The enemy within

Simplifying the vital story of how genes determine our characteristics and chances of mortality

It is no ordinary history of genetics where, midway through, we read the following:

In the Bible, Ham's descendents are cursed because he stumbleth on his father, Noah, drunken and naked, his genitals exposed, lying in a field in the half-light of dawn. In the modern version of that story, you encounter your father, demented and naked, in the half-light of the guest bathroom — and see the true of your own future, illuminated.

Siddhartha Mukherjee is a cancer specialist, whose previous book The Emperor of All Maladies: A Biography of Cancer won the 2011 Pulitzer Prize for general non-fiction. The physician will out: in The Gene: An Intimate History, Mukherjee’s writing and thinking are at their best when his subject is illness. The curse he fears in that bathroom encounter with his eighty-two-year-old father is not the genetic infirmity of old age but the genetic tendency to mental illness that, he reckons, runs in his family. One uncle was undone by manic depression, another by schizophrenia. A cousin with schizophrenia lives out his medicated days in an institution in Calcutta. The book opens with Mukherjee and his father visiting poor Moni, the light in whose pupils “had dulled and nearly vanished, as if someone had entered his eyes with a minute paintbrush and painted them grey”.

Between these absorbing personal vignettes stretches a very long retelling of the growth of scientific knowledge about inheritance, from Gregor Mendel through to the biotech firm Genentech. Again, the physician will out, though here — with less straightforwardly pleasing results. Mukherjee cherishes genetics for having pulled cancer medicine out of the doldrums, and this baseline admiration shines through in his approach to writing history. He treats the past mainly as providing a chronological frame on which to hang the introductory genetics lessons that he wants to impart, together with colourful stories to wrap them up in. There is little concern to avoid anxiousness or re-examine received wisdom. Scale up the historical-embrace passages in a genetics textbook, organize them according to the periodization favoured by the leaders of the Human Genome Project, render the whole in fluent, simile-laden prose, and you have something that reads a lot like Mukherjee’s history. The textbook deals with eugenics, and so does Mukherjee, unsurprisingly though not always subtly (he turns Francis Galton, coiner of “eugenics”, into a pantomime villain). The Gene is very much what Mukherjee tells us it is: a “prequel” to the cancer biography, telling the tale of the thing which cancer is liable to develop.

Up to that bathroom moment, the history-coated genetics that we get goes roughly as follows. Once Mendel’s unjustly ignored discovery of the gene, understood as an atom of hereditary information, was belatedly recognized in 1900, genes, dominant and recessive, were held to explain inheritance patterns on the model of those Mendel had found in his monastery in Brina, among his yellow or green, round or wrinkled garden peas. But nobody could say exactly, what genes were or what they did. That started to change between the 1910s and the 1940s, when genes became known as bits of chromosome responsible for directing the synthesis of proteins, and genetic disease came to be understood as due to chromosomal alterations that disrupt normal protein synthesis. Francis Crick and James Watson’s paper of 1953 announcing that DNA — by then under suspicion as the main genetic chemical — has the structure of a double helix ushered in a new molecular era. Talk of “the genetic code” dates from then, referring to the cell’s rule book for translating sequences of DNA bases into the amino acids making up proteins. Disease-causing mutations were now understood as errors arising in a gene’s DNA sequence. It turned out, for example, that behind sickle-cell anaemia lies just one change in one base pair in the gene encoding the oxygen-carrying protein haemoglobin. In the 1960s, in the wake of François Jacob and Jacques Monod’s demonstration that proteins can turn genes on and off in response to environmental cues, there came a new appreciation of genes’ abilities to regulate their own expression. The 1970s marked the start of a new era again, as geneticists learned to cut and paste genes at will and also to read DNA sequences. Out of these innovations came, among other therapeutically marvellous, synthetic insulin and, at a time when HIV made the blood transusions on which haemophiliacs depended dangerous, synthetic blood-clotting factor VIII.

But then we reach Mukherjee’s discussion of his stricken father’s condition — that other intimate history of the gene — and the triumphalism evaporates. The dementia is not, after all, the family madness striking again, but a symptom of something else: a swelling of the ventricles in the brain, probably due to an excess of fluid. To become intimate with the genetics of normal pressure hydrocephalus (NPH) is to be immersed in a world of complications. Mukherjee is an outstanding guide: it is... quite likely to be a genetic disease... although not "genetic" in the same sense as sickle-cell anaemia or hemophilia. No single gene governs the susceptibility to this bizarre illness. Multiple genes, spread across multiple chromosomes, are involved... Variations in any of these genes may alter the physiology of the aqueducts and ventricles, changing the manner in which fluid moves through the channels. Environmental influences, such as aging or cerebral trauma, interpose further layers of complexity. There is no one-to-one mapping of a gene and one illness. Even if you inherit the entire set of genes that causes NPH in one person, you may still need an accident or an environmental trigger to "release" it (in my father’s case, the trigger was mostly likely his age)... It is a Delphic boat of a disease... determined not by one gene, but by the relationship between genes, and between genes and the environment.

There follows a further, fastidious unpacking of the ways in which this condition is and is not genetic, is and is not environmental, is and is not the product of chance. It is hard to think how these pages could be improved.

This willingness to give complexity and diversity their due lifts a good deal of the second half of the book. Here, Mukherjee brings his growths-of-knowledge story up to the present, with an emphasis on human genetics and occasional stops around the Mukherjee family tree. The coverage of topics is a little quirky — there is nothing here, for example, about genetically modified foods or the use of DNA fingerprinting — but the author touches on the major medically relevant developments. He makes an attractive hero out of Victor McKusick, founder of a Baltimore genetic medicine clinic and compiler of the standard catalogue of genes involved in human diseases.

Just as, in the late 1960s and early 70s, the arrival of prenatal testing for chromosomal conditions, together with the spread of legalised abortion, turned genetic medicine into an intervention science (and refreshed its eugenics roots), McKusick began effectively putting not only "genetic" in quotation marks, but also "disease", which is increasingly understood as a mismatch between constitution and environment. Even haemophilia and sickle-cell anaemia manifest very differently in different individuals depending on what is interacting with what, and how, and when, and where. Mukherjee quotes McKusick in 1991, at a conference on legal and ethical issues surrounding the new Human Genome Project, warning about the "genetic-commercial complex", selling an exaggerated certainty about what genetic tests predict to parents increasingly under pressure to pay for and abide by them. When, ten years later, the full DNA sequence for humans was published, it revealed far fewer genes than expected — considerably fewer than in the
Access highlights from the TLS delivered to your inbox every week.