And as We Moved, We Embraced, and We Absorbed *
A Narrative and Contextualization of the Work of Svante Pääbo, Nobel Laureate in Physiology or Medicine 2022

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A few months after its publication, my friend Naoyuki Takahata presented me with a copy of the book he had written with Jan Klein. The cover of the book was most unusual. It was the reproduction of a portion of the painting of Paul Gauguin’s masterpiece, now in the Museum of Fine Arts in Boston, “D’où Venons-Nous? Que Sommes-Nous? Où Allons-Nous?” (“Where Do We Come From? What Are We? Where Are We Going?”), painted in Tahiti in 1897, six years before his tragic death. Gauguin’s painting (which, interestingly, has to be viewed from right to left) depicts the spectrum of human activity from birth to death. Klein and Takahata titled their book Where Do We Come From? The Molecular Evidence for Human Descent, which I reviewed in Current Science (10 September 2002).

Where do we come from? ... has haunted us for hundreds of years. When and where did modern humans—*Homo sapiens*—arise?

Charles Darwin, to whom we owe our fundamental understanding of biological evolution, wrote his magnum opus *On the Origin of Species* in 1859. The thesis that he expounded was a challenge to the Victorian dogma. Darwin argued that God did not specially create each species. Species were not immutable. One species arose from another, a pre-existing one, with modification by natural selection. In this book, he conspicuously avoided discussing the human species. He had only stated that “light will be thrown on the origin of man and his history”; later, that is. Even twelve

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years later, when he published The Descent of Man, and Selection in Relation to Sex, he did not have much to say about human evolution. He only argued—using embryological, anatomical, and behavioral observations—that different species of the human also evolved in the same way as those of other genera. The arguments were not strong. Fossil record of the Homo at the early stages of their existence was sorely lacking.

However, Charles Darwin made some astute observations. Based on the observations available, he inferred that all humans are one species and that its “races” all descended from a common ancestral stock. Noting that humans and African apes were anatomically considerably similar, he inferred that gorillas and chimpanzees were closely related to humans. He even concluded that the ancestors of humans probably lived in Africa.

Darwin’s inferences have been confirmed by detailed palaeoan-
thropological research. We now know that gorillas, chimpanzees, and modern humans had a common ancestor about seven million (sometime between five and ten million; estimates of dates are often imprecise because of the paucity of data) years ago in Africa. Thus, hominins (us and our extinct relatives) came from Africa. Hominins and the great apes (e.g., gorillas and chimpanzees) evolved along separate lines of descent after separating from the common ancestor. Indeed, the hominins got their start in Africa, where they evolved from a quadrupedal gait to an upright gait and also developed a large-sized brain.

The archaeological record of hominins maps the spread of our ancestors across our planet. The fossils and artifacts reveal that multiple hominin species have walked the earth. Every hominin fossil dated to be older than 2.1 million years—and there are now quite a few of them—has come from Africa. Africa is undoubtedly the birthplace of the genus *Homo*. From the fossils found at the site of Jebel Irhoud in Morocco, we know that our species (*Homo sapiens*) originated in Africa at least 315,000 years ago. We started to make forays out of Africa around 200,000 years ago. In large numbers, possibly from about 100,000 years ago. By 50,000 years ago, we had established ourselves throughout Eurasia.

When we came out of Africa, we realized that we were not alone. Other hominin species had already come out of Africa and had

**Figure 2.** Where Do We Come From? What Are We? Where Are We Going? Painting by Paul Gauguin.
colonized many places in Europe and Asia. But, by about 40,000—30,000 years ago, the last of the hominin species who were not *Homo sapiens*, such as the Neanderthals (*Homo neanderthalensis*) became extinct. We were left alone in the world.

How did we succeed? Two competing theories have dominated this discussion ever since the first fossil of the Neanderthal was discovered in 1956. One held that the Neanderthals were an archaic variant of our own species, *Homo sapiens*, that evolved into or was assimilated by the anatomically modern European population. The other posited that the Neanderthals were a separate species. We waged war against them, killed and exterminated them. A milder variant of the ‘war argument’ is that the Neanderthals ended up competing with the incoming moderns for food and gradually lost ground. We shall not dwell on the arguments and facts used to support these theories. Fossil and other palaeoanthropological evidence are always fragmented and often scanty; hence the support provided by these types of data to competing hypotheses is often equivocal.

The ability to analyze the DNA of modern and ancient humans and other species has revolutionized the study of human evolution. Comparing the human genome with the genomes of the living great apes has shown conclusively that we are most closely related to chimpanzees and bonobos; we share nearly 99% of our DNA with them. Analyses of the DNA of hundreds of thousands of individuals belonging to extant human populations have revealed that we are genetically highly diverse. The populations of Africa are the most diverse. Even though we identify ourselves with discrete groups, the groups are genetically not discrete. Modern human genetic variation is continuous, and most variation exists within populations than between populations. This is a consequence of our demographic history as a species that originated in Africa with populations that mixed continuously as they migrated around the world.

Enabling the analysis of ancient genomes was critical to our understanding of human evolution, especially why and how the various other species of *Homo* that the *sapiens* met when they came
out of Africa rapidly vanished. The most important species that became extinct rapidly was *Homo neanderthalensis*; the Neanderthals.

The Nobel Foundation awarded the Nobel Prize in Physiology or Medicine in 2022 to Svante Pääbo, Director of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, “for his discoveries concerning the genomes of extinct hominins and human evolution.” Pääbo made his discoveries by analyzing ancient genomes. Analyzing the genomes of living organisms is relatively easy. However, obtaining DNA from an ancient extinct individual and analyzing it is quite a different matter. Over time, DNA changes chemically and gradually breaks down into short fragments (see Box 1). So after thousands of years, only traces of it remain among bone samples, and those traces are usually heavily contaminated with foreign (e.g., bacterial or fungal) DNA (see Box 2). Pääbo and his team painstakingly overcame these challenges and developed benchmarks for the analysis of
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Interestingly, Pääbo initiated work on fossil tissues secretly while he was pursuing his doctoral studies at Uppsala University. ‘Secretly’ in the nights because he was not sure whether his doctoral supervisor would approve of his efforts to isolate and analyze DNA from the cells of a 2,400 years old Egyptian mummy. The results of these ‘secret’ studies made it to the pages of Nature magazine on 18th April 1985. Everyone was then talking about his paper, the first paper published on DNA from fossil tissues.

Pääbo never looked back. He and his group perfected the art and science of isolating and analyzing DNA from fossils. They produced the first DNA sequence, although incomplete, with some gaps in the complete sequence of a Neanderthal in 2010 [1]. Subsequently, in 2014, he generated a complete DNA sequence of a Neanderthal woman discovered in a cave in the Altai mountains in Siberia [2]. A floodgate opened. DNA sequences of over 8,000
Neanderthals are now available. These data revealed, not unexpectedly, that there was considerable genomic diversity among the Neanderthals. Comparative analyses of DNA sequences of Neanderthals with those of modern humans helped identify positions in the DNA at which the nucleotide present in the modern human is derived from the Neanderthal. About 135,000 Neanderthal genetic variations were found in modern humans.

Statistical analysis of sequence data of modern humans, specifically in respect of the nucleotides derived from Neanderthals and shared and unshared with them, enabled Pääbo to conclude that interbreeding between the Neanderthals and humans took place. This immediately put to rest the theory that we had waged war against our Neanderthal cousins and exterminated them. A systematic comparison of sequence data of humans resident in different geographical regions of the world with those of the Neanderthals revealed that the Neanderthals contributed about 1–4% to the DNA of non-Africans. (For details of methodology on estimating fraction of DNA introgression, see [3].) Neanderthals evolved outside of Africa and likely did not enter Africa. Yet, a tiny fraction (less than 1%) of Neanderthal DNA has been found in some African populations. It is possible that ancient Europeans, whose ancestors had left Africa, met and mated with Neanderthals and then returned to Africa carrying some DNA derived from the Neanderthals and mixed with local populations.

The story of human evolution that emanated from the ancient DNA studies carried out by Svante Pääbo and his team will not be complete unless we narrate their work on another species of hominin—the Denisovan—who were also resident in Eurasia when the modern human came out of Africa. DNA analysis of small bones found in the Denisova cave in Siberia revealed that the individuals (Denisovans) from whom these bones came were a species different from the Neanderthal and the modern human. Comparisons of the DNA sequences of contemporary humans, Neanderthals, and the two Denisovans (whose sequences were published in 2010) showed that Neanderthals and Denisovans had also interbred and that Denisovans contributed 4–6% to non-African
DNA [4]. Later, Pääbo’s team also sequenced DNA extracted from another bone found in the Denisova cave and identified that bone to belong to a child of a Neanderthal father and a Denisovan mother [5]. Thus, not only the Neanderthals and Denisovans interbred with the modern humans, but the two archaic hominin species also mated and reproduced viable offspring.

What happened to the offspring produced by Neanderthal and modern human matings? The evidence derived from DNA sequence data indicates that the offspring became members of the modern human population and not the Neanderthal population. If the offspring became members of the Neanderthals, then after some generations, it would be expected that nucleotides in the DNA that were specific to modern humans would also be found in some Neanderthal DNA sequences. Such evidence has not yet been found. This inference also leads to the obvious explanation for the extinction of the Neanderthals. Their population size declined over generations, eventually leading to their extinction. Of course, it is possible that additional causes may have accelerated their extinction.

Thus, we—modern humans—moved out of Africa to other continents. And as we moved, we met other species of hominins. We embraced them and procreated. We absorbed the offspring into our own community.

The legacy of admixture between modern humans and Neanderthals has had a subtle but significant impact on modern human biology. Discovery of the impact was made possible by analyzing a database of Electronic Medical Records and Genomics (eMERGE) Network, created by a consortium of nine hospitals in the USA. Medical and genomic data of over 28,000 patients of European ancestry were jointly analyzed, with special attention to what genetic variants each patient carried. Ultimately, the researchers were able to link Neanderthal genetic variants with significantly increased risk of 12 traits [6], including heart attack and thickening of arteries. It is possible that some Neanderthal genetic variants may have been beneficial to modern human populations as they first moved out of Africa thousands of years ago. The same
variants may have later become detrimental in modern, Western environments. One example is a Neanderthal DNA variant that increases blood clotting. A bleeding wound is sealed by the clotting of blood that prevents germs from entering the body. The ‘clotting variant’ played a very beneficial role, especially because wounds must have been very common when Neanderthals and early modern humans were hunter-gatherers. After modern humans became settled agriculturists, wounds probably became less common, and also medicines were discovered to stop bleeding.

The same variant was no longer beneficial for survival from infections and became a ‘risk variant’ for stroke, which is also caused by clotting of internal haemorrhages. More recently, Zeberg and Pääbo [7] have identified that a genomic segment on human chromosome 3 is the major genetic risk factor for severe symptoms after being infected by SARS-CoV-2. This segment, they showed, is inherited from Neanderthals. It is carried by about 50% of people in south Asia and about 16% of people in Europe. These examples show that gene flow from Neanderthals to modern humans have had some tragic consequences for humans.

Suggested Reading


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