COMMENT

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GENE EDITING IN SEARCH OF AN ETHIC

UNDERSTANDING THE RELATION BETWEEN THE GENOME AND THE PERSON

In the rarest of coincidences, shortly after the death of baby Charlie Gard, due to mitochondrial DNA depletion syndrome, came the news of the success of gene editing of single cell human embryos to correct a mutation which causes hypertrophic cardiomyopathy. While this success remains at the experimental stage, with much more to be done before gene editing is ready for clinical application, it is reasonable to consider what if it were possible through gene editing that no baby, including Charlie Gard, might ever suffer what he did. It is this consideration which lies at the centre of an ethics justification of gene editing. What follows will attempt to demonstrate that gene editing may fulfil the fundamental positive injunction – one ought to do what is morally good.

The news of the gene editing success brought with it a flurry of commentary, including that of ethicists. In contrast with the science commentary which has been quite detailed, the ethics commentary has been fragmented and at times ill-informed about the science involved in gene editing. Noticeably absent has been a coherent framework from within which to understand what ethics does to contribute dispositively to the scientific, policy, and public discussion of gene editing. Not surprisingly, members of the scientific, medical community, as well as members of the general public, must come away wondering what to make of ethics.

Put simply, ethics is designed to answer the question, "what ought I to do?"[1] And while it is not to be confused with the question, "what can I do?" it is when we have the ability to do something that it becomes imperative to consider whether we ought to, especially where there are consequences affecting others. Ethics then is a rational analysis based on principle of other-regarding human behaviour, which presumably includes gene editing as human behaviour with substantial consequences for others. The analysis can be conducted retrospectively, as it will be in this case since the editing has already occurred, or prospectively with, in case of gene editing, what further will be undertaken, including clinical applications, if any.

"WHAT WE CAN SAY FROM AN ETHICS PERSPECTIVE AT THIS POINT IS THAT THE RESEARCH IS BEGINNING TO MEET THE NECESSARY ETHICS CONDITION, SCIENTIFIC VALIDITY, TO JUSTIFY GENE EDITING GENERALLY AND THE USE OF CRISPR IN PARTICULAR."

What then is meant when we say, "I ought, ought not to do this or that"? It comes directly from the basic principle of normative human behaviour, that is human beings "behaving as human beings ought to behave,"[2] or as Cicero[3] put it, behaving according to right reason in conformity with nature, with reason listening to nature and nature responding to reason. What might this mean for clinical research scientists?

It means, as Jacob Bronowski[4] put it, that "They ought (as researchers) to behave in such a way that what is true can be shown to be true." As normative for the conduct of scientific research, this requires that scientific behaviour be informed by what he called the 'habit of truth', indicating that science as the pursuit of truth requires the virtue of truthfulness in those practicing science. Science in itself, not necessarily as practiced by individual scientists, is then an inherently ethical enterprise. What might this mean for the conduct of those scientists who reported the findings and outcomes of their recent gene editing, using the editing technology known as CRISPR-Cas9?

Before answering that question, it is necessary first to assess the moral standing of the human genome as the complete set of our genetic code. What are the claims we ought to make to ensure its

integrity essentially and functionally since the use of CRISPR directly affects the genome? There are three relevant considerations to bear in mind. First, the genome influences our mind, body and behaviour. Second, it can unlock new insights into our origins and our history as a species. Third, it can point to new approaches to understanding the origins of disease, its treatment and its possible prevention altogether[5]. There is another important consideration. Since function usually follows form in biological systems and since we are at the mercy of our genes, does that mean that we are our genome?[6] Much, for an ethics assessment of gene editing, depends on how we answer this question. If we are not merely the sum of our genes, presumably we are not our genome, the product of genetic activity and natural selection. We are also the product of a social and physical environment as expressed through personally appropriated behaviour. What then is the relation between the genome and the person?

"Humans have emerged from the blind interplay (natural selection) like all other living beings, but with the unique privilege – and – burden of a brain developed to the point that it can elucidate the mechanisms that underlie this interplay and thereby devise means of manipulating them."[7] By mechanisms, de Duve means "all the instructions" used to "specify a given human being from conception to death." At the same time, he makes two observations that logically entail a question critical to the present discussion. The first observation is that today's human genome results from a lengthy evolution in the face of changing conditions. The second is that the composition of the present genome is not necessarily the best given prevailing conditions. If so, we have to ask whether the genome is inviolable, because if not, protecting it as it is would be pointless in the face of continuous accidental mutations, combined with the unanticipated consequences of our personally appropriated behaviours. On this analysis, de Duve concludes that if our genomic history is one of continuous mutation, then why not our genomic future? If the genome has not been inviolable in the past, what would justify considering it inviolable in the future?

Some, to protect the genome from interference have argued that at conception a unique genotype emerges so that the uniqueness of the genome correlates with the uniqueness of the person. Is this the case? Statistically, given the size of the genetic lottery, the genotype is unique. But genotype uniqueness does not mean, as twinning illustrates, that no one else will evidence it. The biological reality of twinning indicates a difference between genetic uniqueness and the uniqueness we attribute to person. As Maurizio Mori[8] points out, 'unique' is an equivocal concept so that as applied to the genome, it does not signify the same as when applied to the person. However applied, things considered to be unique are usually valued. But 'value' also is an equivocal concept, since things can be valued intrinsically, that is, for their own sake. Or they can be valued instrumentally as a means to securing something else that may be valued for its own sake. If our present genome is statistically unique and the result of continuous mutation, it is reasonable to consider its value as instrumental in the service of something valued intrinsically, our persons. Nothing illustrates this point more clearly than the medical-ethical and legal battle to save the person of Charlie Gard from the fate of his genetic mutation. →

Despite this, to protect the genome from interference, others make a theological argument for genetic uniqueness as intrinsically valuable. For example, Paul Ramsey[9], who concedes that genetic uniqueness depends on randomness, contends that the randomness of genetic composition is the closest scientific equivalent to the concept of divine creation "ex nihilo" (out of nothing). As a consequence, if creation 'ex nihilo' is intrinsically valuable, so too is genetic randomness. However, it remains unclear, as de Duve, observes, how genetic randomness – the cause, for example of cystic fibrosis – can be considered something of intrinsic value.

In light of this, it is reasonable to think, as a matter of principled ethics, that the genome may be manipulated, provided that in doing so, a particular manipulation does not compromise other relevant moral principles, such as respect for persons, human autonomy, and safety of the species. Moreover, if the history of our genome is one of continuous mutation in response to random circumstances, to refuse to pursue gene editing, now that scientifically valid research is beginning to show how this might be done responsibly, would be an abdication of responsibility. It would amount to a preference for "chance over reason, the accidental over the intentional."[7]

Being intentional in medical research today requires technology-based applications. But the use of technology in medicine has been criticised as a surrender to the so-called technological imperative under which we feel compelled to do things simply because we can. Were this the only way to consider technology, it might give us pause. But, there is an alternative to viewing technology as mere instrumentalism which gives way to moral standing in its own right. This is to understand technology as constitutive of knowledge, something Francis Bacon recognised a long time ago. A function of the interdependence of knowledge and instrument, it provides the readable instruments as means for and constitutive of science[10]. We might consider in vitro fertilisation as an example of this. It is in this instrumental and constitutive role that technology moves on a technical and ethical trajectory that, as techno-science starts by representing nature, then objectifying or reifying it and eventually becoming normative of nature, and in this way correcting nature's anomalies[11].

Within this framework, is it possible to justify the experimental gene editing announced by researchers at the Oregon Health and Science University? To correct a mutation in the MYBPC3 gene in human embryos grown in vitro, gene editing components and sperm, half of which evidenced MYBPC3 mutation, were inserted into oocytes without the mutation. Insertion occurred at the metaphase II stage of their cell cycle. Of the 58 embryos tested, 42 (72.4%) showed no MYBPC3 mutation. Analysis of the findings would indicate that the maternal copy of the gene served as the template achieving the repair. The analysis also found strong evidence of uniform gene editing with no mosaicism or off-target incidence, and progression to later stages of embryonic development. In light of these successful outcomes, it remains to be seen whether they can be replicated and what further research is required before this form of editing can move into the clinical setting, starting with clinical trials.[12]

> "IF WE ARE NOT MERELY THE SUM OF OUR GENES, PRESUMABLY WE ARE NOT OUR GENOME, THE PRODUCT OF GENETIC ACTIVITY AND NATURAL SELECTION."

What we can say from an ethics perspective at this point is that the research is beginning to meet the necessary ethics condition, scientific validity, to justify gene editing generally and the use of CRISPR in particular. Ultimately that will require being informed by "the habit of truth" and having arrived on the technological trajectory where it has become "normative of nature". If and when fully met, it will then have to meet sufficient conditions, such as social justice and the legitimacy of purposes beyond therapeutic need. To this end, it would help to not use the phrase 'designer babies'. Its prejudicial connotation begs the question before the scientific evidence is in, compromising intellectual honesty and possibilities for the public good.

We will know when that moment has arrived when, as Jennifer Doudna recalls being told, "Ethically we can't not do this."[13] In the presence of the cruel fate of Charlie Gard, for whom there was no treatment, how unfortunate is it that we are not quite there yet. And even in cases of persons with hypertrophic cardiomyopathy associated with the MYBPC3 mutation, where there are effective treatments, where is the argument based on right reason in conformity with nature that would conclude it will never be the case that ethically we can't not do this?

CRISPR-Cas 9 technology is based on a system of defence naturally employed by bacteria against infection from bacteriophages and active genetic factors. By releasing RNA's that complement threatening RNA, the system, as a matter of course, seeks out the threat to destroy it.[14] If so, then the findings from the Oregon experiment show that CRISPR-Cas 9 is already at the first stage of Ihde's technological trajectory, imitation. With replication, we may soon be at the second stage, objectification. But even now, it is justified to think of CRISPR-Cas 9 as a model of scientific reasoning in conformity with nature. What we ought to do is, what for now, we are doing experimentally, since scientist ought to act in such a manner that what is true is shown to be true.

At this juncture in the public debate over gene editing, we might do well to consider seriously these words, fittingly, given the context of the debate, found in John Milton's[15] Paradise Regained:

"...all my mind was set
Serious to learn and know and thence to do
What might be public good..."
Why not regain Milton's wisdom? ■

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