Commentary: Code Dread?

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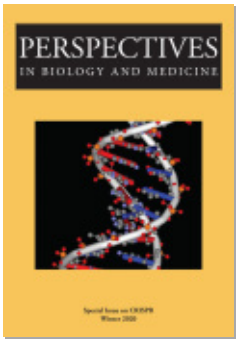

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COMMENTARY

code dread?

NEAL BAER

CRISPR KEEPS ME UP AT NIGHT. I marvel at its potential to cure insidious genetic diseases and scourges like malaria. I shudder at the ways it might be misused to create biological weapons. What frightens me most, though, is what I can't predict: how will we use CRISPR? How will it change evolution? How will it redefine the very nature of our existence?

CRISPR (clustered regularly interspaced short palindromic repeats) is an ingenious cut-and-paste system that homes in on a particular DNA gene sequence and then, using Cas9 enzymes, snips it out. That sequence is then replaced with a new one that rewrites or repairs the original. Two different cells—somatic, from the body, and germline, from gametes—can be manipulated using CRISPR. Yet only germline genome cells can be inherited by future offspring.

In 2019, scientists in the US used this method to treat a patient with sickle cell disease. In Europe, scientists treated one with beta thalassemia. Both patients, suffering from genetic mutations of their hemoglobin genes, underwent bone marrow ablation. Then CRISPR was used to modify their own blood-producing stem cells to make healthy fetal hemoglobin. The CRISPR cells were engrafted in each patient—known as a somatic treatment—without the usual worry of donor rejection. Both patients are reported to be doing well, making healthy fetal

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hemoglobin. These CRISPR-based treatments have kept them from needing transfusions or hospitalization for severe anemia or vaso-occlusive crises. Using CRISPR to treat genetic mutations like these, which cause inordinate suffering and a shortened life span, is nothing short of miraculous.

Why worry, then, about using CRISPR as long as it can be made safe in the clinical setting? Repairing the somatic genetic mutations in an individual means that scientists can do the same to the germline genome, and this could change human evolution. "That raises the possibility, more realistically than ever before," notes Michael Specter (2015), a well-known science journalist, "that scientists will be able to rewrite the fundamental code of life, with consequences for future generations that we may never anticipate" (54). One method for accomplishing such a profound feat of editing is by using a CRISPR-based gene-drive system that preferentially propagates a genetic trait through an organism and its offspring. Imagine using CRISPR to make a female mosquito infertile, causing it to be incapable of laying eggs. Instead of a 50% chance that the disruptive gene is inherited, a CRISPR gene copies itself, making the inheritance 100%, leading to a self-destructing mosquito.

How do we conceive of any unintended consequences that could come from using CRISPR gene drives to make female mosquitoes infertile in order to eradicate malaria? Can we ever be certain of the environmental impact of such an undertaking, even if it means preventing a thousand children from dying of malaria each day? Can we prevent the malevolent use of CRISPR to conjure up bacteria or viruses that can wipe out millions or destroy food crops the world depends on? "If you can edit a creature to solve a problem," declares gene-drive discoverer Kevin Esvelt (2019), "you can edit a creature to create a problem."

CRISPR has vaulted us into a binary world of hope and potential devastation. It can provide us with cures that will alleviate suffering, along with terrifying bioweapons that could destroy us; treatments for diseases that assail humankind, and enhancements that could give the wealthy an even greater societal edge—what the political theorist Michael Sandel (2004) warns could lead to two subspecies, "the enhanced and the merely natural." This dual-use research of concern "could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security" (NIH 2019).

CRISPR is not the first exterminating peril the world has faced. Scientists and inventors have given us nuclear weapons and fossil fuel engines that have posed dire threats of nuclear winter and global warming. Since the atomic bomb was dropped on Hiroshima and Nagasaki, nation-states have operated under the paradigm of mutually assured destruction: if you bomb us with a nuclear weapon, we will retaliate. The threat of mutual annihilation has averted nuclear Armageddon. With CRISPR, this old paradigm has evaporated.

Today a rogue scientist with access to a DNA synthesizer, DNA sequences—which can be easily purchased—and some basic scientific expertise can build genetic weapons of mass destruction. Scientists have already made horsepox, polio, and virulent avian flu. Next, CRISPR was used on embryos, which were not brought to term. Finally, in 2018, twin girls were born with a CRISPR-engineered germline mutation.

Dr. He Jiankui, a Chinese geneticist, used CRISPR to manipulate the germline of embryos that became the twins, claiming to have made them resistant to HIV. An uproar ensued against He among scientists, journalists, and bioethicists. A few, however, like the Harvard geneticist George Church, supported him, claiming in an interview that He was subjected to "bullying" and that "as long as these are normal, healthy kids it's going to be fine for the field and the family" (Cohen 2018). At the end of 2019, He and his two colleagues were sentenced to three years in prison and fined $430,000 for illegally practicing medicine by "knowingly violating [China's] regulations and ethical principles with their experiments. . . . . The court indicated that three genetically edited babies have been born" (Kennedy 2019).

BEFORE AND AFTER

He's manipulation of the twin embryos has changed how scientists and the public view CRISPR. Before his experiment, germline genome editing (GGE) was regarded as verboten by numerous academies and scientists, at least until strict safeguards could be put in place. These twins raise many questions about moving forward with germline editing. What was conceivable has been made real.

Meiosis is nature's way of sorting and resorting the genes of most living organisms, guaranteeing diversity within species and driving evolution to select attributes—in the form of mutations—that benefit the organism and favor survival. Those mutations also inflict some individuals with painful, life-limiting genetic syndromes. Some, like Tay-Sachs, are lethal early in life, and others, like Huntington's, are genetic time bombs. CRISPR has the capacity to harness meiosis, to seek out and destroy genetic scourges, both somatically and heritably.

We must address the ethical dilemmas CRISPR raises, particularly when we begin to genetically tinker with the germline of human beings and any other living plant or organism. Granted, scientists, agronomists, and even dog and cat breeders have been manipulating the germline of species for thousands of years. But not until recently has it been possible to do this in a targeted way. CRISPR has drawbacks because it can cause mutations itself, but newer CRISPR-based tools, like prime editing—"a versatile and precise genome editing method that directly writes new genetic information into a specified DNA site"—offer the possibility of avoiding the errors that CRISPR can make (Anzalone et al. 2019).

I had the good fortune of writing about CRISPR for my Netflix television series, *Designated Survivor*, in which a few rogue scientists, working for a right-wing

presidential candidate's campaign, sought to make ethnic bioweapons. Unfortunately, this endeavor was not as farfetched as it might sound. During Apartheid, the South African government sought to use biologically designed weapons in what was termed Project Coast to differentially attack the indigenous South African population. Particularly worrisome was discovering how easy it is to obtain DNA sequences for designing a CRISPR gene and how DIY labs are not typically overseen by authorities who can assure that CRISPR is used safely. I also learned that the genome of the opium poppy had recently been mapped, and I pondered how CRISPR might be used to inject a virus or lethal gene drive that could disrupt the heroin industry. Farfetched? Perhaps. But not inconceivable.

In light of these quickening advancements in CRISPR technology, we decided to devote this issue of *Perspectives in Biology and Medicine* to CRISPR, engaging renowned geneticists, bioethicists, and philosophers to write about what they think are the most pressing questions CRISPR raises today.

We invited our contributors to consider a number of questions listed below but did not ask them to limit their essays to any particular question or point of view. Owing to space limitations, we did not pursue questions on using CRISPR to change the germline of insects or animals, for instance, by making deer mice resistant to Lyme disease, nor did we discuss its potential use on crops to thwart disease and increase yields. We asked each contributor to write with focus and passion, delving deeply into their own views and those they disagree with. Listed below are the questions each contributor received:

- How do you view CRISPR's impact on human evolution? Are you concerned about how CRISPR will be used in the future?

- What are the short- and long-term prospects for using CRISPR to eradicate genetic diseases like Huntington's, cystic fibrosis, and Tay-Sachs?

- How should we think about the possibility of children having more than two parents when CRISPR is used to eradicate a genetic disease? Are there other reasons for allowing CRISPR to be used? For instance, if gay or lesbian couples wish to have biological children with both same-sex parents' genes?

- What concerns do you have about possible eugenics applications for CRISPR, or is that a science fiction scenario?

- What worries you most about the possible misuse of CRISPR? And conversely, what gives you the most hope about CRISPR's prospects?

- What, if any, controls should be put in place to prevent CRISPR from being used to make biological weapons?

- What governmental oversight, if any, should be established to monitor and regulate CRISPR experiments and treatments?
- What kind of oversight, if any, should universities and research institutes establish for CRISPR experiments and applications?
- What market forces are shaping the use of CRISPR?
- How should we be thinking as a nation about the use and application of CRISPR? What role should the US have in global conversations about its use?
- Should the US be working with other nations on a CRISPR use agreement? What would that agreement entail? How would it be monitored?

CRISPR: A Rose Bearing Thorns

The 12 essays in this special issue probe the challenging questions posed by a genetic editing tool that has the potential to give an individual the power, as Esvelt (2019) warns, to "single handedly genetically engineer a whole species."

Meiosis makes each of us unique. CRISPR could dilute or attenuate that uniqueness by rewriting our genetic code. If that code is rewritten in our germlines, it will be passed on to our progeny, though Esvelt and others are working on daisy-chain gene drives that can put the brakes on CRISPR sequences passed down after several generations—a *kill switch* in case of unforeseen outcomes.

In our first essay, Rosemarie Garland-Thomson presents a series of formidable questions CRISPR raises when we manipulate the genes in somatic and germline cells. While CRISPR is often discussed in terms of relieving human suffering, Garland-Thomson asks us to address what we mean by suffering. Where do we draw the line on remediating *disability* when there's no consensus on that term? "The business of modern medicine is to sort human variations into the opposing categories of disease and non-disease," writes Garland-Thomson, "or what has been considered since the 19th century as 'normal.' Making up new disease categories, or what medical science calls discovering new diseases, is a market-driven growth industry." Garland-Thomson asks us to think hard about how we define and categorize disease and health, lest we slip into a mindset of "liberal eugenics," that "enforces health as an unassailable aim [that] takes precedence over ethical interests." It's a slippery slope when we accept CRISPR being used to treat whatever one feels is *not healthy*. And when money is to be made, one can imagine CRISPR being used for enhancement for short stature or not having the musculature of a top athlete.

Garland-Thomson continues that it's difficult "reimagining *then* through the knowledge of *now*," particularly when we think about whether one would have

terminated a pregnancy or used CRISPR on a fetus born with a genetic syndrome in light of knowledge one has long after that child has been born. And yet, with CRISPR potentially available for clinical use, she cautions us that we need "to make decisions in the present that will yield intended but uncertain future outcomes."

Many scientists contend that the driving question CRISPR poses is whether it fulfills an unmet medical need and can be made clinically safe. Garland-Thomson, along with many of our other contributors, cautions that we must look further to "what the existence of CRISPR technology suggests about the limits of being human." Garland-Thomson worries that GGE approaches a "new eugenics." Using germline editing to enhance or improve future persons, she says, may lead to "morally unacceptable consequences, ranging from producing medical harm to abrogating consent, intensifying genetic discrimination, increasing social inequality, promoting conditional parental acceptance, turning people into products, fostering a commercial medical industrial complex, and encouraging rogue scientific and medical practice."

Garland-Thomson questions the faith we traditionally place in scientific breakthroughs, noting the "collateral damage" from mechanical inventions ranging from nuclear energy, to gasoline-powered engines, plastic, or opioid medication—"all aimed at making a better future for everybody."

Alta Charo counters that what is "often lacking in this debate has been an effort to look back at debates surrounding earlier advances in reproductive technologies, most of which have been accompanied by fears of eugenics, the loss of human dignity, and the disruption of parent-child relationships. While these advances have each had pockets of abusive uses, they have been integrated into modern life without bringing about wholesale destruction of society." Helen O'Neill reminds us that "very little work has ever been done to look at genomic alterations, rearrangements, or unwanted effects caused by the routine procedures [like IVF] carried out clinically on embryos." We might begin there, she cautions, looking more closely at assisted reproduction, before moving forward with GGE.

Accentuate the Positive, Eliminate the Negative, and Don't Mess with Mr. In-Between

After the births of the CRISPR-edited twins, the Organizing Committee of the Second International Summit on Human Genome Editing concluded that "the scientific understanding and technical requirements for clinical practice remain too uncertain and the risks too great to permit clinical trials of germline editing at this time. Progress over the last three years and the discussions at the current summit, however, suggest that it is time to define a rigorous, responsible translational pathway toward [GGE clinical] trials" (NAS 2018).

In their essay, Kevin Doxzen and Jodi Halpern note with trepidation that opening the path for GGE clinical research might allow it to proceed under some conditions. They write that "as detailed recommendations to navigate this unique terrain are under development, we suggest an approach that begins with identifying serious concerns about social exclusion and social justice that arise with GGE. These concerns . . . are not captured by a utilitarian ethics framework, which seeks to maximize positive over negative health outcomes." In contrast, George Church recently stated: "I believe we have an ethical obligation to maximize benefits and minimize harm. . . . If we have an opportunity to eliminate infectious and genetic disease, or some subset of them—even one of them—then we should pursue it" (Hall 2019, 14). Can future generations, who will undergo whatever germline edits we make today, no matter how well intended, consent to these changes? Is it nonsense to think about unborn people consenting? Doxzen and Halpern argue that "these concerns reflect people's rights, rights that have standing independently of outcome assessment and that set constraints on the means to achieving an otherwise positive end like the goal of improving population health."

Doxzen and Halpern review a number of potential outcomes using GGE. They reflect on public access to medically necessary treatments and whether enhancements for one's prospective children should ever be allowed, and they raise deep concerns about eugenics that can be conflated with our quest to improve our health and that of our future children.

As national and international scientific bodies meet to develop guidelines and regulations for using GGE, Doxzen and Halpern argue that a human rights-based approach, rather than a utilitarian one, ought to "ensure that this socially disruptive technology minimizes further marginalization of people with disabilities and does not create a new form of social injustice."

When the Personal Becomes Genetic

One of the arguments against using CRISPR to rewrite the germline is that options already exist for determining whether an embryo might carry a parent's genetic mutation. Parents can undergo genetic testing and through IVF and preimplantation genetic diagnosis implant embryos that do not contain that mutation. Others note that IVF can pose risks to the mother or woman donating eggs, and some object to destroying embryos on religious grounds (though one might presume that they would also object to using CRISPR to change an embryo that nature or God made). George Church, in a recent interview, says we "should be focusing on outcomes . . . rather than methods" when it comes to treating genetic diseases like sickle cell anemia, cystic fibrosis, and beta thalassemia. He concedes that "most of these can be cost-effectively dealt with by genetic counseling" and IVF, but he offers several arguments in favor of using GGE: it's less

expensive to eliminate a genetic disease through the germline than to keep treating it somatically over generations; it's the best system for reaching all cells in the body; and it goes through a single cell rather than millions that involve somatic cell treatments (Davies 2020).

But what about exceptions, or what Peter Mills in his essay identifies as "the most unusual case"? Let's imagine that two parents, both homozygous for deafness, desire to have a child who would not be born deaf. That scenario is not imaginary. A Russian scientist has identified five deaf couples who want to have hearing children, and he's petitioned Russian authorities to allow him to carry out a CRISPR germline treatment on these couples' embryos. This recent push to allow for GGE brings us to a discussion of using CRISPR germline editing by three contributors with personal experience.

Carol Padden, who is deaf, and her daughter, Jacqueline Humphries, who is not, "propose an expansive view of human diversity that recognizes the value of genetic, linguistic, and cultural diversity to the future health of humankind." How one defines a disease, or a medically unmet need, is influenced by the culture and those in power, including the medical-industrial complex that is driven to find cures. Padden and Humphries point out that many in the deaf community do not see themselves as disabled but as valued contributors to human diversity, with a highly developed language and style of communication. Padden herself doesn't want to be "cured" because she is not inflicted, though she and Humphries "worry about the potential for medical overreach and expediency" as "scientists may begin soon to do germline editing with deaf individuals."

Ethan Weiss, in his essay about his daughter, Ruthie, born with albinism, ponders "a future in which children with genetic differences like albinism are gene edited using technologies like CRISPR-Cas9." He details the journey he and his wife, Palmer, have made in raising a child with a genetic disorder that severely impairs her vision, makes her intolerant to sunlight, and causes other medical problems. He also embraces Ruthie for who she is and the joy she brings to her family, friends, and those who meet her. Weiss also says, "beyond a doubt that had we known of Ruthie's condition before she was born, she would not be here today." But that knowledge is predicated on what he knew then; not on what he knows today. He worries that new technologies like CRISPR will stop us from having children like Ruthie in the future as we become better at detecting mutations and eliminating them. He leaves us with a conundrum: "one can't know what it's like to parent a child with a disability until one knows. And without knowing, it is practically impossible to make an informed decision about whether and how to intervene."

Revisiting the Island of Dr. Moreau

CRISPR technology has become democratized, with kits available to DIY biohackers and the scientific methodologies available online. With democratization

and easy access to the materials needed to use CRISPR come biosecurity threats. Rachel West and Gigi Gronvall's essay "outlines potential biosecurity concerns, and recommends actions governments and scientists may take to reduce biosecurity risks." They note that we must come to terms with the possibility that CRISPR could be used for nefarious purposes, where a rogue scientist or highly trained amateur could "edit an existing pathogen to make it more damaging, edit a non-pathogenic organism to incorporate pathogen genes and traits, and even, theoretically . . . synthesize a novel pathogen."

Apart from the nefarious uses of CRISPR to make bioweapons are experimental uses across species. H. G. Wells was prescient when he wrote *The Island of Dr. Moreau* in 1896. Dr. Moreau experimented by combining humans with animals. The ethicist Jason Scott Robert (2018) has written that "scientists have tried to 'humanize' their experimental model organisms (mouse, rat, pig, cow, non-human primate). With the advent of CRISPR-Cas9, the prospects for humanization have increased considerably. . . . With part-human chimeras, one ambition is to transfer human pluripotent stem cells into non-human embryos to assess the potential for cellular functional integration."

Amateur Dr. Moreaus can now purchase kits online that use CRISPR technology to increase the size of green tree frogs or make brewer's yeast fluoresce. Should biohackers be given the tools to do CRISPR experiments in their home labs? Unfortunately, one can imagine any number of dangerous applications for CRISPR. Yet to date, no US presidential candidate has discussed CRISPR—neither its potential to cure disease nor its power to unleash destruction. In light of the power and threat of CRISPR, West and Gronvall note that the US Department of Defense and the Defense Advanced Researched Products Agency (DARPA) must "continue to innovate and engage in biotechnology, but that an assessment framework should also be used to examine novel biotechnology and its potential broader applications in the scientific and public spheres."

West and Gronvall also turn to international governance organizations and scientific academies for leadership in working to ensure that all countries act responsibly in the future use of CRISPR. The World Health Organization is "providing a framework for how gene drives should be responsibly used" in the testing and release of modified mosquitoes. One might turn to the UN for leadership since nearly every country is a member. It's a daunting task; countries cannot agree on efforts to stop global warming. But we must have conversations now, not after disaster has struck.

Another safeguard West and Gronvall suggest to protect the public from "ill-intended" uses of CRISPR is to tightly control the sale of DNA sequences. "In 2010, the US Department of Health and Human Services (HHS) published the *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA,* which outlines how companies should "screen customers and their orders for possible misuse." This screening on a voluntary basis didn't stop David Evans, a

Canadian scientist, from creating horsepox using strands of DNA. Kevin Esvelt thinks that "all such orders should be screened against a database of problematic sequences. . . . A mandatory, universal process could work if publishers or funders boycott work that doesn't abide by it, or if companies build the next generation of DNA synthesizers to lock if a screening step is fixed" (Yong 2018).

Other options for protecting the public include shielding scientists who are whistleblowers and, as West and Gronvall point out, teaching scientists about the "risks and guidelines for biosecurity early in their careers," so that "they will carry this throughout their work in academia, industry, or other careers." At Harvard, Barbara Groez, a professor of natural sciences at the John A. Paulson School of Engineering and Applied Sciences, integrates ethics into the curricula with the goal of encouraging students to develop and nurture the habit of thinking about ethics as a computer scientist and to learn ways to design, build, and test systems with ethical principles in mind. That approach should start early, even before college, to encourage students and the public to think about CRISPR and the bioethical and safety issues it raises.

Who's Responsible?

Sarah Chan, in her essay, writes that He's actions in using CRISPR on the Chinese twins exposed "fault lines in our thinking about human genome editing with respect to risk, harm, and responsibility." Chan interrogates the multiple ways we might think about the meaning of how to assess responsibility in deciding whether we should proceed with using GGE clinically to treat disease or enhance traits. She delves into the prickly question of whether we should take a precautionary approach and not take action, because we cannot fully predict unintentional outcomes, or whether we should be more proactive. "Are we failing to do what would be most responsible, in order to avoid being held responsible," she writes, "that is, held to blame—in the event something goes wrong?" What if we could cure a serious genetic disease at the embryonic stage, Chan asks, and save patients from enduring pain and suffering before they receive a somatic genome cell treatment? She continues: "A further consideration is that the risk of germline editing falls primarily on one individual, while the risk of repeated somatic procedures is distributed amongst many, including persons who do not yet exist."

Scientists and physicians, along with parents who face the prospect of having children with genetic diseases, are in the forefront of determining whether or not we should use germline genome editing. Chan considers "who is responsible, who takes responsibility and who should be held accountable?" Since scientists created CRISPR, she asks if scientists should be "expected to be aware of regulatory requirements across all national contexts and to act as whistleblowers to promote enforcement."

Peter Mills and Josephine Johnston in their essays seek to clarify the "pre-existing lines of inquiry" in which the "treatment-enhancement distinction and the somatic-germline distinction are not as clear-cut as they might initially appear" (Johnston). The lines between what constitutes an unmet medical need and an enhancement are fuzzy at best. What about a gay or lesbian couple who both wish to biologically contribute their genes to a child? That sci-fi scenario is plausible now with CRISPR. But is it an unmet medical need? It might be considered one by the gay couple and therefore calls for a CRISPR treatment, though others might argue that biology naturally constrains two people of the same sex from both contributing genes to their baby. That's true today. But not necessarily in the future. What's more, it's conceivable that a child in the near future could have many parents who have contributed their genes through germline genome editing. How this might change our conception of parenthood and who's responsible for raising that child is daunting. Will we ultimately resort to basing parenthood on the percentage of genes each mother and father has contributed?

The Stories We Tell Ourselves

How we think about CRISPR is determined by many social, cultural, and political factors. Scientists and physicians tell stories different from individuals who haven't had the experience of researching genetic syndromes or treating patients suffering from them. Marcy Darnovsky and Katie Hasson encourage us to refocus our conversations about CRISPR "away from technical, medical, and scientific considerations toward matters of societal meanings, values, context, and consequences." One problem, Darnovsky and Hasson point out, with the stories we tell, is that they are often infused with emotion that "shapes our thinking about gene editing tools and the ways they should and should not be used." Terms like "designer" and "CRISPR babies" can evoke images of monsters or enhanced superhumans that "distort public understanding and undermine genuine debate." We must also be wary of personal anecdotes. Though often powerful, they can be misleading. Darnovsky and Hasson relate the story of a mother speaking at the First International Summit on Human Gene Editing in 2015, whose child died in infancy. She pleaded for heritable genome editing to move forward to save the lives of babies like hers. In reality, her baby suffered from anencephaly, which had "no clear genetic basis," yet that moving story was quoted numerous times in the media.

With so many stories being told about CRISPR, particularly why we should and should not move forward with germline genome editing, Darnovsky and Hasson maintain that it is essential to "develop robust forms of public engagement" that should include "women's health advocates, disabled people and communities, and those working to reduce economic and racial inequalities," along with "scholars from the humanities and social sciences." One might add theolo-

gians, philosophers, and anyone else who wishes to learn more and hear about the prospects of genetic engineering. As members of the human community, we all should have a say in how CRISPR should be used. Bringing all parties to the table requires what I call *innovative conversations*. We must design new formats for including a diversity of voices in discussions about CRISPR.

The debate on CRISPR and germline genome editing to date has been limited to scientific societies and bodies, with little discussion publicly amongst candidates running for political office or from the White House. A topic as critical to our future must be discussed by everyone, not just experts. "Genuine inclusivity in these deliberations," Darnovsky and Hasson write, "will require challenging the technical and medical framings that favor the perspectives and expertise of doctors and scientists, constrain the questions that are asked, and delimit the risks and benefits that are seen as relevant." We must design new innovative conversations to accompany innovative—and potentially disruptive—genetic technologies.

The Forces Be with You

Scientists do not work in a vacuum. They also have aspirations, drives, ethical beliefs, and egos that shape the way they think about doing research and its impact on society. J. Benjamin Hurlbut, in our final essay, examines the forces that influenced He Jiankui, cautioning that the way science is done can lead to an "ill-begotten experiment" like the one performed by He. Underlying the CRISPR-edited twin outcome is what Hurlbut cites as "a familiar sequence: scientific knowledge generates technological applications which in turn produce societal impacts and consequences." Science and innovation race along, and then ethical questions come afterwards. He points out that the First International Summit on Human Genome Editing in 2015 required "broad societal consensus." But "after the He story broke, the Hong Kong summit organizing committee abandoned [the 2015] commitment to seeking 'broad societal consensus' and issued a statement declaring that it is 'time to define a rigorous, responsible translational pathway toward [germline editing clinical] trials.'" Hurlbut is deeply concerned by this shift, which mirrors the paradigm of science racing forward with society lagging behind. After He conducted his experiment, that notion was reinforced: what's done is done; now it's time for society to deal with it.

Hurlbut met He at a scientific meeting in Berkeley, California, in January 2017. Hurlbut's fascinating account of the forces placed on He to be the first scientist to use CRISPR to edit the germline of a human being is profound. Hurlbut contends that He internalized contemporary views in biotechnology that "led him to believe that his experiment would elevate his status in the scientific community, advance his country in the race for scientific and technological dominance, and drive scientific progress forward against the headwinds of ethical

conservatism and public fear." During that meeting in Berkeley, He read about Robert Edwards, who secretly produced the first "test-tube baby," which Edwards revealed in the popular press, years later winning the Nobel Prize. Hurlbut notes that despite prohibitions against germline genome editing, He moved forward, deeply influenced by Edwards's story: that "major breakthroughs are generally driven by one or a couple of risk-taking scientists; heroic scientific achievements are often initially controversial; someone has to break the glass."

Breaking the glass is a powerful metaphor that drives many scientists. Hurlbut, in a stunning revelation, contends that He consulted and confided in dozens of scientists, "including well-known and respected American scientists," the majority of whom expressed support for his project. He told many of those who expressed support that he had "initiated pregnancies or produced babies." In light of Hurlbut's disclosures, it is more imperative than ever for the NAS and International Commissions to take a very hard look at the culture that motivated Dr. He.

HUBRIS

CRISPR makes us imagine the unimaginable, or, at the very least, what was once the provenance of Jurassic Park science fiction. How will it change human evolution? Will it further divide us into the enhanced and the merely normal? Will it privilege medicine to a degree we never dreamed possible, wiping away scourges and devastating genetic diseases? Will we be able to harness the power of CRISPR and still protect humanity from rogue scientists who could wreak havoc, the likes of which we've never seen?

We often act after a crisis—we're not good at prevention. Seventy percent of adult Americans are obese or overweight, and many suffer from type two diabetes, which accounts for 90 to 95% of all diagnosed diabetes cases. The cost is staggering: treating diabetes in 2017 amounted to one in four health-care dollars, or $327 billion (Petersen 2018). Yet we still eat and drink sugar-laden and highly processed foods, even though we know they're unhealthy. Acting takes discipline and courage.

All the essays in this collection share a driving question: what does it mean to be human today and how ought we to think about our future generations? The decisions we make today about manipulating the human germline genome will have a profound—and likely unpredictable—effect on them. We often talk about how technology has changed the world before and after the invention of the internet and cell phone. But cell phones and social media change the ways in which we interact with each other. They don't change our genetic make-up. CRISPR is a game changer.

We're in for a ride that is not fully conceivable. These essays are an attempt to frame the questions that will have a lasting impact on humanity before something dire occurs. Are we smart enough, empathetic enough, and ethical enough to

deal with the complex questions posed by CRISPR? Here I turn to the humanities for an answer. The arts, literature, and music all come from minds and hands and hearts that were not genetically altered. Human ingenuity and compassion have made the world livable and given us hope in times of despair. Evolution has given us an endless assortment of unique human beings and their gifts. Now that we have the power to shape our own evolution, we must think long and hard about how we want to use it.

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