Policy Challenges Posed by New Reproductive and Genetic Technologies

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Throughout human history, sexual intercourse has been inseparable from having a child; the lottery of parental genes recombining in the joining of egg and sperm has been inseparable from the subsequent implantation and growth of a pregnancy in that woman, and inseparable from her bearing of that child. These events have been part of a continuum that occurred inside the body and that was not susceptible to outside manipulation.

Scientific research into human reproductive biology has changed all that. The process is now open to manipulation at every stage of the continuum. Nuclear transfer cloning can separate genetic recombination from reproduction. Now that eggs and sperm can be kept and manipulated outside the body of their sources, it means intercourse is not needed for pregnancy—embryos can be derived from two individuals who have never met and may not even be alive at the same time. Pregnancy can be separated from fertilization, so that the woman who gives birth is not genetically related in any way to her offspring.

This opening up to manipulation of the process of human reproduction means that as a society there are many choices to make and many dilemmas to face that we have never dealt with before. We do not have policies in place to deal with them. Unfortunately, we do not have a choice; Pandora's box is open and we are going to have to decide what to do. We cannot avoid it because even if we do nothing, that is a policy; it simply means the market rather than a social process will decide how the technologies are used.

In the time I have available, I am going to describe the basics of three reproductive or genetic technologies and note some of the issues they raise, both for individuals and society. Later, Dean Young will talk about possible legal responses to deal with some of these issues. Often, although a technology may have been originally developed to solve a particular problem, it is subsequently used for widening purposes, and I am using the three examples to show the kinds of wide ranging consequences that may arise from the availability of a specific

technology. It is not as simple as deciding if a given technology is "good" or "bad." Very often, it will depend on how a technology is used. Because of the complex cascade of issues resulting from the use or non-use of each of these technologies, the law faces many new choices. There are harms and benefits to be traded off and there are usually economic, health care system and social justice issues raised.[1]

I. IN VITRO FERTILIZATION

The first of the technologies I will touch on is in vitro fertilization or IVF. IVF was originally developed to give women who couldn't become pregnant because their fallopian tubes were blocked a chance to do so. As you can see on this diagram, normally, once a menstrual cycles, an egg is released by the ovary and travels down the tube. The sperm journeys, from the vagina through the uterus and up the tube. Fertilization usually takes place in the lateral part of the fallopian tube, with the fertilized egg then continuing its journey to later implant in the uterine wall. Clearly, if the tubes are blocked, this can't happen. But if eggs are taken from the ovary, taken out of the body, they can be fertilized by putting them with sperm in a glass dish, which is where the term "in vitro" (in glass) comes from. The resulting zygote can then be put back into the uterus.

The first IVF child was born in 1978 in Britain and the technology has developed and become widespread in the years since, so that currently about one in 80 infants born in the U.K., and one in 50 in the Scandinavian countries, are after IVF.[2] A cycle of treatment starts with the woman having injections of hormones (for example human menopausal gonadotropin) to induce ovulation. These hormones have both immediate and long term health risks. The most serious immediate side effect is a condition called ovarian hyperstimulation syndrome which can be mild, moderate, or severe. Ovarian enlargement, nausea, vomiting, visual disturbances and fluid retention may occur. Severe cases occur in a few percent (0.4 – 4.0 %) of cycles—and may have complications which on occasion are life threatening or fatal. With regard to the long term, several studies raised the possibility that women who receive these hormones have several times increased risk of ovarian cancer many years

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1 P.A. Baird, *Proceed with Care: Final Report of the Royal Commission on New Reproductive Technologies* (Ottawa: The Commission, 1993).

2 D. Derbyshire, "One in 80 Born in Britain is a Test Tube Baby", *The Daily Telegraph*, London, U.K., June 28, 2000.

later.[3] However, a recent large study has data which suggests this increased risk of cancer is related to the infertility itself.[4] Egg growth in response to the hormone injections is monitored through blood and urine tests or ultrasounds, and the procedure to retrieve the eggs from inside the body of the woman is timed to be done just before ovulation occurs.

For the retrieval, the woman is given either a light anaesthetic, or a sedative and local anaesthetic, and ultrasound is used to guide a needle put through her vaginal wall to her ovary to aspirate any available eggs. This has a small risk of bleeding or infection attached which can cause tubal blockage if it does not already exist. If eggs are retrieved, they are put into culture medium in an incubator. After several hours, a drop of sperm is added to the medium and the eggs returned to the incubator. Within 20 hours, they are examined under the microscope to determine if fertilization has occurred. If it has, (as it has in 70 – 80 % cases), on the third day, at a 2 – 8 cell stage, the dividing fertilized egg, the zygote, can be transferred back to the body. It is put into the uterus through a fine catheter inserted into the cervix.

In about 20 % of transfers, implantation occurs, and a measurable rise in hormone levels in the woman's blood results—a so called "hemical pregnancy." The obverse, of course, is that in most cases, about 80 % of transfers, there is no implantation. The live birth rate, which is what recipients are interested in, is less than the implantation or pregnancy rate because a percentage are lost or miscarried. At each of these stages of the treatment cycle there is a failure rate. The bottom line is that the overall success rate, measured as a liveborn infant delivered per treatment cycle started, is between 10 % and 15 %. That is, classical IVF doesn't work in 85 % to 90 % of cycles of treatment. Somewhat better results can be obtained with additional techniques where, under the microscope a sperm is put into the egg rather than just putting egg and sperm together in a

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3 M.A. Rossing, J.R. Daling, N.S. Weiss, D.E. Moore & S.G. Self, "Ovarian Tumors in a Cohort of Infertile Women" (1994) 331 N. Engl. J. Med. 771; A.S. Whittemore, "The Risk of Ovarian Cancer after Treatment for Infertility" (1994) 331 N. Engl. J. Med. 805.

4 A. Venn, L. Watson, F. Bruinsma, G. Gilles & D. Healy, "Risk of Cancer after Use of Fertility Drugs with In Vitro Fertilisation" (1999) 354 The Lancet 1586.

petri dish.[5] IVF is expensive—currently about $10,000 of direct costs for one cycle of treatment, and more than one is often needed.[6]

An important question is what are the outcomes of IVF pregnancies? The data show they are different than pregnancies conceived naturally in that 27 % of deliveries after IVF are multiple (for example, twins, triplets or quads). This compares to a general population rate of multiple deliveries of about 1 %.[7] This way of counting underestimates the issue, because it is individuals who may suffer problems, and more than one individual child may be born at a delivery. If, instead, we count liveborn individuals, about 40 % of individuals born after IVF are part of a multiple pregnancy.

This is important because multiple pregnancies pose health risks for women and in particular for children, who are more likely to be born prematurely and be of low birth weight. Neonatal care, which is expensive, is more likely to be needed, and the consequences of prematurity and low birth weight, such as developmental delays and cerebral palsy, are more common. A substantial proportion of very low birth weight children will require continuing care and services in varying degrees for a good part of their lives. IVF babies have 3 – 4 times the population rate for still births, and for deaths in early life. Ectopic pregnancies—that is pregnancies outside the uterus—which have to be terminated, and which risk the life of the mother—are about 25 times as common after IVF, possibly partly because women with tubal problems are selected for IVF procedure.

However, a fully informed couple may be willing to knowingly accept these risks, and if a woman has blocked tubes, the evidence shows it will give her an increased chance of having a live born child. Having children is important in the emotional lives of most people, and IVF used to circumvent blocked tubes in order to help a couple have a family is well accepted by the majority of North Americans.

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5 *Human Fertilisation and Embryology Authority: Eighth Annual Report and Accounts*, (London: The Stationery Office, 1999).

6 P.J. Neumann, S.D. Gharib & M.C. Weinstein, "The Cost of a Successful Delivery with In Vitro Fertilization" (1994) 331 N. Engl. J. Med. 239.

7 T. Bergh, A. Ericson, T. Hillensjö, K.-G. Nygren & U.-B. Wennerhold, "Deliveries and Children Born after In Vitro Fertilisation in Sweden 1982-1995: A Retrospective Cohort Study" (1999) 354 The Lancet 1579.

Nevertheless, fertilization outside the body opens up the reproductive process to being manipulated in new and different ways, and some other ways of using IVF are of concern to many people. The zygote produced at IVF may be put into the uterus of a woman who did not provide the egg, so one possible scenario is with regard to post menopausal pregnancies. The eggs of a woman past menopause do not work in IVF—so if post menopausal women are to have pregnancies, eggs have to be provided by younger women, and usually the sperm of the older woman's partner is used. This has opened up a market for young women to sell or barter their eggs, which is flourishing in the U.S. but which is banned in several European countries.

Another example of possibilities opened up by IVF is that if a woman wants to have her own genetic child, but she doesn't wish to carry a pregnancy, she may have IVF with her own egg and then hire another woman to carry the pregnancy. The zygotes produced at IVF can be frozen; and this opens up an even wider range of possibilities.

In summary, IVF is an expensive procedure, which has risks to the health of the women and children involved, but which may give certain people a chance they otherwise wouldn't have to have a baby. But it is being used in a widening variety of ways, and many of these ways are exploitive, commodify reproduction, and are viewed as inappropriate by many. What is an appropriate policy response? Should there be limits on and accountability by clinics?

II. SEX SELECTION

My next example of technology use is sex selection. There are three approaches to sex selection of offspring when one sex is preferred over the other; each method raising somewhat differing social and ethical issues.[8]

The first method is sex selective abortion. This involves doing prenatal diagnosis by one of three methods: by taking a sample of fluid from the womb; by taking a sample of early placenta; or by doing a detailed ultrasound. The least invasive way is to do an ultrasound examination. Prenatal diagnosis of sex can be done by this method when the genitalia have developed sufficiently to be outlined on the ultrasound

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8 *Sex Selection for Non-Medical Reasons: Final Report of the Royal Commission on New Reproductive Technologies* (Ottawa: Canada Communications Group Publishing, 1993) at 885.

scan, after 10 – 12 weeks of pregnancy. Then the fetus of the undesired sex can be aborted. In the dispersed medical community prenatal ultrasound is widely done and most pregnant women in Canada now have at least one ultrasound. Sex selective abortion may occur as a result, although this probably occurs relatively infrequently, at least in Canada, though not in some other countries.

Sex selective implantation: The second method of selecting sex is to do IVF so the zygote is accessible; then test one of the cells of the early zygote to see if it has two X chromosomes or an X and a Y, for example with probes to DNA sequences on the Y chromosome. Then only those of the desired sex can be transferred for implantation in the uterus. This method of sex selection is invasive, posing health risks for the woman because she has to have IVF, and is expensive.

Sex selective insemination is the third method. This treats sperm with the aim of enhancing either the X-bearing or the Y-bearing sperm content of the semen. A sperm sample has to be delivered to the clinic for processing and treatment, the woman has to time a visit to the clinic to coincide with her ovulation, and the couple must abstain from unprotected intercourse during this time. Instead of being approximately 50/50 whether a girl or a boy will occur, the odds can only be changed to something like 70/30. This current approach is unlikely to result in much change in the sex ratio in North America because at present it is not very accurate, it is intrusive, and several cycles, each costing several hundred dollars, are needed on average before a pregnancy results.

Currently, few couples in Canada think the sex of their child is so important that they're willing to undergo any of the three intrusive and expensive maneuvers described above, although we have seen advertising of these services aimed at particular ethnocultural communities where males are valued more highly. But the situation is not static and future developments are likely to make information about the sex of the fetus much more easily available. For instance, fetal cells are normally found in the maternal circulation, and this may mean in future that a maternal blood sample can be tested, the fetal cells in it sorted and examined with DNA probes to reveal the sex of the fetus she is carrying.

We will need to have thought through the issues regarding sex selection and have a policy response. Its use raises many questions. Will we permit people to choose the sex of their children? What cascade of consequences would this have? Would it be used in a gender biased way in terms of the order and number of sons in each family? Would it reinforce attitudes that the sex of a child is very important? What policy

would promote wider adoption of fundamental values such as sexual equality? How would individuals feel who are born after the procedure but turn out to be the "wrong" sex? What will be the legal implications?

III. CLONING

My third topic is human reproductive cloning where nuclear transfer from a body (somatic) cell to produce a child is used. Cloning to produce offspring without using sexual reproduction has now been done in many mammalian species, including sheep, cows, goats and mice. There is no reason to suppose that nuclear transfer cloning would not work in humans. An Oregon group has used nuclei from cells of monkey embryos transplanted into oocytes and produced liveborn animals, so the techniques are in place to do this in primates.[9]

Normally, all the cells of our body have 46 chromosomes, which contain a full complement of DNA. All our cells, that is, except for eggs in women and sperm cells in men. These reproductive cells have only half the genetic complement, contained in 23 not 46 chromosomes. This means when an egg and sperm join at reproduction, the resulting person has the normal complement of 46 chromosomes in their cells—half of them from the mother, half from the father. In nuclear transfer from somatic cells, the usual joining of egg and sperm that is needed to make a new generation is bypassed, and a genetic copy of an adult animal is made without it. What is done to bypass the usual reproductive process, is to take an egg cell (from a sheep for example), and empty that egg of its nucleus. The emptied egg is then fused with a somatic or body cell containing the nucleus of another adult sheep. This is then implanted in the uterus of yet another ewe. The famous lamb "Dolly" doesn't have two genetic parents; the DNA in the nuclei of her cells is a copy of the DNA in the nucleus of an adult animal—in other words—she is a clone of that adult.

In outbred species (such as humans—we do not usually mate with close relatives), there is no way of predicting what the overall characteristics of an embryo will be. In sexual reproduction we are all the result of a lottery, because it is unpredictable which particular combination of our parents' thousands of genes will occur. Cloning is different from sexual reproduction not just in degree—it is a completely

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9 L. Meng, J.J. Ely & R.L. Stouffer, "Rhesus Monkeys Produced by Nuclear Transfer" (1997) 57 Biol. Reprod. 454.

different kind of reproduction—it separates reproduction from the recombination of genes that has always occurred during reproduction. If nuclear transfer is used, the nucleus may come from an adult whose characteristics are known, so it is possible to select by known characteristics which humans will be copied. In essence, the new technology allows the asexual replication of particular human beings, and provides the ability, for the first time, to predetermine the full complement of nuclear genes of a child.

I think we need new vocabulary to deal with this area. For example, the National Bioethics Advisory Committee in the United States refers to Dolly as a "delayed" twin of an adult sheep.[10] Although a clone and its source are genetically as similar as identical twins, identical twins are not produced by deliberate human agency, and they have always developed simultaneously, in the same pregnancy. Dolly is a genetic replica by asexual means of a fully developed adult animal, and "replicand" seems a more accurate term than "delayed twin."

Making a genetic copy of someone does not mean that person is completely identical. Those characteristics that are monogenic or very strongly genetically determined will be identical—for example transplantation antigens or blood types. But those characteristics that are the outcome of a complex interplay between genetic endowment and the rearing social, psychological and nutritional environments will differ. As well, because the cytoplasm of the egg has mitochondrial genes which may be different from those in the somatic cell that was fused with it, the human person resulting from cloning would not be an exact genetic copy.

There is a considerable risk that physical harm would occur to resulting cloned individuals, as there are many unknowns and large uncertainties. In animals, the manipulation of the nucleus and the egg cell leads to increased fetal loss and to congenital malformations. If nuclear transfer is used to produce a human individual, the other related problems such as early death, malformations, and intellectual handicap would only become evident after birth, so it is embarking on a risky course.

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[10] *Cloning human beings: Report and Recommendations of U.S. National Bioethics Advisory Committee* (Rockville, M.D.: National Bioethics Advisory Commission, 1997).

There are some other physical harms to consider.[11] A cloned individual is derived from a single body cell of an adult. Mutations happen all the time in our body cells but most of the time it doesn't matter much, as particular cells are not critical to support life. However, if the body cell used in cloning has under gone a sporadic mutation, that is important, because all the cells of the clone coming from it will have that mutation. The consequences of mutations can be expected to differ, but sporadic mutations in a variety of genes can predispose a cell to become cancerous for example. If the body cell used for transfer had such a mutation, that mutation is transmitted to all cells of the body, including the eggs and sperm of the replicand.

Another unknown outcome is whether individuals produced by nuclear transfer would age normally. Body cells can only divide a finite number of times. So if an "older" cell that has already divided many times is used to clone, does it have implications for the life expectancy in a replicand? Initially, data from Dolly suggested that her cells were "older" than expected (showed telomere shortening), but data from other cloned animals has suggested otherwise. We do not know, as yet.

As well as potential physical harms, potential psychological harms to cloned individuals occur—such as a sense of diminished individuality, foreclosed future, or disturbed sense of identity. An important part of human identity is a sense of coming from a maternal and paternal line while at the same time being a unique individual. Many children who are adopted, or from donor insemination, show a deep need to know about their biological origins. Making children by cloning means they have no chance of having this dual genetic origin; they are not connected to others in the same biological way as the rest of humanity. The first person born this way would be the first of our species not to come from the joining of egg and sperm. Social, family and kinship relationships and obligations that support human flourishing have evolved over millennia—there are no ways evolved for how to place replicand individuals. Is the DNA source the twin? The mother? The father?[12]

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[11] J.Q. Wilson & L. Kass, "The Ethics of Human Cloning" (Washington, D.C.: American Enterprise Press, 1999).

[12] P.A. Baird, "Cloning of Animals and Humans: What Should the Policy Response Be?" (1999) 42 Perspectives in Biol. & Med. 179.

Most of the debate on human cloning has been focused on weighing physical and psychological harms and benefits to individuals, but this is a dangerously incomplete framing. Although looking at the issue as a matter of reproductive technology choice focuses attention on individual autonomy, reproductive freedom, and protection of children, it means that many other issues are completely left out of consideration.[13] We need a framing that reveals how permitting reproductive cloning affects future generations and our society as a whole, because viewing cloning as a personal, private matter inappropriately minimizes potentially serious social consequences. Individual choices in reproduction are not isolated acts—they affect the child, other people, and future generations. These wider consequences need to be taken into account, because we all have a stake in what kind of community we live in; we do not want it to be one where the use of cloning commodifies children, commercializes the forming of families or increases social injustice.

The lottery of reproduction has been a protection against people being predetermined, chosen, or designed by others—including parents. But cloning controls and directs the production of human beings in an unprecedented way. The chance nature of reproduction is changed into "making" individuals with particular genomes. A major impetus to developing nuclear transfer cloning for producing animals has been that it could then be combined with genetic enhancement, because with nuclear transfer cloning, genes can be added to give the animals desired traits.[14]

Cloning makes it possible for the first time to think seriously about genetically enhancing humans. A person's cells could be cultured, and genes inserted into the cells in culture. Screening could be done to identify those cells taking up the desired genes and then those particular cells used to produce a cloned "improved" individual. Theoretically genes could be inserted for viral disease resistance, or to protect against baldness, or degenerative diseases. Genes related to many other traits such as height or intelligence could be inserted in future.

If nuclear transfer cloning is allowed for those people who wish it, what will stop genetic enhancement being used eventually? There would be strong individual motivation to have a taller or disease resistant child. When we start down the path of reproductive cloning, we are taking

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[13] F. Baylis, "Human Cloning: Three Mistakes and a Solution" Dr J.P. Maclean Memorial Lecture, Department of Internal Medicine, University of Manitoba, Winnipeg 1999.

[14] E. Pennis, "After Dolly, A Pharming Frenzy" (1998) 279 Science 646.

human evolution into our own hands. From our record of dealing with hunger, environmental degration or poverty, I do not think we are wise enough to manage it or the social consequences. Most people will want their child to be brighter, taller, disease resistant—so this technology has the potential to make people more alike and standard, based simply on individual choices, no coercion involved, just market forces.[15] If it works, as it has in animals, it is likely to become used more often than just occasionally by those who can afford it.

In considering what we should do about policy regarding asexual cloning to make a human being, it is relevant to know that an exceedingly small proportion of infertile people are so because they do not have eggs or sperm, and such individuals already have options such as assisted insemination, egg and embryo donation, and adoption available to them.

If reproductive cloning were permitted, who would have access to cloning or genetic improvements? Everyone? Or just those who can pay? It is unlikely that most countries would be willing to provide publicly supported cloning, given that there are few social benefits and many potential harms.[16] If it is permitted at all, it is likely that those with financial resources would be able to have access, but not other people. However, if cloning or enhancement technology were provided as a public good in order to ensure equality of access, government would have to decide in what circumstances people may clone themselves, and what traits were desirable. Docility? Height? What would they be? To provide a tissue transplant? To permit infertile couples to reproduce this way? If cloning is permitted, unless the market is to decide, criteria as to who may clone themselves will be needed, as well as a regulatory body. What will be the policy response?

In public policy making, it is inappropriate to subordinate every consideration to whether or not a technology helps a particular couple to have a family. Many effects of permitting cloning cannot be dealt within the framework of individual autonomy and reproductive choice. The current strong focus on autonomy leads us to overlook the collective and transgenerational consequences of leaving the use of reproductive technologies to individual choices.[17] The cumulative impact of individual-

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15 L.M. Silver, *Remaking Eden: How Genetic Engineering and Cloning Will Transform the American Family* (New York: Avon Books Inc., 1997).

16 P.A. Baird, *supra* note 13.

17 P.A. Baird, "Individual Interests, Societal Interests and Reproductive Technologies" (1997) 40 Perspectives in Biol. & Med. 440.

centred choices can result in an unethical system. Society has a legitimate role to play in deciding whether or not cloning will be used. And the far-reaching nature of this choice means the decisions should not be taken pre-emptively by a particular clinical facility or a particular group of scientists who ignore the wishes of the rest of the community. The perspectives, not just of individuals knowledgeable in biology or science, but of sociologists, humanists, and citizens from a variety of life experiences are needed on something that affects our species' future.

Medicine, science and technology are world-wide endeavours, so consequently this is not an issue facing any nation alone, but humans as a species. For that reason, UNESCO is making an effort to develop international agreements to deal with cloning in humans, and WHO has recently started to make policy recommendations in this area for all countries.

However, experience shows that where there is a demand for a novel service and the ability of some to pay for it, unless there is legislation there will be professionals willing to provide it. There is licensing and regulation of fertility clinics in several European countries, but in some countries reproductive technologies are highly commercialized and little regulated. If we do not wish to go down this path, legislation will be needed that does not permit implantation into a woman of an egg cell that has had the nucleus transferred in from a body cell. If such legislation is written, its wording should not inadvertently ban non-reproductive cloning research, which must be addressed separately as the issues are different, or animal cloning research that may be of benefit, and that many people see as acceptable.

CONCLUSION

I have described three examples of technology arising from scientific research and innovation in reproductive biology and genetics. They each have a cascade of consequences resulting from their use or non-use. Human intervention is now possible ever more directly, in the most intimate biological processes which have great meaning in our lives. We need to recognize that "all innovation is not by definition progress, no matter what has to be sacrificed to attain it."[18] It is not Luddite to recognize the harms as well as the benefits, to recognize that dehumanization, exploitation and social injustice will result from some

[18] L.R. Kass, "The Moral Meaning of Genetic Technology" (1999) Commentary 322.

uses of genetic and reproductive technology. In making policies, we need to be aware of the dangers not only to privacy or insurability, but to the way we relate to each other and to our humanity. We will need wise public policy if we are not to be driven by technological innovation to become a society we do not wish to be. Inevitably, the legal profession will be involved in dealing with many of these issues and choices. I hope we are able to manage our way through this maze of choices so that technologies are used in a non-exploitive way that brings benefit, and that we are not driven to do things just because we can.