Bioethics Outlook

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Abusing the new genetic technologies:

Ed Yong explains CRISPR and the case of Dr He Jiankui

It would be unusual not to have heard that, sometime last year, a Chinese researcher used a new genetic technology, called CRISPR, to 'edit' two human embryos. (CRISPR stands for 'clustered regularly interspaced short palindromic repeats'.) Though their father is HIV-positive, neither Lulu nor Nana, who will be born in the next few months, actually has HIV. The researcher 'edited' a normal gene (called CCR5) which the HIV virus uses as a doorway for infiltrating human cells in order to 'lock the virus out' before injecting the cells back into their bodies. The researcher, Dr He Jiankui, proudly described what he had done at the International Summit on Human Genome Editing at the University of Hong Kong in November. And, after his talk, he added that another pregnancy is on the way. He has justifiably been condemned by his colleagues.

What is CRISPR technology?

CRISPR technology is a simple yet powerful tool for editing genomes. CRISPR (its full acronym is CRISPR-Cas9) is a specialized stretch of DNA. The protein Cas9 is an enzyme that acts like a pair of molecular scissors which is capable of cutting strands of DNA.

In this issue

- Bernadette Tobin summarizes an excellent account of the recent abuse of a powerful new genetic technology.
- John Haldane provides another perspective on the use of gene editing.
- Pope Francis addresses the annual meeting of the Pontifical Academy for Life.

The technique has many desirable potential applications including correcting genetic defects, treating and preventing the spread of diseases and improving crops. It allows researchers easily to alter DNA sequences and modify the function of genes.

The technology (which acts like a pair of molecular scissors capable of cutting out strands of DNA) has been adapted from the natural defence mechanisms of bacteria and single-celled micro-organisms. These organisms use CRISPR-derived RNA and various Cas proteins, including Cas9, to foil attacks by viruses and other foreign bodies. They do so primarily by chopping up and destroying the DNA of a foreign invader. When these components are transferred into other, more complex, organisms, it becomes possible to manipulate, or 'edit', genes.

The reaction of the scientific and medical worlds was immediate.

The pioneer of the technology Jennifer Doudna says she was 'horrified'; the Director of the US National Institutes of Health Francis Collins said the experiment was 'profoundly disturbing'. Even Julian Savulescu, the Australian ethicist who has described gene-editing research as 'a moral necessity' described Dr He's work as 'monstrous'.

Why the fuss?

So what is the all the fuss about? Perhaps the best summary yet of what is known (and unknown) about Dr He's experiment has been provided in an article entitled 'The CRISPR-baby scandal gets worse every day' by the writer Ed Yong in *The Atlantic,* a monthly journal from the United States.[1]

In what follows, I summarize Yong's penetrating criticisms of Dr He's experiment, but I recommend the full article as worthy of careful reading. Yong lists a wide variety of forms of irresponsibility in what Dr He has done:

1 Dr He did not address an unmet medical need.

Dr He's team deactivated a perfectly normal gene in an attempt to reduce the risk of a disease that neither child had. The rationale for using a method as extreme and untested as gene editing does not hold up. First, the disease can be controlled in other ways (for example, by the use of antiviral drugs, many of which have been tested for safety and efficacy in clinical trials). Second, the procedure does not confer complete immunity to HIV, since some strains of the virus can enter cells via a different protein. Third, although people with natural deficiencies in the gene appear healthy, they might be more susceptible to West Nile virus, and more likely to die when they catch influenza.

[1] Ed Yong: The CRISPR-baby scandal gets worse every day. *The Atlantic,* 3rd December 2018. https://www.theatlantic.com/science/archive/2018/12/15-worrying-things-about-crispr-babies-scandal/577234/; accessed 5.2.19 All subsequent footnotes are taken from (or summarized from) this article.

2 The actual editing was not executed well.

Dr He's data have not been published or peer reviewed, so many of the details of his experiment are unclear. But based on his presentation at the Hong Kong summit, other scientists have denounced the work for being amateurish.[2]

3 It is not clear what those new mutations will do.

At least two of the three mutations that Dr He introduced into the twins' genomes are substantial changes that could alter how the CCR5 gene works. Typically, scientists would introduce the same mutations into mice or other lab animals to see what would happen. If they felt reassured enough to move into human patients, they could recruit patients with HIV, take out some immune cells, introduce the new CCR5 mutations, transplant the cells back, and monitor the volunteers to see if they remain healthy. This could take months or years.

4 There were problems with informed consent.

It is not clear whether the participants in the trial were actually aware of what they were signing up for. He described his work as an "AIDS-vaccine development project." He claimed that he (and another professor) personally took the volunteers through the informed-consent process. But Dr He has no training in the specific skill of taking informed consent to participation in a clinical trial.

5 He operated under a cloak of secrecy.

Dr He did not tell his institution, the Southern University of Science and Technology, about his experiment. He took unpaid leave in February 2018 to begin work in secret. The university has since said that it plans to launch an investigation into the project, which it called a "serious violation of academic ethics and standards". He also claims that he received ethical approval from Shenzhen Harmonicare Hospital. But the hospital says that the Medical Ethics Committee never met to discuss such a project, and that the signatures on He's approval form "are suspected to have been forged."[3]

[2] For example, it appears that Dr He only managed to edit *half* of Lulu's CCR5 genes; the rest are normal. That could either be because every cell in her body has one normal copy of CCR5 and one edited one (she's heterozygous) or because half of her cells carry two edited genes and half carry two normal ones (she's mosaic). If it is the former, she would not be resistant to HIV. If it is the latter, it depends on whether her immune cells specifically carry the edits. The same might apply to Nana, who, seems to also have normal copies of CCR5 somewhere. In addition, the edited cells don't seem to have been edited in the right way.

[3] Yong, op cit.

6 He organized a public relations campaign.

Even though he kept relevant people and institutions in the dark (and has not yet revealed the actual technical details of his work in any official publication), he simultaneously organized a public-relations campaign, engaging a PR company and creating five YouTube videos describing his actions and the rationale behind them.

7 A few people knew about He's intentions but failed to stop him.

Dr He spoke at scientific conferences about his gene-editing research in other animals. But he discussed his ambitions to edit human embryos with only a select few.

8 He acted in contravention of a global consensus.

The global consensus had in effect been: *Don't rush into it.* In 2017, a report of the US National Academies of Sciences, Engineering, and Medicine did not call for an outright ban on germ-line gene editing—that is, altering the DNA of sperm, eggs, or embryos in ways that could cascade through generations—but said that 'there is a need for caution.' It should only be done in clinical trials with 'rigorous oversight', maximum transparency', an 'absence of reasonable alternatives', only after 'much more research to meet appropriate risk/benefit standards' and 'broad participation and input by the public'.

9 He acted in contravention of his own stated ethical views.

In July 2017, Dr He addressed a meeting at the Cold Spring Harbor Laboratory. He did not mention his plans to edit human embryos, but referred to the case of Jesse Gelsinger, the American teenager who died in a gene-therapy trial in 1999. To avoid such deaths, and the chilling effect that they can have on research, Dr He urged scientists to move cautiously before editing the genome of embryos.

10 He sought ethical advice and ignored it.

It has been reported that Dr He spoke at length with bioethicist William Hurlbut at Stanford University. Hurlbut told Dr He about opposition to the instrumental use of human embryos in the United States, and the grounds for believing that human life begins at conception. [4]

11 There is no way to tell whether He's work did any good.

Both Nana and Lulu will be monitored at least until they turn 18. But as Alta Charo of the University of Wisconsin at Madison said: 'The children were already at virtually no risk of contracting HIV, there is no way to evaluate if this indeed conferred any benefit. If they remain HIV-negative, there is no way to show it has anything to do with the editing.'[5]

[4] Ed Yong, op cit.
[5] Ed Yong, op cit.

12 He has 'doubled down'.

If Dr He has any contrition about how these events have unfolded, it has not been obvious. Speaking at the Hong Kong summit, he apologized, but only because news about his work 'leaked unexpectedly' before he could present it in a scientific venue. Regarding the experiment itself, he said he 'felt proud'.

13 Scientific academies have prevaricated.

In the wake of Dr He's revelations, several scientists have called for a temporary moratorium on similar experiments. By contrast, after the news first broke, the organizing committee of the Hong Kong summit released a bland statement in which it simply restated the conclusions from its earlier report. A second statement, released later, was stronger, calling He's claims 'deeply disturbing' and his work 'irresponsible'.

14 A leading geneticist came to Dr He's defence.

In an interview with *Science*, George Church, a CRISPR pioneer from Harvard University, said that he felt 'an obligation to be balanced about' the affair.[6] Church said that the 'most serious thing' about his experiment was 'that he didn't do the paperwork right'. Alexis Carere, president-elect of the Canadian Association of Genetic Counsellors, disagreed: 'If someone contravenes the rules that we have laid down, we are justified in speaking out about it.'

15 This could easily happen again.

Last year, the world learned that a group of scientists had resurrected a virus called horsepox. Several researchers and ethicists criticized that work, arguing that it would make it easier for others to recreate the related (and far more dangerous) smallpox virus. Regardless of the risks or merits of the experiment, this reveals a vulnerability at the heart of modern science. Small groups of researchers can make virtually unilateral decisions about experiments that have potentially global consequences, and that everyone else only learns about after the fact.[7]

To conclude:

Some years ago, the Catholic Archbishop Sydney, Anthony Fisher op, commented on the use of genetic techniques for truly *therapeutic purposes*.[8] We would not hesitate to act if we knew we could cure a child with Down' syndrome with vitamin therapy or with surgery. So if the only safe and effective way of correcting a grave genetic were by genetic means, then genetic therapy could be something we should consider. But of course, all the normal ethical

[6] Alexis Carere, as quoted in Ed Yong, op cit.

[7] Ed Yong, op cit.

[8] In so doing he distinguished their use for therapy from their use for 'enhancement' – that is, the project of trying to make our children cleverer, more athletic, more beautiful, more ethical, than they would otherwise be, Anthony Fisher expressed deep concern - about 'our desire for control over ourselves and everybody else, our lack of humility, our lack of willingness to accept life as a gift'. *The Australian*, 31.12.2016

principles would apply, including testing safety and efficacy in animals, eliciting genuinely informed consent to participation in a clinical trial, etc. By ignoring those ethical constraints and acting so irresponsibly, Dr He's experimentation has delivered a blow to that whole therapeutic endeavour.

Respecting the human form

John Haldane

Anyone who has had the good fortune to see the magnificent exhibition of paintings by Mantegna and Bellini at the National Gallery in London will have been struck by their attention to the human form: at once expert in rendering contour, proportion and volume but also perceptive in capturing or expressing posture, gesture and meaning.

Some of those depicted such as Loredan, Doge of Venice, are great and famous; others like the shepherds approaching the Virgin and child are humble and anonymous; and in the figure of Jesus, whether as cradled infant, crucified man, or resurrected saviour, the artists endeavour to show us the transcendent in and beyond nature.

However ancient the period, unfamiliar the setting or dramatic the scene, the human form appears as a constant: a common element in art, history, philosophy, politics and religion. Anthropology and the interpretation of ancient texts and artefacts are made possible by, and confirm, the commonality of humankind. As the Roman dramatist and former slave Terence wrote: "I am human and nothing human is alien to me." To endorse this maxim is not to say that no human condition is better or worse than any other, for there is both soundness and defect of body, mind and spirit. But both good and bad are identified by reference to the human form, considered not just physiologically, but psychologically, morally and spiritually.

The patrician figure who appears in Bellini's portrait of the Venetian Doge carries his inherited features as proudly as his official robes, and it did not require the theory of genetics to understand that physical and mental characteristics are inherited. Selected breeding goes back before the Greeks and the Romans, but they certainly favoured it in the shaping of human offspring.

The modern science of genetics dates from the mid-nineteenth century when an Augustinian friar, Gregor Mendel, while hybridising plants, realised that traits are not produced by blending "parental" characteristics but by the combination and interaction of units of inheritance. What those units were

and how many of them there are would only be discovered in the following century with the development of molecular genetics.

As in most areas of scientific enquiry, our knowledge of genetics is growing rapidly. The largest collaborative undertaking in the history of biology was launched in 1990 and completed a little over a decade later. The identification and mapping of the human genome involved determining the molecular components in human DNA and the segments and sequencing of those that constitute genes. Because genes have structural and functional effects, the success of the Human Genome Project prompted questions about the practical application of this knowledge.

The detail and precision of this mapping, together with the influence of causal determinism pervasive within quantitative theories and explanations, encouraged the idea that the genetic make-up of individuals necessarily leads to specific outcomes. But, as Mendel suspected when he criticised the earlier theory that the character of the offspring is a blend of the traits found in the parents, the way in which the character of human progeny is determined by that of their ancestors may be complex and indeterminate.

In the case of contemporary genetics, four factors stand in the way of any simple projections upwards from the genotype to the phenotype (that is in the genes in our DNA responsible for a particular trait to observable physical properties and behaviour). First, there are variations in the genomes of individuals, so one cannot appeal simply to general patterns to be found in the overall human genome. Second, few features are monogenic, but rather depend on interactions between numbers of genes. Third, those interactions, and the expression of individual genes in fixing the structure and function of cells, is subject to external environmental influences. And fourth, individual human bodies themselves contain a vast population of symbiotic microorganisms whose presence and behaviour effect the expression of genes.

But as well as these physical facts, there is the significant difference made by consciousness, reflection and reasoning. Even if predictions are forthcoming about the upward effects of biology on the human form in its physiological and behavioural aspects, there is also efficacy at the level of thought so that as well as considering what is predicted, or what *would* happen there is also the question of what is morally required, or what *should* happen.

I am not suggesting that by channelling our thoughts we can somehow impede or redirect biological processes as some New Age practices and mediative techniques imagine, but that as well as what happens, there is also the issue of how to respond to it. It is in relation to the latter that the idea of the human form, or the form of the human, offers insight and guidance.

The issue of applied genetics is not just a speculative one – in one form or another it has been with us for decades. Preimplantation screening and prenatal diagnosis are routinely used to detect abnormalities and mutations (as well as identifying the sex of the embryo) – generally with a view to intervention, usually destructive. Such intervention can be positive, for example, when it involves gene therapies intended to supply healthy genes, or when it leads to gene editing to correct, delete or modify gene sequences. But all of these procedures give rise to ethical questions.

In the case of gene-editing – which has come to greater notice recently through reports that a Chinese scientist, He Jiankui, altered the genes of twin female human embryos to ensure that they cannot contract HIV – there is the obvious issue of unpredicted and unpredictable consequences.

In the use of cellular repair mechanisms to modify DNA by genome editing offers the prospect of correcting mutations and introducing additional functions. However, it also involves risks of producing harmful mutations. Some of these may result from selecting and cutting genomes that contain unintended sequences. There is the further issue of the resistance of tissues and cells types to infection and transfection. The effects of this resistance and of additional efforts to overcome it are uncertain.

As with cloning, the risks of cellular mutation, physiological and functional malformation and early death provide several good reasons why we should not proceed with these uncertain and potentially hazardous techniques. However – though this research inevitably involves the creation of embryos for experimentation and destruction – these are contingent and consequential factors that may be overcome through further research. We have to look beyond these risks at deeper ethical and philosophical considerations. First, it is necessary to distinguish between actions intended to remedy a defect and thereby restore a normal feature, and those aimed at changing the character of a thing, to give it enhanced qualities or additional powers. The former concern repair, the latter transformation. Aside from unanticipated immediate effects, there is the issue of further collateral consequences. By way of an analogy, by making people ambitious may counter lack of attainment, but it may also remove associated circumstantial benefits, such as contentment.

The study of the physical aspects of the human form is the business of the sciences, but the understanding of human life, and the place of norms, ideals, principles and values is the business of imaginative, ethical, philosophical and religious reflection. Current discussions of how genetic and reproductive technologies should be combined tend to be conducted almost exclusively in terms of harms and benefits. There are two problems with this: first, the calculations are crudely utilitarian; second, they omit non-consequential factors.

For most people the challenges of reproduction are felt to be worthwhile and are accepted as the corollary of the creation of another human being. The sense of otherness felt at the sight of a newborn child registers a combination of continuity and difference that contributes in part to the value of conceiving and having children. By contrast, the deployment of genetic science in the service of enhanced reproduction suggests a wish to overcome human nature as it is, in favour of some unspecified “improved condition”.

It may be said that the application of genetics offers the prospect of creating children whose initial condition and subsequent development are likely to be better than those of natural offspring. But this reply embodies a disregard of the human form that is the condition of our existence, the recognition that binds us to peoples past or far away.

A good human life is not one that tries to overcome the human form, but one that is developed within the context of it. That is why we resonate to the art of Mantegna and Bellini and take hope in the idea that God took on our human form.

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Pope Francis' speech
to the Pontifical Academy for Life
February 25, 2019

My Dear Brothers and Sisters,

Our meeting is taking place during a great Jubilee for the Pontifical Academy for Life - the Twenty-Fifth Anniversary of its Founding. For this important occasion, last month I sent a letter entitled *Humana Communitas* to your President. What lead me to write that letter was first of all to thank all Presidents who have succeeded one another at the helm of the Academy and all the Members for their talented service and generous commitment in protecting and promoting human life over these past twenty-five years.

We all know the difficulties our world is going through. The fabric of family and societal relationships is becoming ever more threadbare and there is growing tendency to close ourselves off within ourselves and our own interests, with serious consequences for the "great and crucial question of the unity of the human family and its future." (*Humana Communitas*, 2) This presents us with a great paradox: just when humanity possesses the scientific and technical ability to procure well-being that is spread fairly, as God would wish, we see instead conflicts that are increasingly bitter and an increase in inequalities.

The Enlightenment myth of progress is disappearing and the capabilities that come one after another in science and technology don't always produce the desired results. In fact, on the one hand technological development has allowed us to solve problems that until a few years ago were insurmountable – and we are grateful to the scientists who made those breakthroughs; but on the other hand, difficulties and dangers have arisen that are sometimes more insidious than what went before. Being "able to do" something threatens to overshadow *who* is acting and *for whom* something is being done. The technocratic system that is based on the criterion of efficiency says nothing to answer the deepest questions that man asks himself. And if indeed we cannot do without technology's resources we must recognise that by using them we subjugate ourselves to it. Still, technology is a sign of humanity. It shouldn't be seen as a force that is outside us and hostile but rather a product of our genius through which we obtain what is necessary for our lives and that of others. It is a specifically human way of living in the world. Nevertheless, today's evolution of technical ability leads to a dangerous bewitchment – instead of providing human life with the tools that improve life, we run the risk of handing life over to be ruled by those tools and they end up deciding the value of life. This reversal is destined to have terrible consequences: not only will machines operate themselves, they will end up operating humans. Human reason is thus reduced to a thought process without effects that is unworthy of human beings.

We see, unfortunately the serious damage that is caused to the planet, our common home, by the indiscriminate use of technology. For this reason, global bioethics is an important front on which to do battle. It reveals our awareness of the profound effects of environmental and social factors on

health and life. This is an approach that is very much attuned with the integral ecology that I described and promoted in the Encyclical *Laudato si'*. In addition, in today's world marked by close interaction among diverse cultures, we must bring to bear our specific contribution as believers to the search for operational criteria that can be universally shared, that can become points of common reference for those who have the serious responsibility of making decisions at a national and international level. This also means getting involved in the question of human rights, and their corresponding duties. This is the field in which to carry out common research leading to a universal ethic, an area where tradition has addressed many questions by drawing on the patrimony of natural law.

The Letter *Humana Communitas* speaks explicitly of "emergent" and "convergent" technologies. The possibility of intervening on living material of ever-decreasing dimensions, of processing even greater volumes of data, of monitoring – and manipulating – cognitive and deliberative cerebral processes has enormous implications. It approaches the threshold of the biological specificity and spiritual uniqueness of humanity. It was in this sense that I stated the "distinctiveness of human life is an absolute good" (*Humana Communitas*, 4).

This bears repeating: "Artificial intelligence, robotics, and other technological innovations are to be used in a way that serves humanity and the protection of our common home, rather than the exact opposite, which, as various studies reveal, unfortunately often happens." (*Message* to the World Economic Forum at Davos, January 12, 2018). The inherent dignity of every human being is to be firmly fixed at the centre of our reflection and our action.

In this regard, it must be noted that the term "artificial intelligence" – even though it produces a certain effect, can be misleading. The term hides the fact that – despite the performance of certain low-level activities (that was the original connotation of the word "robot") – these automatic actions are qualitatively different from the uniquely human activities of knowing and acting. For this reason, artificial beings can become dangerous to society. Likewise there is already the risk that man will become technologized instead of technology becoming humanised. These so-called "intelligent machines" are being too hastily endowed with abilities that are specifically human.

We must understand better what, in this context, are the meanings of intelligence, conscience, and emotivity, affective intentionality and moral action. Artificial devices that simulate human abilities are in fact without human characteristics.

We must be aware of this in order to orient the regulation of the way machines are used, and of related research, toward constructive and fair interaction between human beings and the most recent machines. Their numbers are in fact increasing throughout the world and they are transforming the way we live our lives. If we are able to make their presence beneficial to our lives, the extraordinary possibilities of these new developments will be able to be realised by every individual and all of humanity.

The debate underway among specialists shows the serious problems involved in controlling the algorithms that process great quantities of data. Likewise, the technologies for genetic and cerebral manipulation raise serious ethical questions. In any event, the attempt to explain the whole of thought, sensibility and the human psyche on the basis of the functional sum of their physical and organic parts does not take into account the emergence of the phenomena of experience and consciousness. The human phenomenon surpasses the result of the mere calculable assemblage of its individual elements. Even in this context, the axiom according to which the whole is greater than the sum of the parts takes on a new depth and relevance. (Cf. Exhort. Ap. *Evangelii gaudium*, 234-237).

On the other hand, but in this same line of the complex synergy of *psiche* and *techne*, that which we learn about cerebral activity provides us with new indications about how to understand consciousness (one's own and that of the world) and the human body itself. It is not possible to prescind from the web of multiple relationships if we are to acquire a greater understanding of the entire human dimension.

Certainly, we cannot draw conclusions from the data of empirical science. But we can draw from them, even from theology, certain indications that are instructive for our anthropological reflections, just as we have throughout the history of science. It would be decidedly contrary to our most valid tradition to cling to the anachronistic conceptual apparatus that is unable to dialogue adequately with changes in the concept of nature and constructs, of constraints and freedom, of means and end, that we have been introduced by the new culture of action proper to the technological age. We are called to place ourselves on the path taken with determination by the Second Vatican Council, which calls for a renewal of theological disciplines and a critical reflection on the relationship between Christian faith and moral action, (cfr. *Optatam totius*, 16)

Our commitment- intellectual and specialist – will be a point of pride for us in our participation in an ethical alliance in favour of human life. It is now urgent, in a context in which ever more sophisticated technological means involve directly the human qualities of the body and the psyche, to develop a project that can be shared with all the men and women engaged in scientific research and healthcare. This is a difficult task, given the hectic pace of innovation. The example of intelligent and believing teachers who have embarked with wisdom and boldness on a voyage of discovery with their contemporaries, with the goal of understanding the patrimony of faith to a degree that is worthy of man, should encourage us and give us support .

I ask you to continue your study and research in order that your work of promoting and defending life may be ever more effective and fruitful. May the Blessed Mother assist you and my blessing accompany you. And please do not forget to pray for me. Thank you.

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Deputy Chair, Nuffield Council on Bioethics
Advisor, National Institute for Health & Care Excellence

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