The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race

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Walter Isaacson's latest tome, titled *The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race*, is a tour de force that chronicles the ingenious work of the winners of the 2020 Nobel Prize in Chemistry. The award went to Jennifer Doudna, Ph.D., of Berkely, California, and Emmanuelle Charpentier, Ph.D., formerly of Paris, France (Sorbonne University and Pasteur Institute) and now of the Max Planck Institute in Berlin, Germany. The scientists, only the sixth and seventh women to receive the Nobel Chemistry award, were honored for their transformative discovery in 2012 of CRISPR (clustered regularly interspersed short palindromic repeats)-Cas9 (CRISPR-associated system) as a gene-editing tool. In announcing the accolade, the secretary of the Royal Swedish Academy proclaimed, "This year's prize is about rewriting the code of life.… These genetic scissors have taken the life sciences into a new epoch."

Isaacson cogently argues that the invention of CRISPR and its interface with the COVID-19 pandemic will accelerate our transition to the third great revolution of modern times. These revolutions have been based on the fundamental kernels of our existence: the atom, the bit, and, now, the gene.

Albert Einstein's insights on relativity and the photoelectric effect led to the atom bomb, nuclear power, transistors, spaceships, lasers, and radar. The second half of the 20th century was an information technology era, which was founded on the idea that all information could be encoded by binary digits known as bits and all logical processes could be performed by circuits with on–off switches. This led to the development of the microchip, the computer, and the Internet.

We have entered a third momentous era: a life science revolution. Molecules are becoming the new microchips. (Is it any wonder that medical school applications increased more than 17% in 2020?) Determining if and when to edit our genes will surely be one of the most consequential decisions of the 21st century.

The complexity of the CRISPR-Cas9 story is so intricate that a casual reader may struggle to find a narrative thread among the abundance of researchers, experiments, conferences, and issues involved. Nonetheless, close reading of this book is well worth the effort. The reward is an exciting journey of discovery wherein attentive readers will see how brilliant advances in the basic sciences were brought from the bench to the bedside to fight COVID-19. They will be informed about the exciting potential to control future pandemics, which may be accomplished either by circumventing the next viral plague through better screening and treatment or by engineering human beings with improved disease resistance programmed into their cells. Importantly, they will also learn about gene editing to treat serious diseases or to effect societal "enhancement," with all the bioethical challenges these advances engender. Finally, they will read about the intense competition among, and personal foibles of, scientists engaged in this exciting realm of discovery.

Near the turn of the millennium, a Spanish molecular biologist, Francisco Mojica, from the University of Alicante (Alicante, Spain), observed strange repeating bits of DNA in the genome of several species of bacteria. These bits were not genes, but their repeating pattern suggested that they were not random junk either. Mojica termed these enigmatic regions "clustered regularly interspersed short palindromic repeats," or CRISPRs. Soon thereafter, these segments were identified as an important component of the bacteria's immune system.

Bacteria have been battling viruses for more than a billion years using CRISPRs in their DNA that can remember and then destroy viruses that attack them. CRISPR is a small subsection of the bacterial genome that stores snippets of captured viral code for future reference. When the bacterial cell is reattacked by a virus, an RNA copy of the virus's stored "signature" forms a DNA-splitting complex that destroys the incoming virus. Hence, CRISPR-Cas9, the technique of gene editing that Doudna and Charpentier patented, makes it possible to snip and alter bits of DNA as needed at a predetermined point. CRISPR-Cas9 can be engineered to edit any gene. Using the CRISPR-Cas9 genetic scissors, researchers can change the DNA of humans, animals, plants, and microorganisms with extremely high precision. The CRISPR-Cas9 gene-editing tools have revolutionized the molecular life sciences, introduced new opportunities for plant breeding, contributed to innovative cancer therapies, and led to novel vaccines and may make it possible to cure an array of inherited diseases.

In 2003, the Kass Commission published its 310-page report, *Beyond Therapy,* that was replete with concerns about genetic engineering.[1] It warned of the potential dangers of using technology to go beyond treating diseases to using

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it to enhance human capabilities. The authors argued that altering what is "natural" was hubristic and endangered our individual essence.

With the 2012 discovery of CRISPR that rendered the human genome as easily manipulable as that of a bacterium, it became obvious that thoughtful effort and reflection would be needed to find a prudent path forward. In January 2015, eminent scientists convened in California's Napa Valley to forge a consensus. The group agreed that CRISPR for noninheritable gene editing in somatic cells is a good thing that could lead to beneficial drugs and treatments.

The Napa group also agreed that some restraints should be placed on germline editing. They decided to call for a temporary halt in germline editing—*i.e.*, changing heritable DNA in sperm, eggs, or early-stage embryos—in humans, at least until the safety and social/ethical issues could be better understood. An international summit convened in December 2015 reached conclusions almost identical to those of the Napa meeting: human germline editing should be strongly discouraged until stringent conditions were satisfied. Interestingly, the final report of the international group, issued in February 2017, did not call for a moratorium on germline editing. Rather, it provided a list of criteria that should be met before germline editing is conducted.

In addition to the ongoing debate about somatic *versus* germline editing, another thorny issue involves the distinction between treatments designed to correct dangerous genetic abnormalities *versus* enhancements designed to improve human capabilities or traits. Dr. Doudna currently believes that CRISPR-Cas9 should be used only when medically necessary and there are no satisfactory alternatives. She worries that society may become genetically tiered along economic lines, with inequality increasing, if the wealthy can purchase genetic enhancements for their children.

In summary, we live in an exciting and revolutionary scientific era that holds great promise for development of life-saving and life-enhancing therapies. However, charting our way through the moral minefields highlighted in this masterful book will be complex. And who should decide? Scientists? Lawyers? Governments? The community? Individuals? Experience tells us that context is critically important, and the perspective of individuals and society changes over time. Someday we may consider it unethical *not* to use germline editing to alleviate human suffering. As Dr. Doudna wrote in a 2019 article in *Science,* "[T]he temptation to tinker with the human germ line is not going away…. Ensuring responsible use of genome editing will enable CRISPR technology to improve the well-being of millions of people and fulfill its revolutionary potential."[2]

Walter Isaacson's engaging, provocative, and informative book offers no solutions to the questions "What does 'ensuring responsible use' mean?" and "When, whether, and under what circumstances might it be ethically acceptable to create genetically engineered infants?" This thoughtful volume should stimulate reflection and be obligatory reading for all clinicians who have an interest in the future of the human race.

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