Introduction

Suppose one man has sexual intercourse with one woman. A spermatozoon fertilizes an egg and creates an embryo with 46 chromosomes.[1] These chromosomes are studded with *genes*: discrete passages of deoxyribonucleic acid (DNA) coding for the amino acid chains that form proteins.[2] Proteins build cells; cells create tissues; and, ultimately, tissues become a baby.[3] Other than the choice of mate, no design is involved. Because this process accounts for most births, this book describes it as *standard reproduction*.

An alternative to standard reproduction may soon emerge. In *human germline modification* (HGM), scientists use molecular editing tools to alter the genes in human *gametes* (sperm and eggs) or embryos.[4] Such gametes or embryos can be used to conceive babies with modified traits (*HGM for reproduction*) or to perform lab research (*HGM for research*).

Bioethicists, lawyers, and policymakers have debated the costs and benefits of HGM for reproduction for many years.[5] Until recently, this debate was academic because efficient editing technology did not exist.[6] However, in 2015, Chinese researchers published the results of an experiment in which a molecular editing tool known as CRISPR/Cas9* was applied to human embryos.[7] The goal was to cut the beta-globin gene (HBB), which when mutated causes a blood disorder known as beta thalassemia,[8] and repair the break with a new sequence of DNA. Upon testing 54 surviving embryos, the researchers found that the CRISPR/Cas9 tool cut the HBB

* CRISPR/Cas9 has many uses. For example, in addition to HGM, it can be applied to cells in culture or used to create or cure experimental animals. Elizabeth Pennisi, The CRISPR Craze, 341 Science 833, 834–35 (2013); Margaret Knox, The Gene Genie, 311 Sci. Am. 42, 45–46 (December 2014). Here is a simplified explanation of how it works: suppose a researcher wishes to disable a specific gene in the nucleus of a cell. She creates a synthetic guide ribonucleic acid (gRNA) molecule complementary to the gene's sequence and attaches the gRNA to the Cas9 enzyme. Using one of various methods, she introduces the complex into the nucleus of the cell. The gRNA leads the Cas9 enzyme to the relevant DNA sequence, which the enzyme then cuts and disables. If the researcher wants to substitute a new DNA sequence, she can add it to the gRNA/enzyme complex in the hope that the cell will use it as a template to repair the cut. Andrew Pollack, A Powerful New Way to Edit DNA, New York Times (March 3, 2014), www.nytimes.com/2014/03/04/health/a-powerful-new-way-to-edit-dna.html

gene in 28. However, only 4 took up the new DNA, and those 4 were *mosaic*, incorporating the new DNA in some cells but not others.[9] Seven other embryos repaired the cut on their own using HBD, an endogenous gene with a sequence similar to that of HBB.[10] Also, the CRISPR-Cas9 tool sometimes cut the DNA in the wrong place, leading to off-target mutations.[11] The researchers concluded that further study was needed before the CRISPR/Cas9 tool could be applied to human embryos in a clinical setting.[12]

A stunning reality overshadowed this modest conclusion: the Chinese researchers had dared to modify human embryos.[13] To be sure, they never intended to create babies and used only nonviable embryos in the experiment.[14] Nevertheless, their work was so shocking that when news of it leaked out, scientists and bioethicists immediately began to comment.[15] Some objected that HGM was unsafe[16] and would lead to human enhancement.[17] Others countered that scientists could continue their research as long as they did not conceive babies through HGM.[18]

HGM research did continue around the world. British and Swedish scientists edited genes in healthy human embryos to study embryonic development,[19] while Chinese scientists explored potential therapeutic uses of HGM.[20] Finally, in 2017, two years after the first experiment, an international team of scientists from the United States, Korea, and China reported major advances in editing human embryos.[21]

The international team obtained donor sperm from a man who carried a mutation that causes hypertrophic cardiomyopathy, a dangerous condition in which the heart muscle develops thicker walls.[22] The team hypothesized that mosaicism could be reduced if editing were performed when only a single copy of the mutated gene was present; accordingly, it injected the CRISPR/Cas9 tool together with the sperm directly into eggs.[23] Fifty-eight embryos were analyzed. The team did not detect the mutation in 42 embryos, or 72.4 percent. (In comparison, 47.4 percent of control embryos created with the sperm lacked the mutation.[24]) Only 1 of the 42 embryos was a mosaic.[25] Even better, the team did not detect off-target mutations in the embryonic cells it examined,[26] perhaps because it modified the CRISPR/Cas9 tool so that the cutting enzyme was present in a purified form and dissipated more quickly.[27]

Hard on the heels of this report, Chinese scientists announced that they had applied a new technology called *base editing* to cloned human embryos.[28] Unlike CRISPR/Cas9, which cuts and repairs DNA, base editing uses enzymes to change a mutated nucleotide base into the standard one.[29] The embryos in the experiment contained a mutation that causes beta thalassemia. The scientists found that the mutation was corrected in more than 20 percent of the embryonic cells tested.[30]

While some scientists innovated, others pondered the policy implications. In 2017, the National Academy of Sciences (NAS) and the National Academy of Medicine issued a report about human genome editing, including HGM

(hereinafter NAS Report).[31] The report opined that research on human gametes and embryos could proceed subject to existing ethical rules and legal regulations.[32] Clinical trials performed to conceive children without a serious disease or condition might be acceptable if reasonable alternatives were not available and research subjects were closely monitored for health and safety.[33] However, the report advised that regulators should not authorize clinical trials for other purposes, such as enhancement, at the present time.[34]

These recommendations are generally consistent with federal law in the United States. HGM for research is permitted,[35] and HGM for reproduction is not yet banned (although federal regulators cannot receive applications for clinical trials at present).[36] However, political forces may lead to changes in the law. Conservatives who wish to protect human embryos may demand that the US Congress ban all HGM, including basic research.[37] Liberals who favor research but wish to prevent the birth of modified babies may insist that Congress ban HGM for reproduction,[38] as other countries have already done.[39]

Too often, both sides of the political divide ignore a simple fact: when human beings are motivated to procreate, they do what it takes to circumvent laws that get in the way. For example, within the United States, residents of states that prohibit gestational surrogacy travel to states with more permissive laws.[40] Likewise, citizens of foreign nations that ban donor gametes and gestational surrogacy travel to places where those technologies are legal.[41]

Therefore, this book proceeds on the basis of two assumptions: first, scientists may eventually acquire enough technical expertise and genetic knowledge to make HGM reasonably safe for mothers and babies; and second, if the United States bans HGM, those who wish to use it may travel to China or other nations for treatment. As a consequence, children with modified genomes will be born and raised here, go to school here, and (upon reaching adulthood) work here. This book describes such individuals as *children of HGM*.

Analysis proceeds in three parts. Part I discusses HGM for reproduction as a matter of public policy. Chapter 1 presents hypotheticals in which parents use HGM to conceive children with therapeutic or enhancing modifications. Next, Chapters 2, 3, 4, and 5 collect complaints about such interventions into four categories. The first, the hubris objection, addresses claims that adults who use HGM transgress divine and natural boundaries, leading to bad outcomes. The second, the manufacture objection, asserts that adults who employ HGM transform human reproduction into manufacture. The third, the stratification objection, charges that children of HGM and their descendants will produce class divides and social inequalities. The fourth, the apocalypse objection, includes allegations that children of HGM will bring about catastrophic outcomes, such as the collapse of democracy or genocide. Chapters 2 through 5 subject these objections and related concerns to critical analysis and link them to negative stereotypes about children of HGM.

Some critics may assert a fifth objection: HGM is hazardous to human embryos.[42] Many will die in the lab or be transferred to women but fail to come to term. But harm to embryos is a general concern: it applies to most embryo research and many assisted reproductive technologies.[43] Therefore, this book does not examine this objection in detail, although it mentions it where relevant.

Part II shifts the focus to the psychological origins and consequences of the four objections and related concerns. Chapter 6 explains that the objections are consistent with, and likely the product of, a heuristic called "psychological essentialism." Thus, stereotypes about children of HGM derive or draw power from essentialism. Chapter 7 claims that predictions of social stratification and apocalyptic outcomes encourage people to envy and mistreat children of HGM.

Part III addresses the laws of HGM in the United States. Chapter 8 presents existing federal and state laws that affect HGM for research and reproduction. Next, Chapter 9 describes future laws that Congress or state legislatures may enact in an effort to stop HGM. Finally, Chapter 10 discusses the harms that bans impose on scientists and science, parents, children, foreigners who travel to the United States, and society. This book concludes that education is a safer and more effective means of preventing abuses of HGM.

Notes

1. Kerry Lynn Macintosh, Chimeras, Hybrids, and Cybrids: How Essentialism Distorts the Law and Stymies Scientific Research, 47 Ariz. St. L.J. 183, 192 (2015).
2. Genetics Home Reference, U.S. National Library of Medicine, What Is a Gene? (May 2, 2017), https://ghr.nlm.nih.gov/primer/basics/gene.
3. Kerry Lynn Macintosh, Human Cloning: Four Fallacies and Their Legal Consequences 1–2, 28 (2013).
4. This definition excludes mitochondrial replacement techniques (MRT), even though some classify such techniques as a form of human germline modification. *See* Susannah Baruch et al., Human Germline Genetic Modification: Issues and Options for Policymakers 14 (2005). MRT bypass the defective mitochondria found in some eggs to prevent the birth of children who would otherwise inherit debilitating mitochondrial diseases. MRT are excluded from discussion here because they pose a more limited and technology-specific set of policy and legal issues. The Institute of Medicine recently issued a report opining that clinical trials of MRT could be ethical under specific circumstances. Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases, Board on Health Science Policy, Institute of Medicine, Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations (Anne Claiborne, Rebecca English, & Jeffrey Kahn eds., 2016).

5. Some have embraced HGM as a means of controlling our own evolution. *See, e.g.*, RONALD BAILEY, LIBERATION BIOLOGY: THE SCIENTIFIC AND MORAL CASE FOR THE BIOTECH REVOLUTION (2005); GREGORY STOCK, REDESIGNING HUMANS: OUR INEVITABLE GENETIC FUTURE (2003); LEE M. SILVER, REMAKING EDEN: CLONING AND BEYOND IN A BRAVE NEW WORLD (1997). Others have insisted HGM is an evil to be avoided. BILL MCKIBBEN, ENOUGH: STAYING HUMAN IN AN ENGINEERED AGE (2004); FRANCIS FUKUYAMA, OUR POSTHUMAN FUTURE: CONSEQUENCES OF THE BIOTECHNOLOGY REVOLUTION (2003).
6. *See* NICHOLAS WADE, Scientists Seek Ban on Method of Making Gene-Edited Babies, NEW YORK TIMES (March 29, 2015), www.nytimes.com/2015/03/20/science/biologists-call-for-halt-to-gene-editing-technique-in-humans.html (asserting that until recently, concerns about HGM have been theoretical); *see also* PRESIDENT'S COUNCIL ON BIOETHICS, BEYOND THERAPY: BIOTECHNOLOGY AND THE PURSUIT OF HAPPINESS 37–40 (2003) (dismissing visions of designer babies as improbable given technical challenges and limited knowledge of genetic and environmental factors).
7. PUPING LIANG ET AL., CRISPR/Cas9-mediated Gene Editing in Human Tripronuclear Zygotes, 6 PROTEIN & CELL 363 (2015).
8. *Id.* at 364. The mutation disrupts production of the beta hemoglobin protein, a component of the hemoglobin A that red blood cells need to carry oxygen. If a child inherits the mutated gene from both parents, she will suffer from severe anemia. AMERICAN MEDICAL ASSOCIATION, FAMILY MEDICAL GUIDE 616 (4th ed. 2004).
9. LIANG ET AL., *supra* note 7, at 366.
10. *Id.*
11. *Id.* The source of these off-target effects was unclear. Imperfections in CRISPR/Cas9 technology might have been to blame. JOCELYN KAISER & DENNIS NORMILE, Embryo Engineering Study Splits Scientific Community, 348 SCIENCE 486, 487 (2015). Alternatively, the off-target effects might have stemmed from the use of nonviable embryos in the experiment. DAVID CYRANOSKI & SARA REARDON, Chinese Scientists Genetically Modify Human Embryos, NATURE NEWS (April 22, 2015), www.nature.com/news/chinese-scientists-genetically-modify-human-embryos-1.17378.
12. LIANG ET AL., *supra* note 7, at 364.
13. KAISER & NORMILE, *supra* note 11.
14. The researchers obtained tripronuclear zygotes from fertility clinics. Each of the abnormal zygotes contained two sperm nuclei and one oocyte nucleus. These zygotes had the capacity to mature into blastocysts but not babies. LIANG ET AL., *supra* note 7, at 364, 369.
15. GRETCHEN VOGEL, Embryo Engineering Alarm, 347 SCIENCE 1301 (2015).
16. *E.g.*, EDWARD LANPHIER ET AL., Don't Edit the Human Germ Line, 519 NATURE 410, 411 (2015); *see also* ERIC S. LANDER, Brave New Genome, 373 N. ENG. J. MED. 5, 6–7 (2015) (questioning safety of the technology and expressing opposition to clinical applications that change human gene pool).

17. Lanphier et al., *supra* note 16, at 411. The authors of the article cited in this note have a motive to oppose HGM. They perform research aimed at correcting genetic mutations within somatic cells, which they believe can save lives without transmitting modifications to future generations. They fear that public backlash against HGM could derail their work. *Id.*
18. *E.g.*, in 2015, an International Summit on Human Gene Editing concluded that HGM research could proceed but advised that babies should not be conceived until safety was established, benefits identified, societal consensus achieved, and regulatory oversight imposed. Organizing Committee for the International Summit on Human Gene Editing, On Human Gene Editing: International Summit Statement, National Academies (December 3, 2015), www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a.
19. Norah M. E. Fogarty et al., Genome Editing Reveals a Role for OCT4 in Human Embryogenesis, 550 Nature 67 (2017) (reporting United Kingdom experiment in which scientists disabled OCT4 to study effect on embryonic development); Anneesa Amjad, Swedish Scientist Edits Genomes of Healthy Human Embryos, 870 BioNews (September 26, 2016), www.bionews.org.uk/page_704671.asp (describing Swedish experiment in which scientist edited genes to observe effect on embryonic development).
20. In 2016, one Chinese research team reported that it added a gene variant conferring resistance to HIV infection to nonviable human embryos. Xiangjin Kang et al., Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR/Cas-mediated Genome Editing, 33 J. Assisted Reprod. & Genetics 581 (2016). In 2017, another Chinese team stated that it corrected genetic mutations in viable human embryos. Lichun Tang et al., CRISPR/Cas9-mediated Gene Editing in Human Zygotes Using Cas9 Protein, 292 Molecular Genetics and Genomics 525 (2017).
21. Hong Ma et al., Correction of a Pathogenic Gene Mutation in Human Embryos, 548 Nature 413 (2017).
22. *Id.* at 414; Heidi Ledford, CRISPR Fixed Disease Gene in Viable Human Embryos, 548 Nature 13 (2017). Hypertrophic cardiomyopathy has been implicated in the deaths of young athletes. Unfortunately, the mutation that causes the condition is dominant. Even if only one parent carries the mutation, a child can inherit the condition. *Id.*
23. Ma et al., *supra* note 21, at 415.
24. *Id.* at 416.
25. The mosaic embryo repaired four of its cells using DNA that the team added to the CRISPR/Cas9 tool to serve as a template. It repaired its other three cells with reference to the normal DNA of the egg. *Id.*
26. *Id.* at 417. As another scientist pointed out, however, off-target mutations could be present even if the researchers did not detect them. Ledford, *supra* note 22, at 14.
27. Ma et al., *supra* note 21, at 418; Ledford, *supra* note 22, at 13.

28. Puping Liang et al., Correction of β-thalassemia Mutant by Base Editor in Human Embryos, 8 Protein & Cell 811, doi: 10.1007/s13238-0170475-6 (2017).
29. Jon Cohen, "Base Editors" Open New Way to Fix Mutations, 358 Science 432 (2017).
30. Liang et al., *supra* note 28.
31. National Academy of Sciences & National Academy of Medicine, Human Genome Editing: Science, Ethics, and Governance (2017).
32. *Id.* at 142.
33. *Id.* at 145–46, Recommendation 5–1. This recommendation came subject to other conditions, which can be summarized as follows: the edited genes caused or contributed to a serious disease or condition; the genes were changed to types linked to normal health; data existed to show the risks and health benefits of the procedure; researchers had plans to track research subjects and their descendants over time; the work was transparent without compromising patient privacy; health and social risks and benefits were continually reevaluated with the benefit of public input; and oversight ensured that the technology was not used for purposes other than averting serious diseases or conditions. *Id.*
34. *Id.* at 147–48.
35. Chapter 8, Sections A.1, A.2, A.3.a.
36. For a discussion of the role of the Food and Drug Administration in regulating HGM for reproduction, see Chapter 8, Section A.1.
37. For a discussion of a total ban and who might favor it, see Chapter 9, Section A.1.
38. *E.g.*, Center for Genetics and Society, Genetically Modified Humans? Seven Reasons to Say "No," (May 7, 2015), www.geneticsandsociety.org/biopolitical-times/genetically-modified-humans-seven-reasons-say-no.
39. *See id.* (claiming more than 40 countries ban HGM that affects future generations); Baruch et al., *supra* note 4, at 39 (citing Australia, Austria, Brazil, Canada, Costa Rica, Finland, France, Georgia, Germany, Hungary, Italy, Japan, the Netherlands, Norway, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom as nations that prohibit HGM in most cases).
40. Victoria R. Guzman, A Comparison of Surrogacy Laws of the U.S. to Other Countries: Should There Be a Uniform Federal Law Permitting Commercial Surrogacy? 38 Houston J. Int'l L. 619, 626–28 (2016).
41. Richard F. Storrow, Assisted Reproduction on Treacherous Terrain: The Legal Hazards of Cross-border Reproductive Travel, 23 Reproductive BioMedicine Online 538, 539 (2011).
42. *See* Brendan Foht, Experiments on Human Embryos Offer Little Hope for Curing Genetic Diseases, Nat'l Review (February 4, 2016), www.nationalreview.com/article/430771/genetic-modification-embryos-morally-wrong-still (asserting that HGM for research exploits the unborn); *but see* Christopher Gyngell et al., The Ethics of Germline Gene Editing, 34

J. OF APPLIED PHILOSOPHY 498, 504 (2016) (arguing that HGM for research should proceed even if it is not safe for embryos).

43. *See* MICHAEL J. SANDEL, Embryo Ethics – The Moral Logic of Stem-Cell Research, 351 N. ENG. J. MED. 207, 208 (2004) (discussing embryo losses in stem-cell research and assisted reproduction).