Ethical Currents

The Rapidly Evolving Debate Over CRISPR

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In November 2018, Chinese researcher He Jiankui, Ph.D., made the surprising announcement that he had performed human germline gene editing. Using the CRISPR/Cas9 gene editing technology (which I will refer to as CRISPR), he claimed to have mutated a gene in two zygotes which he then transferred to the mother, who gave birth to them last year. A bioethics scenario debated for the last 70 years may have come to pass with no public, regulatory, or ethical oversight. That seems to be the story at least. What actually occurred is less clear. The details are unpublished, so we are relying on the testimony of a few scientists to whom Dr. He revealed some of the data.[1] It is unclear that they will ever be published, since he disappeared from public view soon after his announcement and is under investigation by Chinese authorities. Given experiences of fraud in the past over supposed breakthroughs, many ethicists are wary of putting too much faith in this announcement.

Whether or not He succeeded though, the mere plausibility of this scenario shows the need for continued reflection on the ethics of gene editing. Over the last three years, researchers in a number of countries have used CRISPR on human embryos with the blessings of regulatory authorities, secular bioethicists, and the scientific community. He's work shows how thin the wall is between research and reproductive gene editing – all it takes is the step of transferring the embryos into a woman's uterus. This case also shows the dangers of depending on the scientific community's self-regulation. A number of U.S. researchers were aware of He's experiments but did nothing to notify authorities or the public.[2] While many scientists, including the inventors of CRISPR, have argued for a moratorium on germline editing, others have seen this as a welcome opportunity to push further ahead.[3]

It is essential that a more diverse group of ethicists, theologians, and the public participate in these conversations. There will be many voices promoting the promise of this technology, but we must also be aware of its dangers and limitations.

My goal in this essay is to first provide a brief overview of developments in this fast-changing field. I will then examine the practical and

ethical risks of this technology from the perspective of Catholic bioethics in light of Dr. He's experiment. With these risks in mind, we must be wary of allowing the promises of technology to reduce suffering override ethical concerns.

CRISPR AND ITS LEGITIMATE USES

In the early 1990s, researchers studying bacteria found strange repeated genomic sequences across many species, which they called "Clustered Regularly Interspaced Short Palindromic Repeats" (CRISPR).[4] These repeated sequences matched viral DNA and were part of a bacterial immune system targeting viruses for destruction. In 2012, a team led by Jennifer Doudna and Emmanuelle Charpentier showed that a modified form of the bacterial system could target (almost) any DNA sequence in other kinds of cells. Soon after, Feng Zheng and his collaborators showed that CRISPR could be used in human cells.

CRISPR consists of two elements. First, there is a guide RNA (gRNA) that contains a ~20 base pair sequence designed by researchers to target a specific DNA sequence. Second, there is a protein, usually CRISPR Associated Protein 9 (Cas9), that cuts DNA. When researchers introduce these two elements into cells, the gRNA binds to Cas9 and directs it to the specific DNA sequence that it matches. Then Cas9 cuts the DNA at that sequence. At this point, cells try to repair the damaged DNA through one of two mechanisms. Usually they just try to connect the two loose ends together, which leads to mistakes. One, two, three, or more DNA base pairs can be lost, introducing mutations in the targeted gene that generally make it nonfunctional. A second mechanism takes advantage of a natural repair mechanism that uses one of the cells' pair of each chromosome (one from the father, one from the mother) to repair the other one (or even just swap elements from one to the other). If researchers introduce a well-designed piece of DNA into cells along with CRISPR, sometimes the repair process will insert this sequence into the cut, allowing researchers to introduce wholly new genetic elements into an organism. This occurs much more rarely than a mutation though.

CRISPR is an exciting technology with many uses that should be celebrated by Catholic bioethicists. Over the last five years, it has revolutionized biomedical research, promising great benefits through new discoveries. It is cheaper, simpler, and more efficient than prior gene editing technologies, and can be used in more organisms and cell types, including human cells. Second, it may be therapeutically useful for individuals with existing diseases through somatic cell gene therapy. Somatic cell therapy targets cells, generally in adults or adolescents, that are not passed on to the next generation. CRISPR would make such treatments easier. While there are risks from such therapies, as I will discuss, these risks can be balanced against current suffering, especially in the case of patients capable of informed consent. Catholic and secular bioethicists have declared these therapies to be ethical in principle.

THE PROBLEMS OF GERMLINE GENE EDITING

The ethical concerns over CRISPR, especially in light of He's experiment, involve germline gene editing. This is when a genetic alteration will enter into a sperm and egg, thus passing to the next generation. Such a change could

happen through editing cells which will give rise to sperm and eggs in an adult or, as He did, by manipulating embryos. One of the remarkable things about CRISPR is that it will act when researchers inject it straight into the single-celled zygote. The concerns that such manipulations raise can be divided into two major classes, those tied to risk and those arising from the misuse of power over the next generation.

There are four kinds of risks to be considered: mosaicism, off-target effects, imprecision, and general lack of knowledge.

Mosaicism. One ongoing problem highlighted by He's experiment is mosaicism. When CRISPR is injected into the newly fertilized egg, it does not always initiate editing right away but sometimes only after a cell division or two. In such cases, the embryo could have some cells that have the desired edit and some that do not, leading to mosaicism. A mosaic is an organism with different genetic variants in different cells. Mosaicism may itself lead to health risks, but it can also make gene editing ineffective. If geneticists want to target a gene that acts in the lungs (as in the case of cystic fibrosis), but the edited cells are only in the neural tissue, then the editing will have no effect. While there may be technical work-arounds, mosaicism has been a problem in almost all of the germline editing experiments so far.

Off-Target Effects. One of the early concerns with CRISPR was that it does not always restrict its activity to the targeted DNA but can cut elsewhere in the genome. These are called off-target effects and are dangerous because they cause unknown mutations in the genome leading to diseases such as cancer. Over the past few years, researchers have addressed these problems by better selection of the target DNA and various alterations to Cas9, meaning that these issues have become less of a concern. While significantly reducing these problems, these modifications have not eliminated them, though, suggesting the need for extensive sequencing of edited cells to ensure that no deleterious mutations have been introduced. These effects can also occur in somatic cell gene therapy, but in such situations, the patient can give informed consent, and frequently, one can sequence the genome of the edited cells to detect any major problems.

Imprecision. Even if CRISPR cuts the correct gene, the results can be imprecise due to the repair process, a problem that has become clearer in the last two years. As noted, the simplest repair mechanism that sticks the ends of the DNA together is error-prone. There is little ability to predict what mutation it will introduce. For example, since every DNA triplet codes for one amino acid, if CRISPR deletes three base pairs, then the gene may still be transcribed and translated into a protein, just into an unpredictable one. The protein may not work, it may work with reduced function, or it may end up with some completely different function. If a larger segment is deleted, it may affect neighboring genes. Through such mechanisms, He seems to have introduced completely novel mutations rather than the one he planned.[5] Further, there are very few cases in which one just wants to eliminate a gene. Most genetic therapies require fixing a disease gene. While the second repair process allows researchers to introduce other DNA sequences, this occurs in a low efficiency manner. In one report, researchers found that zygotes can use the other chromosome for repair but that report is disputed.[6] It is thus unclear that scientists can make the specific edits they want.

Lack of Knowledge. Finally, there is the broader problem of lack of knowledge. In general, we do not know all of the ways individual genes work. Genes are involved in multiple processes, so disruptions have unpredictable effects. For example, many people had thought that the *CCR5Δ32* mutation that He targeted largely affected only HIV susceptibility, since it is a naturally occurring mutation. Further research revealed that people with that mutation have problems with fighting viral infections and may be more susceptible to West Nile virus.[7] We have even less knowledge of how genes affect development. Such lack of knowledge may be acceptable when treating an adult with a serious illness capable of consent but is less acceptable with nascent human life. Moreover, once such a mutation is introduced, it has entered the human gene pool. As the National Academies report on gene editing notes, it is unclear that we will ever have full knowledge of the effects of such edits, since you cannot force the resulting child to participate in follow-up research.[8] This problem affects most fertility experiments, such as when the parents of the three-parent child produced in Mexico City refused to participate in follow-up.[9] More generally, there is evidence that IVF introduces health risks, but there has not been effective research on it.[10]

POWER OVER FUTURE GENERATIONS

This points to the second set of issues surrounding germline modification, those related to power over nascent human life. Magisterial documents express concerns over current methods of germline editing because they require IVF. This opposition is related to the severing of the tie between the unitive and procreative ends of sexuality. More to the point here though is the concern over the attitude to nascent human life expressed in IVF, shown most prominently through the number of embryos discarded in the procedure. Beyond the simple loss of life, *Donum vitae* argues that it "can open the way to other forms of biological and genetic manipulation of human embryos."[11] Originally written in 1987, this statement seems like a slippery slope argument, with all the problems of uncertainty inherent in such arguments.[12] Still, recent events have proved the Congregation for the Doctrine of the Faith (CDF) prescient, as the development of technology after technology that disregard the value of life in its earliest stages: preimplantation genetic diagnosis (PGD), embryonic stem cells, and embryonic genetic manipulation for research, primarily aimed at improving contraception and IVF. There is a self-reinforcing cycle of this technology development. This series of technologies embody what Pope Francis calls the technocratic imperative, treating the embryo as "something formless, completely open to manipulation."[13]

Two developments suggest that germline editing may accelerate this paradigm. First, to avoid the risks discussed above, many commentators have suggested in vitro gametogenesis (IVG).[14] This technique would develop induced pluripotent stem cells from the parents' cells, and then use CRISPR on these cells. After sequencing to ensure that only the correct edit was made, scientists could differentiate the edited cells into sperm or eggs in a dish before using them in IVF. This allows quality control on the edit and prevents mosaicism because the edit would be made before fertilization. While not yet successful in humans, important strides have been made in animal models. Gene editing is only one

application of IVG though, since its use has been suggested for what Julian Savulescu calls procreative beneficence.[15] One of the problems that Savulescu sees with current PGD is that there are too few embryos to choose from because one cannot get many eggs from women. His ideal would be to generate enough gametes from parents to produce hundreds of embryos with the worst traits edited out, so that one could select the embryo with the best traits. Here we see a eugenic mentality. While there is little appetite for this technology for itself, CRISPR creates a compelling reason to develop it.

This points to a second problem area opened up by this technology - the issue of enhancement or making people better than well. The He case was especially worrisome since his goal was not to cure a genetic illness in a person with a specific mutation, but to protect against HIV by introducing a mutation. Due to the problems of imprecision discussed above, these kinds of enhancements may be easier than gene repairs. Though the distinction between therapies and enhancements is contested, most bioethicists (including Savulescu and Peter Singer) agree one should not begin human gene editing with a possible enhancement.[16] Many Catholic ethicists have criticized the goal of enhancement. While there are issues to be raised about how enhancement affects human nature, those are not the primary grounds upon which the church criticizes it. Instead, enhancement efforts "imply an unjust domination of man over man," by choosing arbitrary criteria upon which to value human life, thus undermining human dignity.[17] Although in a less acute way than other genetic modifications and testing, the focus on the perfectibility of the next generation embodied most clearly by enhancement, is ultimately dangerous to the common good.

CONCLUSION

While CRISPR could aid in the treatment of many genetic diseases, we should be wary of germline modifications because of the technical and social risks involved. Many people may argue that this is an obscurantist position: if we have something that might reduce suffering, we should do it. Yet, it is important to remember technological enthusiasts have promised such relief of suffering many times (the human genome project, regenerative medicine, previous incarnations of gene therapy) with few major benefits to show. Catholic health care is right to be skeptical of the glamor of high technology, especially when it asks us to cross moral lines. While CRISPR does offer benefits for research and somatic cell therapy, we should reject current models of germline modification.

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ENDNOTES

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