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Regenerating a Mammoth for $10 Million

By NICHOLAS WADE

Scientists are talking for the first time about the old idea of resurrecting extinct species as if this staple of science fiction is a realistic possibility, saying that a living mammoth could perhaps be regenerated for as little as $10 million.

The same technology could be applied to any other extinct species from which one can obtain hair, horn, hooves, fur or feathers, and which went extinct within the last 60,000 years, the effective age limit for DNA.

Though the stuffed animals in natural history museums are not likely to burst into life again, these old collections are full of items that may contain ancient DNA that can be decoded by the new generation of DNA sequencing machines.

If the genome of an extinct species can be reconstructed, biologists can work out the exact DNA differences with the genome of its nearest living relative. There are talks on how to modify the DNA in an elephant's egg so that after each round of changes it would progressively resemble the DNA in a mammoth egg. The final-stage egg could then be brought to term in an elephant mother, and mammoths might once again roam the Siberian steppes.

The same would be technically possible with Neanderthals, whose full genome is expected to be recovered shortly, but there would be several ethical issues in modifying modern human DNA to that of another human species.

A scientific team headed by Stephan C. Schuster and Webb Miller at Pennsylvania State University reports in Thursday's issue of Nature that it has recovered a large fraction of the mammoth genome from clumps of mammoth hair. Mammoths, ice-age relatives of the elephant, were hunted by the modern

humans who first learned to inhabit Siberia some 22,000 years ago. The mammoths fell extinct in both their Siberian and North American homelands toward the end of the last ice age, some 10,000 years ago.

Dr. Schuster and Dr. Miller said there was no technical obstacle to decoding the full mammoth genome, which they believe could be achieved for a further $2 million. They have already been able to calculate that the mammoth's genes differ at some 400,000 sites on its genome from that of the African elephant.

There is no present way to synthesize a genome-size chunk of mammoth DNA, let alone to develop it into a whole animal. But Dr. Schuster said a shortcut would be to modify the genome of an elephant's cell at the 400,000 or more sites necessary to make it resemble a mammoth's genome. The cell could be converted into an embryo and brought to term by an elephant, a project he estimated would cost some $10 million. "This is something that could work, though it will be tedious and expensive," he said.

There have been several Russian attempts to cultivate eggs from frozen mammoths that look so perfectly preserved in ice. But the perfection is deceiving since the DNA is always degraded and no viable cells remain. Even a genome-based approach would have been judged entirely impossible a few years ago and is far from reality even now.

Still, several technical barriers have fallen in surprising ways. One barrier was that ancient DNA is always shredded into tiny pieces, seemingly impossible to analyze. But a new generation of DNA decoding machines use tiny pieces as their starting point. Dr. Schuster's laboratory has two, known as 454 machines, each of which costs $500,000.

Another problem has been that ancient DNA in bone, the usual source, is heavily contaminated with bacterial DNA. Dr. Schuster has found that hair is a much purer source of the host's DNA, with the keratin serving to seal it in and largely exclude bacteria.

A third issue is that the DNA of living cells can be modified only very laboriously and usually at one site at a time. Dr. Schuster said he had been in discussion with George Church, a well-known genome technologist at Harvard Medical School,

about a new method Dr. Church has invented for modifying some 50,000 genomic sites at a time.

The method has not yet been published, and until other scientists can assess it they are likely to view genome engineering on such a scale as being implausible. Rudolph Jaenisch, a biologist at the Whitehead Institute in Cambridge, said the proposal to resurrect a mammoth was “a wishful-thinking experiment with no realistic chance for success.”

Dr. Church, however, said that there had recently been enormous technical improvements in decoding genomes and that he expected similar improvements in genome engineering. In his new method, some 50,000 corrective DNA sequences are injected into a cell at one time. In the laboratory, the cell would then be grown and tested and its descendants subjected to further rounds of DNA modification until judged close enough to that of the ancient species. In the case of resurrecting the mammoth, Dr. Church said, the process would begin by taking a skin cell from an elephant and converting it to the embryonic state with a method developed last year by Dr. Shinya Yamanaka for reprogramming cells.

Asked if the mammoth project might indeed happen, Dr. Church said that “there is some enthusiasm for it,” although making zoos better did not outrank fixing the energy crisis on his priority list.

Dr. Schuster believes that museums could prove gold mines of ancient DNA because any animal remains containing keratin, from hooves to feathers, could hold enough DNA for the full genome to be recovered by the new sequencing machines.

The full genome of the Neanderthal, an ancient human species probably driven to extinction by the first modern humans that entered Europe some 45,000 years ago, is expected to be recovered shortly. If the mammoth can be resurrected, the same would be technically possible for Neanderthals.

But the process of genetically engineering a human genome into the Neanderthal version would probably raise many objections, as would several other aspects of such a project. “Catholic teaching opposes all human cloning, and all production of human beings in the laboratory, so I do not see how any of this could be

ethically acceptable in humans," said Richard Doerflinger, an official with the United States Conference of Catholic Bishops.

Dr. Church said there might be an alternative approach that would "alarm a minimal number of people." The workaround would be to modify not a human genome but that of the chimpanzee, which is some 98 percent similar to that of people. The chimp's genome would be progressively modified until close enough to that of Neanderthals, and the embryo brought to term in a chimpanzee.

"The big issue would be whether enough people felt that a chimp-Neanderthal hybrid would be acceptable, and that would be broadly discussed before anyone started to work on it," Dr. Church said.