ETHICS & MEDICS
A Commentary of The National Catholic Bioethics Center on Health Care and the Life Sciences

MANIPULATING LIFE AT ITS BEGINNING

"When our son was a little over a year old, he began dropping things and he still couldn't talk. At first, doctors thought he had a cold. But we knew something was wrong. Eventually we learned that our baby boy wouldn't survive his toddler years." The couple were already expecting their second child when they received the diagnosis concerning their first: Niemann-Pick disease type A. No cure. No treatment.

"I was five months pregnant, and doctors wanted me to do an amniocentesis to check our new baby for the same thing. Since we would not consider an abortion under any circumstance, we said no. For the next four months we waited to learn the fate of our second child while we watched our first son's health and abilities slowly deteriorate."

My friend's eyes welled up with tears as she thought about the birth of their second child. Against astronomical odds, their second son was born with the same horrible, fatal disease. "By the time our second son was born, our first son could no longer eat. Day and night, he whimpered. 'Hmmm. Hmmm.' It broke our hearts! We tried everything! I would soft boil an egg for him, and it would take three to four hours to get it down. He just wasn't eating enough."

The next few years of doctor visits could not stop the inevitable. My friends lost both their sons before their fourth birthdays. That was twenty years ago and the pain is still fresh. "Today," I said, "some couples would use IVF to select an embryo that they knew did not have that defect." My friend exclaimed, "Oh my gosh, no! I couldn't! All those dead embryos have souls, and one day I would have to face them in heaven, and I just couldn't do it."

Contrast this heartfelt response with the calculating language of an advocate of genetic engineering. Steven Potter writes,

> The genetics revolution is ongoing, and there may indeed be no stopping it now. The human species is about to undergo an incredible transformation. The forces of natural selection are about to be replaced by the forces of human selection. In the future it will likely be routine for parents to choose the genes of their children. Where this might take us we cannot know. Of course we will quickly remove from the human population versions of genes that result in catastrophic disease. But in addition we will be selecting ideal combinations of genes from the two parents, modifying genes for which neither parent offers a preferred copy, and perhaps even making entirely new kinds of genes never before seen in nature. For the first time humans will have complete control over their genetic destiny. And the process will result in an upward spiral of genetic change, as each generation is more intelligent than the last and better able to choose the genetic makeup of their children. It could well mean the end of the human race as we know it, but perhaps the beginning of something better.[1]

To achieve this aim, Potter knows that he will destroy many embryos and experiment on many others.

CRISPR-Based Gene Editing

Academic researchers, national labs, and private labs worldwide are experimenting with CRISPR-based gene editing. They are editing mice genes to make the mice better models for human disease research. They are editing mosquito genes to make them less able to carry the malaria parasite. Scientists are also experimenting with editing human somatic cells (cells that are not reproductive cells or embryonic stem cells). For example, by editing the bad genes in pancreatic cells that contribute to diabetes, scientists hope to develop better treatments for the disease. Because gene-edited somatic cells live and die inside our bodies and are not passed on to our offspring, there is little chance of passing on unintended consequences.

In 2015, scientists in China went beyond somatic cell research to perform germ-line editing on embryos.[2] Working with scientists around the world, they experimented on eighty-six embryos created by in vitro fertilization (IVF). They edited the DNA in the embryonic cells in an attempt to alter the course of an often deadly blood disorder called beta thalassemia. Although the experiment

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failed because of "off-target" cuts in the DNA, it sent a cold chill around the world.

In part because of that failed experiment, scientists convened the International Summit on Human Gene Editing, which took place in Washington, DC, December 1 to 3, 2015.[3] Although the discoverers of CRISPR and other scientists, researchers, educators from around the world gathered to discuss how to define boundaries around gene editing, the summit did little to slow germ-line editing experimentation. Two months after the UK Academy of Sciences participated in the summit, the United Kingdom granted a license to researchers at the Francis Crick Institute in London to "edit" up to one hundred and twenty human embryos.[4]

Off-Target Effects

An off-target effect happens when a scientist targets a specific sequence of DNA to delete, change, or insert and makes that change but unintentionally executes an additional change somewhere else. Our genes make up only about 1.5 percent of our DNA's 3.2 billion base pairs (paired molecules with the abbreviations A-T and C-G). Targeting a specific sequence of base pairs in a gene doesn't preclude the possibility that the exact same sequence appears elsewhere in the genome.

Editing a second or third sequence could have unpredictable results. An off-target effect in the germ line carries unknown risks. This means that an edited embryo implanted in utero may be born with mutations never seen before.

The summary conclusion statement from the gene-editing summit supported restricting the implantation of gene-edited embryos but not restraining the editing of embryos for research purposes.[5] (It thus supported the recent UK decision.) The US National Institutes of Health, however, prohibit both, because of the bioethical responsibility to gain full consent before attempting any treatment.[6] Since the embryo cannot grant consent, the treatment cannot be allowed. This prohibition considers the embryo a patient and thus leans in the direction of considering the embryo a person.

Other Biological Risks

We will not know the effects of editing eggs, sperm, or embryos until those embryos become adults who procreate. The only way to measure the long-term safety of gene editing is to track edited embryos to adulthood and then track their progeny. Current gene sequencing technology isn't precise enough to measure the multigenerational outcomes of these edits.

The primary reason for editing an embryo is, in theory, to avoid a horrific disease. Yet history and our fallen human nature suggest that once it is possible to edit an embryo, those with different views on research boundaries will edit embryos for other purposes. This is the "designer baby" problem, although Potter calls it an opportunity for parents to "choose the genetic makeup of their children."

To illustrate this inevitability, clinics that used to offer preimplantation genetic diagnosis (PGD) only to avoid serious disease now also offer "family balancing," also known as gender selection. If parents want a girl, a clinic tests several IVF embryos until it finds one that is free of the target disease and is also a girl. The boy embryos that were also completely free of the target disease are frozen or destroyed. This is the tip of the eugenics iceberg.

Allowing a tool like CRISPR to be used on their embryos, parents can design hair, skin, and eye color, height, muscle strength, muscle speed, and many other attributes that are controlled or influenced by one or more genes.[7] This is a new kind of clinical eugenics, which is easy to rationalize because you can't look an embryo in the eye.

But even these designer eugenic edits come with risks. The human genome was sequenced around the turn of the century, but our understanding was limited. We knew genes governed the creation of proteins. We now know that the folding of that protein into its three-dimensional shape can be as important to its function as the gene that created it. In other words, the gene is only part of the puzzle of what the gene controls. Individual proteins often affect more than one bodily process. The same will be true of eugenic edits—only we do not know what the unintended effects will be.

It is important to note three points about gene editing and IVF/PGD. First, it is impossible to edit the DNA of an embryo in the uterus; IVF is the only way. But for every implanted IVF embryo, many more embryos (human beings) are frozen or destroyed outright. Some estimates place that ratio as high as sixteen to one.

Second, editing the DNA of an embryo is tricky and has not yet been done successfully. Third, some argue that, if the goal is to avoid genetic disease, then IVF/PGD can achieve that goal with fewer risks than gene editing.

New Pharmaceuticals and Therapeutics

CRISPR is not just scientific exploration; it is at the center of an exploding and contentious industry. With over two hundred nations on the planet, this is a competitive global issue. Scientists are afraid someone else will make a discovery before they do.

The CRISPR discoverers have become cofounders of several companies: Editas Medicine, Caribou Biosciences, Intellia Therapeutics, and CRISPR Therapeutics. These companies seek to commercialize the CRISPR technology and have received over $398 million in venture capital funding so far.[8] Recently, Editas—a one-year-old company with no products or revenues—raised $94.4 million in an IPO and, as of this writing, is valued at $1.1 billion.[9] Editas also signed a deal with Juno Therapeutics worth up to $700 million.[10] CRISPR Therapeutics inked a deal with Bayer AG worth over $335 million.[11] Venture capitalists and existing companies like Bayer see CRISPR as the foundation of the next generation of pharmaceutical, therapeutics, and food companies.

However, Cellectis, a French biotech company, and others have sued one or more of these companies over patents related to CRISPR and genome engineering. With a collective investment, in one year, of over $1.5 billion and with huge multinationals fighting over patents, the stakes are high. Losers are more likely to press the ethical boundaries to recover their losses.

Considering the Moral Effects

It is tempting to say that those raising the alarm over CRISPR are overreacting. But the alarm isn't only about CRISPR; it's about the steady march of science, which clearly illustrates man's determined pursuit of ways to manipulate life at its earliest stages. It is foolish to think that this trend will stall or reverse without some external motivator.

Scientists discover *how* things work—and with that knowledge manipulate the world around us for our collective good. This has given rise to electricity, medicine, and other important discoveries. Businesses use those discoveries to efficiently manufacture products, increase access, and raise our standard of living.

But when science, government, and business are not restrained by asking *why* within the realm of the philosophical and theological, great atrocities may result.

At the gene-editing summit, only one bioethicist spoke. No theologians were present to ask why. And to date, none of the CRISPR companies have a bioethicist on their board of directors or board of advisors. Why?

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Defibrillators at the End of Life

I recently published three articles on pacemakers.[1] My focus in these articles was to examine the moral permissibility of deactivating a pacemaker at the end of life or letting the pacemaker's battery run out. I determined that both—deactivation and letting the battery run out—were morally impermissible.

Another type of cardiac device is also often used in treating patients with heart irregularities, namely, a cardioverter defibrillator. I address here the issue of whether or not this device can morally be deactivated at the end of life.

Purpose of the Device

A cardioverter defibrillator monitors a patient's heart rate and rhythm to prevent sudden cardiac death due to life-threatening dysrhythmias, or irregularities of the heart beat, such as ventricular tachycardia (rapid heart beat) or ventricular fibrillation (severely abnormal heart beat). A defibrillator restores a normal rhythm by means of antitachycardia pacing, cardioversion, defibrillation, or back-up cardiac pacing.[2] It also administers a shock when necessary to restore the patient's normal rhythm. While very effective in preventing death from sudden cardiac arrest, cardioverter defibrillators are not without their problems, which may be particularly challenging during the dying process.

For our current purposes, I will leave aside the matter of disabling a cardioverter defibrillator in order to cause death. It is never permissible to stop treatment *in order to cause the death of the patient*—an issue I have addressed sufficiently in my articles on pacemakers. My current focus is on whether or not disabling a cardioverter defibrillator is akin to deactivating a pacemaker or letting its battery run out at the end of life. With pacemakers, I tentatively concluded for various reasons that pacemaker deactivation, whether active or passive, is not morally licit. Does the same conclusion apply to the cardioverter defibrillator? No, it does not, for the following reasons.

Reasons for Deactivating

First, unlike a pacemaker, the presence and workings of which are not felt by the patient, a cardioverter defibril-

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lator makes its presence known by delivering a powerful shock or shocks to the patient. This kind of shock therapy at the end of life has no medical benefit and may cause significant distress to the patient, the family, and the health care staff. It is like performing CPR on a dying person.[3] Unwelcome side effects may occur with the shock, such as a transient loss of consciousness, uncontrolled bowel movements, enuresis, nausea, and vomiting.[4]

Second, while pacemakers do not interfere in the dying process, cardioverter defibrillators can and do. In one case a man was shocked thirty-three times the day before he died![5] Many individuals, for sound reasons, may sign a do-not-resuscitate order (DNR) as they approach the end of life. A person suffering from end-stage chronic obstructive pulmonary disease and congestive heart failure, for example, may decide that heroic measures to keep him alive no longer make sense. It is entirely appropriate for him to request that no such measures be taken. However, a DNR will not affect the workings of a cardioverter defibrillator at the very end of life. The only option—and an appropriate one—is for the patient to request that the defibrillator be deactivated so that he can die a natural death without the fear of being shocked back to life when the heart stops or when life-threatening dysrhythmias occur. This discussion should not wait until the last days and hours of a patient's life. It should occur before the patient is already in hospice care.

An important element of treatment with a cardioverter defibrillator is open and frank communication at the time of the device is implanted. The discussion should include information about deactivation of the defibrillator at the end of life. Admittedly, this may be difficult. Who wants to talk about the end of life just when a patient is receiving a device whose purpose is to prolong life? As difficult as the conversation may be, however, it is in the patient's best interests, and it should detail options for end-of-life care, including the possibility of deactivation in the event that the device no longer provides medically sound treatment. In ongoing discussions after implantation, the health care provider and the patient should review the patient's clinical situation and confirm that continuing use of the defibrillator is in harmony with the patient's goals as the disease progresses.[6]

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