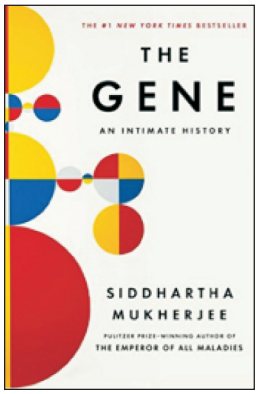
The Gene. An intimate history. Siddhartha Mukherjee. Allen Lane, London, 2016. *593pp, ₹1601*. ISBN: 978–0–670–08714–3.



Dr Mukherjee's books are replete with information, wisdom and thought-provoking asides. This encyclopaedic volume is no exception. The extraordinary feature here is the manner in which he acquaints us with intimate family members and brings to life some of his themes using their medical accounts. We meet some of them in the prologue itself. Eventually we are on nodding acquaintance with his grandfather, grandmother, father, mother, her twin sister, uncles and cousins. The final paragraph of *Prologue* embodies a tender assessment of his admirable grandmother.

Far from hiding mental illness in the family, he brings out details that bear upon his narrative gently and with sensitivity. A telling anecdote illustrates our general lack of sympathy towards someone who is mentally ill. His cousin, Moni was beaten up by goons allegedly for urinating in a public garden. Moni, suffering from schizophrenia later told Dr Mukherjee that an internal voice had commanded him, 'Piss here, piss here.' Dr Mukherjee also gained some interesting insights on his chosen subject. He asked his father for a Bengali word for *genes*. After some thought, he was offered *abhed*—indivisible, impenetrable, inseparable, identity. A flaw in a gene was *abadher dosh*—a blemish that cannot be separated from the self. We continue to encounter members of his family throughout the book. At times their peculiar plight leads to an account of the next rung up the ladder of genetics. The manner in which Dr Mukherjee's grandmother rushed to the rescue of errant but sick Jaggu (pp. 198–200) is especially dramatic. Neurologists and neurosurgeons will empathize with Dr Mukherjee as his father develops 'normal pressure hydrocephalus'.

Sympathy is on display as is scientific gravitas and admirable honesty. 'When I met Sarah … for the fourth or fifth time, I told her about the splintered minds of my cousins and two uncles.' Dr Mukherjee explains: 'It was only fair to a future partner that I should come with a letter of warning.' She chose to marry him even after reading this letter.

A quote from Haruki Murakami's *1Q84* provides an intriguing approach to the subject. 'Human beings are nothing but carriers––passageways—for genes. . . . Genes don't think about what constitutes good or evil. They don't care whether we are happy or unhappy. We're just a means to an end for them …' (Those not in the know will, on exploration, find of interest the explanation of the title *1Q84*.)

The purpose of the book is summarized pithily. It is 'the story of the birth, growth and future of one of the most powerful and dangerous ideas in the history of science …' In the next paragraph Dr Mukherjee explains the use of the adjective 'dangerous' and in doing so cautions us on the current rush to manipulate genes. He also explains the link between his previous book (*The emperor of all maladies)* and this volume on pages 8 and 9. Greater insight will follow the study of the first two paragraphs of the epilogue (p. 497).

He eases the task of the reviewer of this volume. 'The book is organized both chronologically and thematically. The overall arc is historical. We begin in Mendel's pea-flower garden, in an obscure Moravian monastery in 1864, where the gene is *discovered* and then quickly forgotten (the word *gene* only appears decades later). The story intersects with Darwin's theory of evolution. The gene entrances English and American reformers, who hope to manipulate … genetics to accelerate human evolution and emancipation. That idea escalates to its macabre zenith in Nazi Germany in the 1940s.… A chain of post-World War II discoveries launches a revolution in biology. DNA is identified … the *action* of the gene is described … the three-letter genetic code is deciphered. Two technologies transform genetics in the 1970s: gene sequencing and gene cloning.… In the 1980s human geneticists begin to use these techniques to map and identify genes linked to diseases … enabling parents to screen fetuses … multiple genetic mutations are identified in human cancers … these efforts reach their crescendo in the Human Genome Project …' On pages 314–15, Dr Mukherjee sums up progress on our understanding of the gene from Mendel to the sequencing of genomes in four short paragraphs. He condenses 'the book of man in twenty-three volumes' into four and a quarter pages (pp. 322–6). Also see pages 480–3 for his summary of conclusions on the 'post-genomic world'. There is much wisdom here, based on deep study.

The bare bones in this summation are fleshed out in the six parts of his book and culminate with a final account involving his family. The last paragraph poses the question, 'But what is natural?' He provides a brief but poignant answer.

Dr Mukherjee's representations of persons are graphic and memorable.

You must have read several descriptions of friar Mendel and his experiments but have you been introduced to the 'short man with a serious face, myopic and tending toward portliness … (with) little interest in the spiritual life but (blessedly) intellectually curious, good with his hands and a natural gardener' who carried out those epoch-making studies with plants? We owe the terms *dominant* and *recessive* to Mendel. 'A man of few words, Mendel was even more concise in his writing: he had distilled nearly a decade's work into forty-four … pages.' Copies of his paper in the annual *Proceedings of the Brno Natural Science Society* were sent to the Royal Society and the Linnaean Society in England and the Smithsonian in Washington. 'What followed, as one geneticist wrote, was one of the strangest silences in the history of biology. The paper was cited only four times between 1866 and 1900—virtually disappearing from scientific literature.'

Did you know that Mendel had Christian Doppler as his mentor? Dr Mukherjee's brief narrative of Doppler's chief claim to fame is evocative and can be found on page 20.

Dr Mukherjee's final tribute to Mendel is touching. 'Mendel wrote only one monumental paper on pea hybrids. His health declined in the 1880s.… On 6 January 1884, Mendel died of kidney failure.… The local newspaper wrote an obituary but made no mention of his experimental studies. Perhaps more fitting was a short note from one of the younger monks in the monastery: *Gentle, free-handed and kindly … Flowers he loved*.' There is much more on Mendel in the following pages but we need to move on.

Take the description of Richard Owen, the paleontologist '… who hovered over England's natural historians like a patrician falcon' and who 'descended from the Royal College of Surgeons to verify and catalog Darwin's fossil skeletons'. Or this: 'In 1796, the French physicist Pierre-Simon Laplace had proposed that even the current solar system had arisen from the gradual cooling and

condensation of matter over millions of years. When Napoleon had asked Laplace why God was so conspicuously missing from his theory, Laplace had replied with epic cheekiness, '*Sire, I had no need for that hypothesis*.' Humour is used to good effect. Describing the work of Thomas Morgan in the 1920s on how 'units of heredity' enabled the formation of animals and the smooth function of organs, Dr Mukherjee informs us that Morgan once told a student, 'Excuse my big yawn. I just came from my own lecture (on genetics).'

Early in the book, Dr Mukherjee discusses the question of similarities between parents and children and tells us of the concept put forth by 'half scientist, half mystic' Pythagoras around 530 BC. According to Pythagoras, the seminal 'in the most literary sense' hereditary information was carried in male semen. The only role he attributed to the mother was the provision of the womb in which 'this data was transformed into a child'. Dr Mukherjee moves from Pythagoras to the playwright Aeschylus, the play *Eumenides* and Apollo's statement, 'She doth but nurse the seed, new-sown. The male is parent. She … just hoards the germ of life.' The linkage of this concept to Pythagoras' triangle and, a century later, to Plato's view in 380 BC of how perfect children could be derived cannot but captivate the reader. It was left to Aristotle to dismantle Pythagoras' theory in *De generatione animalium*. Dr Mukherjee terms this work a 'foundational text for human genetics' as he proposed that perhaps the female, like males, contributes actual material to the foetus. No surprise then that Max Delbruck joked that Aristotle qualified for a posthumous Nobel Prize.

From Mendel and Pythagoras, on to Charles Darwin, who, we learn aspired to a career in medicine in Edinburgh 'but horrified by the screams of a strapped-down child amid the blood and sawdust of the operating theatre, fled medicine …' He studied theology at Christ College, Cambridge. The loss to our profession was the gain of natural history and philosophy. Eventually, of course, Darwin's work helped propel great medical advances.

Such vivid depictions of scientists, their lives and work, abound and ensure that the reader is held, spellbound, throughout. It must have taken much hard work and strenuous research to uncover facts and anecdotes that make key personalities come alive and narrative lead to fascinating narrative.

Dr Mukherjee solves a riddle that may have puzzled others as well. In the late 18th century, parson-naturalists dominated the discipline of natural history. Mendel and Darwin are but two examples. Why was this so? Dr Mukherjee's answer: nature was god's creation and its study was thus consistent with Christian doctrine. Gardens were cultivated, plant and animal specimens collected to understand and make known the wonders of divine creation. The church provided a safe haven for these scientists. There was a drawback. 'The injunctions against the wrong kinds of investigation were so sharp that parson-naturalists did not even question the myths of creation.… The result was a peculiar distortion of the field … inquiries into the origin of living beings were relegated to the forbidden sidelines.'

Indeed, Darwin was constantly 'gliding along the dangerous edge of the known world, tacking south of heresy. He could have easily ascribed (his findings to) the invisible hand of god. But the answer that came to him in October 1838 in a book by another cleric, the Reverend Thomas Malthus, had nothing to do with divinity.' Malthus' *An essay on the principle of population* led Darwin to the concept of death as nature's culler and onward to natural selection where the fittest survived to drive evolutionary change in a species.

I mentioned thought-provoking asides at the start of this review. Here is one such. At Lyell's suggestion, on 1 July 1858 Darwin presented at a meeting of the Linnaean Society in London his own paper outlining his general theory of evolution and the paper by Alfred Russell Wallace with similar conclusions arrived at after studies in the Malay archipelago. 'The audience was not particularly enthusiastic about either study. The next May, the president of the society remarked parenthetically that the past year had not yielded any particularly noteworthy discoveries.'

Another features the Dutch botanist Hugo de Vries, who coined the term *mutant*. 'De Vries refused to bathe before dinner, (William) Bateson complained. "His linen is foul. I dare say he puts on a new shirt once a week." ' Bateson coined the word *genetics* from the Greek word *genno*—to give birth.

Commenting on Philip Larkin's poetic statement that sexual intercourse began in 1963, Dr Mukherjee blandly corrects Larkin: 'He was off by about two hundred thousand years.'

And there is the tale of the Boston surgeon who lost his memory and could recall his friends by the names of the various operations he had performed on them!

Darwin's cousin, Francis Galton discussed the selective breeding of the strongest, smartest, 'fittest' humans by *unnatural* selection in his book *Inquiries into human faculty and its development*. Needing a word to 'express the science of improving stock' Galton found *eugenics* appropriate. He also coined the phrase *nature versus nurture* to differentiate between hereditary and environmental influences on development.

The pursuit of *the science of improving stock*, when applied to humans, was to have tragic consequences for many. These are vividly described in this volume. The story of Emmett (Emma) Adaline Buck and her daughter Carrie is to be found in the appropriately titled chapter 'Three generations of imbeciles is enough'. I found the statements by Justice Oliver Wendell Holmes Jr (pp. 83–4) especially distressing.

Dr Mukherjee's learning, love for history and literature are in evidence throughout the book. His comments on haemophilia (pp. 98–9) serve as examples. 'The name of the illness—from Greek *haimo* (blood) and *philia* (to like or live)—is actually a wry comment on its tragedy.… The mutation in the hemophilia gene … had likely arisen spontaneously in Queen Victoria at birth. Her eighth child, Leopold, had inherited the gene and died of a brain hemorrhage at age thirty. The gene had also passed from Victoria to her second daughter, Alice—and then from Alice to *her* daughter, Alexandra, the czarina of Russia …' He then moves to Alexandra and the unsuspecting carrier's son Alexei who had life-threatening haemorrhages. These led to Alexandra's dependence on the 'Russian monk of legendary unctuousness, Gregory Rasputin …' and onwards to the Russian revolution and Rasputin's death on 30 December 1916 when he was poisoned, shot, slashed, bludgeoned and drowned. The story does not end there. A fast-forward through time to 2007 takes us to the discovery of a 13-year-old boy's skeleton that was found on genetic testing to be that of Alexei. Alas! the full genetic sequence of the skeleton was not carried out to find the mutant gene that 'had crossed one continent and four generations into a defining political moment of the twentieth century'.

I find Dr Mukherjee's enthusiasm contagious. Like him, I could not help being excited by the English bacteriologist Frederick Griffith's work that solved a major dilemma in genetics. How can genetic information pass horizontally from one organism to another? Vertical transmission from parent to offspring was understandable but how could this happen between two unrelated

strangers. Griffith's experiments on pneumococci helped him understand how, in a culture, a 'smooth' strain was able to induce virulence into the hitherto less harmful and more vulnerable 'rough' strain. After describing Griffith's experiments and observations that showed how the gene that governed virulence slipped out of the bacteria into the chemical soup in which both strains were being grown and, thence, into the non-virulent strain proved that genes were autonomous, material units that could exist in a chemical form outside the cell and could travel from cell to cell. One would have expected Griffith to broadcast this finding from the rooftops 'but Griffith, an unassuming, painfully shy scientist … who barely spoke above a whisper … hesitated for months … (and then) published his data in the *Journal of Hygiene*—a scientific journal whose sheer obscurity might have impressed even Mendel. Writing in an abjectly apologetic tone, Griffith seemed genuinely sorry that he had shaken genetics by its roots …' (pp. 112–14). Likewise is his account of Herman Muller's discovery in the 1920s that X-rays caused mutations in genes proving that genes were made of matter and that they could be altered using energy (p. 115). Almost as a postscript, Dr Mukherjee tells us that in 1932, Muller moved to Berlin. 'He had no inkling that his adopted city would, indeed, witness the unleashing of the new science of genetics, but in its most grisly form in history.' That story is presented in the next chapter, headed 'Lebensunwertes Leben' (lives unworthy of living). In it Dr Mukherjee shows vividly how the gene had emerged as 'a potent political tool and one of the most dangerous ideas in history'. In one of Mengele's experiments on twins, one with a hunchback was sewn to the twin with the straight back to see if a shared spine would correct the deformity. The site of operation got infected and both twins died.

In subsequent chapters we are led to the identification of DNA ('once termed the stupid molecule'), the unravelling of its structure and function, the base pairs that are integral to it, the role of RNA, cell division, programmed death of cells (termed *apoptosis* by John Kerr, the Australian pathologist in the 1970s) controlled by 'the genes of death', plasmids, the use of viruses in genetics, experiments where the nucleus of the egg cell is replaced by that from a fertilized egg or from an embryonic cell or even from another species, the interrelated functions of physics, chemistry and physiology in genetics and onwards to current events in the field, reverse transcriptase, recombinant DNA, gene sequencing, cloning and gene therapy. Dr Mukherjee takes us through the role of single genes, interactions between neighbouring genes and distant genes on the same chromosome, mechanisms by which genes are turned on and off, epigenetics.… At all times, we are made to progress along the time-line that led to each advance, told fascinating details of key players, the tools developed and used by them and brought up to date.

The recounting of the steps through which the three-dimensional structure of DNA was identified is especially fascinating. The description of the principle of X-ray crystallography has Dr Rosalind Franklin being placed centre stage for a while. Dr Mukherjee's finale to her role is touching. 'In 1962, Watson, Crick and Wilkins won the Nobel Prize for their discovery. Franklin was not included.… She had died in 1958, at the age of thirty-seven, from diffusely metastatic ovarian cancer—an illness ultimately linked to mutated genes.' Watson, in turn, had his own personal tragedy. In 1984, while Watson was with scientists discussing the feasibility of sequencing the human genome, Rufus, his 15-year-old son escaped from a psychiatric institution where he was under treatment for schizophrenia. (He was later found and brought back.) 'To Watson, a firm believer in the genetic basis for the disease, the Human Genome Project had come home—literally' (p. 303).

Dr Mukherjee shows us an unexpected side of James Watson when the latter mocked old biologists with their preoccupation with the collection and classification of biological specimens as 'stamp collectors'. Dr Mukherjee rallies to their defence. 'Darwin and Mendel had both bridged the gap between the old and new biology. Darwin had started out as a natural historian—a fossil collector—but had then radically altered that discipline by seeking the *mechanism* behind natural history. Mendel too had started out as a botanist and a naturalist and radically swerved that discipline by seeking the mechanism that drove heredity and variation' (p. 221).

The geographical description in the paragraphs on page 159 covers the area over a few square miles in London where so many epochal discoveries in genetics were made over half a century and more. A walking pilgrimage through it would be in order.

The account of how genes are used to make medicines starts off with the experiments on insulin—'the Garbo of hormones'. The work of Langerhans in 1869 was followed by experiments by Mering and Minkowski that proved the presence of isletin ('island protein') in pancreatic tissue; Banting and Best's extraction of a few micrograms of isletin (renamed *insulin*) and Boyer's plans for its synthesis. The work on somatostatin; the formation of Genentech (an abbreviation of genetic engineering technology); Goeddel's creation of the first molecules of recombinant insulin; the great increase in the need for synthetic factor VIII after haemophiliacs were infected by HIV after being given transfusions followed. The anecdote of the 43-year-old man with haemophilia given the first recombinant factor VIII derived from hamster cells is hilarious (pp. 248–9). I could go on and on but cannot tax your patience further.

As we contemplate the brave new world of gene manipulation and therapy, the words of Erwin Chagall must keep resounding in our minds. 'You can stop splitting the atom, you can stop visiting the moon, you can stop using aerosol.… But you cannot recall a new form of life. [The new genetic hybrids] will survive you and your children and your children's children.… The hybridization of Prometheus with Herostratus is bound to give evil results' (p. 210).

An example of self-regulation in genetics is recounted in the chapter 'Einsteins on the beach'.

As Marianne Dieckmann told Dr Mukherjee, 'The capacity to manipulate genes represented nothing short of a transformation in genetics.… We needed to convince ourselves, and everyone else, that we were responsible enough to use it.'

The book ends with a glossary, a graphic time-line of genetics, exhaustive notes (pp. 505–50), a select bibliography and an index.

I found this book enhancing my sense of wonder even as it stimulated, informed and amused me. You will also find it rewarding.

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