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The Ethics of the Treatment of Spinal Cord Injury: Stem Cell Transplants, Motor Neuroprosthetics, and Social Equity

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Abstract

The intense desire for a “cure” in individuals with spinal cord injury (SCI) has resulted in the transplantation of stem cells and embryonic and other cell types into the injured spinal cord to enable limb function. We review the ethical issues concerning the procurement and use of embryonic stem cells. A brief survey of the current state of human SCI transplantation is presented. We explore the interface between basic science and the clinical management of SCI and discuss the ethical issues of therapy. At what point is it ethical to conduct human experiments when the experimental data is still at an early stage of development? Is it ethical to perform these operations on a vulnerable group of patients without adequate scientific controls and analysis of the results? Motor neuroprosthetics is developing rapidly and will enable limb movement controlled by the paralyzed patient and other device control such as wheelchairs and communication boards. How can there be a more equitable distribution of such expensive technology and other treatments of SCI? Both clinicians and scientists should be mindful of these complex ethical issues when undertaking pioneering therapies for patients with SCI.

Keywords

ethics; neuroprosthetics; repair; spinal cord injury; stem cells; transplantation

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The repair of the injured human spinal cord with resultant functional recovery is one of the major challenges of contemporary neuroscience. The pathophysiology of spinal cord injury (SCI) is complex, multifactorial, and multiphasic and is now being unravelled along with various repair strategies.[1-3] There have been rapid advances in the fields of stem cell biology, experimental strategies for spinal cord repair, brain–computer interface cognitive science, motor neuroprosthetics, and robotics, all of which are likely to make a future impact on the quality of life of patients with SCI. There has been a lot of investment in this basic research in the last few years, which has accelerated the pace of discovery. This has been boosted by advocacy from high profile patients such as the actor, the late Christopher Reeve, who wrote a moving account of his personal quest to find a cure for his quadriplegia.[4] The ethical controversies surrounding neural stem cell research are diverse and range from questions about embryo experimentation and cloning to the conduct of ethical human trials without the

exploitation of vulnerable patients who are desperate for a cure. The ethics of social equity and the support of the patient with SCI are also discussed.

Advances in Stem Cell Science

Stem cell research has been progressing intensely and is undergoing rapid development. The broad areas of research include efficient maintenance of cell line cultures,[5] conditions for successful induction of differentiation into specific cell types,[6] and analysis of functional incorporation of transplanted cells into organs without the development of unwanted side effects such as teratoma. Work has continued concurrently in rodent, primate, and human embryonic and adult stem cells. Unlike many other countries (such as Norway or Germany[7]), Australia has not specifically regulated the importation of human embryonic stem (ES) cell lines outside of general customs laws, leading to the commercial importation of many lines from overseas.[8] This has raised many questions about the use of poorly characterised and potentially unethically harvested cell lines from countries with weaker regulatory control. International initiatives such as the UK Stem Cell Bank aim to produce a standardised approach to such issues.[9] The Australian Stem Cell Centre has now made available two locally produced lines with a plan to release four more in the near future.[10]

Stem cells are not a purely embryonic phenomenon, and populations of precursor cell colonies for the purpose of tissue repair exist in most tissues. These cells, such as bone marrow, skin, and cord blood cells, are collectively termed adult stem (AS) cells. Research into the use of both ES and the less ethically controversial AS cells is being conducted concurrently. It remains scientifically unclear whether the latter will one day have the potential to replace the need for the former.[11] Though certain AS cell types have been shown to have considerable plasticity (i.e., neural,[12] haemopoietic, and bone marrow stromal stem cells), the complex cellular mechanisms for such behaviour remain incompletely understood, and the degree to which AS cells may form an alternative to ES cells remains controversial. Both have shown great potential for the treatment of cardiovascular,[13-15] endocrinological,[16] and neurological disease in animal studies and small clinical trials.

Stem Cells and SCI

The use of stem cells and the emergent field of regenerative medicine provide hope to patients suffering from SCI but also raise a myriad of complex ethical issues. Stem cells have been of great interest to researchers because of the combination of two unique attributes. First, with specific treatment they are capable of prolonged self-renewal through division. Second, controlled physiological exposure may influence them to differentiate into specific cell lineages. Stem cells thus create hope for sufferers of a wide range of conditions through the potential for repair and regeneration of diseased tissue. Stem cells not only show potential in the field of regenerative medicine but also provide a basis for generating experimental models for cells of specific types, thereby allowing close study of features of particular diseases and effects of proposed pharmaceutical or cellular therapies. The potential of stem cells to differentiate into a specific cell lineage is contingent upon their inherent degree of subspecialisation, and they are therefore classified on this basis as totipotent, pluripotent, multipotent, or unipotent (Table 1).

Enzmann et al. have reviewed the functional considerations of stem cell transplantation for spinal cord repair and critically evaluated stem cell sources and their mechanisms of action.[1] Each of the stem cell types pose ethical and technical challenges in terms of origin (embryonic vs. fetal versus adult derived tissue, allograft vs. xenograft), harvesting process (including morbidity of the donor site in autografts), purity of the cell population, immunogenicity, and tumorigenicity. Although each of these cell types may have potential for human application, it is likely that the most effective reparative therapy for spinal cord repair will come from

combinations of strategies such as neuroprotection to counter secondary injury, neural cells to replace lost circuitry, scaffolds to provide support for the regeneration of axons and cells, and methods to enhance axonal regrowth, synaptic plasticity, and inhibit gliosis.[3] These combined strategies are in an early stage of development.

Ethical Issues in ES Cell Procurement and Use

All totipotent and most pluripotent stem cells are derived from embryos and thus involve very difficult questions about the valid use of embryos for the purposes of medical research. Some ethical debate has focused on the question of whether embryos ought to be considered "persons" with all the attendant rights; but it is arguable that even if an embryo is not to be treated in the same way as a complete person, it should be accorded "profound respect."[17] In Australia, the recently reviewed Research Involving Human Embryos Act 2002 (RIHE Act)[18] allows licensed research on donated embryos excess to the needs of in vitro fertilisation (IVF) treatment prior to the 14th day of development. The licence is granted upon application to the National Health and Medical Research Council's (NHMRC) Embryo Research Licensing Committee, which considers, amongst other things, restricting the number of embryos to that necessary to the goals of the proposed application, the likelihood of significant advance that could not reasonably be achieved by other means, the ethical guidelines of the NHMRC, human research ethics committee (HREC) approval, and further matters prescribed by regulations.[8] Requests for embryonic research are thus treated as ethical priority disputes between the value of the embryo and the significance of the outcome of its use—weighing possible disrespect against potential benefits. The United Kingdom has a similar scheme under the Human Fertilisation and Embryology Act (1990),[19] conducted through a licensing scheme instituted by the Human Fertilisation and Embryology Authority (HFEA). So far, four licences have been granted by the NHMRC for research on embryos for the purpose of stem cell extraction.[20]

A currently topical question is whether researchers should be allowed to move beyond the restrictions of using excess IVF embryos and create new embryos solely for the purpose of research. In particular the use of somatic cell nuclear transfer (SCNT), the technique used to clone Dolly the sheep in 1997,[21] can be utilised to create genetically identical (and therefore immune specific) stem cell lines for transplantation research purposes (a process known as *therapeutic cloning*) as well as to create stem cell lines from donors who carry genetic diseases. ES cells have already been harvested from blastocyst stage cloned embryos in the United Kingdom,[22] and the technology is legal also in the United States (though not publicly funded), South Korea, and Singapore. The Australian Federal House of Representatives have recently, on the recommendation of a Council of Australian Government (COAG) Review Committee Report (*The Lockhart Report*),[8] passed a Private Member Bill[23] by conscience vote to overturn provisions of the Prohibition of Human Cloning Act 2002 (POHC Act)[24] and legalise licensed research involving the creation of embryos through SCNT, as well as techniques involving parthenogenetic activation of oocytes and cytoplasmic transfer.[25] Therapeutic cloning is not to be confused with reproductive cloning, which involves the implantation of a cloned embryo for the purpose of birth and remains illegal in Australia and most parts of the world.[8] Therapeutic cloning continues to raise a number of ethical debates including the exploitative and health risks to women involved with altruistic oocyte donation, problems with policing, and the potential for misuse with illegal (and currently scientifically unsafe) reproductive cloning, as well as issues surrounding the creation of new embryos in an unnatural biological context solely as a means to an end in medical research.

A further issue for consideration is whether the ability to create chimeras and hybrids in which human and nonhuman cells are combined should be legally permitted. Human–animal chimeras, involving the mixing of gametes or embryonic tissue with ES or AS, have the potential for improved efficiency of stem cell extraction as well the possibility of using animal

oocytes in favour of human.[26] Such activity is currently prohibited in Australia under the POHC Act.[24]

Therapeutic Ethics

Sufferers of SCI comprise a population of mostly young, previously active, and independent patients who have been struck down by sudden insult. These characteristics combined with a likely prognosis of lifelong dependence and supportive care mean that the potential hope offered by stem cell therapies has been met with extreme enthusiasm. The amalgamation of high stakes, desperation, and what the media portrays as a "stem cell revolution" has lead to considerable advocacy for hastened research in, and uptake of, stem cell technologies. Media campaigning by such celebrities as Michael J. Fox (who suffers from Parkinson's disease) and the late Christopher Reeve has lead to heightened awareness of stem cells as well as increased availability of research funding. As jurisdictions worldwide pass new laws on the regulation of embryo research and SCNT, increasingly advocates are pressing governments with the notion that a denial of access would prevent future relief to sufferers of countless medical conditions. Whilst stem cells offer much potential, as highlighted previously, we are dealing with a relatively new science. The hype surrounding the potential of stem cell research brings with it not only positive but also negative side effects. Of particular relevance to medical practitioners is the potential vulnerability of poorly informed patients, desperate for cure and well stocked on stories of miracle cures from the media. Medical professionals should remain vigilant against persons who seek to take advantage of desperate patients by subjecting them to invasive non-evidence-based procedures with considerable potential side effects, especially where financial incentives are involved.

Before transplantation procedures are performed on humans with SCI, adequate laboratory investigation, preferably in higher mammals, should be undertaken and the neurobiological principles of transplantation of a particular cell type or construct and the best techniques for reparative surgery of the spinal cord should also be established. The ethics for producing animal models of SCI are challenging, particularly in the higher mammals if the lesions become chronic. The animal rights movement is vigorously opposed to any such experiments, nevertheless there may be particular neurobiological questions that are optimally investigated in the higher mammals even if in a limited or hemi-cord model.

A critical question is at what point should transplantation and reparative surgery for human SCI begin. Is it ethically and scientifically sound to move from rodent models straight to the human without any higher mammal or primate experimentation? Whilst it may be preferable that the experiments be conducted on the higher mammals prior to experimentation on humans, we acknowledge this may not be always necessary and may delay the valid assessment of new techniques in humans. A key element is the strength and validity of the experimental neurobiology of the particular strategy before the human application is begun. It could be argued in some circumstances that not trying a new therapy in humans that has shown a lot of promise in the laboratory may be unethical; in situations where there is no alternative, one can legitimately move from a "mouse to a man" as it were. Getting this balance right is very difficult particularly when professional egos and intercollegiate and institutional competition are contributing to the drive to be pioneers in surgery for human SCI. Scientific curiosity and the altruistic aim of improving the human condition are also important motivators. Monetary reward may also be a factor particularly in those centers where there is limited scientific control or audit of these procedures and large sums of money are being charged for the procedures. This activity is to be abhorred and discouraged. There is also clearly great pressure put on the investigators from the SCI patients and their families for the surgery to go ahead. Desperate individuals with SCI will always be prepared to make large financial sacrifices and take significant personal risks to achieve some improvement in their plight. It is the function of

institutional ethics committees to prevent the inappropriate and premature application of these technologies.

Transplantation shortly after SCI or in a very young animal or in a quadruped is very different from transplantation in a human with chronic SCI, and great care must be taken when extrapolating results from animal experiments to humans.[27] Although neural transplantation of genetically engineered embryonic cells has resulted in some improvements in Parkinsonian motor disorder, there have been untoward and unpredicted adverse effects of the grafts, including uncontrolled dyskinesia in up to 57% of patients, which did not occur in the animal models.[28] Untoward effects would also be a consideration in transplantation for SCI. Hofstetter et al. recently observed severe side effects following transplantation of adult spinal cord-derived naïve neural stem cells (NSCs) into mice, with aberrant axonal sprouting and allodynia-like hypersensitivity of forepaws.[29] There is a risk of infection including meningitis with the transplantation of tissue into the spinal cord. Transplantation of cells and connective tissue matrix into the chronically damaged spinal cord may also increase the damage and worsen any residual neurological function. Other questions that remain to be resolved include the potential for immune rejection when nonautologous grafts are utilised, stratification of risks and benefits of therapies based on type and timing of SCI, and variability of study outcomes with animal age. Rejection of allograft material may eventually occur as the central nervous system is not an immunologically privileged site.[27] Considerable further study is required in animals to unlock these answers and also ascertain longer term potential ramifications, including the possibility of tumour formation Such studies should serve as a reminder of the complex nature of both the neural architecture and microenvironment as well as control of stem cell pluripotency.

As stem cell research turns the corner into the domain of human trials, research ethics bodies must remain objective under pressure to ensure that the ethical requirements of scientific validity, fair participant selection, favourable risk-benefit ratio, independent review, informed consent, and respect for potential and enrolled participants is adequately considered.[30] Specifically, institutional ethics committees must ensure that adequate safety has been previously demonstrated through specific animal experiments and that a well-considered system of informed consent is put in place to protect the vulnerable patient group already described. The considerable ethical cost of conducting safety trials on patients means that, where this is justified, researchers should do all that is possible to generate meaningful results with measurements of clear objective outcomes. Objective results of significant statistical power will be particularly difficult to obtain in the area of SCI due to individualistic injury types (likely to cause significant variability in architecture and microenvironment) and the fact that *significant* therapeutic gains might only be demonstrated by subjective patient experience, which may in turn be hampered by the placebo effect.

Although “sham” surgery has been carried out for Parkinson’s disease,[28] this would be impractical and would be unlikely to be accepted by SCI patients because the use of sham surgery randomisation and blinding of trials exposes control patients to medical risk *without* the potential for individual benefit. This creates what has been described as “tension between the highest standard of research design and the highest standard of ethics.”[31(p992)] The ethical allowance of such trials per se is a controversial area of medical ethics; however, they should only be considered in situations where no reasonable alternative research design exists and careful procedures have been put in place to minimise risk and the number of required participants.[32] Access to regular, independent medical review of participants needs to be made available and informed consent of the highest standard only should suffice, with patients being able to voluntarily withdraw from the trial at any point.

Whilst randomised controlled trials are the highest order of evidence-based medicine, these trials would be very difficult and impractical to set up for SCI. Careful evaluation of patients with adequate follow-up by independent assessors will produce an acceptable evidence base for judging efficacy. Because the numbers of cases would be relatively small at most centers, a multicenter trial would be preferred. A core assessment program was developed by committee and consensus for patients having intracerebral transplantation (CAPIT) for Parkinson's disease.[33] CAPIT includes standardized assessment tools and rating scales such that the patients can be compared pre- and postoperatively and across multiple centers to accurately assess the clinical efficacy of the transplantation. A similar assessment program is also needed for patients having experimental grafting or reparative surgery following SCI. We encourage the leaders in the field of human spinal cord repair to work together to produce such a consensus so that clear protocols are developed and a trial network established. The detailed clinical assessment of patients with SCI and the indications and suitability of the patient for surgery are the critical assessment tools that need to be developed and standardized. Assessments of patients should be done by observers who are separate from the surgery team and are therefore independent. An International Clinical Trials Workshop on SCI was held in 2004[34] and recommended guidelines for studies of humans with SCI have been published.[35]

How much should the consent to treatment be influenced by hope of improvement or cure? Exaggerated or distorted reporting to the media by physicians and scientists, and media oversimplification, dramatization, and hyperbole create unrealistic and unfair expectations of cures to those suffering the devastating consequences of SCI and their families. In contrast, Raisman stated, "If it is dangerous to raise hopes, then medical research will have to be either (a) totally irrelevant to human suffering, or else (b) it must be carried out in secrecy. Hope, like truth itself, cannot be qualified as false or true. Hope is hope.… To give hope is surely not a crime. The crime is to take it away."[36(p408)] Whilst we have sympathy for Raisman's argument, the degree to which the hopes of the patients and their families are raised depends on the messages they are getting from their own reading, the media reports, their acquaintances, and how the treatment is explained by the treating physicians and scientists. Getting the balance right in the continuum of unrealistic hope and realistic hope in terms of the explanation of a new treatment and its likely effects may be difficult, but the scientists and the treating physicians must be as honest in their appraisal of their technique and its potential risks as they can be. We believe it is ethical practice to give patients with SCI a degree of hope that a new treatment will help them, provided this is done responsibly and honestly.

Current Status of Transplantation for SCI in Humans

There is tremendous variety in the types of cells being used for transplantation in experimental animal models of SCI. Dr. Wise Young has summarised the types of cells being implanted, and these include olfactory (nasal) mucosa autografts (Portugal), fetal olfactory ensheathing cells and neural stem cells (Russia), adult olfactory ensheathing cell autografts (Australia), fetal olfactory ensheathing glial cell (China), bone marrow stem cell autografts (adult; Brazil, China), fetal spinal cord transplants (USA), fetal Schwann cell transplants (China), porcine fetal neural stem cell transplants (USA), adult activated macrophage autografts (Proneuron Company, Israel, and USA), adult peripheral nerve grafts (Ecuador, Taiwan), and umbilical cord blood transplants (Korea, Mexico).[37]

We know of patients with SCI having transplants of autologous olfactory ensheathing cells in Brisbane, Australia, with no results published as yet. Dr. Carlos Lima from Portugal is transplanting autologous olfactory epithelium into patients with SCI and offers in addition an intensive postoperative rehabilitation program. Lima et al. reported seven patients treated with olfactory mucosa autografts 6 months to 6.5 years after injury. All patients improved in motor function, and six improved in sensory function, two had return of some bladder sensation, and

one had return of voluntary contraction of the anal sphincter. On magnetic resonance imaging (MRI), there was moderate to complete filling of lesion sites. The morbidity was minor, and they concluded that this procedure was feasible, relatively safe, and potentially beneficial.[38]

In Argentina, bone marrow-derived mesenchymal stem cells were co-cultured with the patient's autoimmune T cells (AT) and purported to differentiate into NSCs. AT cells were infused 48 hours before the transplant to generate an "inflammatory environment" for the NSC cells, which were then injected into an artery feeding the lesion site. Two patients with SCI received these NSCs and neurorehabilitation for 6 months. There was a gain in sensory and motor level in both patients. There were no adverse events.[39]

It should be noted that a long period of intensive and regular neurorehabilitation with experienced therapists and a well-motivated patient with a partial SCI may lead to some gains in neurological function irrespective of any graft. There is the need to integrate the prolonged rehabilitation into these studies well before the grafting procedure or as a control group with neurorehabilitation without the transplantation, otherwise it will be very difficult to tease out the inevitable placebo effect and the genuine gain that may follow intensive rehabilitation from the effects of any graft or surgery.

Robert Smith, a 46-year-old paraplegic man from Harrison Township, was the first American to travel to Beijing, China, in 2003 to have a transplant of aborted fetal olfactory cells injected above and below the injury site by Dr. Hongyun Huang. Dr. Huang stated at that time he had performed more than 300 cases; the operation took 2 hours and cost $20,000. Smith said that "within hours of the procedure, [he] could wiggle toes he couldn't move before, breathed better and had a stronger lefthand grip." When asked how much recovery he expects to achieve, Smith said, "I think the sky's the limit."[40] Further personal statements also appear on the China stem cell Web site[41] with reports of less spasticity, improved respiratory function, improved motor and sensory function, improved bowel sensation, improved sweating, and the ability to walk with braces following rehabilitation, whereas this ability was not present prior to the surgery. These Internet blogs will hold significant sway over the vulnerable SCI population and are very similar to the initial enthusiastic personal testimonials that appeared after the first transplantation procedures for Parkinson's disease. Unfortunately the reports of success of this transplantation operation in China are all anecdotal. The lack of vigorous scientific control of these patients including strict follow-up protocols and full documentation render these operations highly questionable with respect to ethical principles.

Three independent physicians from the Geffen School of Medicine, University of California–Los Angeles, have studied seven of the patients having Dr. Huang's surgery in China preoperatively and up to 1 year postoperatively using standard disability rating scales and MRI. One of the patients with a high cervical lesion had a cerebral injection of the cells. Complications including meningitis occurred in five patients, and transient postoperative hypotonia may have accounted for some physical change. No clinically useful sensorimotor, disability, or autonomic improvements were found. The conclusion was that the phenotype and fate of the transplanted cells was unknown. Perioperative morbidity and lack of functional benefit were identified as serious clinical shortcomings. It was recommended that physicians should not recommend this procedure to patients.[42] Dr. Wise Young, the director of Rutgers University's Keck Centre for Collaborative Neuroscience, now plans to set up various trials of SCI therapies in China with careful follow-up and have the trials registered in the United States; he states these trials will be much more economical in China compared with the United States.[41]

Motor Neuroprosthetics and SCI

Staggering advances are occurring in the field of motor neuroprosthetics where a device decodes brainwaves from the motor cortex into electrical signals that are transmitted to a computer, which is in turn connected to a motor device to move the limbs at the intent of the patient.[43] This has application for patients with SCI, stroke, limb loss, and neuromuscular disorders; this application may allow operation of a communication board, a wheelchair, or a prosthesis. Some prosthetic control has been achieved with opening and closing of a prosthetic hand and rudimentary movements with a multi-jointed robotic arm in a patient with quadriplegia.[44] The patient needs to train to control the device. Sensory feedback has not yet been developed but will be necessary for the controlled movement and functionality of paralysed limbs. Although the benefits of these devices for the patient with SCI are incalculable, the cost of these devices is currently prohibitive. Who will receive these devices and who will decide? Will the cost be reduced to generally affordable levels? Will it become a responsibility of governmental health authorities to subsidise the cost of these devices for the individual who cannot afford them? Where does the priority for this cost sit in relation to hospital budgets for the routine care of SCI patients and at a societal level in relation to more pressing health resource issues? How will the SCI group lobbying pressure affect this resource allocation? These are some of the difficult ethical questions that arise from the development of such expensive technology, which can benefit only a few individuals in society.

Social Equity and the Support of the Patient with SCI

Maldistribution of health resources and the divide between the rich and poor is a major ethical and medico-political issue when considering SCI. In Australia, patients who have transport accident or workers' compensation insurance have access to home modifications, equipment, care, and support and have greater social and financial security for the rest of their lives than those people who are reliant upon meager or no government support. This is clearly inequitable and deprives the society of the valuable contribution that the poorly supported patient might make with more support.

The New Zealand Accident Compensation Commission is responsible for all people with SCIs, whether due to trauma or not and whether compensable or not. This universal insurance system promotes equity of medical treatment. Patients have access to the most appropriate equipment, home alterations, assistance to return to work, and access to carer support on an equal basis regardless of the cause of the injury. A similar situation exists in Sweden, where there is universal coverage for all SCI cases. This includes the provision of a pension, housing, transport, attendant care, and support for further education and return to work. It must be remembered that accidents are not respecters of intelligence, physical ability, status in society, wealth, or age. All people are at risk of SCI or of a medical condition that could leave them with paraplegia or quadriplegia. All societies should work toward achieving equity and opportunity for people with SCI.

Overall, very few SCI patients will be able to receive reparative surgery or expensive neuroprosthetics using the brain–computer interface, assuming these therapies are shown to be efficacious and their developmental cost can be reduced. The aid of a nonhuman primate assistant may give a person with quadriplegia some independence but is a very limited resource. In the future, robots will be able to do household chores for the disabled, but this will be an expensive and limited resource for the foreseeable future. There will likely be an increasing disparity in resource allocation for patients with SCI.

On a global scale, many patients with SCI in the developing world are not even receiving the basic care that is readily available in advanced countries; many of these patients, particularly

persons with quadriplegia, will develop multiple complications including joint contractures, pressure sores, and chronic urinary sepsis and renal failure with a significantly shortened life span as a result. Rehabilitation facilities are usually nonexistent or very limited in developing countries. Health aid to the developing world should include provision for the care and rehabilitation of SCI patients and other patients with disability.

Conclusions

Stem cells and regenerative medicine bring new hope to persons with SCI, but practitioners and researchers should be mindful of the complex ethical issues involved with this novel treatment. Difficult questions are being asked about the ethical validity of creating new embryos purely for the purpose of research, as well as new cellular techniques such as SCNT, the creation of chimeras, parthenogenetic activation, and cytoplasmic transfer. Such issues are raised in the context of a global biohealth economy that is more often seeing cellular material as intellectual property, capable of being the subject of trade.

We are moving closer to the day when repair of the injured spinal cord that results in useful functional improvements will be possible. It is the source, the harvesting, and the manipulation of stem and other precursor cells, the translation of the laboratory findings to the human with SCI, the selection of patients, experimental trial design, and issues of resource allocation that provide major ongoing ethical challenges. We hope this article will encourage the pioneers in this field to approach their work with the highest ethical standards and scientific integrity. It is clearly possible from the examples we have given for even the best intentioned ambitious investigator to carry out procedures with little scientific evidence from the laboratory to support their use in a particularly vulnerable group of patients who may have little else to pin their hopes on. It is technically straightforward to inject cells near to or within an SCI site, but those who do this must consider the evidence base and the neurobiology before embarking on such procedures. If stem cells are to be transplanted into the injured spinal cord, then great care needs to be taken with the assessments of the patients ensuring adequate periods of follow-up with standard disability scales that have been chosen by expert panels. The effects of intensive rehabilitation also need to be appraised in any such studies.

There was a great flurry of activity and enthusiasm with adrenal and fetal neural transplantation for Parkinson’s disease that initially showed great promise, but with the lack of efficacy, the ethical problems, and the side effects, the numbers have fallen and the procedures are performed in only a select few specialised centres capable of the careful scientific analysis of these experimental procedures. This is as it should be. There were many desperate and ultimately disappointed patients as a result of this process. Whilst we fervently hope that the promise of these new biologic treatments for patients with SCI will be realised, we also hope that transplantation for SCI does not follow the same pattern as occurred in Parkinson’s disease and that the lessons have been learnt.

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Table 1

The classification of stem cells

Types of stem cells	Potential
Totipotent	From the pre-blastocyst embryo, capable of differentiation into all cell types including placenta
Pluripotent	From the inner cell mass of the blastocyst (embryonic stem cells [ES]), primoridal germ cells (embryonic germ cells [EG]), foetal cells or cord blood, capable of differentiation into endodermal, ectodermal, or mesodermal cell types
Multipotent	Differentiation within a particular cell lineage such as mesenchymal stem cells or bone marrow
Unipotent	Able to produce one cell type only (e.g., respiratory epithelium, cornea, etc.)