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Lessons From the **HE JIANKUI** Incident

He Jiankui's announcement on November 26, 2018, that he had used CRISPR technology to alter the genes of two embryos that resulted in births shocked everyone in China, especially scientists and regulators. Later that day, 122 Chinese scientists issued a statement condemning He for violating scientific, ethical, and legal norms, and hundreds more signed the statement in the next few days. Government research regulators were equally shocked and have launched an investigation to determine exactly what He did and to gather insights into what needs to be done to prevent other scientists from engaging in similar rogue activities.

The well-known Chinese saying *tong ding si tong* (when the pain ceases we have to be thinking of the pain) could imply drawing a lesson from a bitter experience, recalling past pain as a warning for the future, or bringing home the lessons painfully learned. Many Chinese scientists, physicians, regulators, and ethicists have entered a period of soul-searching, trying to draw lessons from the incident and to achieve *huai shi bian hao shi* (transforming a bad thing into a good thing). Chinese physicians and scientists know very well that they have an obligation to respect and protect their patients and research subjects that must temper their quest for fame and fortune. But the nation needs to be certain that these values are reflected in the regulatory system to prevent outliers such as He from misbehaving.

Careful scrutiny should be applied to a variety of emerging biotechnologies such as gene editing, the use of stem cells, mitochondrial transfer, xenotransplantation, synthetic biology, nanomedicine, and the application of artificial intelligence (AI) to medicine. One of the lessons from the He incident is that although we are ignorant of many of the possible indirect effects of gene editing, we regulate as if it were a well-understood conventional technology. It is a mistake to apply what the transhumanist philosopher Max Moore calls the "proactionary principle" of taking a very permissive approach to experimentation with new technologies. This might be acceptable for some technologies with which we have considerable experience, but not for this new generation. Instead, we need to develop a more cautious approach that incorporates an extensive ethical and safety inquiry before scientists take action.

One of the distinguishing characteristics of emerging biotechnologies is that they pose extraordinary risks that may affect future generations as well as tremendous potential benefits to human beings and society. Genome editing may effectively treat and cure intractable genetic diseases and protect future generations from inheriting these conditions. However, it may also introduce genetic changes that will harm our progeny. Synthetic biology could facilitate the development of products that will help meet nutrition, fuel, and medical needs, but it could also enable the creation of vaccine-resistant viruses that could result in a devastating global pandemic on the scale of the 1918 Spanish flu.

A second hallmark is uncertainty. Human reproduction and development is so complex and the factors that influence it so interdependent that it is extraordinarily difficult to predict all the consequences of any intervention in the human genome. After we edit the genome in the egg, sperm, zygote, or embryo, it is quite difficult for us to determine whether editing affects any nontargeted genes, and almost impossible to know the impact of the gene editing on the development process. Even if we perform experiments on humans, it will be a challenge to assess the outcome. Consider the births that resulted from He's experiment, which was designed to make the resulting twin babies immune to HIV infection. If they never become infected, we still cannot be certain that it was the gene editing that protected them, nor will we know whether the genetic intervention made them more susceptible to other infections or affected their health in other ways or what effect it will have on their children and their children's children. Thus, we cannot conduct a reliable risk-benefit assessment or provide necessary and adequate information to parents who might be considering a genetic intervention on an embryo so that they could provide valid informed consent. This explains why He's actions were so irresponsible.

The third critical characteristic of an emerging technology is that it can present unprecedented ethical challenges. New AI systems are using algorithms to analyze vast stores of medical data to identify patterns that could help us make earlier and more accurate diagnoses, support preventive medicine, and guide therapeutic decisions. The use of AI to analyze public health data could help us detect and track the outbreak of infectious diseases, enhance medical monitoring, and lead to optimization of demand management and resource distribution. But some of the data mined by AI include human behavior that is often attributed by race, gender, income, and other groupings. The way these data are then used to predict other behaviors can sometimes build in racist or sexist assumptions that distort the analysis. Besides, the patterns of past human behavior might not be a good predictor of what people will do in an unprecedented event such as a bioterror attack or viral epidemic.

These characteristics of emerging biotechnologies illustrate why a proactionary approach is inappropriate. Instead, we have to take an approach called *lun li xian xing* (ethically thinking ahead of action). Before we launch any project that uses these emerging biotechnologies, we have to develop tentative regulations based on comprehensive inquiry and rigorous ethical discussion. These regulations must be tentative because of our current degree of uncertainty; they will have to be revised as our knowledge and experience expand. One aspect of regulation of which we can be certain is that before scientists launch any project, they should submit their application not only to an institutional ethics review committee but also to provincial/municipal and national ethics committees to be reviewed and approved.

Because each of the emerging biotechnologies has unique characteristics that present specific legal, ethical, and safety challenges, it will not be possible to develop generic regulations that can be applied to all.

After He's incident, China's National Health Commission promulgated draft regulations on novel biomedical technologies. Although this was an encouraging step in the right direction, it is not sufficient. We Chinese bioethicists plan to draft recommended regulations for each of these emerging techs—including genome editing, stem cells and regenerative medicine, xenotransplantation, synthetic biology, and nanomedicine—on the basis of comprehensive inquiry and debate on ethical, policy, and governance issues.

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We have to make clear to the research and medical community that self-regulation is necessary but not sufficient. Research professionals always focus on the importance of scientific and technological innovation and pay less heed to the social, political, and ethical ramifications. We cannot expect these researchers to have expertise in these emerging disciplines, so we need to have participation of those with the relevant knowledge. In addition, we have to be alert to the potential conflicts of interest of those directly involved in research and experimentation. Scientists are as prone as anyone to self-deception when personal fame and fortune are at stake. An effective regulatory system will require top-down authority from government entities as well as bottom-up oversight from the research community, and it must entail participation by political leaders, researchers, humanities and social science

scholars, and public stakeholders.

The previous generation of Chinese research regulations did not specify legal liability or penalties for violating the rules. They were thus a very weak disincentive to scientists who might be willing to violate the norms. We are happy to see that recent draft regulations promulgated by the National Health Commission explicitly prescribe penalties for breaking the rules. In the draft regulations the wrongdoers could be punished by circulating a notice of criticism or warning, fining them, banning their clinical research or/and clinical practices for a given period, or suspending their license. If the case constitutes a crime, the liability should be investigated according to the law.

In He's case, the report on preliminary findings mentioned only that he would be dealt with seriously in accordance with current law and regulations; if he is suspected of committing crimes, he will be handed over to the public security department to handle. For example, if he bribed some officials to dodge the laws or some professionals to fabricate faked documents, he would be faced with criminal allegations. However, the investigation report did not specify what kind of crime he may have committed, so we will have to wait for the final results of the investigation.

Chinese scientists and bioethicists should actively participate in international efforts to standardize regulations among countries.

The old rules also failed to acknowledge the importance of mandating transparency on the part of researchers. He claimed that he had conducted innumerable experiments on animals, but he never published the findings. If he had, we would have known to keep an eye on where his research was heading. Many Chinese scientists do not publish findings during the early stages of their work. They seem to prefer to have the final results arrive as a surprise to the world. But publication and review of research at every stage is necessary to keep it on a reliable path. Too many scientists are publishing final results that cannot be reproduced; without early-stage publications, it is difficult to discover where the research went wrong. We recommend that scientists publish reports on their early stages of research and that they publish negative as well as positive results. This type of transparency will not only provide an opportunity for useful feedback to the research but will also be helpful to other researchers working in that field.

Finally, Chinese scientists and bioethicists should actively participate in international efforts to standardize regulations among countries. This is not now the case. One reason that some people offer for not actively participating is that there is an unbridgeable and incompatible divide between international ethical guidelines and Chinese traditional culture. That is not true. China's national policy for dealing with the relationships between different countries and cultures is "seeking common grounds and reserving differences." Cultural differences are not a justifiable reason to reject international guidelines and refuse to participate in international efforts to develop shared regulations on the innovations, R&D, and applications of biotechnologies. Indeed, Chinese scholars participated in drafting the Universal Declaration of Human Rights, adopted by the United Nations; the Universal Declaration on the Human Genome and Human Rights, adopted by UNESCO; and the International Ethical Guidelines on Biomedical Research Involving Human Subjects, issued by the Council for International Organizations of Medical Sciences, a nongovernmental, nonprofit group established jointly by the World Health Organization (WHO) and UNESCO. Also, one of us (Zhai) is a member of the current WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight for Human Genome Editing.

He's unfortunate experiment should never have taken place. The only upside to his misconduct is that it might have provided the catalyst for China to update its regulations in ways that will preserve the integrity of research and prevent similar misbehavior in the future.

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