

*The DNA Files: Unraveling the Mysteries of Genetics*

**Gene Therapy: Medicine for Your Genes  
Transcript**

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## **Gene Therapy: Medicine for Your Genes Transcript**

**JOHN HOCKENBERRY:** This is *The DNA Files*, I'm John Hockenberry. Imagine a permanent fix for sickle cell anemia or cystic fibrosis. Imagine curing cancer without radiation and without chemotherapy.

**DON HARDY::** I firmly believe that gene therapy, that I went through, is in its infancy. And it's just a matter of time before it's going to be curing many, many of our diseases.

**ARTHUR CAPLAN:** What do people think they're getting when they get gene therapy? Do they understand it? I will tell you, not very well. They really don't. I mean, there isn't any therapy, it's just gene experimentation right now.

**JOHN HOCKENBERRY:** It's a dream if we could swap the genes that make us ill for the genes that make us well, we would have both a medical miracle and a moral crisis. For the next hour *The DNA Files* will explore the promise and problems of Gene Therapy: Medicine For Your Genes.

But first:

**JOHN HOCKENBERRY:** Recombinant DNA was a battleground in the 1970s. Scientists in San Francisco faced demonstrations. Congress heard testimony on the dangers of man-made plagues. Cambridge, home of Harvard and MIT, outlawed recombinant DNA research. But by the end of the decade, a fragile peace prevailed. The Cambridge Moratorium was repealed. Scientists had fended off legislation with their own system of oversight and review. Into this uneasy calm strode an ambitious scientist with an ambitious plan to treat disease by altering the genes...as John Rieger reports.

**JOHN RIEGER:** He was the brilliant 46-year-old director of UCLA's hematology program, who had built his career on bold treatments for cancer and blood disease. Martin Klein believed that gene therapy was the logical, though radical, next step, and he was anxious to take that step.

**MARTIN KLEIN:** Remember, I had been in medicine a fairly long time at that point, and I had grown up in a tradition where an academic physician is a sort of highly responsible individual, where he makes decisions, and presumably his decisions are in the best interest of his patients. I've grown up in a tradition where one didn't stop and pause to go to a committee.

**JOHN RIEGER:** Klein had his sights on a fatal disease called thalassemia, a relative of sickle cell disease. Victims lack one of the genes for normal hemoglobin. Klein proposed an experiment to insert recombinant DNA with the missing gene into the blood-producing cells of the bone marrow. If it worked, it would be a breathtaking advance. But first, Klein needed UCLA's permission. Robert Cook-Deegan is director of the National Cancer Policy Board of the National Academy of Sciences. He says the experiments were so unlikely to work that it simply wasn't worth the risk.

**ROBERT COOK-DEEGAN:** There are always people who are pushing the envelope,

and we want people to push the envelope, and people were pushing those edges...believe me. There was a lot of really innovative hematology going on for the hemoglobin diseases at that time. Gene therapy was not one of the ones that was most likely to help the patients, however. So I actually just flat out reject the contention that this was in their clinical best interest.

**JOHN RIEGER:** Klein waited, chafing, for more than a year. Then, in the summer of 1980, he quietly went abroad. He arranged with hospitals in Israel and Italy to treat two patients. To avoid even more complicated oversight, Klein had promised UCLA that he would use only non-recombinant DNA, a promise he now repeated. But that would make the treatment less effective. So, at the crucial moment, Klein reached for the test tube with the recombinant genes.

**MARTIN KLEIN:** I was trying to cure desperate diseases. And really there was only one area in which I would say I was out of line and I really regretted my actions, and that was in the decision to use recombinant DNA. But in retrospect, scientifically, that was not an unsound decision, but it...it cost a great deal.

**JOHN RIEGER:** Klein's experiments produced a fire storm in the scientific community. By dodging review, he had endangered the hard-won independence of DNA research. He had lied to the foreign hospitals and lied to his patients, provoking ugly comparisons to the century's worst medical abuses. It cost Klein his career. But in the end, Klein's actions strengthened the very oversight mechanism that he had sought to avoid.

**ROBERT COOK-DEEGAN:** Number one, they signaled all the investigators in this field that you are in a fish bowl, so you better be damn sure that you are scrupulous in your attention to detail, not only about the experiment but about the process and the approval and making sure that it's ethical. And number two, it allowed very broad public debate about the first protocols, which would not probably have happened if there weren't such a light shining on the whole field.

**JOHN RIEGER:** Klein's patients were neither helped nor hurt by his treatment. It would be ten years before a human gene therapy experiment earned formal approval. But Martin Klein still doesn't think that his experiments were premature.

**MARTIN KLEIN:** I think I was forced to pay too high a price in the sense that I really could no longer work in that field. I really think that if I could have pursued my studies, we would have cured thalassemia and sickle cell disease by now. And I think the field has gone so slowly that that's probably many years off.

**JOHN RIEGER:** For *The DNA Files*, I'm John Rieger.

**JOHN HOCKENBERRY:** This is *The DNA Files*, I'm John Hockenberry. When you were in high school, do you remember that film they showed in biology class about the miracles of modern medicine?

Merck Pharmaceutical Tape: Throughout the world the life expectancy of the average citizen has improved dramatically, due in part to new health care strategies and the drugs

and vaccines developed by global research over the last half century. It is a profound accomplishment.

**JOHN HOCKENBERRY:** If you went to school in the 50s, chances are the profound accomplishment they were talking about was the polio vaccine. In the 70s it might have been organ transplant operations. The point is, medical breakthroughs have occurred with stunning regularity during the 20th century. Even more dramatic changes are ahead. That's because we are now at the beginning of a new era ... the era of genetic medicine.

Hardly a week goes by without some scientist somewhere announcing that he or she has discovered a gene that may affect human health.

*[Sounds of News Reports]*

No one knows where these discoveries will eventually lead. But scientists do agree on one thing – the only way to cure disease is to attack it at its roots. And you can't find roots any deeper than our genes. This program is about a new and highly experimental form of medicine that aims to eradicate disease by putting new genes into our cells. It's called gene therapy. Since 1980 about three thousand people have been treated with gene therapy for a variety of diseases – cystic fibrosis, heart disease and cancer, to name a few. No one has been cured. Even so, many believe that gene therapy is the medicine of the future.

Correspondent John Rudolph recently visited the Institute for Human Gene Therapy at the University of Pennsylvania. It's one of the many places where scientists, doctors and patients are working to make the promise of gene therapy a reality.

**JOHN RUDOLPH:** These days Don Hardy spends a lot of time in the hospital. But even dressed in a hospital gown he looks fit and healthy. You would never suspect that this 66-year-old man suffers from a disease that is always fatal. In 1995 Hardy learned he had mesothelioma – a rare form of lung cancer caused by inhaling tiny asbestos fibers. For 35 years Hardy worked in construction, installing asbestos insulation in power plants and factories. It was a dusty job – Hardy protected himself by wearing cotton masks fashioned out of baby diapers.

**DON HARDY:** Well...I thought at least I was one of the few that tried to take some precautions to prevent breathing in the fibers and or dust. And whatever means I took were... naturally did not work.

**JOHN RUDOLPH:** Over the years Hardy saw many of his co-workers die from mesothelioma. He was crushed when doctors told him he too had the disease.

**DON HARDY:** Anyway ... I was concerned, devastated, couldn't believe it was happening to me.

**JOHN RUDOLPH:** Most people with mesothelioma live only another year or two after being diagnosed. The lungs fill with fluid and are slowly wrapped in a cancerous membrane that grows like a thin sheet. Breathing becomes harder and increasingly painful. Eventually the lungs can no longer function, and the person dies. In many ways Don Hardy and his wife Joan live an enviable life. Their home near the Jersey shore is in a

retirement community of well-kept houses with tidy lawns. Each winter the Hardys migrate to Florida, where Don can keep up his golf game during the colder months. Come springtime it's back to New Jersey to be near children and grand-children. Despite these comforts Joan Hardy says she and Don are constantly reminded of mesothelioma's grim toll. Three thousand new cases are recorded each year. All incurable.

**JOAN HARDY:** We had a couple we were very friendly with from Atlantic City, and he was diagnosed and died within about a year; and almost a year to the day, his wife died from the same disease, from washing his clothes.

**DON HARDY:** Most of the fellows used to take their clothes home for laundering, and the first thing the women would do is shake them out, and all this asbestos dust was around the washing machines or wherever they did it, even if they did it in a laundromat [sic] out, so they were breathing the asbestos in at that time. And that's how a lot of the wives and/or children of the asbestos workers contacted [sic] the disease.

**JOHN RUDOLPH:** So, Joan, you're . . . you're monitoring, your health is also monitored?

**JOAN HARDY:** Oh, yes. Definitely.

**DR. DANIEL STERMAN and NURSE:** I just CT scanned him. He has this huge mass in the diaphragm, which I'll show you. So I'm not sure he's going to be a good surgical candidate.

**JOHN RUDOLPH:** It's a typical Friday morning at the hospital of the University of Pennsylvania. About 15 doctors and nurses gather in a conference room to discuss patients admitted with lung diseases.

**DR. DANIEL STERMAN and NURSE:** I mean age is certainly an issue, but I'm not sure his disease is beyond that point.

**JOHN RUDOLPH:** Don Hardy's case was presented to this group in 1995. His mesothelioma was discovered at an early stage. But he still faced the fact that there is no cure for this disease. None of the traditional cancer therapies works – including chemotherapy, radiation therapy and surgery. Knowing this, Hardy was reluctant to go through a typical mesothelioma treatment, including an operation to remove his lung. Standing in a hospital corridor waiting for an x-ray, Hardy remembers the difficult choices he was given.

**DON HARDY:** The radiation I knew would not do anything but destroy my lung, so that to me was not even an option. The interferon was marginal and that was only being done over, supposedly, in France. I didn't consider that one. The only one that I was aware of, you know, was the surgery ones. If I go for the big radical, where they take the lung out, the best I could ever expect is fifty percent of what I was. So I thought, let me search and search for other alternatives.

**JOHN RUDOLPH:** Hardy wanted something different – and he found it: a revolutionary treatment that researchers at the University of Pennsylvania had developed

using laboratory animals. Now they wanted to try it on humans. On November 17, 1995 Don Hardy became the first person to undergo gene therapy for mesothelioma.

**JOHN HOCKENBERRY:** We'll hear more of Don Hardy's story in just a moment. But if you're like me, you probably have some questions about gene therapy right now. Like, how exactly does it work? For some answers, we turn to Doctor Gary Nabel. He does gene therapy research at the Howard Hughes Medical Institute at the University of Michigan Medical Center in Ann Arbor. Gary, thanks for joining us.

**GARY NABEL:** Hi, John.

**JOHN HOCKENBERRY:** Now, what I'd like you to do is to take us inside the cells in our own bodies, and explain what it is that gene therapy tries to accomplish.

**GARY NABEL:** Gene therapy tries to get at the fundamental root of diseases. That is, it tries to alter the abnormalities that we have in our genes that cause disease. In the case of Mr. Hardy and most patients who have cancer, we know that the cancer arises from a series of alterations in our DNA. And what we hope to do, by using genes as drugs, is to program the cell, and to program the body, to correct the faulty genetic information.

**JOHN HOCKENBERRY:** Now, when people talk about genetic disease, I always think of illnesses that parents pass on to their children: cystic fibrosis, for instance, that's a hereditary, genetic disease – but as we have heard gene therapy now is being used to treat cancer. So, is there more than one kind of genetic disease?

**GARY NABEL:** That's absolutely correct, John. The initial thoughts, when gene therapy began to be tested, both in the laboratory and initially in patients, was that it would be for genetic diseases, diseases like cystic fibrosis, sickle cell anemia, other inherited diseases. But research in the last few years, particularly in cancer as well as infectious disease, has taught us that our genetic makeup is not stable. It changes, throughout life. And so as a consequence of exposure to drugs, to chemicals, to sunlight, to irradiation, we damage our DNA, and that DNA then is altered during our lifetime. It's not something that we acquire from our parents. And because of that, many diseases that we before thought would not be approached by gene therapy are now considered to be targets.

**JOHN HOCKENBERRY:** Gary, thank you for that explanation. We'll talk to you a little later in the program. Now let's get back to Correspondent John Rudolph, and more of Don Hardy's story.

**NURSE:** Alright Mr. Hardy, you need blood drawn? I think so, yeah. Are you going to give it to me?

**JOHN RUDOLPH:** To many people the idea of gene therapy is frightening. After all, what would happen if the new gene acted in unpredictable ways, and actually made people sicker? But for Don Hardy, gene therapy wasn't scary, it was a chance at survival.

**DON HARDY:** To me this was exciting. No-one that I have talked to over the years, or any of my friends that had gone to any other doctors had expressed any, you know, hope that there is something out there that could be done for mesothelioma, and I felt that it

would work and that it was for me.

**DR. DANIEL STERMAN:** We had no idea whether he'd have an acute reaction where his blood pressure would drop or his heart would stop, or he'd develop severe pain or fever to 105...we had no idea.

**JOHN RUDOLPH:** Dan Sterman is Don Hardy's doctor. He's one of seven physicians who crowded into Hardy's hospital room to deliver that first dose of gene therapy for mesothelioma. Everyone was on high alert. Putting foreign genes into a human body was so new, the staff wasn't sure what would happen.

**DR. DANIEL STERMAN:** Dr. Kaiser, who's the head surgeon of the program came in and, very, you know, authoritatively and dramatically, helped me put the virus into Don's chest cavity, and except for some of it leaking around from the chest tube, nothing happened. It was all of us waiting around for this big explosion to occur, and nothing....

**JOHN RUDOLPH:** What happened at the hospital was this: a plastic tube was surgically placed in Hardy's chest. Then a saline solution was poured into the space between his lungs and the thin sheet-like tumor surrounding them. Hardy was turned from side to side so the solution would slosh over as much of the tumor as possible. Then they waited.

**DR. DANIEL STERMAN:** I remember sitting with Don in his room, you know, for hours that morning staring at him, and finally I just said, you know, you're fine, I'm leaving, you know.

**JOHN RUDOLPH:** The saline solution contained a virus, plus a gene taken from a second virus. Viruses are used for gene therapy, says Dr. Daniel Sterman, because they are very good at getting inside cells.

**DR. DANIEL STERMAN:** You can't just put the gene on top of the cell and hope it gets in in enough quantities to have any effect. You can try that. It doesn't work very well. So you need something to deliver the gene into the cell, and what things are really good at getting into human cells? Well, viruses are really good because they infect all of us. And what we've done is to develop a virus, which is a crippled virus, meaning it can deliver its cargo but it can't reproduce itself to cause illness in a human being.

**JOHN RUDOLPH:** In Don Hardy's case the delivery vehicle came from a virus that causes the common cold. Doctors hoped it would attach itself to the cancer cells and insert a gene taken from another common virus – in this case the virus that causes cold sores. The cancer cells would then be genetically changed. Three days later Hardy began receiving a drug aimed at killing the altered cancer cells.

**DR. DANIEL STERMAN:** In essence what we are doing is infecting cancers with viruses, so to speak, and then treating them with the medicines that we use to treat viral infections. In other words, if we can't treat a cancer with cancer therapy, let's trick it into thinking it's a virally infected thing, and treat it with viral therapy.

**JOHN RUDOLPH:** For the next 21 days Hardy was given the anti-viral drug. The

doctors tested him to see how much of the virus gene had gotten into his cancer cells. At the end of the treatment Hardy left the hospital even though the doctors didn't have any evidence that Hardy had been cured. The only thing Dr. Sterman could say for sure was that the gene therapy hadn't made Hardy any sicker.

**DR. DANIEL STERMAN:** What we've seen is that it seems to be a very safe therapy. There are very few side effects. And the goal of any experimental trial, first and foremost when you're trying out something new, is to prove that it's safe.

**JOHN RUDOLPH:** Since Hardy showed no negative side effects, Dr. Sterman and his colleagues have gone on to give gene therapy to more than two dozen men and women with mesothelioma. Dr. Sterman sees a steady stream of patients who are dissatisfied with traditional cancer treatments, and are willing to gamble on more promising, but as yet unproven alternatives. He tells them all the same thing.

**DR. DANIEL STERMAN:** As terms of hope is concerned, I think that it would be – and I'll be honest about this – unreasonable to expect any of these experimental therapies to cure you, although it's not impossible that they won't. I think the reality is that we don't know what effect these are going to have upon you, but you are lucky because five years ago there would have been no other options.

**JOHN RUDOLPH:** Don Hardy has heard Dr. Sterman deliver this speech many times.

**DON HARDY:** And the doctors, you know, I can understand they have to be cautious, they can't say, okay, it did or didn't help, they're just going to compile their data and let the statistics talk for themselves. You know, we did have quite a few of the guys that – I say guys, men and women – that participated in the study that did pass away. But I think it...it does work, and the fact that it does help, and it does offer anybody that's, you know, stricken with the disease, the fact that they're going to gain some time, and that time is important, because nobody knows when the next thing coming down the road may be the quote, unquote, the "miracle cure". And that's the way I feel about gene therapy.

**JOHN RUDOLPH:** But has gene therapy kept Don Hardy alive? Or does he keep hanging on because of the hope that gene therapy gives him? No one really knows. The only sure thing is that Hardy has defied the odds. And because of this he's become a symbol of hope for other cancer patients, and for doctors and scientists working to turn genes into effective medicine.

**JOHN HOCKENBERRY:** People like Don Hardy are among gene therapy's strongest advocates. They have seen this new technology up close, and they believe in its future. The rest of us can only judge gene therapy from what we read or hear in the news media, or see in the movies. Often the message that comes through is that genetic medicine is dangerous and frightening.

**JOHN HOCKENBERRY:** Genetic experiments, including gene therapy, have always tapped into our anxieties. We worry about safety. We feel uncomfortable about deliberately manipulating human genes, even to cure disease.

*[Various quotes, soundbites, old tapes]*

**JOHN HOCKENBERRY:** Genetic experiments including gene therapy have always tapped into our anxieties. We worry about safety, we feel uncomfortable about deliberately manipulating human genes even to cure disease. To allay these fears gene therapy experiments are closely monitored by government regulators. Many universities and private companies also strive to be extra careful with their gene therapy research. The University of Pennsylvania, where Don Hardy was treated, actually maintains a staff of bioethicists. Their job is to keep tabs on genetic experiments going on at the school. Arthur Caplan heads the university's Center for Bioethics.

**ARTHUR CAPLAN:** Arguments about gene therapy really began quite early. They began back in the 1970s, and they were in the form of concerns about bioengineering. Interestingly, they were not about gene therapy for people; they were about gene therapy for microorganisms.

**JOHN HOCKENBERRY:** In those early days Caplan says people were concerned about what would happen if we tried to genetically engineer different bacteria.

**ARTHUR CAPLAN:** The mayor of Cambridge, Massachusetts, at one point said he was worried if there were scientific institutions in his town that were doing this, he didn't want to see sort of Frankenstein-type microbes coming out of the sewers.

**JOHN HOCKENBERRY:** Today those early concerns seem almost quaint. Now even high school biology classes like this one in Maine do the same gene combining experiments that once struck fear into the hearts of public officials and private citizens.

**BRAD FLETCHER:** Today we're gonna do...probably the simplest of all genetic engineering processes, and really it's, I guess you might say the most basic step in genetic engineering, but was a major milestone back in the 70s when they began doing this procedure. It is supposed to be safe [class laughs], but just as a cautionary remark make sure you don't eat any of this stuff. You know, don't stick this on anything.

**JOHN HOCKENBERRY:** In the 1980s when the first proposals for human gene therapy were presented to government regulators, a whole new crop of safety questions appeared – would the therapeutic genes spin out of control? Would a virus carried into the human body cause the death of a person, even though it was just meant to transport some new genetic information?

**JOHN HOCKENBERRY:** Concerns over safety remain. Each time scientists increase the dose of disabled viruses to new, unprecedented levels the anxiety level also goes up. Meanwhile popular ideas about gene therapy have shifted. There is a growing belief that it is a miracle cure. And that, says Caplan, poses a new set of ethical problems

**ARTHUR CAPLAN:** We've been interested in what do people think they're getting when they get gene therapy? Do they understand it? I will tell you, not very well. Our studies show that they believe they are getting the best available cure, not the sort of first stage, experimental interventions. I mean, there isn't any therapy, it's just gene experimentation right now.

**JOHN HOCKENBERRY:** Caplan says there are plenty of examples of doctors and researchers exaggerating the benefits of gene therapy. It's a criticism shared by many.

**DR. TED FRIEDMAN:** Gene therapy's gone through a little awkward phase, sort of a teenage phase, recently.

**JOHN HOCKENBERRY:** Dr. Ted Friedman is one of gene therapy's pioneers. It was Friedman who coined the phrase gene therapy back in 1972. Not long after, Friedman says, people began making exaggerated claims about this new type of medicine.

**DR. TED FRIEDMAN:** The zeal and the enthusiasm of some of the investigators – and I'm among them – the zeal and enthusiasm and, to some extent, vulnerability of the media, the need for visibility and the misunderstanding of the technology, has led to massively overstated expectations.

**JOHN HOCKENBERRY:** In 1995 the National Institutes of Health issued a report sharply critical of scientists and organizations that fund gene therapy research. Overselling the results of laboratory and clinical studies, the report said, had created the mistaken and widespread perception that gene therapy is further developed and more successful than it actually is. Since that report researchers have generally become more careful when they talk about gene therapy. But this new medicine still has plenty of supporters.

If you were to visit the Institute for Human Gene Therapy at the University of Pennsylvania, you would enter a stately turn-of-the-century building. The institute's director, Dr. James Wilson, is one of gene therapy's biggest boosters.

**DR. JAMES WILSON:** The goal of gene therapy is to correct the genetic defect, and if done properly, this fix will be permanent. What this would mean would be a one-time treatment to fix the defect, to therefore prevent any manifestation of the disease. This begins to resemble what in medicine we aspire to, which is curing an illness, not treating the illness.

**JOHN HOCKENBERRY:** Dr. Wilson's dreams for gene therapy are huge. In an effort to realize them the University of Pennsylvania spends more than 20 million dollars a year on laboratories, special hospital wards – even manufacturing facilities specifically built to make experimental gene therapy drugs.

A lot of the research is conducted on animals in an ultra clean laboratory.

**JAY JACOBI:** You're inside the John Morgan III Animal Facility, where only rodents, which we carry mice and rats...

**JOHN HOCKENBERRY:** You enter the University's animal lab through a wide, dimly-lit corridor. Inside each of the dozen-or-so rooms along the corridor are stacks of small clear plastic cages. Inside each cage is a specially bred rodent. Anyone who enters this lab has to wear protective clothing. This is not, as you might have thought, to prevent some runaway gene from accidentally infecting a research scientist. It's actually to protect the rodents. If they are contaminated it could ruin the experiments they are being used for. Jay Jacobi manages the animal facility.

**JAY JACOBI:** There are investigators that choose to take their mice to their lab, which would be outside of the facility, so we sterilize little individual Chinese-food takeout containers, and it becomes a mouse take-out container and it's a sterile environment.

**JOHN HOCKENBERRY:** These stringent safety precautions are found at most labs involved in gene therapy research. The stakes are high. Gene therapy could potentially solve many of medicines most vexing problems.

In the U.S. alone it's estimated that some 400-million dollars is spent on gene therapy research each year. A remarkable investment, considering that gene therapy has yet to cure a single patient. But, as Dr. Ted Friedman argues, the very concept of gene therapy has already revolutionized the practice of medicine.

**DR. TED FRIEDMAN:** The other sort of revolutions in medicine: antibiotics and surgery and the germ theory, and those kinds of things. The things that have really sent medicine in totally new directions, they came to be accepted and integral parts of medical thinking, more slowly and after demonstrations of efficacy. Gene therapy has had this peculiar upside-down history, where... where it's become so integral and so powerful a part of medical thinking at a time when it still hadn't shown itself in any clinical setting, to work.

**JOHN HOCKENBERRY:** But not everyone shares the view that gene therapy has changed the course of medical history.

**MERCK PHARMACEUTICAL TAPE:** Staffed by over 4,000 scientists and physicians, Merck's Global Network of Research Laboratories conducts what is one of the most costly and time-consuming pharmaceutical R&D processes in the world.

**JOHN HOCKENBERRY:** Like many large drug makers, Merck and Company does some gene therapy research. But Merck's bread and butter is developing and selling traditional drugs. These are medicines that affect chemicals inside the body. They don't attempt to alter the genes. Alan Oliff oversees cancer research at Merck. He admits gene therapy offers the most logical way to attack disease. But Oliff argues the practical problems of making gene therapy work are huge. So, he reasons, it's better to stick with proven remedies.

**ALAN OLIFFP:** If we can get to the ultimate scenario of having a single therapy that is curative, as opposed to something controlling a disease, that would be wonderful, but we haven't done so bad with controlling some of the chronic disorders that people have. Many people with diabetes do quite well taking insulin. I'm not ready to discard that approach yet in favor of the Star Wars approach for molecular genetics.

**JOHN HOCKENBERRY:** Oliff also notes that the side effects of gene therapy are still largely unknown. No one can say for sure that disabled viruses won't act in unpredictable and possibly dangerous ways once they are introduced into a person's body. Dr. James Wilson at the University of Pennsylvania admits these problems need to be solved for gene therapy to enter the medical mainstream.

**DR. JAMES WILSON:** The gene delivery vehicles we're currently using are based on

attenuated or disabled forms of just common viruses. Viruses are very powerful in delivering genes. What we do is we eliminate the disease-causing genes, and in place of those, we insert our therapeutic gene. An important question, though, is have we sufficiently disabled this vector or virus so that it won't cause any problems or side effects in patients? It's the power of the virus that brought us here, but it's also in that power we need to control it.

**JOHN HOCKENBERRY:** Now, I find this idea of using viruses to cure disease a little disturbing. So let's bring in Doctor Gary Nabel of the University of Michigan again to see if he can make sense of it for us. Gary, I thought viruses really make you sick. How can they be made to cure you instead?

**GARY NABEL:** John, you're absolutely right. Viruses, for the most part, do make you sick by reproducing themselves in the body and infecting cells and disturbing their function. In this case, what we do is to remove essential parts of the virus so that they can deliver the genetic information, deliver the package of DNA, but yet, once that delivery occurs, essentially the virus self-destructs.

**JOHN HOCKENBERRY:** So we strip down all the characteristics except this ability to infiltrate other cells, and that's what we use. So my question then is, what's the risk that one of these stripped-down viruses, used for gene therapy, will revert back to its old ways once it's injected into a person's body, and end up infecting that person with some disease?

**GARY NABEL:** Well, the risk is there, but generally speaking, it's felt to be quite low. The reason for this is that there are very strict guidelines in terms of production of virus [sic] that have to be met, and various tests that need to be performed on these altered viral vectors before they're delivered to patients. In many ways, what we're doing with viruses is taming them, in much the same way that one would take a wild horse and train it to be ridden and to deliver packages. We're doing the same with viruses. That's not to say that under no circumstances the horse might not become wild, but if it's well-trained, and you have a lot of experience in understanding the horse, then perhaps the safety margin will be increased.

**JOHN HOCKENBERRY:** Now, you used a technical term there, viral vector. Is that the name you use for one of these viruses that is tamed sufficiently to be very, very predictable when injected into someone?

**GARY NABEL:** Yes, that's correct. A vector is a modified version of the virus. Now, the logical extension of the work that we're doing with viral vectors, though, is to begin to modify them in such a way that they become completely synthetic. And in fact there's substantial work going on in the gene therapy field which is moving away entirely from viruses, and creating new classes of vectors that we call synthetic vectors. Perhaps the best analogy here would be to compare a horse to a car. Clearly, the horse may not be completely predictable and may have a mind of its own, but as we become more sophisticated in the technology and can build synthetic vectors, we can build the equivalent of a car that is much more readily controlled, and certainly can be contained when it is introduced back into the population.

**JOHN HOCKENBERRY:** Gary Nabel, thanks again. We'll continue our conversation

just a little later.

**JOHN HOCKENBERRY:** This is *The DNA Files*. I'm John Hockenberry.

[*Music break*]

Until a few years ago the only people who really thought about treating and curing disease on the genetic level were a handful of scientists working in their laboratories. Now the idea is starting to catch on in the wider world. Patients who believe they have been helped by gene therapy are telling their stories in public. One of the most vocal patient advocates is Don Hardy, who we heard earlier in the program. Again, here's correspondent John Rudolph with more of Don Hardy's story.

**JOHN RUDOLPH:** When the Asbestos Workers Union held its annual convention in Las Vegas, Don Hardy got a hero's welcome.

**ASBESTOS WORKERS UNION SPEAKER:** Here's a guy that's gonna beat it. His name is Don Hardy, and three years ago in September of 1994 he was given some devastating news. Brother Hardy was diagnosed as having mesothelioma. Ordinarily this would have been a death sentence. Now I want Don to come up to the microphone, to say hello. Let's welcome him again, Don Hardy.

**JOHN RUDOLPH:** Hardy, dressed in a jacket and tie, his white hair carefully combed back, spoke to the union membership about his fight against mesothelioma. He told them that gene therapy could, one day, be the cure they have been waiting for.

**DON HARDY:** I firmly believe that gene therapy...that I went through...is in its infancy. And it's just a matter of time before this will be curing many, many of our diseases.

**JOHN RUDOLPH:** The speech to union members is just one part of Hardy's personal crusade to offer hope to people at high risk for mesothelioma. Back home in New Jersey, he says, many of his former co-workers refuse to get tested for the disease because they believe fighting it is a lost cause.

**DON HARDY:** I have a very close friend that was diagnosed and he absolutely refused to get any help, but eight or nine months after he told me, he was gone. There are many of them that I worked with that feel the same way. "Don't tell me. There's nothing you can do. Just let it run its course." You know, a lot of those same people sort of pat me on the back and say, "Oh, you're a courageous guy for doing this," but I'm a selfish guy, too. I want to survive. Someone has to be first. I don't have to be the first as long as I'm in there, as long as I'm in there with the ones that are surviving. But if I have to be first, I'm a risk-taker. I'll do it.

**JOHN RUDOLPH:** Hardy's words are inspiring. But they also might convey the wrong impression of gene therapy. Hardy's doctor Dan Sterman says Hardy has done a great service by offering hope to people suffering from mesothelioma. But Sterman worries that patients who are treated with gene therapy have unrealistically high expectations.

**DR. DANIEL STERMAN:** They've had minimal toxicity, they feel well, they go back to their normal life, and people ask what they've been through, and they tell them they've been through a gene therapy trial. And it may be another six months, to a year, to a year and a half before they have progression and eventually die. So during that time they may be telling others what a wonderful thing it is they have been through, even though we have no documentation that they've had a dramatic response.

**JOHN RUDOLPH:** Sterman worries that too much enthusiasm may compromise gene therapy's future. If this new medicine doesn't live up to people's expectations, the public may conclude that it's never going to work. Sterman is concerned that this could happen before researchers have a chance to prove gene therapy's medical value.

And that's not his only worry. Sterman says some people continue to be uneasy about the whole idea of gene therapy.

**DR. DANIEL STERMAN:** There is a segment of the population that doesn't want scientists, physicians, to manipulate human genes even for potential good.

**JOHN RUDOLPH:** In response to the opposition Sterman and others emphasize that gene therapy experiments need to be conducted as safely and carefully as possible. But these precautions are not likely to satisfy many of gene therapy's harshest critics. And the critics are growing louder as a whole new type of gene therapy begins to emerge.

**JOHN HOCKENBERRY:** The new technique that John Rudolph alluded to is called germ-line gene therapy. It could bring even bigger changes to the practice of medicine, and with those changes more difficult ethical questions. To get an idea of what may be coming, you need to visit, of all places, an animal hospital. A menagerie of pets, and their owners, fills the waiting room at the University of Pennsylvania's veterinary hospital. Along with the usual collection of dogs, cats and hamsters, there's a snake and a lizard waiting to be treated.

**JOHN HOCKENBERRY:** Most people who bring their pets here are unaware that this is also the site of some of the world's most advanced genetic research.

Scientists at this hospital have succeeded in making genetic changes to egg and sperm cells, and the cells that produce sperm. This kind of germ cell manipulation has mostly been done in mice and other laboratory animals. But researchers at the University of Pennsylvania's Veterinary School hope that one day the technique will be used in farm animals – making them stronger, healthier and more productive.

And what about doing the same thing for people? Could humans also be made stronger, healthier and more productive through germ cell manipulation? Absolutely, says Dr. Alan Kotlikoff, the head of the school's Department of Animal Biology.

**DR. ALAN KOTLIKOFF:** Imagine, for example if you did not have cystic fibrosis but you were a carrier of the mutant gene. And you knew that your descendants were all at risk of being born with cystic fibrosis...a fatal and debilitating disease. If your descendants could be freed of that risk, of that Damoclean sword, by selectively modifying the stem

cells that make sperm, and you could go on and live a normal reproductive life, that would be, I think, an extremely attractive proposition to many people, one that many people would desire.

**JOHN HOCKENBERRY:** Maybe, but germ line gene therapy is also very controversial – some say it should not even be associated with the kind of gene therapy that Don Hardy received. While both techniques involve adding new genes to cure disease, the potential effects are very different.

To get a sense of just how different let's again bring in Dr. Gary Nabel. Gary what is germ-line gene therapy?

**GARY NABEL:** Well, John, germ-line gene therapy really attempts to correct a disease – primarily an inherited genetic disease – at its most fundamental level, that is, in the cells that we use to reproduce and give rise from one individual to another. These are the germ cells – the eggs and sperm, or a fertilized egg. Any one of those cells would presumably allow us to correct defects, not only in all cells of the body, but then they would be passed along to the next generation.

I think it's important to stress that although there have been remarkable strides in research in the laboratory, at all levels we still do not have the technical capability to do this kind of genetic correction, or germ-line therapy, at the present time in humans.

**JOHN HOCKENBERRY:** So let's bring this back to the case of Don Hardy, who we've been following, in his cancer treatment in the course of this program.

**GARY NABEL:** Well, in the case of Don Hardy, it's quite possible that we would have no obvious germ-line gene therapy for him. Remember, in his case the disease arose as a consequence of an environmental insult, his exposure to asbestos, and changes in his DNA that occurred as an adult.

It's more likely, though, that we would use this technology to treat diseases where there was a hundred-percent certainty that the disease would occur, and that the consequences would be devastating. Cystic fibrosis, I think, is a very good example where symptoms of the disease are actually shown in a very high percentage of people who have the genetic defect.

**JOHN HOCKENBERRY:** So this is clearly a candidate for germline gene therapy. Any other diseases?

**GARY NABEL:** Yes. Sickle cell anemia would be another example.

**JOHN HOCKENBERRY:** Is there a risk, though, that you'd pass along other characteristics by changing the germ cells?

**GARY NABEL:** Absolutely. And that is really at the crux of the difficulty in thinking about germline gene therapy. At the present time, the technology is not at hand to perform germline gene therapy.

On the other hand, we have seen that technology sometimes surprises even the most optimistic of scientists. And so I think it should remain an object of research in the laboratory, and as we gain more comfort with our technology – both its limitations as well as its potential – we should revisit the question when the risks appear to be coming into a range where they would justify the procedure.

**JOHN HOCKENBERRY:** While searching for his comfort level, Doctor Gary Nabel does – very carefully – gene therapy research at the University of Michigan at Ann Arbor. Gary, thank you very much for joining us.

**GARY NABEL:** Thank you, John.

**JOHN HOCKENBERRY:** Some scientists, like Gary Nabel, are taking a wait-and-see attitude toward germ-line gene therapy, while others are dead-set against it.

Stewart Newman is a fierce critic of this emerging technology. Newman teaches cell biology and anatomy at New York Medical College, a school located about 45 minutes north of New York City.

**STEWART NEWMAN:** Germline modification – and I prefer not to use “therapy” for gene modifications on someone who doesn’t even exist yet – what is it therapy for? – basically, what it is doing is designing individuals in a prospective fashion.

**JOHN HOCKENBERRY:** Newman argues that germline manipulation would really be genetic enhancement. In other words, an attempt to give people special traits that they wouldn’t normally have. He says it’s wrong to use genetic medicine to give some people built-in advantages over others.

**STEWART NEWMAN:** You might start out by saying, Well, you know, this is going to be a terrible disease. Let’s see if we can get the person not to have it. Then you could say: Well, maybe the person would be a little shorter than I would like. Let’s see if we can make them taller. Maybe a little smarter. Maybe a better athlete. After a while, you don’t know whether you’re dealing with a person or with a manufactured object.

**JOHN HOCKENBERRY:** The prospect of germline gene manipulation has prompted deep concern around the world. Research in this area is banned in some European countries with painful memories of Nazi efforts to create a master-race during World War II. Countries including Germany, Austria and Switzerland want to avoid using genetic science to enhance future generations.

The U.S. takes a different approach. The federal government, which funds a great deal of genetic research, won’t even consider proposals to explore human germ-line alteration. But there is no federal law prohibiting this type of research from being done with private money. And so many people believe it’s only a matter of time before experiments in human germ-line manipulation begin.

**JOHN HOCKENBERRY:** In Washington DC, scientists and philosophers gather to discuss germ-line gene therapy. The meeting is part of a study sponsored by the American Association for the Advancement of Science. The questions discussed here are not just

medical in nature. Permanently altering human genes also raises profound ethical and religious questions.

**PROFESSOR LAURIE ZOLOTH-DORFMAN:** The main question that people ask theologically is: should we be playing God?

**JOHN HOCKENBERRY:** Professor Laurie Zoloth-Dorfman studies Jewish ethics at San Francisco State University. To her, germ-line gene therapy is simultaneously exciting and troubling. Exciting because it promises to attack the root causes of inherited diseases, troubling because it could permanently change what many believe to be the God-given world.

**PROFESSOR LAURIE ZOLOTH-DORFMAN:** When you think about altering essential human patterns – if the map, the road map of humanity, is somehow encoded in our DNA, and when we begin to uncircle it, name it, know it, number it, and then begin to rearrange it, it does raise profound questions about why is it given us in this way? That's on the one hand. On the other hand I'm wearing glasses. And I can see even though I really sort of can't see. And that basic not-seeing was what was given to me as my essential human pattern, and I changed it. So are we talking here about a different way of changing one's abilities? Or is it a difference in quality, when we talk about DNA? And that I think is the interesting question that we're gonna have to spend a lot of time thinking about, is it a quantitative or qualitative change in what we always do?

**JOHN HOCKENBERRY:** Zoloth-Dorfman is not alone in her ambivalence toward germ-line alteration. And so, what will happen when the first human germline gene therapy experiment is proposed? The history of genetic science offers a range of possibilities. When the creation of Dolly the sheep was announced in 1997, there was a huge and highly emotional outcry against cloning. On the other hand the public is generally enthusiastic about the promise of genetic medicine. The future of germ-line gene therapy may very well hinge on whether it's perceived as good medicine or a misguided attempt to create a superhuman race.

**JOHN HOCKENBERRY:** For the less controversial form of gene therapy – the one that is not intended to affect future generations – the issues are less theoretical, more immediate. Today gene therapy is being administered in life and death situations. In fact, the rules of gene therapy research dictate that it be given almost exclusively to people with terminal illnesses. This new medicine is so risky that anyone who's likely to survive treatment with traditional drugs is barred from getting gene therapy. Sooner or later most patients who receive gene therapy find out why these rules exist. Again here's correspondent John Rudolph.

**JOHN RUDOLPH:** There comes a time in the life of every person who has been treated with gene therapy when they have to face the limits of this new medicine. For Don Hardy that moment came last winter, during a routine check-up at the Hospital of the University of Pennsylvania. A chest X-ray showed that the tumor around Hardy's lungs had started to grow again. His doctor, Dan Sterman, gave him the bad news.

**DR. DANIEL STERMAN:** We haven't gotten rid of all the tumor. There's still a tumor there, and it's slowly gnawing at you. It's growing, and it's not dramatically large, but it's

there and you know it and I know it.

**DON HARDY:** Sure.

**DR. DANIEL STERMAN:** And I guess the point is that you have a window, now, which... we have opportunities. They are experimental opportunities, but they are opportunities, and the window may close in a few months. And so that's okay.

**JOHN RUDOLPH:** Don Hardy left the hospital that day knowing he had a huge decision to make. Hardy wanted more gene therapy. But that was prohibited under the rules of the experiment. In exchange for being treated Hardy had accepted certain conditions. He wasn't just another cancer patient. He was part of a scientific trial where safety was as big a concern as finding a cure. And for reasons of safety the amount of gene therapy he would receive had been pre-determined. There was, however, another possibility – a different experimental treatment that used lasers to burn away cancer cells. Hardy decided to try the laser technique. He knew it might not cure him. But he hoped it would give him more time – to be with his family, to enjoy his retirement, and if necessary to have another gene therapy treatment when it was permitted.

**DON HARDY:** I wanted to follow the therapy program right to the end because I believed in it, and I got a little setback in the fact that I got some growth, and knowing the nature of the disease, the advice was: don't wait for the second treatment, because it's still down the road. They need approval, from what I understand, because they've changed the delivery system, or they've changed the virus, actually. So I'm pretty confident that I made the right decisions, and whether God's guiding me in my decisions or what, I feel that somebody's helping me to make them, because I seem to have made a couple of good ones here, anyway.

**JOHN RUDOLPH:** Don Hardy's experience with gene therapy has been a delicate dance. Like most cancer patients he's had to make difficult decisions choosing treatments without any guarantees they would work. So far Hardy has made the right choices, and by doing so prolonged his own life.

**JOHN RUDOLPH:** But gene therapy still has not lived up to its promise. Even so, Dr. Sterman is not discouraged.

**DR. DANIEL STERMAN:** I think it's the only way that I can keep going...is to hope that somewhere along the way we reach a certain dose, a certain type of vector, or some other type of therapy altogether, that one time we're going to see the CAT scan in which the tumor does shrink dramatically, and where the patient lives 2 or 3 years longer than expected, or the pain goes away dramatically.

**JOHN RUDOLPH:** It's hard to predict when the first breakthrough will happen, and even harder to say if or when adding or replacing genes to cure disease will become part of mainstream medical practice. But what is certain is that years of research lie ahead before gene therapy gains acceptance. In that time many more people like Don Hardy will have to be willing to take a chance – to bet their lives on what may be the medicine of the future.

**JOHN HOCKENBERRY:** Listening to Don Hardy's story I can't help thinking about

another man who took a gamble on a new and unproven medical treatment. Remember Barney Clark? In 1982 he became the first person to receive a permanent artificial heart. The big clunky machine kept him alive for 112 days.

Don Hardy has done a lot better than Barney Clark. He has lived years longer than expected following his treatment, and his life doesn't depend on being tethered day and night to some noisy contraption.

But gene therapy hasn't cured Don Hardy, and his doctors would be surprised if it did. And so like Barney Clark, Hardy's story shows both the promise and the challenge of medical science. Progress is steady, but truly conquering disease is tough. And in an age when genetic science holds out the hope that we shall one day know the secrets of human health, we discover our bodies do not easily give up those secrets.

I'm John Hockenberry

[Theme music. End.]

**Credits for *The DNA Files*:**

*The DNA Files* is produced by SoundVision Productions in Berkeley, California, and is made possible through the generous contributions of the National Science Foundation, the Department of Energy, and the Alfred P. Sloan Foundation. Additional support from the March of Dimes.

For more information and for an interactive look at some of the issues behind this program, go to our website at [www.dnfiles.org](http://www.dnfiles.org). For tapes and transcripts of this program and this series, contact Visibility, Inc. at 303-823-8000. To contact *The DNA Files*, send your e-mail to [feedback@dnfiles.org](mailto:feedback@dnfiles.org). *The DNA Files* Executive Producer is Bari Scott. The Project Director is Jude Thilman. Today's program, Gene Therapy: Medicine for Our Genes, was produced by John Rudolph and engineered by Lars Hoel. The editor was Anne Donohue.

Managing Editors of *The DNA Files* are Loretta Williams and Catherine Stifter. Production Manager is Catherine Gollery. Technical Director is Robin Wise. Adi Gevins is Director of Research and Creative Consultant. Sally Lehrman is Content Consultant. Original music composed and performed by Bill Frissell. Introductory feature produced by John Rieger and edited by Gary Covino.

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This program is distributed by NPR National Public Radio.

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