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The Brave New World of Gene Editing

Matthew Cobb
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The Gene Machine: How Genetic Technologies Are Changing the Way We Have Kids—and the Kids We Have
by Bonnie Rochman
Scientific American/Farrar, Straus and Giroux, 272 pp., $26.00

DNA Is Not Destiny: The Remarkable, Completely Misunderstood Relationship Between You and Your Genes
by Steven J. Heine
Norton, 344 pp., $26.95

A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution
by Jennifer A. Doudna and Samuel H. Sternberg
Houghton Mifflin Harcourt, 281 pp., $28.00

In recent years, two new genetic technologies have started a scientific and medical revolution. One, relatively well known, is the ability to easily decode the information in our genes. The other, which is only dimly understood by the general public, is our newfound capacity to modify genes at will. These innovations give us the power to predict certain risks to our health, eliminate deadly diseases, and ultimately transform ourselves and the whole of nature. This development raises complex and urgent questions about the kind of society we want and who we really are. A brave new world is just around the

Graeme Mitchell/Redux

The biochemist Jennifer Doudna, a pioneer of the technique of DNA modification known as

corner, and we had better be ready for it or things could go horribly wrong.

CRISPR, at her lab at the University of California, Berkeley, 2015

The revolution began in benign but spectacular fashion. In June 2000, President Bill Clinton and Prime Minister Tony Blair announced the completion of the first draft of the human genome. According to a White House press statement, this achievement would "lead to new ways to prevent, diagnose, treat, and cure disease." Many scientists were skeptical, but the public (who footed much of the $3 billion bill) probably found this highly practical justification more acceptable than the mere desire to know, which was in fact a large part of the motivation of many of the scientists involved.

During the 2000s, Clinton's vision was slowly put into practice, beginning with the development of tests for genetic diseases. As these tests have become widespread, ethical concerns have begun to surface. Bonnie Rochman's *The Gene Machine* shows how genetic testing is changing the lives of prospective parents and explores the dilemmas many people now face when deciding whether to have a child who might have a particular disease. Some of these technologies are relatively straightforward, such as the new blood test for Down syndrome or the Dor Yeshorim genetic database for Jews, which enables people to avoid partners with whom they might have a child affected by the lethal Tay-Sachs disease (particularly prevalent in Ashkenazis). But both of these apparently anodyne processes turn out to raise important ethical issues.

Whether we like it or not, the Dor Yeshorim database and other similar initiatives, such as genetic tests for sickle-cell anemia, which largely affects African-Americans, are enabling us to deliberately change the frequency of certain human genes in the population. This is the technical definition of eugenics and might seem shocking, since eugenics is forever associated with the forced sterilization of the mentally ill and Native Americans in the US or the murder of those deemed genetically defective by the Nazis. But the ability to use genetic testing when deciding whether or not to have children is clearly a form of soft eugenics, albeit one carried out voluntarily by those affected and clearly leading to a reduction of human suffering. With the best of intentions and, for the moment, the best of outcomes, we have drifted across a line in the sand.

The new genetic test for Down syndrome also hides ethical traps. The test detects tiny amounts of fetal DNA in the mother's bloodstream, and in the US it has

largely replaced the widespread use of invasive alternatives (amniocentesis or chorionic villous sampling, in which cells are taken from the placenta) that involve a risk of miscarriage. The advent of a safe way to detect Down is a positive development (in the UK it is predicted that the test will prevent up to thirty invasive test–induced miscarriages each year), but some women feel that its simplicity means they are being inadvertently pressured into having a test for Down, and potentially into having an abortion if the test result is positive.

It is extremely difficult to obtain reliable data on how often identification of Down syndrome in a fetus has led to a decision to terminate a pregnancy, but a recent study in Massachusetts suggested that prior to the introduction of the safer test in 2011, around 49 percent of such pregnancies were aborted. Since many parents opted not to have an invasive test for fear of miscarriage (in the UK the figure was around 40 percent), it is reasonable to expect that an increased rate of identification of fetuses with Down syndrome will lead to more abortions. This has led to criticism from families with Down syndrome children, who understandably want to emphasize the joy they feel living with a child who has the condition. Rochman navigates these difficult waters with skill and compassion, drawing on conversations with families and physicians and setting out the ethical challenges and the range of solutions adopted by different people, without being preachy or moralistic.

In the last few years, genetic testing has entered the commercial mainstream. Direct-to-consumer testing is now commonplace, performed by companies such as 23andMe (humans have twenty-three pairs of chromosomes). Much of the interest in such tests is based not only on the claim that they enable us to trace our ancestry, but also on the insight into our future health that they purport to provide. At the beginning of April, 23andMe received FDA approval to sell a do-it-yourself genetic test for ten diseases, including Parkinson's and late-onset Alzheimer's. You spit in a tube, send it off to the company, and after a few days you get your results. But as Steven Heine, a Canadian professor of social and cultural psychology who undertook several such tests on himself, explains in *DNA Is Not Destiny*, that is where the problems begin.

Some diseases are indeed entirely genetically determined—Huntington's disease, Duchenne muscular dystrophy, and so on. If you have the faulty gene, you will eventually have the disease. Whether you want to be told by e-mail that you will develop a life-threatening disease is something you need to think hard about

before doing the test. But for the vast majority of diseases, our future is not written in our genes, and the results of genetic tests can be misleading.

For example, Heine reveals that according to one test, he has "a 32 percent increased chance" of developing Parkinson's disease. Behind this alarming figure lurks the reality that his risk is only slightly higher than the small likelihood that is found in the general population (2.1 percent for Heine, 1.6 percent for the rest of us). That does not sound quite so bad. Or does it? What does a risk of 2.1 percent really mean? People have a hard time interpreting this kind of information and deciding how to change their lifestyle to reduce their chance of getting the disease, if such an option is available. (It is not for Parkinson's.)

Even more unhelpfully, different companies testing for the same disease can produce different results. Heine was told by one company that he had a higher-than-average risk of prostate cancer, Parkinson's, melanoma, and various other diseases, whereas another said his risk for all these conditions was normal. These discrepancies can be explained by the different criteria and databases used by each testing company. Faced with varying estimates, the average customer might conclude that contradictory information is worse than no information at all. As Heine puts it, "The oracle's crystal ball is made of mud."

More troublingly still, however imperfect its predictive value, the tsunami of human genetic information now pouring from DNA sequencers all over the planet raises the possibility that our DNA could be used against us. The Genetic Information Nondiscrimination Act of 2008 made it illegal for US medical insurance companies to discriminate on the basis of genetic information (although strikingly not for life insurance or long-term care). However, the health care reform legislation recently passed by the House (the American Health Care Act, known as Trumpcare) allows insurers to charge higher premiums for people with a preexisting condition. It is hard to imagine anything more preexisting than a gene that could or, even worse, will lead to your getting a particular disease; and under such a health system, insurance companies would have every incentive to find out the risks present in your DNA. If this component of the Republican health care reform becomes law, the courts may conclude that a genetic test qualifies as proof of a preexisting condition. If genes end up affecting health insurance payments, some people might choose not to take these tests.

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ut of even greater practical and moral significance is the second part of the revolution in genetics: our ability to modify or "edit" the DNA sequences of humans and other creatures. This technique, known as CRISPR (pronounced "crisper"), was first applied to human cells in 2013, and has already radically changed research in the life sciences. It works in pretty much every species in which it has been tried and is currently undergoing its first clinical trials. HIV, leukemia, and sickle-cell anemia will probably soon be treated using CRISPR.

In *A Crack in Creation*, one of the pioneers of this technique, the biochemist Jennifer Doudna of the University of California at Berkeley, together with her onetime student Samuel Sternberg, describes the science behind CRISPR and the history of its discovery. This guidebook to the CRISPR revolution gives equal weight to the science of CRISPR and the profound ethical questions it raises. The book is required reading for every concerned citizen—the material it covers should be discussed in schools, colleges, and universities throughout the country. Community and patient groups need to understand the implications of this technology and help decide how it should and should not be applied, while politicians must confront the dramatic challenges posed by gene editing.

The story of CRISPR is a case study in how scientific inquiry that is purely driven by curiosity can lead to major advances. Beginning in the 1980s, scientists noticed that parts of the genomes of microbes contained regular DNA sequences that were repeated and consisted of approximate palindromes. (In fact, in general only a few motifs are roughly repeated within each "palindrome.") Eventually, these sequences were given the snappy acronym CRISPR—clustered regularly interspersed short palindromic repeats. A hint about their function emerged when it became clear that the bits of DNA found in the spaces between the repeats—called spacer DNA—were not some random bacterial junk, but instead had come from viruses and had been integrated into the microbe's genome.

These bits of DNA turned out to be very important in the life of the microbe. In 2002, scientists discovered that the CRISPR sequences activate a series of proteins—known as CRISPR-associated (or Cas) proteins—that can unravel and attack DNA. Then in 2007, it was shown that the CRISPR sequence and one particular protein (often referred to as CRISPR-Cas9) act together as a kind of immune system for microbes: if a particular virus's DNA is incorporated into a microbe's CRISPR sequences, the microbe can recognize an invasion by that virus and activate Cas proteins to snip it up.

This was a pretty big deal for microbiologists, but the excitement stems from the realization that the CRISPR-associated proteins could be used to alter any DNA to achieve a desired sequence. At the beginning in 2013, three groups of researchers, from the University of California at Berkeley (led by Jennifer Doudna), Harvard Medical School (led by George Church), and the Broad Institute of MIT and Harvard (led by Feng Zhang), independently showed that the CRISPR technique could be used to modify human cells. Gene editing was born.

The possibilities of CRISPR are immense. If you know a DNA sequence from a given organism, you can chop it up, delete it, and change it at will, much like what a word-processing program can do with texts. You can even use CRISPR to introduce additional control elements—for example to engineer a gene so that it is activated by light stimulation. In experimental organisms this can provide an extraordinary degree of control in studies of gene function, enabling scientists to explore the consequences of gene expression at a particular moment in the organism's life or in a particular environment.

There appear to be few limits to how CRISPR might be used. One is technical: it can be difficult to deliver the specially constructed CRISPR DNA sequences to specific cells in order to change their genes. But a larger and more intractable concern is ethical: Where and when should this technology be used? In 2016, the power of gene editing and the relative ease of its application led James Clapper, President Obama's director of national intelligence, to describe CRISPR as a weapon of mass destruction. Well-meaning biohackers are already selling kits over the Internet that enable anyone with high school biology to edit the genes of bacteria. The plotline of a techno-thriller may be writing itself in real time.

A Crack in Creation inevitably focuses on Doudna's work, providing insight into her own feelings as the implications of CRISPR slowly dawned on her and her principal collaborator, the French scientist Emmanuelle Charpentier. However, the book also describes the work of the many laboratories around the world that contributed to the breakthrough. This evenhanded approach contrasts with an article on the history of CRISPR written for *Cell* by the molecular biologist Eric Lander of the Broad Institute. Lander's article was widely seen as unfairly emphasizing the work of the Harvard researchers Zhang and Church and downplaying the contribution of Doudna and Charpentier.* These contesting histories seek to influence not only who will get what seems like an inevitable

Nobel Prize for the discovery, but above all the fortune that can be made, for individuals and institutions, from the patents to CRISPR applications.

Anthony A. James/UC Irvine

Adult female Anopheles stephensi *mosquitoes, important malaria carriers in urban India, transformed in genetic experiments to study whether they can be made inhospitable to malaria parasites*

Frustratingly, Doudna and Sternberg say little about the patent issue, which is currently the focus of a complex legal case between the University of California and the Broad Institute over which group of researchers can rightfully license CRISPR-Cas9. In February, the US Patent Trial and Appeal Board ruled in favor of the Broad Institute, supporting its patent for the use of CRISPR-Cas9 in eukaryotic cells (including humans). The Berkeley team, on the other hand, had previously filed patents on the use of CRISPR-Cas9 in any cell, which, if supported by the courts, would mean that any researcher wishing to use the technology would have to get licenses from both Berkeley and the Broad Institute. The problem—apart from the obvious fact that the main beneficiaries of the US Patent Board's decision will be lawyers, not scientists, and certainly not patients—is that the outcome may limit scientific inquiry by imposing fees for using CRISPR technology. More fundamentally, it can be argued that it is inherently wrong to patent discoveries made through publicly-funded research.

The story is far from over. The Berkeley team is appealing the initial decision; patents in other areas of the world, including Europe, have yet to be decided; other institutions have also filed patents that have yet to be examined in court; and the use of alternative enzymes that are more efficient than Cas9 may render the whole process moot. Initially, the Berkeley and Broad teams were working together on the commercialization of the technology, but something broke down in their relationship, and the current patent dispute is the consequence. What caused that rupture has not been made public, and Doudna and Sternberg give no hints.

The second half of *A Crack in Creation* deals with the profound ethical issues that are raised by gene editing. These pages are not dry or abstract—Doudna uses her own shifting positions on these questions as a way for the reader to explore

different possibilities. However, she often offers no clear way forward, beyond the fairly obvious warning that we need to be careful. For example, Doudna was initially deeply opposed to any manipulation of the human genome that could be inherited by future generations—this is called germline manipulation, and is carried out on eggs or sperm, or on a single-cell embryo. (Genetic changes produced by all currently envisaged human uses of CRISPR, for example on blood cells, would not be passed to the patient's children because these cells are not passed on.)

Although laws and guidelines differ among countries, for the moment implantation of genetically edited embryos is generally considered to be wrong, and in 2015 a nonbinding international moratorium on the manipulation of the human germline was reached at a meeting held in Washington by the National Academy of Sciences, the Institute of Medicine, the Royal Society of London, and the Chinese Academy of Sciences. Yet it seems inevitable that the world's first CRISPR baby will be born sometime in the next decade, most likely as a result of a procedure that is intended to permanently remove genes that cause a particular disease.

Already in the early days of her research, Doudna seems to have been haunted by the implications of her work—she describes a disturbing dream in which Hitler keenly asked her to explain the technique to him. Over the last couple of years, following meetings with patients suffering from genetic diseases, Doudna has shifted her position, and now feels that it would be unethical to legally forbid a family to, say, remove a defective portion of the gene that causes Huntington's disease from an embryo, which otherwise would grow into an adult doomed to a horrible death.

Like many scientists and the vast majority of the general public, Doudna remains hostile to changing the germline in an attempt to make humans smarter, more beautiful, or stronger, but she recognizes that it is extremely difficult to draw a line between remedial action and enhancement. Reassuringly, both *A Crack in Creation* and *DNA Is Not Destiny* show that these eugenic fantasies will not succeed—such characteristics are highly complex, and to the extent that they have a genetic component, it is encoded by a large number of genes each of which has a very small effect, and which interact in unknown ways. We are not on the verge of the creation of a CRISPR master race.

Nevertheless, Doudna does accept that there is a danger that the new technology will "transcribe our societies' financial inequality into our genetic code," as the rich will be able to use it to enhance their offspring while the poor will not. Unfortunately, her only solution is to suggest that we should start planning for international guidelines governing germline gene editing, with researchers and lawmakers (the public are not mentioned) encouraged to find "the right balance between regulation and freedom."

The failure to resolve the issue of how to regulate gene-editing technology is even more striking when Doudna and Sternberg describe what they acknowledge is the most dangerous potential application of their technique: the deployment of what are known as gene drives, especially in species with short generation times, such as insect pests. Gene drives are artificial bits of DNA that rapidly spread through the population, unlike existing GMO techniques in which modified genes spread at a very slow rate and easily disappear from the gene pool. When a gene drive is used, the frequency of the altered gene increases exponentially with each generation, rapidly flooding the whole population. This is the technology that scientists have been proposing as a way of rendering all mosquitoes sterile or preventing them from carrying malaria, and it could clearly have an enormous effect on the epidemiology of some of the most deadly diseases. Over 300,000 children die each year of malaria; CRISPR gene drives could potentially save them by altering the mosquito's genome.

The problem with a gene drive is that it is essentially a biological bomb that could have all sorts of unintended consequences. If we make the mosquito inhospitable to the malaria parasite, we might find that, just as with the overuse of antibiotics, the parasite mutates in such a way that it can evade the effects of the gene drive; this change could also mean that it is immune to our current antimalarial drugs. Meanwhile, the alternative approach of eradicating the mosquito from a particular environment, as Doudna and Sternberg point out, may lead to unexpected changes in the ecology of the region—we simply do not know enough about ecology to be able to predict what will happen.

Claims that a gene drive that goes wrong could be reengineered (this is facilely called "undo" by its advocates) ignore the fact that other species might have been irreversibly damaged by the initial genetic change. Ecosystems are fragile. A vaccine against malaria might eventually become an ecologically safe alternative, but the advocates of gene drives understandably argue that if we carry on with our

current approach, using insecticides and bed nets, malaria will continue to kill those hundreds of thousands of children each year, together with thousands more who are infected with other mosquito-borne diseases, such as Zika, dengue, West Nile virus, and chikungunya.

At the moment, there are no regulations governing if and how gene drive technology should be deployed. Part of the problem is that this is effectively a global question—insects travel easily, and they and the diseases they transmit can mutate as they go. An apparent solution in one part of the world might turn into a catastrophe in another, as manipulated insects and pathogens move unhindered across frontiers and enter new ecosystems. Global regulation of gene drives—much as we have global regulation of other potentially dangerous technologies such as civilian air travel or nuclear power—is crucial, but many governments, and especially the current US administration, have little appetite for international regulation.

Whether these developments excite us or appall us, we cannot unlearn what we have discovered. CRISPR is already speeding up scientific discovery, making it possible to manipulate genes in organisms and providing stunning insights into evolution, such as last year's study by Neil Shubin at the University of Chicago that explored how fish fins were replaced by feet in land vertebrates nearly 400 million years ago. CRISPR will soon be applied to health care, making some previously lethal or debilitating diseases a thing of the past. Not all diseases will be easily cured—for example, the development of a cure for Duchenne muscular dystrophy is likely to be hindered for many years by technical difficulties associated with the delivery of CRISPR sequences to all the affected muscle cells—but we truly are emerging into a new world.

To prevent gene editing from taking a dystopian turn, strict regulation through internationally recognized guidelines must be found to protect our genetic information from unscrupulous states or commercial exploitation, prevent the irresponsible release of gene drives, and prohibit any form of discrimination against people because of their genes. Hostility to such discrimination should become a basic moral principle shared by societies around the world. The first step toward such an outcome is to ensure that the public and lawmakers understand the new technology and its dramatic implications. *A Crack in Creation*—the first book on CRISPR to present a powerful mix of science and ethics—can help in this process. As Francis Bacon said, knowledge is power.

* For a taste of the dispute, see "Heroes of CRISPR"—Lander's article—and "Villain of CRISPR"—the delightfully splenetic response by the Berkeley geneticist Michael Eisen, available at michaeleisen.org. ↩

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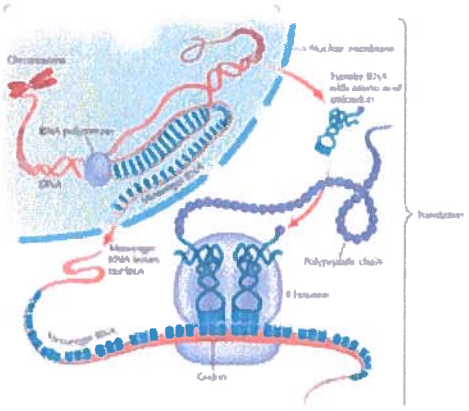

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