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■ Also in this issue: excerpt from “Address to the Pontifical Council for Culture” by Pope Francis ■

HURLING TOWARD GERMLINE GENE EDITING

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In the fall of 2018 twin girls were born in southern China. In November, not long after their birth, He Jiankui, a Chinese researcher, made an announcement that sent shockwaves around the world. Jiankui claimed that he genetically altered the twins as embryos to immunize them against HIV infection. Using in vitro fertilization (IVF) and preimplantation genetic diagnosis, along with a new genetic tool called CRISPR, Jiankui cut and pasted the girls' DNA, permanently changing their germline and that of their potential offspring.¹

While many details of Jiankui's experiment are not fully known or verified, his claim caused great concern due to his injudicious and unprecedented use of a relatively new and untested procedure in humans. Despite this criticism, there is little doubt that his alleged stunning proof of concept will accelerate the research of germline gene editing (GGE) in humans, making this an important issue in the years ahead.

Genetic enhancement runs up against several moral issues, perhaps the chief of which is the inevitable eugenic attitude it would foster and the associated inequality it would create between those who have the “proper” enhancements and those who do not. For simplicity's sake, this analysis leaves aside questions related to genetic enhancement and considers only changes made for therapeutic purposes. Regardless, most of the censure of Jiankui focuses on the results of human modification and often overlooks the prior question of how gene editing research itself conducted. Germline gene editing in humans is not safe or morally licit under current practices and technology because of its reliance on technologies such as IVF, the danger to and destruction of the embryos used, and the unknown consequences of changing the germline.

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Justifying Germline Editing of the New Embryo

Gene editing falls into two main categories: somatic and germline. Somatic changes affect non-reproductive cells and are not hereditary, while germline changes modify the reproductive cells and therefore affect not only the individual, but also his or her offspring. In order to alter the germline, a change is introduced in the egg or sperm cells of the parent or in the embryo before differentiation.

While gene editing has been theoretically discussed for some time, since the advent of CRISPR technology in the early 2000s, the ability to make germline changes has quickly moved from theory to practice. CRISPRs (clustered regularly interspaced short palindromic repeats) are repeating DNA sequences that “remember” viral DNA after infection. On subsequent infection, these CRISPRs activate Cas (CRISPR-associated) genes to cut the viral DNA, neutralizing the virus.² Scientists have harnessed this natural ability and can now remove or add genes to correct genetic defects.

Many scientists and philosophers hold that GGE is morally justifiable or even that we have a duty to future generations to continue this line of research. Along the way numerous objections are swept away in the belief that the promise of future generations born immune to cancer or genetic disease is enough to quash any smaller moral difficulties that may arise. Nevertheless, it is important to consider the multitude of children being wantonly sacrificed to achieve this end.

Proponents of this research argue that GGE poses no problems:

Some will say that the embryo itself is at risk of harm. But it is doubtful that the embryo is the type of entity that can be harmed, or at least, harmed in a morally significant way. . . . It is doubtful whether harms to embryos have enough moral significance to justify prohibition or non-funding of otherwise valuable research. . . . There is, however, an easy way to protect future people from these safety risks: ensure none come into existence . . . by making sure that none of the embryos used in the research are allowed to develop to the point that they are subjects of morally weighty harm.³

They also say that since these embryos are already destined to be destroyed (e.g., “leftover” embryos from IVF), or

would not normally survive to term, no harm is done in experimenting on and subsequently destroying them.

The Waste of Unwanted Embryos

GGE primarily uses “leftover” embryos from IVF and similar reproductive technologies. Leaving aside the dilemma of “leftover” humans, the use of IVF is morally illicit. This technology replaces the marital act. Therefore, it is “contrary to the unity of marriage, to the dignity of the spouses, to the vocation proper to parents, and to the child’s right to be conceived and brought into the world in marriage and from marriage.”⁴ Producing a child through technology denigrates what should be seen as a gift from God, placing it on the level of any other human product.⁵

Furthermore, IVF intentionally creates a larger number of embryos than needed in order to select the best to implant and increase the chance of success in case of initial failure. Overproduction invariably results in the destruction of remaining embryos. “Just as the Church condemns induced abortion, so she also forbids acts against the life of these human beings.”⁶ Finally, if IVF is illicit, it follows that using IVF-generated products—whether embryos, eggs, or sperm—is also morally illicit. By using these products the researcher is cooperating at some level in that moral evil.

GGE research often involves genetic testing to determine whether the embryo is developing normally. Preimplantation genetic diagnosis requires the removal of a cell or cells from the embryo at a very early and vulnerable stage, placing it at risk of mutilation and death.

Since GGE research is still in its infancy, scientists do not deem it safe to bring an edited child to term—hence the furor over the purported birth of the genetically edited Chinese twins. In the future, once it is deemed safe to bring these children to term, some sort of prenatal testing will likely remain a standard to ensure that the developing embryo is not defective. Various post-implantation testing techniques are morally permitted, provided they do not place the developing embryo at undue risk, and the intent in testing is treatment or better preparation for difficulties before or after birth. In modern society, however, the intent is often termination if some defect is found. This use of testing with the intention of abortion is never morally permissible and is an additional ethical problem for anyone developing or using GGE on human embryos.⁷

The Question of Personhood

In germline editing, CRISPR is generally introduced into embryos via injection within the first few days after conception. Any procedure performed at such a vulnerable point in development necessarily places the embryo in great danger. Additionally, the current vectors for delivering CRISPR are neither safe nor reliable and pose a further risk. Such experimentation on human embryos, even for therapeutic reasons, can be done only for proportionately grave reasons.⁸ Anything else is contrary to the human dignity of the embryo, which is made in the image and likeness of God

and which has “a right to the same respect that is due to the child already born and to every human person.”⁹

As noted above, some argue that embryos can be experimented on and destroyed because they cannot be harmed or, at least, because the moral significance of harming them is very small. However, the proponents do acknowledge that at some point the embryo becomes a person, and harming it would be morally significant; hence their test subjects must be destroyed before that point. This thinking, however, is flawed. Who determines when an embryo is person enough to carry moral weight? For some it may be three weeks; for others it may be three months. Any deadline is simply an arbitrary standard based on personal criteria.

A human embryo is human from day one. Despite its pluripotency, the embryo can develop only as a human, never as a goat, lizard, or anything else. So if at some point the human embryo has the moral weight of a human person, and if between day one and that point the human embryo has remained human and has not substantially changed, then the moral weight of personhood was present from the beginning: “Thus the fruit of human generation, from the first moment of its existence, that is to say, from the moment the zygote has formed, demands the unconditional respect that is morally due to the human being in his bodily and spiritual totality.”¹⁰

The only way to deny that human embryos—regardless of age—have the same moral weight as full human persons would be to propose some sort of gradation in dignity and moral significance. Some suggest that early postnatal GGE clinical trials should be “conducted on infants with the severe form of the disease as this would result in less expected harm. . . . If the GGE technique turns out to be lethal, little is lost because that individual had no hope of long-term survival in any case.”¹¹ However, once again, this is an arbitrary standard. Who determines the gradations in personhood, and who judges whether this or that individual has met the correct standard? Yet even if there are some manner of gradations among humans, this “does not allow us to posit either a change in nature or a gradation in moral value.”¹²

Once we see that embryos, even if not yet persons, have the same rights and demand the same respect as persons, several things follow. First, we cannot wantonly endanger them through experimentation, whether or not they are viable or destined for implantation. Second, destruction of embryos before or after experimentation is the same as killing a human person. In a way it is worse than killing an adult, because embryos are completely defenseless. As the very smallest and most vulnerable of humans, they demand our protection in a special way, just as the disabled, the elderly, and those unable to speak for themselves demand our special protection and guardianship. Lastly, some argue that even if the destruction of embryos is morally illicit, the development of GGE could potentially reduce the number of embryo and infant deaths in the future.¹³ Thus, if we really care about embryos, it is better to kill a smaller number now

to save a greater number later. However, one cannot justify a moral evil with promise of a good, no matter how great.¹⁴

Inheriting Germline Changes

Current technology is not advanced enough to guarantee that germline editing will not cause equal or greater harm in future generations (or even to the life of the person whose genes are edited). CRISPR can cut and splice the genome to remove a gene that causes blindness or is linked to high cancer rates. In theory this is wonderful, especially for conditions that are incurable or do not manifest until later in life. Yet in practice there are several difficulties.

CRISPR is not perfectly accurate, and it can cut out the wrong gene in addition to, or instead of, the intended target. Recent studies show that CRISPR works correctly about 20 percent of the time.¹⁵ This does not mean one person is cured and the other four are not. It means one person is cured and the other four incur such catastrophic changes to their DNA that they are even further disabled or do not survive to term.

In addition to problems at the intended site, CRISPR can also cause off-target mutations: additions, deletions, and restructurings at completely different areas of the genome. Some off-target mutations are known, while others are not, potentially going unnoticed until years later. These mutations could have no effect at all, or they could cause cancer or other serious diseases. Furthermore, the vector used to introduce CRISPR into the cell can cause unintended damage or changes. Altogether, in fixing one problem we could easily create ten new ones.

The human genome has three billion base pairs and is full of safeguards and redundancies. We know very little about how most of it works. The danger is that changing small pieces here and there, even just one base letter, can lead to a cascade of effects, some beneficial and others detrimental, some noticed and others overlooked. In the case of the Chinese twins, scientists speculate that the same genetic edit that immunized them to HIV may have also enhanced their intelligence.¹⁶

These difficulties apply to individuals, but GGE poses additional problems because the germline is edited. Not only is the individual changed, but that change will be passed on to his or her offspring. Genetic changes that do not have a great effect on an individual could potentially cause problems in later generations. Further complicating the situation, everyone's genome is unique (except for identical twins). While this is great for crime fighters, it also means that if an individual's germline is edited, it could have a beneficial effect on some offspring but a detrimental effect on others. Removing a certain gene may decrease cancer risk in one individual but increase cancer risk in another.

All of this adds an extra layer of complexity to determining the effects of GGE on individuals and their offspring, and it necessitates more thorough research before using it in humans. Finally, since a greater number of people are affected when the germline is edited, greater care should

go in to making changes to the germline, which should not be made without a proportionately grave reason.¹⁷

It is doubtful that a drug with such a safety record, or lack thereof, would be approved for use by the US Food and Drug Administration. Likewise, in its current state, GGE carries such great risk of unintended and unforeseen harm that it is immoral to continue such research in humans. With current technology, the majority of GGE attempts will be unsuccessful, resulting in the death of the embryos even as successful attempts are terminated for "safety" reasons. In human experimentation of any kind, the benefits should outweigh the risks, but GGE is so experimental that no foreseeable benefit can justify its use in humans at this time. To use an embryo for such research is to reduce it from its proper dignity of a human person to "a pure and simple instrument for the advantage of others."¹⁸

Future Prospects

If we could perform research without using IVF technologies and endangering or destroying embryos, if the technical process were improved to the point of not causing errors or unintended consequences, and if we could ensure that any changes made will not unduly harm current or future generations, then potentially we could use GGE for therapeutic purposes. There may be better, easier, less morally troublesome paths to cure disease that should be pursued first.¹⁹

Still, if these difficulties can be overcome, it will be possible to ethically perform therapeutic GGE in the future. In order to consider editing the human germline, we first need to perform a great amount of research in animal models—starting with lower animals and moving to primates—to better understand the genome and improve the safety of GGE. To use GGE in a strictly therapeutic manner, to safely prevent all future generations from getting cancer or eliminate a devastating hereditary disease, would be in principle an unquestionably laudable and desirable goal.²⁰

Notes

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8. *Ibid.*, dir. 31.
9. CDF, *Donum vitae*, I.4.
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11. Gyngell et al., "Ethics of Germline Gene Editing," 505.
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The views expressed here are those of the individual authors and may advance positions that have not yet been doctrinally settled. *Ethics & Medics* makes every effort to publish articles that are consonant with the magisterial teachings of the Catholic Church.

13. Gyngell et al., "Ethics of Germline Gene Editing," 504.
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15. Janice S. Chen et al., "Enhanced Proofreading Governs CRISPR-Cas9 Targeting Accuracy," *Nature* 550.7676 (October 19, 2017): 407-410, doi: 10.1038/nature24268.
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18. CDF, *Donum vitae*, I.5.
19. Gyngell et al., "Ethics of Germline Gene Editing," 498.
20. John Paul II, Address of His Holiness Pope John Paul II at the Conclusion of the Thirty-Fifth General Assembly of the World Medical Association, (October 29, 1983).

Excerpt from Pope Francis, Address to participants at the international conference organized by the Pontifical Council for Culture on regenerative medicine (April 28, 2018)

We must also acknowledge with deep satisfaction the great strides made by scientific research in discovering and making available new cures, especially those related to the delicate problem of rare, autoimmune and neurodegenerative diseases, as well as of many others. In recent years, advances in cellular research and in the field of regenerative medicine have opened new horizons in the areas of tissue repair and experimental therapies; this significant chapter in scientific and human progress is alluded to in the theme of your meeting by the terms: repair and cure. The more you are committed to research, the more relevant and effective

these aspects will become, thus enabling an increasingly adequate, incisive and even personalized response to the needs of the sick.

Science is a powerful means for better understanding the natural world and human health. It has opened up new possibilities and provided refined technologies that enable us not only to examine the deepest structure of living organisms, including man, but also to intervene in ways so profound and precise as to make it possible even to modify our DNA. Here we see the need for an increased awareness of our ethical responsibility towards humanity and the environment in which we live. While the Church applauds every effort in research and application directed to the care of our suffering brothers and sisters, she is also mindful of the basic principle that "not everything technically possible or doable is thereby ethically acceptable." Science, like all other human activities, is conscious that certain limits must be respected for the good of humanity itself, and that a sense of ethical responsibility is needed. The true measure of progress, as Blessed Paul VI recalled, is that it is directed to the good of every man and the whole man (cf. *Populorum Progressio*, 14).

If we wish to prepare for the future and to ensure the well-being of each human person, we must grow in sensitivity as the means at our disposal become all the more potent. This is our responsibility to one another and to all living creatures. For human health needs to be considered in a broader context, not only in relation to scientific research but also to our ability to preserve and protect the natural environment. There is also a need to take into consideration every member of our human family, especially those experiencing social and cultural hardships that endanger both their health and their access to adequate care.

