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New Machine Sheds Light on DNA of Neanderthals

By NICHOLAS WADE

The archaic human species that dominated Europe until 30,000 years ago is about to emerge from the shadows. With the help of a new DNA sequencing machine that operates with firefly light, the bones of the Neanderthals have begun to tell their story to geneticists.

One million units of Neanderthal DNA have already been analyzed, and a draft version of the entire genome, 3.2 billion units in length, should be ready in two years, said Dr. Svante Paabo, the leader of the research project at the Max-Planck Institute for Evolutionary Anthropology in Leipzig, Germany.

Biologists expect knowledge of the Neanderthal genome to reveal, by its differences with the human genome, many distinctive qualities of what it means to be human. Researchers also hope to resolve such questions as whether the Neanderthals spoke, their hair and skin color, and whether they interbred at all with the modern humans who first arrived on their doorstep 45,000 years ago, or were driven to extinction without leaving any genetic legacy.

Dr. Paabo has shared some of his precious source of Neanderthal DNA with Edward M. Rubin of the Joint Genome Institute in Walnut Creek, Calif., whose team has identified 62,250 units of Neanderthal DNA by a different method. The two teams report their results in the journals Nature and Science respectively, saying they have independent proof of the principle that recovery of the Neanderthal genome now seems possible.

“I think these results are monumental,” said Richard Klein, a paleoanthropologist at Stanford University. The full Neanderthal genome will resolve many longstanding issues about Neanderthals and their relationship to modern humans, including their physical and perhaps behavioral differences, he said.

The Neanderthals, who flourished for 400,000 years, physically resembled modern humans, but the middle of their face jutted forward and their large brain cases had a distinctive bulge or bun at the back. They were heavily muscled and presumably well adapted to the cold conditions of the last ice age. They would probably have been terrifying to the lighter-boned modern humans who first encountered them, except that their weapons were considerably less advanced. The Neanderthals still used a million-year-old stone tool kit that modern humans had abandoned.

Archaeologists have shown that as sites of the first modern humans, known as the Aurignacian culture, moved westward across Europe, those of the Neanderthals receded in parallel. By 30,000 years ago or even earlier, the Aurignacian conquest of Europe was complete, and the Neanderthals had disappeared from their last refuges in what are now Spain and Portugal.

Dr. Paabo began his quest for Neanderthal DNA more than a decade ago, and has had to overcome a daunting array of obstacles. Many extravagant claims were then being made about DNA in old bones, with some scientists

claiming to have recovered DNA from dinosaur bones that were millions of years old. But such bones were often contaminated by the DNA of the people who handled them, and Dr. Paabo saved the field from sliding into disrepute by demonstrating the extreme precautions necessary to avoid analyzing human DNA by mistake.

In 1997 he succeeded in analyzing part of the Neanderthal mitochondrial DNA, showing that it differed profoundly from modern human DNA. Mitochondria, the small organelles that provide the cell's energy, are separate from the main genome in the cell's nucleus. Since the nuclear DNA in old bones is degraded into millions of short fragments, 50 or so units in length, it seemed beyond hope of retrieval.

Enter a new kind of DNA sequencing machine, made by 454 Life Sciences of Branford, Conn. The machine prompts each DNA unit to generate a flash of light by stimulating luciferase, the enzyme found in fireflies. The flashes are captured by a charge-coupled device, the image-sensing plate used in telescopes to capture the light of distant stars. From the timing and position of the flashes, a computer reconstructs the sequence of the DNA units. As it happens, the kind of DNA the 454 machine works best with are tiny fragments the size of those found in old bones.

Dr. Paabo then scoured the museums of Europe for Neanderthal bones that might still retain DNA. Most of the 70 he tested had none, since DNA quickly degrades after the death of the organism. Many others were heavily contaminated with DNA from the curators and scientists who had handled them. Since human DNA is 99.9 percent identical to Neanderthal DNA, the contamination posed serious problems.

Just one bone, retrieved from the Vindija cave in Croatia, turned out to retain DNA and be fairly free of human contamination. Asked what made it so special, Dr. Paabo said that because it was small and uninteresting it had been "thrown in a big box of uninformative bones in the museum in Zagreb and wasn't handled very much."

The original owner of the Vindija bone was a male Neanderthal who died about 38,000 years ago. As with other ancient bones, most of the surviving DNA on this one belongs to the bacteria that consumed it when it was fresh. Less than 6 percent is Neanderthal DNA, and what there is of it has suffered a chemical degradation of the four DNA bases, referred to as A, T, G and C: some of the C's have converted to T's and some G's to A's. Dr. Paabo has developed methods for distinguishing the real Neanderthal DNA and addressing the chemical conversion problem.

Dr. Paabo hopes to find other Neanderthal bones with retrievable DNA. But even if no more turn up, he believes there is enough DNA in the Vindija bone alone to complete a draft of the full Neanderthal genome.

He and his team still have many more problems to overcome, but other researchers are impressed with the progress so far. "He's superbright and superthoughtful, and if anyone's ever going to do it, it's him," Dr. Klein said.

If the full Neanderthal genome is retrieved, biologists may be able to ask if the Neanderthals had language by looking at their version of the human gene known as FoxP2, thought to be one of the last components to evolve in mediating the modern human language faculty. FoxP2 has changed significantly since the human lineage split apart from that of chimps some six million years ago. If the Neanderthal version resembles the chimp version, that would make it less likely they had modern, syntactical language.

The Neanderthal genome should also enable biologists to calculate which aspects of human evolution took place

between 6 million and 500,000 years ago, and which are more recent. The latter is the approximate date at which the Neanderthal and human lineages split apart.

Dr. Paabo also believes the Neanderthal genome will help geneticists identify which human genes have been subject to the pressures of natural selection in the last 500,000 years. This would be of great interest in understanding which are the distinctive genetic attributes of modern humans.

From the data already obtained, Dr. Paabo and his colleagues estimate that the ancestral Neanderthal population was very small, perhaps less than 10,000 individuals. Since the ancestral population of modern humans was much the same size, it seems that all populations of early humans were tiny, expanding only after the ice age ended.