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Three Venues for Discussing Human Gene Editing

Scientists, government leaders, and the public must all be part of the debate, and our challenge is to manage the dynamic integration of these perspectives.

Little did we know when we were writing the Nuffield Council on Bioethics report *Genome Editing and Human Reproduction: Social and Ethical Issues*, published in July 2018, how quickly our call for meticulous research, broad social debate, and the painstaking formulation of governance would be overtaken by events. News only a few months later from China that treatments led by a university researcher, He Jiankui, had produced two (soon, possibly, three) children with modified genomes upended most people's expectations of the pace, order, and context of innovation in this controversial area. Blogging soon after from the auditorium in which He presented his claims to the Second International Summit on Human Genome Editing, held at the University of Hong Kong in November 2018, I suggested that his intervention had reset the initial conditions for the innovation of heritable genome editing and left scientists, policy-makers, and others scrabbling to reinvent the future. Now, a few more months on, it's worth taking stock of where we are.

First, though, some context. *Genome Editing and Human Reproduction* is the Nuffield Council's second report on genome editing. In the first, *Genome Editing: An Ethical Review*, published in 2016, we observed how it was a "distinctive consideration relating to genome editing… that it potentially brings 'basic' biological research and translation to clinical treatment into closer conjunction." One reason for this is that the distinction between research and treatment here does not so much depend on further, technically exacting steps in a developmental pathway, but on other circumstances and choices. It is rather like the distinction between therapeutic and reproductive cloning, which, 15 or so years ago, allowed people with grave misgivings about the potential

uses of that technique to find an uneasy entente with researchers exploring human somatic cell nuclear transfer in human embryos. From the point of view of embryology, the difference is undetectable; it consists, essentially, in whether the reconstructed embryo is subsequently transferred to a woman. Ironically, when I first heard of He's claims I was inclined to dismiss them, recalling how the claims of rogue embryologists to have cloned human beings always melted away before demands for proof. On the eve of big international conferences, in the intoxicating attention of global media, one hears many unfounded rumors and hyperbole. People get jittery. In the case of human cloning, the entente seems to have held, if only because it is hard to imagine why anyone (except, perhaps, the adherents of an obscure extraterrestrial cult) would actually want to carry it through. Not so, apparently, with genome editing.

Pause here for a minute. I want to acknowledge a point that has been made very widely: there are no pressing clinical indications for the use of genome editing in human reproduction. For a start, in almost no cases of heritable genetic disease are there no existing alternatives to achieve the aims of the intervention (or aims that are reasonably close to these). This would make it very hard for any genome editing innovation to meet a standard of proportionality. More important, though, if we want to give proper attention to what is at stake morally with the use of these technologies, is the need to understand these aims. By this I do not mean trying to imagine or penetrate the private motives of any individuals purposing to use the technologies, but rather to understand the technologies' proper modalities.

To be clear, then, the use of genome editing in human reproduction is not a therapeutic intervention (or is so only obliquely). Since the future person does not exist prior to or independently of the conditions in which their conception is brought about, they cannot be being treated for an existing condition. What is at stake in the use of genome editing is bringing about the birth of a human being with one set of genetically conditioned features rather than another set. The important moral question is, therefore, about which of these features, among those for which the prospective parents might have a preference, is a good reason to use the technologies available. Good reasons might include having a genetic connection with both parents and securing the absence of a specific heritable disease. Or they might not.

I would argue that whether genetic connectedness or the avoidance of disease count as good reasons to use genome editing technologies may depend as much on the circumstances of the intervention as on the ontology of the condition the intervention is intended to avoid or secure. Thus, the desire to have children with inbuilt resistance to HIV—the purported reason for He's genome editing—could *conceivably* be a good reason to use genome editing in *some* imaginable conditions. I would maintain, though, that it did not count as a good reason in the conditions that obtained in China in 2018. And the knock-down argument for why it was not a good reason in those conditions was that those conditions included substantial uncertainty about the iatrogenic, or care-induced, risks associated with the procedure. There's undoubtedly still a long way to go before this is likely to change—and no certainty that it ever will. Nevertheless, having genetically related children without genetic disease is evidently seen as a very important reason to pursue it, one that is implicitly, but very widely, socially endorsed, judging by the buoyancy of the in vitro fertilization industry.

It is only when we have understood the aims of the intervention clearly that we are able to consider how these aims should be valued. The point I want to make, however, is not a point about the conditions of *innovation* but about the conditions of *diffusion* of genome editing. The reason we, collectively, need to think about genome editing in human reproduction is not that it answers a pressing unmet need; the reason we need to think about it is that it is a potentially transformative technology. The important question is not "why do we need it?" but, once we have it, as we one day very likely will, "what might we do with it?"—which leads to the inevitable normative question "what *may* we do with it?" The diffusion of genome editing will not depend on it being "necessary" for us to have genome editing but on it delivering a valued outcome as well as or better than incumbent technologies or having desirable features that those incumbent technologies lack.

To resume. What made it more likely that genome editing would be applied in human reproduction is, as we said in our 2016 Nuffield report, the greater accessibility and facility of the genome-editing tool CRISPR-Cas9 than previous techniques for achieving genetic modification in offspring. And what *this* made more likely was that it would be used by someone in the scientific demimonde, someone on the fringes, not strongly socialized into the global scientific elite, not inculcated with or strongly attached to recognized norms and conventions, perhaps even oblivious to them. This is perhaps one of the weaknesses of analogies to the 1975 Asilomar Conference on Recombinant DNA, which has become emblematic of effective scientific self-regulation. Then, it was just about possible to gather everyone who might be in a position to deploy recombinant DNA technologies, along with their camp followers, into a single conference center on the California coast. Not so with genome editing in 2018.

Quest for a unified approach

It has been something of a mission to formulate a unified approach to the international governance of genome editing, to bring everyone into a single tent. Although there have been many initiatives on the part of scientific bodies in many parts of the world, the preeminent sites of debate have been the two international summits in 2015 and 2018, organized

under the aegis of the US National Academies of Sciences and Medicine, the United Kingdom's Royal Society, and the Chinese Academy of Sciences (on the first occasion) and the Academy of Sciences of Hong Kong (on the second). The salient features of the emerging approach to governance have been a principle of separation and a principle of order. These consist, first, in the affirmation that there is a clear and meaningful distinction between basic science, on one hand, and translational research and any potential movement into clinical use, on the other. This separation also implicitly recognizes a distinction between the role of researchers and the business of science relative to the business of innovation. Second, the steps between research and innovation are set out in a determinate order of priority, with elite scientific consensus as the gatekeeper. This does something to shore up the nominal distinction that the emerging technologies of genome editing intrinsically disturb.

The claims that the researcher He had transgressed this separation and circumvented this orderly process were traumatic to the self-conception of the scientific community. The reaction at and after the second summit is worth reflecting on. Of course, He's intervention was repudiated as something no responsible researcher would do. His choice of indication, his technical approach, and his clinical conduct were all denounced. In fact, He's presentation at the University of Hong Kong (just down the road from his erstwhile place of work in Shenzhen) was dramatized in the manner of a confession, and he was summarily anathematized at the summit and in the scientific and popular press.

There is much still to be understood about why He was not dissuaded from his course; about the disinfection of the trail of associations that He left with advisers and collaborators in the United States, China, and elsewhere; about his business interests and the involvement of partners and funders; about the reasons for his choice of indication; about his clinical conduct; and about the response of Chinese authorities to his work and the international reaction. The fact that He was, until that moment, a marginal figure will not be contradicted by anything we may discover about whatever éminences grises turn out to have supported, facilitated, or encouraged his ambitions, whether by commission or omission. But if rumors circulating are true that He has been jailed in China and is potentially facing severe penalties, the distribution of responsibility and the question of whether he is a villain or a scapegoat are important matters. And we must not forget the families and, in particular, the two or three children at the center of all this. For their sake, let me emphasize the recommendation of our 2018 Nuffield report that governments take active steps to affirm that people whose genomes have been edited should be entitled to the full enjoyment of human rights. And let me express the hope that they put this earnestly into practice where these families are concerned.

Here, however, I want to make a couple of brief points about the international governance of reproductive genome editing. The organizing committee's conclusions at the second international summit represented a notable shift from the position that emerged from the first summit. One feature of the altered approach is the shift of emphasis from one kind of regulatory distinction to another. It is as if the ideal of the separate protected space of basic research has been set aside as the primary regulatory concept in favor of the idea of the responsible pathway. The pathway, once defined, is supposed to create a visible, verifiable distinction between those who follow it and those who do not: anyone who is not on the pathway "steps out of line" and is "out of order."

This pathway, the Royal Road, leads out of the enclave of basic science and into the wider world. This raises the stakes, however, because if the ideal distinction is set aside, questions must arise about how far the public interest that is thereby awakened reaches back along the pathway toward its origin. This interest is not new, nor had it been suspended as a matter of right or indulgence, but only held in abeyance. It is as if He's intervention has "broken the fourth wall" of the laboratory and put the conduct of science directly in dialogue with the wider public realm. As a consequence, the notion of "responsibility" in play no longer refers to scientific norms, but rather to broader social norms (or, rather, the way that the subset of scientific norms embedded in broader norms becomes more apparent). A consequence of the events of Hong Kong is that genome editing became a publicly salient phenomenon, and one called to account by the law of the land rather than the norms of scientific research.

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A second shift in the official concluding statement at the second summit was to sideline "broad societal consensus," which had been a key feature of the first summit statement. This, however, now appears all the more relevant to the definition of a responsible pathway, because "responsible" no longer means only (to quote from the first summit's organizing committee) resolving "the relevant safety and efficacy issues…, based on appropriate understanding and balancing of risks, potential benefits, and alternatives" but also taking account of

"broad societal consensus about the appropriateness of the proposed application."

The need for very broad consensus has been reasserted by a group of prominent researchers in the March 13, 2019, issue of the journal *Nature*. Their article ("Adopt a moratorium on heritable genome editing") proposes a voluntary agreement between nations not to approve any clinical use of germ line editing for a defined period, during which they should work toward the establishment of an overarching international framework.

This proposal serves as a counterweight to the position of the summit committee and, it has to be said, to the National Academies 2017 report *Human Genome Editing: Science, Ethics, and Governance*. This line is much more characteristic of most European and international responses, such as those issued in 2015 by the Council of Europe and by UNESCO's Intergovernmental Bioethics Committee. They enjoin that no state should move ahead unilaterally, pending international dialogue on the acceptability of doing so. Perhaps this kind of approach is a consequence of European human rights traditions and systems of civil law in which such strictures are grounded. Notable in this matter, for example, are the mandates enshrined in the Council of Europe's Convention on Human Rights and Biomedicine (the Oviedo Convention), which permits modifications to the human genome only for preventive, diagnostic, or therapeutic purposes and only if their aim is not to introduce any modification in the genome of any descendants, and which is binding law in 29 countries. The basic difference of approach can perhaps be glossed as the difference between leadership and consensus building.

Governance as ecology

In my presentation to the summit in Hong Kong (and elsewhere), I have suggested that we should approach international governance through the dynamic relationship among three venues in which discourses on science and technology are played out. This process may be characterized as "geo-ethics" (by analogy to geopolitics and in contrast to globalizing ethical imperialism).

The first venue may be called (following Michael Polanyi, polymath brother of the economist, Karl) the *Republic of Science*. It is, broadly, enacted in international scientific conferences and professional societies, articulated through a collective research program and structured by a dominant theoretical paradigm. The denizens of this venue are largely the participant list of the international genome editing summits. They play an important role in the education and socialization of future generations, but their primary authority relates to technical standards. This means relatively narrow questions of safety and efficacy, recognizing that even the question of what is an "appropriate understanding and balancing of risks, potential benefits, and alternatives" exceeds this competence. This is not to say that scientists, like others, do not have an important role to play in moral discourse, but as the German philosopher Immanuel Kant memorably averred, when they participate in these public debates, they have no special authority. They are a "public" among others.

The second venue, which may be described as the *Halls of Justice*, is that of international governance, instituted mainly in intergovernmental organizations (such as UNESCO and the Council of Europe). It works ostensibly through the elaboration of legal prohibition and the negotiation of "margins of appreciation" that take account of international ethical differences, although it is a mistake to think that the black letter of the law is its main purpose. Its practical role is to provide a venue to explore agreements and differences using certain principles as a framework for discussion, to weave together an international community that is an essential condition for international cooperation and coordinated action.

The third venue is that of the *Public Sphere,* that of ethics (broadly understood), which explores values and maps contours of possible consensus and conflict within particular social, cultural, and political conditions. It is here that there is a need for social processes that elicit the public interest while attending to voices of dissent, providing opportunities to represent differences of value and vision as a continual critique of orthodoxy in the context of the emerging socio-technological conjuncture. This is the "broad and inclusive public debate" that we call for in our 2018 Nuffield report. Initiatives such as the Global Observatory for Genome Editing (emerging from a 2016 meeting at Harvard University) can offer crucial visibility to the third venue, which, because it lacks formal institution, is always at risk of erasure.

We can recognize certain sorts of pathologies that come from the dynamics and imbalances of power among these three venues. For example, ignoring the third venue can lead to elitism; ignoring the first, to populism. The task, as I see it, is to bring these different discourses together. I do not think that there is a single site for this, some ideal Estates-General, or one that is not structured to favor asymmetries of power and knowledge, but I do think that at a global level, the circulation of people, ideas, and information between these venues can provide a vector for critical reflection. This is why we should support and attend to cross-cutting initiatives such as the one recently established by the World Health Organization. But it is a mistake to imagine that these efforts can ever be encompassed in a single event or institution. They form a rich, dynamic ecology that must be allowed and enabled to evolve openly, inclusively, and justly, and it is the business of us all to see that this is what happens.

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