The New Atlantis
A Journal of Technology & Society

Part Three

The Case Against Cloning-for-Biomedical-Research

While there is currently widespread agreement that cloning-to-produce-children would be unethical, and even fairly broad support for its prohibition, public opinion is much more divided on the moral acceptability of cloning-for-biomedical-research.[1] This fact is partly attributable to confusion and partly to the different moral arguments that apply to the different ends cloning may serve.

Disputes over terminology surely compound the confusion. Some of the laws proposed to prohibit cloning-to-produce-children while permitting cloning-for-biomedical-research identify the act of "cloning" not with the creation of a cloned human embryo for research purposes, but only with the transfer of such an embryo to the uterus of a woman.[2] By contrast, many scientists, ethicists, and advocates use the term "cloning" for both practices—calling one "therapeutic cloning" and the other "reproductive cloning." Though both these terms use the word "cloning," they are still not entirely accurate. So-called "therapeutic cloning" will not be therapeutic for any patients in the near future, and will never be therapeutic for the cloned embryo, which will be destroyed. Furthermore, the distinction between the two implies that "therapeutic" cloning is not "reproductive," when both are in fact forms of reproduction—both create new human life.

Unlike cloning-to-produce-children, which would be pursued only by those with a distorted understanding of the goods of procreation and family, cloning-for-biomedical-research serves a noble aim—the discovery of new knowledge that might make possible new modes of healing. But, like cloning-to-produce-children, and arguably to an even greater extent, cloning-for-biomedical-research involves immoral *actions*. In cloning-to-produce-children, after the embryo is cloned, it is transferred to a woman's uterus so that it can develop into a child and be born, while in cloning-for-biomedical-research, the embryo is destroyed.

The availability of morally acceptable alternatives makes cloning-for-biomedical-research less justifiable. In the following pages, we show what is at stake in the debate over cloning-for-biomedical-research, and why it is important to reject human cloning whatever its purpose is.

Exploitation of Embryos

The central moral objection to cloning-for-biomedical-research is that it involves the deliberate killing of human embryos. Much of the debate over cloning-for-biomedical-research therefore concerns the question of the moral status of the embryo. Is the embryo "one of us," despite its apparent lack of distinctively human features and capacities? Do these youngest of human beings deserve our care and protection, or are there purposes that are sufficiently important to warrant killing them or using them in experiments?

We maintain that, because human embryos are human beings, they must "never be used as a mere means for the benefit of others."[3] Human embryos are members of the human species at the earliest stage of biological development. They are tiny in size and unfamiliar in appearance, but they are unmistakably individual human organisms—they do not become human at some later developmental stage. Occasionally scientists will aver that "science does not offer a hard-and-fast answer to the question of when human life begins."[4] The notion that it is impossible for science to answer the question of when human life begins, or even that the question is meaningless, can be convenient for scientists who want to use embryos as raw materials in their technological projects, but it also represents an abdication of the responsibility of science to provide us not only with technological power over nature but also with answers to questions about nature, including answers that might make us reconsider the moral implications of some of our growing technological power over nature.

Cloning is not the only area of research that involves the deliberate destruction of human embryos. Most other forms of embryo-destroying research rely on embryos originally created for reproductive purposes left unused, stored frozen in IVF clinics.[5] But in the case of cloning-for-biomedical-research, human embryos are created for a purpose that requires their destruction. While the abandonment of one's embryonic offspring represents one of the most morally vexing aspects of modern reproductive technologies, the creation of new human lives solely to produce biomedical research materials is a further, distinctive form of human exploitation.

Cloning-for-biomedical-research is a deeper violation of the meaning of the procreative act and the obligations we owe to future generations than cloning-to-produce-children. Both involve seeing offspring as products of our will, made to serve our purposes. But the direct aim of creating human lives in cloning-for-biomedical-research is the destruction of those lives, and the transformation of their bodies into biomedical research

supplies. It literally involves manufacturing and commodifying human life: biotech companies advertise human embryonic stem cells as having been "derived under current Good Manufacturing Practice (cGMP) conditions."[6] Advocates of such embryo-destroying research speak not of "embryos" but of the "products" of techniques like IVF or cloning.[7] In cloning-for-biomedical-research, the act of human reproduction is transformed entirely into a means of satisfying the desires and furthering the projects of autonomous adults, in complete indifference to the interests of the new human beings created.

As we will argue below, there are other serious moral problems associated with cloning-for-biomedical-research, including the exploitation of women who will be needed to provide eggs. And cloning-for-biomedical-research will lay the technical and practical groundwork for cloning-to-produce-children and a number of other morally troubling acts. But we should not forget that cloning-for-biomedical-research is already at the bottom of the slippery slope—it is an act of deliberately creating human beings solely so that they can be destroyed for the benefit of others.

Ethics of Egg Procurement

Procuring human egg cells for cloning research is both practically complicated and ethically problematic. Unlike some forms of human embryo research that can use embryos donated by fertility patients, cloning-for-biomedical-research involves the manufacture of embryos, which requires collecting oocytes from women—a process with significant medical risks to women that inherently exploits and commodifies women's bodies.

Collecting eggs from women requires stimulating their ovaries to release more than one egg cell during ovulation. Women are prescribed a regimen of hormones that induce superovulation.[8] This procedure can result in a condition called ovarian hyperstimulation syndrome; researchers estimate that 3 to 10 percent of the egg-retrieval procedures performed in IVF clinics result in moderate or severe forms of the syndrome.[9] Severe cases can result in nausea; ovarian cysts; the enlargement of ovaries; changes in the viscosity, volume, or coagulation rate of blood; thromboembolism;[10] and even death.[11] The surgical procedure used to extract eggs also poses risks of pelvic infections and injuries, and internal bleeding.[12] Women providing eggs for research may be at lower risk for some of these complications than women undergoing fertility treatment,[13] but they are also undertaking these risks not as part of a course of treatment but for the sake of scientific research.

Obtaining human egg cells is an obstacle for cloning researchers, since it is not easy to find women willing to undergo the risk-laden and onerous procedures necessary to provide eggs. Whether or not scientists should be permitted to pay women for their eggs is one of the more hotly disputed policy questions concerning cloning-for-biomedical-research, since such payments may provide an inducement for women, especially poor women, to take on medically unnecessary risks. For that reason, some jurisdictions and institutions have placed limits on whether or how much scientists can pay women to provide eggs. While there are no federal laws in the United States restricting payments for egg donors (beyond limits on when and how federal dollars can be spent), some states have laws prohibiting payments for anything beyond reimbursement for direct expenses.[14] The National Academy of Sciences guidelines for stem cell research also endorse compensating women "only for direct expenses incurred as a result of the [egg-procurement] procedure,"[15] though these guidelines are not binding.

Guidelines from other professional associations, however, have been more permissive. The American Society for Reproductive Medicine guidelines allow that egg providers may be paid as much as $10,000 to "reflect the time, inconvenience, and physical and emotional demands associated with the oocyte donation process," whether the women are providing eggs for fertility treatments or research.[16] The International Society for Stem Cell Research guidelines suggest that the research-oversight bodies at each institution decide for themselves whether to permit compensation,[17] on the grounds that such groups are able "to distinguish undue inducements from payments that appropriately acknowledge the interests of the subject."[18] (For a brief survey of the policy debates over egg donation, see "Regulation of Egg Collection" in Part Four of this report.)

Some scientists and bioethicists who endorse cloning-for-biomedical-research have sought to loosen or eliminate restrictions on payments to women for eggs. Many human research subjects are compensated for their participation, and many women who provide eggs for fertility treatments are also paid for their eggs. So, the argument goes, for the sake of consistency women providing eggs for research should also be paid.[19] But the fact that human egg cells have been commodified in one instance does not justify their further commodification in other instances.

Advocates of cloning-for-biomedical-research also argue that payments do not represent "undue inducement" for women to undergo egg-collection procedures.[20] But it is somewhat disingenuous to downplay the incentive effect of payments, since the presence of payments clearly makes

a difference in the decisions women make about whether or not to provide eggs: researchers report that it is difficult to find women willing to provide eggs if they will not be compensated, and women cite the absence of compensation as a chief reason for their decision not to undergo egg-collection procedures.[21] A survey of 230 women enrolled in a Columbia University program that paid them each $8,000 for their eggs found that just 2 percent of the women said they would have been willing to provide eggs without getting paid.[22]

Ethicists who endorse payment for eggs argue that following procedures for informed consent and limiting the amount of money paid for eggs can allow scientists to avoid exploiting women.[23] But as bioethicists Françoise Baylis and Carolyn McLeod argue in a critique of payment-for-eggs schemes, in practice it is impossible to eliminate exploitation, especially of the poor.[24] "There simply is no way to ensure, and no reason to expect, equitable participation in egg selling by rich and poor women," they write.[25] Doing so would require researchers or review boards to track the economic situations of all egg sellers and ensure an impartial distribution, because simply showing that recruitment methods do not *intentionally* target poor women would not be enough to prevent the exploitation of the economically vulnerable.[26] The fact that a woman may freely consent to egg retrieval in full knowledge of its risks does not prevent undue inducement and exploitation, because the woman would most likely not have chosen to take on such risks had she been more financially secure. Exploitation of women providing eggs for fertility treatments is already too common, and more extensive commodification of eggs for research will only aggravate this problem.[27]

It is also necessary to respond to the claim that women are not being paid for their eggs but rather are being compensated for the risks and stress they undergo. For example, the American Society for Reproductive Medicine recommends that

> Compensation based on a reasonable assessment of the time, inconvenience, and discomfort associated with oocyte retrieval can and should be distinguished from payment for the oocytes themselves. Payment based on such an assessment is also consistent with employment and other situations in which individuals are compensated for activities demanding time, stress, physical effort, and risk.[28]

But this argument, that it is the time and effort and not the eggs themselves that are being compensated for, is just a bit of rhetorical drapery obscuring the real purpose of the financial payments: securing more

eggs. What researchers want is not the active participation of women in a shared research enterprise, but to extract valuable resources from women's bodies—the raw materials for a biotechnological manufacturing process.

Future Prospects

Cloning-for-biomedical-research is itself a grave moral evil, but if it is actively pursued it will also make possible a host of other evils.

Most obviously, cloning-for-biomedical-research will lay the foundations for cloning-to-produce-children. The process of creating cloned embryos is the most technically challenging part of cloning-for-biomedical-research and also of cloning-to-produce-children. The act of transferring a cloned embryo to a woman's uterus so that it can grow to term is likely to be little different from the act of transferring any embryo produced through IVF (although as of now, because of embryonic defects associated with cloning, cloned human embryos transferred to a uterus may not be able to survive to term[29]). So progress in the practice of cloning-for-biomedical-research necessarily contributes to expertise in cloning-to-produce-children. Furthermore, were cloning-for-biomedical-research allowed to progress, prohibitions on cloning-to-produce-children would become increasingly difficult to justify. It is safe to assume that some individuals and scientific organizations that support the prohibition of cloning-to-produce-children do so today in order to allay public concerns about cloning in general; their motivation to support such a ban would subside as cloning-for-biomedical-research advances and becomes entrenched. At the same time, it is difficult to imagine that, in a world in which cloned human embryos were being created for research in ever-growing numbers, no one would begin to implant them in wombs to bring babies to term. Indeed, were cloned embryos to become a commonplace part of biomedical research, not only would it be practically difficult to enforce laws or regulations prohibiting their transferal to wombs, especially in the largely unregulated U.S. assisted reproduction industry, but such laws or regulations would be morally odious, since they would consign all cloned human beings to death. (The immorality of these "clone-and-kill" laws is discussed further in Part Four.)

If research on human cloning were to become more acceptable to Americans and more engrained in the careers and projects of the scientific community, other biotechnological developments, as we shall see, may come to be regarded as permissible, desirable, or even necessary.

The existence and acceptance of scientific techniques influences moral sensibilities about future techniques, and is often used as justification for setting aside moral objections. (For example, as mentioned above, many ethicists who advocate paying women for eggs point to the precedent of buying and selling eggs for fertility treatments as a justification for the further commodification of eggs for research.)

While it is worth exercising caution in appealing to the distant consequences of cloning research, the stakes in bioethical debates of this kind are high enough to justify taking seriously even some speculative worries. As the philosopher Hans Jonas argued in an essay on the implications of biological engineering:

> Since no less than the very nature and image of man are at issue, prudence becomes itself our first ethical duty, and hypothetical reasoning our first responsibility. To consider the consequences before taking action is no more than common prudence. In this case, wisdom bids us to go further and to examine the use of powers even before they are quite ready for use. One conceivable outcome of such an examination could be the counsel not to let those powers get ready in the first place, i.e., to stop certain lines of inquiry leading to them, considering the extreme seducibility of man by whatever power he has.[30]

In the subsections that follow, we examine several morally troubling scientific and technological possibilities that may follow on cloning-for-biomedical-research and prove too seductive for humankind to resist.

Creeping extensions of embryo research. One of the medical possibilities most commonly cited as a rationale for pursuing cloning-for-biomedical-research is the prospect of using cloning as a large-scale source of patient-specific embryonic stem cells for cell-replacement therapies. The use of cloned human embryos for biological spare parts might become as regular a part of medicine as bone marrow transplantation is today. Even if some versions of such a future—like the possibility of "personalized biological repair kits" for every American[31]—seem exaggerated, that such a hypothetical is proposed at all by advocates is telling.

However, embryonic stem cells, taken from very young human embryos, are not the only possible medical applications of human cloning research. Scientists could grow cloned embryos in laboratories for longer periods in order to perform experiments on embryonic and fetal development, or to aid in the creation of technologies for growing fetuses outside the womb, or to develop organ primordia for transplantation.

Since the early days of the embryo debates, there has been a broad consensus among researchers and ethicists that embryos should not be experimented upon more than fourteen days after fertilization (discounting days spent frozen in storage). Countries that have used the fourteen-day limit in their laws and regulations governing research on human embryos include Australia,[32] Canada,[33] India,[34] Japan,[35] and the United Kingdom.[36] While the United States has no national laws prohibiting research on human embryos beyond fourteen days, professional societies[37] and the National Academies of Sciences[38] have adopted the fourteen-day limit as a guideline. (California's state stem cell research agency uses a twelve-day limit for its funding decisions, on the same principle as the fourteen-day limit.[39])

The basis for this fourteen-day limit is that this is roughly when *gastrulation* occurs, a process after which the cells of the embryo lose their pluripotency, making it no longer possible for the embryo to split into identical twins. According to an influential 1984 British government report on human fertilization and embryology, the formation of the primitive streak in the embryo, a sign that gastrulation has taken place, "marks the beginning of individual development of the embryo."[40]

The widespread adoption of this standard is somewhat surprising, considering its flimsy moral and scientific basis. Embryos are individual human beings from fertilization on—they do not acquire individuality with the emergence of new cell types or the first visible signs of a vertebrate body plan, or even with the loss of the ability to give rise to an identical twin.[41] The fact that early embryos can at times split into two genetically identical embryos does not mean that the embryo was not a single individual prior to becoming two individuals. The divisibility of early embryos is one of their unique biological features, comparable in some respects to the ability of animals like flatworms to grow as distinct individuals when cut in two.[42] As unusual as such biological divisibility may seem, there need be no confusion about whether a flatworm is a single biological individual prior to its being cut in two, just as there need be no confusion about the biological individuality of an embryo that has the potential to divide into genetically identical twins.

The British government's report itself admitted that "biologically there is no one single identifiable stage in the development of the embryo beyond which the *in vitro* embryo should not be kept alive"[43] and that the decision to demarcate a limit was made "in order to allay public anxiety."[44] So the fourteen-day limit on embryonic research is largely arbitrary, both morally and scientifically. And notwithstanding its wide adoption, it is not legally

enforced in the United States. If promising research opportunities were to emerge that required experimenting on older embryos, it is likely that the ethical standards of the scientific community in the United States would shift to accommodate them, accepting research on older and older embryos.

Embryonic and fetal farming. One of the longstanding goals of regenerative medicine is to build organs from pluripotent stem cells. But growing organs from stem cells is an extremely complex matter, even more so than the difficult task of differentiating stem cells into particular cell types. Instead of deriving organs from stem cells, it may be more technically straightforward to culture embryos for longer periods of time. There are already biotechnology companies developing methods for transplanting organs from aborted fetuses,[45] but using cloning to produce genetically identical fetuses could well be a more attractive option. Cloned embryos could be grown past the fourteen-day limit to yield organ primordia, tissues, or stem cells that could be used for transplantation.

This possibility is less strange than it may seem. From a medical perspective, one reason to go in this direction is that transplantation of organ primordia to replace diseased organs seems to have therapeutic advantages over replacing diseased organs with healthy mature organs (such as in kidney transplants).[46] Researchers have explored this possibility by harvesting kidney primordia from aborted human fetuses and implanting them in immunodeficient mice, demonstrating that the organ primordia developed into semi-functioning kidneys.[47] The viable time to transplant kidney progenitors has been determined to be between 7 and 14 weeks of development.[48] There have already been several animal studies in which tissue from fetuses was harvested for the purpose of treating diseases in mature animals.[49] Considering the pressing need for viable human kidneys—there are more than 100,000 names on the U.S. waiting list as of this writing[50]—it is conceivable that in the future we will see increasing pressure to create cloned fetuses for the purpose of harvesting organs.

In 2006, Congress passed the Fetus Farming Prohibition Act to prohibit the deliberate production of fetuses for the sake of harvesting tissues or organs for medical or research purposes.[51] However, the law prohibits the use of fetuses *gestated* for research purposes, and so if researchers developed the means to grow embryos to the fetal stage *in vitro*, this law would likely not prohibit such actions.

Ectogenesis. The idea of growing prenatal human beings outside of the womb, or ectogenesis, is often associated in the public mind with science

fiction, but in recent years it has been inching toward reality, as scientists have improved the ability to keep unborn human beings alive outside of the womb.[52] On the early side of the developmental spectrum, researchers have invented culturing methods that enable the growth of human embryos up to the fourteen-day limit.[53] And on the other side, we already have incubators for caring for premature infants born as early as 22 weeks.[54] Much of the research today is focused on developing technologies to save the lives of babies born prior to 24 weeks, before which the survival rate using existing incubators greatly decreases. However, some people are interested in developing artificial wombs to allow women who are unable to have children to do so without requiring a surrogate—or simply to allow women to have children without undergoing the burdens and inconveniences of biological pregnancy.[55]

Progress in cloning-for-biomedical-research could accelerate the move toward ectogenesis. The desire to obtain patient-specific organs for transplantation could make it attractive to grow cloned fetuses outside the womb. The Fetus Farming Prohibition Act, mentioned above, does not in fact prohibit growing fetuses outside of the womb in order to harvest their organs for research or transplantation.[56] Even if the law were repealed entirely, however, developing ectogenesis technologies may be easier than finding surrogates willing to become pregnant for the gruesome task of supplying doctors with spare parts.

If artificial womb technologies are developed significantly further, there would be far more harvesting of fetal tissues and organs, as the key technical obstacle to "fetal farming" would be removed. Further, the development of artificial wombs would potentially encourage people to argue that, in the interest of saving the lives of patients, we ought to permit the cloning and artificial cultivation of fetuses for the purpose of harvesting tissues.

Deliberately creating headless babies. It is with some trepidation that we raise the next scenario—already realized in animal experimentation—that might arise in an era of widespread cloning-for-biomedical-research: the possibility that cloning may lead to the deliberate creation of headless humans for growing organs.

The creation of headless clones as a source of organs seems gruesome and fantastic. But it also conforms all too well to some of the dominant attitudes in our society concerning the exploitation of prenatal human life. It is not hard to imagine a day when growing demand for sources of cells and organs for transplantation could lead to the creation of not just

embryos but fetuses and infants; the deliberate engineering of these clones to lack human brains may be seen as a compassionate measure. Biologist and futurist Lee Silver endorsed the creation of headless clones in 1997, saying that he saw "nothing wrong, philosophically or rationally," with the practice.[57]

This prospect may seem very far from any reputable scientific work, and indeed, it is far from clear that it will ever be feasible, technically. But scientists have spent decades studying the genes necessary for development, and in some cases the disruption of just one gene can prevent the development of whole organs or parts of the body. In 1995, scientists were able to create headless mouse fetuses by knocking out a single gene,[58] and research on the genetic basis of the development of the brain and head has continued in the years since.[59] Much of this work, conducted on animals, could provide medically useful knowledge of developmental disorders,[60] but it could also, at least theoretically, be used to produce headless human clones as well. So it is not inconceivable that scientists could create embryos that would be unable to develop certain organs or features that are taken by some to be definitive of human personhood, such as the brain, despite the fact that headless fetuses may sound like mere science fiction.

These entities would presumably lack many of the higher capacities of human beings, and might be thought by Silver and others as being less than human and having less than the moral standing of human fetuses, infants, or adults. In fact, this is one of the common arguments in favor of destroying embryos for research—embryos are clumps of cells that have not yet developed the brain functions necessary for thought and sensation that some see as underlying moral standing, and so it is morally justifiable to kill them to provide patients with medical treatments.[61] If it turns out that fetuses or infants are a more effective source of cells and organs for therapy, then ensuring that these fetuses will lack the capacities to think or feel will presumably, in this calculus, make them morally equivalent to the embryos we are already willing to kill in the name of medical research.

The repugnant thought of creating headless clones and the unsettling similarity of such an idea to how we already treat unborn human beings should give us reason to strengthen our commitment to the protection of unborn life by rejecting all forms of embryo exploitation now, before such grotesque possibilities come to seem more plausible.

Interspecies cloning. If cloning research programs continue to be frustrated by the lack of human egg cells, scientists may turn to creating

cloned embryos by combining human cells with enucleated animal cells. Cell lines that showed quite similar properties to human embryonic stem cells have already been generated by transferring human somatic nuclei into rabbit oocytes, as long ago as 2003.[62] This kind of technique would result in embryonic stem cells that have the nuclear DNA of a human and the mitochondrial DNA of an animal.

Since interspecies cloning could potentially provide a means of producing patient-specific embryonic stem cells, many researchers have already proposed its use to make up for the difficulty of procuring human egg cells.[63] Interspecies cloning has also been suggested as a research tool to provide a better understanding of nuclear-mitochondrial interaction and to provide *in vitro* models to study late-onset diseases (such as Parkinson's).[64]

It is still not clear if this kind of cloning will be an effective source of embryonic stem cells for either research or medicine. A report of the President's Council on Bioethics in 2004 pointed out that more research would be required to know if mitochondrial proteins from animals persist in interspecies embryonic stem cells.[65] A 2009 study involving interspecies cloning using human neural stem cell nuclei and goat oocytes found that human mitochondrial proteins were expressed in the resulting cells, but that the incompatibility of the human genome with the goat cytoplasm meant the cells were not able properly to express genes necessary for mitochondrial function.[66]

Whether such methods could be effective or not, would they be morally better or worse than human cloning? Creating and killing human embryos is always wrong. The mixture of human and non-human life is in itself disturbing, although there are some cases in which mixing human and non-human cells or DNA can be morally acceptable. (A full moral analysis of interspecies research is beyond the scope of this report.) However, creating cloned embryos with uncertain standing as members of the human species in order to avoid the moral problems of human cloning is deeply troubling. Overcoming our sense of repugnance at the idea of creating human-animal hybrids only to use the creation of such hybrids as an excuse to overcome our moral judgments about the sanctity of human life would be not a form of sophisticated moral progress but would rather an example of moral evasion.

Artificial gametes. Another development that cloning-for-biomedical-research will both facilitate and increase the demand for is the creation of "artificial gametes"—egg and sperm cells, made to order. Researchers

have laid out three potential applications for artificial gametes: to create *in vitro* models for the study of how human gametes develop and of germline diseases, to enable genetic manipulations of the human germ line, and to create a supply of gametes to use in research and assisted reproductive therapy.[67] But like interspecies cloning, the production of artificial gametes would provide a way to overcome the limited number of human eggs available for cloning research.

Already, researchers have used mouse embryonic stem cells to derive "sperm-like" and "egg-like" cells *in vitro*.[68] Researchers have also been able to derive cells that express markers similar to mature germ cells from human embryonic stem cells.[69] More recently, researchers were able to transform bone marrow stem cells into sperm-like cells.[70] Based on these studies and others, it is quite possible within the next several years that researchers will be able to derive large quantities of gamete cells from stem cells (either embryonic or induced pluripotent stem cells) *in vitro*.

While there are many related concerns about what such a technique might lead to, it is worth highlighting one in particular here. *In vitro* gametogenesis (IVG) increases our ability to design and produce the most genetically desirable gametes and embryos, because it greatly increases the quantity of gametes (especially oocytes) that can be used for IVF. Using such a technique to produce an embryo and create a human being would be a form of eugenic selection. Some bioethicists have instead proposed calling this kind of selection "procreative beneficence," and have argued that "the ability to create large numbers of eggs or sperm through IVG greatly increases our capacity to select the best child possible."[71] They point out that the mass production of artificial gametes would greatly increase the number of embryos available for selection. If gametes were used to create 10,000 embryos, they write, it is virtually guaranteed that parents will find an embryo that has their desired selection of, say, twenty different single-gene traits.[72]

Even if embryos are not created and destroyed on this scale, artificial gametes would still represent a significant increase in the eugenic ability to select desired traits in comparison to today's techniques of IVF and preimplantation genetic diagnosis. And the use of artificial gametes in this way would result in the creation of untold thousands of embryos that will be discarded as failing to meet genetic quality-control standards.

Genetically engineered children. Creating genetically engineered children would be made much easier if cloning were a widely available technology. Cloning is already used by scientists to create genetically

engineered animals, particularly large animals like pigs and cows.[73] One of the major challenges of producing genetically engineered animals is introducing specific genetic modifications into embryos without damaging or destroying them.[74] It is easier to introduce genetic modifications into somatic ("adult") cells, and those modified somatic cells could be used through cloning to produce genetically modified offspring. For instance, scientists could keep cultures of skin cells in a dish and use genetic-modification techniques to introduce specific genetic changes, and then test the resulting cells to see if the genetic modifications have been successful—that is, to see whether the targeted genes have been modified and whether other sites in the genome may have been inadvertently modified. After this process of genetic modification and testing, the scientists could then use the modified somatic cells to create cloned embryos with specific desired genetic changes.

With the development of new genetic-modification techniques that offer increasingly precise means of editing the genome, demand may grow to use them to produce genetically modified children. In April 2015, Chinese researchers announced that they had for the first time genetically modified human embryos using a technique called CRISPR-Cas9,[75] and though the experiment was condemned by many in the scientific community,[76] some scientists have expressed a willingness to consider genetically engineering human beings with these methods.[77]

Genetic modification will always be a highly risky experiment—the human genome is immensely complex, and deliberately changing one gene is likely to have unpredictable effects. A full analysis of the risks and ethical implications of genetic-modification technology is beyond the scope of this report, but if the technology improves alongside research on human cloning, more and more scientists may be tempted to use the two in conjunction to produce genetically engineered children.

Another quite strange application of cloning combined with genetic engineering has been proposed by bioethicist Carson Strong in order to overcome ethical concerns arising from the fact that cloned children will not have unique genomes. In a 2005 article, Strong argued that by genetically modifying embryos, "the objection [to cloning] based on lack of uniqueness would no longer be applicable."[78] Strong went on to speculate that genetic modification could be used "to give the child a nuclear DNA relationship to both members of an infertile couple" by introducing genetic modifications that would "duplicate certain selected genetic characteristics of the other member of the couple, such as hair or eye color," so that "the child would possess nuclear genetic characteristics of both

parents."[79] This argument, however, fails to respond to cloning critics' actual concerns. As we argued in Part Two, what is most repugnant about human cloning is the way it puts control over the genetic properties into the hands of the adults who choose to create them and distorts the relationship between the generations; Strong's proposal to perform genetic modifications would only aggravate this problem.

Cloning and genetic engineering might also be combined with the creation of IVF embryos and embryonic stem cells. Consider this scenario: A couple who want a genetically modified child first use IVF to produce embryos, which they then destroy to derive embryonic stem cells, which can in turn be genetically modified and used to produce cloned offspring. Embryonic stem cells are already more efficient than ordinary somatic cells for cloning,[80] and the resulting cloned children would be genetically related to both "parents" (though, in some sense, the couple initiating this grisly reproductive procedure would be better understood to be the child's grandparents, with the destroyed embryo from which the child is cloned being its parent).

Alternatives to Cloning-for-Biomedical-Research

Human cloning once appeared to be an essential part of the promising field of regenerative medicine. Without cloning, it was argued, researchers would be unable to create patient-specific stem cell lines, making it difficult to produce tissues for therapy or for studying particular diseases. As we described in our previous report *The Stem Cell Debates: Lessons for Science and Politics*, both the urgency and the promise of regenerative medicine were notoriously overhyped during the period from 2001 to 2006.[81] But that supposed urgency and promise put critics of embryo-destructive research in a difficult position: approving of cloning-for-biomedical-research would mean condoning the ethically unacceptable exploitation of women and of embryonic human life, but stopping cloning would mean forgoing a promising route toward treatments for numerous serious diseases and conditions.

This moral dilemma was never entirely stark—cloning was never more than a promising tool for research, not a certain source of cures. And there was always some hope that alternative forms of research that did not require the creation or destruction of embryos would be developed. Shinya Yamanaka's 2006 discovery of a way to make induced pluripotent stem (iPS) cells in mice[82] (followed by their discovery in humans the next year[83]) gave the world hope that the medical promise of regenerative

medicine could be achieved without pursuing ethically troubling research on human cloning.

And yet, while the availability of iPS cells has dampened interest in human cloning,[84] research on human cloning has not ceased (as shown by scientists' successes in 2013 and 2014 in creating stem cells from cloned human embryos[85]).

Here we examine some of the reasons scientists have offered to justify continuing work on human cloning despite the availability of alternatives, and we show why the comparative advantages of pursuing human cloning are so minimal that they cannot surmount the ethical problems associated with that research.

Supposed advantages of cloning. Some scientists and advocates of embryo-destroying research believe that embryonic stem cells represent the "gold standard" for stem cell research.[86] Some have argued that cloning "mimics human physiology more faithfully" than the methods used to create iPS cells, because cloning "emulates normal fertilization."[87] Two major studies were published in 2014 comparing stem cells produced through cloning to iPS cells; the first found that iPS cells were more likely to have epigenetic abnormalities,[88] but the second found that there were no significant epigenetic differences between iPS cells and embryonic stem cells produced through cloning.[89]

Cloning reprograms cells much faster than the methods for creating iPS cells, with cloning transforming the somatic cell into an embryo within hours, whereas iPS cells generally take weeks to reprogram.[90] Whether or not this makes iPS cells more vulnerable to the accumulation of genetic defects is largely unknown.[91] Some scientists have suggested that, because the production of iPS cells involves many rounds of cell division, iPS cells may have a higher risk of proliferating like cancerous cells than stem cells produced through cloning.[92] This higher risk of cancerous proliferation for iPS cells remains largely speculative, however.[93] And as shown by a recent study reporting that iPS cells and cloning-derived stem cells have similar numbers of mutations,[94] the risk of becoming cancerous may not be substantially different between iPS cells and stem cells produced through cloning.

Advantages of iPS cells over cloned stem cells. The difficulty of procuring human eggs means that cloning-based therapies may never be viable as mainstream medical treatments. Extrapolating from recent experiments, it appears that roughly a dozen or more eggs would be required

to use cloning to create a single stem cell line.[95] And because each cycle of egg-retrieval procures an average of around twelve eggs,[96] about one retrieval procedure would be required for there to be enough eggs to give a good chance of deriving a therapeutic stem cell line to treat one patient. Further research may improve the efficiency of this process, but working from this fairly conservative calculation, in order for cloning to become the basis for widespread stem cell therapies—say, providing personalized stem cells to 100,000 patients per year—there would have to be approximately 100,000 egg-retrieval procedures per year. This would likely only be possible if there were a massive market for human eggs, on the order of hundreds of millions of dollars per year.[97] Alternatively, artificial eggs might someday be produced, as discussed above. Either of these scenarios would be morally troubling and practically complex, and unlikely to come to pass without major scientific and social changes.

The impracticality of a medical cloning enterprise of course does not provide justification for eschewing cloning research *per se*; it merely implies that we should not dedicate our medical resources toward cloning-derived stem cell therapies. It makes much more sense to dedicate those resources to therapies based on iPS cells, which do not require human eggs, thus avoiding the risks to women and concerns about exploitation that an egg market would entail. The potential for widespread availability is one of the most significant practical and moral advantages of iPS cells.

From a therapeutic perspective, a further advantage of iPS cells over cloning-derived stem cells is that the latter may have a higher chance of triggering an immune response.[98] Even though cloning-derived stem cells used for therapy would have the same nuclear DNA as the patient, they would have different mitochondrial DNA, and a recent study in mice showed that this difference in mitochondrial DNA can cause immune reactions.[99] (While iPS cells also sometimes cause immune responses, they would not have immune problems connected to differences in mitochondrial DNA.) Relatedly, there may be immune reactions and other problems resulting from "heteroplasmy" in stem cells derived from cloning—mitochondrial DNA incidentally brought along with the somatic-cell nucleus that differs from the bulk of the mitochondrial DNA found in the egg cell.[100]

Do we need to pursue both lines of research? When iPS cells were discovered, some scientists expected that cloning, in the words of one journalist, "may one day become a history lesson."[101] However, with the first successful derivation of stem cells from human cloning in 2013, the

scientific community has once again come to see cloning as an important research program,[102] a view reinforced by the successful cloning experiments in 2014.[103] Many scientists believe that both lines of research should be pursued, arguing that cloning could improve our understanding of how to produce iPS cells.[104]

One reason that has been given in support of simultaneously pursuing cloning and iPS cell research is that the former might indirectly make the latter more effective. Research on cloning could, some scientists have argued, be used to improve the techniques for producing iPS cells.[105] This stands to reason: there are obvious similarities between the fields, both of which involve reprogramming cells, and it would be surprising if there weren't at least *some* findings of value to both.

Still, the crossover of knowledge between cloning research and iPS cell research should not be overstated. In a 2011 paper, bioethicist Insoo Hyun claimed that Shinya Yamanaka, the first researcher to produce iPS cells, may have used results of cloning research to identify factors that can be used to improve iPS cell reprogramming.[106] But the influence of the cloning study on the Yamanaka paper in question was minimal.[107] (In fact, the insights about cloning that Yamanaka depended on could justly be attributed to knowledge that dates back to the early 1960s, when John Gurdon first performed cloning experiments with frogs; as we noted in Part One, Yamanaka and Gurdon shared a Nobel Prize in 2012 for their discoveries related to cell reprogramming.) Moreover, in the Yamanaka study Hyun points to, the scientists who were supposedly dependent on the findings of cloning research still needed to go through a library of 1,473 transcription factors to identify a particularly effective factor for reprogramming somatic cells[108]—so it is difficult to believe that advances in cloning research contributed much to that work on iPS cells.

The idea that cloning research is necessary for progress in iPS cell research is something of a convenient myth. If all cloning research stopped, iPS cell research would hardly grind to a halt. And of course, if only *human* cloning research were stopped, the basic science of reprogramming could still be studied through animal cloning—indeed, the cloning study Hyun refers to which supposedly influenced Yamanaka was conducted with mice, not humans.

The issue of whether to pursue both iPS cell research and cloning research must hinge on whether the potential knowledge acquired through cloning overrides the ethical concerns raised by cloning, including especially the destruction of human embryos.

If we regard embryos as having inherent value—a dignity or sanctity linked to their status as human organisms at the earliest stage of life—then we ought to be committed at least to the claim that there should be no unnecessary destruction of human embryos. It is worth noting that this point has been acknowledged even by some supporters of embryonic research. For instance, the Ethics Advisory Board counseling the U.S. government on embryo research in 1979 wrote that "the human embryo is entitled to profound respect."[109] An influential 1984 British report on embryo research also found that "the human embryo is entitled to some added measure of respect beyond that accorded to other animal subjects."[110] Although this concept of "respect" is notoriously fuzzy and often has been used merely as rhetorical cover,[111] supporters of embryo research will sometimes gesture at its practical consequences. To give but one example, the bioethicist Dan W. Brock, a supporter of embryo-destroying research including cloning-for-biomedical-research, has written that

> human embryos could be shown the special respect that [their] intermediate moral status requires by limiting their use to equally important human purposes. That special respect would justify guidelines limiting embryos' use and destruction to research with reasonable promise of alleviating serious human disease and suffering.[112]

Anyone who accepts the position that the human embryo has at least *some* intrinsic value can only condone the destruction of human embryos if it is necessary for achieving some good of greater value. Since some say that the future medical benefit of stem cells provides such a value, this potential benefit is usually taken to justify the destruction of human embryos in scientific research.

However, in iPS cells we have a means of developing stem cell therapies that does not require the destruction of embryos. While iPS cells may have certain limitations, as reviewed earlier in this section, those limitations do not appear to undermine the merit of the technique. Anyone who regards the human embryo as having some kind of non-instrumental value must recognize that cloning-for-biomedical-research should not continue.

Altered nuclear transfer. Another widely discussed alternative to cloning-for-biomedical-research is altered nuclear transfer (ANT), a proposal developed Dr. William B. Hurlbut as an outgrowth of his work as a member of the President's Council on Bioethics.[113] As the name suggests, ANT is similar to somatic cell nuclear transfer, the technique used for cloning,

but it would involve modifications either to the oocyte, the somatic-cell nucleus, or both, so that the nuclear transfer operation would produce a biological artifact that could serve as a source of pluripotent stem cells, but would not be an embryo. Hurlbut prefers to call the products of ANT simply "entities" instead of embryos, and has said that they would lack the moral status of a human embryo since they would have "no inherent principle of unity, no coherent drive in the direction of the mature human form."[114] If he is correct to say that these entities lack the integrated organization of a living being—that they are equivalent to disordered collections of cells that result from failed fertilization like teratomas or hydatidiform moles[115]—then ANT could offer a morally acceptable alternative to cloning for producing genetically identical pluripotent stem cells, since it would not require the destruction of human embryos.

The methods of ANT were designed through a combination of moral reasoning and philosophical and scientific reflection about the meaning of embryonic human life. ANT therefore offers not only a promising alternative to the particular moral problems of cloning-for-biomedical-research, but also holds out the promise of cooperative dialogue between scientists and moral philosophers, recognizing that moral philosophy concerning human life must be informed by science, and also that, to borrow medical ethicist Paul Ramsey's remark about physicians, scientists "must in greater measure become moral philosophers."[116]

Not everyone agrees with Hurlbut that the products of ANT are not embryos. In a 2004 letter to the *New England Journal of Medicine*, three Harvard-based stem cell researchers argued that the presence of defects could not settle the ethical question concerning the moral status of the embryo.[117] They argue that the inherent principle of unity and coherent organismal drive that Hurlbut cited "are ill-defined concepts with no clear biologic meaning."[118] Whether or not these concepts are scientifically meaningful is at the crux of the debate over ANT, and indeed of the debate over human embryo research more generally. Can science tell us whether embryos are biological individuals with lives that begin at conception, or must an empirical biological science reject such questions about what biological entities *are* as scientifically meaningless and focus only on what can be *done* with biological materials?

In principle, by modifying key developmental genes in the oocyte and in the somatic cell, ANT could produce an entity that will not have the organized unity of a human embryo. As biologist Maureen L. Condic has argued, ANT results in the production of entities unable to undertake "the first globally coordinated event in human development, the formation of

trophoblast and inner cell mass lineages," which is "the earliest act of the embryo *qua* embryo."[119] Addressing gravely important considerations like these, which arise from a confrontation with the question of what the embryo is, should be a much higher priority for developmental biologists and embryologists as they seek to develop new biotechnological powers over human life.

As of this writing, no attempts at ANT have yet been reported with humans, although there have been some attempts involving animals. In 2006, biologists Alexander Meissner and Rudolf Jaenisch attempted to use one ANT method with mice. The researchers noted that the products of ANT were "inherently unable to implant into the uterus" because they lacked the ability to form the outer layer of the embryo necessary for implantation.[120] The authors also observed that the products of ANT lacked a number of features necessary for embryonic development.[121] The scientists were nonetheless able to derive pluripotent stem cells, holding out the promise that, should there ever be general acceptance that the products of ANT are not embryos, ANT could be a useful and morally acceptable alternative to cloning.[122]

Are embryonic stem cells a "gold standard"? Many writers and scientists describe embryonic stem cells as the gold standard for stem cells.[123] Because cloning-derived stem cells come from embryos, the notion of the gold standard is sometimes taken to imply that they are of a higher quality than iPS cells.[124]

Both of those assumptions—that embryonic stem cells represent a gold standard for comparison and that cloning-derived stem cells are functionally superior to iPS cells—are scientifically dubious. To understand why, let us begin by pointing out that the term "embryonic stem cells" is something of a misnomer. Unlike somatic ("adult") stem cells, which are found in the body—so, for example, neural stem cells can be found in the brain—embryonic stem cells are not found in the embryo. As Rudolf Jaenisch stated at a meeting of the President's Council on Bioethics in 2003, embryonic stem cells "have no counterpart" in actual animal embryos.[125] Rather, they are *made out of* cells found in embryos. It would be more precise to call them "embryo-derived stem cells."[126] This terminology would highlight the fact that what we refer to as "embryonic stem cells" do not occur in nature—they are artificially produced. Extracting cells from the inner cell mass and culturing them in an artificial tissue-culture environment induces changes to the cells. As some developmental biologists have emphasized, the notion that embryonic

stem cells represent an *in vitro* equivalent to cells of the inner cell mass is unjustified, since embryonic stem cells have a number of important properties not found in any cells of the early embryo.[127]

One such useful property is long-term self-renewal. In a natural bodily setting, no embryonic cell demonstrates long-term self-renewal.[128] But embryonic stem cells (and iPS cells) in their artificial environment do. As one review put it,

> embryonic cells, once brought into tissue culture, are exposed to numerous extrinsic signals to which they never would be exposed… *in vivo*. ES [embryonic stem] cells certainly adapt to selective tissue culture conditions and acquire novel functions that allow them to proliferate in an undifferentiated state indefinitely, and, because of this, ES cells are in some sense tissue-culture artifacts.[129]

The exposure to artificial tissue-culture conditions is an inevitable aspect of embryonic stem cells (as well as iPS cells). Embryonic stem cells are not somehow more natural than iPS cells; both are shaped in important ways by technical intervention.

Furthermore, there is little reason to treat embryonic stem cells produced through cloning as a gold standard for patient-specific stem cells. Cloning-derived stem cells and iPS cells should be compared on dimensions pertinent to medical therapy, such as the immune reactions they instigate and their ability to successfully differentiate into various useful cell types. While the degree of similarity between embryo-derived and non-embryo-derived stem cells may turn out to be an indicator of these qualities, the degree of similarity itself cannot be the ultimate basis for evaluating the therapeutic prospects of stem cells.

Evidence from studies looking at the clinically relevant features of stem cells suggests that iPS cells could be effective replacements for embryonic stem cells. For example, in a paper published in 2014, researcher Douglas Melton and his colleagues reported developing a method for making insulin-producing cells on the scale necessary to treat type 1 diabetes. Melton's team was able to use both human embryonic stem cells and iPS cells to generate these insulin-producing cells, indicating that iPS cells were at least adequate for this clinical purpose.[130] In September 2014, scientists in Japan began clinical trials for a treatment for macular degeneration, a condition that can lead to blindness, using cells derived from human iPS cells.[131] While the results of these trials have not yet been published, data from pre-clinical studies on the safety and quality of iPS cells is promising, with experiments in animal models showing that

iPS cells seem not to cause tumors or immune rejection, two of the main safety concerns.[132] The actual use of iPS cells in therapy and in research strongly suggests that they represent a viable alternative to using cloning to produce patient-specific stem cells.

Conclusion: Scientific Research and the Need for Ethics

The discovery of human embryonic stem cells in 1998, just a year after the cloning of Dolly was announced, transformed the debate over human cloning. The project of regenerative medicine seemed to give cloning a morally serious purpose, moving it from the controversial fringes of reproductive autonomy to the heart of the medical research enterprise. By 2004, although scientific success with human cloning was still very limited, prominent supporters of embryonic stem cell research were calling for the mass-production of cloned human embryos for spare parts.[133] Although the discovery of induced pluripotent stem cells in 2006 seemed to have eliminated the need for cloning-for-biomedical-research, and numerous scientists turned away from cloning in favor of the more practical and ethical new technique, scientific work on human cloning did not cease, as the experiments in 2013 and 2014 demonstrate. For scientists who believe that the destruction of human embryos is morally acceptable, cloning remains another promising avenue of research. For such scientists, even if human cloning no longer seems necessary, so long as it is possible it should still be pursued.

While the availability of alternative sources of pluripotent stem cells makes cloning-for-biomedical-research unnecessary, it does not make prohibitions against human cloning unnecessary—rather, it makes the decision to prohibit human cloning easier. We no longer face the hard choice of either forgoing promising medical research or maintaining some level of commitment to the sanctity of human life. Scientific progress has, in this case, given us the opportunity to draw apart the goods of medical progress from the harm of destroying human life, but we must take advantage of this opportunity with resolute political action—prohibiting all forms of human cloning now. Doing so will require careful attention to the past two decades of policy and political debates over cloning legislation and regulation, a matter to which we turn next.