

The road to the code...

... and the cast who brought genetics to centre stage.

Cracking the Genome: Inside the Race to Unlock Human DNA/The Sequence: Inside the Race for the Human Genome

by Kevin Davies

Free Press/Weidenfeld & Nicolson: 2001.

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In 1901, William Bateson, the biologist who coined the word genetics, presented his first "Report to the Evolution Committee of the Royal Society". It included a footnote on "extraordinarily interesting" observations by Archibald Garrod, a physician at the Hospital for Sick Children in London: "Recently Garrod has noticed that no fewer than five families containing alkaptonuric members ... are the offspring of first cousins ... exactly the conditions most likely to enable a rare and usually recessive character to show itself."

A century after this first description of mendelian human genetics, *Nature* and *Science* contain the first reports of the 'complete' sequence of the human genome. This is a tremendous accomplishment, and even more remarkable when set in the context of those 100 years.

Human genetics was not an instant hit. Geneticists found fruitflies and other 'simpler' organisms more tractable material for analysis, and physicians had little interest in obscure disorders that affected so few people. (The eugenicists' interest in human genetics was another matter, being driven by social and political goals, rather than by scientific curiosity or medical necessity.) There were some early successes — notably the foundations of population genetics, laid by Ronald Fisher, J. B. S. Haldane and Sewall Wright (1908–50); the molecular nature of sickle-cell anaemia discovered by Linus Pauling (1949); and electrophoretic studies of inherited protein variations by Oliver Smithies (1955).

It was not until 1956 that the number of human chromosomes was determined correctly by Jo Hin Tjio and Albert Levan, and, some 20 years later, the first human gene (β -globin) was cloned. But modern human genetics did not begin until 1980, when David Botstein, Ray White, Mark Skolnick and Ron Davis showed how so-called restriction fragment length polymorphisms (RFLPs) could be used to find human disease genes.

Then, in the mid-1980s, discussions began on the desirability of sequencing the complete human genome. The project that was funded by the US Department of Energy began in 1987. It was followed in 1990 by that from the National Institutes of Health, under the directorship of James Watson.

the human gnome project...



Hard sell: Jim Watson woos Leroy Hood, David Botstein, Sydney Brenner and Charles Cantor.

Robert Cooke-Deegan wrote a scholarly account of these early years of the Human Genome Project (HGP) in *The Gene Wars* (W. W. Norton, 1996). Now Kevin Davies' book *Cracking the Genome* covers the period from 1991 to the present. During those years, we were as likely to learn of the progress of the HGP from the pages of *The New York Times* as from those of *Nature* or *Science*. And if these accounts were to be believed, the twists and turns of the HGP were worthy of a Wagnerian epic.

The central characters in Davies' account are Craig Venter and Francis Collins. Venter founded the non-profit Institute for Genome Research before establishing the for-profit company Celera. His forte has been to see what needs to be done, and then to do it. Sydney Brenner and Ham Smith proposed very different ways in which the sequencing could be carried out, but it was Venter who acted decisively. Davies recounts how Venter and Smith began sequencing a microbial genome even before they had submitted a grant application to the National Institutes of Health. By the time the proposal was rejected as "impossible", the sequence was 90% complete.

Francis Collins, as the leader of the publicly funded sequencing efforts — Eric Lander called them the "Forces of Good", leaving

us to supply the equivalent phrase for Celera — was constrained by his position from pushing ahead as decisively as Venter. The international battalions of the public genome effort, although fighting on the same side, did not always agree on how the war should be fought. There were also leaders in Congress to be cajoled, and here Collins was adept at keeping funds flowing to the project by persuading congressional committees of the benefits that would flow from it.

There is a large cast of characters, all equally worthy of taking centre stage. They include John Sulston and the Wellcome Trust in England. Both wielded tremendous influence — the former through his insistence on hewing to a gold standard of sequencing and the immediate public release of sequence data, and the latter through its financial clout and irrepressible envoy, Michael Morgan. At the 1998 genome meeting at Cold Spring Harbor Laboratory in New York, Morgan's announcement that the trust was to double its support of the Sanger Centre in Cambridge won a standing ovation from the assembled troops. The Sanger Centre is sequencing one-third of the human genome, a task paid for primarily by the Wellcome Trust.

Davies discusses the controversies over the patenting and commercial exploitation

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of the sequence. There continue to be irreconcilable differences between the demand by publicly funded laboratories for immediate and unrestricted release of data and the necessity for Venter to maintain some degree of secrecy in order to sell genomic information. The most recent manifestation of this controversy is the failure of the participants to agree on joint publication.

I am not sure who Davies sees as his audience. He includes a chapter on DNA that is aimed at non-scientists, yet much of the book requires familiarity with the genomics research world. Davies tries to show why sequencing the genome is both useful and fascinating by including chapters on the implications for clinical genetics, human evolution and gene therapy, but I found that these broke the flow of the central story of sequencing the genome. It could be argued that Davies' US title is not quite on the mark. So far, we have read the letters of the genome without much understanding; cracking the genome is yet to come.

Davies tells the story with verve, but tends to lapse into hyperbole, as if he feels the need to reassure the reader that this is a big story; for example, the double-helix paper stands "above the entire rest of the pantheon of scientific literature", and the completion of the human genome sequence is "perhaps the defining moment in the evolution of mankind". And there are mistakes; it was Robert Sinsheimer at the University of California at Santa Cruz, rather than Charles DeLisi of the Department of Energy, who first considered sequencing the human genome. Davies' claim that DNA was "virtually ignored" in the period between Friedrich Miescher (1871) and Oswald Avery (1944) displays a disappointing lack of knowledge of the studies of Albrecht Kossel, Phoebus Levene and William Astbury.

Davies closes the book with the charming story of Bateson's conversion to mendelism while travelling by train to give a talk at the Royal Horticultural Society. According to Bateson's wife, Bateson's reading of the experiments performed by the little-known monk 35 years previously transformed his view of heredity. Bateson revised his presentation en route to include Mendel's findings. Unfortunately, historian Bob Olby's recent research suggests that Bateson was reading, not Mendel, but the Dutch geneticist Hugo de Vries.

Davies did not set out to write a definitive record of the politics of the genome project, which is a pity; genome scientists are likely to be left wanting more behind-the-scenes details and scuttlebutt. *Cracking the Genome* is a good start, but the epic that is the Human Genome Project awaits its Boswell, or Watson. ■

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Happy together? Einstein was said to have treated his first wife Mileva Marić with undisguised contempt.

Affairs of the heartless

Einstein in Love: A Scientific Romance

by Dennis Overbye
Viking: 2000. 416 pp. \$27.95

Lewis Pyenson

Seeking the laws of nature, physicist Albert Einstein invoked the Deity's love of harmony. For more than a decade, however, we have been aware that Einstein, the man, surrendered celestial harmony to earthly passion and engendered domestic dissonance. Einstein was the great defender of cause-and-effect in physics, but from his youth, he sought the affection of women, in parallel and in series, with little concern for the consequences. Celebrated as a gentle pacifist, Einstein treated his family with heartless disdain and his first wife with undisguised contempt. He raised large sums for charity while depriving his children of a tranquil existence. In *Einstein in Love*, science writer Dennis Overbye has provided an engrossing narrative of the personal and professional life of *Time* magazine's "Man of the Century".

Einstein's attraction to his first wife Mileva Marić, a free-thinking Serb of Austro-Hungarian nationality, echoed his sceptical attitude towards authority. Both were irreverent and unconventional students of physics. Early in their courtship he called her

Doxerl (Dollie) and she called him Johanzel (Johnny), perhaps allusions to characters in *A Doll's House* (Henrik Ibsen was a notable figure in Munich when Einstein was a boy there). Notwithstanding doubts expressed by the editors of the Einstein papers, there is circumstantial evidence that Marić shared in the genesis of relativity theory.

Just as Einstein took time to obtain a doctorate — failing several times in the attempt — he was also slow to reach maturity in personal relations. Shortly before he finally broke with Marić, when Europe was careening towards war in 1914, Einstein drew up a list of demands for keeping up appearances with her that reads uncannily as if it were the marriage contract of the emotionally crippled scholar Peter Kien in Elias Canetti's 1935 novel *Auto da Fé*.

When Einstein's station in life permitted it, he gave libido free rein. Women became, for him, an anodyne for the rigors of pure thought. Overbye portrays Einstein's second wife Elsa Einstein as a bourgeois comfort, suiting his station as a world-famous professor at Berlin University. Through her efforts, he ate well and recovered his Jewish heritage.

The charming affair between Einstein and Marie Curie, portrayed by Yahoo Serious in his underrated 1988 comedy film *Young Einstein*, is entirely fictitious, but it invites us to consider how Einstein loved. If we may infer from his correspondence, his love is largely sexless; momentous thoughts find little place in it. In addition to cute nothings, letters sent to his wives refer to