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The Evolutionary Biological Implications of Human Genetic Engineering

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A common worry about the genetic engineering of human beings is that it will reduce human genetic diversity, creating a biological monoculture that could not only increase our susceptibility to disease but also hasten the extinction of our species. Thus far, however, the evolutionary implications of human genetic modification remain largely unexplored. In this paper, I consider whether the widespread use of genetic engineering technology is likely to narrow the present range of genetic variation, and if so, whether this would in fact lead to the evolutionary harms that some authors envision. By examining the nature of biological variation and its relation to population immunity and evolvability, I show that not only will genetic engineering have a negligible impact on human genetic diversity, but also that it will be more likely to ensure rather than undermine the health and longevity of the human species.

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I. THE EVOLUTIONARY HARM ARGUMENT AGAINST HUMAN GENETIC ENGINEERING

The term "monoculture" has become increasingly pejorative in recent years, particularly among the ranks of environmentalists, anthropologists, and other vehement critics of globalization. But it has more congenial roots in the context of agricultural practice, where it refers to the growing of a single cultivated crop (or "cultivar") over a relatively large swath of land. Because of the high genetic relatedness of the cultivars in a monoculture, their planting, maintenance, and harvesting can be standardized, increasing the efficiency of crop production and (consequently) reducing the cost of

food. As it turns out, however, the benefits of monoculture come at a substantial price—namely, an increased risk of catastrophic crop failure. Genetic uniformity in agricultural practices increases the chance of crop loss for two chief reasons: first, high levels of relatedness increase the vulnerability of a cultivar population to large-scale epidemics, which can spread rapidly in genetically homogenous populations, and second, low levels of biological diversity can impair the flexibility of cultivar lineages to respond to changing environmental conditions, such as fluctuations in temperature, moisture level, or soil composition.

Perhaps, the most famous illustration of the perils of monoculture is the Great Irish Potato Famine of the middle 19th century, which led to the death of nearly one-fourth of the Irish population. The proximate biological cause of the potato epidemic was a single-celled, host-specific infectious organism (*Phytophthora*) that has been linked to numerous plant pathologies, including (and especially) potato blight. But a deeper explanation of the tragedy makes use of *evolutionary* biological facts: namely, that in planting clones of the "lumper" potato variety in vast numbers and over wide areas, farmers unwittingly reduced host species diversity (Bourke, 1993). In so doing, they effectively rolled out the genetic red carpet for this voracious eukaryotic parasite.

A similar but more recent anecdote relates to the Californian winery debacle that occurred near the end of the 20th century, and from which an analogous precautionary moral can be drawn. Years before the catastrophe, agricultural experts at the University of California (Davis) had recommended that winemakers in the Napa Valley region use a productive rootstock cultivar called AxR1. This cultivar was thought to be resistant to the insect pest *phylloxera*, which had single-handedly wiped out nearly all the vineyards of 19th century Europe (Campbell, 2004). As it happened, however, although AxR1 did retain its original resistance, the aphid-like pest had evolved into a form that could thrive on the AxR1 monoculture. This oversight, in addition to a lack of appreciation for the dangers of host crop uniformity, led to the replanting of 2 million acres of vines, resulting in a financial disaster to the tune of 1 billion dollars.

The moral of the monoculture story can be read in two different (though not mutually exclusive) ways: "know thy mortal ignorance" and "know thy evolution." Regardless of the chosen emphasis, the basic message is clear: it is dangerous to put all of your agricultural eggs into one genetic basket. Why should the same precautionary maxim not apply with equal force to the genetic modification of humans, a technology that (ostensibly) threatens to narrow the range of human genetic variation (HGV)? Critics contend that given our unfortunate experiences with monoculture, the burden of persuasion should be on those who seek to demonstrate the safety of human genetic modification rather than on those who merely purport to identify its risks. I disagree with this allocation of the rhetorical burden, but I believe that the arguments in this paper will rise to the challenge in any case.

In a certain sense, there is nothing new in the idea that reproductive technologies and social practices could combine to decrease human genetic diversity, either in the aggregate or in any subset. This might happen, for example, if it became increasingly common to choose a mate or to abort a pregnancy on the basis of information obtained through genetic screening. But these technologies and practices could not result in anything even approaching a monoculture scenario since they do not affect background rates of recombination and mutation, the two primary sources of genetic variation. However, the same may not be said for *robust* genetic technologies, such as gametal genetic engineering, which can alter the genome—and by implication the gene pool—to an extent and with a degree of efficiency that is unprecedented in the history of life on earth.

Thus far, the ethical analysis of germ line genetic engineering technology (GET) has focused primarily on its social, psychological, or aesthetic-moral implications (see, e.g., Kass, 1998, 2002; Habermas, 2001, 2003; President's Council on Bioethics, 2002, 2004, respectively). Rather than retread this well-worn territory, I will concentrate on a challenge to GET that is commonly advanced but which has received far less critical attention in the literature: namely, the argument that GET will reduce the range of existing HGV, creating a biological monoculture that could not only increase human susceptibility to disease but also hasten the extinction of our species. Insofar as this paper explores the *phylogenetic* implications of GET, it compliments a recent paper in which Powell and Buchanan (forthcoming) examine the *ontogenetic* ramifications of the same technology. Although both papers consider GET in an evolutionary biological context, Powell and Buchanan focus on the development of traits during the lifetime of an organism, whereas the present paper is concerned with the evolution of human populations.

As I see it, there are two major areas of evolutionary concern that, taken together, comprise what I will refer to as the "evolutionary harm argument" (EHA). Both components of the EHA hinge on the premise that GET will substantially reduce HGV. The first contends that a progressively homogeneous human population will become increasingly susceptible to disease (e.g., Rifkin, 1983); the second claims that a shrinking range of biological diversity will reduce the human species' flexibility in responding to novel adaptive challenges (Baylis and Robert, 2004). In broad form, the EHA entails that the regulation or blanket prohibition of GET is necessary to protect the diversity of the human gene pool and, by implication, to prevent the aforementioned evolutionary harms.

I will show that once properly fleshed out, the EHA is unpersuasive since it is premised on several key misconceptions about the nature of genetic variation and its relationship to phenotypic diversity, disease resistance, evolvability, and the mechanism of natural selection. In this paper, I argue that the widespread use of GET is unlikely to reduce HGV and that even if it did, this would neither increase the human species' susceptibility to

disease nor prevent it from responding effectively to the shifting demands of selection. By rejecting GET in order to preserve the health of humanity and its valued characteristics, we may be jettisoning the most powerful weapon in our adaptive arsenal for ensuring the long-term survival of our species (see Buchanan, forthcoming).

II. THE NATURE OF BIOLOGICAL VARIATION

Thus far, the EHA has proven difficult to vet due to its lack of theoretical and empirical specificity. In order to cure this defect, we need to get a firm grip on the nature of biological variation. The presence of ample, heritable variation is a crucial premise in Darwin's "one long argument" for descent with modification. When we speak broadly of "human variation," we are referring to all the characteristics that make people different from one another, including traits that are culturally transmitted. *Biological* variation is a particular subset of human variation that refers to any and all genotypic and phenotypic diversity that is biologically transmitted. At the genomic level, measures of diversity include the number of alleles per locus or the overall proportion of genetic polymorphism; at the populational level, diversity is measured in terms of character trait variance; and finally, at higher taxonomic levels, diversity is indicated by species number, functional differentiation, or morphological disparity.[1]

Darwinian evolution requires that heritable variation be the *cause* of a propensity for differential survival and reproduction. For the most part, natural selection acts directly on an organism's phenotype and only indirectly on its genotype (Brandon, 1990; Hull, 2001). Because selection tends to operate at or above the organismic level, it only "sees" the functional phenotype, and thus it is insensitive to the genetic substrate from which that function is realized. It stands to reason that HGV is important for adaptive purposes only insofar as it has, or will at some future time have, a tangible effect on the phenotype.

Because the EHA is typically couched in terms of genetic rather than phenotypic variables, the first thing we need to do is to consider the relationship between genotypic and phenotypic diversity. Philosophers tend to focus on HGV because they assume that phenotypic variation maps neatly onto genotypic variation. But in doing so, they succumb to the "gene-for" fallacy or the idea that each gene codes for a single trait and (conversely) that each trait arises from the operation of a single gene. The landscape of the genotype-phenotype map is actually far more complex, for several reasons.

The first is *phenotypic plasticity*. The phenotype is a product of the genotype and its interaction with the grab bag category we refer to as the "environment." Because many phenotypic traits are highly plastic, they will develop disparately in dissimilar environments despite their underlying

genetic identity. A single genotype can produce an array of phenotypes, each varying in accordance with the environmental context in which it unfolds (Via et al., 1995). The result is phenotypic diversity without a corresponding level of genotypic diversity. For example, consider the pupae of eusocial insects (such as ants, bees, and wasps). These undifferentiated larvae kin, despite their high genetic similarity, can develop into members of the worker, soldier, or queen castes depending on the temperature, nutrition levels, and other environmental factors in which they are reared. The upshot is that high levels of phenotypic diversity can be maintained in a population without correspondingly high levels of genetic diversity.

The second is *multiple realizability*. Not only are we unable to infer much about genotypic diversity on the basis of phenotypic diversity alone, but the reverse also holds true. Many phenotypes are multiply realizable in that they supervene on a range of underlying genotypes. Natural selection will treat all variants equally so long as they have the same effect on the phenotype. Consequently, phenotypic uniformity can overlay substantial amounts of genetic diversity.

The third is *pleiotropy*. This one-to-many relationship, effectively the inverse of multiple realizability, describes the situation where a single gene produces a wide range of functionally unrelated phenotypes. Pleiotropy is different from phenotypic plasticity in that the resultant trait diversity is due not to environmental heterogeneity but rather to compound gene function. But like phenotypic plasticity, pleiotropy allows phenotypic diversity to supervene on genetic homogeneity.

The fourth is *nonlinearity*. Because of the complex causal dynamics of the genotype-phenotype map, changes in genetic sequence will rarely have a linear or proportionate effect on the phenotype. In some instances, small genetic perturbations can have enormous ontogenetic consequences. For instance, mutations that occur early in ontogeny (i.e., "upstream" in the developmental cascade) can be amplified in the unfolding of the organism (Carroll, 2005; Davison and Erwin, 2006). In other cases, large genetic disturbances can be of minor phenotypic significance. Some functions are so well buffered against developmental noise and genetic error that even large perturbations do not affect the resulting phenotype; in addition, large portions of the genome are nonfunctional and thus can be modified without altering organismic development.

Each of these phenomena is discussed in greater detail below. For now, what matters is that because of the nonsymmetrical mapping of traits onto the genome, phenotypic diversity cannot be reliably inferred from genetic diversity, and vice versa. Failing to causally connect up HGV with phenotypic diversity, and the latter with natural selection, is one of the major oversights of the EHA. Another is that it lumps all types of genetic variation under a single generic heading. This conflation poses a problem for several reasons. First, nuclear DNA is only one type of genetic material that is

transmitted into the next generation. The subcellular organelles, such as the mitochondria, possess their own genetic code as a relic of their free-living prokaryote days. It is unclear how this type of DNA would bear on any of the phenotypic traits that the critics of genetic engineering are worried about.

But simply excluding the genes of organelles does not solve the conflation problem. This is because the nuclear genome itself is not a homogeneous reference class for the purposes of evolution by natural selection. The category of nuclear DNA can be further broken down into two different types of genetic diversity. The first is *neutral genetic variation*, which refers to genotypes that have no bearing on fitness, and the second is *adaptive genetic variation*, which describes genes that are actively under selection (Kimura, 1983). Given that this distinction is rarely acknowledged outside of the biological literature (Holderegger, Kamm, and Gugerli, 2006), it is not surprising that it is entirely absent from philosophical discussions of the evolutionary implications of GET.

In diploid organisms, or those containing two homologous copies of each chromosome, three different genotypes can occur at a given locus (e.g., aa, ab, bb). If the locus is nonadaptive (i.e., neutral), then it does not matter for the purposes of selection which of these genotypes is present, and the locus will accumulate mutations stochastically. If the locus is under selection, however, then it does matter which variant is present, and selection will eliminate the relatively less fit ones thereby reducing genetic diversity at that locus. The fact that selection tends to *reduce* variation poses an ostensible paradox for Darwinian theory since descent with modification requires a steady stream of variation to draw upon in response to changing environmental conditions. There is still much controversy as to the mechanisms that maintain genetic diversity in natural populations. Research over the last few decades, however, points to neutral variation as a critical ingredient in, and genetic drift as a central mechanism of, biological variation. This may sound counterintuitive, for although random drift (i.e., sampling error) tends to increase variation between populations, it is generally thought to decrease variation within them by bringing certain variants to fixation.[2] But in portions of the genome that have no effect on fitness, diversity can accumulate at a steady rate over time, thanks to mutation, drift, and other stochastic forces that go "under the radar" of natural selection. These nonadaptive genetic sequences have been given the (misleading) sobriquet "junk DNA" and appear to constitute the vast bulk of protein variation (Reich et al., 2002; Nozawa, Kawahara, and Nei, 2007). When we choose any two people at random from the entire human population, we find that 99.9% of their DNA is identical. Of that one-tenth of 1% of remaining variation, a large proportion (~70%) is effectively neutral. To put it crudely, the majority of HGV is junk.

In contrast to junk DNA, which has only captured researchers' attention in the last few decades, adaptive genetic variation has been the focal point of evolutionary thought since its inception. In practice, however, adaptive genes are more difficult to identify than their neutral counterparts. This is because adaptive variation is inferred from patterns of complex traits, most of which are produced by nonlinear interactions of gene networks. These complex developmental dynamics make it extremely difficult to infer levels of adaptive genetic variation from observed phenotypic diversity (Conner and Hartl, 2004). Were adaptive and neutral variation correlated, this would provide a tractable means for measuring the former. But no such correlation has been revealed, and thus junk DNA cannot be used as a proxy for adaptive diversity.

Selection will tend to purge less fit variants from the gene pool, whereas neutral sequences will accumulate mutations steadily over evolutionary time. In fact, it is the absence of expected variation that is the most reliable indicator that a gene or trait is under selection. It follows (somewhat counterintuitively) that change, not stasis, is the null expectation in biology. Unlike Newtonian physical systems, which when at rest tend to stay at rest unless acted upon by an external force, biological systems have a tendency to change (i.e., drift) unless acted upon by an evolutionary force, such as natural selection (Brandon, 2006). It follows that biological diversity should not be viewed as a goal to be achieved or a state to be actively maintained but rather as an inherent disposition of replicating systems. GET may act to reduce genetic variation and thereby offset the propensity to drift, but in this respect it is no different than natural selection.

III. WILL GET REDUCE HUMAN BIOLOGICAL DIVERSITY?

Having sketched out the landscape of biological variation, we are now in a position to consider the likely impact of GET on human genetic diversity. As noted in the previous section, one of the major shortcomings of the EHA is that it focuses on genetic variation per se rather than partitioning this class into the causally differentiated categories of neutral and adaptive variation. This conflation is more than a simple oversight—it amounts to a fundamental flaw in the EHA, for several reasons.

First, although the EHA touts the value of diversity, it is abundantly clear that not all biological variations are desirable. This may seem obvious, given that the very business of natural selection is to weed out unfavorable variants from the population. But the idea goes deeper than this. Beyond a certain age, humans will contribute little to the gene pool of the next generation, and thus (with some rare and controversial exceptions) natural selection will tend to ignore the post-reproductive period of life. Consequently, as the human organism ages, it invests less and less in the physiological repair

mechanisms that would otherwise eliminate harmful genetic variation. Like a neglected house left to fall into disrepair, the body begins to accumulate genetic and ontogenetic variation, leading to disease and eventually death. Surely, we do not desire the kind of genetic variation that leads to functional disintegration, such as that wrought by cancerous cell lines, neural degeneration, or recessive diseases. Thus, to make its case, the EHA must zero-in on the beneficial subset of variation, while excluding the diversity associated with conditions that we would treat as pathology.

Second, because the vast majority of HGV is neutral, and since biological systems will continue to accumulate variation in the absence of selection, it is unlikely that GET (targeting phenotypes like eye color or attention span) will have a significant effect on the overall level of genomic diversity. Recall that in biology, diversity arises "for free" in systems that are not under selection. For obvious reasons, GET will be geared toward engineering traits that make a difference to consumers of the technology. It will not waste time modifying unexpressed genetic sequences that have no palpable effect on the architecture or function of the organism. For this reason, GET will leave the lion's share of genetic diversity intact.

But even if we remove junk DNA from the equation and focus only on adaptive variation, it is unlikely that GET would have a greater homogenizing effect than ordinary background selection. Although adaptive variation comprises a smaller fraction of the genome than junk DNA, at any given moment the number of genes that are under selection is vast. Even if we did manage to homogenize a subset of adaptive variation, the impact on overall functional diversity would be negligible. Those who think otherwise tend to overestimate the degree of genetic homogeneity that can be inferred from casually observed phenotypic traits. As studies in the biology of race have shown, the variation *within* putative racial groups is greater than the variation *between* them (Cavalli-Sforza, 1994). Everyone in a society could look like either Ken or Barbie, and yet their underlying genetic diversity could rival that of any two randomly selected people on earth. The set of traits that human beings tend to notice is but a tiny fraction of existing phenotypic variation.

Third, even if we assume that GET will lead to uniformity in a wide range of *phenotypes*, this need not entail a corresponding uniformity in their underlying *genotypes*. As we saw in the previous section, the same phenotype can be produced from disparate genetic substrates, given the many-to-one and one-to-many dynamics of the genotype-phenotype map. This is especially true for complex traits, the prime targets of GET, which rarely correlate with and only with a specific subset of the genome (Nijhout, 2003). The implication is two-fold: first, the targeting of a particular phenotype by GET need not result in the homogeneity of its underlying genotypic generators, and second, the targeting of a particular genotype need not increase the uniformity of its protein product (given *epistasis* or the interaction between

regulatory networks in relation to their effect on the phenotype). For example, we can increase phenotypic variance in the domestic dog population, producing an astounding array of forms from the Chihuahua to the Newfoundland, while at the same time decreasing total genetic diversity.

Fourth, even if GET did produce temporary pockets of genetic uniformity, whether they would be maintained is highly contingent on human population structure and the extent of gene flow between natural populations. Revolutions in transport and information technology have led to unprecedented levels of global exchange, not only in relation to goods and services but also with respect to genes as well. With the exception of the occasional uncontacted Amazon tribe discovered accidentally by loggers, there are few behaviorally or geographically isolated human populations. As a result, any homogenization due to GET will likely be dampened and ultimately swamped out by invading variants. This scenario is particularly compelling, given that access to and usage of GET will be far from uniform, allowing localized pockets of homogeneity to be easily reabsorbed into the genetic mainstream.

Finally, even if GET did bring certain genotypes to fixation, causing the extinction of competing alleles and hence a reduction in overall genetic diversity, this would not be irreversible. In the wild, extinction represents a true absorbing boundary, particularly in the case of complex functional pathways whose iterated independent origin is extremely improbable. By contrast, human-initiated gene banks (akin to the Global Seed Vault that recently debuted in Norway) can be maintained, and from which genes can be retrieved, long after their extinction in the wild. Extinct genotypes can be "resurrected" (as it were) in order to introduce favorable variants into the population or control for levels of genetic diversity. In conjunction with other reproductive technologies, such as nuclear transfer cloning, GET could be used to facilitate the rapid redeployment of genes (Buchanan, 2008).

The factors I have been discussing thus far are all biological. But whether GET is likely to increase or decrease human biological variation, and the extent to which it will do so, turns not only on biological facts but also on the psychological, social, and political framework in which the technology is used. Broadly speaking, the impact of GET will depend on the nature of the genetic technology at issue, its demographic penetrance, the extent of individual/cultural convergence in application, and the existence of regulatory regimes that constrain its proliferation or use.

Let us begin by distinguishing cloning, or the crude duplication of an existing genome, from GET, which involves the precise manipulation of existing genes. In terms of its effect on levels of HGV, the pervasive cloning of a small number of individuals lies on one extreme end of the homogeneity spectrum. But even in this most extreme and unlikely scenario, it is perfectly possible to limit cloning to the *functional* components of the genome, while allowing for background diversity in neutral DNA. In this way, even the

widespread cloning of a small subset of individuals could preserve a substantial proportion of existing HGV. It could turn out, of course, that the evolutionary value of nonfunctional DNA is negligible (a proposition that I contest in the final section), but the point is that one need not clone the entire genotype in order to reproduce the same phenotype. On the other hand, if cloning technology was both accessible to and utilized by a wide range of persons, then the reductions in HGV would be far less severe. The higher the penetrance of cloning technology, the less impact it would have on human biological diversity. For instance, if every living human cloned himself/herself only once at time *T*, then the resulting genetic pool would be no more or less diverse at time $T + 1$ and presumably no more or less susceptible to risks associated with homogeneity than the human population at T.

Nevertheless, most authors assume that access to sophisticated reproductive technology will, at least initially, be limited to the wealthy, thus skewing the gene pool in favor of the upper echelons of society. This is the crux of the skeptic concern—namely, the mass production of a small number of genetic types. But it fails to take into account the strong negative correlation between income level and expected reproductive fitness. Despite their superior resources, richer people tend to have fewer children than those of the less privileged classes. This forces the EHA to overcome a double difficulty: if cloning is (for economic reasons) restricted to the privileged few, then it will be confined to an elite demographic with far lower rates of reproduction than the rest of humanity; if, on the other hand, cloning is ultimately accessible and widespread, achieving a degree of penetrance on the order of cellular phones, then its effect on HGV would be minimal since there would be relative parity in its use across disparate demographics. A final possibility is that cloning could be administered in combination with GET to increase the diversity of the resulting offspring (Strong, 2005).

Although these questions are interesting, the focus of this paper is on GET and not cloning largely because the potential gains from precision manipulation dwarf those associated with the crude duplication of naturally existing genomes. The notion that GET will reduce HGV turns on another critical (and highly dubitable) sociological premise: namely, that individuals presented with the opportunity to engineer their own offspring will tend to choose the *same or a similar set of interventions*. Some fear that this collective convergence will lead to a brave new world of blonde-haired, blue-eyed, and unhealthily proportioned people. The trouble with this idea, of course, is that it assumes that there is a common conception of the good, when it is absurd to think that there is anything approaching consensus on the value and content of complex human dispositions (such as aesthetic taste, sexual attractiveness, or moral virtue). Although there are certain organizing principles that are stable across cultures (such as morphological symmetry), they represent atolls amidst a sea of different strokes for different

folks. Even if there is widespread access to GET, disparate economic, religious, moral, political, and other cultural preferences will prevent the fixation of a small subset of phenotypes. In fact, by enabling people to act on these divergent preferences, GET could actually increase human biological diversity, allowing for new (and otherwise inaccessible) combinations of desired characteristics.[3]

Another reason to doubt that individuals and cultures will converge on a common use of GET is that the "garden variety" is not always the best way to guarantee mating success. Although there is some evidence that people are attracted to traits whose values fall close to the arithmetic mean, conformity to the morphological or behavioral status quo can also have negative reproductive consequences. A wide range of animals show an affinity for rare phenotypes in their mating decisions, a curious fact that forms the basis of an evolutionary hypothesis called "rare male advantage," a type of *sexual selection*. The latter refers to differential survival and reproduction due to mate preference, which can be a powerful evolutionary force particularly in species with reduced predation pressures (such as birds and humans). Although the selection for or against a trait usually does not depend on the distribution of similar traits in the population, in *negative frequency-dependent* selection, the selective advantage of a variant is inversely proportional to its frequency. In the case of negative frequency-dependent sexual selection, this advantage is due to female mate preference for rare or minority males (Singh and Sisodia, 2000).[4] The result is a "balancing" selection regime that maintains high levels of polymorphism in the population. Interestingly, most of the traits that are candidates for genetic enhancement are either directly or indirectly implicated in mate selection. This is not surprising, given the extraordinary ontogenetic burdens people endure in order to increase their appeal to the opposite sex or to advance their standing among members of the same sex.

In sum, whether GET will reduce genetic diversity depends on the type of variation in question. Because the bulk of HGV is neutral, it will remain unaffected by GET, steadily accumulating variation in the absence of selection. Only the tiny fraction of functional DNA that actually matters to consumers would be subject to modification. And even if the same traits were singled out for modification, their character states would not be uniformly chosen, given that different cultures, and individuals within cultures, do not share a singular conception of the good. Finally, sexual balancing selection, global gene exchange, and human-maintained gene banks can prevent the few homogenized traits from becoming irrevocably fixed in population. For all these reasons, it is unlikely that GET would reduce human genetic diversity to any significant extent, especially if reproductive decisions are reserved to the individual in the private sphere rather than mandated from the top-down by coercive political institutions.

Nevertheless, some authors contend that even small declines in HGV could have grave evolutionary consequences (Lederberg, 1966; Suzuki and Knudtson, 1990). This seems reasonable enough. The central issue should not be whether there is a *net* change in HGV since an average increase in total human diversity is consistent with there being highly homogenous subpopulations that incur evolutionary costs. For the remainder of this paper, therefore, I will simply assume arguendo that GET will lead to substantial reductions in HGV, either locally, globally, or both. The question I want to address is whether this lack of biological diversity would, as some bioethicists claim, (a) increase our susceptibility to disease or (b) impair the adaptive flexibility of our species. I will show that neither scenario is plausible, let alone ineluctable.

IV. WILL GET INCREASE OUR SUSCEPTIBILITY TO DISEASE?

Skeptics frequently invoke agricultural disasters in issuing bleak prognoses about the potential evolutionary consequences of genetic engineering. If the widespread cloning of potato varieties or grape vines (discussed in Section I) could result in ecological catastrophe, why should the same lessons not apply equally to human beings? To understand why GET is unlikely to increase the susceptibility of human populations to disease, we must delve deeper into the mechanisms of biological variation and its relationship to pathogen resistance.

In sexual organisms, the two major sources of genetic variation are mutation and recombination. Although the sexual combination of genomes (referred to as "outcrossing") can generate a perpetual stream of selectable variation, doing so runs the risk of producing deleterious variants and breaking down salutary gene combinations that would otherwise go to fixation under selection. The risk was apparently worth it, however, at least for complex multicellular animals virtually all of which combine genomes instead of reproducing asexually. The ubiquity of sex presents an evolutionary paradox: why would organisms rest content with getting only half of their genes into the next generation, when asexually they could pass on *all* of them? To put it slightly differently, why should animals invest so much time, energy, and risk in mate search and copulation, only to relinquish 50% of their genome? Selection would not have countenanced such a massive cost to fitness were it not offset by some greater gain.[5]

Although the origin of sex is controversial, there are two widely received and mutually nonexclusive explanations. The first is that sex evolved to repair DNA damage from X-rays, UV light, and coding errors that could be detrimental to the phenotype (Michod and Long, 1995). During the crossing-over phase of meiosis, the chromosomes align, enabling the repair of damaged portions of the genome by copying the "correct" opposing sequences.

The second explanation of sex, and the one more pertinent to the present discussion, is that recombination evolved as a means of conferring resistance to pathogens or parasites (Hamilton, Axelrod, and Tanese, 1990). This explanation is premised on a "matching-alleles" model of infection genetics (Agrawal and Lively, 2002), according to which an exact genetic match is required for infection (in contrast to "universal virulence" models, wherein a pathogen can infect all host genotypes). The strategic evolutionary interaction between host and parasite leads to the so-called "Red Queen" effect, according to which coevolving lineages must constantly evolve in order to maintain their present fitness levels (Van Valen, 1973; Ridley, 2003). Anti-parasite adaptations are bound for obsolescence, particularly given the short life cycle of parasites that gives them an evolutionary rate advantage over their relatively long-lived hosts.[6]

It is widely accepted that genetic diversity is an important factor in protecting populations from infectious agents (Coltman et al., 1999; Meagher, 1999; Altizer, Harvell, and Friedle, 2003; Spielman et al., 2004). In the wild, inbreeding, founder effects, and habitat fragmentation can all serve to decrease gene flow between natural populations. In the context of GET, however, the fear is that pervasive genetic modification will lead to biological uniformity, rendering human populations more susceptible to pathogens. But a closer examination will reveal that it is not genetic diversity per se, but rather a *particular sort* of genetic diversity, which bears on host-parasite dynamics. The upshot is that only a minute fraction of potential genetic interventions could impact on disease resistance, and even these not incurably so.

Most studies investigating the role of variability in disease resistance have used neutral genetic markers as the metric for populational diversity. However, variability in neutral loci is only an indirect measure of the correlation between diversity and disease resistance since it essentially serves as a proxy for variation in functionally important sequences, such as those that comprise the major histocompatibility complex (MHC). The MHC is a group of closely linked genes in the mammalian genome responsible for immune recognition, and it is a major determinant of susceptibility to infectious and autoimmune disease. The MHC produces molecules that bind to the antigens of intra/extracellular pathogens, presenting them for appropriate T-lymphocyte response.[7] In the course of coevolution, pathogens develop novel forms of antigenicity to evade host immune recognition, and hosts, in turn, evolve new combinations of MHC genes in order to identify and destroy the immune-dodging pathogens.

Given its essential role in immune response, it should come as no surprise that the MHC cluster is the most diverse of its kind in the vertebrate clade (Robinson et al., 2003). Host organisms with more MHC alleles and allelic combinations can recognize a wider range of pathogen-derived antigens, reducing the incidence and intensity of parasitic infection (Alberts and

Ober, 1993; Kurtz, 2003). In contrast, variability in junk DNA alone (without a corresponding diversity in functional material) is not associated with pathogen resistance (Holderegger, Kamm, and Gugerli, 2006; Schwensow et al., 2007).

Therefore, it is not genetic variation per se, but rather *adaptive* genetic variation, which confers disease resistance on a population. To be even more precise, it is not adaptive variation per se, but *immunorelevant* adaptive variation, which underwrites host resistance to pathogens. A more targeted approach to GET and cloning—one aimed at maintaining the right sort of genetic diversity—could substantially reduce the risk of infectious disease. Therefore, even if we assume that GET would narrow the range of HGV, we can significantly reduce the chances of an epidemic by deliberately preserving high levels of polymorphism in the immunorelevant sections of the genome.

Finally, maintaining a large pool of naturally existing genetic variation may not even be a crucial asset in disease prevention and control. In contrast to other animals, and to those unfortunate individuals living prior to the germ theory of disease, contemporary human society need not sit idly by as its population are ravaged by a virulent epidemic. Unlike medieval Europeans, we are not forced to wait patiently until favorable variants have spread throughout the population and herd immunity is achieved. To rely on HGV to see us through the coming plague would be not only epidemiologically absurd but also morally tragic. Ancestral human populations had to sustain enormous death tolls from small pox and bubonic plague in order to attain pathogen resistance. The most effective way of curtailing, containing, and ultimately eliminating an outbreak, however, is through a rapid *environmental-behavioral* response, not by waiting for the gradual process of Darwinian evolution to run its course (a process that can take hundreds, thousands, or even millions of years, depending on mutation rates, population structure, selection pressures, and the type of the adaptation in question). Canonical methods of disease control include a speedy assessment of the threat, public education on ways to prevent transmission, the provision of clean water, food, and sanitized shelter, the disinfection and proper disposal of waste products, vector control, timely burials, hand washing, quarantine, and mass vaccination (Connolly, 2005).

Add to these "low-tech" containment practices the molecular power of GET, and you have an extraordinarily capable defense against infectious disease. Unlike prophylactic measures that rely solely on environmental modulation, GET enables us to identify and synthesize the chemical functions of resistant genotypes and to produce and distribute vaccines in the prevention and treatment of epidemics. Collectively, these methods are far more effective than natural selection in controlling an outbreak, and none are contingent on the range of HGV. Most importantly, they allow us to avoid the myriad unnecessary deaths that would inevitably occur along the winding and treacherous road to a Darwinian solution. Genetic diversity can conquer virtually any epidemic, but its victory will always be a pyrrhic one.

Although the *phylogenetic solution* is nasty, brutish, and long, the eminent flexibility of human cognition and behavior offers an *ontogenetic solution* that cannot only realize the same ends that natural selection is capable of achieving, but it can do so much more quickly, reliably, and with far less human carnage. GET can introduce favorable variants "laterally" (outside of reproduction), offering a powerful mode of genetic transmission that is otherwise inaccessible to complex organisms (Powell and Buchanan, forthcoming). In this way, GET can combine and integrate variation from different human lineages, as well as genes found in other species and even those synthesized in the laboratory.

Another advantage of GET relates to human intentionality. When biologists say that variation is "random," they do not mean that mutation is equally likely in all directions but rather that it is statistically unrelated to adaptation. The EHA presupposes, however, that variation is blind not only to natural selection (which it is) but also to intentional beings like ourselves (which it is not). It assumes that humans are in no better position than Mother Nature to determine which variants are fit or will be fit in the future. Despite its muddled ontology, there is little doubt that intentionality injects a forward-looking element into the evolutionary process that the "blind watchmaker" will never benefit from.

The argument in this section may be summed up as follows. Even if genetic engineering reduced the range of adaptive HGV (a prospect that I find unlikely for the reasons offered in Section III), there is no reason to believe that doing so would necessarily affect levels of immunorelevant variation. Because only the latter type of genetic variation affects pathogen resistance, a carefully monitored GET regime can substantially reduce the risks of human biological monoculture. At any rate, cultural-behavioral response is a far more efficacious and morally acceptable way of dealing with an outbreak than waiting for natural selection to run its deadly course. By combining GET with established methods of disease control, we can overcome many of the physiological and moral obstacles that confront the natural origination, spread, and fixation of disease-resistant variation.

V. WILL GET IMPAIR THE EVOLVABILITY OF OUR SPECIES?

Even if a decrease in HGV will not render us more susceptible to disease, it is still possible that a shrinking sphere of genetic diversity could ultimately diminish the evolvability, or adaptive potential, of the human species (Suzuki and Knudtson, 1989). One fear is that GET could position *Homo sapiens* in such precise congruity with the environment that it becomes a hyper-specialist species, unable to roll with the punches as they are thrown in the ordinary (and extraordinary) course of evolution. Another worry is that GET will operate on shortsighted motivations and flawed scientific beliefs, resulting

in the elimination of potentially favorable variation. In order to evaluate these claims, we must examine the relationship between biological diversity and evolvability.

One of the central questions of macroevolution concerns the differential survival and reproduction of taxa across deep evolutionary time. Why do some groups persist for hundreds of millions of years, whereas others go extinct almost as quickly as they appeared? Although there is no uncontroversial answer to this question, it is becoming increasingly clear that the notion of *evolvability* will be integral to any complete explanatory picture of macroevolution. Although its precise definition is contested, in the most basic sense evolvability relates to adaptive potential or the tendency of mutations to increase the fitness of a lineage. Generally speaking, the more variation that selection has to work with, the more creative it can be in navigating the adaptive landscape (Wagner and Altenberg, 1996); this in turn increases the chances that the lineage will conduct a successful evolutionary "search" and catch the gradient of a superior fitness peak.[8] In one sense, host-parasite coevolution is a subset of evolvability since it entails that the host respond to new adaptive challenges initiated by the parasite, and vice versa, in perpetuity. But above and beyond facilitating strategic maneuvers in a local evolutionary arms race, evolvability-conferring traits can, in Dawkins' words, act as "evolutionary watersheds" that open the "floodgates to future evolution" (Dawkins, 1989, 218).

Evolvability is affected not only by the existing range of variation but also by how that variation is causally distributed. The more interdependencies there are between functional developmental systems, the more likely it is that mutations will damage the phenotype and the less wiggle room there is for viable phenotypic variation. For this reason, evolvability depends in large part on various deconstraining mechanisms that reduce the number of links between organismic processes (Raff, 1996), preventing small genetic changes from having a catastrophic effect on the phenotype.[9]

Developmental robustness not only affords the phenotype with an ontogenetic margin of safety but also allows for the accumulation of hidden but potentially useful variation (Wagner, 2003), which can subsequently be co-opted in the service of a new functional task (Kirschner and Gerhart, 1998). The larger and more diverse this cache of genetic potential, the greater the adaptability of a lineage (Schlichting 2008; Gibson and Dworkin 2004). Stephen Jay Gould (2002) referred to this stock of evolutionary potential as the "exaptive pool" (1277). The exaptive pool is composed of three types of variation: (1) neutral variation that has accumulated in buffered/redundant developmental networks, (2) adaptive variation, or genes that are currently under selection but whose function can be diverted in the service of a new task, and (3) spandrels, or the nonadaptive by-products of adaptive variation. Together, these provide the necessary raw materials for future evolutionary change (Chipman, 2001).

Of these three types of variation, neutral genetic evolution is arguably the most important factor in evolvability, for several reasons. First, as discussed above, neutral sequences make up an enormous fraction of the total gene pool. Second, genotypes that code for important functions are typically bound up with the phenotype and thus effectively off-limits to directional selection (gene duplication scenarios may be an exception). It is precisely because of their nonfunctionality that neutral portions of the genome are more amenable to selective co-optation. Third, neutral evolution allows natural selection to explore a much wider range of phenotypic search space, preventing a lineage from becoming ensnared in a local optimum. By drifting around the adaptive landscape and away from its local pedestal, a lineage increases its chances of stumbling upon the gradient of a superior fitness peak (Ebner, Shackleton, and Shipman, 2002).

The fact that junk DNA is a vital component of the exaptive pool has important implications for the present discussion. Because consumer capital and (hence) engineering effort will not be expended in order to modify genomic sequences that have no tangible effect on the phenotype, this vast source of co-optable diversity will remain unaltered by GET. In fact, by modifying genes that mediate developmental correction mechanisms, GET could be used to significantly *increase* the levels of neutral variation and hence the evolutionary flexibility of a lineage.

Most important of all, evolvability and the co-optable HGV on which it depends may be a less important factor in the survival of our species than other sources of diversity, such as phenotypic plasticity. In contrast to evolvability, *phenotypic plasticity* is the property of an organism, not a lineage; it refers to the ability of a single genotype to generate an array of phenotypes (including behaviors). Humans are not among the most *morphologically* variable species—compare, for example, the average human family with that of the social insect colony, which features a caste-based system of soldiers, workers, and queens. Nor do we occupy a particularly arborescent branch of the tree of life—indeed our lineage is maximally depauperate, as we are the only remaining species of our genus. We do, however, boast the most robust cognitive and behavioral repertoire in the history of life. We are symbol manipulators, cultural transmitters, and niche constructors par excellence. We deliberately and radically transform our selective environment, and we transmit those changes "vertically" (to offspring), "horizontally" (to conspecifics in the same generation), and "obliquely" (to unrelated offspring of subsequent generations) (Boyd and Richerson, 1985). In this way, phenotypic plasticity buffers the species against environmental fluctuations, obviating or at least significantly diminishing the evolutionary "need" for HGV.

Even more fundamentally, we must be careful not to equate either survivability or evolvability with the good, or for that matter, with each other. The fact that GET could reduce the longevity of the species is not an irrefragable or even peremptory reason for rejecting it (Powell and Buchanan, forthcoming).

Everyone who travels in an automobile, plays a sport, or eats a cheeseburger recognizes that life is not simply about maximizing one's life span. Likewise, the costs associated with phylogenetic persistence may be outweighed by the gains to be had over a shorter but more agreeable span of time.

But even if we assume that the survival of the human species is an absolute moral goal, it still does not follow that evolvability is a desirable characteristic. This is because the concept of evolvability is different from, and perhaps even antipodal to, the notion of survivability. The latter refers to the tendency to persist, whereas the former entails the disposition to change. These two tendencies can run in tandem, but they can also come into conflict. The ability to persist may require some flexibility for future change, but there is a point at which the requisite change is so overwhelming that it may be said to negate persistence. At what moment this happens I cannot say; but there is no shame in this confession, as neither have philosophers in thousands of years been able to agree on when the famous ship of Theseus, remodeled plank by plank over Athenian generations, ceases to be the same ship. The only point I wish to make is that the disposition to evolve can in some circumstances entail the disposition to go extinct.

To understand how this could be so, one must recognize that "extinction" in macroevolutionary terms is very different from that term as it is used in the more colloquial sense or for purposes of moral consideration. When most people are asked to think of a "species," they will tend to conjure the *biological* version of the concept (due to Mayr, 1942), which defines a species as the most inclusive set of (potentially) interbreeding organisms. However, many evolutionary biologists have rejected the notion that species are (or *only are*) sets of organisms with shared characteristics, in favor of a *phylogenetic species concept* that conceives of species as individuals and groups them according to common ancestry (Hull, 1987). On this view, the same phylogenetic species at time T may be phenotypically distinct (or even wholly unrecognizable) at time $T \pm 1$ since a shared ancestry does not imply a shared set of characteristics. The upshot is this: that the human species persists in macroevolutionary terms does not imply the survival of any of the attributes that we associate with "human nature" or that we otherwise deem worthy of preservation. And likewise, that the human species goes extinct in the biological sense does not entail the annihilation of those characteristics we value in ourselves. Would we consider evolvability a desirable thing if it meant a future without beings that we could even loosely call human? In an interesting twist, consider that GET could actually be used to buffer the human species *against* its tendency to evolve, preserving the valued attributes of human nature.

If the preceding analysis is correct, then GET does not pose an unavoidable or even colorable risk to the immediate health or long-term survival

of the human species. To the contrary, we should protect GET much as our early ancestors' cradled fire—for it may be the key to our survival in a hostile world. I do not expect (nor do I desire) that the skeptical reader stop worrying and love GET—but I do hope that together we have the courage to think clearly about the risks and benefits of this awesome technology.

NOTES

1. It is important to note that variation is not the same thing as *variance*, which refers to the distribution of variation around a mean. One population might have a large amount of variation tightly clustered around the mean, whereas another might have a smaller amount with a wider distribution in variation space. It could turn out that the range of existing variation, sometimes called *disparity*, is a more significant factor in disease resistance and evolutionary flexibility than the sheer volume of diversity itself.

2. Not all traits that evolve are adaptations. Many are the product of random drift or cross-generational sampling error (i.e., deviation from expected frequency) that is unrelated to relative adaptedness. Both selection and drift are sampling processes, but selection is sensitive to the relative fitness of the sampled lineages, whereas drift is not. Although both selection- and drift-based theories can predict changes in gene frequencies over evolutionary time, they differ in that the former allows for predictions regarding the direction as well as the rate of change, whereas the latter is directionless (although it entails a measurable rate). On the conceptual and methodological distinction between selection and drift, see Brandon (2005).

3. These ideas emerged from series of fruitful discussions with Allen Buchanan.

4. Frequency-dependent survival and mate advantage have been observed in guppy populations in which rare color morphs and patterns apparently confer a fitness advantage. Whereas ordinary selection favors duller and more cryptic color patterning (which helps to avoid detection by predators), sexual and negative frequency-dependent selection favor more conspicuous and rare variants, respectively, thereby maintaining high levels of diversity within the population. For a review of this phenomenon, see Nosil (2006). A hypothetical example of rare male advantage in humans is a scenario in which blue-eyed males are relatively more successful than brown-eyed males at securing mates when the former trait is rare but less so when the trait is common. Likewise, under negative assortative mating regimes, individuals tend to mate with conspecifics that are unlike themselves in relation to some phenotypic characteristic (such as height in humans). Both frequency-dependent mating and assortative mating can act to maintain biodiversity and heterozygosity in a population.

5. The mystery of sex surrounds not only its origins but also its maintenance. For reasons that are largely unknown, unisexual vertebrate lineages are rare and evolutionarily short-lived in the wild, despite the accessibility of parthenogenesis-conferring mutations (Adams et al. 2003).

6. To avoid a potential cross-disciplinary confusion, note that the terms "parasite" and "parasitism" are defined *functionally* in evolutionary biology, where they refer to a physically intimate and fitness-asymmetrical relationship between two species, and thus include organisms ranging from bacteria to the cuckoo. By contrast, in medicine and public health (including the field of "parasitology"), the term refers exclusively to *eukaryotic* parasites and excludes viruses and bacteria.

7. Initially, MHC protein polymorphism may have arisen in single-celled eukaryotes in order to maintain cell membrane diversity, which can obstruct viral "grafting," or the passing of viral material from one host cell membrane to another (Forsdyke, 1991).

8. The "adaptive landscape," introduced by Sewall Wright in the 1930s, is a topographic representation of the function between possible genotype/phenotypes and their fitness values. The fitness landscape is composed of fitness peaks and valleys, and populations will tend to climb the nearest peak. The assumption is that if selection (and only selection) is operating on a population, mean fitness will not decrease.

9. These mechanisms include (inter alia) modularity, canalization, buffering, gene duplication, and functional redundancy, all of which increase the robustness of the phenotype against microenvironmental perturbations, such as mutations or developmental noise (Wagner and Schwenk, 2000).

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