

[CRICKETS CHIRPING]

[MUSIC PLAYING]

[LAURA TROXEL:] We were aware that Molly had a vision impairment, because when I was breastfeeding Molly, she would look away from me to see a light somewhere else in the room.

[BABY VOCALIZATIONS]

[NARRATOR:] When their daughter was just a few months old, Laura and Ryan Troxel got heartbreaking news. Molly had symptoms of an inherited disease, a form of blindness. She would probably lose what little sight she had by the time she became an adult.

[RYAN TROXEL:] Oh, it was devastating. I remember trying-- I still tear up now thinking about it here-- just knowing that your daughter is not going to be able to see.

[NARRATOR:] Molly's blindness was due to a mutation in the genetic instructions for a protein in her eyes. Ever since biologists first cracked the genetic code, they imagined that someday this knowledge would help cure diseases like Molly's.

[SCIENTIST:] Bingo.

[NARRATOR:] That time has finally come.

[BENNETT:] When I first realized that we could make a blind dog see, it was the first hope that we could actually do the same thing to children and make blind children see.

[OFF CAMERA:] And you did it.

[NARRATOR:] This is the story of how gene therapy developed from a dream in the lab to a revolution in medicine.

[MUSIC PLAYING]

[BENNETT:] Your injections look fabulous. That looks really exciting.

[SCIENTIST:] I have even more encouraging stuff to show you, actually.

[BENNETT:] I first began to be interested in gene therapy when people began to clone genes and transfer them to animals. This was in 1980. They were transferring genes to mice and altering their appearance and their growth. And I realized, wow, this approach could be used to treat humans. Fantastic. That's great. And I realized, this is what I want to do.

[NARRATOR:] Most genes are instructions for producing proteins that perform important functions in different cells of the body. Inherited diseases come from mutations in genes. Those mutations result in the production of a faulty protein or sometimes no protein at all. The principle of gene therapy is to provide cells with a corrected copy of the mutated gene that will produce the functional protein.

[BENNETT:] The big idea of gene therapy is that you're treating a disease at its root. You are stopping the disease in its track by altering the instructions that the cell is given. The benefits are

that one can potentially correct the basic problem that is causing the disease and allow the cells to function normally, and thus, allow the person to function normally.

I met my husband in medical school, and he knew early on that he wanted to study neuroscience. And his biggest interest was in the retina.

[NARRATOR:] The retina is a light-sensitive layer of neural tissue at the back of the eye. It converts light energy into signals that are carried to the brain by the optic nerve.

[MAGUIRE:] People don't realize the retina is a very integral part of the brain. And essentially, what it is is the brain is squeezed out like toothpaste into the eye socket. And it forms a film, and that's the camera film, the retina, that you and I see with.

[NARRATOR:] Maguire's focus on eyes and Bennett's expertise in genetics naturally came together.

[RESEARCHER:] So just walk directly ahead--

[NARRATOR:] In the 1980s, while they were still students, Maguire wondered if blindness might be treated with genes.

[BENNETT:] Albert asked me in medical school whether the eye would be a good target for gene therapy, and I said, yeah, sure. What I didn't tell him is, we didn't know any of the pieces that we needed to be able to do this. There had been no genes identified which, when mutated, caused that condition. We didn't know how to clone those genes.

[MAGUIRE:] If I had known all the issues, I probably would have walked away.

[NARRATOR:] It would take decades to assemble the necessary tools and know-how, but the eyes were a good potential target for developing a gene therapy. Eyes are easy to access, and two eyes means that in an experiment, one can be treated while the other acts as a control. For Bennett and Maguire, the next question was, how can you get the corrective genes into the cells you want to treat?

[BENNETT:] It may seem crazy, but viruses are now used. Because viruses have evolved to do what they do really well, and that is to move DNA or RNA across cell membranes.

[NARRATOR:] Viruses contain packets of genetic information. They can invade cells and deliver their genes inside. Then they hijack the cells' machinery to make copies of themselves. Scientists strip away the viruses' harmful genes and those needed for the viruses to replicate. Then they insert a copy of a corrected gene. Attached to the gene are regulatory sequences which direct it to be expressed in specific cells.

Next, scientists inject huge numbers of the modified viruses into the tissue that needs the therapy. The viruses invade those cells and deliver the corrected gene but without replicating.

[BENNETT:] Our first animal model for testing the ability to use viruses to deliver DNA was the mouse.

[NARRATOR:] Through the 1990s, Bennett and her collaborators tested different types of viruses and methods for injecting them into mouse eyes until they showed the procedure could work. But mouse eyes are small compared to human eyes.

[BENNETT:] You can imagine the surgery to deliver a gene to a mouse eye is a lot different than if you are going to inject the eye of a human, which is 100 times bigger.

[MAGUIRE:] You with me?

[BENNETT:] Yes.

[NARRATOR:] To be sure that a sufficient number of genes could be delivered and expressed in human-sized eyes, the researchers needed to develop procedures in a large animal model.

[BENNETT:] Come on, come on, come on.

[NARRATOR:] One breed of dog turned out to be the perfect model. Briard Shepherds have eyes about the size of humans. And remarkably, some Briard Shepherds suffer from the same form of blindness that's a leading cause of blindness in children. The couple adopted this pair of dogs after they retired from work in the lab.

[MAGUIRE:] The Briard dog has the exact same genetic condition as humans who have child-onset blindness called Leber amaurosis. So they match up almost perfectly with the human condition.

[DOG PANTING]

[NARRATOR:] In both humans and dogs, Leber amaurosis can be caused by mutations in a gene called RPE65.

As a result of the mutation, the light-detecting cells in the retina, called photoreceptors, progressively malfunction and die.

The symptoms typically show up in infancy.

Molly Troxel inherited the disease-causing mutation from her parents. They each have one working copy of the RPE65 gene, so their vision is fine. But in each parent, the other copy contains a rare mutation that leads to a non-functioning protein. Molly inherited two mutated copies of the RPE65 gene, one from her mother and one from her father. So her cells have no functioning RPE65 protein.

The odds of two people with a rare mutation in the same gene having a child together are remote, indeed.

[RYAN TROXEL:] You know her and I, just somehow our genes ended up creating Molly, which was a great thing. But you know, with her having the eye disease, it's just a really rare thing also.

[LAURA TROXEL:] I think Molly was around age 6 when they were able to define that she had the RPE65 mutation. Gene therapy would be an option for her someday. So that was a lot of wonderful hope.

[NARRATOR:] The research that could turn hope into reality came together with the help of Briard Shepherds.

[BENNETT:] It wasn't until we had the Briard dog that we actually had all of the pieces in place, the know-how of how to deliver the genes and the appropriate animal model, which is critical.

[NARRATOR:] But while Bennett and Maguire assembled the components for treating Leber amaurosis in dogs, researchers had already begun testing gene therapies for other diseases on humans. In 1999, tragedy struck. Jesse Gelsinger entered a gene therapy trial at the University of Pennsylvania for the treatment of a rare liver disease. Doctors injected Jesse with a virus that carried copies of a corrective gene, but his immune system reacted to the viral invasion with overwhelming force, damaging his organs. Four days after the procedure, Jesse Gelsinger died. He was 18.

[BENNETT:] This was a tragic event for this young man and his family, but it was also a tragic event for the field of gene therapy itself, because everything came to a screeching halt. People withdrew their interest and their support for gene therapy. There was no more funding.

[NARRATOR:] With human clinical trials shut down, Bennett and Maguire pushed on with attempts to restore sight in Briard Shepherds. Dogs with mutations in the RPE65 gene would grow up to be blind, unable to navigate simple environments.

[RESEARCHER:] Oh, good girl.

[BENNETT:] So we took advantage of all the things that we had learned over the preceding decade or so and injected three puppies.

[NARRATOR:] Then they waited. Would the therapy restore some sight to the dogs, or would failure send the scientists back to the drawing board?

[BENNETT:] At the two-week time point after injection, I got a call from the animal facility. The vet tech taking care of them said, "gee, they're watching me as I walk through the facility. I think they can see." And they could, and it was miraculous. It was absolutely just one of the most exciting moments I've had in science. It was the first hope that we could actually do the same thing to children and make blind children see.

[NARRATOR:] Bennett, Maguire, and their collaborators successfully repeated the experiments with more dogs. The next step would be to try it in people. But in the wake of the Gelsinger tragedy, moving forward with human trials would be difficult.

[HIGH:] There had been a general sense that this was a therapy that was not ready for prime time, that there were too many things we didn't understand, and that it was not ready for development. All the companies that had been involved in gene therapy were either turning away from it, or they were failing.

[HIGH:] And now they want several examples of this.

[NARRATOR:] But as companies left the field, gene therapy pioneers like Katherine High persisted. In 2001, she was setting up a gene therapy facility and looking for candidate diseases when she came upon Bennett's work.

[HIGH:] So I was always looking for things where there was good proof of concept in a large animal model. And she clearly had it.

[RESEARCHER:] So I'm looking at retinal ganglion cells.

[HIGH:] When we had our facilities set up, I went over to talk to her.

[BENNETT:] She walked into my office, and I looked up, and she said, "Jean, how would you like to run a clinical trial?" I was just-- I was totally floored. I was not expecting that at all.

[BENNETT:] And so that was the beginning of a whole infusion of energy, and enthusiasm, and support, and led to incredible success.

[NARRATOR:] It took Bennett and High years to adapt the virus-delivery system to be safe and effective in humans. In 2007, they recruited the first patients for human trials. In 2013, the Troxels threw a party for Molly. Now 11, she was about to be enrolled in a later trial.

[MOLLY TROXEL:] I was really excited and a little scared, because, you know, it's surgery on your eyes. But then I was thinking, you know, it's going to be OK. It's going to work.

[LAURA TROXEL:] Molly was gung-ho. She was going to do this. She wanted it. I was afraid. The hope was that she would have more vision, but there was a possibility that it could make her vision worse.

[NARRATOR:] The surgeon first injected one of Molly's retinas with 6 drops of a liquid containing billions of gene-carrying viruses. Later, if the procedure worked, they would inject the other eye. Each virus contained a copy of the RPE65 gene. The viruses invaded the retina cells and delivered their genetic payload. The cells' machinery produced the RPE65 protein to restore function.

When the patch came off, Molly couldn't tell if anything was different. But then--

[MOLLY TROXEL:] I saw the moon.

[RYAN TROXEL:] I went, wow, Molly, you can see that? For her to see the moon and stars-- things you would take for granted-- was just huge for us. Now, there's just no stopping her.

[RYAN TROXEL:] I think the biggest surprise for me is just her independence. She could ride her bike up on the circle without us, you know, being right there and, you know, pins and needles that she's going to hit a mailbox or something.

[LAURA TROXEL:] She's hit a lot of mailboxes.

[MUSIC PLAYING]

[RYAN TROXEL:] Around the horn.

[LAURA TROXEL:] Even though to an outsider she still looks visually impaired, I'm so thankful that she can see better and if nothing else, that it stopped the progression of this disease.

[RYAN TROXEL:] Nice. Yeah. Good job, Molly.

[MOLLY TROXEL:] I was hoping for perfection. But that's hard to do. But what I have now is perfect.

[BENNETT:] I feel extraordinarily lucky to actually see our research move from the bench all the way to treating humans and then see these humans benefit.

[LAURA TROXEL:] Good job, Molly.

[BENNETT:] All science builds on previous science. And science involves so many different areas of expertise. This whole study is a perfect example of the importance of collaboration in science.

[NARRATOR:] More than 40 patients, most of them children, have taken part in RPE65 clinical trials, with excellent results.

[RESEARCHER:] Open the door. And you did it. Bravo.

[NARRATOR:] In 2017, RPE65 gene therapy was recommended for approval by a panel of the Food and Drug Administration for the treatment of congenital Leber amaurosis.

This success brings therapies for other inherited diseases one step closer to reality.

[MUSIC PLAYING]

[BENNETT:] And you did it.