Tissue and Cell Donation

AN ESSENTIAL GUIDE

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12 Ethical and Consent Issues in the Reproductive Setting: The Case of Egg, Sperm, and Embryo Donation

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Introduction

Ethical questions about egg, sperm, and embryo donation that arise in the reproductive setting are among the most complex encountered by clinicians, policy makers, and social scientists because of their manifold and far-reaching personal, familial, and social implications. Uniquely, gamete and embryo donation did not originate in order to preserve existing lives, but to assist in the creation of new lives. More recently, the prospect of using germ cells and embryos to develop an entirely new field of therapeutic intervention – through regenerative medicine, tissue engineering, and stem cell science – raises an additional set of complex ethical issues. Determining best practice in this context is thus dependent on the expertise gained from more well-established human donation sectors, such as blood banking, as well as innovative thinking about patient information and consent, the risks of exploitation and commodification, donor screening and feedback, reversible anonymity, and the standardization of best practice.

A considerable literature now surrounds the formation of new families through assisted conceptive technologies such as in vitro fertilization (IVF), surrogacy, gamete donation, donor insemination, and preimplantation genetic diagnosis, including their social, legal, and ethical dimensions [1–4]. Less attention has been paid to the post-IVF context of tissue donation, namely coordination of the large numbers of "surplus" embryos created during clinical treatment for infertility, which, if a couple so desires and consents, may be donated for scientific research, although specialist literature addresses this topic [5–9]. Increasingly, procedures to enable couples to donate surplus embryos from IVF treatment for a range of scientific and clinical procedures, including stem cell research, have become the focus of efforts to define and standardize best practice [10].

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Background: IVF and stem cells

IVF was first successfully practiced in the United Kingdom in 1978 by the consultant gynecologist and surgeon Patrick Steptoe and the developmental biologist and research scientist Robert Edwards [11]. This clinical application in humans of basic mammalian developmental biology techniques was itself the product of a uniquely productive period of embryological research in the postwar period [12], which enabled increasingly sophisticated understanding of the precise events involved in the biological reproduction and development of higher vertebrates. Increasingly, technological means of intervening into mammalian reproduction and development – initially aimed at population control and agricultural improvements rather than infertility – began to lay the groundwork for assisted human reproduction as early as the 1950s.

Despite its ethically controversial prehistory and debut, IVF quickly became an acceptable and popular technology. Although there is no authoritative source for the numbers of children born worldwide as a result of IVF, the International Committee for Monitoring Assisted Reproductive Technologies reported at the European Society for Human Reproduction and Embryology Conference in 2006 that IVF had been responsible for the births of three million children. During the 1980s and 1990s, IVF expanded rapidly, becoming an established and routine sector of public and private healthcare services worldwide, and the basic technique in an expanding fertility industry. As its applications widened, IVF began to be used to respond to an ever-widening spectrum of diagnoses, from male infertility to genetic disease. A consequence of this expansion in uses of IVF, and of the way in which IVF is routinely practiced (in which hormonal stimulation is relied upon to produce a much larger yield of eggs during a single cycle), is the preservation and cryogenic storage of fertilized eggs that may be used in a future treatment cycle. Cryopreservation enables a couple to thaw and transfer embryos over the course of more than one IVF cycle without the need for additional superovulation, thus maximizing the use of their embryos. This reserve supply of embryos may be stored indefinitely (although some countries such as the United Kingdom limit storage to 10 years) and may or may not be used for further treatment (for example, if a couple achieve a pregnancy and their goals are met). Frozen embryos thus comprise a

unique potential source of donated human tissue – and one that has come to be of increasing scientific interest as well as of ethical concern.

As we are now aware, IVF was not the only revolutionary outcome of the postwar boom in developmental biology, reproductive physiology, and mammalian embryology. Other spectacular firsts were accomplished in mice, monkeys, cattle, sheep, and humans, resulting in the derivation of stable, pluripotent mouse and primate cell lines in the 1980s, human embryonic stem cell (hES) lines in the 1990s, and the cloning of a higher vertebrate from an adult cell in the famous "Dolly" experiment of 1996 (for a review, see Parson [13]). Together, these experiments overturned some of the most elementary scientific principles formerly assumed to govern biological development in general, and the diminishing course of cellular developmental potential in higher vertebrates in particular [14]. The confirmation, for example, that adult mammalian cells never lose their pluripotent potential – that is, their ability to become any kind of cell, as if they were an embryo – and that they can, as a result, be reprogramed to become any kind of specialized cell, has created significant prospects for new treatments for a wide range of diseases. These include degenerative, metabolic, genetic and congenital (e.g. spontaneous noninherited translocations), and other diseases; many previously unable to benefit from any form of therapy.

In sum, the unexpected regenerative capacities now known to be recoverable from most cells and tissue, such as adult skin cells, combined with the sophistication of modern molecular genetic and cell culture technology, have meant that all human tissue and cells, but in particular gametes and embryos, have literally, in the context of stem cell science, been given a new lease on life. Improved knowledge of the precise genetic and epigenetic events involved in germ cell differentiation and embryogenesis has become the "gold standard" against which cellular developmental potential can be most accurately understood. Despite the emergence of new techniques such as induced pluripotent stem cells (IPSCs), the human embryo retains a unique importance in both medicine and science.

Coordination and consent: the UK example

This chapter draws primarily on the experience of the United Kingdom, where assisted conception and human embryonic stem (hES) cell research are both highly regulated and scientifically advanced. The United Kingdom is a pioneer of the "combined approach," whereby extensive regulation enables a permissive research climate. This approach is based on a form of social contract devised by the philosopher Mary Warnock, who chaired the Consultation Committee on Human Fertilisation and Embryology from 1982 to 1984 in the wake of the birth of Louise Brown: in exchange for allowing

research on human embryos, such research would be subject to strict statutory limitations enforced through criminal law [15]. As a result, in the UK system public confidence in the necessity for "lines to be drawn" is supported by a robust and active regulatory authority (the Human Fertilisation and Embryology Authority [HFEA]), which oversees all clinical and scientific work involving human embryos as well as treatment involving their creation. At the same time, the public desire to see scientific advances in the pursuit of improved (and less expensive) health care can also be met through promotion of a highly permissive research climate of experimental science [16].

The HFEA was established in 1991 as a licensing authority and regularly updates its licensing criteria through a Code of Practice. Since the early 1980s, the United Kingdom has continually revised and updated the ethical governance of assisted conception and embryo research (including embryo donation to stem cell research), including their regulatory oversight, quality control, and scientific standardization. Initially through the HFEA, later under the auspices of its publicly funded national stem cell bank (completed in 2004), and most recently under the new parliamentary and European Union (EU) directives, the process of providing statutory regulation, ethical infrastructure, and quality control has undergene a rapid evolution that is ongoing [17].

Unlike the United States, where legislative initiatives to oversee reproductive biomedicine have historically been haphazard, a series of UK governments has devoted parliamentary time to the establishment of legislation governing both clinical and scientific conduct related to the human embryo. In accordance with the conclusions of a Department of Health (DH) consultation paper, published in 2000 [18], new regulations were introduced into the parliament to amend the 1990 Human Fertilisation and Embryology Act in order to widen the criteria for research on human embryos, including the creation of embryos through cell nuclear replacement (CNR) for research purposes. Under the Human Fertilisation and Embryology (Research Purposes) Regulations (2001), three new criteria for embryo research were added to the existing Act (a) to widen the possibility for understanding the cellular bases of serious diseases, (b) to permit research that might lead to their treatment, including (c) through the method known as "therapeutic cloning" (i.e. CNR).

In 2002, following the recommendations of the DH and also those contained in a special report of the House of Lords Select Committee on Science and Technology [19], the UK Stem Cell Bank was commissioned and publicly funded as a joint endeavor between two of the United Kingdom's national research councils, the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (together £2.3 million). Housed at the National Institute for Biological Standards and Control (NIBSC) near London in a purpose-built facility, the UK Stem Cell Bank was charged with "providing ethically sourced, quality controlled

adult, fetal, and embryonic stem cell lines for research and for the development of therapies by the national and international research and industrial communities." A steering committee chaired by Lord Naren Patel was established to develop a series of guidelines including Codes of Practice for the bank and the use of stem cell lines. These codes were closely modeled on the 2001 Department of Health Code of Practice [20] for Public Sector Tissue Banks and were the subject of an extensive consultation exercise in late 2003. They have been updated and revised regularly since (see www.ukscb.org). The first licenses from the HFEA were granted in 2002 for hES cell derivation, and in 2003, the first UK-derived lines were announced by King's College in London [21].

Thus, whereas in Europe and the United Kingdom considerable effort has been made to establish a robust ethical and legislative context for guidance concerning clinical and scientific manipulation of human fertilization and embryology, the United States has relied largely on the nonstatutory guidelines provided by professional bodies such as the American Fertility Society, the National Academy of Science, and the American Society of Reproductive Medicine. The lack of a more systematic regulation of the US IVF industry, or "baby business," has been explicitly criticized by some [22], while its consumerist tendencies have been lamented by others [1]. Apart from the federal ban introduced by former president George W Bush in 2001 curtailing hES cell research, the regulation of the human reproductive sciences and medicine in the US context is largely charged to the United States Food and Drug Administration (USFDA) and focused on product safety and prevention of disease transmission. This oversight is limited to donor eligibility requirements such as donor screening and donor testing for anonymous reproductive cell/tissue donation situations, and labeling expectations for all donation scenarios. These regulations are codified as 21 CFR 1271 and are included within requirements applicable to all cells, tissues, and cellular and tissue-based products (HCT/Ps) transplanted, implanted, infused, or transferred in the United States. The USFDA does not regulate consent or gifting practices and currently does not require reproductive HCT/Ps to follow good tissue practices or to report adverse events. In the United Kingdom, where legislation exists but must be continually reinterpreted and amended, the key regulatory bodies are the aforementioned HFEA and the newly established Human Tissue Authority, as well as the UK Stem Cell Bank and the associated NIBSC. Both authorities work closely with the medical and scientific regulators and advisors, including the Medical Healthcare Products Regulatory Agency (MHRA), the National Institute for Health and Clinical Excellence (NICE) and professional organizations such as the British Association for Tissue Banking (BATB), and the National Blood Service (NBS) within the National Health Service Blood and Transplant (NHSBT) to ensure UK legislation remains in step with other national and international protocols determining best practice.

Ethical issues: informed consent

As in all areas of tissue and cell donation, ethical consideration must be given to a wide range of issues raised by the possibility of embryo donation leading to stem cell research. From the position taken by national governments on this issue, such as the US ban on federal funding for embryonic stem cell research, to media coverage and religious prohibitions, to intimate personal and familial questions of identity and shared reproductive substance, as well as in relation to basic questions of clinical care and best practice, this context represents a highly challenging ethical arena in which innovation is a constant, if laborious, requirement. The lessons to be learned in this sector are consequently likely to have a significant impact both within and beyond the tissue banking profession as this sector increases in prominence and professionalization.

The successful translation of stem cell science into actual treatments for diseases such as diabetes, cancer, Alzheimer's, or Parkinson's depends on the maintenance of public confidence and support for what is, in global terms, a highly controversial field. In the post-Hwang context [23], as well as in the wake of the earlier misconduct involving human tissue in the Alder Hey pathology department in the UK [24], the question of accountability for robust consent procedures for donation of embryos and other human tissue and cells, and their credibility to patients and the wider public, has gained increasing prominence [10]. While debate about informed consent, patient screening, anonymization, feedback, and paid donation continue to indicate the lack of a uniform frame of reference internationally concerning best practices in the regulation of egg and embryo donation, the imperative to provide clear standards of best consenting practices is increasing. Thus, in addition to the fact that consent procedures for embryo donation for stem cell research must respond with due diligence to novel sources of patient concern, the development of such procedures is also required to conform to a new and, in some senses, higher standard.

For example, although informed consent remains a core principle in clinical practice, and for any scientific research involving human subjects, including stem cell research, its meaning in the context of the reproductive setting is complicated by a number of factors, such as the fact that an embryo is not readily conceptualized in terms of either its "own" or its donors' individual autonomy. Embryos created in the context of IVF inevitably must be thought of as embodiments of shared reproductive hope and investment, often for couples whose primary experience is of reproductive loss or disappointment [25]. For many such couples, the opportunity to "give something back" to medical research is an attractive possibility, offering as it does a form of reciprocity or altruistic satisfaction. It may even be the case that couples who have failed in their attempt to conceive a child through IVF (as remains the fate of the majority of couples who undergo IVF) can gain some sense of

reward from potentially helping others, thus contributing toward a generalized social good even when their own immediate reproductive aspirations have been unfulfilled. In all cases, both members of a couple must consent to the donation, and the precise terms and conditions of such consent must be rigorously established and protected.

CASE 1

Patient motivations

Mr. and Mrs. X have attended the assisted conception clinic for their first cycle of IVF. They have a niece aged 3 who was born from IVF. As part of their initial consultation, they are asked to fill in consent forms indicating whether or not they would be prepared to donate embryos to research. The consent coordinator explains that these would only be embryos not suitable for treatment, e.g. ones that had not shown signs of appropriate development and could not be used for embryo transfer, or which would not be considered of high enough quality to survive the freeze-and-thaw process. Anticipating this decision, Mr. and Mrs. X have discussed the issues involved in embryo donation prior to attending the clinic. They consider themselves fortunate to be given the opportunity to receive treatment and feel that they would not be able to do so if other people before them had not donated their embryos for research. They would like to be able to help others do the same. They view discarding their embryos as a waste of a potentially valuable medical resource. Even if they do not become pregnant themselves, they suggest, some good may come of their treatment for others. Mrs. X expresses a specific interest in speaking to a member of the research team about stem cell derivation as her grandfather had had Parkinson's disease, and she would like to specifically help this cause if it is possible.

In addition to the fact that embryos come from couples, and that many couples undergoing IVF have never considered the question of what they might do with any surplus embryos left over from their treatment, consent for embryo donation for stem cell research is complicated by technical factors intrinsic to this field of biomedical innovation. A number of unique aspects of this form of tissue donation – in particular the potential for amplification, regeneration, and transformation of the original cellular material – create areas of uncertainty about best practices that remain under debate. The fact that a single embryo could be the basis for a cell line potentially used to treat thousands of people, and the possibility to immortalize, and endlessly divide such a line, creates unprecedented ethical difficulties, as do issues of screening donors and providing feedback. As we shall see in the following sections, the establishment of novel and effective ethical protocols for many forms of live donation in the contemporary reproductive setting

has by no means ensured that uncertainty will not continue to characterize various implications of this increasingly important biomedical domain in the future.

Determining best consenting practices

Under both UK law and the EU Tissues and Cells Directive, consent for embryo donation to stem cell research must be requested by a professional who is independent of both the clinical and research staff in his or her assisted conception unit in order to avoid conflicts of interest. The ability to meet this standard is essential, much as the acute economic pressures on the health service may make it difficult. The beginnings of a more professionalized relationship to consent in the reproductive setting, in part because of the momentum generated by successful hES cell derivation, have begun to become more apparent in the context of a higher level of national coordination in the United Kingdom, in a manner that is likely to be replicated elsewhere.

Since 2004, the British initiative to coordinate the scientific effort of hES cell derivation and banking with the clinical service of providing assisted conception, in other words at the IVF–stem cell interface, has been facilitated by the establishment of a national network of Human Embryonic Stem Cell Coordinators (HESCCO). Funded by the MRC, and building on the momentum created by the UK government's enthusiastic support for the stem cell field (publicly stated priorities of both past and present Prime Ministers Tony Blair and Gordon Brown), the HESCCO network was the first group to devise, pilot, and confirm standardized national consent procedures for embryo donation to hES cell derivation. The establishment of a networked, interdisciplinary peer group for work in this sensitive area has been shown to facilitate continuous improvement in the development of policies and practices and coordination of many aspects of derivation, such as quality control and consent protocols. Such networks, which are likely to become better established, facilitate support of frontline, administrative, and laboratory staff who work in these types of facilities, often enabling a streamlining of procedures that can reduce donors' vulnerabilities to bureaucratic inefficiencies, inadequate or incorrect information, or "consent fatigue." Similarly for staff, networked affiliations boost morale and create wider opportunities for information sharing and cooperation.

CASE 2

Staff issues

Z is an experienced nurse aged 28 who works in a large fertility clinic. She

basis, she counsels female patients about their treatment and performs scans to assess their progress. These include early pregnancy scans. Sometimes, these scans show that the baby has no heartbeat and Nurse Z must inform the patient, provide emotional and clinical support, and arrange aftercare. Presently, she is finding this part of her job very difficult as she has recently had a miscarriage herself. She and her partner had been trying unsuccessfully to conceive for over a year. Having miscarried at 7 weeks, no one at work is aware of her pregnancy loss, and she has not informed them. Increasingly, she finds it difficult to cope with patients with infertility problems and especially those who are having an ongoing, successful pregnancy. Her partner has urged her to move on. However, she cannot rid herself of the fear that, as she approaches 40, her chances of conceiving are rapidly decreasing. Recently, she has been tempted to take the day off sick when she knows that she is scheduled to undertake pregnancy scans for patients. Nurse Z has access to a hospital staff counseling service, which she may attend soon (see Chapter 10 on staff support). Unfortunately, the longer time passes, the more difficulty she has confiding in others, addressing her concerns directly, or performing her job effectively.

Consent criteria in the United Kingdom

Free and informed consent are key principles of the Human Tissue Act (2004), the HFE Act (1990), and the EU Tissue and Cells Directive (EU TCD) (2004), as well as being standard principles of best practices in clinical medicine, randomized controlled trials, and scientific research involving human subjects. For consent to be robust, legitimate, and ethically sound, comprehensive information must be given to the donors in a form that is readily accessible and allows a free and informed decision to be made by potential donors [26]. In the United Kingdom, all patient information provided with consent forms must be approved by local ethics committees. This is also required for research involving embryos.

The criteria devised by the steering committee of the UK Stem Cell Bank for provision of information *prior to discussion of consent to donate embryos to stem cell research* are divided into two components: oral and written information. Correspondingly, the discussion between the consent coordinator or research nurse and patients who are potential donors must cover the following points:

1 the research project is directed toward the derivation of hES cell lines
2 very few such cell lines are derived from donated embryos at present
3 any hES cell lines that are derived will be deposited in the UK Stem Cell Bank, may be used for other projects within the United Kingdom and/or overseas, and may eventually be used for treatment
4 the research will not lead to any direct medical benefit to the donor

5 the UK Stem Cell Bank is overseen by an independent steering committee that has the responsibility to ensure legal and ethical accountability for all hES cell lines accessioned by the bank
6 donation to research will in no way affect donors' treatment, and the decision whether to donate is voluntary
7 donated embryos will be anonymized, although this anonymity must be reversible under exceptional circumstances when grave matters of public health may be at stake
8 no information emerging from tests done on the cell lines will be fed back to donors (unless under the exceptional circumstances mentioned earlier)
9 donors can withdraw their consent until the point that the embryos are used for research
10 cell lines, or discoveries made using them, may be patented and used for commercial purposes, but the donor will not benefit financially from any future profit generated by them.

These minimum criteria, which must be provided in the patient information leaflet accompanying the consent form, are also fully discussed with potential donors by an independent party who is not part of either the clinical or the research team. They are considered by patients for a suitable period of time to allow reflection, then each gamete or embryo provider must consent *in writing* to the following:

1 that they consent to the use of embryos created using their gametes or embryos in a specified research project for the derivation of hES cell lines
2 that they understand that a sample of any successfully derived hES cell line(s) will be deposited in the UK Stem Cell Bank, and that these cell lines may be used in other research projects
3 that they are aware they are under no obligation to donate gametes or embryos to research, and that a decision not to participate in research projects will not alter their treatment in any way
4 that they understand that they have a right to withdraw their consent without giving any reason, at any stage until the gametes and/or embryos have been used for research
5 that they understand that any cell line derived from their donated gametes/embryos may eventually be used for treatment purposes (including cell replacement therapies) in the future, but that donors will not personally benefit from such treatment
6 that they understand that cell lines or discoveries made using them may be patented and used for commercial purposes, but that donors will not benefit financially from any future profits of such commercial activity

7 that they agree to be contacted in the future in the unlikely event that the stem cell steering committee considers it necessary to confirm test results performed on stem cell lines that are of direct relevance to their own, their family's, or the public's health.

In the establishment of minimum consent criteria, clarity and brevity must be balanced against the need to retain a substantial core of necessary information. Best consenting practices are enhanced by ensuring that the patient information and consent form is attractive and accessible, easy to read, and easily completed. The forms may be supplemented by a public website, including resources, links, and frequently asked questions. In the United Kingdom, the HESCCO consent forms received approval from the HFEA in 2005 and have since been adopted by numerous clinics nationwide (Figure 12.1).

CASE 3

Patient concerns #1

Mr. and Mrs. W have spoken to a member of staff at their assisted conception unit and are trying to decide whether they would like to donate their embryos for stem cell research. The staff member has explained that any stem cell line derived must have a sample of cells sent to the UK Stem Cell Bank so that they can be accessed for secondary research by people who may not be deriving stem cells themselves. Mr. and Mrs. W asked whether this was just in the United Kingdom or could people apply from abroad? The staff member explained that the lines can be released to researchers worldwide and that it is the stem cell bank steering committee that evaluates the suitability of applicants on a case-by-case basis. Mr. and Mrs. W have read newspaper stories about the fraudulent work in South Korea by Mr. Hwang and are very concerned about cells derived from their embryos being exported abroad. They want to know if they can donate their embryos on the condition that any successfully derived cell lines can only be used in the United Kingdom, but the staff member has explained this kind of conditional consent is not possible. The couple decline to donate their embryos.

Moving toward the future of stem cell translation

The combination of rapid worldwide expansion of IVF over the past three decades and equally substantial developments in stem cell science, with their promising clinical potential, all but ensure that the practice of embryo donation for stem cell research will gain momentum as a distinct sector of tissue and cell banking internationally. Although rapid progress has been made, particularly in the United Kingdom and Europe, to ensure that

your hospital logo

The generation of human embryonic stem cells

RESEARCH INFORMATION SHEET

Introduction

We would like to invite you to participate in a project to generate human embryonic stem cell lines that could eventually be used in treatment or therapy. This project will use human embryos unsuitable for your current treatment or freezing (for possible use in a later treatment cycle), and that would normally be discarded.

Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us (contact details below) if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

Why have I been chosen?

We are approaching all couples undergoing in-vitro fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI) who have said they are agreeable with research.

What does this involve for me?

During your current IVF cycle, one or two embryos (if they are of sufficient quality) will be selected for replacement into the womb. The remaining embryos may be frozen and stored for your future use, if you wish. The decision to freeze embryos is based on their quality as observed under the microscope. This decision is made by clinical embryologists who are not directly associated with this project and therefore your decision of whether to take part in this research will have no impact on your treatment or chances of conceiving. Embryos that are not frozen because they are not of sufficient quality, would normally be allowed to perish or donated to research. We are now seeking your permission to use these embryos to try to generate embryonic stem cells. If you wish to contribute to this research project you will need to sign a consent form (which you will also be given a copy of).

Will I benefit from this research?

If you give embryos for this project, you should be aware that the results of the research are not intended to directly benefit any treatment you might have. However, this research will help us understand how embryos develop and may in time improve treatment for infertility. In addition, the major goal of stem cell research is to find treatments and/or cures for many other diseases such as Parkinson's disease, heart disease and some types of cancer. Therefore this research may help to treat other patients in the future.

Will participating in the research affect our treatment?

No. You will receive the same treatment whether you donate embryos or not. All embryos that you donate would otherwise have been allowed to perish. This is ensured by making sure that research staff are not involved in your treatment and that clinical staff are not involved in the research.

Do we have to take part?

No. Participation is entirely voluntary.

Date Created: 30 September 2005 HESCCO Review Date: 30 September 2006 / Version 1

Figure 12.1 Page one of the two page HESCO patient information and consent form illustrates the question and answer format assigned to assessibility.

robust and workable legislative guidelines and ethical protocols are agreed upon and implemented, a number of areas continue to demand further refinement and clarification. At present, the most challenging areas of debate concern the following topics:

1 reversible anonymization
2 conditional consent (and artificial gametes/embryos)
3 feedback to patients
4 payment of donors
5 donor screening

In the following sections, these issues are illustrated through case studies and discussion, and are supplemented by current guidelines and regulation, where relevant.

Reversible anonymization

Under the EU TCD, the provenance of all clinical grade cell lines must be fully traceable and documented at every stage. Potential donors need to be made aware not only that so-called reversible anonymization will be used to ensure that in the event of a major health threat (commonly imagined to be a xenopathic agent such as Bovine Spongiform Encephalopathy (BSE)), but also that they may be contacted in the event that future screening identifies them as a carrier of a disease potentially transmissible by human embryonic stem cell lines (ESC). While the justification for this measure is all but unassailable on public health grounds, the mechanisms for implementing these criteria vary. In particular, the questions of the degree of reversibility that needs to travel with the hES cell line sample, how far down the path of postderivation dissemination donor identity information needs to pass, or where such information is retained (in the clinic or in the lab) remain subject to local, regional, national, and international variations. Donors may be reassured if specific information can be provided about the mechanism of "reversibility" that will be employed, especially, for example, if donor information does not leave the clinic. The feasibility of national and international databases of all embryos donated to research, their provenance, and the outcomes of such research are being explored [27].

Conditional consent

One of the most common and widespread concerns expressed by patients in the context of assisted conception in general, and equally by patients who are approached about the possibility of donating their eggs or embryos to hES derivation in particular, is the *reproductive misuse* of such material. The prospects of their reproductive substance being sold or made available to other couples, mislabeled or otherwise inadvertently used to create a child for another couple, or, in a more futuristic vein, employed in scientific

experiments leading to a cloned offspring, are among the most common and widespread concerns expressed by patients. For potential donors to stem cell research, such concerns have additional dimensions. For example, the growing scientific literature suggesting that it may be possible for germ cell lines, or "artificial gametes," to be derived from embryonic cell lines [28] has proven to be a concern for a small but growing number of patients. The possibility of introducing conditional consent, a decision that would respond to the legitimate concerns of potential donors, is one to which the HFEA has devoted serious consideration in the United Kingdom. To date, the HFEA has refrained from endorsing conditional consent, as to do so would establish a new precedent of "fettering" consent to tissue donation, which many regard as contrary to best practices in terms of either experimental research or tissue banking. Many believe it is also not in the patients' best interests, as the feasibility and, therefore, authenticity of such a guarantee of unknown duration cannot presently be reliably assured. An additional objection to making an "exception" of embryo donation as a candidate for the unprecedented use of conditional consent is that adult cells can already be made into embryo-like cells and gametes and that too little is known about the distinction among these various types of cells. To date, the consent to donate embryos for hES cell research has remained unconditional in the United Kingdom.

CASE 4

Donor emotional aspects

Many assisted conception units (and all such clinics in the United Kingdom) enforce storage limits on frozen embryos, for example, five or 10 years. In such cases, it is necessary to contact patients to determine their wishes for their frozen embryos before the storage expiry date. Contact is usually maintained on a yearly basis, but for a variety of reasons (such as change of address), contact may be more infrequent or interrupted. Mr. and Mrs. X were contacted after four years by telephone to check their address details and to explain that it was necessary to send out forms about their frozen embryos. They confirmed address details and were posted the forms. However, months went by and the forms were not returned, so a telephone call was made to check that they had received the forms. They said that they had received the forms but were still uncertain about what to do. They were finding the decision very difficult as they had had successful IVF treatment and now had twin girls. Since their treatment, they had also conceived naturally themselves and have a son. They said that they could not consider letting their frozen embryos perish at the end of the legally allowable storage limit as they saw them as possible siblings for their existing children. However, they also felt that they did not want more children as three were enough. They had continued to discuss their options but had failed to reach a decision. In time, they reached a decision to donate their embryos for research. However, they noted on their form that they

had found the decision highly unsettling and made worse by the gap in contact of four years.

Feedback to patients

Feedback of information to patients raises issues in relation to both the short and long term. At one end of what might be called the "feedback spectrum" is the increasingly influential principle drawn from human rights law and bioethics that personal information belongs to the donor and that no agency should retain identifiable information of relevance to the individual's health in secret or without that individual's knowledge and consent. However, information such as possible genetic predisposition to disease may only come to light through research many years after donation and may or may not be welcomed by former patients, especially as the clinical implications might be unclear, unreliable, or simply unknown, having been derived from tissue grown in vitro through many passages. How and by whom such information would be imparted also presents difficulty. Beyond the requirement of reversible anonymity discussed previously (which is restricted to the most extreme cases of a public health risk), current best practice as recommended by the UK Stem Cell Bank Code of Practice for the Use of Human Stem Cell Lines (2006) is for donors to be informed that "no individual feedback will be given on tests performed by the UK Stem Cell Bank or research results of subsequent studies" although "general information . . . including the results of research using embryonic stem cell lines will be published on the [Bank's] website" [29: 2]. Hence, while the option to be informed if their embryos develop into cell lines has largely been foreclosed, the possibility that patients would be contacted either in the event of a public health concern, or indeed should "test results of direct relevance to the donor or the donor's family" be discovered, remains open.

CASE 5

Patient concerns #2

Mr. and Mrs. Y have decided to donate their spare embryos for research and have just finished talking to the research nurse about the issues involved as part of their routine induction at the clinic. They have decided to sign the consent form to donate their surplus embryos to three of the hospital's research projects but, after much deliberation, have decided not to contribute to hES stem cell derivation. During their consultation, staff members have explained that a sample of any hES cell line derived by the research team must be placed in the UK Stem Cell Bank and that these lines may last for a very long time (possibly indefinitely). The couple have also learned that there is a slim chance that future research on the stem cell lines may reveal a public health issue, and that in those circumstances, they are legally required to be traceable by the stem cell bank. Mr. and Mrs. Y, who are in principle keen to help, feel uncomfortable about the future uncertainty this possibility of contact would create. Such contact would both confirm an hES line had been derived from their embryo, and that it was affected by a serious disease. They are unsure of how they, or their offspring, might react under such circumstances. They are also concerned about implications the feedback might have on their life insurance policies. Reluctantly, they conclude that the indefinite nature of the stem cell research project precludes their participation.

Payment to egg and embryo donors

In July 2006, the HFEA set a new precedent in the United Kingdom by granting a license to Newcastle University for "egg sharing for research" – a practice designed to reduce the cost of IVF treatment in exchange for the donation of eggs for research purposes [30]. The authority simultaneously announced a public consultation into the wider question of "whether it is appropriate for women to donate their eggs for use in scientific research," and what safeguards might be needed were such a practice to become more widespread. Egg sharing for research, which is based on the model of clinical egg-sharing programs, in which discounted IVF treatment is offered in exchange for donating eggs to other couples, has been the subject of debate because of the potential for exploitation, and the specter of commodification that attaches to any kind of remuneration for tissue donation and especially to the perceived sale of tissue. In February 2007, the HFEA [31] confirmed its decision to license egg sharing for research, stating,

> "Having considered all the information on donating eggs for research, including the risks to women and the outcomes of the public consultation, the Authority has decided that women will be allowed to donate their eggs to research, both as an altruistic donor or in conjunction with their own IVF treatment. Given that the medical risks for donating for research are no higher than for treatment, we have concluded that it is not for us to remove a woman's choice of how her donated eggs should be used."

By confirming its support for increased levels of remuneration for egg donation to research, the Authority's position now closely resembles that of the Ethics Committee of the American Society for Reproductive Medicine, which in its published guidelines of 2000 endorses payment to donors provided that "payments to women . . . should be fair and not so substantial that they become undue inducements that will lead donors to discount risks" (estimated to be >10 k USD [32: 218, 33]). However, both of these positions are now in conflict with that of the US National Academy of Sciences "Guidelines for Human Embryonic Stem Cell Research," which stipulates that no payment should be provided to egg donors – a view recently adopted as part of the California stem cell initiative, and by major international providers of hES lines, such as Singapore-based ES Cell International. A compromise option, such as that adopted by the International Society of Stem Cell Research allowing each individual country to determine its own laws may be a suitable interim measure (2006).

Donor screening

The large-scale amplification involved in the clinical application of hES cell line therapies in the future, whereby several thousand patients might receive hES cell products from a single line, poses significant challenges at the level of determining appropriate screening procedures throughout the derivation process. Which aspects of donor screening are paramount for hES cell derivation (as opposed to blood donation), and how should the screening, testing, and documentation of donor characteristics be facilitated logistically, technically and ethically? This question has been handled differently in the United States and the United Kingdom, with the former relying on USFDA requirements, which are specifically designed to emphasize that its xenotransplantation regulations are not intended to prevent the clinical use of hES cells derived using animal products (Title 21 Code of Federal Regulations Part 1271 [35–37]). Whereas this policy will require greater reliance on microassays of preclinical lines, rather than on samples taken from the donor at the time of donation, a consensus has not been reached in the United Kingdom about the suitability of such "passive" detectors of potential contaminants – particularly in the context of variant Creutzfeldt–Jakob disease. In the United Kingdom, preexisting standardization of IVF patient screening, under the mandatory HFEA Code of Practice, overlaps considerably with existing NBS testing in terms of HIV, Hep B, and Hep C screening. However, there is, at present, no requirement in the EU TCD or the UK Stem Cell Bank guidance for donor screening to ask the lifestyle questions routinely applied by the blood service to screen donors. Considerable debate thus continues to surround the adequacy of molecular assays to detect any infection or contamination by testing the cell lines directly, particularly for master stocks.

Conclusion

As one of the newest arenas of tissue banking, the reproductive setting remains a site of emerging policy and protocols which continue to evolve in the context of high-profile scientific advances and accompanying political debate. An ethically sensitive setting, the context of assisted conception, from which the vast majority of eggs and embryos are donated for stem cell research, raises important questions for patients and tissue coordinators, as well as clinicians, embryologists, scientists, and policy makers. Although the highly charged moral debate surrounding research involving human embryos appears unlikely to diminish, this chapter also notes the importance of the discovery that all tissue and cells are likely to retain far more regenerative and differentiating potential than previously imagined. This discovery has implications for the entire field of tissue banking, and though the highly charged moral debate surrounding germ line tissues and cells may initially arise in the reproductive setting, it is by no means restricted to that arena.

Like genetic fingerprinting, the science of cellular regeneration has the potential to change the status of tissue samples en masse, as individual samples become newly valuable as potential master stocks, or perpetual populations of named cell colonies, such as the famous Hela line of immortal cells used in cancer research. While it is highly unlikely that ethical uniformity will ever be reached concerning the moral status of the human embryo, it is entirely possible that many individual countries seeking to combine the possibility of beneficial scientific and clinical advances with respect for the "special" qualities of human reproductive material will devise combined approaches, such as that found in the United Kingdom, in which not only rigorous and standardized, but also flexible and tolerant, systems of enabling those patients who wish to donate gametes and embryos to research can do so knowing that some of the very highest standards of practice in tissue banking have been established in this sector.

However, no amount of regulation or even best practices can eliminate some of the profound risks of gamete and embryo donation, in particular, the risks women face of hyperstimulation syndrome in the context of IVF, a potentially fatal condition affecting as many as 1 in 100 cycles. The risk of exploitation of women and couples whose consent to donate is almost exclusively acquired in the highly stressful context of the assisted reproduction clinic is also significant. Increasing commercialization of this sector, which is differently evident in both the United States and the United Kingdom, should remain of concern in terms of its exploitative potential. As definitions of best practices change in concert with evolving regulations, and as tissue donation from this sector increases in volume, the need for robust assessment of donor safeguards – preferably on the basis of empirical research – will remain at a premium.

KEY LEARNING POINTS

- In the United Kingdom, assisted conception and hES cell research are both highly regulated and advanced scientifically and represent a pioneer exemplar of the "combined approach," whereby extensive regulation enables a permissive research climate.
- Consent procedures for embryo donation to stem cell research must respond with due diligence to novel sources of patient concern.
- An embryo is not readily conceptualized in terms of either its "own" or its donor's individual autonomy. Embryos created in the context of IVF inevitably must be thought of as embodiments of shared reproductive hope and investment, often for couples whose primary experience is of reproductive loss or disappointment.
- Couples who have failed in their attempt to conceive a child through IVF (as remains the fate of the majority of couples who undergo IVF) can gain

some sense of reward from potentially helping others, thus contributing toward a generalized social good even when their own immediate reproductive aspirations have been unfulfilled. In such cases, both members of a couple must agree to the specific terms of donation.

- The fact that a single embryo could be the basis for a cell line potentially used to treat thousands of people, and the possibility to immortalize, and endlessly divide, means that such a line creates unprecedented ethical difficulties, as do issues of screening donors and providing feedback.
- Consent for embryo donation to stem cell research must be undertaken by a professional who is independent from both the clinical and research staff in his or her assisted conception unit, in order to avoid conflicts of interest.
- Having a peer group for work in this sensitive area will facilitate continuous improvement in the development of policies and practices in consent discussions with potential donors. It will also facilitate support of the frontline and administrative and laboratory staff who work in these types of facilities.
- The risk of exploitation of women and couples, whose consent to donate is almost exclusively acquired in the highly stressful context of the assisted reproduction clinic, is also significant. For consent to be robust, legitimate, and ethically sound, comprehensive information must be given to the donors in a form that is readily accessible and allows a free and informed decision to be made by potential donors.
- In the establishment of minimum consent criteria, clarity and brevity have been emphasized, while retaining a substantial core of necessary information. Best consenting practice is enhanced by ensuring that the patient information and consent form is attractive and accessible, easy to read, and easily completed. Potential donors need to be made aware that the so-called reversible anonymization will be used to ensure that in the event of a major health threat, they may be contacted.
- One of the most common and widespread concerns expressed by patients in the context of assisted conception in general, and equally by patients who are approached about the possibility of donating their eggs or embryos to hES derivation in particular, is the *reproductive misuse* of such material.
- The possibility of introducing conditional consent may not be in the patients' best interests, as the feasibility and, therefore, authenticity of such a guarantee of unknown duration cannot presently be reliably assured.
- The large-scale amplification involved in the clinical application of hES cell line therapies in the future, whereby several thousand patients might receive hES cell products from a single line, poses significant challenges at the level of determining appropriate screening procedures throughout the derivation process.

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13 Clinical Governance in Cell and Tissue Banking

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This chapter will take the reader through, and place in context, the general processes that are developing in the United Kingdom and the United States to ensure patients receive safe and high-quality care. These general principles can also apply to the clinical and laboratory aspects of tissue banking. Quality and improvement aspects in clinical care provision include standards of good practice equivalent to the principles of "good manufacturing practice" and "good laboratory practice" that apply in donor selection and tissue processing facilities. The terms used reflect the vocabulary used in the United Kingdom, and similar terms are often used elsewhere in the world. The glossary provides simple definitions of the terms used throughout the chapter.

Introduction

Clinical governance refers to an interdisciplinary oversight that ensures that the practice of individual clinicians, their clinical teams, and support services provide clinically effective, up-to-date, efficient, and equitably available health care. Peer review plays a key role in ensuring that individual clinicians and teams are accountable for the care they provide. Tissue banks and their physicians do not provide direct patient care, but clinical governance includes the application of governmental laws and regulations through the setting of professional standards and accreditation for organizations.

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