Stem cell treatments and multiple sclerosis

Benefit through immunosuppression is realistic, but regeneration is more difficult

Few subjects in contemporary medicine have generated more excitement and controversy than stem cells. The potential of stem cells to generate different cell types opens up the possibility of new treatments for regenerating damaged tissue. Stem cells have attracted particular interest for their potential to treat neurological disease because tissues within the central nervous system cannot regenerate.

Multiple sclerosis is an autoimmune disease where the immune response targets myelinating cells (oligodendrocytes) within the central nervous system. It is characterised by focal inflammation, demyelination, and axonal damage. Multiple sclerosis differs fundamentally from the “classic” neurodegenerative diseases—Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease—in which neurones are irreversibly destroyed, because lost oligodendrocytes and thus myelin can be replaced spontaneously by adult brain stem cells. This natural regeneration (called remyelination) can be widespread during the early stages of multiple sclerosis, but it is not sustained, and the increasing failure of remyelination underlies the loss of axons that characterises disease progression.

Effective treatments for multiple sclerosis must therefore be able to limit damage by inhibiting the immune response and repair damage by replacing lost myelin, should intrinsic regeneration become inadequate. Stem cells potentially have a role in both areas, and treatments that limit damage are already used in clinical practice as detailed below.

Three types of immunomodulatory stem cell are being explored. The first type—haematopoietic stem cells—are bone marrow stem cells that generate all blood cell types. Intravenously delivered autologous haematopoietic stem cells have been used successfully to reconstitute the immune system after self reactive lymphocytes are removed by chemotherapy, which promotes self tolerance because the immune system no longer recognises the body’s own antigens as foreign, and effectively resets the immune system. This treatment carries the substantial risks associated with myeloablative therapy, and although it is used in many countries it is not currently licensed in the United Kingdom. Although the recent experience of using a non-myeloablative regimen before transplanting autologous human stem cells into patients was encouraging, the pretransplant regimen included drugs that may be effective immunomodulatory treatments in their own right (alemtuzumab and cyclophosphamide), which makes it difficult to work out the exact contribution of the transplant.

The second type—mesenchymal stem cells—are widely distributed in adult tissues and generate osteoblasts, adipocytes, and chondrocytes. They produce a wide range of factors that are immunosuppressive (and may also enhance endogenous remyelination), and it is these effects that have generated interest. Several trials to evaluate the use of systemically transplanted autologous mesenchymal stem cells in early relapsing and remitting multiple sclerosis are currently under way, including one funded by the Medical Research Council that is based in Cambridge and London.

Thirdly, neural stem cells are multipotent cells present in the developing and adult central nervous system that generate neurones and glia. Neural stem cells delivered systemically in animal models of multiple sclerosis have a negligible direct effect on repair but have unexpected immunosuppressive effects in the central nervous system and in peripheral lymph nodes. Phase I clinical trials using fetal neural stem cells are likely to be initiated in Italy in the next few years.

Stem cell treatments for repair in multiple sclerosis have not yet reached clinical practice, although they are effective in animal models of myelin diseases. Systemically delivered stem cells do not contribute sufficiently to direct repair, so injection of stem cells (or other cells with the capacity to myelinate such as Schwann cells or olfactory ensheathing cells) into areas of damage is the only currently feasible method for transplant mediated remyelination. However, such an approach presents obvious difficulties in a multifocal disease like multiple sclerosis, which explains the recent conceptual shift away from transplant based treatments towards drug based treatments aimed at enhancing remyelination. The recognition that many chronically demyelinated lesions already contain stem cells capable of carrying out repair has led to a phase I trial of antibodies that block lingo-1, a cell surface molecule that inhibits central nervous system stem cells from becoming oligodendrocytes, in an attempt to promote endogenous remyelination. The wnt intracellular signalling pathway also inhibits the differentiation of brain stem cells; drugs that inhibit wnt signalling might accelerate remyelination.

Three key messages emerge. Firstly, the main therapeutic benefit provided by current clinical approaches using stem cells is based on immunosuppression. However, the emergence of new drugs that have the same effect, such as natalizumab and alemtuzumab, means that it is essential to compare the risks and benefits of cell based immunosuppressive strategies with those of drug based approaches. Secondly, regenerative treatments based
Diagnosing serious bacterial infection in young febrile children

Measuring vital signs and assessing a child’s overall state of illness are the priority

In the linked prospective cohort study, Craig and colleagues present new evidence to guide clinicians who assess children with acute infections. Young children often attend emergency departments and primary care with acute infections. Most of these infections are self-limiting, yet identifying the small proportion of children who have a serious or life threatening infection can be challenging and a source of great anxiety for parents. Although routine childhood vaccinations have decreased the incidence of serious bacterial infection (currently 1% in primary care, 20% in emergency departments), the consequences of misdiagnosing the most serious infections can be dire.

We have reasonably good evidence for the diagnostic value of clinical features for conditions such as pneumonia and to a lesser extent meningitis, but for others such as urinary tract infections, we know little about which clinical features predict serious outcome. However, because children do not always present with discrete clinical conditions, more generic tools have been developed to identify children do not always present with discrete clinical conditions, more generic tools have been developed to identify those at greatest risk of serious illness. Some such as the Yale score have fallen from use, others such as the Manchestertriage system have limited discriminatory value, but overlooks the important group of children who lie between these extremes, and who may be the ones that clinicians have most difficulty deciding how to manage.

The diagnostic accuracy of these models expressed as the area under the curve ranged between 0.8 and 0.9 for pneumonia, urinary tract infection, and bacteremia, suggesting good predictive value. The strongest positive predictors of serious bacterial infection were a generally very unwell appearance, high temperature, chronic disease, and prolonged capillary refill time. For children with pneumonia, other predictors were coughing, difficulty breathing, abnormal chest sounds, and to a lesser extent tachypnoea, chest cracksle, and tachycardia. For urinary tract infection, the presence of urinary symptoms was by far the strongest indicator, whereas for bacteremia, tachycardia and crying were also strong indicators. However, only 64 cases of bacteremia occurred, so this result should be treated with caution, especially because other studies found conflicting results for crying. This is

on drugs that can mobilise endogenous stem cells are more promising than transplant mediated remyelination. Progress in this area is essential for patients with progressive disease where neurodegeneration, rather than neuroinflammation, dominates the clinical presentation. Thirdly, professionals must communicate to patients the fundamentally different applications of stem cells in the treatment of multiple sclerosis.

Failure to explain the distinction between stem cells for immunosuppression and for (currently unattainable) regeneration will increase the allure of unlicensed stem cell clinics offering (at great expense) treatments that have little realistic prospect of benefit.

In the linked study, Chamnan and colleagues estimate the effect of different screening strategies for identifying and treating people at high risk of cardiovascular disease.\(^1\) The study is a clear exposition of some simple ideas—that to get the most from the money spent on preventing heart disease, we should use all the information available to identify and target those most likely to benefit. Compared with universal screening of untreated individuals aged 40-74, the study shows that using a targeted strategy to identify the 20% of the population at highest risk can prevent 50% more cardiovascular disease; targeting the 40% at highest risk can prevent 74% more; and targeting the 60% at highest risk can prevent almost all cardiovascular disease. They may have overestimated the number of people treated under a universal strategy, however, because it is unlikely to be fully implemented. Targeted case finding is more manageable and may be more effective than untargeted screening.

Simple ideas can be big ideas. The simple idea in this study contradicts current government policy.\(^2\)

About 5% of people in the United Kingdom with cardiovascular disease are undiagnosed but eligible for preventive treatments. The best way to identify these people has prompted much research. Even knowing only age, sex, and diabetic status is enough to preselect those patients in the health survey for England who are most likely to need treatment.\(^3\) UK general practice records generally have more than this minimum amount of information on risk factors.\(^4\)

So how far have we got with implementing the obvious? In 2006, Sandwell Primary Care Trust started a programme of cardiovascular disease prevention based on targeted case finding.\(^5\) This programme identifies those
Few research studies have tackled the question of whether people bereaved in sudden or traumatic circumstances should view the body of the deceased. The linked qualitative study by Chapple and Ziebland found no hard and fast evidence about the therapeutic value of this practice, and their interviews with 80 respondents highlight a range of experiences and preferences. Above all else, their research shows how complex the subject is.

Previous interview-based research, psychological outcome measures, and expert opinion are conflicting, with some people arguing that viewing is necessarily conducive to healthy grieving, and others being more circumspect. Bereavement theories based on the notion that people move through stages of grief argue that a successful outcome depends on them accepting the reality of death before they can mentally and emotionally move back into their familiar world in a functional way. Those who, for one reason or another, become “stuck” in their grief have been considered at risk of pathological or complicated grieving that may require clinical treatment. It could easily be assumed that the sudden or traumatic death of someone close is more likely than other forms of death to lead to complicated grief.

Research into the Australian Granville train crash found that people who viewed the body had better outcomes in terms of psychological recovery, whereas a study of the Zeebrugge ferry disaster suggested that viewing may increase anxiety and distress in the short term, but that people who viewed the body tended to be less distressed in the longer term.

Yet these studies do not provide clinicians and other professionals with a model or framework to help them with advice about the benefits or problems associated with viewing, so it is still unclear whether viewing the body in these circumstances facilitates or complicates the grieving process, and whether the effect of viewing changes over time. Professionals are generally sensitive to the needs of the families and wish to protect them from further distress; encouraging people to view the severely...
Intelligence, education, and mortality

Are linked in several ways, so strategies to reduce inequalities should be broadly based

Socioeconomic status can be indexed in a variety of ways, but usually on the basis of an individual’s occupational social class, income, education, and housing tenure. Data accumulated over several decades show that these characteristics are associated with differences in health, particularly within affluent societies. But studies that take these socioeconomic variables—including psychological characteristics—also need to be considered.

6. Hodgkinson P. Viewing the bodies following disaster: does it help? Cruise Bereavement Care 1995, Part 1, 2A.
cause of social class inequalities in health.” This idea is based on two observations. Firstly, intelligence test scores—measured by individually or group administered tests—are socially patterned, whereby children and adults from socially deprived backgrounds typically have worse results. Secondly, lower intelligence test results across the life course, even in youth, are associated with higher mortality and rates of disease many years later. This is exemplified by data from a cohort of one million Swedish men who were administered an IQ test in late adolescence. After two decades of mortality surveillance during which 15,000 deaths occurred, we see a stepwise gradient between mortality and intelligence across the full range of intelligence scores such that lower intelligence is associated with the greatest risk (figure).

If Gottfredson’s thesis is correct, statistically adjusting the association between socioeconomic position and health for intelligence would eliminate any gradient. In framing her hypothesis so provocatively, Gottfredson has probably asked too much: it is unlikely that any single characteristic will completely explain the socioeconomic gradient in mortality. In addition to testing this hypothesis, Lager and colleagues also ask the opposite question: is the intelligence—mortality gradient explained by socioeconomic status? The answer to both of the above questions seems to be that controlling for either intelligence or education, partially but not completely “explains” the respective associations with mortality; these observations are supported by the current literature. However, using education as their primary marker of socioeconomic status raises concerns regarding colinearity: the correlation with intelligence is strong, so educational outcomes probably capture differences in cognitive ability.

Observational evidence should be interpreted cautiously because the extent to which one construct explains the effect of another depends on how precisely these two entities have been measured. In the US national longitudinal survey of youth, for example, the effect of a single measurement of intelligence on mortality disappeared completely after statistical control for socioeconomic circumstances that were measured 19 times during follow-up. In contrast, the effect of socioeconomic position was little affected by adjustment for the one-off measurement of intelligence. Presumably, if intelligence had been measured with much higher precision than socioeconomic position these data would have supported a reverse conclusion.

Surprisingly, Lager and colleagues also report a higher risk of mortality in older women with higher rather than lower intelligence in childhood. Being based on sub-group analysis, where spurious findings can surface by chance, this result remains suggestive. Furthermore, given that, in both men and women, education and mortality, and education and intelligence, have similar magnitudes of association, it is surprising to see an association between intelligence and mortality only in men. In female participants in the 1932 Scottish mental surveys, higher scores on intelligence tests administered at 11 years were associated with lower death rates up to 76 years later—Lager and colleagues’ discussion stated that this finding was limited to deaths occurring only during the second world war, but this was not the case. Until the apparent sex differences in these results are resolved, it is probably also too early to use Lager and colleagues’ results to make a conclusion about the state of the system integrity hypothesis—the notion that higher intelligence may be a marker of a general latent trait of a well functioning body.

If intelligence contributes to observed socioeconomic inequalities in mortality through a variety of mechanisms, then the efforts to reduce inequalities should continue to be broadly based, including educational opportunities and interventions initiated in early life. These may also elicit improvements in intelligence, although efforts to do so have so far yielded disappointing results.

Relation between IQ score and total mortality in 994,262 Swedish men (14,498 deaths). Multiple adjustment comprises age at testing, conscription testing centre, birth year, parental social class, height, body mass index, blood pressure (systolic and diastolic), and illness (psychiatric and somatic). The referent is the highest scoring IQ group (category 9). Reproduced, with permission, from Batty et al.

12 Whitty LJ, Deary IJ. Longitudinal cohort study of childhood IQ and survival up to age 76. BMJ 2001;322:1-5.