On 12 February 2009, researchers at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, led by Svante Pääbo, announced in a press conference that they had completed a first draft of the Neanderthal genome, the first to be sequenced from an extinct type of human. This book is Pääbo’s account of how that remarkable scientific achievement came about. But it is much more than that. It is also the brilliantly written account of the founding of an entirely new scientific discipline (paleogenomics), an instructive case study of the power of the scientific method and the story of Pääbo’s own scientific career with all its twists, turns and serendipities, along with occasional glimpses of the sometimes happy but often complicated and messy personal life of its author. This review will focus on Pääbo’s scientific story.

Chapter 1 begins with the moment that Pääbo and his team realized they had managed to retrieve mitochondrial DNA (mtDNA) from a Neanderthal bone. We are then introduced to the Neanderthals and the questions that arose concerning their relationship to modern humans following their discovery in the nineteenth century. The author explains the problem of post-mortem DNA degradation, meaning that very little DNA is present in most ancient samples, and the dramatic advance represented by the development in 1983 of the polymerase chain reaction (PCR). This technique allowed a single piece of DNA to be “amplified”, generating thousands to millions of copies. However, one of the biggest challenges in ancient DNA studies is minimizing the contamination of samples, thus ensuring that what is being amplified is DNA endogenous to the individual or organism being studied. The problem of contamination becomes a recurring theme of the book and serves to highlight just what an achievement the sequencing of the Neanderthal genome really was.

In Chapter 2 the reader is taken back to the earliest stages of Pääbo’s scientific career, when he was a medical student at the University of Uppsala in Sweden. His interest in ancient DNA began as a secretive sideline, with “proof-of-principle” experiments confirming that DNA could be extracted from artificially mummified calf liver and subsequently from authentic Egyptian mummies.

During Pääbo’s time as a postdoc at UC Berkeley improvements were made to the PCR method, and Chapter 3 charts his successful application of the method to samples from extinct animals (the quagga and the thylacine), to museum specimens of kangaroo rats and to Native American remains. Pääbo also notes his growing awareness of the limitations of ancient DNA preservation and the techniques for extracting and studying it.

In the early 1990s Pääbo was increasingly frustrated by “flashy” publications in high-profile journals claiming, for instance, that DNA had been retrieved from Miocene magnolia leaves, from insects in Dominican and Lebanese amber, and even from dinosaur bones. In Chapter 4, he explains his dismissal of these claims of “super-old” or “antediluvian” DNA, especially when attempts to replicate the findings under more rigorous laboratory conditions proved to be a failure. He and his colleagues introduced what they called “criteria of authenticity”, procedures that had to be carried out before a DNA sequence obtained by PCR could be regarded as truly old. Eventually, Pääbo and his team decided to ignore the dubious results and concentrate on their own work.

The next chapter describes Pääbo’s sequencing of the mtDNA of the extinct giant ground sloth, in order to elucidate its evolutionary relationships with modern tree-dwelling sloths. The field of ancient DNA studies had become sufficiently well-established by the mid-1990s that Pääbo could return to the challenge of human remains, applying sequencing methods to Oetzi the Ice Man and to mummies from the American southwest. Chapter 5 concludes with Ralf Schmitz of the Bonn Museum in Germany agreeing to provide a small piece of the right upper arm bone of the Neanderthal type specimen, from which the groundbreaking mtDNA sequence was retrieved.

Chapter 6 resumes the story following publication of the Neanderthal mtDNA sequence. An immediate priority was to
sequence mtDNA from other Neanderthals to estimate how much mtDNA variation was present in the group as a whole. Small samples of Neanderthal and cave bear bones from the Vindija cave in northwestern Croatia were obtained for this purpose. However, Pääbo and his colleagues were beaten to publication by a UK-based group reporting a second Neanderthal mtDNA sequence from Mezmaiskaya cave in the northern Caucasus. With three sequences now available, it became clear that Neanderthal mtDNA showed little variation, suggesting that the Neanderthals, like modern humans, had expanded from a small population.

Pääbo tells the story in Chapter 7 of how he was invited by the Max Planck Society to set up a new evolutionary anthropology institute in Leipzig. The new facility included custom-designed clean rooms for ancient DNA extractions. Chapter 8 recounts the reactions of multiregionalists to the Neanderthal mtDNA results, which broadly supported the out-of-Africa model of modern human origins. In particular, Erik Trinkaus argued that the mtDNA results might be biased if DNA sequences resembling those of modern humans were erroneously discarded as contaminants. This chapter shows how Pääbo’s team was able to demonstrate that Trinkaus’ concerns were misplaced.

The focus then shifts in Chapter 9 towards the need to sequence the Neanderthal nuclear genome. Initial attempts were made to extract nuclear DNA from the Vindija cave bear bones, rather than the scarcer and more valuable Neanderthal bones. However, these efforts failed. Success was achieved with Pleistocene mammoths recovered from the Alaskan permafrost, but this was discouraging because there were no Neanderthals preserved in permafrost!

Despite these setbacks, Pääbo was convinced that nuclear DNA had to be present in Neanderthal bones even if the PCR could not retrieve it. Two alternative approaches presented themselves: second-generation sequencing and the cloning of DNA in bacteria. Chapter 10 outlines the decision to test both approaches head-to-head using Neanderthal DNA. To this end, collaborations were established with Michael Egholm of biotech company 454 Life Sciences and Eddy Rubin of the Lawrence Berkeley National Laboratory in California. The chapter concludes with Pääbo setting out a “roadmap” for sequencing the entire Neanderthal genome at the Cold Spring Harbor genome meeting in 2006.

Chapter 11 describes Pääbo’s dawning realization that the bacterial cloning method was too inefficient to get the project done and the termination of his collaboration with Eddy Rubin. Pääbo nevertheless boldly promised at a press conference in July 2006 to sequence the entire Neanderthal genome within two years. The urgent quest for more and better Neanderthal bones is the theme of Chapter 12. The right upper arm bone from the Neander Valley had yielded 4% Neanderthal DNA, and it was hoped that other bones might yield as much or even more. However, analyses of additional samples from the Neander Valley and other sites did not prove encouraging. Yields from these bones ranged from 0.1 to 1.5 percent Neanderthal DNA. Then a developing collaboration with the Croatian Academy of Sciences and Arts led to the acquisition of eight more bones from Vindija. Nearly all contained Neanderthal DNA; three yielded more than 1% Neanderthal DNA and one almost 3%.

Every step in the laboratory procedures was re-evaluated to minimize the loss of DNA during processing. Chapter 13 explains that the result was a “game-changing advance” with the development of a protocol that was several hundred times more efficient than the previous one. Another significant advance was the use of restriction enzymes to separate bacterial DNA in the bone extracts from endogenous Neanderthal DNA. This increased the yield of Neanderthal DNA from 4% to 20%.

Chapter 14 moves on to the next challenge the team faced: mapping the genome by matching the short Neanderthal DNA fragments to a human reference sequence. This required the development of mapping algorithms that struck a careful balance between being too stringent (which would make the Neanderthal genome look too similar to the modern genome) and too permissive (which would make it look too different to the modern genome). Next, the mapping algorithms were tested by sequencing and mapping all the nucleotides in the Neanderthal mtDNA (Chapter 15). However, the accumulation of nuclear DNA sequences was going much more slowly than hoped, and in mid-2008 this led to the termination of the collaboration with 454 Life Sciences. New technology acquired by biotech company Illumina would allow completion of the nuclear genome sequence within reasonable time. Both Science and Nature began to court Pääbo’s team for the Neanderthal genome paper.

Chapter 16 begins with all the nuclear DNA needed to complete the project now sequenced. This achievement allowed important questions to be answered, such as whether Neanderthals had contributed DNA to people living today, especially in Europe where Neanderthals are known to have coexisted with early modern humans. The mtDNA data and the first nuclear genome analyses suggested no admixture, but could only exclude a very large genetic contribution from Neanderthals. By February 2009, however, there was strong evidence that Neanderthal genomes more closely resembled those of modern non-Africans than Africans and that interbreeding outside Africa must therefore have taken place.

At a research meeting in Croatia, Pääbo and his colleagues hammered out how they would analyse and publish the genome paper (Chapter 17). Their studies had confirmed that the data quality was excellent, with estimated levels of contamination in the mtDNA data of about 0.3% and in the nuclear DNA data of less than 1%.

Chapter 18 describes additional work confirming that Neanderthals and early modern humans had interbred. Furthermore, the data suggested that the direction of gene flow had been from Neanderthals into modern humans. If gene flow had occurred in the other direction it was now undetectable. One outstanding puzzle was thrown up by the data: Neanderthal DNA seemed to be present not only in modern Europeans, but also in the Chinese and in the inhabitants of Papua New Guinea. Pääbo’s solution to this puzzle was the “Middle Eastern” scenario, in which early modern humans leaving Africa mixed with Neanderthals in the Middle East and then carried Neanderthal DNA into regions where the Neanderthals had never been present.

Chapter 19 discusses the “Middle Eastern” scenario in a little more detail. Fossil evidence shows that early modern humans had coexisted with Neanderthals for some time in the Carmel mountain range of present-day Israel. The two populations shared the same stone tool technology and in all likelihood interbred with one another. But then a “replacement crowd” of more expansive early moderns with a more sophisticated tool technology spread out
rapidly from Africa and absorbed the modern human populations that already existed in the Middle East. In this way, Neanderthal DNA passed indirectly into the replacement crowd and through them into modern European and Asian populations.

In 2009, work began to construct a catalogue of the genetic differences between modern humans and Neanderthals (Chapter 20). This was seen as a crucial step in understanding what sets the two groups apart. However, there were limitations to how complete the catalogue could be since only 60% of the genome had been sequenced at that time.

Chapter 21 tells the story of the publication of the Neanderthal genome and the reception it received from the scientific community. *Science* published the paper on 7 May 2010, along with 174 pages of supplementary material. At the same time, the reconstructed genome was made freely available in online databases. Most reactions from fellow scientists were positive, although Erik Trinkaus was a notable exception. Pääbo even notes the welcome given to the paper by young-age creationists, almost all of whom consider the Neanderthals to be “fully human”, while old-age creationists (and specifically Hugh Ross’ Reasons to Believe organization) did not like the discovery that Neanderthals and modern humans had interbred, regarding this as evidence of “animal bestiality” in human history.

In Chapter 22 the book turns from the Neanderthals to the discovery of another extinct type of human. Early in 2009, Pääbo’s team had acquired a miniscule fragment of finger bone that had been found in Denisova Cave in the Altai Mountains of southern Siberia. Sequencing of its mtDNA revealed that it represented neither a modern human nor a Neanderthal, but seemingly another extinct human group. During a research visit to Russia an unusual molar tooth from the same cave was also acquired. The mtDNA analysis of the finger was published in *Nature* in April 2010.

The final chapter describes the nuclear DNA sequencing of the finger bone, which contained surprisingly low levels of contamination (Chapter 23). An entire mtDNA sequence was also reconstructed from the molar tooth. The results indicated that the finger bone and the tooth came from different individuals but the same type of human, subsequently named “Denisovans”. Analysis of the nuclear DNA sequence revealed that the Denisovans were more closely related to Neanderthals than to modern humans, although, as with the Neanderthal genome, there was evidence of gene flow from Denisovans into the ancestors of some modern populations. The team concluded that “low levels of mixing with earlier humans seemed to have been the rule rather than the exception when modern humans spread across the world” (p.246).

So what do we now know as a result of this extraordinary research project?

1) We have a pretty good idea of what the Neanderthal genome was like and how it differed from the modern human genome. A near-complete catalogue has now been compiled of nucleotide positions that distinguish modern humans from Neanderthals, Denisovans and living apes, and it contains 31,389 changes, 125 insertions and a few deletions. What is not yet known is the functional significance of these differences. On page 208 Pääbo highlights what he calls “the dirty little secret of genomics”, the fact “that we still know next to nothing about how a genome translates into the particularities of a living and breathing individual.”

2) We have strong evidence that both the Neanderthals and the Denisovans contributed a small percentage of genetic material to modern-day populations. In the case of the Neanderthals, this flow of genetic material into early modern humans most likely happened while the two groups coexisted in the Middle East, early modern humans then carrying the Neanderthal DNA with them when they migrated into regions where no Neanderthals had ever been present. In the case of the Denisovans, it seems likely that early modern humans met and mixed with them while migrating out of Africa and along the southern coastlines of Asia.

3) Like modern humans, the amount of mtDNA variation in Neanderthals is very low, suggesting that both groups began as small populations that later underwent expansion.

From a young-age creationist perspective, the data from these genome studies (and from the fossil record) are consistent with the claims that human diversity was significantly greater in the early post-Flood period than today and that both the Neanderthals and the Denisovans were members of the human baramin. What is not clear is how the genetic differences between these groups arose so quickly after the Flood (and, presumably, after Babel). Conventional estimates of divergence times suggest much longer time scales than the Biblical chronology allows. A major prediction of the young-age model is that there must be as-yet undiscovered mechanisms of rapid genomic change.

A few other points pertinent to creationism can be drawn from the book:

1) *The human nature of the scientific enterprise*. On page 191 the author writes: “Science is far from the objective and impartial search for incontrovertible truths that nonscientists might imagine. It is, in fact, a social endeavor where dominating personalities and disciples of often defunct yet influential scholars determine what is ‘common knowledge.’” Pääbo makes these comments in the context of the once-prevailing consensus that no interbreeding between Neanderthals and modern humans had ever taken place. However, his words serve as a useful and more general reminder that scientists are subject to biases of many kinds (not least worldview, philosophical and religious biases).

2) *The excitement of the scientific enterprise*. This book reads like a detective story and vividly conveys the excitement of a life in science. As in any life, there are ups and downs, successes and failures. Advances in scientific knowledge are hard-won. But overall, science is a joyous and fulfilling activity, and one that brings glory to God as we study the Creator’s handiwork. One of our tasks as creationists is surely to cultivate in the church a healthy attitude to scientific discovery, and help to dispel the fear and suspicion that too often prevails.

3) *The practical realities of the scientific enterprise*. There are also lessons for us in this book about how good science is done. Pääbo’s story helps us to see the importance of developing and testing our own models (not simply criticizing those of our opponents), the need for self-criticism, the value of collaborations with others, the necessity of rigorous peer review, and the unfortunate way in which headline-grabbing (but ultimately wrong-headed) ideas can eclipse more careful, systematic work. Of course, as creationists we can only dream of having a research budget of $6 million and the facilities of the Max Planck Institute at our disposal, but there is much to learn here despite our limited resources! One final thought: the Neanderthal genome project
challenges the popular creationist claim that “origins” science is somehow inferior to “operations” science, by showing that multiple competing hypotheses about unobservable past events (e.g. the Neanderthals did/did not contribute genetic material to modern humans) can be successfully evaluated in terms of how well they explain observable phenomena in the present. While there may be some differences in methodology (e.g. Cleland 2001), it is difficult to maintain that there is a hard-and-fast distinction between “historical” science and “experimental” science.

This is an unfinished story, as the postscript to the book makes clear. Indeed, as I was writing this review the latest edition of *Nature* landed on my desk, with a report by Pääbo and colleagues of nuclear DNA sequenced from bones found in Sima de los Huesos in northern Spain, which may have belonged to *Homo heidelbergensis* (Meyer et al. 2016). About the same time, Pääbo’s team published a further analysis of Denisovan and Neanderthal DNA persisting in modern individuals from the Pacific Melanesian islands (Vernot et al. 2016). As creationists we ought to welcome the results of such research as we seek to develop young-age models to explain the fossil record of early humans. In this endeavour, more data is better than less and it is clear that new and exciting discoveries await us.

References

