CCC Ethics Study #4:

Life Scientists and CRISPR-Cas9: An Ethics Commentary on "Human Nature"

by

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I. Introduction

CCC's 2020 Annual Retreat included a showing of "Human Nature," Adam Bolt's 2019 documentary about CRISPER-Cas9. In what follows, I will comment on the film from *an ethics perspective*. Hopefully my comments will complement CCC members' own reactions to the film and enhance appreciation of its ethical dimension.

The film has an Introduction and six "Chapters": 1. "Needle in a Haystack"; 2. "CRISPR"; 3. "The Gene Machine"; 4. "Brave New World"; 5. "Good Genes"; and 6. "Playing God." Chapter 1 introduces the concept of genetic disease. It does so via the case of David Sanchez, a sickle-cell anemia patient who is part of a clinical trial in which CRISPR-Cas9 is being used to try to cure that malady. Chapters 2 and 3 relate the history and workings of the CRISPR system and identify some current uses of CRISPR-Cas9. Chapters 4-6 explore ethics issues raised by possible applications of this potent gene-editing tool. I will focus here on views about these ethical issues expressed in the film by biologists, biochemists, and geneticists.

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II. Ethics-Related Issues in Chapters 4-6[2]

A. Engineering human heredity. The first ethics issue explored in Chapter 4 surfaces initially at the beginning of the film. In a 1966 talk at Cal Tech, biologist and Human Genome Project progenitor Robert Sinsheimer stated,

> The dramatic advances of the past few decades have led to the discovery of DNA and to the decipherment of the universal hereditary code, the age-old language of the living cell. And with this understanding will come the control of processes that have known only the mindless discipline of natural selection for two billion years. And now the impact of science strikes straight home, for the biological world includes us. We will surely come to the time when man will have the power to alter, specifically and consciously, his very genes. This will be a new event in the universe. The prospect is, to me, awesome in its potential for deliverance or equally for disaster. (03:53)

The issue raised here is a general one: whether humankind's use of its newfound "power to alter, specifically and consciously, [its] very genes" – put differently, the use of science and technology to engineer human heredity -- is justifiable and advisable. Undertaking to engineer changes in human heredity raises an ethics issue because proponents and opponents of doing so in contemporary society disagree about whether proceeding with that project will yield immense benefit and/or cause significant unintended harm to humans, human society, or the human species in general. For Sinsheimer, the prospect of this power being used to alter human genes is "awesome in its potential for deliverance or equally for disaster."

Biologist George Daley calls CRISPR-Cas9 "sobering" (45:40) because it makes the hitherto theoretical and remote prospect of engineering human heredity "actually feasible" (45:49). This calls for the envisioned project to be seriously assessed rather

[2] With one exception, the ethics-related issues explored in section II are taken up in the order in which they emerge in the film. The exception is explored in section II.G.

than kept on the back burner. Geneticist Fyodor Urnov underscores the urgency of making such an assessment with his claim that the scope of changes to humans that will prove achievable via gene editing is likely to increase significantly in coming years, eventually embracing some controversial mutations. As genetic engineering advances...

> people will be able to order a change in their genetic makeup to create an outcome of interest to them: in their metabolism; in their appearance; in principle, potentially in who they are as people, personality changes. (46:25)

Daley and Urnov do not invoke ethics ideas or principles in discussing the general project. Neither argues that undertaking to engineer human heredity using CRISPR-Cas9 will yield medical benefits that far outweigh any projected costs, hence that the project is ethically justifiable. Neither claims that the risk of causing significant harm to humans or human society from undertaking that project is sufficient to make going down that path ethically ill-advised or unjustifiable. Some scientists subscribe to one or the other of those claims, but only one interviewed in the film does so.[3] Is *any* ethical justification given in the film for pursuing the general project of engineering human heredity? We will return to this question in section II.H.

B. Access. The second ethical issue that surfaces in Chapter 4 pertains to a specific aspect of engineering human heredity: access to its results.

After noting that genes could be engineered to reduce the level of the protein myostatin, something "that could potentially make us all more muscular" (46:51), Daley asks, "...should we make that [option] universally available?" (46:58) That is to say, should the option of undergoing the genetic intervention that results in becoming more muscular be open to all humans who seek it? Daley does not answer the question he

[3] Stephen Hsu briefly discusses benefits and risks of "designer babies" starting at (57:35).

poses. In general, for *any* genetic mutation under consideration for being engineered into the human genome, at least two ethics questions must be asked and answered: 1. who *should* have access to the process for effecting it?; and 2. what criterion *should* be used to determine eligibility for access to it? Neither question is seriously addressed in the film for any mutation.

Access to an engineered genetic mutation raises an ethics issue because, depending on who gets access to which mutation, the outcome could make those able to access it better equipped to compete for important social and economic goods than those unable to do so. Such a result would likely exacerbate existing social inequality, arguably an incremental social harm. If access to an engineered genetic mutation is allowed to hinge solely or primarily on ability to pay its going market price, something that differs substantially from person to person in contemporary societies, then the resultant pattern of access would arguably be distributively unjust. For not all individuals have an equal opportunity to acquire that on which access to the mutation, hence to the desired good, depends. We will return to the access issue in section II.E, when exploring views about using genetic science and technology in human reproduction.

C. Specific mutations. A third ethics issue emerges in Chapter 4 when Urnov invites the viewer to consider the possibility of using gene-editing to effect two specific mutations: one that enables the patient *to get by on 4 hours of sleep per night*, and one that makes the patient *unable to feel pain* (47:02). For each, he imagines a situation in which bringing it about seems ethically justifiable. In the case of being able to function normally on 4 hours of sleep per night, the situation is one in which the would-be patient is an air-traffic controller, on whose continuous alertness human lives depend. In the

case of being unable to experience pain, the situation is one in which the patient is in excruciating pain from terminal cancer. Whether deliberately or not, in offering these examples and situations, Urnov effectively discredits any proposal to categorically ban *all* such mutations.

Having indicated a specific circumstance in which having the sleep-related mutation seems ethically acceptable, Urnov asks, “Do I want the world to go there?” (47:22). This suggests that he may have doubts or be unsure whether, all things considered, it would be ethically advisable or justifiable to allow that genetic mutation to become commonplace. About the pain-disabling mutation, he asks, “do I want a scenario where there are parts of the world where special forces [have been] made immune to torture [by gene editing]?” (48:30) The implication of this question seems to be that while there are circumstances in which this mutation is ethically justifiable – viz., someone’s being in excruciating pain from terminal cancer – under other circumstances effecting the same mutation would be ethically objectionable. It could be that Urnov favors neither categorical banning nor universal permissibility as that which should determine the proper scope of access for the mutations he cites. Perhaps he regards whether engineering a specific gene mutation is ethically justifiable as *mutation- and circumstance-specific*.

D. Engineering human heredity as a function of purpose and cell type.

The fourth ethics issue that emerges in Chapter 4 is a critical one. It involves exploring whether the ethical acceptability of gene editing depends on the values of two

independent variables[4]: 1. the *purpose* for which a gene-editing intervention is undertaken, and 2. the *type of cells* on which the gene editing is carried out.

John Zhang, founder of Darwin Life (50:03), stated, "Everything we do is a step toward designer babies... With nuclear transfer and gene editing together, you can really do anything you want." (50:06) For example, he claims that in the future, parents will be able to select their child's hair or eye color, or perhaps improve her/his IQ. (50:06) To grasp the importance of such provocative statements, it is imperative to recognize that some of the traits that Xhang supports engineering would involve attempts at genetic intervention for purposes of *enhancement or parental preference*, rather than for *therapeutic* purposes.

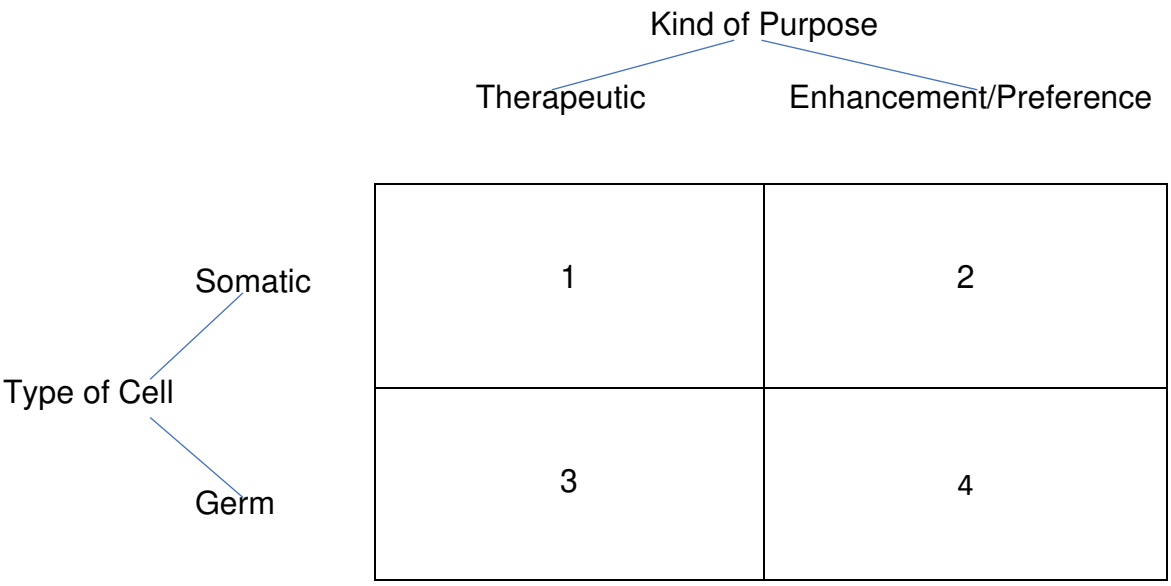
Moreover, some of Zhang's efforts would presumably be carried out on *germline* rather than *somatic* cells. Germline (or germ) cells are sperm, egg, and embryonic cells, genetic changes in which will be passed on to their descendants in future generations. In contrast, somatic cells are cells of a particular body that die when the individual expires; changes made in the genes of an individual's somatic cells are not inherited by their descendants.

These two key distinctions give rise to four categories of gene-editing interventions: ones undertaken for...

1. therapeutic purposes on somatic cells
2. enhancement or preferential purposes on somatic cells
3. therapeutic purposes on germ cells
4. enhancement or preferential purposes on germ cells

These categories of options can be conveniently represented by a 2 X 2 matrix:

[4] Besides 'mutation' and 'circumstance.'



Interventions that fall into Box 1 are the least ethically controversial and most widely regarded as ethically acceptable in the U.S. at this point. This is understandable, since (i) the objective of such edits is to help people overcome genetic disease, (ii) they physically affect only patients with the disease, and (iii) given accurate information, patients can freely give their informed consent to undergoing such gene editing.

Interventions that fall into Box 4 are the most ethically controversial and are widely regarded as ethically unacceptable in the contemporary U.S. This is because, among other reasons, (i) the intended outcome could give the patient an advantage over people who have not undergone the procedure, (ii) access to the procedure is likely to hinge on the (decidedly unequal) ability to pay its going market price, and (iii) the germ cell changes effected in the individuals will be inherited by their descendants. Such beings, since they do not yet exist, cannot consent to changes in their genomes.

The CRISPR-based clinical trial that Matthew Porteus is conducting in which sickle-cell patient David Sanchez is enrolled, is being done on his somatic blood cells, not his germ cells. Thus, this intervention falls into Box 1. However, editing the somatic

cells of a sickle-cell carrier leaves its germ cells unchanged and the carrier's children and their children remain vulnerable to the same disease. Some ask, in Porteus' words, "...why not just do it so that the diseased gene never gets passed along to future generations?" (52:13) In fact, "...there are some people out there who think that's all we should do." (52:20) In other words, some contend that gene editing should be done on the sickle gene carrier's *germ* cells, e.g., its embryonic cells, a Box 3 intervention, rather than on its somatic cells. There is serious disagreement in the medical community and in society at large over the ethical acceptability of doing so. Porteus offers one reason underlying this disagreement: in pursuing gene editing of germline cells, "we may be creating things that we can't put back in the bottle." (52:24)

Is that the only reason why gene editing of human germline cells is ethically controversial? Urnov and four colleagues offered two other reasons in a "Comment" published in 2015[5], part of whose text is shown in the film:

> In our view, genome editing in human beings using current technologies could have unpredictable effects on future generations. This makes it dangerous and ethically unacceptable. Such research could be exploited for non-therapeutic modifications. We are concerned that such an ethical breach could hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited. (53:03)

Urnov here regards the gene editing of human germline cells, even for *therapeutic* purposes, as ethically unjustifiable, but not because he believes such an intervention is *inherently* ethically wrong. Rather, his view is based on two considerations. First, gene

[5] Edward Lanphier, Fyodor Urnov, Sarah Ehlen Haecker, Michael Werner, and Joanna Smolenski, "Don't Edit the Human Germ Line," *Nature*, Volume 519, March 26, 2015, pp. 410-411. https://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111.

editing human germ cells would have "unpredictable effects on future generations."[6] Second, progress in research on gene editing of human germ cells for *therapeutic* purposes (Box 3) could tempt some researchers to take the next step and edit the genes of human embryos for *enhancement* purposes (Box 4). Urnov and his co-authors "proposed that there be an unconditional moratorium: don't edit human embryos, don't use edited sperm and eggs to make human embryos, just nothing." (53:21) Why did they propose such a moratorium?

> We must understand that when we authorize research on human embryo editing, we are enabling, ultimately, human embryo editing for human enhancement. That's what we're doing. We're putting the recipe out into the world. (53:33)

To clarify what is implicit in "ultimately," the problem is that researchers would be diffusing knowledge about human-embryo editing widely in the absence of social structures able to effectively regulate such research, thereby facilitating its use by other scientists for more controversial purposes, e.g., human enhancement. Moreover, research on human germ cells would, Urnov believes, elicit a public outcry and risk reactive restriction or prohibition of gene editing of *somatic* cells for *therapeutic* purposes (Box 1).

[6] Urnov's concern that "genome editing in human beings could have unpredictable effects on future generations" gains weight from a recent paper by Columbia University researchers. The authors claim that gene editing human embryonic cells for therapeutic purposes risks producing heritable unwanted changes in the embryo being edited through causing unexpected damage to the DNA of some of its cells. See Katherine J. Wu, "Crispr Gene Editing Can Cause Unwanted Changes in Human Embryos, Study Finds," *New York Times*, October 31, 2020, https://www.nytimes.com/2020/10/31/health/crispr-genetics-embryos.html?searchResultPosition=1. See also Michael V. Zuccaro, *et al.*, "Allele-Specific Chromosome Removal after Cas9 Cleavage in Human Embryos," *Cell*, Volume 183, Issue 6, December 10, 2020, pp. 1650-1664.e15. https://www.cell.com/cell/fulltext/S0092-8674(20)31389-1.

In 2017, the National Academy of Sciences Committee on Human Gene Editing took a quite different position. In 2016, it was tasked with looking into "whether or not there was something intrinsically unethical about manipulating genes in a way that makes [the changes made] heritable." (1:12:11) The Committee concluded that editing the genes of human germ cells...

> '...is not intrinsically evil.' It is what we called 'ethically defensible,' but we understood that this was now a break from the past in the thinking on this topic." (1:14:06)

It is curious that the Committee framed its conclusion in this way, viz., that gene editing human germ cells is *not* intrinsically wrong but *is* ethically defensible. For, in all likelihood, most Committee members had Box 3 *therapeutic* interventions in mind, not Box 4 *enhancement* interventions, when voting for a conclusion that sanctions both. The film sheds no light why individual Committee members voted as they did.

E. "Designer babies." A fifth ethics-related topic explored in Chapters 4 and 5[7] is "designer babies." This expression refers to human newborns who, prior to birth, have had selected genetically based traits deliberately altered to reflect the priorities and/or preferences of their parents.

For Stephen Hsu, co-founder of Genomic Prediction, "...sex is for recreation and science is for procreation." (57:35) He contrasts the "crazy, old-fashioned way" of determining the qualities of one's child, which he views as tantamount to "rolling the dice with their kids' lives" (57:49), with new science- and technology-based ways of determining those traits. As he sees it, there are two ways in which a baby's genome will eventually be determined: in the short term, with ever improving pre-implantation

[7] From (55:09) to (1:09:39).

genetic diagnosis (PGD), and, in future, via gene editing. In the case of PGD, parents will commission “multiple viable embryos” (58:05), have “some fancy [diagnostic] genetic tests” (58:24) run, pick out the embryo with the trait set they most prefer (or the traits that are most important to them), and have that embryo implanted to be brought to full term.

According to bioethicist Hank Greely, “with today’s technology, you’ve been limited to look at only a handful of traits. But soon, genetic sequencing will be cheap enough, easy enough, and accurate enough that you’ll be able to learn everything that genetics can tell you.” (58:46) Thus, Greely anticipates that the set of traits able to be chosen or rejected by PGD will expand considerably and become more affordable.

However, Hsu envisions a more radical idea: “In the future, let’s imagine that CRISPR gets really, really good. Maybe you don’t need to produce lots of embryos, maybe you’ll only need to produce one and make whatever edits you want to.” (59:13) Realizing that neither mode of intervention will be widely affordable, at least in the short run, the interviewer asks Hsu, “what about the cost of it?”, presumably referring to PGD, but possibly also to gene editing. Hsu responds:

> In the short term, there’s a disturbing possibility that people with means will be availing themselves of this technology, and people who don’t have the means will not. So, I kind of hope for a future when government makes it free for everybody. You would have a healthier population, maybe a longer-lived population, maybe a slightly smarter population on average. So, if you have a smaller fraction of your population with Down Syndrome, the average intelligence is a little bit higher and, you know, society might run a little bit more efficiently if people are a little bit smarter. (1:01:04)

Most of the benefits Hsu cites sound plausible and could become widely recognized.[8] However, it is extremely unlikely that government will ever make PGD or gene editing "free for everybody" – and, in this writer's view, unrealistic to suggest that it might. It is conceivable that government could decide, on economic grounds, to make PGD or gene editing free to all when it comes to preventing or deleting seriously harmful traits for therapeutic purposes. But it is implausible to think, when it comes to selecting traits that serve only enhancement or parental-preference purposes, that government will cover the cost of that intervention for all citizen-parents. If so, then either such interventions will be universally prohibited – even more unlikely – or only parents of considerable means will have access to genetic selection technologies for enhancing their children's traits or ensuring that their traits reflect parental preferences. This too would exacerbate social inequality, arguably a social harm.

I am also concerned about the possibility that the dominant culture of the society in which gene editing of human germ cells for enhancement purposes is permitted could exert pressure on parents to select mutations that would manifest themselves in specific, widely desired attributes or capabilities, such as tall height, blond hair, and exceptional memory. Were the culture to do that, the diversity of future generations could be diluted. Hsu, however, strongly disagrees. When he has given talks to the public about futuristic science,

> I've had tall, blonde trophy wives come up to me after the talk and say, 'Wow, that was incredible. That was an incredibly interesting talk, but don't you think there's a problem with all this? Won't every parent just select their kids to be tall and blonde?' The geeks all come up to me and say, 'Isn't this dangerous, because all the parents are going to select for the smartest kid they can possibly get?' Because that's what the

[8] However, I doubt that broad use of CRISPR-Cas9 would make society "run a little bit more efficiently."

> geeks think is cool. You know, probably if you were talking to some NFL coaches, they'd say, 'Oh, everyone's gonna select their kid to be 6'5" and run a 4.2 [second] 40 [yard dash], you know?' So, there will be a wide range of what people think is the right thing to select for or engineer for. And, actually, there's nothing wrong with that, right? Let a million flowers bloom. (1:08:48)

Hsu could be correct in predicting that there would be considerable variety in the mutations preferred by parents, although that is not obviously true and doesn't follow from his three examples. But, even if he is correct, there could also be wide convergence on a set of *culturally validated traits*, ones relevant to the preferences of all parents. Heterogeneity in the mutations selected first by parents does not preclude wide agreement on a subset of other chosen genetic mutations. It is interesting that in each of Hsu's examples – tall blondes, nerds, and NFL coaches – he projects that the parent in question would choose traits that would either make the child resemble the selecting parent in one of its distinguishing features (tall blondes and nerds), or endow the child with traits that would equip it to succeed in the profession of the selector (NFL coaches). Perhaps so, but it is at least as likely that many commissioning parents who *lack* traits validated by the dominant culture would prioritize mutations that would engender traits that *are* culturally validated, even over mutations that they already have. To the extent that this happened, it would decrease diversity.

F. The aging reversal and wooly mammoth projects. In Chapter 6, geneticist George Church discusses two of his controversial ventures that involve gene-editing: the "aging reversal" and "woolly mammoth" projects. To Church, these projects are not "quixotic or misguided" science-fiction visions of a "mad scientist," but potentially "quite useful" endeavors.

Regarding aging reversal, the 63-year-old researcher believes it is absurd for him to have finally reached the point of being fully qualified to do his job well and then for society to "pull the plug and recycle me." (1:17:28) It makes much more sense to him to have beings in society that combine "the body and mind of a 22-year-old" and "the experience of a 130-year-old" (1:17:32). He believes this is achievable through gene-editing.

Church recognizes that the ethical acceptability of his aging-reversal project depends on society's population level: "We need to be cautious in that, you know, there's this whole population problem." (1:17:37) But he seems to think it would be ethically acceptable to pursue that project "if we have a place to put all those people" (1:17:42), presumably meaning those who would live considerably beyond the normal human life span as a result of the project's success. However, in the film Church does not address several important questions:

- what quality-of-life conditions would have to exist in the "place" set aside for the aging-reversed people (or those displaced by them) for the project to be ethically justifiable?
- how many and which individuals should be allowed to undergo aging reversal?
- who would decide 'how many' and 'which'?
- what criteria should be used in answering the preceding questions?

In short, having "a place to put all those people" is *not sufficient* to make the project ethically acceptable. Church does not appear to have thought through the full range of conditions that would have to be fulfilled for his aging reversal project to be ethically justifiable. The technical feasibility of a project does not settle the question of its ethical acceptability.

Regarding bringing back the woolly mammoth, Church describes the process he has in mind thus:

> So, in the Mammoth Project, we read the ancient DNA, decide which genes we're going to resurrect, put those into the Asian elephant's cells, and then -- we're developing technology that's not yet working – to make, take those embryos all the way to term. Then we scale that up to make a herd of these things, maybe 80,000 of them, to repopulate the tundra.

He appears to see this project as a useful way of bringing back selected extinct species and of preserving or rescuing species that are endangered. However, one ramification of this project seems ethically problematic. If the project succeeds, it could well undermine an important incentive that humans currently have for striving to preserve endangered species, viz., 'we'd better take good care of the remaining members of this species because if they disappear, the species can never be recovered.' The success of Church's Mammoth Project would demolish that incentive and probably make humans more willing to acquiesce in species extinction for the sake of, say, economic development. For, if needed, an extinct species can always be resurrected through genetic science and technology. Hence, its demise is no cause for concern.

However, once nascent economic development takes root, calls to abandon it in order to recover a lost species via gene editing may go unheeded, not least because familiarity with and appreciation of the extinct species are likely to have waned in its absence. Thus, although gene editing might make the recovery of an extinct species technically possible, it might also dampen the resolve to abandon the economic development that arose after a species' demise. Paradoxically, gene editing could be conducive to the endangerment or extinction of species, only some of which would be actually restored, possibly in suboptimal, non-wild environments, e.g., zoos. To the

extent that this scenario is plausible, the ethical acceptability of species resurrection or recovery through gene editing is unclear.

G. Xenotransplantation. The only significant ethics issue in the film that does not appear in Chapters 4-6 arises from an application of gene editing covered in Chapter 3.[9] Luhan Yang, formerly a student in George Church's academic lab, founded eGenesis "to revolutionize how we transplant organs" in order to "overcome [human] organ shortages." (39:07) The company plans to use "CRISPR to engineer immuno-compatibility by knocking out and knocking in genes" (41:17) in the pig genome, such that the organs of the gene-edited pigs are more likely to be accepted by the immune systems of their human recipients.[10]

Nothing in the film's segment on gene editing and xenotransplantation shows or suggests that Yang or her research colleague Yinan Kan recognizes that their project might warrant ethical scrutiny. Let us briefly consider this matter.

If the project proves successful, many humans at imminent risk of dying will have their lives extended, and many gene-edited pigs (and possibly animals from other "lower mammalian species"[11]) will be killed and their organs harvested for transplantation. This raises a general ethics question: is a research project that would culminate in harvesting vital organs of gene-edited non-human mammals and transplanting them into humans to extend lives at imminent risk of ending ethically acceptable or justifiable?

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[9] From (38:42) to (42:56).
[10] For a useful overview, see Megan Sykes *et al.*, "Transplanting organs from pigs to humans," *Science Immunology*, Vol. 4, Issue 41, eaau6298, November 29, 2019. https://immunology.sciencemag.org/content/4/41/eaau6298.
[11] *Ibid.*

Yang and Kan presumably aim to extend otherwise lost human lives through their work. While that intention is laudable, it does not by itself guarantee that the project in question is ethically justifiable on consequential grounds.

Most would probably contend that the only thing that matters in evaluating the ethical justifiability of Yang's project and related transplant practice is whether the project works and, as a result, human lives are extended that would otherwise have soon ended. However, some might argue that the ethical justifiability of the project and practice hinges on one or more contingent features of the situation in question. What features might be relevant to making a thoughtful judgment about whether the project and the related practice are ethically justifiable? Two that come to mind are (i) the *sources* of the transplantable organs; and (ii) selected characteristics of their would-be *recipients*. Let us consider each.

Regarding the sources of the pig organs, most would probably argue that where the substitute organs come from is ethically irrelevant, as long as they are not from other humans -- unless they were donated voluntarily. However, in response, it is worth noting that pigs are sentient creatures with interests in continuing to live and not being subjected to pain and suffering. As such, they are ethically relevant parties whose interests deserve to be taken into account in assessing the acceptability of the project and practice. Confronted with this point, most who have no ethical qualms about taking the lives of gene-edited non-human mammals (in order to harvest their transplantable organs for humans in need) would probably either deny that pig interests deserve to be taken into account, or assign those interests much lighter weights than they would assign to the same interests in the case of human beings.

Some who acknowledge that both pigs and humans have those interests in common might argue that for the gene-editing project and transplant practice to be ethically justifiable, not only must the interests of the humans substantially outweigh those of the pigs, but it must also be the case that the pig-organ harvesting must be *necessary*, in the sense that no viable alternatives exist to harvesting them from gene-edited pigs. Being more convenient or cost-effective to the researchers than other alternatives would not suffice to make the pig organ harvesting necessary.

As for the second factor – the identity of the would-be pig-organ recipients -- many would contend that, other than need, no distinctions should be made amongst would-be recipients that would lead to judgments that some would-be recipients should get organs from gene-edited pigs while others should not. They would argue that the ethical justifiability of the project and practice should be *independent* of anything about the would-be recipients other than need. If the would-be respondents are in dire need of such organs, then that suffices to make the project and practice ethically justified.

However, others might respond that it is ethically appropriate if not obligatory to differentiate the candidate organ recipients based on whether or not they have one or more some specific properties or attributes. The idea would be that only those candidates who had those properties would be eligible to receive a pig organ. They would further argue that the ethical acceptability of the project and practice would *depend* on whether the target recipients had the relevant property or attribute. Examples of possible relevant properties are ones revolving around the candidate

recipient's age, post-transplant prognosis, and degree of responsibility for being in a health situation in which a substitute organ is needed.[12]

I view Yang's project and related practice as neither always nor never ethically justifiable. That is to say, I view them as neither ethically *acceptable* regardless of prevailing conditions and attributes, nor as ethically *unacceptable* regardless of prevailing conditions and attributes.[13] This view parallels my position on the ethical issue of whether it is ethically acceptable or justifiable to use animals, such as dogs, rodents, and chimpanzees, in traditional medical research labs in projects intended to benefit humans. Doing so is *neither always nor never* ethically justifiable. For me, the issue in both cases is *under what conditions is such an endeavor ethically justifiable*. In short, Yang's xenotransplantation project is *conditionally ethically justifiable*, i.e., it is ethically justifiable if and only if certain specific conditions are satisfied. Extended discussion would be needed to determine what those precise conditions are and why, but they could involve whether there are viable alternatives to harvesting the organs, how the source mammals are treated, and selected attributes of the would-be recipients.

The aim here is not to persuade the reader to agree with the writer's stance, but to invite her/him to join the writer in reflecting on the issue of gene-editing-based xenotransplantation by exploring the question of whether the gene-edited organ transplantation project-cum-practice is unconditionally or conditionally ethically

[12] For example, those who oppose making any distinctions (other than need) amongst would-be recipients would presumably object to making a decision about eligibility to receive a gene-edited pig's organ based on conduct like smoking, abuse of drugs, or abuse of alcohol. They would call attention to the difficult, perhaps insuperable obstacles to making such judgments fairly.
[13] I do *not* view Yang's project as *inherently* ethically wrong or unjustifiable.

justifiable. To the writer, such reflection would usefully complement the sunny enthusiasm exuded by the researchers in the film's segment about their pioneering work.

H. Engineering human heredity revisited. In Chapter 6, Fyodor Urnov expands on his prior remarks[14] about the project of engineering human heredity via gene editing:

> The things that make us most human are some of the most genetically complex, which is kind of a relief. Creativity. Emotionality. Love. Now I want to be clear. They all have a biological basis. They are all written in our DNA. But we are a very, very, very long way away from being able to edit the person." [Interviewer: "Do you think that day will come?"] "I do, but I'm hopeful that we will mature as a species before we get this inevitable technology to play with for our own detriment. I am hopeful for that, yes. Is that hope based in fact? We'll see. (1:29:53)

Urnov first seems to want to allay public concern about this general project, saying that researchers are still very far away from being able to edit the genome so as to produce humans with prized traits like creativity, emotionality, and the capacity to love.[15] But he admits that he *does* believe the day will come when gene editing will be able to produce humans with those traits, with unknown consequences. Having kindled concern over this prospect, Urnov tries to reassure by saying he is "hopeful" that before gene editing becomes capable of engendering those traits, the human species will have matured sufficiently so that that the new technology will not be used to the species' detriment. He closes on a candid note by acknowledging that his hopefulness is not

[14] See above, section II.A.

[15] Urnov's remark that "we are a very, very, very long way away from being able to edit the person" is misguided. Genetic endowment does not determine an individual's characteristics as a person. Environment and life experience are also key contributory causal factors. While it is already possible to edit the genome of an individual, it is and will remain impossible "to edit the person," just as it is impossible to "clone a person," only a being whose genetic endowment is identical to that of the donor.

grounded on established facts; for the moment, it's just an optimistic feeling or belief. Eventually, "we'll see" whether that hope proves to be more than wish fulfillment.

No life scientist in the film offers a clear ethical justification for the general engineering-human-heredity project. Some clearly believe it is ethically justifiable to use gene-editing to engender specific traits in some humans, especially traits with therapeutic value, and some foresee that such intervention will become widespread for multiple specific traits. The interviewed researchers go no further.[16]

Biochemist and CRISPR pioneer Jennifer Doudna deserves credit for encouraging her life science colleagues to convene and think deeply about the implications of CRISPR-Cas9 for "what it means to be human" (1:29:48), and about the terms under which this technology can be responsibly used. While she does not take an explicit position in the film about the ethical justifiability of the general engineering project, Doudna relates a nightmare she had in which Hitler appeared and said, "So, tell me all about how Cas9 works." (51:07). Thus, she is well aware of and concerned about worst-case scenarios, ones that arguably call for serious precautionary measures.

Urnov *et al.*'s 2015 proposal for a moratorium on germline gene-editing was followed by another in 2019. Thirteen life scientists, four ethicists, and a health advocate from seven countries published a journal "Comment" that stated, "A global moratorium and [international] framework are...necessary to ensure proper consideration of the relevant issues surrounding clinical uses of germline editing."[17]

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[16] Stephen Hsu, whose optimistic views about "designer babies" were discussed above, may seem to be an exception. However, he is a physicist, not a life scientist, by training.

[17] Eric Lander, Françoise Baylis, Feng Zhang, Emmanuelle Charpentier, Paul Berg, *et al.*, "Adopt a moratorium on heritable genome editing," *Nature*, March 13, 2019, Vol. 567, pp. 165-168. https://www.nature.com/articles/d41586-019-00726-5.

As developments between 2012 and 2018 suggest, some life scientists see the possibilities opened up by CRISPR-Cas9 as too exciting to forgo.[18,19] Viewing a project as posing "a sweet intellectual problem"[20] can induce a researcher to become preoccupied with its technical details and neglect the social context and implications of her/his work.

Had a life scientist in the film offered a facilely optimistic ethical justification of the paradigm-shifting, engineering-human-heredity project, I would have noted that claiming that forging ahead with this project is ethically justified assumes that...

A. no serious problems will arise as a result of forging ahead with it; or that
B. for any problem that arises downstream in society as a result of forging ahead, an effective 'band-aid' will always be found in time to resolve it; or that
C. any such problems that eventuate will be greatly outweighed by the benefit delivered; or that
D. engineering human heredity is intrinsically ethically justified.

I regard assumptions A and B as naive. Even if C was true, it is not clear that in every case the greater benefit would ethically justify incurring the lesser cost. Whether it did

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[18] "First, in China, biophysicist He Jiankui reportedly edited embryos to create at least two babies. Second, scientists who were apparently aware of this work did not take adequate measures to stop it. Third, there has been growing interest in proposals for genetic enhancement of humans. Fourth, some commentators have interpreted subsequent statements as weakening the requirement for broad societal consensus; such statements include a 2017 report from the US National Academies of Sciences, Engineering, and Medicine, and a 2018 statement from the organizing committee following the Second International Summit on Human Genome Editing...Finally, no mechanism was created in the ensuing years to ensure international dialogue about whether and, if so, when clinical germline editing might be appropriate." *Ibid.,* p. 166.

[19] Uncritical researcher excitement and enthusiasm over a paradigm-shifting technology is not a new phenomenon. For example, re the first test explosion of the atomic bomb, Richard Feynman wrote, "After the thing went off, there was great excitement at Los Alamos. Everybody had parties, we all ran around. I sat on the end of a jeep and beat drums and so on. But one man, I remember, Bob Wilson, was just sitting there moping. I said, 'What are you moping about?' He said, 'It's a terrible thing that we made.' I said, 'But you started it. You got us into it.' You see, what happened to me—what happened to the rest of us—is we started for a good reason, then you're working very hard to accomplish something and it's a pleasure, it's excitement. And you stop thinking, you know; you just stop. Bob Wilson was the only one who was still thinking about it, at that moment." Richard Feynman, *Surely You're Joking, Mr. Feynman! Adventures of a Curious Character* (Norton: New York, 1985), p. 135.

[20] *In the Matter of J. Robert Oppenheimer: Transcript of Hearing before Personnel Security Board,* Washington D.C., April 12-May 6, 1954, U.S. Atomic Energy Commission (Government Printing Office: Washington, D,C., 1954), p. 31.

would depend on, among other things, the magnitude of the cost, how equitably the benefits and costs/risks were distributed, and the extent to which the harms in question were reversible. Assumption D is indefensible. In short, while I hope that assumption is valid, I am skeptical about it.

The other life scientist in the film who comes close to expressing concern about the ethics of the engineering-human-heredity project is Matthew Porteus. Besides invoking the 'it's-hard-to-get-the-genie-back-in-the-bottle' argument, toward the end of the film he states, "The relationship between our genes and our environment is incredibly complex and we don't understand that" (1:27:56), not least because "environment" can include society as well as nature. This statement, the two moratorium proposals, and Doudna's public and professional initiatives sound the alarm about proceeding with CRISPR applications in "full speed ahead, damn the torpedoes" style. They suggest that ethical justifiability for the general project hinges on adherence to carefully thought out and rigorously enforced precautionary measures.

III. Conclusion

No life scientist interviewed in the film is as ambivalent about the overarching engineering-human-heredity project as Robert Sinsheimer. Earlier, I quoted his remark that humanity's new power to control genes is "awesome in its potential for deliverance or equally for disaster." The film ends with a remark of his about the new era of genetics, "Ours is, whether we like it or not, an age of transition. After two billion years, this is, in a sense, the end of the beginning" (1:31:26). After a long childhood, during which human heredity was not engineerable, genetics is now entering its exciting but more risky adolescence, in which human heredity will be increasingly engineerable.

Regarding the emerging era of potent genetic science and technology, bio-engineer Feng Zhang's statement is apt: "I think we have to have humility." (1:28:15) A critical micro- and macro-level ethics-related question involving CRISPR-Cas9 now confronts U.S. society:

> *Will life scientists, bioengineers, physicians, entrepreneurs, industrialists, legislators, and regulators demonstrate humility in practice by taking and respecting appropriate precautions in proposing, testing, authorizing, and applying CRISPR-Cas9, or will considerations of fame and fortune, political power, and/or corporate profit trump those precautions and shape CRISPR-Cas9-based gene editing in ways that hinder it from becoming a blessing for humanity as a whole?*