OPINION

Ethics of testicular stem cell medicine

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The ethical issues raised by advances in reproductive technology allowing the transplantation of testicular stem cells to enable infertile men and cancer patients, including the pre-pubertal, to have children, and to provide new contraceptive prospects for fertile men are discussed. Consideration of respect for the patient’s autonomy, the need for informed consent and the health of any offspring resulting from such a procedure are included. Topics covered include: the problems raised by cases needing consent for the transplantation of testicular stem cells from pre-pubertal and adolescent patients; the legal status of stem cells; the arguments for treating such tissue as property which might serve as a means of guaranteeing respect for patients’ rights in disputed cases; aspects of patents and the ethics of allowing commercial traffic of such material; questions relating to health and safety, as well as xenotransplantation technology in humans; and posthumous procurement use of germ cells from minors. Proposals are made to enhance informed and effective consent, while supporting patient determination, choice, autonomy and technological advances. The paper appeals to the emerging EU directives in relation to tissue procurement, storing and use of tissue and cells to adopt a pragmatic and meaningful position which will help enhance patient determination and autonomy in relation to the emerging technologies in reproductive medicine, whilst providing a pragmatic way forward for fertility clinics and laboratories to function.

Key words: assisted reproduction/cancer patients/ethics/risks/safety/testicular stem cells

Scientific background

The earliest developments in the field of testicular stem cell medicine came from work on rat (Deansley, 1954) and mice (Parrott, 1960) models. The possibility that spermatogonial stem cells could be used to restore fertility in males after banking was established by analogy with routine clinical practices in bone marrow transplants. Brinster’s group (Brinster and Zimmerman, 1994) has shown that when a suspension containing gonocytes from immature mouse testes is injected into the seminiferous tubules, the testes can be repopulated and spermatogenesis restored; in some cases, fertility returns after sterilization with busulphan (Brinster and Zimmerman, 1994; Ogawa et al., 2000). What is more, the germ cells could be cryopreserved in advance (Averbock et al., 1996). The cells are apparently able to transmigrate between Sertoli cells to their normal location in the basal compartment of the tubule.

Work in other species and in humans aims to develop this strategy for practical purposes (Schlatt et al., 1999; Brook et al., 2001a), including applications for cancer patients. It is anticipated that testicular tissue biopsies could be cryopreserved for autologous transfer when the patients are in full remission (Bahadur et al., 2000). This method could serve as a back-up for routine semen cryopreservation already offered, as it provides the potential for reinitiating spermatogenesis, especially in boys receiving total body irradiation. The efficacy of recolonization of germ cells in rodents (Nagano et al., 1999) provides hope for sterile men. Recently, mice have been born after the use of frozen immature testicular tissue taken from one set of mice and matured in others, and a rabbit was born after using rabbit testicular tissue that had been matured in host immunodeficient mice. The recipient host mice who had the testicular tissue transplanted into their testes had their own spermatogonial cells destroyed by cancer drugs. This study provides an important impetus for work on human testicular stem cell transplantation (Kanatsu-Shinohara et al., 2003). In the latest innovations, testicular stem cells have been derived from embryonic stem (ES) cells in various species, leading to newer prospects for male infertility (Toyooka et al., 2003; Clark et al., 2004; Hong et al., 2004; Nayernia et al., 2004).

Introduction

Advances in reproductive technology have brought new possibilities for patients unable to have children normally. The ultimate goal of testicular stem cell technology is to create healthy offspring and to create new possibilities in male contraceptive design. Typically the kind of patients who may utilize the technology are infertile men who present with azoospermia, Sertoli cell-only syndrome or cryptorchidism,
and men with cancers who are unable to ejaculate, as they seek to propagate their own genetic line rather than using the donor sperm available. Recently, the technique has been extended to preserve gonadal tissue for pre-pubertal children. The prospect of a male contraceptive designed through specific stage germ cell immunization seems a further promising prospect. The safe use of such material inevitably requires considerable research, and the limitations of the process should be recognized. Equally, we need to recognize that if patients were to exercise autonomous choice when faced with a possible loss of fertility, preservation of testicular tissue or the germ cells may need to be followed through despite the fact that the technology is still in early stages of research and the best approach may not be clear.

When working with sensitive reproductive material, it is important to understand the social, legal and ethical ramifications. This is to ensure that scientific and medical progress is made transparent, in tune with and acceptable to society’s expectation. As a minimum, we need to express the value of ‘beneficence’, ‘maleficence’ and ‘autonomy’ concerning respect for self and autonomous choice. In order to relay a sense of public acceptance, we need to be able to either provide answers or be seen to have addressed concerns and problems well before these became a reality. On the whole, these concerns will encompass safety, commercialization, health and disturbance or deviation from normal reproduction. The public will need to be convinced of the appeal of xenotransplantation techniques (Schlatt et al., 1999; Kanatsu-Shinohara et al., 2003) in research when clinical application is sought. Our scientific world is increasingly under public scrutiny and the public needs to have its share in decision making. Public disquiet covers wide areas of science, including genetically modified (GM) foods, nanotechnology (Glover, 2004) and man-made pollutants; reproductive technology in humans and agricultural animals has continued to attract significant media reports, including interest in testicular stem cell medicine (Reaney, 2002). Scientists recently have been described as ‘a high priesthood serving a tutelary god which is science and claiming a comprehensive and exclusive understanding of God’s intention’ (Glover, 2004). It is therefore important that reproductive technologists retain their sense of proportionality and a perspective of public concerns while progressing with their scientific advances. The field of reproductive medicine remains highly sensitive, with complex legal and ethical issues.

**Ethical issues**

The ethical issues relate directly to the core notion of respect for human beings. The main ethical issues involve the need for an avoidance and limitation of injury, balanced against considerations of benefits, safety, autonomy and consent. The consideration of avoidance of harm is vague in the case of testicular stem cell transplantation; the taking of tissue cannot currently be justified for clinical use, although the technology to do so exists. The experimental nature of the whole field of assisted reproductive medicine requires us to exercise our judgement. In this case, the amount of tissue to be extracted, the mode in which it is to be removed and the issue of informed consent all need to be taken into account. It would be unacceptable for clinics merely to jump on the bandwagon by offering services such as stem cell cryopreservation on a commercial basis. It is unclear at present whether the transplantation of stem cells could be done safely without long-term harm, and many in vitro models will need to be evaluated, especially for genetic safety. We need to be able to monitor the effects of an abnormal repopulating mechanism on the patient’s welfare given that this is something difficult to prove in laboratory experiments. Appropriate safety aspects should be fully explored, and there should exist safeguards for people from whom testicular tissue is removed, for example in commercial and patent aspects of testicular stem cell technology.

As for injury, in the context of stem cell transplantation research, if a boy protested at having tissue taken from him, despite parental consent, then there could be scope for the charge of having caused bodily harm. This is something clearly to be avoided by engaging the child in the decision-making process, especially as the procedure to preserve and infuse testicular stem cells cannot currently be justified as essential, even if it is desirable (Bahadur and Ralph, 1999).

There are clearly unacceptable and unethical uses of human tissue or its extracts, and these may include the production of leather, cosmetic products or herbal aphrodisiacs. Perhaps more difficult to evaluate is whether human tissue can be bought and sold, and whether the donor has any rights to or say over the tissue. Practitioners are also known to court the media prematurely in order to report on unfounded or weakly based information, such as recovery of sperm after stem cell transplantation, without distinguishing this from what could be natural recovery. This type of approach can have a profound effect on vulnerable patients, especially in the commercial sector. The taking of testicular stem cells from minors after death is unacceptable as the interest of the patient cannot be justified. Likewise, the use of previously stored testicular stem cells from minors in posthumous procreation to recreate a lost son is unethical, given that the overriding reason is likely to be parental bereavement. Philosophers find these issues difficult to resolve, and they are discussed in the context of rights and utilitarianism or, more broadly, consequentialism.

**Legal status of stem cells**

To date, courts in England and Wales have not addressed the issue of the legal status of human reproductive material outside the human body. Although we know there is no property status in corpses, and although since the abolition of slavery, living persons cannot be the subject of property, the status of tissue has never really been decided; today even biopsied tissue falls into a grey area (Wright, 2004). A corpse may, however, still be accorded property status if it has undergone a process or the application of human skill, such as that involved in stuffing or embalming. Gametes and embryos have an undefined status where questions such as accidental damage, modification or destruction arise. An embryo or
fetus has no legal status, and this position in European law was reinforced recently for the fetus (Anonymous, 2004a). By the same token, a disproportionate status of a ‘living baby’ was described when sperm frozen 21 years ago was utilized (Anonymous, 2004b; Horne et al., 2004), highlighting a public sensitivity and respect for reproductive material. Testicular stem cells, whilst having a status no different from that of embryos, still represent half of the unique coding of potential human beings. In the case of testicular tissue, the presence of immature sperm would warrant special consideration, especially if they were derived from very ill cancer patients or children. Careful attention must be paid to ensure that autonomy of individual patients or the need for ‘informed consent’ is not in any way diminished.

Children and adolescents present a new challenge to our understanding of informed consent; in the case of pre-pubertal subjects, parental or proxy consent may be inevitable. The fiduciary duties of doctors should represent a sufficient safeguard of patients’ interests, but the history of reproductive medicine is littered with examples when patients’ interests have not come first, such as in the misappropriation of embryos, or embryo freezing programmes disproportionate to embryos used in research.

Some cases in the USA, however, have come close to answering such questions. An individual’s interest in protecting his tissue could not be granted concerning a cell line produced from a patient’s tissue (Moore v Regents of University of California, 1990). In a case specifically centering on reproductive material, namely a cryopreserved embryo, a bailor–bailiff relationship was deemed to have formed, which suggested a proprietary interest (York v Jones, 1989). This suggestion was criticised in the Davis v Davis, 1992, where the embryo was seen to be neither property or persons but sui generis.

A recognition of proprietary interests in reproductive material would not be incompatible with UK law as it stands. The fact that an embryo is not a legal person has been reiterated in several cases and reinforced by the Warnock Committee in the report of their enquiry into fertilization and embryology. Although it does not automatically follow that the same principles as apply to the embryo in utero should apply in vitro, it is difficult to imagine courts deciding in favour of the dichotomous legal position which would arise if the embryo in vitro were classified a person. Therefore, if not a person, the embryo risks being classified as a chattel. In addition, it should be recalled that a fetus is not accorded the status of a person. The management and trade of sperm, especially across borders, makes the treatment of it as a chattel more of a likelihood.

Against this background, public feeling is likely to be against classifying the embryo as property, which raises the spectre of commercialization of entities with the potential to become human beings. The special status accorded to embryos appears to be more a public relations exercise than one with any legal substance. It is only a matter of time before the property status of sperm, egg and embryos becomes subject to court application or clarification, especially if inheritance disputes arise.

Although it may be perceived that testicular stem cells will have a somewhat lesser status than embryos, the reality is that they are not different. Testicular stem cells generated from donated embryos may also bring an added double-edged sensitivity and attention, given the level of global attention to ES cells (Toyooka et al., 2003; Clark et al., 2004; Hong et al., 2004; Nayernia et al., 2004).

If the process of testicular stem cell culture finds a use in a novel system of hormone production, for example, the issues of patenting and intellectual property rights will undoubtedly be involved. Interest will be heightened further if therapeutic gene modification occurs at the stem cell level.

Oncology and pre-pubertal patients, adolescents and adults lacking capacity

The purpose of gaining informed consent requires the practitioner to disclose all the facts which mutually affect his rights and interests to the patient, so as to protect the rights of the patient while promoting bodily integrity and self-determination among patients. Obtaining consent in pre-pubertal and early adolescent patients remains a contentious topic (Bahadur et al., 2001), beset by confusing legal precepts and advice (Bahadur and Hindmarsh, 2000). These have implications for the patient, parents or legal guardian, and for their involvement in the decision-making process leading towards the acquisition of consent.

Normally consent models refer to treatment but, as stated above, the freezing of sperm is preventative and normally requires no surgical intervention. The consent model which appears most appropriate to the needs of early adolescent cancer patients considering the storage of sperm is that covered in the Gillick case (Anonymous, 1985).

Interestingly, in the USA, the concept of ‘assent’ has been developed. Early adolescents are considered ‘to assent’ (or, its converse, ‘dissent’) when they have sufficient competence to have some appreciation of a procedure, but not enough to give fully informed consent. The age of assent is currently estimated as being 12 (Anonymous, 1977; Sigman and O’Connor, 1991; Committee on Bioethics, 1995).

If a patient is unable to produce semen by masturbation, the possibility of preserving testicular tissue arises, and two issues are at stake. Where the patient is pre-pubertal, and therefore the testicular tissue does not contain ‘gametes’ as defined by the Human Fertilization and Embryology Association (HFEA; haploid sperm only), the legal, practical and ethical considerations are covered by the Children’s Act 1989 and the Tissues Act 1961. Under these circumstances, parental consent is essential (Bahadur et al., 2000). Secondly, where in the opinion of the medical practitioner, ‘gametes’ are present and the patient has reached Tanner Grade 2 maturity, then under the provisions of the UK Human Fertilization and Embryology (HFE) Act, consent must come from the patient.

A ‘family rule’ model (Foreman, 1999) of consent for early adolescents has been developed. When practitioners seek consent they usually want to perform some action and the subject therefore consents to experiencing an event.
Whilst this model does seem appropriate to medical intervention, it should be noted that any coercive influence affecting a decision on testicular stem cell donation and cryopreservation should be avoided; if the patient refuses, then this should be respected.

The basic abilities required to give consent are developed by 2 years of age with an understanding of basic requests and behaviour towards others. By age 7, emotional factors are more important than developmental factors in predicting comprehension of medical procedures, and the use of appropriate techniques can significantly improve younger children’s comprehension of them. Children between 6 and 12 can understand, for example, the idea of psychiatric hospitalization. This fits the model age at which UK patients, parents and practitioners think children can make decisions about surgery, and the age of assent. On the other hand, early adolescents are perceived to lack the social independence needed to make a fully autonomous decision, being vulnerable to external pressures and benefiting from firm guidance (Bahadur et al., 2001).

Therefore, whilst not with respect to medical intervention per se, testicular stem cell biopsy, cryopreservation and transplantation in pre-pubertal cancer patients require delicate, sensitive handling. The UK statutory elements should be taken into account if in vitro mature, haploid, sperm cells are to be produced. We also have a duty of care to the patients’ relatives and guardians, who should ultimately respect the confidentiality accorded by statute to the patient if he so chooses. If the patient refuses at any stage, then this must be respected.

It might at some time occur that an adult who is normally healthy and has the capacity to consent suddenly develops a serious illness, or is involved in an accident, which results in the loss of capacity to consent. The question of freezing ovarian or testicular tissue may arise at short notice. Although ovarian tissue is unlikely to contain gametes as defined by the UK’s HFEA, adult testicular tissue may have such gametes. Strictly in the UK, no gametes can be frozen without informed written consent. However, it is thought that common law principles concerning the removal of gametes from an incapacitated adult should not be changed. If there is doubt about the person’s future recovery, about the potential effects of his or her condition and/or treatment on fertility, or removal of gametes is proposed as being in the individual’s best interests, the courts should determine the lawfulness of any removal. Where the courts have declared removal to be in a person’s best interests, the HFEA should have the power to waive the HFE Act’s consent requirements for the duration of the donor’s incapacity (Anonymous, 2002). The practical downside of this is that little time is available when such requests have to be made to enable the letter of the law to be followed, and this type of problem was presented in the now well known case of Diane Blood in the UK (Bahadur, 2002).

Around the world where the consent requirements may not exist or be strict, cases need to be looked at individually and, for their own protection, practitioners should follow what they perceive as best possible practice in the interest of the incapacitated.

Rights
This leads us to the place of rights in testicular stem cell transplantation technology, which remains equally controversial in an ethical debate. In most cases, when we say that someone has a right to do something, we imply that it would be wrong to interfere with his doing it, or at least that some special grounds are needed for justifying any interference (Bahadur, 2001; Dworkin, 1991: Scott, 1998). Rights can also be described as claim rights (positive rights) or liberty rights (negative rights). The Human Rights Act 1998, article 12, incorporates the right to form a family, thereby acknowledging the unacceptability of obstructing someone in the exercise of that right, rather than demanding positive action. A young cancer patient can decide not to do anything in terms of cryopreserving his testicular tissue before cytotoxic treatment, and this wish has to be respected.

In general, a person from whom tissue is removed has no interest in making any claim to the removed tissue. In the celebrated case of Californian John Moore, the courts decided there were no property rights. English law is silent on the issue of whether a person can claim property rights in tissue which has been removed. The Polkinghorne Committee took the view that a woman having an abortion must give express and unconditional consent to the use of aborted fetal tissue.

The HFE Act, 1990 adopted a scheme requiring consent so as to avoid addressing the issue of property and ownership. The traditional view has been that a body is not property and this view will undoubtedly be subject to further debate as new technologies and possibilities arise, especially in cases when tissue contains reproductive stem cells for personal use. It has to be said that consent to removal does not entail an intention to abandon. Still, however, some support for the property approach can be derived from the various statutes in existence. The HFE Act, 1990 considers that the control and disposal of gametes and embryos rests with the donors. It further allows for the transfer of reproductive material between those having a licence to deal with it, or granting an import–export licence.

The statutory provision, S25, of the National Health Service Act 1977 also seems implicitly to adopt a property approach. The section provides that: ‘where the Secretary of State has acquired: (a) supplies of blood...or (b) any parts of human body..., he may arrange to make such supplies or that part available (on such terms, including terms, as charges, as he thinks fit) to any person....’. The statutory language, therefore, refers to body parts as things, property or goods. Reconsidering the property status of tissue is a logical extension to according rights.

In France (Parpalaix v CECOS, 1984), the wife of a deceased sperm depositor argued that she had a right to her husband’s frozen sperm, which he had deposited before cancer treatment. The court rejected the argument that frozen sperm was property, on the grounds that reproductive material was not inheritable nor an object of commerce. However, the court ruled that the sperm bank must return the frozen sperm to the wife of the depositor, as a result of an understanding between the depositor and sperm bank.
Property and commerce

Practically all court cases involving reproductive material have come close to considering property status. It is all the more compelling that this issue is clarified in the case of the law for reproductive material. ‘Property rights’ are equivalent to a ‘bundle of rights’ such as right to possess, right to exclude, right to use, right to dispose, rights to enjoy the fruits or profit and right to destroy. The codification of the property concept would better protect individual autonomy, as well as clarifying legal rights and duties regarding the control of human tissue in particular circumstances. For example, if a clinic were to destroy tissue without consent, common law property principles concerning the destruction or spoilage of materials rightfully in one’s possession might prove helpful in defining legal rights, duties and grounds of recovery. Some courts and jurisdictions refer to the right of possession as a ‘quasi-property’ right. It empowers spouses or next of kin who are wronged by interference to sue for damages. There are a handful of English decisions in which human tissue has been treated as property: a theft and assault charge in a case where a quantity of hair was taken; a conviction for theft when urine was thrown down the sink in the case of an individual being tested for sobriety; and a similar verdict concerning a blood sample taken from a police station. It cannot possibly be argued that University College London does not own the skeleton of Jeremy Bentham, the renowned philosopher. A hospital which has tissue in its possession, for example for transplant purposes, has such property rights over the tissue as to exclude any claim of another to it, as does a coroner or pathologist who has carried out a post-mortem and retains body parts for examination. To conclude, the fact that the user acquires property rights over removed tissue does not, of course, mean that the user can do whatever he likes with the tissue. In this sense, English law is familiar with the notion of constraints on what an owner may do to or with property.

Perhaps the limitation of greatest concern has to do with commercial dealing in tissue. The HFE Act, 1990 provides that ‘no money or benefit may be given or received in respect of any supply of gametes or embryos unless authorised by directions’. Individual donors of gametes may be paid £15 plus reasonable expenses. The Recommendation on Human Tissue Banking of the Council of Europe’s Directing Committee on public health [Recommendation No R(94)1] specifically recommends that activities associated with human tissue ‘should be carried out by non-profit making institutions’.

Patents

Additional problems may be encountered with intellectual property rights. The requirements for patentability are as follows: novelty, inventiveness, industrial applicability, sufficiency of description and the absence of any feature that makes for inherent unpatentability. The exclusions are as follows: mere discoveries, immoral inventions, and biological, animal and plant varieties. A patent is always granted for a limited period, and in Europe this is currently 20 years, giving the inventor effective monopoly rights.

The European Patent Office (EPO) has granted patents relating to inventions covering the use of processes from human tissue. These have included the production from human tissue of cell lines, e.g. a human lymphoblastic cell line, and a human hepatocyte culture process; human cell-derived protein products (e.g. interferon); and DNA fragments, e.g. genes coding for useful proteins such as the hormone relaxin. A highly purified sample would meet the novelty requirement, as would a glycosylated derivative of the natural form, e.g. the tissue plasminogen activator t-PA, the enzyme active in dissolution of blood clots. The use of relaxin, which relaxes the uterus in childbirth, created opposition in so far as the DNA for relaxin could be obtained from pregnant women, and the use of pregnancy for human profit was judged an offence to human dignity; patenting DNA was considered to be patenting ‘life’. The EPO rejected this opposition and noted that the original ovarian tissue had been donated during the course of necessary gynaecological operations. This use of donated tissue was no more immoral than using donated blood as a source of life-saving substances, such as blood clotting factors. It held that DNA amounted to a chemical substance rather than ‘life’.

It is not clear to what extent the exclusion of patents on grounds of morality may apply. Germ cell modification for germline therapy is perhaps one area, and advances in animal sperm modification to alter progeny is perhaps another area of contention. It is envisaged that patent applications for testicular stem cell technology will follow, especially where gene therapy may be involved, and where male infertility may be reversed (Toyooka et al., 2003; Clark et al., 2004; Hong et al., 2004; Nayernia et al., 2004). Recent advances in a mouse model show that sperm cells can be derived from ES cells which, when injected into oocytes, are capable of restoring the somatic diploid chromosome complement and develop into blastocysts (Geijsen et al., 2004; Azim Surani, 2004). The prospect of asexual reproduction becomes possible.

Health and safety

The well-being of the patient and of any offspring born with the assistance of new technologies will undoubtedly be one focal point from the public. An integral part to offering such services is also the quality and well-being of the service and its providers. These aspects will be analysed from the standpoint of offering testicular stem cell technology. The purpose of gaining informed consent requires the practitioner to disclose to the patient all the facts, which mutually affect the rights and interests of the patient.

The size of the biopsy or the effect of repeated biopsies need to be assessed in terms of trauma and how this may manifest itself in the health of the testes. Taking a normal biopsy from a child with a very small gonad may border on castration, and whether there are long-term well-being implications and the need for testosterone therapy need to be discussed. There are issues for patients with blood-borne cancers and the manner in which the sample may be used or not
used if transplantation of tissue has to be considered. If a disaster were to occur from the use of potentially ‘flawed’ genetic material, then a ‘wrongful birth’ action or ‘wrongful life’ action could follow in some states of the USA. An action for ‘wrongful birth’ is one brought by parents of a child born with some defect or disease, who allege that the negligence of prenatal health care providers or genetic counsellors deprived them of their ability to make an informed decision about whether to have the child who had a likelihood of being born in an impaired state (Kasama v Magat, 2002). This action is brought by parents to recover damages accruing from having to endure having an ‘impaired’ child. The only way a person who had taken advantage of the proposed service would be able to sustain this cause of action is if he/she were not properly warned of the risk of passing cancer onto his/her potential child. Therefore, if practitioners properly warn of any risks associated with an individual who had cancer passing it onto his/her offspring, a ‘wrongful birth’ cause of action should be precluded. A ‘wrongful life’ cause of action, however, would not necessarily be unavailable. ‘Wrongful life’ claims, as they would apply to this scenario, would be claims by ‘abnormal’ or ‘unhealthy’ children (or the parents on their children’s behalf) asserting that but for the practitioner’s negligent advice or treatment, the child would not have been born to experience the pain and suffering of living with such an impairment (Hayman v Wilkerson, 1987).

The very patients’ testicular stem cell technology could benefit also present a double-edged dilemma of transmitting to the offspring, for example, a cancer gene or the infertility gene, and the unavoidable application of ICSI. The transmission of the deletion on the Y chromosome too has implications for children born from testicular stem cells (Katagiri et al., 2004). We also need to recognize in relation to the indiscriminate use of ICSI that the calcium oscillation patterns which are thought to be genetic regulatory features are completely altered compared with normal IVF, and with less mature sperm (Kurokawa and Fissore, 2003), and doubts about the long-term health of offspring produced by the procedure are constantly commented upon. Longer term but limited studies on children born from IVF technology appear to show growth retardation, although overall they are apparently fine (Koivurova et al., 2003; Ludwig, 2004). For patients with Sertoli cell-only syndrome or testicular cancer who could benefit from testicular stem cell technology, there may be specific observations which need to be considered. In most tubules devoid of germinal cells or lacking spermatocytes and spermatids, the Sertoli cells’ nuclei showed an increase in histone H4 acetylation. A similar observation was made in the peritumoral seminiferous tubules of testicular tumour tissue that lacked germinal cells, with carcinoma in situ (CIS) cells being hypoacetylated. The global hyperacetylation of elongating spermatids during spermatogenesis could be part of an intercellular signalling pathway involving Sertoli cells and germinal cells, which could be disturbed in cases of severe spermatogenesis impairment, as well as in tubes surrounding germ cells in testicular tumours (Faure et al., 2003).

We need to recognize that the testicular stem cells need to mature to at least the late stage haploid spermatids for ICSI to take place. Maturing the sample by orthoptic transplantation or germ cell infusion seems reasonable, and in animal models shows promise. However, such a strategy for blood-borne cancer and testicular cancer patients must be avoided, even if there are biochemical or mechanical ways of flushing out such tumour cells, as the flushing may not always be efficient. The effects of an unusual reverse population mechanism of germ cells into the existing testes need to be noted, as well as any long-term effects this may pose to the health of the testes. Reaction to transplantation on a non-reproductive site, such as an ‘arm’ in humans, for reproductive purpose, has been mixed. With ovarian tissue, the logistics of additional internal surgery and intrusive follicle aspiration seem a practical reason, but this reasoning cannot be evenly applied to testicular germ cells. Overall, the idea of unusual transplantation sites seems to be met publicly with caution, and the effects of altering the pertinent long-term developmental ‘genetic and biochemical switches’ in an unnatural biological environment seem to be ignored. Strong concerns and reservations have been expressed by the public and scientists on xenotransplantation and xenomaturatation per se, and in particular the possibility of releasing a new virus or bacterium into the environment. The clinical application of producing human gametes by xenotransplantation or xenomaturatation has added concerns in so far as genetic contamination or mismatches may occur, and how these may manifest in the offspring. However, research application of both these techniques, xenotransplantation and xenomaturatation, ought to be allowed in a controlled environment as interesting, safe and effective developments may one day arise.

The other approach is to in vitro mature the testicular stem cells; unlike mature sperm, these cells undergo meiosis, thereby maintaining genetic diversity in the main germline. Likewise, germ cells have more potential to be altered by different maturation processes, and disruption of methylation patterns could have possible long-term health implications for the offspring, in particular in relation to genomic imprinting diseases (Clayton-Smith, 2003). Consideration of methylation patterns also applies to isolated germ cells (Aslam et al., 2000), as any protective cells are removed thereby making the cells more prone to DNA fragmentation or chemical changes by external agents. Furthermore, the dialogue between the germ cells and Sertoli cells seems relevant (Jegou et al., 1992). Paternal DNA integrity also appears to be important in development of the human embryo (Tesarik et al., 2004). In this sense, it is worth noting that human testicular germ cell infusion has already been reported (Brook et al., 2001b) with dye solution via the rete testes. Any recovery of spermatogenesis would be difficult to distinguish from normal recovery, which occurs in a number of cancer patients.

The storage of tissue, including gonadal tissue, comes under the Medical Devices Agency set up so as to ensure the safety of tissue storage and use. In the UK, it has just been announced that a new ‘Regulatory Authority for Fertility and Tissue’ is to replace the HFEA and the Tissue Authority,
highlighting the increasing importance of tissue (Anonymous, 2004d). Concerns are understandable, given that the donated tissue is for heterotopic transplantation and hence pharmaceutical grade tissue is required. Gonadal tissue and germ cells are likely to be used for orthotopic transplantation. There is a need to screen patients for hepatitis B, hepatitis C and human immunodeficiency virus (HIV), so that mixed storage of samples does not cause cross-contamination. Nitrogen vapour-only freezing does not give added reassurance as vapours circulate carrying any airborne pathogens. The use of automated alarms and fillers, too, has proven to offer false reassurances, and banks have gone dry due to the malfunction of complicated structures. It is important that banks are physically maintained and checked in order to avoid a false sense of security.

The Health and Safety of Work Act 1974 imposes important duties on employers with regards to health and safety. The Control of Substances Hazardous to Health (COSHH) Regulations 1994 relate to exposure of employees and their environment to toxic substances. Records and auditing of samples along with good laboratory practice and accreditation collectively contribute towards staff and patient welfare. More transparency is expected with the Freedom of Information Act. In cases of unproven technologies, it is prudent to draw up contracts which recognize the limits of the application of such reproductive germ cells for the purpose of procreation. These wider issues are equally important in ensuring standards are maintained in any testicular stem cell work.

Most recent developments in Western Europe relate to EU Directives on Tissue Banking (Anonymous, 2004c) with well meaning standards, but which most clinics in the UK are currently unlikely to attain without very significant laboratory and staffing investment. The EU commission has about 312 million Euro to deal with this tissue issue, and one can imagine the European clinics will need to match at least that sort of expenditure to fulfil their demands. One has to bear in mind that cryopreserved sperm has been used for nearly three decades and with overall satisfaction. The standards currently required for tissue appear disproportionate. It is akin to saying that ‘if this option was the last possible option for a patient to preserve his fertility then this should not occur as the facilities are not up to scratch’. From the welfare of the child consideration, this apparently translates as, ‘his or her safety is so important that it is better not to be born’. There is no basis for such a rash decision and it would appear that in the UK, no clinic has gained an ovarian or testicular tissue licence, to date. It is important that this option is made available to patients as advances seem promising. New laws cannot be applied retrospectively to already stored tissue and provisions have to be made for its use. It is important for EU politicians to understand that a pragmatic balance needs to be struck to enable laboratories and clinics to function normally, and be able offer the possibility to keep the fertility options for patients open. Clinics and laboratories are already mindful of litigations and hurt to patients. There is an increasing danger of over-regulation, where practitioners and reproductive tissue are increasingly separated by excessive paperwork and bureaucracy, notwithstanding reduced patient choice and autonomy. It is especially important that the EU commission take heed of this message.

**Practical aspects**

What constitutes an informed consent will always be a moot point. The following types of facts are typically required for consent to be considered informed: (i) the diagnosis or prognosis; (ii) the nature and purpose of the treatment or procedure; (iii) the expected outcome and probability of success; (iv) the material risks, benefits and consequences of the proposed treatment or procedure; (v) the alternatives to the proposed treatment or procedure and supporting information regarding the alternatives; and (vi) the effects of no treatment or procedure, including the effects on the prognosis and material risks associated with no treatment or procedure. Beyond ‘informed consent’, the ‘effectiveness of consent’ needs to be maintained. This can be done by encouraging the patient (and partner) to review their consent regularly and make amendments to their changed circumstance in the light technological advance. Children who may have stored testicular stem cells under proxy or parental consent will need to be re-counselling as adults and be allowed to re-consent and afforded greater autonomy, but within the limits of existing national laws. Children and adolescents are expected to have longevity, and time limits of storage may need to be tailored accordingly. Where proxy or parental consent is concerned, the disposition agreements should stop short of the posthumous procreation of ‘grandchildren’ or ‘replacement children’ with surrogates. Appropriate support and therapeutic counselling may better serve such parental bereavement.

When it comes to the use of such material, the transition from research phase to clinical application is always going to reveal difficult dilemmas. These may, for example, include: when do we know it is safe to use it for procreation and how many cases should be carried out before the technology can be declared safe for routine use? It would be prudent to avoid the use of dyes in cell infusions, which are inevitably carcinogenic. The various safety views and concerns need to be relayed to patients if litigation is to be avoided in future. It would always be best to consult the relevant national or professional bodies for up to date advice and guidance, and to voice local hospital and ethics committee’s views. All risks, no matter how trivial or hypothetical, need to be explained for ethical and legal reasons.

**Conclusion**

Testicular stem cell technology and transplantation represent a new dimension to reproductive medicine for male infertility and cancer patients, particularly for pre-pubertal boys. Newer developments in stem cell technology could lead to reversing male infertility and enable couples to have children by natural conception. The ethical issues are complex and complicated further by the possible application of the technology to pre-pubertal boys. Safety concerns are foremost and, in the case of patients who have previously undergone cancer treatment, one must err on the side of caution; germ cell
mutation, with its effects on future generations, cannot be ruled out. Xenotransplantation and xenomaturation in humans, despite potential concerns of genetic mismatches and contamination, may lead to interesting developments, which may become safe and effective for use. However, the posthumous taking and use of testicular stem cells in minors is unacceptable.

The issues of consent, rights, the application of the technology, technical preferences, commerce, property status, patents, and health and safety all raise ethical questions which need to be taken into consideration in instances of testicular stem cell transplantation. These ethical dilemmas involve considerations of respect for the patient’s autonomy, the need for informed consent, and the health of any offspring resulting from such a procedure. The issue of consent is particularly complicated in the case of pre-pubertal cancer patients, for whom the technology may prove useful.

While there are no property rights in tissue under the current legislation, to treat such tissue as property might serve as a means of guaranteeing respect for patients’ rights. It is likely that patent applications for testicular stem cell technology will follow. The field is in the research phase and it would be unethical to make commercial gain from those seeking help from this technology.

The emerging political position and directives in Europe need to take account of the need to enhance patient determination and autonomy in relation to the new technologies in reproductive medicine, whilst providing a pragmatic way forward to enable fertility clinics and laboratories to function. Technological advances are breathtaking and, even if the facilities were allowed freely to patients, no significant demand can be expected to put pressure on routine services. The latest proposal in the UK to merge the HFEA with a tissue authority highlights the growing importance of tissue technology in medicine.

References
Davis v Davis (1992) 842 SW 2d 588 (Tenn Sup Ct).


