The Polarization of Responses to The First Human Clinical Trial Involving Gene Therapy

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

In 1990, Dr. Michael Blaese and Dr. French Anderson conducted the first clinical trial utilizing genetic engineering techniques in humans. The public's response to the use of genetic engineering technology in humans were polarized. Since the first discussions of genetic therapies in the 20th century, concerns regarding the ethics and role of bioengineering in society have been expressed. While scientific leaders and bioethicists have analyzed the ethical and social implications associated with genetic engineering technologies, they fail to identify the underlying cause for the polarization of responses. Instead, they identify numerous controversies associated with genetic engineering and attempt to rank their contribution to the opposition.

However, understanding the origins of the public perceptions of gene therapy is essential to overcome obstacles that continue to hinder such therapies from reaching their full potential. The opposition towards research involving genetic engineering has significantly impeded progress within the field and remains an obstacle for life-saving gene therapies. I argue that the polarization of reactions to the first clinical trials using gene therapy to treat adenosine deaminase deficiency (ADA-SCID) results from the technology's fusion of culturally distinct categories. More specifically, I demonstrate how gene therapy combines the mutually exclusive categories of 'nature' and 'culture' using Martijntje Smit's monster theory. Using Dr. Blaese and Dr. Anderson's use of genetic engineering to save the lives of two young girls, I show how despite the overall success of the clinical trial, public responses strongly opposed the underlying technology due to the 'monstrous' characteristic of gene therapies.

Literature Review

Scholars have attempted to explain the polarization of the social perspectives on the use of gene therapies in humans. However, such analyses are largely focused on the underlying

ethical and social implications of genetic engineering technologies. These arguments tend to focus on specific ethical concerns or societal implications and attribute the divergence of responses to individual opinions. Additionally, scholars have considered the development of biotechnologies with respect to current social and political context. For example, Martin (1999) analyzes the progression of gene therapy using concepts from the sociology of technology, in particular the construction of socio-technical networks. More specifically, he details the construction of a socio-technical network around gene therapy and how new disease and therapeutic concepts are co-constructed. Since Martin's analysis of the technology over 20 years ago, the significant advancements of genetic engineering have challenged numerous claims his argument is based off of. For example, he states that while germline editing being deemed unethical did contribute to the shift towards somatic gene editing, he primarily attributed the shift to the low success rate of current germline editing technologies. Furthermore, while Martin does include how ethical concerns regarding genetic modification influenced the trajectory of gene therapies, he does not detail why.

In contrast, Gast (2007) explains the polarized responses to transgenics, however, his argument is applied to mice. He uses Martijntje Smit's monster theory to discuss how the transgenic mouse ultimately became accepted despite being a 'monster'. He argues that the genetically engineered mouse was at first perceived as a Frankenstein-like monster, unnaturally created by the abuse of science, but simultaneously fits into societies culturally accepted biomedical laboratory animal. He explains how the monster's nature-culture contradiction can be resolved by reconsidering how we define nature. Furthermore, he explains how overtime, society becomes accustomed to monsters and undergoes 'monster taming'. The argument presented in Biotech Pioneers is similar to my claim about gene therapies in that the solution to the inherent

social contradiction lies within the outdated definitions of relevant medical and ethical terminology (Gast, 2007).

By directly considering Dr. Blaese and Dr. Anderson's approved and successful use of genetic engineering to treat an extremely fatal disease in two humans, my analysis will not be distracted by additional bioethical concerns. Similarly, as Dr. Blaese and Dr. Anderson's trial was granted official FDA approval, the socio-technical network can be ignored in the analysis of opposition to the technology. Like Gast, I explain how Smit's monster theory best explains the reactions to genetic engineering as it challenges the current nature-culture dichotomy. However, I focus my analysis on the first approved use of gene therapy techniques to treat humans suffering from an extremely fatal disorder.

Conceptual Framework

The polarity of public perceptions regarding human genetic engineering can be best explained using Martijntje Smit's monster theory. Monster theory applies to new technologies that challenge current cultural categories, such as nature and culture or human and animal, that are traditionally considered to be mutually exclusive. New technologies that do not fit into existing cultural categories are considered 'monstrous' and generally invoke extreme reactions of fascination or abhorrence. Monster theory can not only be used to explain the polarization in perspectives regarding human genetic engineering but also how it has achieved a place in society.

According to Smit, the four different methods of 'monster treatment' are monster exorcism, monster adaptation, monster embracing, and monster assimilation. These approaches vary in their tolerance for the abnormal. Monster exorcists reject the technologies place in society and believe it does not fit within symbolic order. This perspective implies rigid and fixed

cultural boarders. Similarly, monster adaptation attempts to eliminate the technology's inherent contradiction by adapting the technology to better fit into existing categories. In contrast, monster embracing represents total acceptance of the technology and excitement for its potential applications and benefits. This perspective implies a disregard for the cultural challenges the new technology poses. Lastly, monster assimilation refers to a strategy of adapting both the cultural boarders and the technology to allow the 'monster' to fit and be incorporated into society (Smit, 2006).

I apply Smit's monster theory to Dr. Blaese and Dr. Anderson's use of gene therapy in humans by showing how the new technology's fusion of distinct cultural categories, nature and culture, instigate polarized responses. More specifically, I use "nature" to refer to elements of the natural world. In contrast, I use "culture" to refer to artifacts constructed by society, that do not exist in nature. First, I analyze the exorcist and embracing perspectives regarding human genetic modification. I will then use the concept of monster assimilation to explain how Dr. Blaese and Dr. Anderson's gene therapy has been domesticated to be used clinically.

Background

Germline Genome-Editing

Genetic editing of the germline specifically refers to genetic modification of germ cells. Germ cells give rise to the gonads, eggs or sperm, and gametes, mature haploid male or female germ cell that form a zygote when united with another gamete of the opposite sex in reproduction. As such germline edits are present in the offspring of a treated organism. Germline genetic modification is achieved by applying gene editing techniques to an embryo resulting in the edited genome in every cell. Germline editing is generally criticized due to its inherent incompatibility with informed consent requirements. Considering foreign DNA is delivered to

embryos and passed down to future generations, it is impossible to receive true consent from the subjects of the treatment.

Somatic Genome-Editing

In contract, somatic genome editing only modify genes and gene expression in somatic cells rather than one's entire genome. Somatic cells are mature and differentiated cells. Thus, unless gonad cells are directly targeted by gene therapies, the genome of the offspring will not be modified. As such, the bioethical concern about informed consent does not apply to somatic gene-editing. Additionally, people are generally less concerned with the risks of somatic gene editing as only specific cells are targeted.

First Unapproved Gene Therapy Trial

Martin Cline, an American physician, conducted the world's first experiment in 1980 using gene therapy to cure thalassemia in two humans despite a lack of approval from the review board (Martin, 1999). Dr. Cline's treatment sparked a rise in social pressure for a ban on gene therapy research, primarily from religious organizations and environmental activists. While Dr. Cline's trials instigated the debates on using genetic engineering technology in humans, concerns regarding the safety, efficacy, and approval of this trial dominate discussions on his use of gene therapy.

Analysis

During the early 20th century, the developing concept of biological engineering fascinated scientific leaders and attracted a lot of research. In 1984 the National Institutes of Health created the Recombinant Advisory Committee (RAC), comprised of scientists, clinicians, lawyers, and policy makers, given the responsibility of establishing a framework for clinical research in genetic engineering. In 1990, the FDA's Recombinant DNA Advisory Committee

(RAC) approved the first gene therapy clinical trial in humans (Wirth et al., 2013). At the time, babies with adenosine deaminase severe combined immunodeficiency (ADA-SCID) rarely survived past age two and treatments for ADA-SCID were limited and largely insufficient. At age four, Ashanti DeSilva was the first patient to undergo an approved gene therapy. The procedure involved removing blood cells from the patient and infusing them with viral vectors to introduce functional ADA genes. In 1991, nine- year-old Cynthia Cutshall was the second patient to undergo this treatment. Nearly 30 years later and both patients are alive and living relatively normal lives. Gene therapies for ADA-SCID continue to be used today and have been fully approved in multiple countries (Wirth et al., 2013).

Monster Exorcism

Despite the undeniable success of the first clinical trial involving gene therapy, 'monster exorcists' continued to disapprove of and protest gene therapies due to its synthesis of the socially constructed boundaries of 'nature' and 'culture'. While many scholars have attributed the opposition of emerging biotechnologies to the bioethical complications involved in numerous genetic engineering techniques, these arguments are not applicable to this use of gene therapy to treat ADA-SCID (Martin, 1999). More specifically, bioethical complications commonly addressed in gene therapy debates include safety, preclinical testing, risk-benefit tradeoffs, and alternative approaches. The opposition to Dr. Cline's unapproved treatment of thalassemia using gene therapy can be largely attributed to these bioethical complications considering his treatment proposal was denied. In contrast, Dr. Blaese and Dr. Anderson presented strong enough evidence for their case, including results of preclinical testing and risk-benefit analysis, to become the first approved attempt to introduce foreign DNA into humans.

Similarly, the incompatibility with informed consent requirements and fear of human enhancement applications are predominant amongst popular arguments against utilizing genetic engineering techniques in humans. Arguments regarding consent are based on the principal that informed consent cannot be given if manipulated genetic material is given prenatally or passed down to future generations. The protocol for the ADA-SCID clinical trial included isolating blood cells of interest and introducing foreign DNA *ex vivo*. Considering only specific somatic cells were manipulated and the virus containing the foreign DNA was delivered to target cells *in vitro*, the arguments regarding compromised informed consent do not apply. Additionally, since only the functional ADA gene was introduced to patients as final life-saving efforts, arguments regarding the abuse of genetic engineering techniques for non-medical purposes also do not apply.

The most common contributors to gene therapy opposition are religious and nature-disrupting arguments. When debates on synthetic biology began at the start of the 1970's, social and ethical concerns regarding the consequences of 'playing god' were primarily expressed by religious organizations and environmental advocates (Martin, 1999). In reality, religious claims that gene therapy takes medicine too far by 'playing god' and environmental arguments are manifestations of the troubling contradiction between nature and culture associated with the technology. A survey conducted by Pew Research Center in 2019 found that more religious individuals are less willing to utilize gene therapies to improve the health of themselves or their children (Funk et al., 2019). When individuals were asked why they believe preventative gene therapies in babies is morally unacceptable, 34% specifically referenced changing God's plan and 26% said it crosses a line we should not cross by disrupting nature (Funk et al., 2019). Surprisingly, while the survey specifically identified the patients as babies, issues regarding

informed consent was not in the top five responses. The results of this survey indicate that individuals extremely opposing gene therapy struggle with the new technology's inherent 'unnaturalness'.

Days after DeSilva officially became the first patient to begin a gene therapy clinical trial, The New York Times published an article titled "Why Gene Therapy Is Considered Scary But Cell Therapy Isn't" (Kolata, 1990). In this article, Kolata writes, "The key to the paradox is the word 'gene'. The muscular dystrophy therapy, with its more benign name, 'cell therapy' or 'myoblast therapy', slipped by unnoticed because it did not conjure up Frankenstein images of messing with genes." She claims that the fear of gene therapy stems from its negative association with the Frankenstein narrative of scientists creating life and disrupting nature. As stated by Dr. Arthur Caplan, the director of the Center for Biomedical Ethics at the University of Minnesota, "Genetic manipulation seems artificial or manipulative in ways that aren't representative of the natural order" (Kolata, 1990). This article demonstrates how the extent of opposition regarding the first gene therapy clinical trial can only be explained by the nature of the biotechnology, or lack thereof.

In spite of the success and benefit of gene therapy trials, 'monster exorcists' continue to resist the use of genetic engineering techniques and advocate for an outright ban on its research for humans. While concerns regarding the use of gene therapies in humans range from safety and bioethical fears to religious values, individuals in complete opposition to the new technology share the belief that genetic engineering crosses the line of medical intervention by interfering with nature. 'Monster exorcists' consider gene therapies a threat to the natural world by fusing the cultural boundaries of medicine or 'nature' and 'culture'.

Monster Embracing

In contrast, others are extremely fascinated by advancements in genetic engineering and embrace the technology's immeasurable potential to benefit humanity. Initially, gene therapies were presumed to be plausible treatments for inheritable genetic disorders. Those suffering from genetic disorders and their loved ones strongly support gene therapy research. In 1990 the Human Genome Project was funded with the goal of sequencing the entire human genome in 15 years and was completed two years ahead of schedule. While in its early days there were many critics, in hindsight, the project's overwhelming success made it clear that the benefits greatly outweighed the cost (Chial, 2008). With technological advancements in genetics, we now know so much more about the human genome and molecular biology. As a result, biomedical research and medicine is heavily relying on genetic information to understand and ultimately treat all types of medical conditions. Now the possibilities and applications of gene therapies seem endless. Gene therapies provide hope for millions of individuals worldwide.

Geneticists appreciate the magnitude and organization of the human genome, thus separate medical genetic therapies from genetic enhancement: the transfer of genetic material to modify nonpathological human traits (National Human Genome Research Institute, 2017). Similarly, with the extensive understanding of many human genes, geneticists and molecular biologists are very confident in their ability to predict the effects of specific modifications. While many people directly associate identity and individuality to one's entire, unique genome, others do not, especially with respect to distinct, disease-causing mutations. These people, particularly medical professionals have a very different perception of genetic therapies; rather than viewing gene editing as 'playing god', it is seen as the simplest approach to treating almost any medical condition directly at the source.

Despite the controversy regarding Cline's unapproved human experiment using gene therapy techniques, many people viewed his trials as a success (Jacobs, 1980). Additionally, support for gene therapies grew after the success of Dr. Blaese and Dr. Anderson's clinical trial. In the New York Times article following the clinical trial, Kolata argues that this use of gene therapy is no different from many generally accepted medical procedures with respect to bioethical concerns and societal implications. The director of the Center for Biomedical Ethics at the University of Minnesota, Dr. Arthur Caplan, specifically stated that the ethical problems regarding this form of gene therapy are not categorically different in degree or kind from any other innovative form of invasive human experimentation (Kolata, 1990). George Annas, the director of law, medicine, and ethics at Boston University School of Medicine, agrees that "The bottom-line answer, concluded by most who have looked at it, is that gene therapy is not qualitatively different from other medical treatments and should not be treated as if it is" (Kolata, 1990). The perspectives of both Dr. Caplan and Annas exemplify the 'monster embracing' approach common amongst scientists and medical professionals.

The majority of people who embrace gene therapy do not consider it to be too unnatural for a place in society. A survey conducted by Pew Research Center in 2019 found that the majority of Atheist and Agnostic people believe gene editing in babies is morally acceptable, suggesting that non-religious individuals are less likely to view gene therapy as disrupting nature (Funk et al., 2019). Dr. Anderson directly responded to the arguments that genetic engineering techniques are unnatural, stating, "We learned we can't fiddle around with bacteria and make them do things that nature hadn't already figured out" (Kolata, 1990). There is a common misconception that genetic engineering techniques are based on man-made technologies that abuse nature. As referred to in Dr. Anderson's response, the techniques involved in genetic

engineering are not man-made. Rather, they are natural biological processes that have been discovered through research on other organisms, such as bacteria, and applied to biomedicine. While the exploitation of biological processes specific to other organisms, even if naturally occurring, can also be considered unnatural, 'monster embracers' do not view gene therapy differently from other forms of medicine similar in that regard.

Monster Assimilation

Scientists and policy makers have employed Smit's monster assimilation strategy to overcome numerous obstacles against gene therapy research. More specifically, gene therapies continue to be 'domesticated' by adapting the technology to fit within redefined cultural boarders. Gene therapies challenged the mutually exclusive categories of 'medical' and 'non-medical'. The first example of how gene therapies resisted 'exorcism' by constructing the technology within carefully defined cultural boundaries occurred when the concept of genetic therapies was first discussed in the early 20th century. In its early phases, there were two competing visions of gene therapy. The first involved improving future generations socially, intellectually, and by curing genetic disorders. As this vision was inspired by eugenics, the younger generations strongly opposing the principle of eugenics proposed the second vision of gene therapy: genetically altering affected patients, not their offspring, for medicinal purposes only (Martin, 1999). The second vision of gene therapy proposed by the younger scientists was the first step in assimilation of gene therapies, as their depiction of the technology was the foundation for the careful distinctions between germline and somatic editing for medical and non-medical purposes.

Around the 1970's when social and ethical concerns about the consequences of 'playing god' grew, 'monster exorcists' demanded a total ban on research involving genetic engineering.

Protests against research involving genetic engineering of human DNA prompted the establishment of the President's Commission for the Study of Ethical Problems in Medicine, and Biomedical and Behavioral Research. Arguments against gene editing often focused on the inability to achieve true, informed consent if foreign genetic material is given or passed down to future generations. The Commission responded to protests by making the distinction both between germline verse somatic gene therapy and for enhancement verse medical treatment of life-threatening genetic diseases (Martin, 1999). While they declared germline therapy unethical, they argued it was acceptable to proceed with somatic therapies for life threatening conditions. The Commission's response to protests exemplifies the 'monster taming' strategy of assimilation by not only making a clear distinction between germline and somatic editing but by also forcing the trajectory of gene therapies away from manipulation of the germline.

Conclusion

Society continues to face a severe contradiction regarding human genetic modification that cannot be resolved by a true consensus amongst all. On one hand, there are the millions of individuals afflicted by diseases that currently can only be cured or treated by genetic therapies and technologies. On the other hand, there are countless individuals that are against gene editing because they conflict with their cultural principles. The recent advancements in bioengineering and genetic engineering call for reevaluation and redefinition of relevant biomedical and bioethical terminology to illuminate impeding contradictions. While many scholars have attributed the opposition of emerging biotechnologies to the bioethical complications involved in numerous gene therapies, such as risk-benefit analysis, these arguments are not applicable to Dr. Blaese and Dr. Anderson's use of somatic gene techniques to treat ADA-SCID. Their clinical trial was explicitly approved by the FDA and RAC after carefully evaluating the risks and

benefits. Instead, Smit's monster theory highlights the underlying challenge gene therapies face: the ambiguous cultural characteristics of the new technology. I demonstrated how gene therapy technologies fuse the distinct categories of nature and culture instigate opposition to show how this contradiction has and can continue to be resolved through monster assimilation.

References

Bostrom, N., & Sandberg, A. (2009). Cognitive Enhancement: Methods, Ethics, Regulatory Challenges. *Science and Engineering Ethics*, *15*(3), 311–341. doi: 10.1007/s11948-009-9142-5

Bostrom, N., & Savulescu, J. (2009). Human Enhancement Ethics: The State of the Debate. In *Human Enhancement* (pp. 1–24). Oxford University Press.

Center for Genetics and Society. Human Genetic Modification. Retrieved from https://www.geneticsandsociety.org/topics/human-genetic-modification

Chial, H. (2008) DNA sequencing technologies key to the Human Genome Project. *Nature Education* 1(1):219

Coady, C. A. J. (2009). Playing God. In *Human Enhancement* (pp. 71–91). Oxford University Press.

Dever, D. P., Bak, R. O., Reinisch, A., Camarena, J., Washington, G., Nicolas, C. E., … Porteus, M. H. (2016). CRISPR/Cas9 β-globin gene targeting in human haematopoietic stem cells. *Nature*, *539*(7629), 384–389. doi: 10.1038/nature20134

Funk, C., Kennedy, B., & Sciupac, E. P. (2019, December 30). U.S. public opinion on the future use of gene editing. Retrieved from https://www.pewresearch.org/science/2016/07/26/u-s-public-opinion-on-the-future-use-of-gene-editing/

Gast, E. T. (2007). *Biotech pioneers. A philosophical inquiry concerning the genetically engineered mouse* (Doctoral dissertation, Amsterdam: RTODTO).

Genetics Home Reference, NIH. (2019, September 3). What are genome editing and CRISPR-Cas9? Retrieved from https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting

Harris, John. (2009). Enhancements Are a Moral Obligation. In *Human Enhancement* (pp. 131–155). Oxford University Press.

Hughes, T. P. (1994). Technological momentum. *Does technology drive history*, *101*.

Jacobs, P., & Times, L. A. (1980, October 8). Doctor Tried Gene Therapy On 2 Humans. Retrieved from https://www.washingtonpost.com/archive/politics/1980/10/08/doctor-tried-gene-therapy-on-2-humans/c95d4b44-3e5c-4a48-904c-4bbefe52391b/

Kamm, Frances. (2009). What Is and Is Not Wrong With Enhancement. In *Human Enhancement* (pp. 91–131). Oxford University Press.

Klein, H. K., & Kleinman, D. L. (2002). The Social Construction of Technology: Structural Considerations. *Science, Technology, & Human Values*, *27*(1), 28–52. doi: 10.1177/016224390202700102

Kolata, G. (1990, September 16). Ideas & Trends; Why Gene Therapy Is Considered Scary But Cell Therapy Isn't. *The New York Times*. Retrieved from https://www.nytimes.com/1990/09/16/weekinreview/ideas-trends-why-gene-therapy-is-considered-scary-but-cell-therapy-isn-t.html

Lanphier, E., Urnov, F., Haecker, S. E., Werner, M., & Smolenski, J. (2015). Don't edit the human germ line. *Nature*, *519*(7544), 410–411. doi: 10.1038/519410a

Martin, P. A. (1999). Genes as drugs: the social shaping of gene therapy and the reconstruction of genetic disease. *Sociology of Health & Illness*, *21*(5), 517-538.

Menuz, V., Hurlimann, T., & Godard, B. (2011). Is Human Enhancement also a Personal Matter? *Science and Engineering Ethics*, *19*(1), 161–177. doi: 10.1007/s11948-011-9294-y

National Human Genome Research Institute, NIH. (2017). What are the Ethical Concerns of Genome Editing? Retrieved from https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/ethical-concerns

Rodriguez, R. (2017). Beyond Dr. Frankenstein's Monster: Human Germline Editing and the Implications of Waiting to Regulate. *N. Ill. UL Rev.*, *38*, 585.

Wirth, T., Parker, N., & Ylä-Herttuala, S. (2013). History of gene therapy. *Gene*, *525*(2), 162-169.