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Germ-line Engineering, Mitochondrial Transfer, and Three-Parent Embryos: Part I

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In this two-part article I shall discuss what human germ-line engineering is as well as the recently legalized mitochondrial transfer procedure in the UK that results in "three-parent embryos." Both involve hereditary changes, meaning that the alteration on the individual embryo's DNA will be passed down to all his or her ensuing children (thus affecting generations). I shall explain the science behind both procedures, as well as their pros and cons, and then raise some typical ethical considerations.

In Part II, I shall explore the more fundamental issue of assisted reproductive technologies (ARTs), which both procedures require. Although ARTs are now seen as commonplace, their existential effect on the resulting child merits a deeper examination of this method of transmitting human life—revealing deep implications upon the meaning of life's origin and destiny.

GERM-LINE EDITING

Since April 2015, the biotech world has been exploding with media attention concerning a more precise DNA editing technology known as CRISPR-cas9. It is a protein and DNA complex that is able to target and then cut and replace a desired sequence of DNA, enabling specific base-pair changes to be made in ways that were not previously as successful.[1] The goal of such a technology is to edit (i.e. eliminate) disease genes for people with devastating genetic illnesses, such as Huntington's, sickle-cell anemia, or cystic fibrosis.

CRISPR technology makes it possible to "search and replace" DNA down to the letter so that a faulty gene could be fixed, such as the genes of **somatic cells** (non-reproductive cells, for instance, the malformed blood cells of people with sickle-cell anemia). However, if the DNA edits are made in **germ cells** (the sperm or egg cells that constitute an embryo's **germ-line**), then the changes made are **hereditary** (passed down to every subsequent generation).

BENEFITS AND HARMS

The modification of the human genome—"germ-line editing"—holds enormous potential benefit for the elimination of genetic diseases, which can be inherited in various ways.[2] The benefits of CRISPR-cas9 technology include being relatively inexpensive, easy to use, and familiar—as it's already in widespread use on somatic cells.

However, there is concern even amongst scientists who pioneered the technology that its use for germ-line modification is currently

unacceptable, as it carries *entirely unknown* consequences:

> The fact is we have identified relatively few naturally occurring alleles in the human population with sufficient penetrance that we would want to target … [Essentially] germline genome editing today would be to carry out a series of blind human experiments.[3]

The reality of DNA is that internal and external environmental factors affect the expression of gene to protein to phenotype in ways that are not entirely calculable or foreseeable. This phenomenon of epigenetics means that the very substance of our life remains mysterious.

Currently, a major issue with the use of CRISPR is the presence of off-target changes, meaning that the intended allele is not the only one altered. This could affect the modified offspring later in life in ways that are unknown. In addition to the transformative changes in humanity's genome, the social factors of employing such a technology would be that it's only accessible to the wealthy, therefore creating "classes" or social strata of genetically modified persons.

MITOCHONDRIAL TRANSFER AND THREE-PARENT EMBRYOS

A similar kind of embryonic genetic modification is the case of three-parent or three-person embryos now legal in the UK as of February 24, 2015.

This IVF-based technique involves combining three sets of DNA—that of two parents plus a donor woman's mitochondrial DNA (mtDNA)—resulting in a mitochondrial (or spindle) transfer.

The procedure involves transferring the nucleus of the mother's ovum (egg) into an enucleated ovum of a donor woman, which is then fertilized by the first woman's husband.[4] This prevents the transmission of diseased mtDNA (the cause of mitochondrial disease: an incurable, inherited condition maternally passed on to around 1 in 6,500 children worldwide).[5] The mitochondrial transfer aims to re-house the genetic information of the mother (who has faulty mtDNA in her egg), into a donor egg with healthy mtDNA, so that the affected mother can have a biological child without passing on the disease. However, the resulting child will carry the DNA of *three* parents, and will pass down this altered DNA to ensuing generations.

Apparently, however, transferring the genetic information to the un-affected donor egg *prior* to fertilization results in increased chromosomal abnormalities during the embryo's division, which are less likely to occur with a second method: pronuclear transfer.[6]

PRONUCLEAR TRANSFER

In this method, IVF is used to create an embryo (a fertilized egg) between the intended parents, containing the affected mother's faulty mtDNA. A second "donor embryo" is created from a donor woman's egg and (usually donor) sperm. At the one-cell stage of development, the pro-nuclei of both embryos are removed: the parents' nucleus is transferred into the enucleated donor embryo, and the donor embryo nucleus (as well as the parent's enucleated embryo) is

destroyed.[7] The resulting embryo now contains the pronuclear DNA from the intending parents, and healthy mtDNA from the donor egg.[8]

ETHICAL CONSIDERATIONS I: WHAT IS THE PURPOSE OF MEDICINE?

The desire to prevent the suffering of children who inherit devastating genetic conditions is very real. Yet *treating* a disease and *preventing* its existence are two different things. Much of the thrust of biotechnology is precisely the latter aim: to prevent the existence of genetic disease through technological intervention. However, with biotechnology we can go much further: not only preventing disease via elimination, but also "perfecting" by inserting or selecting more desirable genetic traits. This raises a fundamental question that has deep implications for many practical outcomes, and that is: what is the goal or purpose of medicine?

A scientist who views the goal of medicine as reducing or *eliminating* suffering will come to very different conclusions about the use of genetic technologies than a scientist who sees the goal of medicine as *healing* patients and providing care/comfort where full healing is not possible. The questions of what is health, suffering, healing, and wholeness point to the broader, metaphysical realities that underlie the biotech issues we are facing. It makes a radical difference whether health (the practice of medicine) has to do with *healing* in terms of restoring the body to its wholeness within the context of life and death *or* whether health concerns the prevention of untimely death and/or the prolongation of life—as long as it's deemed worth living.

What is the role of technology and medicine in terms of heritable diseases? Elimination of disease is neither prevention nor treatment/cure, but something "other"—a different category than the first two—precisely as "elimination" (eradication via germ-line engineering). By virtue of being an entirely different and unprecedented form of "medical care," its ethical meaning and implications ought to be explored within the greater context of what is human health, how is it measured, and what does it mean to care for someone who is suffering?

The questions concerning the meaning of suffering, of life and death, and of health, healing, and medicine are obviously big questions that cannot be explored in the context of one article. Yet the nature of medicine and healing is of crucial importance to understanding the way in which a patient ought to be treated: what is required of medicine and treatment based on what health and healing *are*? In this way, these questions have radical bearing on how biotechnological discoveries ought to be used on human life.

And yet, prior to the question of medicine and health is the more fundamental anthropological one: *who and what is the human being* to which these procedures are performed upon*?* In Part II, I will raise these anthropological and ontological questions latent within biotechnology, showing why they are of utmost importance. ■

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[1] CRISPR technology has existed since 2012, but its recent dominance is due to its use on human subjects this past year, where scientists from Sun Yat-Sen University in China used the tool to modify the genome of non-viable human embryos, published in *Protein & Cell*'s April 2015 issue. For CRISPR's history, see: Ledford, Heidi. CRISPR, the disruptor. *Nature.* June 4, 2015. 522, 20-24. Accessed at: http://www.nature.com/news/crispr-the-disruptor-1.17673#/rise. For a fascinating read on the technology's discovery and the areas it's being used today (including disease prevention, malaria-resistant mosquitoes, agricultural bioengineering, and pharmaceutical research) see: Maxara, Amy. Easy DNA Editing will Remake the World. Buckle Up. *Wired.* July 22, 2015. Accessed at: http://www.wired.com/2015/07/crispr-dna-editing-2/

[2] Autosomal recessive conditions are the result of inheriting a disease gene from both parents; autosomal dominant from one parent; sex-linked (if the disease is associated with the X or Y chromosome); genetic diseases can also occur spontaneously through mutations in the genome *or* in the formation of chromosomes. Note that chromosome related diseases occur when there are an abnormal number of chromosomes (i.e. more or less than 2), and these conditions are not inherited.

[3] See: Bosley, Katrine, et al. CRISPR germline engineering – the community speaks, *Nature Biotechnology* 33, 478 - 486, May 2015. http://www.nature.com.proxycu.wrlc.org/nbt/journal/v33/n5/pdf/nbt.3227.pdf and also: Next generation genome editing, *Nature Biotechnology*, May 12, 2015: http://www.nature.com.proxycu.wrlc.org/nbt/journal/v33/n5/pdf/nbt.3234.pdf

[4] Ahuja, Anjana. "Three Parents? Five Parents? All That Really Matters is Healthy Babies." The Telegraph. March 21, 2013. Accessed at: http://www.telegraph.co.uk/health/women_shealth/9946441/Three-parents-Five-parents-All-that-really-matters-is-healthy-babies.html; cf. Somerville, Margaret. The Ethical Imagination: Journeys of the Human Spirit. Anasai Press, 2006. Pp 126-7.

[5] Mitochondrial disease conditions include fatal heart problems, liver failure, brain disorders, blindness, and muscular weakness. Kelland, Kate. "Three-Parent Embryos Unnerve Ethicists." The Globe and Mail. September 19, 2012. Accessed at: http://www.theglobeandmail.com/life/health-and-fitness/three-parent-embryos-unnerve-ethicists/article4553114/

[6] Coghlan, Andy. "Three-Parent Embryo Could Prevent Inherited Disease." New Scientist. October 25, 2012. Accessed at: http://www.newscientist.com/article/dn22425-threeparent-embryo-could-prevent-inherited-disease.html

[7] Nuffield Council on Bioethics. "Background: Pronuclear Transfer (PNT)." Accessed at: http://www.nuffieldbioethics.org/mitochondrial-donation/mitochondrial-donation-background-pronuclear-transfer-pnt; Gallagher, James. " 'Three People, One Baby' Public Consultation Begins." BBC News: Health. September 16, 2012. Accessed at: http://www.bbc.co.uk/news/health-19597856

[8] For a comprehensive, recent summary on everything concerning 3P IVF see *The Center for Genetics and Society:* http://www.geneticsandsociety.org/article.php?id=6527