4 New Frontiers of Reproductive Science and Medicine

4.1 Areas of Inquiry

In chapter 3, we introduced several ethical principles germane to any discussion of reproductive technologies and biomedical research. We have also provided a few illustrations of how these principles may inform political choices. In this chapter, we turn our attention to several recent developments in reproductive medicine and biomedical research and discuss some of the ethical concerns they may raise. We do so by characterizing each of these developments as an instance of a broader class of cases – in other words, by adopting a taxonomy of reproductive treatments and biomedical research. This approach represents a significant departure from the practice, common among policy-makers and legal scholars, to focus narrowly on just one or perhaps two specific applications of a medical or scientific development.

There are obvious reasons for taking a broader approach to discussing controversial ethical dilemmas. When the Congress decided that aviation needed a separate administrative entity responsible for ensuring its safety, it did not charged the newly established FAA with regulating only the types of aircrafts existing at the time. The FAA was responsible for aviation safety in general, i.e., for the safety of all existing and future aircraft models. Similarly, the FDA is charged with ensuring the safety and efficacy of most current and future drugs, biologics, and medical devices, not just of those in existence at the time its enabling legislation was passed. Translated to our context, this means, for example, that we consider intracytoplasmic sperm injection (ICSI) an instance of a standard reproductive technique, while pre-implantation genetic diagnosis (PGD) is better described as a technology of reproductive customization. The former type of reproductive treatment raises mainly health and safety concerns. The latter is controversial for reasons other than just health and safety.

Standard reproductive techniques and technologies of reproductive customizations are two of four distinct policy domains to be discussed in this chapter. The other two are innovative reproductive treatments and biomedical research involving human reproductive tissues. Taken together, these four policy domains define the scope of possible legislative and regulatory interventions to be discussed in this report. As for any other typology, there may be instances of reproductive treatments or biomedical research that cannot unambiguously be assigned to a specific category. Some would probably consider ICSI an instance of an innovative rather than a standard reproductive technique. Other examples could be found. These difficulties are intrinsic to any classificatory scheme, and must be dealt with on a case-by-case basis. It is also worth mentioning that ours is certainly not the only possible categorization. Other equally useful

taxonomies are likely to exist. For example, in "Reproduction and Responsibility," the President's Council on Bioethics adopts a similar but by no means identical taxonomy.[1]

The commercialization of reproductive treatments would require a separate discussion. By this term, we mean both the commercial trade of human reproductive tissues and the various contractual arrangements made possible by the market for reproductive tissues. Many reproductive treatments, standard or otherwise, raise distinctive ethical and legal questions if the gametes involved stem from one or more third parties. Also to be included in this category is surrogacy, or the delegation of a pregnancy to a surrogate mother. While these questions are by no means trivial or negligible, in this report we will not discuss them in detail. The transformation of human procreation from an intimate act to a set of contractual obligations is a tendency that certainly does not leave us indifferent. At the same time, this trend is not new, and does not raise fundamental new ethical dilemmas. For this reason, in this report we focus mainly on new technological possibilities in the narrow sense of this term.

Our classificatory scheme is designed to emphasize what we believe are distinctive attributes of various reproductive technologies and lines of biomedical research. By classifying a new reproductive technique as an instance of a familiar type of reproductive treatment, policy-makers would have at their disposal several tried and tested ethical arguments. Reliance on ethical precedents would of course greatly simplify the task of identifying the most appropriate regulatory response. This is an important benefit, considering the often puzzling nature of new bioethical dilemmas. A quasi-judicial approach to the resolution of controversial ethical questions would also minimize the opportunities for interest groups to influence or distort the regulatory process. In the process, it would make judicial review a less attractive option. Finally, a classificatory scheme would discipline regulators by encouraging the adoption of consistent policies, thus reducing the scope for arbitrary and capricious agency behavior. In sum, a taxonomy of reproductive treatments and biomedical research would increase both the consistency and fairness of the rule-making process.[2]

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[1] There are considerable similarities here between resolving classificatory ambiguity and the task faced by common law judges (and the Supreme Court, for that matter) in determining exactly which precedents are relevant to judicial case. We will return to this question in chapter 7.

[2] Ethicists may find the approach proposed here reminiscent of casuistry. Cf. Carson Strong, *Ethics in Reproductive and Perinatal Medicine: A New Framework* (New Haven, CT: Yale University Press, 1997). Social scientists could point out that classificatory schemes have been at the center of heated debates in the sociology of science for many years. See Barry Barnes, "On the Conventional Character of Knowledge and Cognition," in *Science Observed. Perspectives on the Social Study of Science*, ed. Karin Knorr-Cetina and Michael Mulkay (London: Sage Publications, 1983); Barry Barnes, David Bloor, and John Henry, *Scientific Knowledge: A Sociological Analysis* (Chicago, IL: University of Chicago Press, 1996); David Bloor, *Wittgenstein, Rules and Institutions* (London: Routledge, 1997); Harry M. Collins, *Changing Order: Replication and Induction in Scientific Practice* (Chicago, IL: University of Chicago Press, 1992); Harry M. Collins and Trevor Pinch, *The Golem. What Everyone Should Know About Science* (Cambridge, UK: Cambridge University Press, 1993); Mary Douglas, *Risk and Blame: Essays in Cultural Theory* (London: Routledge, 1992).

4.2 Standard Reproductive Techniques

Standard reproductive treatments are the first type of reproductive treatment to be discussed in this chapter. These are treatments that have been in use for many years, are quite familiar to ART practitioners, and are part of the curriculum of any medical school. In addition, there is widespread agreement among ART practitioners on how to perform these procedures, at least with regard to their main steps. Standard reproductive procedures include IVF, gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), intrauterine insemination with washed sperm (IUI), and intravaginal culture (fertilization of oocytes in an air-free plastic capsule placed into the maternal vagina).[3] In this category, we also include well-established procedures such as embryo and sperm cryopreservation and micromanipulations such as ICSI. Strictly speaking, these are not reproductive treatments; they may be regarded as preliminary or ancillary procedures performed prior to an actual reproductive treatment. ICSI, for example, is not a reproductive procedure; it is often used to overcome male infertility, and may be performed as part of an IVF cycle.

The constitutive attribute of standard reproductive procedures is their largely uncontroversial nature. The ethical concerns raised by these procedures are limited mostly to the health and safety risks for the mother and the child.[4] The child's well-being and the health and safety of the woman undergoing ART treatments are two of the guiding ethical principles identified in chapter 3. It is not our intention to examine in great detail possible health and safety risks associated with standard reproductive techniques, but a few observations are in order.

Thirty years after the first "test-tube" baby was born, it remains very difficult to reliably quantify the health and safety risks associated with ART procedures. In the United States, a robust system of health and safety monitoring for ART children does not exist. Implementation costs, lack of government funding, excessive professional fragmentation in the medical profession, and logistical difficulties all have contributed to exacerbating this problem. ART practitioners, for example, follow a pregnancy only for the first three months – they do not examine the newborn baby, nor do they conduct follow-up examinations.[5] In addition, a meaningful comparison of children born through ART and naturally conceived children requires a matched parental control group. In practice, this requirement can rarely be met, as couples seeking ART services by definition are not representative of the general population. This means

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[3] Centers for Disease Control and Prevention, "Survey of Assisted Reproductive Technology: Embryo Laboratory Procedures and Practices. Appendix G: Survey Summary Responses," (Atlanta, GA: 1999).

[4] Mostly, but not exclusively. Case in point is the wish of an Australian woman to become pregnant with the sperm of her deceased husband, a wish the Australian Supreme Court in 2005 granted her after an eight-year legal battle. Similar cases have been reported in the United States and Britain.

[5] Laura A. Schieve et al., "Assessment of Outcomes for Assisted Reproductive Technology: Overview of Issues and the U.S. Experience in Establishing a Surveillance System," in *Current Practices and Controversies in Assisted Reproduction. Report of a Meeting On "Medical Ethical and Social Aspects of Assisted Reproduction" , September 17-21 2001*, ed. Effy Vayena, Patrick Rowe, and David P. Griffin (Geneva, Switzerland: World Health Organization, 2002), p.364-65.

that an investigator may not be able to ascertain with a high degree of confidence whether an observed higher incidence of certain conditions among ART children is attributable to the ART treatment itself, or whether the cause lies with the parents.

Partly motivated by the recommendations contained in "Reproduction and Responsibility," and partly triggered by studies reporting a significantly higher percentage of birth defects in children born through IVF and ICSI,[6] the American Society for Reproductive Medicine (ASRM) announced in 2003 that it was convening a panel of experts to thoroughly review the available empirical evidence on the health and safety risks of ART treatments. The panel presented the study's main findings at the 2004 Annual Meeting of the American Society of Human Genetics (ASHG). It identified more than 2,400 studies pertaining to the health and safety of ARTs, selected 169 studies for further scrutiny, and ignored more than 2,000 studies that did not meet the panel's criteria for inclusion in the study.[7] Based on this evidence, the panel concluded that there is no reason for concern, with a notable exception – they found "suggestive but not conclusive evidence" that ART children may suffer from a higher incidence of two rare disorders, Angelman and Beckwith-Wiedemann syndromes.

In theory at least, this review should have provided definitive answers to the question of whether ART treatments expose ART children to elevated health and safety risks. Unfortunately, definitive answers are not forthcoming. Although the study's main conclusions have been reported widely by the news media, as of this writing the report has not been made available to the public, and it has not been published in a peer-reviewed journal. In addition, the experts selected by the Genetics and Public Policy Institute to conduct the study represent the ART industry itself; thus, the study in essence amounts to a self-evaluation. While this is not necessarily a reason to dismiss the report's findings, the self-evaluatory nature of this report does cast some doubts on its credibility. In fairness, evaluative efforts often face a trade-off between recruiting the best experts in a given field of inquiry and ensuring independence and credibility. At the same time, the public release of this report certainly would have increased the credibility of the panel's findings.

As our report is focused on new reproductive technologies rather than on standard reproductive treatments, we won't delve into health and safety issues in great detail. Conversations with reproductive endocrinologists have shown that the profession generally is dismissive of any concerns about the health and safety of assisted reproductive technologies. These same conversations also show that practitioners seem to be unaware of studies showing a statistical relationship between ART treatments and increased health risks. For this reason, we felt it important to include in this report several illustrations of elevated health and safety risks associated with ART treatments, which are included in Appendix C. (Appendix C focuses exclusively on IVF, which remains by far the most common standard ART treatment in the

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[6] Michèle Hansen et al., "The Risk of Major Birth Defects after Intracytoplasmic Sperm Injection and in Vitro Fertilization," *New England Journal of Medicine* 346, no. 10 (2002).

[7] Tracy Hampton, "Panel Reviews Health Effects Data for Assisted Reproductive Technologies," *Journal of the American Medical Association* 292, no. 24 (2004).

United States. According to a 2002 CDC survey of ART success rates, IVF accounts for more than 90 percent of all performed cycles involving fresh non-donor eggs.)[8]

IVF safety has received considerable attention in the clinical literature, though mostly abroad. Among the risks associated with IVF mentioned in the literature are birth defects, low birth weight, neurological disorders, ectopic pregnancies, craniosynostosis, Beckwith-Wiedemann syndrome, Angelman syndrome, and the cloacal-bladder exstrophy-epispadias complex. Some of these risks are minute, while others are quite large. In most cases, however, it should be remembered that these risks reflect statistical associations and not causal relationships.

Before turning our attention to innovative reproductive treatments, a few words about what has become known as collaborative reproduction are in order.[9] Collaborative reproduction ranges from fairly prosaic procedures, such as sperm donation, to medical interventions, such as oocyte and embryo donation. In the United States, sperm donation is a well-established practice, facilitated by numerous sperm banks. (Interestingly, no one seems to know just how many, even though the FDA now requires sperm banks to be registered.)[10] From a public health perspective, this practice is by no means unproblematic. In the late 1990s, the need to prevent the spread of infectious diseases prompted the FDA to regulate the trade of human tissues, including sperm, oocyte, and embryo donation.[11]

Sperm donation does raise some important ethical questions that go beyond considerations of safety and efficacy. There remains considerable skepticism about the wisdom of tolerating a free market for sperm. Much more controversial and problematic from an ethical standpoint are oocyte and embryo donation. Collaborative reproduction involving oocytes is far less common than anonymous sperm donation, partly because retrieving oocytes is a costly and painful medical procedure, but also because oocytes are far more difficult to preserve, though as we show below, cryopreservation technologies are making progress. The use of third-party embryos remains very uncommon, in large measure because a full-fledged market for embryos seems to many to be a very problematic proposition. Not coincidentally, only approximately two percent of cryopreserved embryos have been put up for adoption – less than number of embryos donated for research.[12]

In some extreme cases, four individuals may be involved in the reproductive process: the prospective legal parents and the oocyte and the sperm donor. A surrogate mother may also

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[8] Centers for Disease Control and Prevention, "2002 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports," (Atlanta, GA: National Center for Chronic Disease Prevention and Health Promotion, Division of Reproductive Health, 2004).

[9] Helen M. Alvare, "The Case for Regulating Collaborative Reproduction: A Children's Rights Perspective," *Harvard Journal on Legislation* 40 (2003); Kenneth Baum, "Golden Eggs: Towards the Rational Regulation of Oocyte Donation," *Brigham Young University Law Review* (2001).

[10] Note that "donation" in this context should not be interpreted literally. Sperm donation in the United States is a lucrative business and an industry, complete with its own trade association.

[11] The FDA has promulgated three main new rules: the "establishment registration and listing" rule, the "donor eligibility" rule, and the "good tissue practice" rule. See chapter 5.1.2 for details.

[12] William Saletan, *Leave No Embryo Behind* (June 3, 2005 [cited March 14, 2006]).

become part of this complex transaction, raising the total number of individuals involved to five. These contractual arrangements raise numerous legal questions, for which few if any legally binding answers have been provided. For example, how should the rights and obligations of prospective parents vis-à-vis a surrogate mother be defined? Should the anonymity of the sperm and oocyte donors enjoy unqualified protection? What rules, if any, should apply to embryo adoption? As this brief discussion demonstrates, collaborative reproduction may raise a host of difficult ethical questions. These are not new questions for the most part, and they are issues that have been debated frequently by bioethicists and legal scholars, though as is often the case, there has been very little consensus. In this report, we discuss these questions only tangentially, mainly in the chapter 7.

4.3 Innovative Reproductive Treatments

The term "innovative reproductive treatment" identifies any procedure performed by a reproductive endocrinologist designed to induce a pregnancy. While the aim of standard and innovative reproductive treatments remains the same – namely, achieving a pregnancy – innovative reproductive treatments differ significantly from the standard reproductive procedures discussed in the preceding section: The nature and the magnitude of the health and safety risks involved differ significantly. When performing an innovative reproductive treatment, an ART practitioner is very unlikely to know the precise nature of the risks to the mother and the baby. To the extent that the nature of the risks involved is familiar, very little is known about statistical probabilities. This is in marked contrast to standard reproductive procedures, where the nature of the risks involved is usually well-known and the magnitude of the risks is also familiar, though not always with a high degree of accuracy. This situation reflects a simple fact: While standard reproductive procedures have been the subject of numerous epidemiological studies, innovative reproductive treatments, by their nature, are performed largely without the benefit of clinical information.

The innovative reproductive treatments discussed below raise more than just health and safety concerns. These concerns range from the allegation that ART practitioners, for all intents and purposes, are experimenting on human subjects, unconstrained by the usual regulatory checks, to the view that children should not have more than two genetic parents, or that children should not be created from unborn mothers. Whatever the nature of the specific ethical concern raised in each case, innovative reproductive treatments can easily be distinguished from standard reproductive procedures precisely because they are very likely to raise significant ethical concerns.

Unlike standard reproductive procedures, innovative reproductive treatments tend to be poorly documented and often are not familiar to ART practitioners. This is not entirely surprising, as these treatments generally are attempted only when the usual standard techniques have been tried and have failed. The controversial nature of innovative reproductive treatments may also induce some ART practitioners to avoid publicity. When information about a novel

treatment surfaces, it is usually an indication that the treatment has been performed with some success, as has been the case for ooplasm transfer.[13]

The cases discussed below were gleaned from the news media or obtained from targeted bibliographic searches. Not coincidentally, despite our best efforts, we have not been able to obtain first-hand information about these treatments from industry representatives. The following discussion is intended to provide a sense of what constitutes an innovative reproductive procedure, and what ethical concerns these procedures might raise. How policy-makers should respond to these challenges is the topic of chapter 10.

4.3.1 Tinkering with Biological Parenthood

Over the last few years, several reproductive technologies have been developed to address specific forms of infertility or to prevent passing on genetic diseases. These novel treatments have two attributes in common: The children so conceived have three genetic parents, and the treatments produce inheritable genetic modifications, though they are not instances of human genetic engineering in the narrow sense of this term.[14] These treatments include ooplasm transfer, a technique developed in the early 1990s, and various forms of reproduction by nuclear transfer. (The term "reproduction by nuclear transfer" is ours. Surprisingly, these techniques have not been associated with a specific medical term – another indication perhaps of their experimental nature.)

Reproductive specialists developed ooplasm transfer in an effort to remedy a form of infertility attributable to shortcomings in the cytoplasm of the egg. In this procedure, the egg is fertilized as in any other IVF cycle, but before it is transferred back to the uterus, its cytoplasm is replaced with the cytoplasm of a younger, healthy egg. According to news stories, the technique has been quite successful.[15] Worldwide, at least 30 women have become pregnant through ooplasm transfer. However, in July of 2001, the FDA effectively banned this procedure by declaring ooplasm transfer as a "clinical investigation." Conducting a clinical investigation requires the submission of an investigational new drug (IND) application, a requirement that has since discouraged ART practitioners from performing this experimental medical procedure.[16]

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[13] Jason A. Barritt et al., "Mitochondria in Human Offspring Derived from Ooplasmic Transplantation," *Human Reproduction* 16, no. 3 (2001).

[14] Erik Parens and Eric Juengst, "Inadvertently Crossing the Germ Line," *Science* 292, no. 5516 (2001).

[15] Leila Abboud, "FDA Seeks Rigorous Review of New Fertility Treatment," *Wall Street Journal*, October 7, 2002; Gina Kolata, "Babies Born in Experiment Have Genes from Three People," *New York Times*, May 5, 2001; Helen Pearson, *Egg Injection Boosts Fertility – New Mitochondria May Pep up Ageing Eggs, without Creating 'Three-Parent' Babies* (news@nature.com, October 20, 2004 [cited April 26, 2006]); available from http://www.nature.com/news/2004/041018/full/041018-10.html; *Treatment for Infertile Women Yields Babies with Three Sets of Genes* (Kaiser Family Foundation, May 7, 2001 [cited August 2, 2005]); available from http://report.kff.org/archive/repro/2001/5/kr010507.11.htm.

[16] See the letter to sponsors and researchers, available at http://www.fda.gov/cber/ltr/cytotrans070601.htm. How the FDA managed to prohibit ooplasm transfer provides an illustration of the limits imposed by the current statutory framework on this agency. The FDA does not have jurisdiction over surgical and medical procedures, and it is therefore not entirely clear whether its authority extends to the field of reproductive medicine in general,

These concerns are not unfounded, as two embryos created by this technique but later aborted had Turner Syndrome.[17]

The same FDA requirements apply to a form of nuclear transfer developed at a New York City hospital in the early 1990s. In this case, cytoplasm is not merely replaced. Researchers fertilize not one but two eggs, one from the prospective mother, and one from an anonymous donor. The nucleus from the donated egg is then removed and replaced with the nucleus from the prospective mother's egg. In an effort to circumvent FDA regulations, a leading U.S. scientist in 2001 decided to outsource the procedure to colleagues in China. The Chinese researchers transferred two embryos. The procedure was successful, but the fetuses died at weeks 24 and 29, respectively, due to complications apparently unrelated to the technique used in the experiment.[18] Had a child been born with this technique, he or she would have had genetic material not from two, but from three individuals – his or her genetic parents as well from the egg donor. This is so because the cytoplasm of the donor egg (or any other cell) contains mitochondrial DNA.[19]

Slightly different concerns are raised by a very similar procedure recently proposed by British scientists.[20] In this case, only one embryo is created, from the gametes of the two prospective parents. To avoid health risks associated with the egg's mitochondria, the nucleus is removed and inserted in a healthy egg from an anonymous donor. Unlike the preceding procedure, this technique is meant to benefit both the parents and the child, who otherwise might have been born with degenerative genetic diseases.[21] These children would also carry genetic material from three persons.

All of these procedures raise ethical concerns above and beyond health and safety considerations. A reproductive procedure that creates babies carrying DNA from three individuals – and therefore with three genetic parents – is problematic enough to preclude its wide adoption based exclusively on effectiveness. Scientists have pointed out that the amount of

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and to ooplasm transfer in particular. Be that as it may, until ART professionals successfully challenge the FDA in court, for all intents and purposes, ooplasm transfer cannot be performed in the United States.

17 *Ooplasm Transfer as Method to Treat Female Infertility* (FDA's Biological Response Modifiers Advisory Committee Meeting, May 9, 2002 [cited August 2, 2005]); available from http://www.fda.gov/OHRMS/DOCKETS/ac/02/briefing/3855B1_01.pdf

18 Shaoni Bhattacharya and Sylvia Pagàn Westphal, *Controversial Three-Parent Pregnancy Revealed* (New Scientist, October 14, 2003 [cited August 2, 2005]); available from http://www.newscientist.com/article.ns?id=dn4266 ; David Derbyshire, *Foetuses Had Three Genetic Parents* (Telegraph Group, October 13, 2003 [cited August 2, 2005]); Denise Grady, "Where Anti-Clone Collides with Pro-Baby," *International Herald Tribune*, October 15, 2003; Steve Kirschner, "The Ooplasm Transfer Debate," *Genomics and Proteomics*, November 1, 2002; Rick Weiss, "U.S.-Banned Fertility Method Tried in China: Woman Became Pregnant through Egg Transfer Technique but Lost All Three Fetuses," *Washington Post*, October 14, 2003.

19 Mitochondria can be described as a cell's energy source.

20 James Randerson, *Scientists Seek to Create 'Three-Parent' Babies* (New Scientist, October 19, 2004, 2004 [cited August 2, 2005]); available from http://www.newscientist.com/article.ns?id=dn6547; Ian Sample, "Can a Baby Have Two Mothers?," *The Guardian*, October 21, 2004.

21 For an extensive discussion of ooplasm transfer for therapeutic uses, see John A. Robertson, "Oocyte Cytoplasm Transfer and the Ethics of Germ-Line Intervention," *Journal of Law, Medicine & Ethics* 26 (1998).

inherited foreign DNA is minuscule, and it is therefore a gross exaggeration to claim that a child has three genetic parents. In our view, the fact that these children receive only approximately 35 genes from a third party is largely irrelevant. What is disturbing is that these reproductive treatments undermine a fundamental biological principle – namely that every human being has a biological mother and father. At stake in this case is not only the health of these children, but also their well-being and the impact that having three genetic parents may have on their psychological development and on the development of their identities.

Whether the implications of departing from this principle are serious enough to justify a ban remains to be seen. What is clear is that this question should not be settled by ART practitioners and patients, nor should it be decided simply in instrumental terms or portrayed as a purely private choice removed from public scrutiny.[22] Its resolution entails making a choice among competing goods, a choice that should be made at the legislative or more likely at the regulatory level, and not delegated to a profession and its clients. The fact that the U.S. scientist who developed one of these techniques decided to circumvent FDA regulations by conducting the experiment in China only underscores the need for a broader involvement of governmental authorities.

4.3.2 Oocyte Cryopreservation (Freezing of Human Eggs)

For a variety of reasons, including the large size of eggs, freezing human oocytes is considerably more difficult than cryopreserving sperm or embryos. According to ART practitioners, only approximately 100 women to date have become pregnant using a thawed egg. The procedure is universally considered experimental. Its success rate compared to standard reproductive techniques is low, approximately 15 percent, though researchers are hard at work to improve it.[23] The main rationale for developing this technology is therapeutic: Freezing eggs could help certain patients, especially young women, preserve their fertility despite devastating conditions or treatments with damaging side effects such as radiation therapy.[24]

Because of the experimental nature of oocyte cryopreservation, the procedure's health and safety risks to women and their offspring are largely unknown. What makes oocyte

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[22] This approach usually translates into an excessive preoccupation for informed consent, to the detriment of any other considerations. See for example Andrea Bonnicksen, "Innovative ARTs and Informed Consent," (Gaithersburg, MD: FDA's Biological Response Modifiers Advisory Committee Meeting, 2002).

[23] Sarah Boseley, "Frozen Egg Baby Hailed as Fertility Milestone," *The Guardian*, October 11, 2002; *First Frozen Egg Babies to Be Born in May* (Xinhuanet (Xinhua News Agency), March 30, 2004 [cited August 2, 2005]); available from http://news.xinhuanet.com/english/2004-03/30/content_1391270.htm; Christina Ianzito, "Putting Your Eggs in a Different Basket," *The Washington Post*, September 21, 2004; Jeremy Laurance, "Italian Births Raise Hopes for Egg-Freezing Treatment," *The Independent*, September 15, 2004; Linda Marsa, "Frozen Eggs Yield Promising Results," *Los Angeles Times*, September 20, 2004; Helen Pearson, "Infertility Specialists Counsel Caution over Frozen Eggs – Reproduction Techniques Not Ready for Prime Time," *Nature* 431, no. 7011 (2004); Shari Roan, "Fertility in Reserve," *Los Angeles Times*, February 2, 2003; Sally Wadyka, "For Women Worried About Fertility, Egg Bank Is a New Option," *New York Times*, September 21, 2004.

[24] On the state of this technology, see Brandon Bankowski et al., "The Social Implications of Embryo Cryopreservation," *Fertility and Sterility* 84, no. 4 (2005), p.829-30.

cryopreservation a good example of an innovative reproductive procedure, however, is its unclear but potentially far-reaching societal impact. Oocyte cryopreservation is beginning to transform itself from a purely therapeutic procedure to an elective one. ART practitioners, while cautioning that this technology is still very much under development, are already considering the possibility that egg freezing could also be an attractive solution for professional women trying to reconcile career goals and the desire for a family. Not surprisingly, some entrepreneurs have already caught on and started offering egg cryopreservation as a commercial service.[25]

It is easy to anticipate at least a few of the consequences that the broad availability of this reproductive option might have on society.[26] Over time, egg cryopreservation may lead to a reduction in the number of frozen embryos. While many would welcome this development, its impact may not be unambiguously positive. For example, the availability of cryopreserved embryos for research is likely to diminish. The exact number of cryopreserved embryos currently donated for research is unknown, but it is likely very few. Further reducing this limited pool of available embryos might undermine the delicate political compromise negotiated in many industrialized countries on stem cell research, and may also induce scientists to advocate a much more liberal (and much more controversial) policy for deriving new stem cell lines.

Egg cryopreservation would also stimulate the emergence of a whole new and very lucrative industry devoted to the retrieval, storage, and sale of human oocytes. This is certainly not a development that many would welcome. The free trade of oocytes could expose women – especially young, poor, or uneducated women – to significant risks. But perhaps the most troubling and the least discussed consequence of making oocyte cryopreservation widely available is precisely what is currently being touted as one of its main benefits – the woman's ability to choose the precise time of procreation.[27] What to well-educated and ambitious women understandably appears to be a very attractive option could have several less desirable consequences. For example, the average parental age would likely increase, perhaps dramatically so. Whether having older parents would be detrimental to a child's development is unclear, and we are not suggesting that is necessarily so, but it is certainly a question worth pondering.

Delayed reproduction may also turn into less reproduction or no reproduction at all. A successful professional career may dissuade many women from considering motherhood at a later age. Some may argue that if this development makes it easier for women to pursue a professional career, it should be a reason for celebration, not a possible cause for concern. Others may disagree. Also worth pondering is whether oocyte cryopreservation might further weaken

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[25] For example, on its Web site, the Fertility Institutes in California aggressively promotes their "frozen donor egg bank." See http://www.fertility-docs.com/egg_freezing_right.phtml.

[26] For a fuller discussion, see Baum, "Golden Eggs: Towards the Rational Regulation of Oocyte Donation"; Margaret Jane Radin, "Market-Inalienability," *Harvard Law Review* 100 (1987).

[27] Not everyone agrees. See John A. Robertson, "Technology and Motherhood: Legal and Ethical Issues in Human Egg Donation," *Case Western Reserve Law Review* 39 (1989).

the institution of the family, as increased individual autonomy may make it more difficult for prospective parents to reach a consensus on when to have a baby.[28]

That egg cryopreservation is rapidly becoming a matter of public concern is demonstrated by the interest that the American Society for Reproductive Medicine has taken in this issue. In a recently published report titled "Ovarian Tissue and Oocyte Cryopreservation," the ASRM discusses whether egg freezing should serve exclusively therapeutic purposes, or whether it should also be recommended as a means to defer procreation. The report concludes that oocyte cryopreservation should be offered exclusively for therapeutic reasons,[29] based exclusively on health and safety considerations. The ASRM does not explore the potential broader societal implications of widespread adoption of this technology – in our view, one more reason to broaden the debate on new reproductive technologies.

4.3.3 Co-Culture

The FDA considers co-culture an instance of xenotransplantation.[30] In co-culture, human embryos come into contact with animal cells outside the human body. In FDA terminology, the recipient of an embryo cultivated on non-human tissues is therefore the recipient of a xenotransplantation "product." As a laboratory technique, co-culture is not new. According to news reports, fertility clinics started offering co-culture to select patients as early as 1989. The technique is actually older than that. It was developed in the 1960s and tested on mice and rats, but never on humans before it was offered as a reproductive service.

Co-culture meets all the requirements of an innovative reproductive procedure. It only came to regulators' attention in 2002, although it has been around for much longer.[31] It is not commonly used and it is certainly not considered a standard reproductive procedure by the CDC or by ART professionals. To our knowledge, the long-term health and safety impact of this technology on children has never been studied. Clearly, co-culture is likely to meet with considerable resistance both on safety and ethical grounds.

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[28] Some may argue that this argument is discriminatory, as men, for all intents and purposes, already have the ability to delay reproductive choices. However, this argument is not entirely convincing, as men's ability to procreate well into old age is not the result of any medical progress.

[29] Practice Committee of the American Society for Reproductive Medicine, "Ovarian Tissue and Oocyte Cryopreservation," *Fertility and Sterility* 82, no. 4 (2004).

[30] See http://www.fda.gov/cber/infosheets/humembclin.htm.

[31] Medical researchers have been experimenting with co-culture as a means to improve ART success rates for quite some time, but it appears that they have done so mostly on animal models. See H.L Feng et al., "Fertilization and Early Embryology: Effect of Different Co-Culture Systems in Early Human Embryo Development," *Human Reproduction* 11 (1996); F.S. Nietro et al., "The Effects of Cocolture with Autologous Cryopreserved Endometrial Cells on Human in Vitro Fertilization and Early Embryo Morphology: A Randomized Study," *Journal of Assisted Reproduction and Genetics* 13 (1996); J. Thibodeaux and R. Godke, "In Vitro Enhancement of Early Stage Embryos with Coculture," *Archives of Pathology and Laboratory Medicine* 116 (1992); K.E. Wiemer et al., "Embryonic Morphology and Rate of Implantation of Human Embryos Following Coculture on Bovine Oviductal Epethelial Cells," *Human Reproduction* 8 (1993).

A 2003 news story published in *Popular Science* magazine describes in some detail the motivation for performing this procedure, and the procedure itself.[32] The technique is used to cure particularly difficult cases of infertility. In this case, the wife's reproductive organs were severely dysfunctional, and her immune system had rejected her husband's sperm. In addition, the husband's sperm count was very low and of poor quality. After traditional reproductive treatments failed to result in pregnancy, the couple was persuaded to try co-culture. The woman's eggs were retrieved, fertilized in vitro, and grown for several days on tissue obtained from a cow uterus. The embryos were then transferred back into the woman's uterus. The technique was quite successful. The couple now has three children, all of them conceived through co-culture.

The story provides an excellent illustration of both parental desperation and of the risky choices parents and their doctors are willing to make. According to the news story the couple is not apologetic for trying a largely untested technique. Asked whether he was concerned about possible long-term effects on his children the father replied:

> Is there a possibility of long-term effects? Yeah, there is. And that worries us. But even if we'd found the kids would be at higher risk, we would have still done it all. [33]

As this quote illustrates, there seems to be some justification to the view that parents do not necessarily or always have the best interest of their offspring at heart. More generally, our discussion of co-culture suggests that innovative reproductive treatments should not be performed on a routine basis until safety and ethical concerns have not properly been addressed. To this end, it is necessary to broaden the debate about the future of reproductive technologies beyond the narrow circle of ART practitioners and patient groups.

4.3.4 Other Experiments

That some reproductive endocrinologists and scientists are willing to push the ethical envelope is illustrated by the following two instances of (failed) innovative reproductive treatments. In the first case, a group of Israeli scientists demonstrated that oocytes retrieved from aborted fetuses can be fertilized and may be viable. In the second case, a U.S. researcher created a chimeric human embryo by adding cells from a male embryo to a female human embryo.

Oocytes grown from aborted fetuses – to our knowledge – have not actually been used in a clinical setting. Had the fertilized eggs in the aforementioned case been transferred to a woman's uterus, a child might have been conceived by an unborn mother – a very problematic proposition at best, and an utterly unacceptable procedure at worst. As for other innovative treatments, there is a perfectly plausible, if purely instrumental, reason for developing this procedure. The Israeli scientists argued that aborted fetuses are a precious source of human tissue, and that retrieving oocytes from these fetuses would circumvent many of the ethical problems normally associated with the retrieval of human oocytes from adult females. That this argument is incomplete goes

[32] Rebecca Skloot, "Sally Has 2 Mommies and 1 Daddy," *Popular Science*, March 1, 2003.
[33] Ibid.

almost without saying. Children born through this procedure could suffer severe psychological harm, as a crucial aspect of their personal identity – a biological mother – would be missing. Interestingly, the scientists in question were not prepared to re-examine the rationale for conducting this line of research despite the outcry that the experiment generated among their peers.[34] They simply acknowledged the strong negative reactions their experiment produced, noting that "probably, in some places, it will be ethically acceptable."[35]

Another case of an innovative reproductive treatment that met with considerable resistance from the ART community was the announcement by a U.S. researcher that he had added cells from a male embryo to a female embryo, thus creating a chimeric human embryo.[36] The creation of chimeras is nothing new in biology, but this appeared to be the first documented case of a researcher actually creating and growing, albeit for only a few days, a *human* chimera.

The justification offered by the researcher for creating the chimeric human embryo was rather nebulous. The experiment was designed to test an innovative therapy to cure severe combined immunodeficiency (SCID), also known as "bubble boy disease." By adding healthy embryo cells to a diseased embryo, the resulting baby is likely to acquire healthy cells that might be able to fight the disease. This, at least, was the hope expressed by the researcher in this case. The scientist decided to add male embryo cells to a female embryo because male embryo cells are easier to track. The researcher was hoping that the male embryo cells would distribute homogeneously over the female embryos, which apparently they did. In this narrow, sense the experiment was successful.

The sharply negative reaction the announcement of this experiment produced is both a testimony to a shared sense of professional responsibility among the members of the ART community and a demonstration of the limits of professional self-regulation. Many of the researcher's colleagues questioned the scientific rationale for conducting this experiment. They also emphasized the damage that the announcement of this experiment might cause to the reputation of the entire ART industry.

Some may interpret these statements as an illustration of reputational incentives at work.[37] In a narrow sense, this is true, but it would be misleading to draw broad lessons from this

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[34] Shaoni Bhattacharya, *Aborted Fetuses Could Become 'Unborn Mothers'* (New Scientist, July 1, 2003 [cited August 2, 2005]); available from http://www.newscientist.com/news/news.jsp?id=ns99993889; Ian Sample, "Prospect of Babies from Unborn Mothers," *The Guardian*, July 1, 2003; Jeevan Vasagar, "Use of Foetal Eggs Grotesque, Say Campaigners," *The Guardian*, July 2, 2003.

[35] Bhattacharya, *Aborted Fetuses Could Become 'Unborn Mothers'* ([cited).

[36] Shaoni Bhattacharya, *'She-Male' Embryos Created in Lab* (New Scientist, July 3, 2003 [cited April 26, 2006]); available from http://www.newscientist.com/news/news.jsp?id=ns99993905; Steve Connor, "Scientists Outraged over Fusion of Male and Female Embryos Condemn Attempt to Combine Male and Female Cells," *The Independent*, July 3, 2003; Emma Ross, "European Group Denounces Chimera Embryo," *Associated Press*, July 2, 2003; Ian Sample, "Scientists Hit out at Creator of 'She-Males'," *The Guardian*, July 3, 2003.

[37] See, for example, David Charny, "Nonlegal Sanctions in Commercial Relationships," *Harvard Law Review* 104 (1990); Ronald J. Mann, "Verification Institutions in Financial Transactons," *Georgetown Law Journal* 87 (1999); Eric A. Posner, "The Regulation of Groups: The Influence of Legal and Nonlegal Sanctions on Collective Action," *University of Chicago Law Review* 63 (1996).

episode. Reputational incentives are an effective sanctioning mechanism only when highly visible controversies erupt. As mentioned earlier, innovative reproductive treatments generally are conducted discreetly; the news media, regulators, and the public learn about these experiments only sporadically, and sometimes not at all. In this sense, the role of reputational incentives as an effective sanctioning mechanism must be regarded as quite limited.

4.4 Reproductive Customization Technologies

While the reproductive technologies discussed so far were initially developed exclusively for therapeutic reasons, in this section we turn to ART treatments that are not designed to treat a physiological condition, though they do have some specific medical applications. The primary use of these reproductive technologies is simply the accommodation of parental wishes of one kind or another. In this sense, these are reproductive customization technologies rather than reproductive treatments, in the narrow sense of this term. They are intended to provide prospective parents with the means to exercise control over the reproductive process rather than simply to help them conceive.

With this type of technology, we enter into one of the most controversial areas of reproductive medicine. Unlike innovative reproductive treatments – where the technical means may be controversial but the goal served (procreation) remains the same – in the present case we are dealing with technologies that are beginning to redefine the very meaning and nature of procreation. They do so not in a dramatic or spectacular way, to be sure. Some uses of these technologies, considered in isolation, could even be described as prosaic. From a pragmatic perspective, it is difficult to quarrel with a mother who, after having three boys, wishes to have a girl. But, as is so often the case in the field of artificial reproduction, things are not quite so simple. Many people feel uncomfortable with suggestions that conception could be customized, though they may not be able to articulate the precise reasons for their discomfort. Others, fearing the degradation of human reproduction to a commercial transaction, will find any technology of customization altogether unacceptable. Still others take the opposite stance, advocating freedom of choice in matters considered purely private.[38]

An obvious example of the non-therapeutic use of a reproductive technology is elective sex selection. Currently, two options exist to choose the sex of a child – pre-implantation genetic diagnosis and MicroSort®. While MicroSort is still being tested, PGD is already available. Reliable data is hard to come by, but according to industry insiders, PGD is rapidly gaining popularity as a sex-selection technology. Another example of a reproductive technology's non-therapeutic use is genetic engineering, i.e., germ-line genetic modification. Human genetic engineering, just a few years ago derided by many scientists as en entirely speculative and utterly irrelevant scenario, is becoming a reality much more rapidly than was initially anticipated, as a

[38] In this regard, some of the ethical principles introduced in chapter 3 – such as privileging therapeutic over enhancing uses of reproductive technologies and protecting the health and well-being of children, but also promoting access to reproductive technologies – may be able to structure these controversies.

recent review of the scientific literature conducted by the Johns Hopkins University Genetics and Public Policy Center indicates.[39]

The notion of reproductive customization raises the question of whether it is actually possible to accurately distinguish between therapeutic and enhancing uses of reproductive technologies. Professional bioethicists have often criticized this distinction has being conceptually weak and incapable of resolving most ethical dilemmas. Technically, these criticisms may be correct, but it would be utterly misleading to conclude that ambiguous conceptual categories should play no role in public debates and in policy-making. Were all categorical ambiguities to be banned from public discourse, it would no longer be possible to pass laws or craft policies. As the human growth hormone case discussed in chapter 2 has shown, even two seemingly straightforward categories like safety and efficacy are not free of ambiguities. This has not prevented the FDA from routinely using safety and efficacy as its main guiding principles in rule-making.

Against this background, whether a general audience finds the distinction between therapeutic and enhancing applications of reproductive technologies useful is a question of some import. Two surveys, one conducted in the United States and the other in Germany, shed some light on this issue. The Genetics and Public Policy Center has conducted extensive research on public attitudes toward new reproductive and genetic technologies in the United States. In 2002, it surveyed the awareness of 1,211 Americans ages 18 and older about genetic technology. Of particular interest to our discussion is the following question:

Would you approve or disapprove if parents were offered a way to use pre-implantation genetic diagnosis to:	*Approve*	*Disapprove*	*Don't Know*	*Refused to Answer*
(a) make sure their baby does NOT have a serious genetic disease?	74	22	4	*
(b) make sure their baby would be a good match to donate his or her blood or tissue to a brother or sister who is sick and in need of a transplant?	69	25	5	1
(c) make sure their baby does NOT have a tendency to develop a disease like cancer when he or she is an adult?	60	33	6	*
(d) choose the sex of their child?	28	68	4	*

[39] Germ-line genetic modification is possible in laboratory animals, and some techniques could be adapted for use in humans, although none have been tried. Scientists are able to replace a faulty gene with a "normal" copy in mouse embryonic stem cells, and then introduce those stem cells into an early mouse embryo, where they can give rise to genetically modified sperm or eggs. The next generation of mice that results from the modified sperm or eggs contains the "normal" copy of the gene. It is now possible to replace a gene in human embryonic stem cells, overcoming a huge obstacle to human germ-line genetic modification. In addition, scientists have been able to derive genetically modified sperm directly from mouse stem cells. Together, these developments suggest that human germ-line genetic modification may not be as far off as we thought even five years ago. Cf. Baruch et al., "Human Germline Genetic Modification: Issues and Options for Policymakers," p.5.

Would you approve or disapprove if parents were offered a way to use pre-implantation genetic diagnosis to:	*Approve*	*Disapprove*	*Don't Know*	*Refused to Answer*
(e) make sure their baby has desirable characteristics, such as high intelligence and strength?	22	72	5	*

Table 1: Attitudes toward various uses of pre-implantation genetic diagnosis.[40]

As this table demonstrates, U.S. respondents seem to make a clear distinction between therapeutic uses of PGD (questions a, b, and c) and reproductive customization (questions d and e). A two-thirds to three-quarter majority supports therapeutic uses, while a very similar proportion rejects customization. Similar results emerged from a survey recently conducted in Germany. The detailed results have not yet been published, but a summary is available.[41] Researchers interviewed 416 former East Germans and 1,694 former West Germans ages 18 to 50 in late 2003. Of all respondents, 76 percent favored legalizing therapeutic uses of PGD, such as screening for genetic diseases, a procedure that is banned in Germany. Only 20 percent of respondents favored maintaining a strict ban on any use of PGD. It is noteworthy that the proportion of respondents supporting legalizing therapeutic uses of PGD is very similar to the proportion of U.S. respondents who favor the use of PGD for the same therapeutic purposes. In sum, its conceptual ambiguities notwithstanding, the distinction between therapeutic and enhancing uses of PGD (and of genetic engineering more broadly) provides a useful framework for structuring public debates on the acceptable uses of this technology.

In the next two sections, we discuss some of the ethical concerns that technologies of customization could raise. The technologies in question are MicroSort, a technique specifically designed to select the sex of a child, and pre-implantation genetic diagnosis for non-therapeutic reasons.

4.4.1 Technologies of Sex-Selection: MicroSort

MicroSort is a technology designed to select the sex of embryos. Male and female embryos come in slightly different sizes, a difference that MicroSort depends on to separate them. According to the technology's developer, the Genetics & IVF Institute located in Fairfax, Virginia, MicroSort has a success rate of 91 percent for female and 76 percent for male embryos.[42] The Genetics & IVF Institute is currently in the process of conducting an FDA-approved clinical trial. When the FDA will approve MicroSort is unclear.

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[40] Genetics and Public Policy Center, "Public Awareness and Attitudes About Genetic Technology," (Washington, D.C.: Johns Hopkins University, 2002), p.7.

[41] Ada Borkenhagen et al., "Was Denken Die Deutsche Bevölkerung Und Kinderwunschpaare Über Die PID? Eine Vergleichende Studie," (Fertility Center Berlin, DRK-Clinics Westend, Leipzig University, Department of Medical Psychology and Medical Sociology, 2004).

[42] See http://www.microsort.com/. See also Joseph G. Schenker, "Gender Selection: Cultural and Religious Perspectives," *Journal of Assisted Reproduction and Genetics* 19, no. 9 (2002), p.403.

Aware of the controversial nature of this technology, the institute currently offers its services only for the purpose of "family balance." This term identifies families that, after having several children of one sex, desire to have a baby of the opposite sex. According to the institute, the demand for sex-selection services is very strong and is by no means limited to families seeking "balance." This suggests that the market for this technology is much larger than the demand for family balance indicates, though it is unclear just how large this market might be. It is certainly large enough to make investors in the Genetics & IVF Institute very rich. For this reason, it is very unlikely that the institute will continue offering its services exclusively for the purpose of family balance once it receives FDA approval for this sex-selection technology. The FDA, for its part, has no authority to limit the use of MicroSort if it has deemed the technology both safe and effective.

Should anyone be concerned about the widespread use of sex-selection technologies such as MicroSort? Providing a definitive answer to this question is surprisingly difficult. Some commentators have pointed out that in countries where sex-selection technologies (of any kind) have been available for some time, male and female birth ratios have experienced dramatic distortions. In Korea, Taiwan, China, and India, for example, patriarchal values and perverse economic incentives have produced strong familial preferences for boys; female infanticide has often been the result. In more recent times, the increasing availability of medical technologies such as ultrasound imaging and amniocentesis has produced an astounding number of selective abortions, shifting birth ratios from a normal 102-103 boys to 100 girls to 120 boys for 100 girls and higher. The consequences are predictable – pervasive scarcity of females and an associated increase in social unrest and crime attributable to a growing population of young, unattached males.[43]

One may argue that Western industrialized countries are very unlikely to face this problem. The empirical evidence in this regard is mixed. A handful of European surveys have consistently shown that the sex of the first-born child is largely a matter of indifference. In Germany, only 14 percent of respondents have a clear preference for a boy, 10 percent for a girl, and 76 percent of respondents claims to be indifferent.[44] Similar results were obtained in the United Kingdom, where 12 percent of respondents would prefer a boy as their first-born child, and 19 percent a girl, the rest being indifferent.[45] On the other end, a survey of 17 European countries found a

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[43] M. Ansari-Lari and M. Saadat, "Changing Sex Ratios in Iran 1976-2000," *Journal of Epidemiology and Community Health* 56 (2002); Cecilia L. W. Chan et al., "Gender Selection in China: Its Meanings and Implications," *Journal of Assisted Reproduction and Genetics* 19, no. 9 (2002); Elizabeth Hervey Stephen, "Demographic Implications of Reproductive Technologies," *Population Research and Policy Review* 19, no. 4 (2000).

[44] E. Dahl et al., "Preconception Sex Selection for Non-Medical Reasons: A Representative Survey from Germany," *Human Reproduction* 18, no. 10 (2003).

[45] H. Statham et al., "Choice of Baby's Sex," *Lancet* 341, no. 8844 (1993).

strong preference for a mixed family,[46] suggesting that there may indeed be a significant demand for sex-selection services, at least for the purpose of "family balancing."

Policy preferences seem consistent with general attitudes. A recently released consultative report on sex selection prepared by the British HFEA shows that 82 percent disagreed with the statement "The use of sperm sorting should be permitted in sex selection for non-medical reasons."[47] Even sex selection for the purpose of "family balancing" did not gather much sympathy – 82 percent again rejected this option.[48] Similar results were obtained by a much more rigorous survey conducted in Germany,[49] where 92 percent of respondents were not interested in using sperm-sorting technology to select the sex of a child. Postulating that the sex-selection process could be carried out in a much more straightforward way did not change this pattern.[50]

The data for the United States is somewhat more ambiguous. A study conducted in the early 1990s, along with a 2002 survey, suggests that the preference for a male first child in the United States is much higher than in Europe, ranging between 58 percent for men and 40 percent for women.[51] The 2002 study puts the proportion of respondents that would be willing to use sex-selection technologies, if available, at 21 percent. Of this 21 percent, men would overwhelmingly prefer a boy (75 percent), whereas women had only a slight preference for boys (56 percent). These results were obtained from a non-random sample of undergraduate students, and should not be taken at face value. A much more rigorous and recent study produced somewhat different results.[52] A representative sample of 1,197 individuals ages 18 to 45 was asked five questions designed to elicit possible preference for a sex and interest in using a sex-selection technology. As with prior studies, participants in this survey expressed a fairly strong preference for a male first born (39 percent), 19 percent would prefer a girl and 42 percent were indifferent. The actual interest in using sex-selection technologies, however, is modest. Only 8 percent of respondents, given its estimated cost, would consider using a sex-selection technology. This figure increases to 18 percent if the sex of a child could be chosen simply by medication, whereas 59 percent were still uninterested. A somewhat similar pattern emerges from a large, comparative survey of practitioners and the general population on the acceptability of potentially controversial

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46 Karsten Hank and Hans-Peter Kohler, "Gender Preferences for Children in Europe: Empirical Results from 17 FFS Countries," *Demographic Research* 2, no. 1 (2000).

47 Human Fertilisation and Embryology Authority (HFEA), "HFEA Annual Report 2003/04," (London: 2004), p.24.

48 Ibid.

49 Dahl et al., "Preconception Sex Selection for Non-Medical Reasons: A Representative Survey from Germany."

50 "Suppose there was a medication enabling parents to choose the sex of their children. Couples simply had to ingest a blue pill to ensure the birth of a boy, or a pink pill to ensure the birth of a girl. Would you take advantage of such medication?"Ibid., p.2232.

51 Roberta Steinbacher and Faith Gilroy, "Sex Selection Technology: A Prediction of Its Use and Effect," *Journal of Psychology* 124, no. 3 (1990); Doreen Swetkis, Faith Gilroy, and Roberta Steinbacher, "Firstborn Preference and Attitudes toward Using Sex Selection Technology," *The Journal of Genetic Psychology* 163, no. 2 (2002).

52 Edgar Dahl et al., "Preconception Sex Selection Demand and Preferences in the United States," *Fertility and Sterility* 85, no. 2 (2006).

diagnostic technologies. This study found that there is strong opposition to elective sex selection in all countries, but less so in the United States.[53]

What should we make of this data? There is no strong empirical evidence to suggest that at the present time, the broad availability of sex-selection technologies such as MicroSort would induce prospective parents to systematically choose one sex over the other. At the same time, this finding does not render superfluous a broad public debate about the use and abuse of sex-selection technologies. Some commentators, though not necessarily worried about skewed sex ratios, are concerned about the impact that the broad availability of this technology might have on our very understanding of procreation, reducing it to an act of design – an expression of parental whims. Still others fear that sex selection may fuel sexual discrimination.[54] These are all legitimate concerns that should be examined in some detail before moving forward with this technology on a grand scale.

4.4.2 Pre-Implantation Genetic Diagnosis for Therapeutic Uses

To date, pre-implantation genetic diagnosis is the one reproductive procedure that comes closest to the ideal of a technology of reproductive customization. First tested in 1989, PGD consists essentially of removing one cell from a blastocyst at the eight-cell stage. The cell so removed allows the ART practitioner to conduct a variety of genetic tests. Embryos can be screened for genetic diseases, for the predisposition to a genetic disease, and for sex-linked diseases. They can also be selected for specific physiological attributes such as blood type. In principle at least, PGD could also be used to screen embryos for any physiological attribute or higher trait, provided science could identify the genetic foundations of these attributes.[55] Even under the best of circumstances, however, PGD is a very cumbersome technology of customization, and a passive one: It only allows the screening of existing embryos, but not the creation of embryos with specific physiological attributes. In this sense, PGD is a far cry from true genetic engineering.

Much has been said and written about PGD, and we will not rehash that discussion here other than to note that the ethical import of genetic screening is not determined simply by its limited ability to serve as a tool of procreative customization. The practice of genetic screening is

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[53] Dorothy C. Wertz et al., "Has Patient Autonomy Gone Too Far? Geneticists' Views in 36 Nations," *The American Journal of Bioethics* 2, no. 4 (2002).

[54] Lisa Belkin, "Getting the Girl," *New York Times Magazine*, July 25, 1999; Ethics Committee of the American Society for Reproductive Medicine, "Preconception Gender Selection for Nonmedical Reasons," *Fertility and Sterility* 75 (2001); Charles Hanson, Lars Hamberger, and Per Olof Janson, "Is Any Form of Gender Selection Ethical?," *Journal of Assisted Reproduction and Genetics* 19, no. 9 (2002); John A. Robertson, "Preconception Gender Selection," *American Journal of Bioethics* 1, no. 1 (2001); E. Scott Sills and Gianpiero D. Palermo, "Preimplantation Genetic Diagnosis for Elective Sex Selection, the IVF Market Economy, and the Child – Another Long Day's Journey into Night?," *Journal of Assisted Reproduction and Genetics* 19, no. 9 (2002).

[55] For an overview, seeGenetics and Public Policy Center, "Preimplantation Genetic Diagnosis. A Discussion of Challenges, Concerns, and Preliminary Policy Options Related to Genetic Testing of Human Embryos," (Washington, D.C.: Genetics and Public Policy Center, 2003).

controversial not because it provides an effective means to customize conception (which currently it does not), but rather for its potential ability to undermine widely shared cultural conceptions of equality and tolerance, those intangible values so often taken for granted but indispensable to any functioning democracy.[56]

A second instance of customized conception is the use of PGD for tissue matching. Typically, this procedure is attempted when parents with a child affected by an incurable disease are unable to find a compatible tissue donor. In these cases, ART specialists may resort to PGD to screen for specific physiological attributes. For example, doctors may try to strengthen the failing immune system of a child affected by Diamond Blackfan Anemia (DBA), a painful and incurable disease, by extracting stem cells from the umbilical cord of a baby selected to be a tissue match.

What should we make of this practice? Are we facing a deplorable application of PGD, or are we simply using PGD for therapeutic purposes? Is the well-being of the children created solely to benefit an older sibling imperiled, or can we assume that they will be welcomed into the family? Do these manipulative medical procedures prepare us to more readily accept future reproductive techniques expressly designed to customize conception rather than to treat a medical condition? Medical professionals offer the following rationale for performing this procedure: Tissue matching is a straightforward case of a therapeutic use of PGD. A young child would die if the procedure were not performed. In addition, the older sibling is not saved at the expense of the younger one. The life of the younger child is not traded against the life of his or her afflicted older sibling. Furthermore, what reasons could possibly justify losing a child if he or she could indeed be saved?

Pro-life groups offer a very different assessment. They point to the instrumental nature of this procedure, i.e., a child being conceived exclusively to benefit an older sibling. They also are disturbed by the need to create (and discard) numerous embryos before a suitable one is found. Advocates for the disabled, for their part, have vehemently criticized genetic screening and tissue matching, arguing that it amounts to a eugenic program against the disabled. According to these groups, PGD likely will foster a culture of perfection incompatible with liberal values of mutual tolerance and respect. The news media, for its part, has fueled these controversies by characterizing tissue matching as the creation of "designer babies."[57] The term is obviously meant to provoke, but it is not entirely without justification.

It is useful to examine how the British Human Fertilisation and Embryology Authority has addressed this dilemma. The British Parliament established the HFEA in 1990 when it passed the Human Fertilisation and Embryology Act. Among other things, the Parliament delegated to the HFEA responsibility for addressing the ethical controversies generated by new developments in

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[56] Francis Fukuyama, *Our Post-Human Future: Consequences of the Biotechnology Revolution* (New York: Farrar, Straus and Giroux, 2002).

[57] Shaoni Bhattacharya, *Banned 'Designer Baby' Is Born in UK* (New Scientist, June 19, 2003 [cited April 26, 2006]); available from http://www.newscientist.com/news/print.jsp?id=ns99993854; Colin Blackstock, "Matched and Hatched, Britain's First 'Designer Baby' Born to Save Brother," *The Guardian*, June 19, 2003.

reproductive medicine (See chapter 6.4 for a more detailed discussion of the act and the agency). Whether the use of PGD for tissue matching should be allowed, and if so under what circumstances, is exactly the kind of controversy the HFEA was designed to settle.

Until recently, it was HFEA policy to authorize PGD only when the procedure would also benefit the future baby, for example, by preventing the birth of a child with an inheritable disease. Thus, the HFEA favored a view of PGD that emphasized therapeutic applications, but only in a very narrow sense. Not every therapeutic use of PGD is designed to benefit the child-to-be, and under HFEA policy, certain applications were prohibited. For instance, Diamond Blackfan Anemia is not an inheritable condition, so performing PGD to produce a tissue match for a child affected by DBA would benefit the older sibling but not the future baby. Consistent with its policy, the HFEA turned down demands to authorize the use of PGD to save children affected by DBA.[58] By contrast, the HFEA approved performing PGD to cure cases of Thalassemia. Unlike DBA, Thalassemia is an inheritable disease. In this case, PGD benefits the child-to-be as well as the older child.

Not surprisingly, parents whose PGD applications were turned down challenged the HFEA policy in court. In July of 2004, following a string of judicial decisions, the HFEA changed its policy regarding tissue matching to allow this procedure to be performed even when no inheritable disease is involved.[59]

One may or may not agree with HFEA policies, but there is one important benefit from resolving this and similar controversies through the regulatory and judicial system rather than through private choices. One provision of the British Human Fertilisation and Embryology Act of 1990 requires the HFEA to explicitly include in its consideration the well-being of children. While the parents of children affected by Diamond Blackfan Anemia understandably disagreed sharply with the earlier HFEA policy on PGD, the policy was clearly informed by the HFEA obligation to balance parental interests and the well-being of future children. As we have shown in this chapter, private choices tend to privilege parental interest, to the detriment of ART children. In this sense, a regulatory approach to deciding what at first may appear as purely private choices is preferable to delegating these choices to parents and the medical profession.

4.5 Biomedical Research Involving Reproductive Tissues

The fourth and last policy area to be examined in this chapter is research involving reproductive tissues. By reproductive tissues we mean oocytes, sperm, and embryos, either human or animal. The lines of research discussed in this section can be grouped into two distinct categories. On the one end, we find research aimed at exploring issues pertaining specifically to human reproduction and infertility. This kind of research may loosely be referred to as ART

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[58] According to news reports, parents whose applications were turned down by the HFEA were able to get the treatment in the United States.

[59] "High Court Ban on 'Designer Babies' Overturned," *The Guardian*, April 8, 2003; *'Saviour Sibling' Perfect Genetic Match for Brother* (BioNews, 320, August 8, 2005 [cited April 26, 2006]).

research. On the other end are situated research protocols that involve the use and manipulation of human reproductive tissues but focus on medical research more broadly. Stem cell research provides an illustration; it depends on the availability of human embryos but is largely unrelated to questions pertaining to the study of infertility, though advances may come about as an unanticipated benefit.

This ambiguity cannot easily be eliminated. Both areas of research touch upon the beginning of human life, and both types of research make use of human reproductive tissues. In addition, there is a considerable amount of organizational and institutional overlapping; many scientists involved in one kind of research are also involved in the other. Both kinds of research often are conducted at the same research organization. And, as we show below, experimentation in these two areas of research raise significant ethical concerns. For all these reasons, we decided not to distinguish explicitly between medical research involving the use of reproductive tissues and ART research proper.

Research protocols in this area raise a fairly unique set of ethical questions. By its nature, research on reproductive tissues is very unlikely to have an immediate impact on children and/or their parents. It is also not very likely to affect the practice of medicine, at least in the short term, nor does it undermine important societal values. In this sense, the immediate, short-term risks associated with these research activities are relatively modest. The destruction of human embryos for research purposes of course remains a very contentious and problematic proposition. It is certainly an important (if not the most important) ethical concern raised by biomedical research involving reproductive tissues. On the other hand, excessive attention to research involving human embryos tends to ignore other important research developments. These research protocols are problematic not because of immediate ethical concerns, but for difficult ethical dilemmas they are likely to produce in the not-too-distant future.

Before discussing actual cases of problematic scientific protocols, we need to respond to an important criticism. Science advocates insist that regulatory interventions should be explored only in the presence of immediate and clear harm. In this view, harmful effects that have yet to manifest themselves do not justify government interventions.[60] The concept of the slippery slope, a metaphorical term used to identify a technological trajectory associated with undesirable societal consequences, has been described by these critics simply as a rhetorical device invoked by technology skeptics unable to muster specific reasons for opposing a scientific or technological development.

We submit that this argument is itself the manifestation of an unreconstructed faith in another kind of slope – the virtuous slope. If we apply the critics' reasoning to a potentially beneficial line of research, we may say that as long as the research has not produced any useful results, there is simply no reason to assume that these results will materialize. Therefore, there is no *prima facie* reason to shield research activities from governmental interventions. Rejecting

[60] John A. Robertson, "Two Models of Human Cloning," *Hofstra Law Review* 27 (1999); Eugene Volokh, "The Mechanisms of the Slippery Slope," *Harvard Law Review* 116 (2003).

this argument implies that there is a causal connection between today's research protocols and tomorrow's cures, i.e., a virtuous slope that connects the current research to future beneficial outcomes, or at least a very strong presumption that today's research will produce tomorrow's cures. But if a virtuous slope exists, why should we assume that a slippery one does not? Technological optimism denies the relevance of the slippery slope – the view that a technology could move in a detrimental direction in a fairly predictable way – but does so by assuming that science and technology indeed move in a predictably beneficial fashion, developing along a virtuous slope. To put it in cruder terms, it is simply incoherent to argue that science and technology are riding a virtuous trajectory and therefore should be protected from governmental intervention, but to deny that science and technology could actually find themselves on a trajectory to societal harm. Why should harm presumptively be proved if benefits cannot presumptively be demonstrated?

We are not suggesting that the slippery slope concept necessarily implies early and aggressive regulatory interventions. What it does suggest is that scientific research should be monitored much more systematically. We shouldn't regulate research lightly, but we don't want to be surprised by problematic and perhaps irreversible scientific developments. A system of monitoring serves not only as an early warning system – it may also help identify unanticipated interactions among seemingly independent lines of research. Considered in isolation, many of the experiments discussed in this section may not raise significant concerns. Their significance changes dramatically if examined in the context of other scientific experiments.[61] A few experiments on mice demonstrating that it is possible to derive sperm cell precursors from stem cells may not mean much. If we learn that it is also possible to derive oocytes from stem cells, and that it has been demonstrated that sperm cells can be genetically manipulated, the original research results begin to appear in an entirely new light.

Much of the information used in the remainder of this section was gleaned from science magazines and news reports and through extensive online research. Efforts to obtain first-hand information about these experiments have produced very modest results – another indication, perhaps, of the need to more closely monitor research involving reproductive tissues.

4.5.1 Cloning Technologies

Cloning (or somatic cell nuclear transfer, as some leading scientists would like the rest of the world to call this process)[62] provides a good illustration of a procedure that is of considerable import both to assisted reproduction and to medical research: Whether one contemplates reproductive or research cloning, the actual process is identical. In essence, it consists of removing the genetic material (the nucleus) from a donated oocyte and replacing it with the

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[61] Not coincidentally, unanticipated interactions among the components of a technical system are one key attribute of technological complexity. Cf. Charles Perrow, *Normal Accidents: Living with High Risk Technologies* (New York: Basic Books, 1984). See also Nathan Rosenberg, "Why Technology Forecasts Often Fail," *The Futurist* July 1 (1995).

[62] Bert Vogelstein, Bruce Alberts, and Kenneth Shine, "Please Don't Call It Cloning," *Science* 295 (2002).

nucleus of a somatic cell, such as a skin cell. To trigger the process of cell division, the "unfertilized embryo" is exposed to a short burst of electricity.[63] If successful, somatic cell nuclear transfer produces an individual that is an almost perfect genetic replica of the somatic cell donor – almost perfect because the clone will share with the egg donor the genetic material contained in her mitochondria, genes that are obviously not present in the somatic cell of the individual that has been cloned.

Reproductive and research cloning raise distinct ethical questions. Reproductive cloning in particular has received considerable attention.[64] Many arguments have been put forward both in favor of and against what some have described as a reproductive procedure, and what others have more accurately but unsuccessfully characterized as human replication.[65] These questions have been extensively debated, and we see no reason to contribute to that debate here, other than to point out that it is very unlikely that the general public will ever consider this procedure an acceptable procreative option, even if it can be performed safely.[66]

With regard to research cloning, the situation is more interesting. In the last few years, the rationale offered by scientists for conducting somatic cell nuclear transfer in humans has changed significantly. Initially, the scientific community described this procedure as an indispensable prerequisite for creating organs compatible the recipient's immune system. But critics have pointed out that scientists are many years away from being able to precisely control the development of stem cells, a situation that apparently has been the source of considerable frustration among developmental biologists.

Public skepticism has induced the scientific community to adopt a different rationale for research cloning – that it is an important technique that would allow scientists to develop a much better understanding of the development of genetic diseases that cannot otherwise be studied. An example is Parkinson's disease, a degenerative condition of the brain that obviously cannot be studied in adult subjects. The emphasis thus has shifted from applied to fundamental medical research.

Other scientists are not ready to abandon the initial vision of growing replacement organs just yet. It has been shown that if human embryonic germ cells are derived from five-, six-, seven-, and 11-week-old primordial germ cells (i.e., germ cells of a fetus several weeks old), they can be injected or grafted onto a diseased organ, where they continue their development.[67] Other experiments have demonstrated that cloning makes it possible to produce specialized

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[63] Strictly speaking, the term "unfertilized embryo" is meaningless. Unfortunately, a proper technical term for this biological construction does not exist.

[64] See, for example, Glenn McGee, ed., *The Human Cloning Debate* (Berkeley, CA: Berkeley Hills Books, 2002); President's Council on Bioethics, "Human Cloning and Human Dignity: An Ethical Inquiry," (Washington, D.C.: 2002).

[65] George J. Annas, "Human Cloning: A Choice or an Echo?," *Dayton Law Review* 23 (1998).

[66] In this regard, see also the survey data in chapter 8.

[67] Michael J. Shamblott et al., "Human Embryonic Germ Cell Derivates Express a Broad Range of Developmentally Distinct Markers and Proliferate Extensively in Vitro," *Proceedings of the National Academy of Sciences* 98, no. 1 (2001).

cellular tissue compatible with the somatic cell donor. For these techniques to work effectively, however, it is necessary to grow a cloned embryo well beyond the customary 10 to 14 days. In addition, these embryos, for now at least, must be grown in vivo (in other words, in a mother's uterus) and subsequently aborted; embryos grown in vitro, for reasons not entirely understood, have not shown the same effectiveness.[68]

These experiments have been conducted on animal models. Exactly how long cloned human embryos would have to be grown in vivo is not clear. What is clear is that the derivation of suitable cellular tissue would require aborting a developing human embryo at a fairly advanced stage, or perhaps even a fetus, to "culture" an embryo well beyond the customary 10 to 14 days. What is interesting about this case is that no one really can say with a high degree of confidence that these experiments have not already been replicated in humans. Also telling is the fact that while public debates about new biomedical research in the last several years have focused almost exclusively on stem cells derived from early-stage embryos, several research groups were already experimenting with stem cells derived from animal embryos several weeks or even a few months old.[69]

What should we make of these developments? As a perceptive reporter has noted, these experiments may challenge the notion that stem cell lines should only be derived from 10- to 14–day-old embryos. Why stop at 14 days? What are the specific reasons for this constraint? It appears that the justification for the 14-day rule is pretty thin – thin enough, in any case, to convince many that it may be worthwhile exploring the possibility of extending the cutoff date for experimenting on human embryos to three weeks or a month. We are certainly not advocating this measure. What this story suggests is that the concept of a slippery slope is not simply a rhetorical device invoked by opponents to stymie scientific and medical progress. It is a concern expressed even by leading scientists, as the following statement made at a 2003 meeting of the President's Council on Bioethics implicitly illustrates:

> […] I am concerned, I mean, as a biologist I'm concerned. I'm concerned about a number of issues. It makes it sound as if most of the time that scientists aren't concerned, that we're just going along in a fashion that, you know, science for science sake.
>
> And I only have to remind you over the last few months to see the use of human embryonic stem cells in mouse chimeras, the use of chimeric human embryos that has been done, that you say there's no reason that these things should have been done. I mean, there's no scientific basis for this.

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[68] Benjamin Dekel et al., "Human and Porcine Early Kidney Precursors as a New Source for Transplantation," *Nature Medicine* 9, no. 1 (2003); Robert Lanza et al., "Regeneration of the Infarcted Heart with Stem Cells Derived by Nuclear Transplantation," *Circulation Research* 94 (2004); Robert P. Lanza et al., "Generation of Histocompatible Tissues Using Nuclear Transplantation," *Nature Biotechnology* 20 (2002); Robert Lanza et al., "Long-Term Bocine Hematopoietic Engraftment with Clone-Derived Stem Cells," *Cloning and Stem Cells* 7, no. 2 (2005).

[69] A fuller account of this story can be found in William Saletan, *The Organ Factory* (Slate, July 25, 2005 [cited September 27, 2005]); available from http://slate.msn.com/id/2123269/entry/2123270/.

> And we have to have some degree – and I'm not going to call it regulation, I don't like that term, obviously, but there has to be some consensus as to what should be permitted and shouldn't be permitted in almost a global way.[70]

As for other lines of medical research discussed in this chapter, there is no reason to entertain immediate radical regulatory interventions. The sense of unease that these experiments are likely to trigger in many readers is, however, a clear indication that potentially controversial medical research can only move forward if adequate legal safeguards are put in place and if Congress takes the necessary steps to ensure compliance. That we learned about these experiments serendipitously only underscores just how precarious our ability to identify and monitor momentous scientific developments is. There is a subtle but important difference between trust and blind trust. A much more systematic approach to monitoring scientific activities would go a long way toward restoring public confidence in the scientific enterprise.

4.5.2 Making Sperm

Over the last few years, science magazines and scientific journals have reported on several important experiments pertaining to the creation of human sperm. Like other research protocols discussed in this section, none of these experiments, taken in isolation, is of immediate relevance to clinicians, and they do not, therefore, raise immediate ethical concerns. All of them, however, are suggestive of momentous future clinical applications.

The first two experiments involved growing sperm in mice. Already, in 2002, a research group had succeeded in grafting testicular tissue from goats and pigs under the skin of mice.[71] The experiment showed that the immature testicular tissue does indeed develop into normal sperm. In the fall of 2004, researchers at Yale University conducted a similar experiment, this time using human testicular tissue. They were able to growth testicular tissue taken from adult humans with immature testes under the skin of mice. The tissue was still viable after 19 weeks, when it was retrieved for analysis.[72] According to the researchers, these experiments eventually should allow development of a technique that could restore fertility in children undergoing chemotherapy. More generally, this line of research should lead to more effective cures for male infertility.

Should anyone be concerned about this line of research? From a narrow, utilitarian point of view, these experiments, per se, do not seem to raise any serious ethical concerns. After all, their declared goal is purely therapeutic, and it would be difficult to argue that anyone would be harmed by the clinical applications of these techniques. At the same time, the claim that these experiments have no broader significance presumes that the technology in question will be used

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[70] John P. Gearhart, Rudolf Jaenisch, and David Prentice, *Stem Cell Research: Recent Scientific and Clinical Developments* (Session 3, President's Council on Bioethics Meeting, July 24-25, 2003 [cited September 16, 2005]); available from http://www.bioethics.gov/transcripts/july03/session3.html.

[71] James Meek, "Mice May Provide Human Sperm Bank," *The Guardian*, August 15, 2002.

[72] James Randerson, "Human Testicular Tissue Grown in Mice," *New Scientist*, October 19, 2004.

exclusively for the purpose it was developed for, an assumption obviously not supported by the history of science and medicine.

A far more consequential research protocol involving the production of sperm was reported from Japan in 2003.[73] In this experiment, the Japanese researchers cultivated embryonic stem cells in a culture known to stimulate the growth of sperm. They then took these cells and implanted them in mice testes, where apparently they fully developed into sperm. The researchers retrieved the sperm and fertilized mice eggs, which began to divide.

According to the Japanese researcher, the study should improve our understanding of embryonic development. The scientists were not secretive about what this generic statement may mean. Their goal, according to one news story, was to enhance our ability to engineer sperm – i.e., to produce artificial sperm based on specific genetic criteria. This could become possible because, as the researchers pointed out, scientists already know how to insert genes into stem cells.

Engineering sperm? Perhaps the Japanese scientist was simply naïve; or perhaps he sincerely believed that engineering sperm is a research proposition as legitimate and unproblematic as any other. Whatever the case may be, the view that human sperm could in the not-too-distant future be genetically engineered to meet specific parental desires is qualitatively different from the kind of rationales offered by scientists involved in potentially controversial medical research. Whether there may be reasons good enough to justify engineering sperm remains to be seen, but this question certainly cannot be decided by the scientific community alone.[74]

A more advanced version of the Japanese experiment was conducted by Harvard University scientists in 2003.[75] In this case, the scientists were able to grow sperm cell precursors entirely in a lab dish; implantation in testes was not necessary. They then injected these sperm-like cells into a mouse egg cell. In some cases, the fertilized egg developed into an early-stage embryo, or blastocyst. The scientists then tried to impregnate a mouse, without success. The Harvard group is now replicating these results in human embryonic stem cells. The researchers were careful to emphasize the scientific nature of their experiment and explicitly downplayed the possibility of developing cures for male infertility. In essence, this method for producing sperm cell precursors allows scientists to study imprinting, the process that regulates which genes are turned on or off during embryo development, depending on whether they are inherited from the mother or the

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[73] *Stem Cells Stimulated to Be Sperm* (Associated Press, September 15, 2003 [cited August 2, 2005]); available from http://www.wired.com/news/medtech/0,1286,60454,00.html; Rick Weiss, "Sperm Made from Stem Cells: Development in Mice Raises Issues for Human Reproduction," *Washington Post*, September 16, 2003.

[74] That this research was conducted at a privately funded university only underscores the need for public oversight.

[75] Josh Chamot and Leslie Fink, *Researchers Engineer Mouse Embryonic Stem Cells to Form Sperm Cell Precursors* (National Science Foundation, Office of Legislative and Public Affairs, December 10, 2003 [cited August 3, 2005]); available from http://www.nsf.gov/od/lpa/news/03/pr03142.htm; Sylvia Pagàn Westphal, "Stem Cells Can Become 'Normal Sperm'," *New Scientist*, May 7, 2003; Gretchen Vogel, "Embryonic Stem Cells: Scientists Make Sperm in a Dish," *Science* 302, no. 5652 (2003).

father. The experiment could also lead to a better understanding of cancer development, and of the causes of birth defects and of male infertility.

Another suggestive experiment was conducted in 2004 by a group of U.S. and Japanese scientists. The researchers managed to insert foreign DNA into the spermatogonia (or immature sperm cells) of zebra fish and to growth them to maturity. This was the first time that researchers had succeeded in culturing entirely in vitro spermatogonia of a species other than mice. The zebra fish is a popular animal model in developmental biology because it shares many of the same genes with humans, and because its embryos are transparent.[76] The researchers used the cultivated sperm to fertilize zebra fish eggs. Of 1,100 eggs exposed to the genetically modified sperm, 104 were fertilized and 89 grew into zebra fish. Of these, five carried the foreign gene.

One possible clinical application of this research is gene therapy. If perfected in humans, this technique would enable scientists to genetically modify sperm, either by adding a specific gene or by removing a defective gene, so as to prevent passing on a genetic disease. Clinical applications, however, are many years away. A much more likely application of this technique is the efficient creation of transgenic animals. Current techniques to engineer transgenic animals are not very effective. Many animals so created display "mosaicism," i.e., only a fairly small fraction of the animal's cells carries the foreign gene.

The experiments described in this section raise several important ethical questions. Is research on human sperm simply another form of medical research, or is it necessary to scrutinize this line of research more carefully? Should bright lines be drawn only when this research comes to fruition? Should these research efforts succeed in producing viable human sperm from embryonic stem cells, what kind of constraints, if any, should society impose on the production of sperm from embryonic stem cells? For example, should it be permissible for ART practitioners to create embryos using sperm derived from stem cells? In other words, should it be possible for children to be born from unborn parents? We think not. The fact that many children have been born from anonymous sperm donors does not provide a rationale for creating children without biological parents or with ambiguous biological roots. Not coincidentally, in recent times, the news media has reported on the concerted (and increasingly successful) efforts by teenagers born through anonymous sperm donations to track down their biological parents – another indication of the powerful role and the importance of biological origins on one's sense of identity.[77] On the other end, would it be acceptable to offer young boys affected by leukemia a chance protect their reproductive chances? Certainly. A regulatory agency is in an excellent position to proscribe the former procedure and regulate the latter.

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[76] Philip Cohen, "Test-Tube Sperm Get New Genes," *New Scientist*, January 26, 2004; *Human GM Sperm Will Be Possible One Day, Researchers Indicate* (Medical News Today, January 28, 2004 [cited August 3, 2005]); Tim Radford, "Scientists Modify Sperm to Add New Fish to the Gene Pool," *The Guardian*, January 27, 2004; Geoff Spencer, *Transgenic Animals Produced Using Cultured Sperm: Study Opens New Possibilities for Biological Research, Gene Therapy* (NIH News, National Institutes of Health, January 26, 2004 [cited August 3, 2005]); available from http://www.nih.gov/news/pr/jan2004/nhgri-26.htm.

[77] Amy Harmon, "Hello, I'm Your Sister. Our Father Is Donor 150," *The New York Times*, November 20, 2005; Rob Stein, "Found on the Web, with DNA: A Boy's Father," *The Washington Post*, November 13, 2005.

4.5.3 Making Eggs

After twenty years of research on mouse embryonic stem cells (ESCs), scientists have been able to coax these cells into just about any kind of cell. Since a group of researchers at the University of Pennsylvania announced in 2003 that they had succeeded in transforming mouse ESCs into eggs, it has now been demonstrated that mouse ESCs can indeed be converted into any kind of mouse cell – i.e., that they are totipotent.[78] Coaxing mouse stem cells into becoming oocytes did not require a sophisticated cocktail of growth factors, a fact prompting optimism in the scientific community about replicating these results in higher mammals, primates, and humans. The eggs were produced through a process similar to ovulation. The oocytes underwent meiosis, the process by which eggs and sperm give up half of their genetic material, and produced embryo-like structures through a process known as "parthenogenesis." Interestingly, eggs were produced by both female *and* male ESCs.

What is the scientific rationale for this experiment? According to the University of Pennsylvania scientists, the experiment could defuse many concerns surrounding research cloning. Somatic cell nuclear transfer is notoriously very inefficient and requires a large number of oocytes to succeed. Retrieving human oocytes in large numbers is an ethically questionable undertaking at best and an unacceptable proposition at worst. The researchers hope that dramatically increasing the availability of oocytes will change the terms of the debate about research cloning: If embryos could entirely be produced in vitro, many opponents of research cloning might find this line of research far less objectionable. A large supply of artificial eggs would also prevent a market for natural oocytes from emerging; the scientists also indicated that their research could advance our understanding of infertility and of menopause.

The rationale offered by these scientists for attempting to produce artificial oocytes is laudable and hopefully not entirely unrealistic. But as pointed out earlier, important scientific experiments often have applications not anticipated by the researchers. In the present case, it is not too difficult to identify some of these unanticipated consequences. As noted above, scientists have made eggs not only from female, but also from male embryonic stem cells. Conceivably, then, a gay couple may be able to produce their own genetically related children through IVF and surrogacy. In this scenario, one man would contribute the sperm and the other the eggs. While some in the gay community may salute this development as an important step toward equal access to parenthood, others may point to possible deleterious consequences for the well-being and the personal identity of children. In allowing men to become mothers, this procedure would also undermine the principle that each child should have a genetic father and mother.

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[78] Claire Ainsworth, "Artificial Human Eggs Created," *New Scientist*, July 2, 2001; Rachel Nowak, "Mice Born from Rat-Matured Eggs," *New Scientist*, September 28, 2002; Sylvia Pagàn Westphal, "Embryonic Stem Cells Turned into Eggs," *New Scientist*, May 1, 2003; Azim Surani, "Stem Cells: How to Make Eggs and Sperm," *Nature* 427 (2004); Nicholas Wade, "Pennsylvania Researchers Turn Stem Cells to Egg Cells," *New York Times*, May 2, 2003; Rick Weiss, "In Laboratory, Ordinary Stem Cells Are Turned into Eggs," *Washington Post*, May 2, 2002.

The availability of oocytes in large numbers would also make it much more attractive for prospective parents seeking an egg donor to consider genetically engineered eggs. As noted elsewhere, scientists have already developed the ability to insert and remove specific genes in embryonic stem cells. Genetically modified stem cells could be used as means to produce eggs with specific genetic traits, in the process making genetic modifications inheritable. A more realistic consequence of this line of research is the postponement of motherhood. Being able to replenish their own supply of eggs through somatic cell nuclear transfer could become a proposition too attractive for many women to resist.[79]

4.5.4 Remaking the Machinery of Gestation

"Ectogenesis" is the technical term used to identify the gestation of a baby outside a woman's womb. Two recent experiments suggest that this possibility may not be as hypothetical as it seems. In one experiment, a group of scientists at Cornell University Medical College in New York took human uterine tissue samples and grew them on a model uterus. To the scientists' amazement, embryos implanted in this tissue survived and developed for six days before the experiment was terminated.[80] Japanese scientists, for their part managed, to gestate goats in a fully artificial womb for three weeks.[81] Whether these experiments are consequential in any way is not entirely clear. Some have argued that it is impossible, for a variety of physiological reasons, to actually design a fully functional human ectogenetic chamber.[82] Detailed information about scientific and medical progress in this area is sparse, and clinical applications appear to be years away. If the debate about genetic engineering is any indication however, progress in this area may occur much faster than anticipated. A brief discussion of possible societal consequences is therefore appropriate.

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[79] Incidentally, there is some evidence that the natural supply of eggs, contrary to common opinion, may not be limited after all. In mid-2004, it was widely reported by the news media that ovaries – at least in mice – are capable of producing fresh eggs throughout their adult life Helen R. Pilcher, *Could We Defeat the Menopause? Mouse Ovaries Offer up Secret of New Egg Cells* (News@nature.com, July 1, 2004 [cited April 26, 2006]); available from http://www.nature.com/nsu/040628/040628-18.html. Whether this result can be reproduced in humans is unclear, but the researchers who conducted the experiment pointed out that female flies, fish, birds, and now mice all do make new eggs throughout life, and that there is no reason to assume that this would be different in humans

[80] It is unclear whether the scientist in question, Dr. Hung-Ching Liu, has published the results of this experiment.

[81] An account of the Japanese experiments can be found in N. Unno et al., "Development of an Artificial Placenta: Survival of Isolated Goat Fetuses for Three Weeks with Umbilical Arteriovenous Extracorporeal Membrane Oxygenation," *Fetal Diagnosis & Therapy* 5 (1990). and Ronald Bailey, *Babies in a Bottle: Artificial Wombs and the Beginning of Human Life* (Reason, August 20, 2003 [cited April 26, 2006]); available from http://reason.com/rb/rb082003.shtml; Y. Kubawara et al., "Long-Term Extrauterine Incubation of Isolated Goat Fetuses," *Artificial Organs* 13 (1989); Robin McKie, "Men Redundant? Now We Don't Need Women Either," *The Guardian*, February 10, 2002; Jeremy Rifkin, "The End of Pregnancy," *The Guardian*, January 17, 2002; Sacha Zimmerman, "Fetal Position: The Real Threat to Roe V. Wade," *The New Republic*, August 13, 2003.

[82] See Bailey, *Babies in a Bottle: Artificial Wombs and the Beginning of Human Life* ([cited).. Curiously, this author's skepticism is in stark contrast to his otherwise enthusiastic support for many other controversial medical and technological developments.

As for many other medical technologies, experiments involving ectogenetic chambers have been conducted with a narrow therapeutic goal in mind. In this case, scientists had hoped to save the lives of extremely premature babies and to help women with uterine malformations to become pregnant. The possible applications of an ectogenetic chamber do not stop here, however. Once this technology has been fully developed, some perfectly healthy women may find it attractive to avoid the hassles and the pains, not to mention the forced temporary retirement, associated with pregnancy by "outsourcing" it to a machine. Women may not be the only ones to find this option attractive. The availability of ectogenetic chambers may induce business firms to adopt policies that strongly encourage their female employees to accept artificial pregnancies. Health insurance companies may find an artificial pregnancy more cost-effective and less risky than a natural one. An entirely artificial gestation could also have a dramatic impact on the abortion debate. A key argument of the pro-choice camp – that the state cannot impose on women the physical and emotional burdens associated with an unwanted pregnancy – would suddenly be removed from the equation.[83]

Also of considerable import are possible risks to the health and well-being of the babies. These risks are all but unknown, but they may well be significant. For example, we know that fetuses respond to the mother's heartbeat and to her emotions. Can we really dispense with these subtle but perhaps critical interactions? One may also wonder whether an artificial pregnancy would weaken the bond between mother and child. How can we be so sure that we will be able to redesign in just a few years what took nature millions of years to create and perfect? Even if we could accomplish this feat, should this practice be indulged or even encouraged for the sake of avoiding stretch marks, weight gain, and overall inconvenience? Is economic efficiency reason enough for tolerating this practice? Is this technology really liberating, as some feminists no doubt will claim? Or should it rather be viewed as a particularly perverse attempt by a male-dominated society to marginalize women?

It is neither our intention nor our desire to provide definitive answers to these questions. More important to the present discussion is the observation that the broad availability of ectogenetic chambers is likely to spark a variety of applications, ranging from the purely therapeutic to the dubious and the downright unacceptable. And as for other scientific and medical developments discussed in this report, only a regulatory agency would have both the expertise and the legitimacy to distinguish between acceptable and unacceptable uses of this technology.

4.5.5 Hybrids and Chimeras

Their vaguely menacing names notwithstanding, we are all familiar with hybrids and chimeras. A hybrid is simply the result of the fertilization of one species' egg with another species' sperm. Mules, the offspring of a female horse and a male donkey, are a classic example. In Greek mythology, a chimera is a monstrous animal with the head of a lion, the body of a goat,

[83] Zimmerman, "Fetal Position: The Real Threat to Roe V. Wade."

and the tail of serpent. In biology, chimeric animals consist of cells from at least two genetically distinct progenitors, either two different animals or a human and an animal. They can be created in a variety of ways – for example, by inserting cells from one species into the embryo or the fetus of another. Stem cells have also been used for this purpose. Chimeras can be conceived naturally, such as when twin embryos fuse (a rare but not unknown phenomenon).

If there ever was a truly horrifying scenario to the average person, it is the possibility that scientists one day could create entities that are neither clearly human nor animal. The term "humanzee" evokes precisely this kind of imagery. The "humanzee" is a creature that is half human and half chimpanzee. Why anyone would want to create a humanzee is of course a very important question that has not received convincing answers. Some have suggested that humanzees could perform degrading and dangerous tasks; others, that they could be designed to serve as soldiers. A more realistic proposition is the possibility that chimeric individuals could be created for superior athletic performance. Whatever the rationale for creating a human-animal chimera, should a suitable technology become available, it is not at all implausible that some individuals may want to use it, despite the unanimous opposition of the scientific community and the ART industry. This situation is reminiscent of reproductive cloning, and raises similar ethical concerns.

It is relatively easy to justify banning the creation of anything resembling a humanzee or a super-athlete. The ethical arguments in this case are not too dissimilar from those offered to ban reproductive cloning. Respect for individual autonomy prevents us from establishing in advance the ultimate purpose of any human life, including human chimeric life. Creation of such a hybrid furthermore raises nightmarish questions of moral status, such as what kinds of political rights such a creature would have. On the other end, there may well be lines of research involving chimeras and/or hybrids that could be justified, both from a scientific and an ethical standpoint.

To our knowledge, there have been only two published experiments involving the creation of human-animal hybrids, both conducted in 2003. In one of these experiments, a Chinese scientist removed the nuclei from rabbit eggs and replaced them with human nuclei obtained from the skin of two five-year-old boys, two men, and a 60-year old woman.[84] The experiment is noteworthy not only because human-animal embryos were created for the first time, but also because it was the first documented case of somatic cell nuclear transfer in humans. It was, in other words, a cloning experiment. As disturbing as this experiment may appear, it was conducted for a straightforward reason. The Chinese scientist was hoping to develop a technique for producing what may be called ethical embryos – embryos that could be produced in large numbers and used as a source of human stem cells without stirring public controversies. Predictably, the experiment did trigger a controversy, but not because of the procedure involved.

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[84] "China's Human-Cloning Policy Fudges Law on Cross-Species Fusions," *Nature* 427 (2004); Carina Dennis, "Chinese Fusion Method Promises Fresh Route to Human Stem Cells," *Nature* 424 (2003); Antonio Regalado, "Chinese Scientists Report Advance in Stem-Cell Work," *Wall Street Journal*, August 13, 2003; Rick Weiss, "Cloning Yields Human-Rabbit Hybrid Embryo," *Washington Post*, August 14, 2003; Richard Yallop, "Professor Backs Use of Hybrid Embryos," *The Australian*, October 28, 2004.

Several scientists expressed serious doubts about the claim that the cells derived from these embryos were indeed embryonic stem cells, because the Chinese researcher failed to demonstrate that the resulting cells were indeed able to self-replicate indefinitely.

One possible way to interpret this line of research is to compare it to xenotransplantation. The transplantation of animal organs into the human body is now common practice in the United States and abroad. Numerous tissue banks exist, and the FDA has thoroughly regulated this field of medicine. Perhaps this experiment could be described as an instance of xenotransplantation; as controversial as transplantation of animal organs into the human body once was, it now has become an accepted medical practice.

In a similar direction points a line of research involving the creation of chimeric sheep.[85] In these experiments, a group of scientists at the University of Nevada in Reno injected human embryonic stem cells into the fetuses of sheep. What is distinctive about these experiments is that the proportion of human cells in some organs (including the skin, the liver, the heart, and the pancreas) is unusually large – between 7 and 15 percent. The researchers hope eventually to be able to grow animals whose organs will not be rejected by humans. Clinical applications remain a distant goal, however.

An important open question is whether the injected human stem cells might end up in the brains of these animals in significant numbers. At this time, scientists are simply unable to provide definitive answers, though they do not exclude this possibility. Nor is it clear that an animal with a significant proportion of human brain cells would have any human cognitive capacities. That scientists at this time are unable to provide even the beginning of an answer to this question is certainly a good reason to carefully monitor these experiments. Precisely this question was raised at a conference organized in October of 2004 by the National Academy of Sciences in Washington, D.C.[86] The question was prompted by research being conducted at Stanford University involving the injection of diseased human embryonic stem cells into animal models.[87] To this end, scientists have created mice with a substantial proportion of human-derived brain cells. This raises, of course, the possibility that mice could acquire human-like cognitive capabilities, a possibility that some scientists participating in the conference seemed to take seriously. Also problematic to participating scientists was prospect that male and female chimeric mice could mate. Other scientists expressed doubts about the wisdom of creating chimeric mice to study disease development.[88]

The discussion among participating scientists showed that researchers are not of one opinion about the wisdom of quickly moving forward in this area. Some have argued, quite reasonably in

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[85] Sylvia Pagàn Westphal, "'Humanised' Organs Can Be Grown in Animals," *New Scientist*, December 17, 2003.

[86] Erika Check, "Biologists Seek Consensus on Guidelines for Stem-Cell Research," *Nature* 431 (2004).

[87] For a moderately technical overview, see the presentation by Professor Irving Weissman prepared for the Conference on Guidelines for Human Embryonic Stem Cell Research, organized by the National Academies and held in Washington, D.C., on October 12-13, 2004 (available at http://dels.nas.edu/bls/stemcells/powerpoints.html).

[88] Nicholas Wade, "Is the World Ready for a Man-Mouse?," *International Herald Tribune*, November 28, 2002.

our view, that the scientific community, as part of its self-regulatory efforts, should first try to determine which experiments involving chimeric animals should be considered unproblematic, which ones are questionable, and which ones should be avoided entirely before moving forward. That this suggestion was ignored is more evidence that a regulatory intervention in this area may indeed be necessary.

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