commentary

Stem Cells: Public Policy and Ethics

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Abstract

Debate on the regulation of human stem cells needs to bring together scientific, ethical and policy considerations if it is to be adequately informed. Scientific issues of importance include the relevance of the environment in appreciating the extent of stem cell plasticity, and the relative potential of embryonic and adult stem cells to produce other cell types. An awareness that blastocysts (early embryos) and stem cells in the laboratory are pluripotential and not totipotential has implications for ethical and policy debate.

The regulations on stem cell research are reviewed, showing that four positions have emerged. Position A corresponds to the prohibition of all embryo research, position B confines the use of embryonic stem cells to those currently in existence and therefore extracted prior to some specified date, position C allows for the use and ongoing isolation of embryonic stem cells from surplus in vitro fertilization embryos, and position D approves of the creation of human embryos specifically for research. Position B which has been adopted by the United States, Germany and Australia (with subtle differences between them) and which is regarded as a compromise position, is critiqued. This is principally on the basis that, in spite of claims made about it, the ongoing destruction of human embryos will continue. This is because these countries allow in vitro fertilization programs, inherent within which is embryo destruction. It is argued that position C would be a more consistent ethical position for these countries. The possibility of moving to position D is also raised.

Keywords
Human embryonic stem cells; Adult stem cells; Stem cell plasticity; Blastocyst; Human embryo research; Policy guidelines

Introduction

Human embryonic stem (ES) cells burst into the limelight in 1998, with their first successful derivation. The attention they have subsequently received, on account of their potential to alleviate a range of debilitating illnesses, and give rise to a new genre of medical therapies, has been bewildering (Towns and Jones, 2004). These positive vistas have been counter-balanced by a welter of concerns, ranging from the ever-present ethical dilemmas precipitated by the moral status of the human embryo, to a confusing array of conflicting claims regarding the scientific superiority of adult stem cell sources. Unfortunately, the calibre of ethical debate has been detrimentally affected by failure to appreciate the subtleties of the scientific background.

For many the least controversial course of action would be to use adult stem cells, and so the pressures on scientists to emerge with evidence demonstrating that their potential is at least as great as that of ES cells are formidable. Such a course of action is appealing to some since it appears to circumvent the ethical problems raised by using human embryos as the source of the stem cells. Unfortunately, scientific uncertainty abounds in this very young field, where core concepts are

being refined almost daily. Consequently, it is of concern when policy makers and governments, in addition to ethicists, philosophers and theologians, demand definitive scientific answers in this rapidly changing terrain. These demands demonstrate a profound misunderstanding of the intimate interrelationship between science, ethics and public policy. The results of this misunderstanding are clearly seen when the manner in which societies regulate stem cell technology is examined.

The Science of Stem Cells

It is now well recognized that stem cells are unspecialized cells, which have the ability to renew themselves indefinitely, and under appropriate conditions can give rise to a variety of mature cell types in the human body. They have multiple sources, ranging from embryos (the inner cell mass [ICM] of blastocysts), to umbilical cord blood, fetal tissues, and a variety of adult tissues. For the sake of simplicity stem cells from all sources other than embryos are termed adult stem cells (as opposed to ES cells). While this distinction is a fundamental one, especially in ethical debate, it is less clear than frequently thought, since the identification of stem cells is far from cut-and-dried, and depends to some extent upon the environment. Indeed, there appears to be a dynamic relationship between stem cells and their immediate microenvironment – the stem cell niche (Watt and Hogan, 2000).

This niche is characterized by numerous external signals, including those derived from chemical factors, cell-cell interactions, and relationships between cells and the surrounding tissue (Watt and Hogan, 2000). These, in their various ways, all have an impact on stem cells, because they affect the precise directions in which they subsequently develop. It is also interesting to note that stem cells taken out of their original niche and exposed to an entirely new environment can potentially differentiate into the cell types typical of that new environment (Wu *et al*, 2002). In other words, stem cells demonstrate considerable plasticity.

While this is a fascinating finding, it would be foolhardy to jump to the conclusion that it renders the use of ES cells unnecessary. There are a number of scientific reasons for this (Towns and Jones, 2004). Even though there are a few confirmed reports of truly pluripotential adult human stem cells (National Institutes of Health, 2001; Committee on the Biological and Biomedical Applications of Stem Cell Research, 2002), what is required is far more understanding of the fundamental biological issues raised by this research. Scientifically, therefore, research with both adult and embryonic sources should continue, bearing in mind that adult stem cells are more problematic than their embryonic counterparts.

In light of this evaluation, considerable care should be employed in advocating, on allegedly scientific grounds, the advantages of adult over embryonic cells as the source of replacement tissues. In other words, it is short-sighted to attempt to circumvent discussion of the moral status of the blastocyst by concentrating on the scientific potential of adult stem cells alone. What is even more important is that ethical debate and policy regulations need to take into account whether the blastocysts in question are located within an environment appropriate to their further development. If the environment is not conducive to such development, this may have considerable ethical implications for research aimed at isolating ES cells from such blastocysts. Unfortunately, up to the present, the role of the environment has failed to feature in debate on policy development.

Providing a Context for Blastocysts and Stem Cells

This confronts us with the notion of the importance of both the micro- and macro-environments on the identification and plasticity of stem cells. These have implications for notions of totipotency (capability of forming a new individual) and pluripotency (capability of creating all an individual's cell lines but not the individual itself). This distinction is more limited than frequently thought, since it fails to take account of the environment, a factor relevant to our assessment of both the blastocyst (the early embryo at 5-7 days gestation) and ES cells.

Before any cells can be considered to be totipotent, it has to be established that they are capable of giving rise to all three germs layers and, therefore, to all the major organ and tissue types of the individual. This requires the presence, not only of the ICM from which the germ layers and hence future individual are formed, but also of the trophectoderm cells which give rise to the layers of the placenta. These extraembryonic tissues are a crucial source of signaling molecules and must function optimally for the differentiation of both embryonic somatic cells and for the establishment of germ lines (Surani, 2001). In other words, the trophectoderm

as well as the ICM cells are required to establish totipotency (Jones and Telfer, 1995). However, if a viable fetus is to result, totipotency also requires successful implantation and development within a woman's uterus.

In the absence of all these conditions ES cells are merely pluripotent, possessing the capacity to create all the cell lines of the fetus, but not the fetus itself. In the laboratory environment they are incapable of totipotency, since they have been removed from the context of the trophectoderm, let alone that of the uterus (Towns and Jones, 2004). It is inaccurate, therefore, to view ES cells as totipotent (Abkowitz, 2002).

What emerges from these considerations is that, within the laboratory environment, blastocysts are 'potentially totipotent' rather than 'actually totipotent' (Towns and Jones, 2004). In this, they stand in stark contrast to their counterparts within a woman's body. It is unfortunate that ethical debate has concentrated almost exclusively upon blastocysts (embryos) as discrete autonomous entities, as though their potential to become future individuals can be realized regardless of environmental considerations. Since a notion such as totipotency is a function of the environment both at the microscopic and macroscopic levels, the consequences of context for moral debate are considerable.

We are now in a position to assess some of the policy issues encountered in regulating stem cells. It will emerge that some of the above scientific points play little if any part in the formulation of policies. We shall return to this in the final section.

Overview of Public Policy

In an extremely helpful review of regulatory practices, Knowles (2004) divided countries into three groups: embryo research is prohibited; *in vitro* fertilization (IVF) embryos can be used for human ES cell research; embryos can be explicitly created for human ES cell research by fertilization and/or somatic cell nuclear transfer (SCNT or 'research cloning'). In discussing the variation in regulations, Knowles (2004) considers that in Europe the more liberal regulations are found in countries with Protestant religious traditions, and the more conservative or restrictive ones in Catholic countries. However, this simple distinction is beginning to break down with some of the traditional Catholic countries, like Spain and France, beginning to allow research on human embryos. It is also of note that the Protestant – Catholic distinction does not apply in the United States.

Knowles (2004) regards a number of Asian countries as having lenient regulatory provisions and suggests, along with Gershon (2003), that in Singapore at least this may be due to the significant commercial potential of stem cell technologies. No hint is given as to any cultural or religious reasons underlying these liberal regulations. By contrast, in Iran and other Islamic countries, Knowles (2004) recognizes that, by placing ensoulment of the fetus at around 120 days, the use of surplus IVF embryos in research is permissible within a Muslim context. Israel's liberal regulations are put down to the government's enthusiasm for the commercial potential of stem cell research, although Jewish theological stances on early development may prove equally important.

Useful as this summary of current (and rapidly changing) regulations is, it leaves unanswered pertinent questions regarding the nature of the ethical, theological and cultural debate behind the regulations themselves. Even this brief summary highlights the inadequacy of generalizations, and provides no hint on the consistency or otherwise of the ethical arguments employed to back up the various positions. Use of the designations conservative and liberal is also unhelpful, since they are far too crude to provide substantive insight into individual positions. Further, the use of just three categories ignores a major theme in much current debate – the presence of a time element in some of the regulations.

Four Underlying Positions

We argue that four regulatory positions can be identified. These vary from position A, the prohibition of all embryo research, to position D, the creation of human embryos specifically for research – encompassing both fertilization and SCNT. In addition, there are two intermediate positions. Of these, position B confines the use of ES cells to those currently in existence, in that they were extracted prior to some specified date, thereby prohibiting the extraction of ES cells and the utilization of ES cells derived in the future. Position C allows for the use and ongoing isolation of ES cells from surplus IVF embryos.

Of these four positions, we shall concentrate on position B, which has been adopted by the United States, Germany and Australia (with subtle differences between them). This is a

particularly interesting position since it can be regarded as a classic compromise stance, with its dual aims of purportedly protecting the human embryo, while also encouraging some scientific research on human ES cells.

Current legislation in Germany prohibits any research on embryos that leads to their destruction. However, the import of existing cell lines (those extracted prior to 1 January 2002) derived from surplus IVF embryos is allowed, provided that the intended research has clinical goals unachievable by other means (Deutscher Bundestag, 2002). Australia allows embryonic stem cell research to be conducted as long as it is on existing stem cell lines derived from embryos surplus to IVF requirements, and created before 5 April 2002 (*Research Involving Human Embryos Act 2002*).

While the United States government has no legislation as such to regulate embryonic stem cell research, federal funding is restricted to research that uses ES cells derived from surplus IVF embryos prior to 9 August 2001. These guidelines prohibit the ongoing extraction of stem cells, and the creation of embryos for research (National Institutes of Health, 2003). In contrast, there are no federal restrictions on privately funded research, which is subject to state laws alone. States vary in their guidelines, with some, such as California and New Jersey, encouraging both embryonic and adult stem cell research.

Position B – An Assessment

Position B is an alluring one, since in one stroke it gives the impression of placating both sides of an exceedingly contentious argument. Research can continue, with at least a modicum of governmental support, although the severity of the scientific limitations under which it is being carried out will not be evident to most people. What is more, those advocating protection of human embryos can feel that their case has been supported, by the prevention of the destruction of any more embryos for research (and possibly therapeutic) purposes. However, we view this way forward as little more than a political construct, with a very unconvincing ethical basis.

The striking feature of this position is that, while it is based on the moral unacceptability of embryo destruction, it allows the use of existing cell lines. Since these have been obtained through the destruction of embryos, the policy implicitly accepts the legitimacy of embryo destruction, albeit in the past. If this were not the case, no research of any description utilizing human embryos or ES cell lines would be tolerated. Position A, with its prohibition of any such research, would be the stance of choice. On the other hand, an unwillingness to move to position C, permitting the extraction and utilization of ES cells, demonstrates that the destruction of human embryos is deplored. Position B represents an uneasy compromise, made possible only by accepting the use of 'ethically tainted/unethically-derived' material.

This is not a new phenomenon, but is one that has been debated in various forums since the events of the 1930s and 1940s in Germany. Examples include the use of anatomical specimens or data derived from unethical experiments on human beings during the Nazi era, or more recently, the use of neural tissue obtained from aborted fetuses for the treatment of patients with Parkinson's disease. These are examples of instances that raise the concept of moral complicity.

These are relevant for the ES cell debate since, if it is contended that the extraction of stem cells from embryos is unethical (necessitating, as it does, the destruction of embryos), moral complicity demands that any subsequent use of the extracted tissue will also be unethical. There is an indissoluble ethical link between the two, with the origin of the material affecting whatever may later be done with it. Its unethical origins in embryo destruction ensure that any resulting ES cell research is mired in maleficence. Is there any way around this?

There may be. A long-established position is to argue that the unethically-derived material from the Nazi era can be used ethically on condition that the wrongs are acknowledged and recurrence is prevented (Weitzman, 1990). A similar argument, but omitting these provisos, has been employed to justify the use of aborted fetal tissue in fetal neural grafting (Jones, 1991). The German, Australian and United States regulations provide parallels with this approach, since although they imply moral wrong-doing, they also aim to legitimize restricted use of ES cells.

However, if moral complicity is accepted in its entirety, no separation exists between the embryo destruction and the ES cell research; the latter is as unethical as the former. Prohibition, as in position A, is the only acceptable path. On the other hand, if a separation can be forged between the two, and if the unethical nature of the embryo destruction is

acknowledged with efforts being made to prevent further embryo destruction, it may prove possible to allow limited research on embryos. This is what the German, Australian and United States guidelines set out to accomplish, by confining research to embryos or stem cell lines already in existence (position B). The prohibition of any future ES cell extraction means that any further destruction of embryos is outlawed. In a very neat way, past wrongdoing is acknowledged and future wrongdoing is prevented. But, in our view, there is a problem.

The prevention of future embryo destruction, which lies at the heart of this response to moral complicity, fails miserably. And this is for one major reason. Embryo destruction is accepted in all these countries as part of their extensive IVF programs. All such programs are responsible for the production of surplus embryos, most of which will be discarded and hence destroyed. Given the frequency of this practice, what is the rationale for basing stem cell regulations on the premise that embryo destruction is unacceptable? The linkage between the two situations is inescapable, leading to the ironic conclusion that restrictive ES cell guidelines do nothing other than prevent research on embryos that are slated for destruction.

In the case of the United States guidelines an additional consideration applies. The intense debates over these guidelines, and the Herculean efforts to protect the human embryo have limited applicability, that is, to the public sector. This is the domain of federally funded research. The private sector, where so much of the research is being undertaken, is exempt, and researchers here are free to use human embryos for research purposes, and therefore extract ES cells. Consequently, in the United States, despite the vociferous high-level political machinations that are undertaken, human embryos will continue to be destroyed in both IVF programs and in privately funded ES cell research. The ethical dissonance is notable.

Surplus Embryos as a Source of Embryonic Stem Cells

There are additional issues to be considered. The model provided by neural grafting in Parkinson's disease has already been alluded to, because similar arguments occur here with respect to moral complicity. What is significant about the neural grafting model is that complicity in the original abortion is avoided because consent to abort the fetus is given on the grounds of maternal or fetal welfare. Quite clearly, the reasons for the abortion and the manner in which it is carried out have nothing to do with the research or therapy on the patients with Parkinson's disease. Indeed, the ethical parameters ensure that there is complete separation in practice between the two (Jones, 1991). What lessons can be learned from this for ES cell research?

At first glance there is a problem, since the separation cannot be nearly as distinct in ES cell research. This is because the process of acquiring ES cells actually destroys the embryo (Doerflinger, 1999). The parallel in neural grafting would be if the process of acquiring the neural tissue from the fetus killed the fetus, whereas in practice it is the abortion that does this.

However, this ignores the source of the embryos. ES cells can either be obtained from embryos created specifically for research purposes, or from embryos surplus to IVF programs (Thomson *et al*, 1998; Reubinoff *et al*, 2000). The objection raised above only applies to embryos deliberately created for research; the research kills embryos that would not have existed if it were not for this particular research program. By contrast, quite a different situation holds when the embryos in question are surplus to the requirements of IVF treatment. Their existence is independent of this or any other research program, and they will eventually be destroyed regardless of any research interests. A decision to use such embryos for research purposes is completely separate from a decision to discard them, because they are surplus to the reproductive needs of the couple from whom they were obtained.

What are the reasons against using embryos from IVF sources for research purposes, and in particular for extracting ES cells? There appear to be no convincing ethical reasons against this. Nevertheless, what we have seen is that some countries have adopted an intermediate position with built-in time-lines (position B). Surprisingly, this position does not seem to stem from a clearly formulated ethical base, but amounts to a desire to protect the human embryo while also allowing the continuation of potentially important research. Unfortunately, it fails on both counts. Its lack of a convincing ethical base opens it to criticism from the conservative side on the grounds that it fails adequately to protect human embryos. Alongside this, the restriction of scientific research to a set number and type of embryos or stem cell lines hampers the dimensions of this research (Roccanova *et al*, 2001; Kennedy, 2003). Such

restrictions may have profound implications for scientific understanding and the development of scientific concepts, and even for therapeutic applications. In other words, it is a compromise that is fundamentally flawed on both ethical and scientific counts.

In terms of the principles outlined, a more consistent approach for position B countries would be to adopt position C regulations. This would allow them to hold a protective view of the human embryo, within the framework of a more consistent ethical stance. This is because ES cell research is limited to surplus embryos from IVF programs, with a procedural separation between the initial decision to discard embryos and the subsequent decision to donate them for research. This allows both the utilization and extraction of new ES cells, and eliminates arbitrary time limits on extraction. This is not an ideal solution, but in terms of the principles so far outlined, it is a far more satisfactory one than that enshrined in position B.

Ways Ahead

From this account it emerges that, in scientific terms, there is a need to experiment upon ES cells as well as adult stem cells. While any country is at liberty to prohibit such research, the state of the science points to its necessity if optimum progress is to be made in understanding the scientific and clinical potential of stem cells. For all other countries regulations are needed to cover their use. It has also emerged in the preceding sections that environmental considerations are integral to ethical debate. How are these considerations to be taken note of in policy regulations?

We have already argued that position B cannot be supported on ethical grounds, even in countries that do not wish to destroy further embryos. Hence, even for them, position C appears to be an interim position of choice. But what about the creation of embryos for research purposes, either by fertilization or SCNT, and the move to position D?

The environmental argument demonstrates that blastocysts in the laboratory are not totipotent, regardless of their source. They have no chance of becoming individuals unless transferred to a woman's uterus. Since this is not the intention when dealing with surplus IVF embryos or those created for research purposes, research on these embryos will not destroy embryos that would have become fully-fledged humans. Even their pluripotency will be lost if they are not used for research or therapy.

Even if embryos (blastocysts) that could never realize their totipotency are considered to be persons, they will never realize that personhood if they exist as surplus IVF embryos or embryos created specifically for research purposes. The differences between these two groups appear minimal, in that they reside in an environment that precludes the realization of human development. Surplus IVF embryos will be destroyed once the need to produce children has passed, regardless of the possibility of being utilized in ES cell research. If used in the latter manner they may contribute to improvements in therapy. Embryos created for specifically research purposes will be destroyed in an attempt to benefit others through improvements in therapy. The move to position D (as found in the United Kingdom) may be the most consistent position ethically and the most advantageous scientifically.

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References

Abkowitz, J.L. (2002). Can human hematopoietic stem cells become skin, gut, or liver cells? *Nature Medicine* 8, pp. 213-214.

Committee on the Biological and Biomedical Applications of Stem Cell Research (2002). *Stem Cells and the Future of Regenerative Medicine,* Washington DC: National Academy Press.

Deutscher Bundestag (2002). Entwurf eines Gesetzes zur Sicherstellung des Embryonenschutzes im Zusammenhang mit Einfuhr und Verwendung menschlicher embryonaler Stammzellen (Stammzellgesetz - StZG). Berlin: Bundestagsdrucksache 14/8394.

Doerflinger, R.M. (1999). The ethics of funding embryonic stem cell research: a Catholic viewpoint. *Journal of the Kennedy Institute of Ethics* 9, pp. 137-150.

Gershon, D. (2003). Complex political, ethical and legal issues surround research on human embryonic stem cells. *Nature* 422, pp. 928-929.

Jones, D.G. (1991). Fetal neural transplantation: placing the ethical debate within the context of society's use of human material. *Bioethics* 5, pp. 23-43.

Jones, D.G. and Telfer, B. (1995). Before I was an embryo, I was a pre-embryo: or was I? *Bioethics* 9, pp. 32-49.

Kennedy, D. (2003). Stem cells: still here, still waiting. *Science* 300, p. 865.

Knowles, L.R. (2004). A regulatory patchwork – human ES cell research oversight. *Nature Biotechnology* 22, pp. 157-163.

National Institutes of Health (2001). *Stem Cells: Scientific Progress and Future Research Directions*. Maryland, Bethesda: Department of Health and Human Services. http://www.nih.gov/news/stemcell/scireport.htm

National Institutes of Health (2003). *Stem Cell Information: Pending Stem Cell Research and Cloning Legislation*. Maryland, Bethesda: Department of Health and Human Services. http://stemcells.nih.gov/fedPolicy/NIHFedPolicy.asp

Research Involving Human Embryos Act 2002. Canberra: Parliament of Australia.

Roccanova, L., Ramphal, P. and Rappa, P. (2001). Mutation in embryonic stem cells. *Science* 292, pp. 438-440.

Thomson, J. A., Itskovitz-Eldor, J., Shapiro, S. S., Waknitz, M.A., Swiergiel, J.J., Marshall, V.S. and Jones, J.M. (1998). Embryonic stem cell lines derived from human blastocysts. *Science* 282, pp. 1145-1147.

Reubinoff, B.E., Pera, M.F., Fong, C.Y., Trounson, A. and Bongso, A. (2000). Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro. *Nature Biotechnology* 18, pp 399-404.

Surani, M.A. (2001). Reprogramming of genome function through epigenetic inheritance. *Nature* 414, pp. 122-128.

Towns, C. and Jones, D.G. (2004). Stem cells, embryos and the environment: a context for both science and ethics. *Journal of Medical Ethics* [in press].

Watt, F.M. and Hogan, B.L. (2000). Out of Eden: stem cells and their niches. *Science* 287, pp. 1427-1430.

Weitzman, M. (1990). The ethics of using Nazi medical data: A Jewish perspective. *Second Opinion* 14, pp. 27-38.

Wu, P., Tarasenko, Y.I., Gu, Y., Huang, L.M., Coggeshall, R.E. and Yu, Y. (2002). Region-specific generation of cholinergic neurons from fetal human neural stem cells grafted in adult rat. *Nature Neuroscience* 5, pp. 1271-1278.