinson, George
Huntington and Alois Alzheimer between 1816 and 1904, and multiple sclerosis. These conditions, which affect the nervous systems of many young adults and an increasingly large number of older people, represent an enormous burden for patients, their carers and for society.

The starting point for strategies which will lead to repair of the central nervous system in these and other situations is to understand the rules of development, recreating in the context of disease a system that works well during embryogenesis and early post-natal life. Possible explanations for the relative lack of spontaneous repair in the adult human brain and spinal cord include a relative (or absolute) deficiency of neuronal and glial stem cells, the emergence with maturation of growth factor conditions that do not favour cell proliferation, and active inhibition of axon regeneration which characterizes disease of the adult human central nervous system. But of equal importance is the fact that the application of sophisticated strategies for repair makes little sense, and is likely to fail, if attempts are not also made to understand and limit the degenerative process.

**The neurobiology of brain repair**

**Cell lineages**

Pluripotential cells are found in the ventricular and subventricular zones of the developing nervous system. Later, in response to growth factors, these stem cells become committed to a particular developmental lineage and, with differentiation, lose the ability to migrate and proliferate. Recreating the responsiveness of neurones and glia in the mature central nervous system so that these cells resume their developmental phenotype and patterns of behaviour will be an important factor in success of the brain repair strategy. In this respect, the observation that precursor cells that retain the ability to differentiate either into neurones or glia—responding to combinations of basic fibroblast factor (bFGF), nerve growth factor (NGF) and epidermal growth factor (EGF)—are present in the adult (murine) brain [1], is an important discovery.

As these stem cells differentiate, the first recognizable change in the glial lineage is the appearance of radial cells that span the subventricular zone to the developing cortex [2]. Neurones destined for the cortex migrate along this scaffold: the growth cones of their axonal processes then seek appropriate targets and extensive connections are formed at sites that are remote from the cell of origin. In following an awkward path, many axons seek boundaries and orientations established by regional variation in the availability of adhesion and repulsion molecules [3].

Oligodendrocyte precursors arise from subventricular zones of the lateral and fourth ventricles; at about the time of birth, these differentiate, contact naked axons and form the myelin sheath. In *vitro*, a bipotential glial progenitor (O-2A) differentiates either into an oligodendrocyte or an astrocyte (type 2) depending on culture conditions [4], and this cell can also be recovered from the adult nervous system [5]. Although controversy still surrounds the status of the O-2A cells in *vivo*, glial precursor cell lines differentiate into oligodendrocytes or astrocytes following transplantation into the rat spinal cord [6], and cells that migrate away from germinal zones in *vivo* also retain this bipotential developmental plasticity [7]. Experimentally, accumulation of proliferating oligodendrocytes occurs during recovery from gliotoxic lesions of the rodent nervous system, but whether these cells are the progeny of migrating progenitors or dedifferentiated mature oligodendrocytes is uncertain.

Myelination occurs in the central nervous system when the membranous processes of mature oligodendrocytes contact axons, spiral and compact to form the myelin lamellae needed for saltatory conduction. This sequence depends upon proliferation of progenitor cells and differentiation of their progeny. In glial-neuronal cocultures, bromodeoxyuridine (BrdU) labelling shows that neurones increase the mitotic index of glial progenitors and this effect can be reproduced, in part, by supernatants from neurones grown in culture and added to purified O-2A cells. In the presence of axons, there is a shift in the pattern of differentiation of O-2A cells with the development both of oligodendrocyte and astrocyte progeny [8]. It is to be expected that during development axons produce signals which influence the differentiation of glial progenitors, and promote the growth of each cell type needed for myelination and anatomical arrangements at the node of Ranvier. Differential regulation in the expression of adhesion molecules, including janusin, tenascin, laminin and fibronectin, occurs during myelination and is required for stability of the emerging glial-neuronal unit. Although astrocytes fulfil an important metabolic role at the node of Ranvier, they also determine
the limits of the central nervous system; their foot processes create the glial limiting membrane and, with microglia, contribute to the tight junctions which form the blood–brain barrier.

Growth factors

The recently described family of factors that determine the growth, survival and protection of neurones includes NGF, brain-derived nerve growth factor (BDNF), and the neurotrophins (NT)-3, NT-4 and NT-5 [9]. Nerve fibres survive by selectively transporting these factors from sites of target innervation and connectivity, and growth factor dependence continues during the life of individual neurones, although this may diminish with time [10]. Failure to secure appropriate growth factor support soon leads to cell death, although various rescue strategies can be adopted. NGF, BDNF and NT-3 all act as survival factors for neural-crest-derived sensory neurones and some motor neurones, and sympathetic neurones require NGF. BDNF supports retinal ganglion cells, and both NGF and BDNF are survival factors for cholinergic neurones. Basic FGF promotes the survival of tyrosine-hydroxylase-positive neurones derived from the ventral mesencephalon, and influences the rate of division of their precursors. Ciliary neurotrophic factor (CNTF) acts as a survival factor for motor neurones. Both CNTF and leukaemia inhibitory factor (LIF) promote cholinergic differentiation of sympathetic neurones, and influence survival of motor and sensory neurones. The most recently described factor is glial cell-line derived neurotrophic factor (GDNF), which stimulates foetal dopaminergic neurones in tissue culture [11].

One important discovery for the brain repair strategy is that growth factors also protect from injury those neurones that they support during development. This suggests an economy of approach, in that protecting brain cells from injury may at the same provide the environmental conditions required to assist the restoration of normal cellular architecture in the central nervous system [12]. BDNF protects dopaminergic neurones from the toxic metabolite MPP+ and from axonal injury; hippocampal neurones are saved from excitotoxic injury by bFGF; this and other growth factors protect a range of hippocampal, septal and cortical neurones from hypoglycaemic and hypoxic injury, and their tissue expression increases following ischaemic and other insults in vivo. NGF and bFGF released close to the striatum reduce the excitotoxic effects of glutamate receptor analogues in a model of Huntington's disease. NT-3 selectively prevents the degeneration of adrenergic neurones within the locus coeruleus, which normally follows exposure to 6-hydroxyparkine in a model that mimics the pattern of nerve cell loss seen in Alzheimer's disease. Finally, CNTF is transported in increased amounts to the cell body after axotomy, and may determine the fate of motor neurones threatened by injury. Many of these effects are mediated by stabilizing the rise in intracellular calcium that characterizes excitotoxic and other potentially lethal mediators of cell injury [13]. From this analysis emerges the general principle that the signals transduced by cells during growth and physiological activity are the same as those that become overloaded during pathological events leading to cell injury and death. The extent to which a cell can survive injury is modulated by its growth factor dependent state of health; it follows that cell death may occur in response to a state of injury from which protection would be anticipated under more favourable growth factor conditions. Conversely, optimal growth factor conditions may save cells from otherwise lethal events occurring at the cell membrane.

Glia also depend upon growth factors for development, survival and protection from injury. Glial O-2A progenitors and their progeny respond to platelet-derived growth factor (PDGF), bFGF, insulin-like growth factor (IGF-1), interleukin 6 (IL-6), LIF, and NT-3. NT-3 and PDGF induce DNA synthesis in oligodendrocyte precursors in vitro and cause these cells to proliferate both in vitro and in vivo; more mature cells also need IGF-1 to stimulate cell division, and once this developmental ritual is complete, CNTF is required for cell survival [14, 15]. Although this evidence suggests that PDGF is mitogenic for O-2A precursors, in vitro they escape from this stimulus after a number of divisions unless grown in the presence of bFGF. It now transpires that the inhibitory effect of bFGF on O-2A cells can be over-ridden by astrocyte-derived factors, which promote differentiation without inhibiting proliferation [16]. IGF-1 and IGF-2 stimulate proliferation of partially differentiated oligodendrocytes, and both act as long-term survival factors for O-2A cells and oligodendrocytes. In vivo, reduction in the availability of survival factors during development leads to strategic loss of a high proportion of newly formed neurones.
oligodendrocytes [17]. Preliminary evidence suggests that CNTF protects oligodendrocytes from injury by tumour necrosis factor alpha (TNF-α) but not complement attack [18]. Taken together, it is clear that cocktails of growth factors are required to orchestrate glial growth and survival in vitro, and proliferation, migration, differentiation, survival and protection of glia are under the control of separate growth factors. Many of these are produced by astrocytes, as are some neurotrophins: conversely, some molecules which influence glial differentiation are derived from neurones [8], and oligodendrocytes secrete autocrine factors which regulate their own development. Less is known about the growth factor requirements of astrocytes, but transforming growth factors beta (TGF-β) inhibit astrocyte proliferation [19].

**Axon regeneration**

Axon regeneration in the adult mammalian central nervous system is limited by the ability of nerve cells to extend new growth cones and the nonpermissive environment in which growth must occur. Axonal potency is prominent during embryogenesis: it diminishes with age and there are inherent restrictions imposed by the overall size of nervous systems. Human embryonic neurones cover greater distances than equivalent rodent cells transplanted into the rat striatum [20]. These differences may relate to variations in the cytoskeleton of the growth cone, and to the nerve cell adhesion molecule (N-CAM) expression by its advancing tip. Although reversal to a developmental growth cone cytoskeletal structure may not be possible, growth factors do enhance regeneration of those axons that they nurture during development.

One important feature of mammalian glial neurobiology that relates to axonal growth is the inhibitory effect of glia on axon regeneration. The astrogliosis that characterizes injury in the central nervous system presents a physical barrier to axon penetration, and the extent to which embryonic and adult growth cones penetrate their surrounding matrix depends on local secretion of protease, which is increased by bFGF and interleukin 1 (IL-1) [21]. Mature oligodendrocytes also inhibit neurite outgrowth as a result of the expression of two molecules, designated NI-35 and NI-250 [3, 22]. Perhaps the need for axonal guidance during development and the advantages of restricting plasticity in the fully wired nervous system outweigh the survival advantage of being able to regenerate axons. *In vitro*, axons are distributed around oligodendrocytes so as to maximize the number that can be contacted by any one myelinating cell [8], and axonal growth cones collapse on contact with an oligodendrocyte or its processes [23].

**Applications of neurobiology for clinical practice**

**Spinal cord injury**

When the brain or spinal cord has suffered an injury in which disability results from discontinuity of nerve fibres in the major pathways, structural and functional repair will depend on whether axons successfully regenerate: the situation presents some urgency because axotomy soon leads to retrograde neuronal degeneration. Experimentally, axon sprouts increase around an area of spinal cord damage stimulated with NT-3, and axonal regeneration towards denervated targets, which is routed around the lesion, is enhanced by infiltrating spinal lesions with antibodies that block the inhibitory molecules expressed on the surface of mature oligodendrocytes: nerve fibres then advance a substantial distance beyond the site of injury [3, 23]. These inhibitory molecules are not present on Schwann cells, which myelinate peripheral nerve, and the permissive environment that they provide for axon regeneration has been exploited by encouraging central axonal regeneration through implanted Schwann cell channels, engineered to improve the availability of growth factors that support repair.

More recently, the enhanced ability of embryonic neurones to grow and reach distant targets has been used experimentally to show that both ends of a foetal spinal cord graft will connect, and restore function, across a complete spinal lesion [24]. With the introduction of techniques for engineering fibroblasts to secrete growth factors in the vicinity of local lesions, the recreation of a permissive environment for regeneration paves the way for clinical applications in the management of spinal cord and, perhaps also, head injury.

**Motor neurone disease**

The demonstration of mutations in the gene for superoxide dismutase associated with familial motor neurone disease suggests that premature death of
motor neurones results from oxidative stress [25]. Free radicals capture electrons, causing lipid peroxidation and this process precipitates cell death; protection from free radicals requires superoxide dismutation, and is increased by vitamins C and E. By reacting with conserved nitrate tyrosine residues, oxygen radicals could interact with tyrosine kinase receptors and deprive motor neurones of the growth factors, BDNF and NT-3. Calcium overload mediated by the excitotoxin glutamate has been proposed as an alternative mechanism of injury, based on evidence for motor neurone toxicity [26], and has prompted clinical trials of drugs which interfere with neuronal excitotoxicity: the pre-synaptic glutamate release inhibitor riluzole is reported to slow the progression of motor neurone disease and to improve survival in patients with bulbar onset of symptoms [27].

Because CNTF is a survival factor and salvages motor neurones in genetically determined neuromuscular disorders of mice [28, 29], the trophic and survival effects on motor neurones have suggested therapeutic studies of CNTF in animal models of motor neurone disease. CNTF and BDNF have complementary effects in reducing the progression of genetically determined neuronal degeneration and given the otherwise predictably poor prognosis; this work has stimulated clinical trials of CNTF and BDNF in motor neurone disease.

Neurodegenerative disease

One hypothesis for the pathogenesis of Parkinson’s disease is that dopaminergic neurones projecting from the substantia nigra to the putamen are damaged by exposure to environmental factors analogous to 6-hydroxydopamine or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its MPP⁺ metabolite [30]. Alternative theories emphasize the experimental evidence for a decrease in complex 1 of the mitochondrial respiratory chain, and oxygen radical injury has also been proposed to account for cell death in Parkinson’s disease [31], especially because metals readily donate electrons and iron accumulates in affected tissue. These rival, but not necessarily competing theories for the mechanism of tissue injury in Parkinson’s disease have led to trials assessing the disease-modifying effects of the free radical scavenger alpha tocopherol (vitamin E) and the selective monoamine oxidase B antagonist deprenyl. First results suggest that they may slow the rate of accumulation of neurological disability [32].

Although these and other treatments that increase the availability of dopamine in the striatum have improved the quality of life for many patients with Parkinson’s disease, they can do nothing to repair lost nerve cells, and it may be unrealistic to hope that symptomatic treatments will ever be satisfactory in those degenerative disorders where large numbers of neurones have already been lost. These situations may require cell implantation both as a source of neurotransmitter release and to restore connectivity. Dopaminergic neurones have successfully been implanted in experimental forms of Parkinson’s disease but there are practical problems: ideally, cells should be implanted at the site from which they normally project, but they must then extend axons and grow through a nonpermissive environment to restore the extensive connectivity of normal nigro-striatal circuits. Ectopic placement of grafts overcomes the requirement for growth, but implanted cells then fail to explore the target area and form appropriate connections [33]. Schwann cells might enhance regeneration of central axons acting as peripheral nerve bridges which span degenerate gaps in neuronal pathways [34]; and, as expected, the viability of transplanted dopaminergic neurones is enhanced by the local infusion of growth factors such as bFGF, which normally promote growth and survival of dopaminergic neurones [35].

More than 140 patients have already received brain cell implants as treatment for Parkinson’s disease [36–39]. Graft survival seems to have improved with time, and this is matched by evidence for improved survival of the implanted material, as shown by positron emission tomography with fluorodopa as the ligand. Most importantly, these grafts are associated with steady improvement in function starting several months after treatment; this rather suggests that viability of the engrafted material and local production of dopamine only have clinical manifestations when local connectivity has also been restored. For the future, the logistic and ethical difficulties of using a human tissue source for treating Parkinson’s disease have prompted the development of cell lines for implantation therapy. Improved graft survival and function through growth factor infusion also seem logical, but precisely which cocktail will optimize graft survival remains to be determined.

Although neural transplantation has only been carried out systematically in patients with Parkin-
son's disease, experimental studies have prepared the way for similar applications in a variety of other situations. In Huntington's disease, excitotoxic injury of the rat striatum with ibotenic acid produces a behavioural syndrome that resembles Huntington's disease and has a comparable neuropathology. Local grafts of striatal neurones survive, connect into local circuits, and restore some of the motor and cognitive deficits of the excitotoxic injury [40]. Although the gene for Huntington's disease has been identified and cloned [41], there will be a delay before predictive testing or gene therapy reduce the incidence and expression of the disease in at-risk individuals. Until then, strategies that aim to restore structure and function in the neuronally deprived caudate will remain relevant to this otherwise inexorably progressive neurodegenerative disorder.

Ideas are also beginning to develop on the possibility of repairing focal areas of cortical damage resulting from ischaemic injury. Preliminary experimental studies [42] have used a model causing focal ischaemia, which leads to degeneration of local neurones and those that normally form cortical connections. Foetal neocortex grafts have been assessed using sensory stimulation followed by deoxyglucose utilization studies of the engrafted cortex, and these show increased metabolic activity; histological evidence suggests that thalamic projections capture and connect with the engrafted neurones, but the extent to which these restore independent cortical activity remains to be determined. Surveying the entire range of experimental situations in which neural grafting has been assessed, it is clear that a wide variety of systems can be reconstituted, and these include visual, endocrine, cognitive and several motor pathways [43].

Multiple sclerosis

At first sight, the most difficult disease to tackle by the brain repair strategy is one, such as multiple sclerosis, in which damage occurs repeatedly, randomly and unpredictably throughout the nervous system. In this, the commonest demyelinating disease in man, disability results both from the inflammatory process and from its failure to repair. For many patients, limiting the inflammatory process without also making attempts at restoring glial-neuronal interaction is a poor ambition, but repair without limiting the damage makes little sense. However, recent developments in therapeutic immunology suggest that it may soon be possible to stabilize the disease process.

Damage to the blood–brain barrier allows inflammatory cells to enter the central nervous system. Migration depends on alterations in the expression of selectins on the endothelial cell surface and the induction of integrins on infiltrating lymphocytes. Together, these enable activated lymphocytes to adhere to the surface of cerebral vessels and to move transendothelially or between gaps in the tight junctions formed by astrocyte and microglial foot processes. In multiple sclerosis, the perivascular lymphocytic infiltration provides a source of cytokines that further increase permeability of the blood–brain barrier and result in microglial activation: in turn, this leads to phagocytosis of opsonized oligodendrocytes and their myelin sheaths. In-vitro studies of rodent glia suggest that these interactions can be a result of binding between receptors for C1q, C3b (CR1) and iC3b (CR3) and corresponding complement ligands on the surface of oligodendrocytes; under these circumstances, the lethal cytotoxic signal is delivered by local release of TNF-α [44]. In fact, other receptor–ligand interactions may be more important than complement in mediating damage by microglia to human oligodendrocytes, and hence in the context of multiple sclerosis. In particular, antibody in low concentration coating the surface of the oligodendrocyte or its myelin sheath may opsonize the target cell for lytic damage using the Fc receptors constitutively present on microglia [45].

The entry of immune cells into the central nervous system can be prevented experimentally by inhibiting the expression of integrins present on activated lymphocytes [46], and it should soon be possible to deliver immunological therapy that effectively inhibits T-cell accumulation in the central nervous system without compromising more general immune responsiveness, using cytokines [47, 48] or lymphocytotoxic monoclonal antibodies.

The effect of antibody-based systemic lymphocyte depletion has recently been assessed in a small number of patients with multiple sclerosis using gadolinium-DPTA enhanced magnetic resonance imaging as a marker of disease activity [49]. CAMPATH-1H, which targets the CDw52 antigen present on lymphocytes and some monocytes, causes a lymphopenia that lasts for several months, and this is associated with marked suppression of disease activity. The phase of lymphocytotoxicity is complicated by transient exacerbation in pre-existing, or
previously experienced symptoms, and circumstantial evidence implicates the cytokines TNF-α and IL-6 as mediators of conduction block in these partially demyelinated axons, perhaps through an effect on ion channels exposed by paranodal demyelination.

The possibility of effective treatments that limit the inflammatory process adds extra impetus to the development of strategies for repairing glial–neuronal arrangements in the demyelinated nervous system. Preliminary studies suggest that the adult human nervous system does contain oligodendrocyte precursors [50], and the failure of glial precursor cells to repopulate and usefully repair damaged nerve fibres may result either from lack of appropriate growth factor signals or from difficulty in penetrating the astrocytic scars that form around areas of demyelination. Even those cells that successfully penetrate gliopaenic areas in vivo might encounter naked axons and, in the context of inappropriate growth factor signals, differentiate inappropriately [8].

Should lack of precursors or physical impediments to migration prove an insuperable obstacle to endogenous repair of post-inflammatory lesions, remyelination will require cellular implantation of O-2A cells or pre-oligodendrocytes. Remyelination does occur experimentally when oligodendrocyte precursors are transplanted into gliopaenic regions. Astrocytes seem necessary in order to recreate local cellular arrangements of the damaged region, excluding Schwann cells, from competing for naked axons and acting as a local source of growth factors; and grafts need to contain sufficient numbers of oligodendrocytes, or their precursors, that are capable of differentiating and remyelinating naked axons [51, 52]. Growth factors can first be used to stimulate and increase the number of grafted cells, and it is worth speculating on the possibility of engineering the expression of cell surface receptors and the proliferative potential of grafted cells so as to maximize their capacity for accomplishing the biologically and metabolically complex tasks of restoring glial–neuronal arrangements in the adult central nervous system. One approach would be to harvest oligodendrocyte progenitors from the nervous system of individuals who are themselves to benefit from transplantation, and expand these in vitro using growth factors before restoring differentiated cells in increased numbers to strategically placed gliopaenic lesions.

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