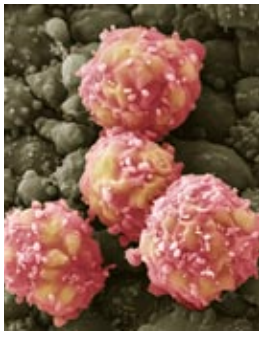
Stem cell treatments and multiple sclerosis

Benefit through immunosuppression is realistic, but regeneration is more difficult



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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.[1] This natural regeneration (called remyelination) can be widespread during the early stages of multiple sclerosis,[2] 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 myeloablation after chemotherapy, and although it is used in many countries it is not currently licensed in the United Kingdom.[3] 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.[4]

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.[5 6] 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.[7 8] 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.[1] Systemically delivered stem cells do not contribute efficiently 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.[9] The wnt intracellular signalling pathway also inhibits the differentiation of brain stem cells; drugs that inhibit wnt signalling might accelerate remyelination.[10]

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

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.

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Diagnosing serious bacterial infection in young febrile children

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

RESEARCH, p 842

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In the linked prospective cohort study, Craig and colleagues present new evidence to guide clinicians who assess children with acute infections.[1] Young children often attend emergency departments and primary care with acute infections.[2] 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.[3] 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.[4 5]

We have reasonably good evidence for the diagnostic value of clinical features for conditions such as pneumonia and to a lesser extent meningitis,[6] but for others such as urinary tract infections, we know little about which clinical features predict serious outcome.[7] However, because 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 Manchester triage system have limited discriminatory value, so recently more pragmatic systems such as the National Institute for Health and Clinical Excellence's "traffic light" system have been suggested.[8-10]

In the largest single study to date of clinical predictors of serious infection, Craig and colleagues examined 15 781 febrile illnesses in 12 807 children under 5 years of age presenting to a teaching hospital in Australia. Emergency department doctors recorded 40 clinical features and followed children for up for 14 days to ascertain clinical outcomes. Most illnesses (86%) were not bacterial infections (mostly non-specific viral illnesses), and 7.2% were clinically diagnosed bacterial infections (for example, abscess, impetigo, mastoiditis, and periorbital cellulitis). Serious bacterial infection occurred in 7.2% (1120) of febrile illnesses, of which urinary tract infection (543, 3.4%) and pneumonia (533, 3.4%) were the most common, followed by bacteraemia (64, 0.4%). Only 12 children had osteomyelitis, eight had septic arthritis, and six had meningitis.

Using a statistical modelling technique, the authors developed a diagnostic model that used 28 variables to discriminate children with serious bacterial infection from those with no bacterial infection or a clinically diagnosed infection. This approach of dichotomising outcomes (serious *v* not serious) is common to many diagnostic studies, 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 bacteraemia, 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 crackles, and tachycardia. For urinary tract infection, the presence of urinary symptoms was by far the strongest indicator, whereas for bacteraemia, tachycardia and crying were also strong indicators. However, only 64 cases of bacteraemia occurred, so this result should be treated with caution, especially because other studies found conflicting results for crying.[6] This is

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further illustrated by the lower area under the curve for bacteraemia in the validation set (5584 illnesses, 33 with bacteraemia), which reflects possible overfitting of the model.

Generally the prediction models were better at ruling out serious bacterial infection than were clinicians' judgments. Clinicians seemed to be as good as the model in regions of the receiver operating characteristic curve with high specificity (90-100%), which suggests that they are better at ruling in serious bacterial infections than ruling them out. Children with serious bacterial infections would usually be treated with antibiotics. In fact, Craig and colleagues found that only 66-81% were given antibiotics during their visit to the emergency department, and ultimately 108 children with such infections were not given antibiotics, and only eight of these children appeared to be unwell.

So what should we do differently now? This study reinforces the importance of measuring vital signs and assessing a child's overall state of illness. When evaluating children with difficulty in breathing, many of us rely on observing the chest for increased work of breathing, but these new findings suggest that auscultation for crackles or altered breath sounds might still be valuable. Crucially though, before relying on these signs in clinical practice, more specific definitions of these predictors and evidence of their inter-rater reliability are needed.[11]

The children in the study had a higher incidence of serious bacterial infection than those typically found in primary care, so it is unclear how well the models would operate in lower acuity settings. It was unfortunate that the model could not include the children with meningitis or bone or joint infection—these are rare but crucial to identify, so excluding them may limit the model's usefulness. This may explain why some features that clinicians should still search for, such as neck stiffness or petechial rash, were not included in the final model. In practice, clinicians use many different diagnostic strategies.[12] Calculating the probability of a condition on the basis of 28 predictors is only feasible with a computerised algorithm, for which popular handheld electronic devices and computerised records are invaluable. But before widespread implementation, we will need to have evidence showing the effect of using such a model on patient management and outcomes.

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Targeted case finding for cardiovascular prevention

The obvious and sensible choice compared with universal screening

RESEARCH, p 842

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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 75% 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.[3]

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.[4] This programme identifies those


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people most likely to be at high risk and invites them for assessment in their own practice by a project nurse. The pilot has been rolled out across the primary care trust and expanded to other areas. Similar programmes have emerged elsewhere. Software companies have helped by developing tools to preselect those at highest risk. National Institute for Health and Clinical Excellence (NICE) guidelines on lipid lowering recommend targeted case finding to identify people who are eligible for statins.[5] Cost effectiveness analysis comparing universal screening with targeted screening showed that the small additional benefits of universal screening could not justify the additional cost.[6]

So why does the Department of Health require primary care trusts to implement universal screening? Although their own modelling implied that universal screening was cost effective they chose not to compare it with targeted screening.[6] Universal screening is cost effective compared with no screening but not compared with targeted screening. Because the decision to advocate universal screening had already been taken, the appropriate questions were not asked of the model.

Where do we go from here? Primary care trusts that have implemented targeted case finding can continue to do so in good faith. Given that universal screening will take years to implement, it makes sense to prioritise people who are most likely to benefit. Are there better ways of targeting case finding? Chamnan and colleagues stratify patients for assessment using the Cambridge risk score.[7] It may be more efficient to use the same score for stratification and for treatment decisions, so using a cardiovascular risk equation might have advantages. Better still, benefit (or cost-benefit) equations could be devised to identify those likely to benefit most.

Cardiovascular disease is not the only underdiagnosed and untreated condition affecting patients—many others exist—and there are also grounds for using existing data to identify these. But before we investigate the complicated ideas we should implement the simple ones. There are untreated patients at high risk of cardiovascular disease, most of whom can be identified from their electronic primary care records. We should act on this information.

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Viewing the body after a traumatic death

Relatives should be given the choice, and time to consider their decision

RESEARCH, p 842

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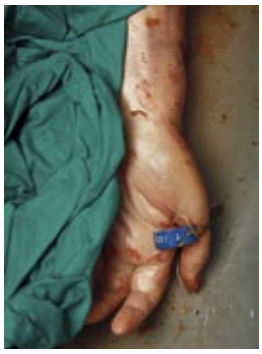
Few research studies have tackled the question of whether people bereaved in sudden or traumatic circumstances should view the body of the deceased. The linked qualitative study by Chapple and Ziebland found no hard and fast evidence about the therapeutic value of this practice, and their interviews with 80 respondents highlight a range of experiences and preferences.[1] 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,[2] and others being more circumspect.[3] 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.[4] 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,[5] 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.[6]

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



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damaged body of a loved one is a high risk strategy, and research to date has shown that although some people find viewing therapeutic others regret it (in the short term at least).

Chapple and Ziebland's study helps with this dilemma, because it finds that the value of viewing is significantly affected by whether or not the person thought that they had been given a real choice in the matter; those who regretted seeing the body were more likely to have been "forced" to see it. Although they do not specify situations in which choice may be lost, the most likely circumstance would be when identification is required. This is an important point that professionals would do well to reflect on when routinely asking a family member to identify the body. In such traumatic circumstances families do not always realise (and often do not take in the information given to them) that identification is a choice; this legal requirement can be fulfilled in other ways. This does not mean that families should be protected from the distress of seeing the body, but that if viewing is to be a choice it can occur in more conducive circumstances at a later time, when they have had the opportunity to consider properly whether they wish to view. That said, some family members are anxious to see their loved one as soon as possible in whatever circumstances (as reported by Awoonor-Renner in her autobiographical article on the death of her son [7]), but this is a choice rather than an obligation and, as such, should be respected wherever possible.

A further important finding from Chapple and Ziebland's study is that the language that bereaved people use when referring to the deceased may help professionals when guiding them about viewing. Speaking of the deceased by name or using a personal pronoun points to a continuing sense of relationship. In these circumstances viewing the body, if it is handled slowly and sensitively, may facilitate grief. Indeed, bereavement theories now suggest that people do not resolve their grief by "letting go" but may continue to engage in some form of relationship with the deceased that intensifies or lessens over time.[8] Being able to view the body and to "talk" with the deceased person is one way of dealing with "unfinished business," such as telling the person that you love them, or simply saying goodbye. To some people this may sound strange or morbid, but sociological studies of dying and death have shown that social death (and the termination of social relationships) rarely coincides with clinical death.[9]

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Listen to an interview with lead researcher Alison Chapple at http://podcasts.bmj.com/bmj/

Intelligence, education, and mortality

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

RESEARCH, doi:10.1136/bmj.c654 and doi:10.1136/bmj.b5282

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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. With the exception of few outcomes—incidence of breast cancer in women and selected injuries—poorer health is more common in poorer people.[1] Moreover, this gradient seems to be apply across the full socioeconomic range, rather than being confined to the most disadvantaged end of the spectrum. A worldwide reduction in these differentials has become a priority for many governments, including that of the United Kingdom,[1] and for the World Health Organization, which in 2005 launched the Global Commission on Social Determinants of Health.[2]

In endeavouring to ameliorate health inequalities, it is important to understand the underlying causes; two *BMJ* studies attempt to describe the gradient more clearly[3] and understand what factors explain it.[4] In a study from Norway (doi: 10.1136/bmj.c654), Strand and colleagues assess the relation between educational inequalities and mortality from 1960 to 2000.[3] In the second study (doi: 10.1136/bmj.b5282), Lager and colleagues investigated the association between early IQ, educational attainment, and mortality in Sweden.[4]

Despite these two studies being carried out in egalitarian societies, which have free national healthcare provision that is widely regarded as being among the best in the world, as has been shown elsewhere, socioeconomic gradients persist, even though they are less pronounced. So how does poverty "get under the skin" to exert its deleterious effect on health? Possibilities include access to resources, environmental exposures, health related behaviours, and their physiological correlates. But studies that take these preventable behavioural and physiological risk factors into account fail to eliminate socioeconomic gradients in health.[5] This raises the possibility that as yet unmeasured variables—including psychological characteristics—also need to be considered.

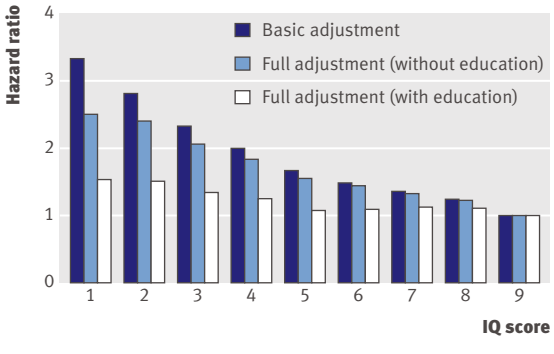
Recently, Linda Gottfredson proposed that intelligence might be "the epidemiologists' elusive 'fundamental

cause' of social class inequalities in health."[6] 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.[7] Secondly, lower intelligence test results across the life course, even in youth,[8] 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.[9] 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).[9]

If Gottfredson's thesis is correct, statistically adjusting the association between socioeconomic position and health for intelligence would eliminate any gradient.[10] 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?[4]

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.[10] 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.[9]

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.[11] 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.



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[9]

Surprisingly, Lager and colleagues also report a higher risk of mortality in older women with higher rather than lower intelligence in childhood.4 Being based on subgroup 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 deaths rates up to 76 years later12—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.[13]

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