Germ-Line Genetic Engineering and the Precautionary Principle

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Background

In its simplest definition, genetic engineering (GE) is the set of molecular techniques for locating, isolating, altering, combining, and studying DNA segments (also known as recombinant DNA technology) (Pierce 508). By altering the genes in a given organism, scientists can produce a new genotype, or set of genes that an individual possesses (Pierce G-8). A genome is the set of genes that an organism has, and genes are instrumental in the expression of proteins, cells, and tissues in the body. Genes are the blueprint from which an organism is built. Scientists can modify the genotype in several different unique ways, much like erasing a section of wall from the blueprint and replacing it with a doorway. They can form a transgenic organism (or chimera) by inserting genes from one species into another; they can alter a current gene so that the gene expresses a different product such as a different protein; or scientists can even change the rate at which a particular gene is expressed from over expressing a given gene to not expressing it at all ("Genetic Engineering").

How can we even manipulate something we can only see in the nucleus of a cell at specific points during cell division? The simple answer is: by using the same machinery that makes, breaks, and replicates DNA naturally in an organism. The machinery or tools that are used by organisms to manipulate their own genetic material are enzymes, proteins, and nucleic acids. Although the ultimate goal for GE is for a specific gene to be expressed as desired in the organism, a large portion of the "engineering" process deals with isolating the desired gene and

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then making many copies of it, in essence photocopying the blueprints for the use of the construction workers of the organism. In order to complete any kind of genetic engineering project or research into genes, a few basic steps need to be followed. First, one must identify the gene of question or interest which codes for a particular protein or enzyme. Then, this gene must be isolated, "cut" from its surrounding DNA, and removed. This snippet of DNA is then placed or "glued" into the vector by which the DNA will be placed into the organism or area desired. From the vector, the desired piece of DNA or gene is passed from the host organism to the desired organism including locale. This is effectively how genetic engineering is done.

By using these methods and techniques, the specific gene of interest can be isolated, duplicated, and inserted into an organism. In the human body, there are two types of cells that are targeted for by these methods of GE: somatic cells and germ-line cells.

Somatic cells are the cells that make up the vast majority of the human body. When GE is performed upon somatic cells, only those cells are directly affected by the change in genotype. These alterations will not be passed down to subsequent generations of cells. Somatic genetic engineering (SGE) or somatic gene therapy is used to incorporate a gene into a person's somatic cells. For example, using a virus as the means of transferring the desired genes into the diseased cell genome, certain genetic illnesses can be treated. The easiest and most effective types of genetic illnesses to treat with somatic GE are diseases like cystic fibrosis, in which the genetic defect alters a particular and particularly accessible part of the body. The gene for cystic fibrosis causes the cells lining the respiratory tract to produce excessive mucus. This overproduction leads to breathing problems such as wheezing and shortness of breath. Somatic gene therapy becomes much harder to administer, more invasive, and less successful when the genetic diseases afflict deeper and more heavily buried tissues.

Germ-line cells are the cells that can directly pass their genetic makeup or disposition on to future generations. These gametic cells include the sperm of the male and the egg of the female as well as the combined zygote upon fertilization of the egg by the sperm. After the zygote has divided into partially differentiated cells known as the embryo, certain cells are set aside to perpetuate the genetic lineage of this embryo

by later becoming the gonads (either the ovaries or testes). Germ-line genetic engineering (GLGE) would transfer the desired gene into the genome of a gametic cell such as the sperm or egg before fertilization, into the newly formed zygote, or possibly into the next generation gonadal tissue. Germ-line Genetic Engineering is the "introduction of a fully functional and expressible gene into germ-line cells resulting in a permanent correction of a specific genetic defect not only in the individual treated but potentially all future offspring" (Boylan and Brown 147). If, and when, GLGE is perfected to the point of being clinically utilized, it will show marked advantages over SGE. GLGE's genetic modifications would be integrated into every cell of the body, even those currently inaccessible through SGE techniques ("Germ Line Gene Therapy"). GLGE would also prove to be a more permanent solution as the changes would perpetually be a part of the organism as the new genome is found in every cell. Current SGE techniques often need recurring implementations due to the types of surface cells that they are targeting. As the epithelial cells are sloughed off and new cells are brought to the surface, these cells too need to be modified to battle the genetic disease. Therefore, GLGE will be the most effective and most enduring type of genetic engineering that can be undertaken, and it is this type of genetic modification that this paper will specifically target as its focus.

If GLGE is perfected, it will become possible to actually insert any type of gene or base pair that scientists can dream of into the human genome or biological blueprint. With this type of technology, we will even be able to direct what genes offspring will inherit from their parents. This area is a frightening frontier of what-ifs, cautionary science-run-amok tales, and doomsday predictions. With the seemingly limitless expanse of possibilities that germ-line genetic engineering will afford the human race in the foreseeable future, what should be done? What limits should be placed on this area of study? Though many do and will call for an all-out ban on research into human genetic engineering to prevent disastrous future scenarios, a more moderate approach can show that the precautionary impulse behind these demands for a ban actually supports a limited role for GLGE in the treatment of genetic diseases. Employing a reformed version of the Precautionary Principle set forth by David Resnik, I will argue that instead of being an overly

cautious and risk-aversive plan of inaction, this principle can and should be understood as a technology-friendly principle which will support the application of GLGE.

Framing the Argument: Enhancements and Safety

From the first mention of the words "genetic engineering," an average person's thoughts immediately jump to the types of beings that littered every child's imagination and filled every sci-fi movie's creature repertoire, lizard men and giants, super strong men who could fly and super geniuses whose intellect surpassed anything imaginable. These common figures display the notion that manipulation of our genetic material will lead to an increase in the natural endowments that we can find already existing in nature such as stature, strength, or intelligence. The prevalent opinion assumes that scientists will use genetic engineering such as GLGE to create enhancements for the human race. However, there is a very large distinction between enhancements and treatments using genetic engineering.

Enhancements are designed for "improving the body or soma type even though there is no life-threatening illness" (Boylan and Brown 120). Treatments for therapeutic means, on the other hand, are for "correct[ing] the nonfunctioning or malfunctioning of a single gene in either a monogenic disease or a multifactorial disorder" (Boyland and Brown 108). Many adversaries of genetic engineering worry that GLGE will be used to create traits and characteristics above and beyond the current "normal" standards of human genetic variance. An example of the blurred line between the two can be seen in the use of HGH, human growth hormone. In the beginning, HGH was administered only to individuals that were significantly below the "normal" standards of height for both males and females. This type of use of HGH was intended for treatment purposes only. However, in recent years, those who could afford the treatments and who wished to be just a little taller than they currently found themselves also underwent HGH supplementation. These individuals were not in need of HGH to achieve a sense of normalcy, but were interested in its properties for a purely cosmetic or aesthetic appeal. This utilization of HGH can be seen as the prototypical application for enhancement.

Many individuals are concerned with the dangers of utilizing germ-

line genetic engineering for these types of enhancements. What types of enhancements would be possible? Which ones would or should be utilized? What unintended consequences of the human genome would be a result of this kind of "tampering?" Would these enhancements not cause strife and genetic stratifications or castes among humans? These questions and concerns are all valid, but I will not be able to discuss them here. Instead I will assume that the distinction between enhancements and treatment needs to be made, and focus strictly on applications of GLGE to clear cases of treatment.

A second crucial issue is safety. In order for any new technique or procedure to be allowed for human clinical use, a very arduous and demanding series of tests and experiments are necessary. Before any experimentation or broad based employment on humans, a drug or procedure's efficaciousness must be determined to be medically safe. Even though research is being conducted in order to create methods and techniques that can accurately and safely implement the genetic changes to human germ-lines, GLGE currently is unsafe to administer to human subjects. However, in considering the ethical issues raised by GLGE, we need to set this issue to the side. The main issue that we are concerned with is: what should society do if GLGE becomes safe enough to employ as a treatment for human subjects?

The Precautionary Principle

In applying the developing technologies afforded by scientific discoveries, nations, organizations, and policy makers have sought models that would be both safe and effective, to gain maximum possible benefits while keeping individuals out of harm's way. A popular and oft-employed stratagem for securing both of these goals has been a concept called the Precautionary Principle (PP). The Precautionary Principle calls for humanity to "never engage in a technological development or application unless it can be shown that this will not lead to large-scale disasters or catastrophes" (Engelhardt and Jotterand 303). The origins of the PP reach back to the 1970's in Germany, where the *Vorsorgeprinzip* was established as a government policy for regulating the production of agents that might harm or threaten clean air. Since then the PP has become an important part of the United Nations' approach to environmental issues. The 1992 Rio Declaration on Environment and

Development states that the "lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation" (United Nations 10). Here the possibility of environmental catastrophe is invoked to set aside scientific certainty about the likelihood that the catastrophe will occur. For this reason, the PP has been criticized as a vague and ambiguous strategy for handling future decisions, and for being an "extremely risk-aversive, anti-science rule" (Resnik 282).

One problem with common versions of PP is their dependence on action. The versions of PP that are most prominently defended all seem to take as granted that civilization has in the past done some action A. After a while, it is claimed that the repercussions of action A *may* not be favorable or good for humanity for whatever reason. It then becomes justifiable, even without "scientific certainty," to act once again, to perform the preventative and "cost-effective" measure B. So the common versions of the PP hinge on an initial action that may yet bring about bad things; they see harm deriving only after an initial action has occurred. But what are they overlooking? Isn't it possible and sometimes even likely that failing to act will lead to untoward consequences? The answer is an overwhelming and resounding yes.

Take, for example, a typical Friday night bar fight. The cocky, diminutive fellow who has had one too many drinks during the night should reasonably be assured that after he mouths off to the big biker dude and errantly takes a swing at him, a harmful consequence is sure to come. This scenario is the typical viewpoint of most renderings of the PP. However, what if this scenario is viewed from a slightly different angle? After verbally and physically assaulting the behemoth and seeing his balled fist and raised arm, what would occur if our little Napoleon did nothing? What if he just stood there instead of running for fear of his life as he should? Obviously, this option or course of *inaction* will indeed also lead to harmful consequences, namely missing teeth and broken bones. This standpoint that many precautionary principlists forget or ignore is that "[o]ne must not only fear catastrophes that will flow from a technology, but also the catastrophes that will flow from its absence" (Engelhardt and Jotterand 307).

If it is reasonable to assume that after carrying out a specific action, harmful consequences may arise, then it is also reasonable to assume

that failing to carry out or purposefully choosing inaction could also lead to equivalent levels of damage. Holding this posit as true, the PP should and must also be applied to *inactions* as well as *actions*, because the PP "invites us to give at least as much weight to the catastrophes we face from not developing a certain technology as from developing the technology" (Engelhardt and Jotterand 308).

The PP and GLGE

But how does the question of *inaction* vs. *action* apply to the case of the PP and GLGE? Let's consider two different scenarios.

Scenario 1: Many protagonists of GLGE are worried that in the process of engineering our genome, scientists may inadvertently do more harm to the genome than good. What harms could possibly be done to a genome? If the technology is present to manipulate the genes and the likelihood that a given gene will be expressed in the population, many fear a reduction in variability of the human genome in which there are fewer genotypes or kinds of genes expressed in the human population. Another concern which is most often touted as a major concern is the unknown and unanticipated "side-effects" of engineering specific genes. What kinds of effects are these modified genes going to have on the entire genome in the future if some of the adverse affects occur in the long-term? What will a build up of these genes do if they are slow in developing or interact in a complex or unpredictable way? Therefore, many propose that GE be banned outright or to a lesser extent, slowing down the pace of research and funds into this field of knowledge by limiting research and experimentation to animals until, and only when, safer and better techniques are available. While these techniques are being developed, Somatic Gene Therapy can be used in order to fill the medical needs of the patients suffering from specific genetic disorders.

Scenario 2: Imagine that a deadly pandemic virus has begun to spread throughout the world (say, from flu being passed among birds and then jumping to humans). Since these flu viruses originate mainly in Asia, the Western hemisphere has time to "predict" what form the next virus will take, and the technology to produce a vaccine that nullifies its effects. Having the ability to create such a vaccine would save millions of lives, and GE techniques may be an invaluable tool in saving the

human race from this type of threat. One of the most threatening dangers facing humanity in the near future are newly emerging viruses, variations on old viruses, and those strains of microbes that have become resistant to known treatments or that have become harmful to humans in different ways.

Scenario 1 with its given threats and harms has the PP justifying the banning or at least limiting the scope of GLGE. Scenario 2 with a different threat has the PP justifying the unprohibited use of GLGE in order to prevent catastrophic viral illness. Which scenario is correct? The answer depends on attitudes toward risk. Most versions of the PP are overly cautious and risk-aversive in their attitudes towards science and scientific technologies. Without any scientific certainty to back their decision with either evidence for or against, these precautionists choose to refrain from making use of the science in order to prevent a *possible* catastrophic outcome from supposed risks and threats of harm.

Everyday we risk our lives just by heeding the shrill call of our alarm clocks and getting out of bed. At any moment any number of unfortunate mishaps and accidents may injure or even kill any of us. Humans deal with the consequences of their "risky" actions hundreds of times in a twenty-four hour period. The root of this "bravery" derives from our assumptions about the nature of the world in which we live and unconsciously weighing the risks associated with our next step.

If humans are so ready to jeopardize themselves without knowing or realizing that they are participating in calculated risks, how can they cringe at taking risks when they are fully aware of the possible consequences? In normal usage, the word "risk" maintains a negative connotation. It is assumed that risk implies the potential for physical harm or damage to the subject. This assumption is not always accurate. When we invest our money in the stock market, we risk our financial future in the well-being of a particular company. If the stock goes down or the stock market crashes, nothing physical happens to the individual; instead, it is merely the subtraction of wealth. Wealth is simply a cultural contrivance, a concept, an abstraction. The individual will continue to live and breathe. Another example more universally understood is the concept of love. When we profess our feelings towards another individual, we are risking emotional investment and also rejection.

If our paramour does not reciprocate, we are injured not physically, but emotionally. We will live (though we may well feel like dying).

Unlike these "normal" risks, human biotechnology is scarcely seen as having such mundane or trivial consequences. Scientific breakthroughs fall under the stigma of calamitous falls and setbacks that can and, more than likely, will cost someone his or her life: the "collective consequence of the ways in which genetic engineering technology is being misapplied is one of many human influences...that will soon mean a world devoid of a whole earth" (Fox 141). Many critics of technology suspect that "technological interventions carry with them an unassessable prospect of an unanticipated, large-scale, catastrophic side effect" (Engelhardt and Jotterand 306). At the slightest hint of a possible danger or unintended consequence, many people are more than happy to pull the plug on science's life support system. Without "scientific certainty" or other actual causal link, any mishap from the application of technology can cause the immediate restriction or cessation new technologies that are linked, however remotely, with the same kind of scenario.

Thus some critics argue that the PP would "forbid anything but the most gradual introduction of most new technologies" and, even to the mighty chagrin of diligent and careful experimenters, "the suspension of technological interventions for which there has not been ample time to assess unforeseen risks" (Engelhardt and Jotterand 304). With even a vague threat of harm, great suspicion and doubt can cast a pall over all biotechnology. Other critics of the formulation of the Precautionary Principle, however, buck this trend and attempt to offer a different, middle-ground stance on applying the PP to biotechnology.

A New Standard Operating Principle

In his article "The Precautionary Principle and Medical Decision Making," David Resnik attempts to reshape and redefine the PP. Resnik begins by contrasting the PP with expected utility theory (EUT). "EUT provides a scale for comparing the expected costs and benefits" for different choices (282). EUT is a beneficial system to apply when, and only when, there are definitive probabilities for specific outcomes following particular choices. The PP, on the other hand, is applied when there is not enough evidence for EUT and uncertainty abounds.

Resnik cites a popular formulation of the PP based on the European Commission's version of 2000, which states that a "lack of scientific proof should not be used as an excuse for failing to take reasonable measures to avert a serious threat." According to Resnik, this interpretation of the PP is "extremely risk-aversive, anti-science," and so in order to make better decisions with this concept in mind, a more reasonable and less risk-aversive form should be articulated. Resnik notes that there is a reliable consensus stating that scientific knowledge is not certain; it "may be confirmed, verified, proven, accepted, justified, reliable or entrenched, but it is not certain" (285). Therefore, the notion of "scientific certainty" is a pretense to begin with and so, Resnik replaces it. For purposes of his essay, Resnik adopts a probabilistic interpretation of "scientific proof." This interpretation then raises the question: what degree of probability counts as scientific proof? Though the particular applications of the scientific claims determine the probabilities involved, the assignment of probabilities must nevertheless be "objective probabilities" that are independent of subjective beliefs. If we are unable to affix an objective probability to a particular statement, it subsequently lacks scientific proof: "Without probability, there can be no scientific proof" (Resnik 287).

This leads Resnik to confront a main critique of the PP from its many opponents: the PP is used in order to "justify taking actions against threats that are not probable or even plausible" (287). Resnik makes an excellent, if a little sophomoric, reference to the hysterical scenarios professed by Chicken Little. But what is a *plausible* threat as opposed to one that is *probable*? Resnik reminds us that probability implies the ability to place an objective probability on an outcome. A plausible threat then is one on which we cannot yet place a probability but which does have some evidence pointing towards it. The example he gives is the plausible occurrence of his having a flat tire on the way to work. There is evidence that it could happen, but not enough data to place odds on its occurring.

Even when a threat is plausible, Resnik argues, our response to it must be reasonable: as many versions of the PP hold, the should be "proportional to the level of the threat." Resnik surmises that responding to a threat that we are unable to prevent is unreasonable. It is just as unreasonable to take inadequate and ineffective means to stop

a preventable threat. To clarify the notion of reasonableness, Resnik again returns to his example of a plausible threat, the possibility of his getting a flat tire. What should he do about this threat? He has several options: (1) do nothing; (2) don't go to work; and (3) take a jack and spare tire (Resnik 289). Option one is insufficient to the threat; two is just a little bit of an overreaction; and three appears to be the most *reasonable* of the three. However, reasonableness, like scientific proof, is not a very exact term. Then what good does this notion do? It is a vital because it "involves the careful balancing and weighing of competing norms and goals that characterize moral and political decision-making" (289). An advantage of this reasonableness is the consideration of multiple easonable responses to a given threat.

Finally, Resnik argues that to invoke the PP, a plausible threat must also be "serious." How is one threat more serious than another? According to Resnik's intuition, which seems plausible, seriousness hinges on two things: a threat's potential for harm and its reversibility. A threat that is reversible, even if it has great potential for harm, may turn out to be dangerous and problematic than a seemingly less harmful but irreversible threat.

Putting these points together, Resnik proposes the following as an alternative formulation of the PP: "One should take reasonable measures to prevent or mitigate threats that are plausible and serious" (Resnik 290). This new version of can have a direct application for GLGE.

To see this, let's return to the example of cystic fibrosis. Again, cystic fibrosis is a genetic illness that affects the cells in an individual's body that produce mucus, sweat, saliva, and digestive juices by making these liquids much more viscous and less fluid than normal. Because of this excessively thick and sticky mucus, the most common dire consequence of this disorder is respiratory failure. So far, all treatments for cystic fibrosis have focused on its symptoms and complications because aiming at the cause has been difficult. Somatic Gene Therapy can be applied to the epithelial cells in the lungs, but since these cells are naturally sloughed off, this kind of treatment needs to be continually repeated.

How would Resnik's PP apply to this example? Cystic fibrosis is without a doubt a very "plausible" malady, since it afflicts 30,000 Americans, and since 1 in 38 (more than 10 million) are unknowing,

symptomless carriers of the defective gene (Statistics and CF). And of course, the tragic outcome of patients with cystic fibrosis makes this disease all-too serious. If and when GLGE technology becomes available for clinical use in humans and is shown to be a medically safe option for the treatment of a given genetic disease, it will be thereby shown to be a "reasonable measure" to lessen or even prevent the illness. Since GLGE would be a reasonble response to a serious and plausible threat, on Resnik's account, the PP would itself justify the use of GLGE.

The Precautionary Principle on Its Head

It is a common misconception that the PP is averse to supporting genetic engineering in general and GLGE specifically. For instance, as Gary Comstock notes, the United Nations and the European Union have invoked the PP to justify a moratorium on genetically modified crops. On the other hand, Comstock then proceeds to develop a scenario in which the world is under climatological distress from global warming, and we are forced to take drastic measures to continue food production such as clear-cutting forests, hunting endangered species, and cultivating previously unused land. Though Comstock himself admits that this is "not a likely scenario," he argues that "GM crops could help to prevent it [the dire scenario], by providing hardier versions of traditional lines capable of growing in drought conditions…or unusual climactic stresses" (Comstock 177). Depending on whether we were focused on the threat of genetic disaster or widespread famine, the PP would demand that we must not or must certainly develop GM crops. Since these two courses of action are incompatible, Comstock sees the PP as inconsistent.

However, if we look closer, we will see that these two arguments are quite different. Comstock is actually applying the PP to two different conditions. The first scenario, that stressed by the UN and the EU, involves uncertainty about the effects genetically modified plants will have on the environment or long-term effects of human consumption. The second scenario, Comstock's own, starts with a bleak situation that is presumed to be a reality: the earth is in dire need of plants to feed its populace in the face of extreme climate changes brought about by global warming. It is plain to see that these two circumstances are quite

different, but Comstock lumps them together.

On the other hand, the two scenarios I put forth earlier in this essay are different in both their approaches to the problem as well as the problem that each faces. In actuality, these two earlier scenarios create a third scenario with a third kind of threat, namely a threat where both scenarios are possible. Therefore, in order to assuage both threats, we need to take a balanced reflection of the wide range of possible threats that can be generated from both action and inaction. There are risks and threats associated with performing GLGE such as decreased genomic variability or long-term accumulations of adverse "engineered" genes as well as risks and threats associated from withholding GLGE such as falling victim to a virulent microbe or suffering the continuing rampage of genetic illnesses. Even if it may be a mistake to go full ahead with GLGE, defensible versions of PP will, in all likelihood, support some use of GLGE as one reasonable approach. When the future and its future human descendants are factored into the moral equation, biotechnology will become a central tool for the perpetuation and survival of the human species and genome. Therefore, a fair application of the precautionary principle should, instead of forever locking the door to GLGE and biomedical technologies, "transform the principle from being central to an anti-technological ethos to a principle that when rightly understood is a cardinal foundation of an ethos supportive of biotechnological innovation" (Engelhardt and Jotterand 308). With a careful application of the Precautionary Principle as proposed by Resnik, this principle, which is usually worded to be strongly anti-technology, can and will show the wisdom in utilizing the exponential benefits that come with GLGE and other such technologies. Without any other form of treatment as a safe alternative, people will surely suffer without its power to heal.

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