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Part One

Scientific and Historical Background

We begin with a brief history of cloning, highlighting some of its technical aspects and showing how the science and technology of cloning have fit together in the wider history of biotechnology as well as in the imagination and the actions of scientists and the public. We draw particular attention to a conceptual shift that first emerged in the late 1990s, in which the conventional understanding of cloning as a new mode of reproduction came to be replaced by an understanding of cloning as a form of biomedical research. In an important sense, the distinction between "reproductive cloning" and "therapeutic cloning" is spurious: all cloning is "reproductive," and the act of "therapeutic cloning" represents a profound transformation in the meaning of human procreation.

What Is Cloning?

One point of contention in the debates over human cloning has been the definition of the word "cloning" itself, with many advocates of certain forms of cloning seeking to circumvent debate through terminological obfuscation.[1] Rather than using the word "cloning," advocates of cloning-for-biomedical-research have sometimes preferred to use specific technical terms like "nuclear transplantation to produce stem cells,"[2] or to speak not of human cloning but of "therapeutic cloning,"[3] "cloning stem cells,"[4] or "cell reprogramming."[5] Understanding what cloning really is means looking at cloning not in narrow technical terms, but from a broad, conceptual perspective.

The noun *clone* comes from the Greek word for twig or branch, and was originally used in something like its current biotechnological context in 1903 by American plant physiologist Herbert J. Webber for plants that are propagated by cuttings or grafts and that are therefore "not individuals in the ordinary sense, but are simply transplanted parts of the same individual, and in heredity and in all biological and physiological senses such plants are the same individual."[6] The noun *cloning*, the adjective *cloned*, and the verb *to clone* came on the scene around 1930, all originally limited to plant physiology.[7] In subsequent decades, however, these words

came to refer to the replication of various kinds of biological entities, particularly cells and biological molecules, especially DNA. In today's scientific literature, the noun *clone* generally refers to each individual molecule, cell, or organism propagated from the original ancestor or template.[8]

Because the terms "clone" and "cloning" are used in so many different ways, an etymological survey will not do much to clarify their meaning. Whatever the moral implications of cloning molecules of DNA, even human DNA, it is clear that they will be very different from the moral implications of cloning human beings.

What concerns us is of course not cloning in general, but *human cloning*, which we can briefly characterize as *the biotechnological replication of human organisms*. This is the sense in which we will use the term human cloning in this report. The idea of "replication" must admit of some vagueness—cloned animals are not simply copies, nor "simply transplanted parts of the same individual," but the similarity between a clone and its genetic progenitor is much greater than the similarity between children resulting from sexual reproduction and their parents.

One of the early precedents for asexual reproduction in animals was the American biologist Jacques Loeb's discovery in 1899 of artificial parthenogenesis, a technique that could be used to transform some species' egg cells into embryos without fertilization by sperm.[9] Although this technique could not be used to produce genetically identical embryos (and so could not be considered a kind of cloning), the announcement of asexual reproduction in animals inspired a wave of controversy and enthusiasm similar to that which greeted the cloning of Dolly a century later. Loeb, who was dedicated to a mechanistic and reductionistic understanding of biology, saw this discovery as a step toward reducing the phenomena of life to "physico-chemical explanation" and transforming biology into an engineering discipline that would enable scientists to manipulate life at the most fundamental level.[10] He believed he had made an important step toward "the chemical theory of life and may already see ahead of us the day when a scientist, experimenting with chemicals in a test tube, may see them unite and form a substance which shall live and move and reproduce itself."[11] Though scientists were divided on whether or when artificial parthenogenesis could be achieved in higher animals, including humans, there were evidently at least some women enthused by the prospect of Loeb's discovery "having finally freed the woman from the shameful bondage of needing a man to become a mother."[12]

Artificial parthenogenesis would never lead to the kind of mastery over human reproduction that many longed for or feared. But it has

become an important research tool for experimental embryology, and in recent years it has been defended by some prominent cloning scientists as a potentially valuable source of human embryonic stem cells.[13] Some bioethicists have argued that the products of parthenogenesis are not really embryos—on the grounds that mammal embryos created through this technique are not viable—and so it would be less morally problematic to use them to study human embryology.[14]

The history of artificial parthenogenesis presages important features of the history of cloning—in particular, the way a reproductive biotechnology went from inspiring vague ambitions for transforming the human family to becoming another tool in an incremental scientific research program.

Early Cloning Experiments

Unlike Jacques Loeb, whose experiments with artificial parthenogenesis were motivated by grand ambitions, the researchers whose experiments laid the groundwork for cloning were more concerned with solving specific puzzles in embryology and developmental biology. In the early twentieth century there was uncertainty and controversy in these fields over whether the differentiated cells in an adult animal's body all contained the same basic genetic information as the original single-celled embryo, or whether the differentiated kinds of cells of the body each only received the information necessary to carry out its own specialized functions.

The German embryologist Hans Spemann sought to address this question by investigating whether individual parts of a sixteen-celled salamander embryo could go on to grow into embryos on their own. Spemann found that an individual cell isolated from these embryos would develop as a normal individual embryo, rather than grow into one-sixteenth of an embryo. In his 1938 book *Embryonic Development and Induction*, Spemann proposed the cloning technique we now call somatic cell nuclear transfer—which he admitted "appears, at first sight, to be somewhat fantastical"—as an experiment that could help determine whether "even nuclei of differentiated cells can initiate normal development in the egg protoplasm."[15] The experiments Spemann proposed would in fact be carried out through the 1950s and 1960s, and while the history of science tends to be more incremental than a timeline of milestones and landmarks can represent, the most historically significant of these early cloning experiments is generally agreed to have been developmental biologist John Gurdon's 1962 work with frogs, for which he would receive the Nobel Prize five decades later.[16]

In his landmark experiment, Gurdon transferred the nuclei of intestinal cells taken from tadpoles into frog embryos that had had their nuclei removed; these cloned embryos went on to develop into tadpoles. Gurdon later showed that nuclear transfer using frog somatic cells could even produce mature adults.[17] Previous work by other scientists seemed to indicate that differentiated cells, like those taken from a tadpole rather than an embryo, would not be able to support the development of clones through nuclear transfer.[18] Though Gurdon's cloning experiment did not use nuclei from fully mature adults, the tadpole intestinal cells he used were thought to be as fully differentiated as any in an adult frog's body, and were certainly more differentiated than cells used in previous experiments. The experiment seemed to prove that whatever caused the differentiation of adult tissues, the process could be reversed by transferring the cell nucleus into an egg that had had its nucleus removed.

Eugenics and Other Early Ethical Debates

In the early 1960s when the technology of animal cloning was being pioneered, the term "cloning" was still not yet in wide currency, either among scientists or the public. (Neither Gurdon nor the other scientists performing nuclear transfer experiments used the term "cloning" in their papers at the time.) One of the earliest references to human cloning that actually used the term was by the biologist J. B. S. Haldane in a 1963 speech at a symposium on "Man and His Future."[19] Haldane used the term to refer to what is still perhaps the best known literary representation of human cloning, his friend Aldous Huxley's dystopian *Brave New World*.[20] As it happens, Huxley did not use the term "cloning" in that 1932 novel, and the reproductive technology he did describe is somewhat different from what we now think of as human cloning, both in technical respects and in terms of what it is said to accomplish.

In the novel's "Bokanovsky's process," a single embryo was transformed into a large batch of genetically identical embryos, yielding "standard men and women; in uniform batches."[21] In real life, modern techniques for embryo splitting can achieve a somewhat similar goal, and have been used in the production of genetically identical livestock. However, these techniques are not so different from the natural phenomenon that results in identical twins, and are not capable of producing more than four or perhaps eight genetically identical embryos.[22] Proposals to use these techniques to improve the efficiency of in vitro fertilization (IVF) were entertained in the mid-1990s, and continue to be considered by some IVF

practitioners,[23] but unlike contemporary techniques for cloning such as the one used to create Dolly, Huxley's fanciful Bokanovsky's process could not be used to replicate any particular individuals.

In his speech, Haldane criticizes the fictional society's policy of creating clones from a single fertilized embryo as being "of little social value."[24] Instead, Haldane advocates producing clones "from cells of persons of attested ability"—just what Gurdon's nuclear transfer technique, if it could be used in humans, would enable.[25]

Some scientists in the 1960s also thought that cloning offered a superior path to achieving eugenic aims widely embraced by geneticists in the early twentieth century. For example, the Nobel-laureate geneticist Joshua Lederberg would go on to advocate the use of cloning (which he also called "vegetative" reproduction) for human beings in an influential 1966 essay.[26] Lederberg argued that cloning, more than the emerging methods of genetic engineering, would answer "the technical specifications of the eugenicists in a way that Mendelian breeding does not."[27] Cloning, unlike sexual reproduction, would allow eugenicists to copy superior individuals directly "rather than suffer all the risks of recombinational disruption, including those of sex."[28] Furthermore, cloning would permit the "free exchange of organ transplants with no concern for graft rejection" and cloned people would, like identical twins, perhaps have an easier time communicating with one another, making teams of clones well suited to high-stress occupations.[29]

Paul Ramsey, ethicist and theologian, responded with a highly critical analysis of cloning, arguing that "to attempt to soar so high above an eminently human parenthood . . . is inevitably to fall far below—into a vast technological alienation of man. . . . setting sexual love and procreation radically asunder entails depersonalization in the extreme."[30] In 1971, James Watson (of Watson and Crick fame) attempted to stimulate a public debate about cloning, concluding that "if we do not think about it now, the possibility of our having a free choice will one day suddenly be gone."[31] In 1972, Dr. Leon R. Kass argued that the surrender of procreation "to the demands of the calculating will" would be "seriously dehumanizing no matter how 'optimum' the product."[32]

As is so often the case with advanced science and technology, the general public initially learned more about cloning from fiction than from scientists or journalists. Starting especially in the mid-1970s, cloning appeared as a central theme or plot device in many novels, movies, and television shows. Often the technical aspects of cloning were glossed over, but sometimes they were described with surprising detail and accuracy, as

in the case of the 1976 novel and 1978 film *The Boys from Brazil*.[33] The typically dark depictions of cloning in fiction have done a great deal to shape public opinion,[34] although it is possible that the decades of frightening stories have counterintuitively had the effect of making the public more accepting of, or even indifferent to, real-life developments.

One of the chief obstacles to applying Gurdon's cloning research to humans was the challenge of obtaining unfertilized human egg cells (oocytes). Gurdon had used frogs for his initial cloning research in part because of the easy availability of unfertilized frog eggs. But the development of in vitro fertilization in the 1970s, culminating in the birth of the world's first IVF baby in 1978 and the creation soon thereafter of the IVF industry, brought with it new techniques for extracting large numbers of human oocytes—making it easier to imagine how scientists could obtain enough eggs to apply cloning to humans.

Cloning and the Embryo Debates of the 1990s

Debates over embryo research in the early 1990s helped lay the political and moral groundwork for some of the controversy that would come later. In 1994, the National Institutes of Health (NIH) convened a panel to help develop guidelines for government funding of research conducted on human embryos. The Human Embryo Research Panel discussed several kinds of research, including "nuclear transplantation" and the possibility of producing embryonic stem cells.[35] However, the panel did not draw out the connections between these two areas of research that would soon become so important. In its final report, the panel's discussion of cloning was limited to techniques "for producing genetically identical copies, or clones of a single mammalian embryo"—in contrast to techniques for creating embryos that are genetically identical to adult mammals.[36] Several techniques for such "embryo twinning" were debated by scientists and ethicists in the early 1990s,[37] and even today there are some who believe that it could be a useful method for improving IVF outcomes.[38] Troubling as they are, these embryo-twinning techniques are not what most Americans have in mind when they think of human cloning. (The panel dismissed broader public concerns about cloning in a footnote, stating that "Popular notions of cloning derive from science fiction books and films that have more to do with cultural fantasies than with scientific experiments."[39] It is not clear to which "popular notions" this sentence refers.)

The Human Embryo Research Panel did examine nuclear transplantation, but here again, its analysis was limited to the transfer of nuclei from

embryos rather than from adults.[40] In hindsight, we can see that this was a significant lapse, as the first successful cloning of an adult mammal, Dolly, occurred less than two years after the panel's report was published. The panel did, however, anticipate other important developments. For example, it raised the possibility of using nuclear transplantation for the "correction" of certain kinds of defects in oocytes, by transplanting the nucleus of one embryo into the nucleus of an oocyte from which the genetic material has been removed.[41] A similar procedure, which would result in the creation of children with three genetic parents, was approved in the United Kingdom in early 2015, and, as of this writing, U.S. government agencies are considering whether and how to regulate these technologies.[42]

In its discussion of producing human embryonic stem cells—a possibility then still a few years away from becoming a reality—the panel's final report predicted that patient-specific pluripotent stem cells could be obtained by a variation on nuclear transplantation.[43] What the panel meant was not cloning, but rather the transfer of the nucleus of a patient's cell into an embryonic stem cell, in hopes that the stem cell would retain its pluripotency while becoming a genetic match for the patient. This line of investigation was pursued in the early days of embryonic stem cell research, and while the method achieved some preliminary success with animal stem cells,[44] it was never demonstrated to work with human stem cells.

The Human Embryo Research Panel recommended the use of federal funding for a wide range of research that involved the destruction of embryos, including research that would create embryos specifically for the purpose of experimentation that would destroy them. The panel's work met with immediate opposition, including thousands of letters from the public and criticism in the press.[45] President Bill Clinton rejected part of the panel's recommendations, saying, "I do not believe that federal funds should be used to support the creation of human embryos for research purposes, and I have directed that NIH not allocate any resources for such research."[46]

Following the 1994 election that brought Republican majorities to the House and Senate, Congress in 1995 passed and President Clinton signed the Dickey-Wicker Amendment, a law prohibiting the use of federal funding for "the creation of a human embryo or embryos for research purposes" or for research "in which embryos are created or destroyed."[47]

Cloning After Dolly

In February 1997, a team of Scottish researchers led by Ian Wilmut announced it had created Dolly the sheep, the first live-born mammal

cloned from adult tissue.[48] This announcement implied that human cloning might be imminent, and so a political debate ensued, one that brought out many of the public's longstanding anxieties over biotechnology. Immediately after the Dolly news broke, President Clinton instructed the National Bioethics Advisory Commission (an entity his administration had created two years earlier) to "undertake a thorough review of the legal and ethical issues" associated with cloning and to report back "with recommendations on possible federal actions to prevent its abuse."[49] The next week, the president ordered in a memorandum that "no federal funds shall be allocated for cloning of human beings."[50] "Any discovery that touches upon human creation," he said, "is not simply a matter of scientific inquiry, it is a matter of morality and spirituality as well."[51] (Given the Dickey-Wicker Amendment's prohibition on federal funding for research involving the creation of human embryos, President Clinton's ban on funding was largely symbolic.)

President Clinton also called for a moratorium on any private-sector cloning efforts, urging

> the entire scientific and medical community, every foundation, every university, every industry that supports work in this area, to heed the federal government's example. I'm asking for a voluntary moratorium on the cloning of human beings until our Bioethics Advisory Commission and our entire nation have had a real chance to understand and debate the profound ethical implications of the latest advances.[52]

Legislation was soon introduced in the U.S. Congress addressing human cloning, including one bill that would make "it unlawful for any person to use a human somatic cell for the process of producing a human clone."[53] The House and Senate held hearings on the ethics of cloning and on whether and how human cloning could be prohibited, with committees seeking testimony from scientists, theologians, and ethicists.[54] While opposition to cloning was widespread, legislators were also concerned lest they unduly restrict medical research. For example, at one hearing, Representative Constance Morella (D.-Md.) advised, "We must be careful not to outlaw or restrict potentially positive scientific developments with overly prescriptive legislation aimed at aspects of cloning which we don't support or condone, such as human cloning."[55] Later, when calling upon Congress to pass a law banning cloning-to-create-children, President Clinton explained that "Banning human cloning reflects our humanity."[56]

The National Bioethics Advisory Commission issued its report three months later. The pages of that report offer the first prominent attempt

to draw bright moral distinctions between different ends to which cloning might be directed. On one hand, the commission concluded that "at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning."[57] The commission recommended that the federal moratorium and the voluntary private-sector moratorium be extended until Congress could pass a law prohibiting the creation of children through cloning.[58] (However, even this recommendation was tentative: the commission recommended that the law should sunset after "three to five years," so that the country could revisit the issue.[59]) On the other hand, the commission took great pains to emphasize the "many applications that nuclear transfer cloning might have for biotechnology" and "new medical approaches."[60] Because of these potential uses of cloning, the commission recommended that any legal "prohibition on creating a child by somatic cell nuclear transfer should be carefully written so as not to interfere with other important areas of scientific research."[61]

Just a year and a half after the Dolly news, the debate over cloning shifted with the announcement by James Thomson's team at the University of Wisconsin that it had succeeded at deriving lines of human embryonic stem cells.[62] Embryonic stem cells seemed to hold enormous promise for medical research, as scientists could use them to make any kind of tissue in the human body. However, creating human embryonic stem cells requires the destruction of human embryos. And using embryonic stem cells to provide patients with genetically matching cells, tissues, or organs for therapeutic purposes would require creating cloned embryos and then destroying them. This is how the cloning and stem cell debates converged.

Scientists and those who closely followed scientific research were aware of this potential application of human cloning before Thomson's discovery was announced in November 1998. Embryonic stem cell lines from mice were first established in 1981,[63] and the idea of using human embryos to acquire stem cells had been endorsed by the Human Embryo Research Panel in its 1994 report.[64] Scientists and biotech-industry advocates used the prospect of regenerative medicine to argue against federal laws or regulations prohibiting cloning research after the Dolly announcement.[65] And the National Bioethics Advisory Commission report even imagined a future in which everyone would have a cloned embryo created and destroyed in order to produce "an embryonic stem cell line for each individual human" to provide us tissue we might someday want for medical reasons.[66]

Despite the commission's recommendation, no federal law was passed prohibiting human cloning in the United States. The only noteworthy piece of federal legislation on cloning to become law in the aftermath of the Dolly announcement was an alteration to the Dickey-Wicker Amendment adding cloning to the list of practices for which federal funding cannot be used.[67] (Cloning law and policy are discussed at greater length in Part Four of this report.)

Cloning, Fraudulent and Real

In the late 1990s and throughout the administration of President George W. Bush, the issue of human cloning remained entangled with the debates over embryo-destructive experimentation and medicine. However, scientific developments continued apace.

The hype and controversy surrounding human cloning attracted several hucksters and hoaxers who made extravagant, unverified, and unlikely claims about having been the first to clone human embryos or even to bring cloned children to term.[68] But the most important fraud during this era came from a respected scientist, the South Korean researcher Hwang Woo Suk.[69] Hwang manipulated images and fabricated data, deceiving the scientific community into believing that he had cloned human embryos from which he subsequently acquired stem cells. While Hwang had created embryos and embryonic stem cell lines, later examinations of Hwang's stem cells showed that he had generated embryos not through cloning, but through parthenogenesis.[70] In addition to his scientific fraud, Hwang also violated a number of the ethical rules South Korea had enacted to protect egg donors: he pressured a number of his own technicians and lab members to donate their own eggs for the procedure, and he offered cash payments, in violation of South Korea's Bioethics and Safety Act.[71]

Other human cloning experiments had been conducted both before and after Hwang's fraudulent work, but they did not succeed at obtaining embryonic stem cells from cloned embryos. In 2001, scientists from the biotech firm Advanced Cell Technologies reported that they had created three cloned embryos from adult skin cells, though none of them developed past the six-cell stage.[72] In 2005, after Hwang's work was published but before it was revealed to have been fraudulent, another team of scientists announced that it had created a cloned human embryo that developed to the blastocyst stage—the stage at which the embryo can be transferred to the uterus of a woman or destroyed to generate stem cells. However, these scientists did not create an embryonic stem cell line from their

cloning experiment, and in fact the cells the embryos were cloned from were themselves embryonic stem cells.[73] Creating embryos using embryonic stem cells is not an impressive demonstration of the power of cloning techniques, and it is of little practical benefit if the goal is to generate *new* embryonic stem cell lines that genetically match a patient.

In 2008, scientists at the California-based Stemagen Corporation reported that they had cloned human blastocysts from adult cells (in fact, they used cells from one of the scientists), however the experiment did not result in the production of any stem cell lines.[74] More cloned human embryos were created by scientists in 2011, but, again, they were unable or did not attempt to create embryonic stem cells.[75] A team led by Dieter Egli at the New York Stem Cell Institute in 2011 succeeded in generating embryonic stem cells via somatic cell nuclear transfer,[76] but the scientists were only able to succeed by using egg cells that had *not* had their nuclei removed—resulting in embryos and stem cells that had three, rather than the normal two, sets of chromosomes, meaning that this nuclear transfer experiment could not be called "cloning," since the embryos would be far from genetically identical to any other individual, and would be of limited utility because of their genetic abnormality.

Scientists faced not only technical challenges while they were working on their human cloning research, they were also hampered by the difficulty of finding egg donors—especially in jurisdictions where paying women for their eggs was prohibited. Scientists' frustration with these ethical and legal limitations was palpable in their public advocacy on the issue and even in the pages of scientific journals.[77]

Alternatives to Cloning-for-Biomedical-Research

The most important development in the field of regenerative medicine in the first decade of the twenty-first century was the discovery that adult cells could be "reprogrammed" to have properties similar to embryonic stem cells. The resulting cells are called induced pluripotent stem cells (iPS cells).[78] Producing them does not require the creation or destruction of human embryos, nor the use of human eggs, meaning that iPS cells are far less morally problematic than embryonic stem cells. And because iPS cells would be genetically identical to whatever patient they were derived from, they offered precisely the advantage cloning was supposed to provide: patient-specific pluripotent stem cells.

It was widely thought that iPS cells could help resolve the embryo debates. However, embryo-destroying research, including cloning research,

has continued. Some scientists have offered a number of reasons for why cloning may be superior to the reprogramming methods used to generate iPS cells,[79] while others have simply argued that we should pursue all possible lines of research.[80] (For an overview of the scientific debate regarding iPS cells and stem cells produced through human cloning, see Part Three of this report.)

In this context, it is interesting to note that the 2012 Nobel Prize in Physiology and Medicine was awarded not only to Shinya Yamanaka, who was the first researcher to create iPS cells, but also to John Gurdon, for his 1962 cloning experiments with frogs. The work of both these researchers, though their experiments were separated in time by decades, demonstrated a similar basic scientific claim—that the biological development through which the cells of the embryo become the myriad specialized cells of the adult body is, in principle, reversible.

It is clear that the discovery of iPS cells has diverted scientific attention from cloning. For instance, Ian Wilmut, the scientist who cloned Dolly, announced in 2008 that he was moving away from cloning research toward iPS cell research, citing the practical, ethical, and political difficulties associated with obtaining human oocytes and creating human embryos, as well as the surprising technical simplicity of the methods involved in creating iPS cells.[81] But an important lesson can be drawn from the fact that cloning research did not stop after the breakthrough with iPS cells: it shows that technical innovation cannot by itself solve an ethical dilemma. Moral argumentation and political pressure are needed to turn the *less ethically problematic alternative* into the *alternative preferred by scientists.*

Background to the 2013 Cloning Breakthrough

Before we turn to the 2013 cloning breakthrough reported by Shoukhrat Mitalipov and his colleagues in Oregon, it is worth briefly surveying some of the work he and his team did in the years leading up to their landmark research.

Scientists at the Oregon National Primate Research Center, a research center affiliated with Oregon Health & Science University, have been working on cloning non-human primates since the late 1990s. In 1997, this lab was the first to use nuclear transfer technology to clone primates (although the clones were copies of embryos, not adult monkeys).[82] In the early 2000s, Mitalipov and his colleagues attempted to extend these embryo-cloning techniques to cloning adult primates, either to produce embryonic stem cells or to produce cloned rhesus monkey offspring that

could be used as model organisms for studying human disease—but these attempts did not succeed.[83]

Perhaps the most important milestone on the road to human cloning was reached in 2007, when Mitalipov and his team reported that they had produced embryonic stem cells from embryos cloned from rhesus monkeys.[84] One of the techniques they refined in their cloning experiments was the ability to remove the genetic material from oocytes without causing so much damage as to render them unable to support embryonic development.

Using the techniques they developed for manipulating primate oocytes to produce cloned embryos, Mitalipov and his team also experimented with a new reproductive technology called "spindle transfer" that would make it possible for mothers with heritable mitochondrial diseases to have genetically related children who do not have those diseases.[85] This new method creates embryos that have three genetic parents, but it bears some similarities to cloning, both in the techniques it employs, in the aims it could serve, and in the ethical problems it raises. In a technical sense, both cloning and spindle transfer require removing the genetic material from a human egg cell and replacing it with genetic material from another cell, so improvement in one of these techniques can contribute to improvement in the other. And both cloning and spindle transfer could enable parents to prevent the transmission of genetic disease to their children while at the same time controlling the genetic identity or genetic parentage of their children. One related method—developed not by Mitalipov's lab but by scientists in the United Kingdom—actually *is* a grotesque form of human cloning, wherein nuclear DNA is extracted from one embryo, killing it, before putting the DNA into another embryo that has also been killed by having its nuclear DNA extracted.[86] Like cloning, these reproductive technologies are radical forms of experimentation that put unknown and unknowable risks on unconsenting subjects—the children—who will not themselves benefit from these procedures.

Another cloning-related area that Mitalipov's team explored was the creation of primate "chimeras"—animals that are composed of tissues derived from more than one genetically distinct individual, whether of the same species or from different species. Biologists have artificially created mouse chimeras since the 1980s,[87] and the Oregon experiments with chimeras in 2012 were in part an attempt to apply those methods to a species more closely related to humans.[88] By combining six different embryos, the researchers produced chimeras that were found to have grown up to be composed of cells from at least three different embryos, with genetically

distinct cells in all of their tissues and organs.[89] They were apparently normal and healthy.[90] The three chimeras that were born were males, though at least one was found to have a small proportion of genetically female cells.[91] Such experiments could be used to test the pluripotency of primate embryonic stem cells by showing that they are capable of contributing to all of the body's tissues in the resulting chimeric animals.

While Mitalipov and his team were able to create monkey chimeras, they were unable to do so using stem cells, leading them to speculate that primate embryos lend themselves less readily to supporting the development of chimeras than do mouse embryos.[92] (An alternative interpretation would be that primate embryonic stem cells, presumably including human stem cells, are less than fully pluripotent—a finding suggested by other scientists comparing human stem cells to mouse stem cells.[93]) Mitalipov's research on chimera formation in primates has two chief implications for human cloning. First, it suggests that some of the animal-cloning techniques that scientists had believed might also work on humans might not work after all.[94] But at the same time, the ability to create primate chimeras could contribute to our understanding of how cloned embryos develop.[95]

The Oregon team has also made progress in producing cloned monkey offspring. In a 2010 paper, the researchers noted that they had used 67 cloned rhesus monkey embryos to attempt to produce viable cloned offspring; from these attempts, only one pregnancy developed to the fetal stage, and although the researchers were able to detect a heartbeat, the pregnancy "failed to go to term and was [spontaneously] aborted at day 81 of gestation" (about half the normal gestation period for that species).[96] As of this writing, this appears to be the closest that any scientist has come to bringing a cloned primate offspring to term.

Building on all of this primate embryo research—related to cloning, chimera formation, and transferring chromosomes between oocytes—Mitalipov and his team went on to perform their landmark 2013 human cloning experiments. As noted above, cloned human embryos had been produced earlier, but Mitalipov's work was the first to successfully use cloned human embryos to produce embryonic stem cells, which has long been a major goal of human cloning research.[97]

One important finding in Mitalipov's 2013 paper is that the procedure is more efficient than many people expected. Researchers' previous experience indicated that cloning would have a very low success rate, requiring perhaps hundreds of eggs to produce just one embryonic stem cell line.[98] But one of Mitalipov's procedures had a much higher success rate—a rate

of nearly one in five.[99] The researchers also found that cloning attempts were much more successful using eggs from some women rather than others.[100] And the authors noted that eggs collected via a less-intensive hormone treatment, one that resulted in the collection of fewer eggs per cycle, seemed to be more effective for cloning than those collected using more strenuous ovarian-stimulation treatments.[101] All these findings are relevant to the political debate about cloning, since they suggest that egg collection can be made more efficient and less dangerous—perhaps mitigating, though by no means eliminating, concerns about the large numbers of egg donors needed and the potential risks they face. However, it is also worth noting that all of these findings are very far from conclusive, and are based on the most tentative and preliminary of evidence.

As of this writing, only two other research teams have succeeded at human cloning since the 2013 breakthrough, both publishing reports of successful human cloning in 2014. While the somatic cells used in the Oregon cloning experiment in 2013 came from commercially available fetal and newborn cell lines, the teams behind the two 2014 papers both obtained somatic cells from older adults, including a 32-year-old woman affected by type-1 diabetes[102] and a 75-year-old man.[103] As with Mitalipov and his team, these scientists also found that eggs from some donors resulted in more efficient cloning than others.[104] Contrary to Mitalipov's results, however, the 2014 papers did not find any relationship between the efficiency of cloning and the number of eggs donated or the method of egg collection.[105] It would seem probable, as with IVF, that the quality of oocytes matters a great deal and that the eggs of different women vary in their usefulness for cloning—but predicting which women will make better egg donors or discovering better egg-collection methods would likely involve an extensive and morally dubious research project requiring harvesting and testing eggs from a very large number of women.

Conclusion: Cloning for Science and Reproduction

Scientists and the public have different understandings of what is important about human cloning. Most scientists seem to consider cloning a promising albeit difficult technique for studying genetics and developmental biology or for producing cells and tissues that can be used for research or for treating patients. Since the development of embryonic stem cells, with their alluring promise of personalized regenerative medicine, the biomedical applications of cloning have come to captivate the

imagination of much of the American public as well. However, moral concerns remain about obtaining stem cells through such a troubling technology. And scientists, regardless of their moral views, face a range of political and technical challenges when attempting to pursue cloning research. Meanwhile, the idea of using cloning to produce children, which most scientists profess to be uninterested in, continues to hold the public imagination—most often as a source of concern, indignation, and fear.

In Parts 2 and 3 of this report, we discuss the ethical issues raised by cloning and its applications, beginning with the use of cloning to create children.