Grady, Denise, and Gina Kolata. "Gene Therapy Used to Treat Patients with Parkinson's." *New York Times* 2003.

Do I have a hard head?" asked Nathan Klein. "My wife always says I have a hard head."

"No, it's pretty average," said Dr. Michael G. Kaplitt. "This is one of the few situations in life where you want to be average."

Dr. Kaplitt had just bored a hole about the size of a quarter through the top of Mr. Klein's skull, in preparation for an ambitious experiment: the infusion deep into the brain of 3.5 billion viral particles, each bearing a copy of a human gene meant to help relieve the tremors, shuffling gait and other abnormal movements caused by Parkinson's disease.

Yesterday at New York-Presbyterian Hospital, Mr. Klein, 55, an independent television producer from Port Washington, N.Y., became the first person to undergo gene therapy for Parkinson's. Despite the checkered history of gene therapy experiments, the Food and Drug Administration approved this procedure for 12 people with severe Parkinson's.

The experiment is a Phase 1 trial, meaning that its main goal is to determine safety, not efficacy. But of course the researchers and their subjects will also be looking for signs that the treatment works. That should become clear within three months, said Dr. Kaplitt, who is an assistant professor at Weill Cornell Medical Center and director of stereotactic and functional neurosurgery at New York-Presbyterian Hospital. "My goal is not to try to cure Parkinson's disease," Dr. Kaplitt said. "It's to provide a better treatment that we can build on to make the next advance."

But some leading experts in gene therapy and Parkinson's disease expressed concern.

They said the experiment was going forward without evidence in monkeys that it could work and that it held the possibility of harm: viruses spreading in the brain, or gene-treated cells churning out huge quantities of proteins that inhibit brain cells from firing.

"This is a crazy experiment," said Dr. C. Walter Olanow, who is a professor and the chairman of the department of neurology at Mount Sinai School of Medicine.

In an interview before the operation, Mr. Klein said he had been fully informed of potential risks.

"I do hope that it does something, whether it will be 10 percent better, 25 percent, 50 percent or more, I hope that this will work," he said. "But I'm the first and I'm their monkey."

About 1.5 million Americans have Parkinson's disease. Tremors are its hallmark, familiar to anyone who has seen the shaking limbs of people with the disorder, like the actor Michael J. Fox or former Attorney General Janet Reno. But other symptoms can be just as troubling, if not more so: people become stiff and can suddenly freeze, unable to move, and many find that they can walk only by shuffling along in tiny steps, which sometimes accelerate beyond their control and send them sprawling. Some develop cognitive problems or dementia.

The disease occurs because nerve cells die in a part of the brain, the substantia nigra, leading to a shortage of dopamine, a chemical messenger that helps carry signals between various brain regions involved in movement.

Drugs can help to control the abnormal movements for a time. The best known, L-dopa, turns to dopamine in the body. But all drugs have side effects. Mr. Klein, for instance, who has had Parkinson's for 10 years and tried 8 or 10 drugs, has suffered from constipation, weight gain, insomnia, dry mouth and fatigue. Other patients develop new movement disorders from L-dopa. And over time, the drugs can lose their effectiveness.

Surgery to destroy bits of the brain that touch off tremors can help, but has its own risks. Fetal cell implants have not helped patients overall and have led to severe movement problems in some. Pacemaker-like devices known as deep brain stimulators have shown promise for some patients who have run out of drug options. But implants pose a risk of infection, and devices can fail.

Dr. Kaplitt and Dr. Michael During, a professor of molecular medicine at the University of Auckland, in New Zealand, with whom he has been collaborating for 10 years, saw plenty of room for improvement in treating Parkinson's.

They and their colleagues suspected that dopamine was not the best target for gene therapy, because patients would probably have been taking dopamine for years and might be resistant to it.

They decided that it made more sense to provide a gene that would enable cells in an overactive region of the brain, the subthalamic nucleus, to make a different messenger chemical, one that would calm the cells themselves and other overstimulated brain regions. The gene they chose is called GAD, for glutamic acid decarboxylase, an enzyme that helps produce a chemical messenger called GABA, for gamma aminobutyric acid.

Genes alone cannot get into cells, but viruses can, and in gene-therapy experiments viruses are commonly used to carry genes to their destination. Dr. Kaplitt and Dr. During chose the virus AAV, or adeno-associated virus. It does not cause disease in people, Dr. Kaplitt said, and its genetic material is removed.

In experiments in mice with a disorder that is intended to mimic Parkinson's, the gene therapy helped all the animals somewhat and helped about half of them a great deal, Dr. Kaplitt and Dr. During reported last October in the journal Science. They have also tested the treatment in monkeys but have declined to discuss the results, because they have not yet been published.

Dr. Kaplitt and Dr. During founded a company, Neurologix, to produce the gene therapy. The company, run by Dr. Kaplitt's father, is paying for the Phase 1 study. Dr. During is a paid consultant to the company. Dr. Kaplitt is not, though he was in the past. He and Dr. During do not recruit patients for gene therapy. Patients are referred by — and followed by — Dr. David Eidelberg and Dr. Andrew Feigin from North Shore-Long Island Jewish Hospital. Neither has any connection to Neurologix.

Many researchers have had qualms about gene therapy since 1999, when a teenage boy, Jesse Gelsinger, died in a gene therapy experiment at the University of Pennsylvania. More recently, several children in France who were successfully treated with gene therapy for an immune disorder later developed a leukemia-like disease.
In this case, some experts say a gene therapy experiment is particularly questionable because Parkinson's patients could have brain stimulators implanted instead.

"You don't have to take the risk of putting in a virus and you don't have to take the risk that it's uncontrollable," Dr. Olanow said. "The danger is that if you inhibit too much you can induce wild, flinging movements which people have been reported to die from." Once the virus is in the brain, there is no way to get it out or turn it off, he and others pointed out.

But Dr. Kaplitt said the study was being limited to patients who did not like the idea of having a device put in their brain.

Another potential danger is that the virus could spread to other areas of the brain, wreaking destruction, said Dr. Inder Verma, a gene therapy researcher at the Salk Institute, in San Diego, and past president of the American Society of Gene Therapy.

Animal studies indicate that the virus can spread from nerve to nerve, said Dr. Howard Federoff, the director of the Center for Aging and Developmental Biology at the University of Rochester School of Medicine and Dentistry. "That's one thing I felt personally needed to be carefully examined to make sure there weren't going to be any adverse effects," he said.

Even if the virus does not spread in the brain, it could elicit an immune reaction. "You may get a brain inflammation and swelling," Dr. Verma said. "You may lose some neurons."

But Dr. Kaplitt said there was no evidence of any adverse effects in the animal studies except a few transient fevers — no brain inflammation, and no signs of overproduction of brain chemicals.

Other experts not involved in the trial doubted that the gene therapy would do anything at all.

Dr. Ole Isacson, a professor of neuroscience at Harvard Medical School, said he was not convinced that changing just a single enzyme, with gene therapy, could fundamentally change a nerve cell's nature.

Yet, Dr. Isacson said he was ambivalent about the experiment. "I agree about the many questions," he said. But, he added, "one can say that unless you try bold things in clinical trials it will be very difficult to find what are the most useful paths in the clinical world."

Others, however, said flatly that the experiment was ill advised.

"As a careful and very rigorous person approaching clinical trials, I'd like to see a great deal more data in a nonhuman primate model that the treatment is efficacious and very safe," Dr. Federoff said. He worried that an experiment gone awry could set back gene therapy for years.

So do others.

"I have real theoretical concerns," said Dr. J. William Langston, director of the Parkinson's Institute in Sunnyvale, Calif. "This is really terra incognita, and I'm not sure we're ready to go there yet, particularly with this strategy."

Mr. Klein did not see it that way. As soon as his doctor told him about the study, he said, he wanted to participate. He found the side effects of the drugs intolerable, his Parkinson's was worsening and a deep brain stimulator did not appeal to him because he did not much like the idea of hardware being left in his brain. He called his doctor every few weeks to check on the project, and did not give up until he was in.

During the procedure yesterday, he was wide awake and in good spirits, joking with doctors and nurses despite having had a metal scaffolding screwed into his head and bolted to the operating table to keep him still and aid in the mapping of his brain. The procedure took about five hours, including an hour and a half to pump the genes into his brain. Soon after it was over, Mr. Klein was settled into a regular hospital room, eating fruit salad, asking for ice cream and getting ready to stroll the corridors.

And hoping for results in the months ahead.

"If it helps me out that's great," Mr. Klein said. "If it helps other people with Parkinson's that's even better."

Wade, Nicholas. "Why Humans and Their Fur Parted Ways." *New York Times*, August 19 2003.

One of the most distinctive evolutionary changes as humans parted company from their fellow apes was their loss of body hair. But why and when human body hair disappeared, together with the matter of when people first started to wear clothes, are questions that have long lain beyond the reach of archaeology and paleontology.

Ingenious solutions to both issues have now been proposed, independently, by two research groups analyzing changes in DNA. The result, if the dates are accurate, is something of an embarrassment. It implies we were naked for more than a million years before we started wearing clothes.

Dr. Alan R. Rogers, an evolutionary geneticist at the University of Utah, has figured out when humans lost their hair by an indirect method depending on the gene that determines skin color. Dr. Mark Stone- king of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, believes he has established when humans first wore clothes. His method too is indirect: it involves dating the evolution of the human body louse, which infests only clothes.

Meanwhile a third group of researchers, resurrecting a suggestion of Darwin, has come up with a novel explanation of why humans lost their body hair in the first place.

Mammals need body hair to keep warm, and lose it only for special evolutionary reasons. Whales and walruses shed their hair to improve speed in their new medium, the sea. Elephants and rhinoceroses have specially thick skins and are too bulky to lose much heat on cold nights. But why did humans, the only hairless primates, lose their body hair?

One theory holds that the hominid line went through a semi-aquatic phase — witness the slight webbing on our hands. A better suggestion is that loss of body hair helped our distant ancestors keep cool when they first ventured beyond the forest's shade and across the hot African savannah. But loss of hair is not an unmixed blessing in regulating body temperature because the naked skin absorbs more energy in the heat of the day and loses more in the cold of the night.

Dr. Mark Pagel of the University of Reading in England and Dr. Walter Bodmer of the John Radcliffe Hospital in Oxford have proposed a different solution to the mystery and their idea, if true, goes far toward explaining contemporary attitudes about hirsuteness. Humans lost their body hair, they say, to free themselves of external parasites that infest fur — blood-sucking lice, fleas and ticks and the diseases they spread.

Once hairlessness had evolved through natural selection, Dr. Pagel and Dr. Bodmer suggest, it then became subject to sexual selection, the development of features in one sex that appeal to the other. Among the newly furless humans, bare skin would have served, like the peacock's tail, as a signal of fitness. The pains women take to keep their bodies free of hair — joined now by some men — may be no mere fashion statement but the latest echo of an ancient instinct. Dr. Pagel's and Dr. Bodmer's article appeared in a recent issue of The Proceedings of the Royal Society.

Dr. Pagel said he had noticed recently that advertisements for women's clothing often included a model showing a large expanse of bare back. "We have thought of showing off skin as a secondary sexual characteristic but maybe it's simpler than that — just a billboard for healthy skin," he said.

The message — "No fleas, lice or ticks on me!" — is presumably concealed from the conscious mind of both sender and receiver.

There are several puzzles for the new theory to explain. One is why, if loss of body hair deprived parasites of a refuge, evolution allowed pubic hair to be retained. Dr. Pagel and Dr. Bodmer suggest that these humid regions, dense with sweat glands, serve as launching pads for pheromones, airborne hormones known to convey sexual signals in other mammals though not yet identified in humans.

Another conundrum is why women have less body hair than men. Though both sexes may prefer less hair in the other, the pressure of sexual selection in this case may be greater on women, whether because men have had greater powers of choice or an more intense interest in physical attributes. "Common use of depilatory agents testifies to the continuing attractions of hairlessness, especially in human females," the two researchers write.

Dr. David L. Reed, a louse expert at the University of Utah, said the idea that humans might have lost their body hair as a defense against parasites was a "fascinating concept." Body lice spread three diseases — typhus, relapsing fever and trench fever — and have killed millions of people in time of war, he said.

But others could take more convincing. "There are all kinds of notions as to the advantage of hair loss, but they are all just-so stories," said Dr. Ian Tattersall, a paleoanthropologist at the American Museum of Natural History in New York.

Causes aside, when did humans first lose their body hair? Dr. Rogers, of the University of Utah, saw a way to get a fix on the date after reading an article about a gene that helps determine skin color. The gene, called MC1R, specifies a protein that serves as a switch between the two kinds of pigment made by human cells. Eumelanin, which protects against the ultraviolet rays of the sun, is brown-black; pheomelanin, which is not protective, is a red-yellow color.

Three years ago Dr. Rosalind Harding of Oxford University and others made a worldwide study of the MC1R gene by extracting it from blood samples and analyzing the sequence of DNA units in the gene. They found that the protein made by the gene is invariant in African populations, but outside of Africa the gene, and its protein, tended to vary a lot.

Dr. Harding concluded that the gene was kept under tight constraint in Africa, presumably because any change in its protein increased vulnerability to the sun's ultraviolet light, and was fatal to its owner. But outside Africa, in northern Asia and Europe, the gene was free to accept mutations, the constant natural changes in DNA, and produced skin colors that were not dark.

Reading Dr. Harding's article recently as part of a different project, Dr. Rogers wondered why all Africans had acquired the same version of the gene. Chimpanzees, Dr. Harding had noted, have many different forms of the gene, as presumably did the common ancestor of chimps and people.

As soon as the ancestral human population in Africa started losing its fur, Dr. Rogers surmised, people would have needed dark skin as a protection against sunlight. Anyone who had a version of the MC1R gene that produced darker skin would have had a survival advantage, and in a few generations this version of the gene would have made a clean sweep through the population.

There may have been several clean sweeps, each one producing a more effective version of the MC1R gene. Dr. Rogers saw a way to put a date on at least the most recent sweep. Some of the

DNA units in a gene can be changed without changing the amino acid units in the protein the gene specifies. The MC1R genes Dr. Harding had analyzed in African populations had several of these silent mutations. Since the silent mutations accumulate in a random but steady fashion, they serve as a molecular clock, one that started ticking at the time of the last sweep of the MC1R gene through the ancestral human population.

From the number of silent mutations in African versions of the MC1R gene, Dr. Rogers and two colleagues, Dr. David Iltis and Dr. Stephen Wooding, calculate that the last sweep probably occurred 1.2 million years ago, when the human population consisted of a mere 14,000 breeding individuals. In other words, humans have been hairless at least since this time, and maybe for much longer. Their article is to appear in a future issue of Current Anthropology.

The estimated minimum date for human hairlessness seems to fall in reasonably well with the schedule of other major adaptations that turned an ordinary ape into the weirdest of all primates. Hominids first started occupying areas with few shade trees some 1.7 million years ago. This is also the time when long limbs and an external nose appeared. Both are assumed to be adaptations to help dissipate heat, said Dr. Richard Klein, an archaeologist at Stanford University. Loss of hair and dark skin could well have emerged at the same time, so Dr. Rogers' argument was "completely plausible," he said.

From 1.6 million years ago the world was in the grip of the Pleistocene ice age, which ended only 10,000 years ago. Even in Africa, nights could have been cold for fur-less primates. But Dr. Ropers noted that people lived without clothes until recently in chilly places like Tasmania and Tierra del Fuego.

Chimpanzees have pale skin and are born with pale faces that tan as they grow older. So the prototype hominid too probably had fair skin under dark hair, said Dr. Nina Jablonski, an expert on the evolution of skin color at the California Academy of Sciences. "It was only later that we lost our hair and at the same time evolved an evenly dark pigmentation," she said.

Remarkable as it may seem that genetic analysis can reach back and date an event deep in human history, there is a second approach to determining when people lost their body hair, or at least started to wear clothes. It has to do with lice. Humans have the distinction of being host to three different kinds: the head louse, the body louse and the pubic louse. The body louse, unlike all other kinds that infect mammals, clings to clothing, not hair. It presumably evolved from the head louse after humans lost their body hair and started wearing clothes.

Dr. Stoneking, together with Dr. Ralf Kittler and Dr. Manfred Kayser, report in today's issue of Current Biology that they compared the DNA of human head and body lice from around the world, as well as chimpanzee lice as a point of evolutionary comparison. From study of the DNA differences, they find that the human body louse indeed evolved from the louse, as expected, but that this event took place surprisingly recently, sometime between 42,000 and 72,000 years ago. Humans must have been wearing clothes at least since this time.

Modern humans left Africa about 50,000 years ago. Dr. Stoneking and his colleagues say the invention of clothing may have been a factor in the successful spread of humans around the world, especially in the cooler climates of the north.

Dr. Stoneking said in an interview that clothing could also have been part of the suite of sophisticated behaviors, such as advanced tools, trade and art, that appear in the archaeological record some 50,000 years ago, just before humans migrated from Africa.

The head louse would probably have colonized clothing quite soon after the niche became available — within thousands and tens of thousands of years, Dr. Stoneking said. So body lice were probably not in existence when humans and Neanderthals diverged some 250,000 or more years ago. This implies that the common ancestor of humans and Neanderthals did not wear clothes and therefore probably Neanderthals didn't either.

But Dr. Klein, the Stanford archeologist, said he thought Neanderthals and other archaic humans must have produced clothing of some kind in order to live in temperate latitudes like Europe and the Far East. Perhaps the body lice don't show that, he suggested, because early clothes were too loose fitting or made of the wrong material.

Dr. Stoneking said he got the idea for his louse project after one of his children came home with a note about a louse infestation in school. The note assured parents that lice could only live a few hours when away from the human body, implying to Dr. Stoneking that their evolution must closely mirror the spread of humans around the world.

The compilers of Genesis write that as soon as Adam and Eve realized they were naked, they sewed themselves aprons made of leaves from the fig tree, and that the Creator himself made them more durable skin coats before evicting them. But if Dr. Rogers and Dr. Stoneking are correct, humans were naked for a million years before they noticed their state of undress and called for the tailor.