ADRIAN WOOLFSON

Gene Genie

A Crack in Creation: The New Power to Control Evolution
By Jennifer Doudna & Samuel Sternberg
(The Bodley Head 281pp £20)

Whereas in the past philosophers could only speculate about the source of human nature, we now know that the foundations of our humanity lie within the genetic instruction manuals situated in our genomes. These provide the raw material and substrate for our morphology, behaviour and culture. The information in genomes is digitally represented in combinatorial sequences of the four chemical bases from which DNA is made. The 3 billion or so bases of the human genome are parsed into twenty-three separate chromosomal pairs. One of the most remarkable findings of the Human Genome Project, completed at the beginning of this millennium, was that the human genome contains just 21,000 protein-encoding genes, 10,000 fewer than that of the water flea.

The fact that *Homo sapiens* was preceded by multiple now-extinct hominid species tells us that evolution has experimented with a number of different ways of being human. One of the most ancient and best characterised of these prior forms of human existence, *Ardipithecus ramidus*, is a case in point. It lived roughly 4.4 million years ago. Extracted from the reddish-brown sediment of the Ethiopian desert in the late 20th century, fossil remains – including a partial skeleton nicknamed 'Ardi' – show that it shared many characteristics with modern humans but, like a character from a *Star Wars* movie, differed in fundamental ways.

Rather than being immutable, human nature is fluid, changing significantly over time, a result of chance alterations to genomes. Darwinian evolution by natural selection fixed some of these into the genetic record while discarding others. The random manner in which natural mutations are generated, coupled with the unpredictability of historical events, makes it unlikely that modern humans would ever evolve in the same way if time were repeated. But what if, instead of relying on random mutations to generate the substrate of evolution, genomes could be made to measure?

In this wonderful book, *A Crack in Creation*, cowritten with Samuel Sternberg, Jennifer Doudna recounts how her curiosity and pursuit of science for no other reason than the thrill of unravelling life's secrets led her, by chance, to discover a method for editing the genomes of living things. Working in her biochemistry laboratory in Berkeley, California, where her studies focused on the structure of RNA, she received a request to collaborate on a project to determine how bacteria defend themselves against a class of viruses known as bacteriophages. The project rapidly snowballed, culminating in the discovery of a simple, robust, low-cost and accurate method for editing the genomes of humans and other species. As a result of this, the human genome may no longer be transformed solely through natural selective processes involving the random generation of genomic variation. Instead, a new form of technology, known as CRISPR, could be used to rewrite the chemical texts of genomes with surgical precision according to the prespecified mandates of the programmer.

The name CRISPR is derived from some of the peculiarities of the complex defence system employed by bacteria to detect and destroy invading bacteriophages. Pieces of DNA corresponding to previously encountered viruses are stored by bacteria like the images of outlaws in a 'most wanted' gallery. This genomic record serves both as an *aide-mémoire* of prior viral infections and as a command and control centre from which to coordinate new attacks. In the event of an infection, CRISPR sequences synthesise corresponding RNA molecules. These function as GPS-like devices that seek out chemical postal addresses within bacteriophage genomes. Once located, the targeted DNA sequence is corrupted with the help of an enzyme associated with CRISPR sequences called Cas9.

Doudna realised that this mechanism could be readily subverted to construct a programmable DNA-editing system, capable not just of deleting human genes but also of overwriting their abnormalities. The momentous implications of this technology, which makes genomes almost as editable as a piece of text, were initially lost on her. But she soon found herself embracing the technology that she helped invent, rapidly transforming herself from a laboratory biochemist into a global CRISPR spokesperson. She intuited that it was essential to communicate the discovery of this immense power, which had the potential to crack open and redefine all of nature's creations, so that appropriate preparations could be made in a timely manner.

Gene editing with CRISPR will have profound and far-reaching implications for human diseases, especially for the 'monogenic' diseases caused by single genetic abnormalities. Conditions such as sickle cell disease, caused by the change of a single base from an A to a T, could be cured. Doudna reminds us, however, that genes often have multiple functions. The sickle cell gene may, for example, protect against malaria. The situation with diseases caused by multiple genes is even more complex. One of the genes predisposing individuals to schizophrenia, for example, also plays a central role in the human immune system. It may prove hard to untangle these conflicting functions. Ultimately, however, it is clear that every aspect of the way we are is negotiable. A manifesto for life will ultimately be necessary to prescribe the ethical boundaries of genetic manipulation.

Perhaps the most important question of all is whether we should tamper with our DNA. Although CRISPR is not currently safe enough to be used to modify eggs and sperm, it soon will be. Doudna's views here are sobering. She argues that the 'line between natural and artificial blurs to the point of disappearing'. Indeed, is changing a gene using CRISPR so different from using the more traditional method of selective breeding? There are some who argue that it would be unethical not to fix genetic abnormalities permanently if we had the ability to do so. Doudna and Sternberg's simple but compelling exploration of this hugely important subject offers an excellent overview of this startling and unprecedented discovery.

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