CLINICAL ETHICS

Stem cells, embryos, and the environment: a context for both science and ethics

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Debate on the potential and uses of human stem cells tends to be conducted by two constituencies—ethicists and scientists. On many occasions there is little communication between the two, with the result that ethical debate is not informed as well as it might be by scientific insights. The aim of this paper is to highlight those scientific insights that may be of relevance for ethical debate.

Environmental factors play a significant role in identifying stem cells and their various subtypes. Research related to the role of the microenvironment has led to emphasis upon "plasticity", which denotes the ability of one type of stem cell to undergo a transition to cells from other lineages. This could increase the value given to adult stem cells, in comparison with embryonic stem cell research. Any such conclusion should be treated with caution, however, since optimism of this order is not borne out by current research.

The role of the environment is also important in distinguishing between the terms totipotency and pluripotency. We argue that blastocysts (early embryos) and embryonic stem cells are only totipotent if they can develop within an appropriate environment. In the absence of this, they are merely pluripotent. Hence, blastocysts in the laboratory are potentially totipotent, in contrast to their counterparts within the human body which are actually totipotent. This may have implications for ethical debate, suggesting as it does that arguments based on potential for life may be of limited relevance.

Since their first successful derivation in 1998, human embryonic stem cells have received almost unprecedented attention. Hailed as the next revolution for medicine, they have been described as the future of molecular biology and the biggest development since recombinant DNA.¹ It has been predicted that their successful derivation will have a more profound impact on health than even the advent of anaesthesia and the development of antibiotics.² They are set to create a whole new genre of medical therapies.³ Their potential availability has also, however, opened a Pandora's box of ethical dilemmas, ranging from ongoing issues surrounding the moral status of the human embryo to the conflicting claims of alternative stem cell sources. Although integral to ethical discourse, these dilemmas demand understanding and assessment on scientific grounds. It is our contention that the ethical debate is being hindered by failure to appreciate the subtleties of the scientific background.

Since the ethical problems accompanying destruction of human embryos are well recognised, the advantages of bypassing these by employing adult stem cells are obvious. For many, the ethical conflicts would be avoided, while all the potential benefits to patients with severe diseases would be retained. Consequently, perceived ethical problems would be resolved if it could be demonstrated that adult stem cells are superior to embryonic stem cells as therapeutic agents.

Unfortunately, resolution is far from clear, for this research field is in its infancy. Scientific uncertainty abounds, and yet societies are demanding definitive scientific answers on stem cell technology. Since the least controversial course of action would be to use adult stem cells, the pressures on scientists to emerge with evidence demonstrating that their potential is equal to, or even greater than, that of embryonic stem cells are formidable. Scientific data and interpretation have become integral to the ethical debate, perhaps in inappropriate ways.

An understanding of the most fundamental aspects of stem cell identity and function is required, from the

identification of stem cells to the role of environmental factors at both the microscopic and macroscopic levels. Recognising the role of environmental factors has ramifications both clinically and ethically. Acknowledgement of these factors will provide for greater understanding of the obstacles that have to be overcome if the clinical potential of stem cells is to be realised. It will also help clarify the notions of totipotency and pluripotency, concepts central to delineating the moral value of embryonic stem cells and their parent blastocysts.

IDENTIFYING STEM CELLS

Stem cells are unspecialised 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. Some stem cells can give rise to a wide range of mature cell types, whereas others give rise to only a few. Stem cells can be derived from a variety of sources including early embryos, fetal tissue, and some adult tissues, of which bone marrow and blood are the best known examples. Hence, there are two populations of stem cells: embryonic and adult stem cells. Of these, embryonic stem cells are derived from the inner cell mass (ICM) of the blastocyst at five to seven days after fertilisation. At this point the blastocyst has differentiated into two cell types, ICM cells (some of which will give rise to the future individual) and the surrounding trophoblast cells (which will later form the placenta).

The distinction between embryonic and adult stem cells raises the issue of accurate identification, a prerequisite to testing the claims frequently made for the abilities of both embryonic and adult stem cells to produce a wide array of cell and tissue types. Scientifically, the problem is a fundamental one: defining stem cells solely on the basis of their structure—that is, the specific markers they carry on their outer surfaces, is inaccurate and potentially misleading. Identification may—for example, be complicated by some stem cells expressing markers from several kinds of lineages and may be further confused by the possibility that marker

expression changes throughout development.⁴⁻⁵ The potential for misidentification is of considerable importance for the scientific community, which has called for functional as well as structural testing.

Placing far more reliance on the functional properties of stem cells opens up a wider debate, namely, the role of the environment in an understanding of stem cell function. The ability of the structure of stem cells to change points to the existence of a dynamic relationship between stem cells and their immediate microenvironment, the stem cell niche.

THE STEM CELL NICHE

The niche concept was first developed in blood cells, where proliferation, differentiation, and survival of distinct progenitor populations were found to be dependent on factors secreted by other cell types.⁶ This microenvironment is characterised by numerous external signals, including those derived from chemical factors, cell/cell interactions, and relationships between cells and the surrounding tissue.⁶ These, in their various ways, all have an impact on stem cells, affecting the precise directions in which they subsequently develop.

This microenvironment is governed by regulatory mechanisms, the molecular nature of which is complicated and elusive. Schuldiner *et al.*,⁷ in their study of the effects of eight growth factors on the capacity of human embryonic stem cells to form other cell types, found that while these factors altered developmental outcome, they did not produce uniform differentiation of the stem cells. Consequently, although the structural markers and functions of stem cells appear to be dependent upon their environment, defining the nature of this environment will be far from straightforward.

An increasing awareness of the role of the niche on stem cell structure and function has led to an evolving concept of the stem cell. For instance, there is now the suggestion that stem cells should be viewed, not as undifferentiated cells, but as appropriately differentiated cells with the potential to display diverse cell types in alternative niches.⁸ An excellent illustration of this point is provided in a recent study by Wu *et al.*⁹ where human neural stem cells were primed in a cocktail of chemical factors and then implanted into various regions of the adult rat brain. Not only did the implanted stem cells give rise to a larger number of neurons than previously reported, but most significantly they gave rise to different neuronal types depending upon the region of the brain into which they were grafted. It is possible that the distinctive nature of the local environment in each brain region instructed the neural stem cells to adopt such different fates.

Furthermore, stem cells taken out of their original niche and exposed to an entirely new environment can potentially differentiate into the cell type(s) typical of that new environment. Human neural stem cells—for example, produced muscle cells when introduced into skeletal muscle¹⁰ and human bone marrow cells differentiated into neural cells when transplanted into a neural environment.¹¹ The above two studies were carried out in rodents, but more recently Mezey *et al.*¹² have demonstrated that a similar scenario is possible in humans. Following bone marrow transplants in patients with various forms of cancer, bone marrow stem cells entered the brain and generated neural cell types including neurons. In many of these studies, where stem cells have been “transformed” into cells from different lineages, there has been some form of injury to the stem cell’s new environment or niche. In light of this, it is possible that various factors, signals, or chemicals normally present in damaged or disrupted tissue may play a role in governing stem cell fate.

The above findings reflect the increasing influence being attributed to environmental factors, acknowledgement of

which has led to the view that stem cells are dynamic rather than static entities. This view underpins the concept of stem cell plasticity, whereby stem cells from adult sources have the ability to dedifferentiate or redifferentiate into cells from other lineages. This may blur the absolute distinction so frequently made between embryonic and adult stem cells (let alone between specific types of adult stem cells), a determinative factor in much ethical debate.

POTENTIAL AND LIMITATIONS OF ADULT STEM CELLS

Adult stem cells include stem cells from bone marrow, blood, fat, and both fetal and adult organs. Plasticity is particularly characteristic of bone marrow. Stem cells from this source can differentiate into neural cells,¹¹⁻¹⁵ (see above for further discussion) while other research has indicated that such cells can be incorporated into skeletal muscle.¹⁶

While these reports indicate that interest in the potential of adult stem cells is justified, they should be interpreted cautiously. It would be unwise to jump to the conclusion that these studies render the use of embryonic stem cells (with destruction of human embryos) unnecessary. There are a number of reasons for this.

First, accurate identification is a prerequisite for determining the presence and extent of plasticity. For instance, although Jackson *et al.*¹⁷ presented data to suggest that a group of muscle cells could turn into blood cells, they later found they were dealing with a subpopulation of cells that normally reside in muscle tissue.¹⁸ What is required are more rigorous standards for determining stem cell plasticity.¹⁹⁻²¹ If—for example, cardiac cells developed from stem cells are to contribute to heart function, they would have to demonstrate “synchronous” contraction within the heart itself. Similarly, neural cells derived from neural stem cells would have to generate electrical impulses and release and respond to chemicals normally found within the brain.¹⁹⁻²⁰

A second issue concerns frequency of occurrence. Failure to replicate previous experimental work showing that blood cells are capable of differentiating into neural cells, suggests that, if transformations are occurring, they are very rare.²² Consistent with this conclusion is the work of Jackson *et al.*,²³ who demonstrated plasticity in human blood stem cells, although the change to the desired heart and blood vessel cells occurred in only 0.02% of cells. Thus, as Winston²⁴ notes, even in apparently rich sources, the cells capable of change may be very few in number, and this may ultimately diminish their therapeutic value.

A third point of concern with clinical applications in mind, is that transformations may occur via hybrid cells, that is, by the fusion of two distinct cell types. Such spontaneous fusion was observed when embryonic stem cells were grown in the laboratory in the presence of neural cells²⁵ or bone marrow cells.²⁶ Such hybrids, however, show chromosomal abnormalities that may preclude them from being used in therapeutic applications.

The apparent formation of such hybrid cells may have important implications for interpretations of stem cell plasticity. Such a phenomenon presents an alternate explanation for the claims that stem cells from one tissue type are able to produce the progeny of another tissue type—that is, bone marrow into muscle, blood into brain, and vice versa. In other words, adult stem cells may not be as plastic as early reports have suggested. Thus, as pointed out by Ying *et al.*²⁵ future stem cell plasticity studies should ensure that any “transformed” cells are examined and tested to see if they display properties of both the original and the introduced cell types.

A final note of caution is that it has become clear that there is far more data to show that embryonic stem cells are

capable of indefinite growth and pluripotency than adult stem cells. Mouse embryonic stem cells—for example, have been renewing for 10 years,²⁷ a capacity yet to be demonstrated in cells from adult sources. If adult cells have a restricted renewal potential, this will have negative implications for therapeutic applications, which rely on the ability to expand cells accurately in the laboratory in order to provide enough material for effective transplantation. Furthermore, embryonic stem cells exhibit high levels of the enzyme telomerase which indicates their “immortality”,²⁸ whereas adult stem cells grown in the laboratory do not exhibit this in the same way. This property renders embryonic stem cells important in the study of cellular ageing and stem cell renewal. Work with neural stem cells from biopsies and autopsies suggests that embryonic stem cells may be easier to coax into specific cell types than adult stem cells.¹⁸

Overall, there are few confirmed reports of truly pluripotent adult human stem cells,^{3, 29} while even apparently convincing reports³⁰ may raise serious queries when assessed in a critical manner.³ Nearly a dozen teams have reported adult stem cell plasticity³¹ and it seems unlikely that random mutation or hybrid fusion can explain all these results. What is required is far more understanding of the fundamental biological issues raised by this research. Even as Winston²⁴ outlines the advantages of embryonic stem cell research—for example, he recognises the benefits of adult stem cells in regard to safety, possible efficacy, and accessibility. Adult sources have the added advantage of not requiring an intermediate embryo for immunocompatibility. Similarly, while the UK Department of Health³² argues that the therapeutic potential of embryonic stem cells outweighs that of adult stem cells, it acknowledges that in the long term both may be useful. The UK government reiterated this point in 2002 by stating that it wishes to advance research with stem cells from all sources.³³

Scientifically, therefore, research with both adult and embryonic sources should continue, although caution should be exercised in evaluating the results. Currently, however, 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. The impetus behind such a sentiment stems principally from a desire to protect the status of the human embryo than from any demonstrated superiority of adult stem cell sources.^{14, 34}

Confusion at this point will do nothing to advance the cause of ethical analysis, since the current state of the science and its likely future directions are integral to serious ethical assessment. In other words, it is short sighted to attempt to circumvent discussion of the moral status of the blastocyst by concentrating on the potential of adult stem cells alone. Until it is accepted that this latter approach is a *cul de sac* for ethical discourse, the imperatives of some ethicists will continue to come into conflict with current scientific perspectives.

TOTIPOTENCY VERSUS PLURIPOTENCY

It is generally asserted that totipotency denotes the ability of a cell or group of cells to give rise to a complete individual, whereas pluripotency refers to the capacity to give rise to all the cell types constituting the individual—but not the individual as a whole. Helpful as this distinction is, it is limited, in that it neither acknowledges nor emphasises the importance of environmental influences in defining these abilities.

As we have seen, embryonic stem cells are derived from the ICM of the blastocyst. These ICM cells have the capacity to form all three embryonic germ layers: endoderm, which will

form the lungs, liver, and gut lining; mesoderm, which will form the bone, blood, and muscle, and ectoderm, which will form the skin, eyes, and nervous system. Outwardly, these cells appear to give rise to a complete individual and are considered by some to be totipotent.³⁵

The claim of totipotency requires a number of conditions, however, whether this be for blastocysts or embryonic stem cells. The latter must be undifferentiated and, hence, capable of giving rise to all three germ layers, a condition that is met when embryonic stem cells are derived from the ICM of the blastocyst. In addition, there is a requirement for trophoblast cells, which will eventually form the layers of the placenta. The extraembryonic tissues are a crucial source of signalling molecules and must function optimally for the differentiation of both embryonic somatic cells and for the establishment of germlines.³⁶ Since both trophoblast and ICM cells are required for successful development of the fetus, both cell types are required to establish totipotency.³⁷ Thus, totipotency becomes a function of the immediate environment of the embryonic stem cell. If a viable fetus is to result, totipotency also requires successful implantation and development within the uterus of a woman.

In the absence of all these conditions embryonic stem cells are only pluripotent, since they are capable of creating 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 trophoblast, let alone that of the uterus. It is inaccurate, therefore, to refer to embryonic stem cells as totipotent rather than pluripotent.³⁸

These criteria for establishing totipotency also have ramifications for the ethical evaluation of the human blastocyst. While the blastocyst has intact trophoblast cells and, therefore, the capacity to produce all three germ layers, plus the extraembryonic material necessary for its survival, totipotency is still dependent on the wider environment—successful implantation in a uterus. Hence, blastocysts within the laboratory are only “potentially totipotent”, in contrast to their counterparts within the body.

A blastocyst or even a later embryo in the laboratory lacks the capacity to develop into a human individual. Unfortunately, this simple observation is frequently overlooked, and moral discussion focuses on the potential of an embryo to grow into a fully developed human without any reference to its context. Ignoring context in this manner inevitably overlooks the crucial importance of an appropriate environment necessary for the realisation of totipotency, changes to which may also alter the moral debate. Just as stem cell identity and arguably moral value depend upon the microenvironment, so too the human embryo is intimately dependent upon its wider environment.

CONCLUSIONS

Much opposition to the use of embryonic stem cells relies upon the argument that adult stem cells could serve as a viable source of tissues for regeneration and therapy. In the light of this, the argument continues that embryonic stem cells, with their debatable ethical credentials, should no longer feature in attempts to produce replacement tissues. This stance uses alleged scientific evidence to bolster an ethical position, and stands or falls on the strength of the scientific case.

Apart from the validity or otherwise of this approach, definitive evidence will not be forthcoming for some time (possibly years), since the scientific issues are complex ongoing ones. As outlined above, the potential of adult stem cells remains a matter for debate and further experimentation. Additionally, the dynamic nature of stem cells, both embryonic and adult, points to a close interrelationship

between their potential and the environment in which they are located. The possibility of cell lineage change also has to be taken into account when the suitability of different stem cell types is being advocated. From a scientific perspective none of this is surprising, and yet it fits uneasily alongside any stance that is a mixture of scientific, ethical, and political rhetoric.

The necessity of paying attention to the scientific framework of the debate, such as we are doing, has implications for other stances as well. With the advance of scientific understanding and, specifically, the advent of a genetic level of understanding, has come a tendency to view the life of an individual on the basis of DNA alone. This too, however, ignores the dependence of the embryo upon a competent environment. The context within which the embryo develops, like the niche for the stem cell, is integral to all aspects of its functioning. The environment provides nutritional requirements as well as numerous cues to ensure the healthy development of the embryo and subsequent fetus. Consequently, the preservation of DNA cannot be equated with the preservation of an individual's life, as has been suggested by McGee and Caplan.³⁹ Adherence to such a reductionist mode of thinking is only made possible by ignoring completely the contribution of the environment. Essential as DNA is for development, it requires an appropriate context if its potential is to be realised.

From this it follows that a notion such as totipotency is a function of the environment both at the microscopic and macroscopic levels. This suggests that ethical debate cannot be reduced to "potential for life", since inherent within the potential of an embryo is an assumption regarding the appropriateness of its environment. This means that the context of blastocysts and later embryos is crucial, ethically as well as scientifically and clinically.

In light of this, it is appropriate to ask whether it is useful to continue thinking of the blastocyst as an independent entity with a moral status stemming entirely from its organisation and perceived potential. We have argued that neither blastocysts nor stem cells are to be viewed in isolation from their context. Given that the claim is frequently made that moral value and status are closely associated with embryonic potential, recognition of the importance of the environment will have major implications for ethical thinking.

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