TEASE
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TEASE

ALAN ALDA Somewhere down there could be the genes that construct a baby, that grow new blood vessels, that help you remember a kiss, or that make you grow old.

ALAN ALDA (NARRATION) I learn how to read a gene.

ALAN ALDA Mm, thank you.

ERIC LANDER That's all there is!

NANCY HOPKINS Of course we'd like to use humans…

ALAN ALDA (NARRATION) And what fish can tell us about babies. In flies we discover a memory gene…and in worms a gene for youth.

CYNTHIA KENYON You change one gene and you cure this disease of aging.

ALAN ALDA (NARRATION) But we also find out why using genes to cure disease is still mostly hope.

JIM WATSON I'll only be truly happy if we stop cancer or stop schizophrenia.

ALAN ALDA I'm

ALAN ALDA. Join me as we look for the genes that make us or break us, on "The Gene Hunters."

A PASSION FOR DNA

ALAN ALDA (NARRATION) When we decided to make a show about DNA -- the stuff genes are made of -- we naturally wanted to start with some of the best DNA we could find. So we came here to the DNA Learning Center on Long Island.

INSTRUCTOR The first thing we're going to do is swoosh our cheek pockets really good.

ALAN ALDA Now I have to tell you you're going to get the DNA of the tuna I had for lunch a little while ago. So my DNA's right there in that little cup, huh?

INSTRUCTOR Take a look in the microscope, you'll see thousands of cheek cells that just sort of slough off.

ALAN ALDA That blue dot in the center. That's the nucleus?

INSTRUCTOR That's the nucleus.

ALAN ALDA This is my nucleus.

ALAN ALDA (NARRATION) It's the nucleus that houses the DNA, so we have to break it up and shake it up to release my genes.

ALAN ALDA OK, I got it.

ALAN ALDA (NARRATION) Unlike me, the high schoolers whose class we've dropped in on aren't in the least amazed that you can get your hands on your own genes, chop them up, multiply them, even read what they have to say. They've grown up during the years when scientists have pretty much deciphered the entire human genome…

ALAN ALDA I'm a nervous wreck.

ALAN ALDA (NARRATION) … the three billion letter instruction manual for making a person.

ALAN ALDA You want more? Science is hard, I tell you.

ALAN ALDA (NARRATION) Our show is about the people who are picking through the DNA -- not just of humans but a strange menagerie of other creatures-- to find out how this unimpressive looking gook has within it some of life's most precious secrets.

ALAN ALDA What'll you give me for this?

ALAN ALDA (NARRATION) One of the first people to imagine that DNA was worth anything was

JIM WATSON, who with Francis Crick 50 years ago discovered the double helix structure of DNA -- a structure now echoed in this staircase outside Watson's office at Cold Spring Harbor Laboratory, just down the street from the DNA Learning Center on the north shore of Long Island.

JIM WATSON first came here in the late 1940s as a 20-year-old graduate student, obsessed with finding out what genes are made of, and how they work.

JIM WATSON I thought it was the only problem worth solving. Of course that wasn't true, but it was the only one I thought worth solving. And luckily, except for Francis Crick, I don't think there was anyone who was as high about DNA as we were.

ALAN ALDA (NARRATION) Watson and Crick discovered their mutual passion for DNA when Jim went to Cambridge, England in 1952. But most biologists didn't share their enthusiasm, and dismissed the pair as arrogant and irrelevant. Watson later wrote about this period in his famously gossipy account of their discovery, The Double Helix.

JIM WATSON No one predicted, you know, thought we were ever going to succeed. And England is too polite to have too much ridicule, but no one was betting on us, and… our obsession about DNA… Prove it. And why are you so excited? And so you've got to be not happy that other people don't believe you, but just… I wrote in the Double Helix and it still offends people that… when you get into science you realize that most scientists are stupid. And… because…

ALAN ALDA Now, come on.

JIM WATSON Yes, I think that's a correct way of looking at it, because they don't see the future. You know, it's a relative matter whether you call them stupid or not, but you know, how can anyone with a Ph.D. be stupid, but most people with PhDs aren't doing anything. You know, doing anything breathtaking. So you have to be prepared, not to care that most people think you're going in the wrong direction, and that means you have to… well, one it pays to have someone else who agrees with you, so Francis and I could talk to each other, and we never tried to persuade anyone else. There was no point of trying to persuade anyone else.

ALAN ALDA (NARRATION) One Saturday morning in early 1953, Watson was fiddling with a model of a possible DNA structure based on a double helix.

ALAN ALDA That Saturday, when things fell into place, what piece was missing from this? What did you…?

JIM WATSON Well, we didn't have this.

ALAN ALDA This was missing.

JIM WATSON We had the backbone but we didn't know how to fill in the center.

ALAN ALDA (NARRATION) The center had to accommodate the four different chemical units, or bases, DNA is made from, known by their letters as A, T, G and C. Watson was trying to make matching pairs of bases -- but they just wouldn't fit.

ALAN ALDA So you were pretty sure it was a double helix, but you didn't know how these base pairs fit together, huh?

JIM WATSON Yes. And in the books the chemistry was written wrong.

ALAN ALDA In what way?

JIM WATSON Well, they had an atom in the wrong… a couple atoms in the wrong place. And so someone said, well the chemistry in the books is wrong.

ALAN ALDA Well that must have thrown you…

JIM WATSON At first I said no, I don't believe you. But then the next day I thought, well, we'll see what happens if you, you know…

ALAN ALDA Change it from the way it is in the books.

JIM WATSON Yeah, and then the whole thing fell out. So if we hadn't had that chemist in the room with us there wouldn't have been someone to say, well, it's wrong.

ALAN ALDA (NARRATION) But it wasn't just that the corrected As and Ts, Cs ad Gs, fit together snugly in the center of the double helix. The structure immediately suggested the answer to the gene's central mission -- carrying information and copying it from generation to generation. The information could be carried in the letters, and the copying achieved by each strand of the helix becoming the template for a new matching partner. So in one stroke, Watson and Crick had the answer not only to how genes are made, but how they work.

JIM WATSON This was just much bigger than anyone expected and in a way, it was so beautiful... there wasn't the usual jealousy of us. You know, people could rejoice in the answer. People just liked that discovery.

ALAN ALDA They found it so beautiful that their natural jealousy faded away in the glare of its beauty.

JIM WATSON Everyone hoped it was right because if it was right we finally had the molecule of heredity, because while Francis and I were very… we believed strongly that DNA was going to be the genetic molecule. Most people didn't. And it wasn't until people saw the double helix that, sort of the world of science accepted DNA as a genetic molecule. And that then led to the, a lot of people suddenly coming in and following up our work and the explosion of molecular biology.

ALAN ALDA (NARRATION) In the years that followed, many of which

JIM WATSON spent here as director of Cold Spring Harbor Laboratory, he continued to play a central role in unraveling how genes work. When in the late 1980s, a group of biologists began to consider the then outrageous idea of deciphering the all the genes in the human body, it was to

JIM WATSON that they turned to lead the project.

JIM WATSON I was in favor of it because even though it seemed premature, it seemed to be the only way to understand a lot of disease, and I was then in my 50s. By that stage, when you're in your 50s, you're seeing your parents die or dead, and you're conscious of disease. When you're 25, hopefully you're not. You're not thinking, you're thinking in terms of life, not death or sickness. And so I saw getting the human genetic information as a big plus toward moving medicine. And that's how we helped sell it to Congress. It was really disease.

GENE READER

ALAN ALDA (NARRATION) Back at the DNA Learning Center, I'm finding out for myself why many biologists originally opposed the Human Genome Project -- even if it promised to revolutionize our understanding of human disease.

ALAN ALDA Oh, there it is.

ALAN ALDA (NARRATION) The techniques of handling and reading DNA were slow and cumbersome. Reading three billion letters-worth would involve thousands of people working, literally, for decades. But then came a revolution. This is the Whitehead Center for Genome Research -- the largest of the 16

laboratories around the world collaborating on the Human Genome Project. There are people here, but they are far outnumbered by machines.

ALAN ALDA Wow, this is amazing. Look at this.

ALAN ALDA (NARRATION) The director of the Genome Center is

ERIC LANDER.

ALAN ALDA This is some kind of robot?

ERIC LANDER Yeah, over there are all these little spots on those plates, those are each separate bacterial colonies. Every one of them has a little piece of human DNA that we've got to sequence. It might have 2000 letters of human DNA. The first thing we've got to do, we've got to pick up and grow each bacterial colony up so that we get enough DNA out of it.

ALAN ALDA I presume this robot is doing this because its doing it a lot faster than humans could.

ERIC LANDER We used to do this not so long ago ourselves with toothpicks. So this is simply a highly automated toothpick. Somewhat more expensive, much more efficient. Every one of those is a different sentence in the human genome. And so we've got to go collect these random shreds of sentences and sequence them. That's pretty much what the entire operation here does.

ALAN ALDA (NARRATION) The machines in this room diligently prepare a hundred thousand sentences a day of the three billion letter book that's the human genome. The next trick is to read those sentences. That's done here -- in another huge room crowded with bland-looking machines tended by a handful of humans. The human's job is to feed the sentences into the machines -- 96 at a time, in these little cartridges. In order to read the order of the letters -- the As, Ts, Gs and Cs -- in the sentences, the machines make use of something extremely weird.

ERIC LANDER Well it turns out that the little sentences are faster than big sentences when you put them through jello, in essence. Now, what is jello?

ALAN ALDA You have this giant scientific laboratory devoted to putting sentences through jello. I'm amazed I didn't come up with that.

ERIC LANDER We like to use fancier words because it's impressive, it costs a lot of money. But basically you're taking little molecular sentences and putting them through jello. The point about jello is that it's this very complicated network, the

little sentences can wiggle through better than the bigger sentences. And in fact what's really cool about this is that the guys that are 51 letters long get there just ahead of the guys that are 52 letters. And then the sentences that are 75 letters long are lagging behind. And there's this little detector that reads the letters as they go by. So in fact if we find a machine… Guys, have we got a machine where we can bring up the letters as they go by? Let's take you to see the letters go by.

ALAN ALDA Great.

ALAN ALDA (NARRATION) The letters, it turns out, have colored tags to identify them -- red for a T, green for an A, blue for a C and yellow for a G.

ERIC LANDER So you can read out the DNA sequence -- GATTCG -- because we attached the right colors to the right sentence. It's a beautiful trick.

ALAN ALDA (NARRATION) Understanding the trick took about 10 minutes in front of a convenient whiteboard.

ERIC LANDER I'm just going to make up some letters of DNA here…

ALAN ALDA (NARRATION) But to save time, we'll summarize. The DNA sequencing machines are actually making copies of the DNA sentences -- but every time one of those colors is stuck on, the copying grinds to a halt. So there are lots of sentence fragments floating around, each one ending in a different color. By reading both the fragment length and its color, you get the sequence.

ERIC LANDER So the number 6 is purple.

ALAN ALDA Right, right.

ERIC LANDER And the number 7 is green, and the number 8… That's it.

ALAN ALDA OK, thank you.

ERIC LANDER That's it. That's all there is. This whole place here is to stick in these things.

ALAN ALDA OK, OK, well let's go, I'll run one of those machines now.

ERIC LANDER That's it. You've got it. It takes an hour in freshman biology. You've got it. That's it!

ALAN ALDA (NARRATION) Well, that's a relief. But there was still one nagging question. Just who exactly is the human whose genome is being read?

ALAN ALDA If you took my blood cells and went through this whole process, do you need to get a lot of other people's blood cells to get a comprehensive picture of the human genome?

ERIC LANDER Your DNA and my DNA are 99.9% identical. We differ at one letter in a thousand. So if what we're trying to do is find all the genes in the genome, all the sentences, we can do that just fine whether it's your DNA, my DNA or anybody else on the planet. Once you've read one person's DNA, you then become interested in this one letter in a thousand variation. Now that matters. I mean, between you and me I said we're 99.95 identical, but we still have three million differences…

ALAN ALDA And one of us might have something that's off that might cause disease, is that right?

ERIC LANDER One of those letters could be breast cancer, one of those letters could cause early onset Alzheimer's disease. You want to know the differences. But it's as if you had many different editions of the same book, and they differed by, you know, a comma here, or the British spelling of some word here instead of the American spelling. So when you say, well what do you mean to read the book, anybody's copy of the book will be fine if you want to get the story line down. If of course we really care about the punctuation -- and at the end of the day in medicine we really do care about the punctuation -- then we've got to read your book. But the Human Genome Project was about reading the first copy of the book. We're now in an age when biology is about information…

ALAN ALDA (NARRATION) In February 2001,

ERIC LANDER was the lead author on the scientific paper that announced the first draft of the human genome. This laboratory continues to pour out 50 to 60 million letters of DNA code every day as the details of the human codebook are filled in. And unlike the companies that are also sequencing our genes, the data streaming out of these machines are free.

ERIC LANDER Every 24 hours, the 50, 60 million letters we produce here get posted on the Web. And they go flying around the databases in Japan and Europe and Washington and then from there to databases in tens of thousands of biology laboratories. So in fact there's this huge information shuffling going on constantly, because if you were studying a particular thing about diabetes, you could have searched the world's databases last week to see if there was a gene like what you were looking for, and there was nothing. You better make sure you have an automatic program searching again next week, because it might have

shown up. So people have these automatic demons running on their computer. So they say, I'm interested in this. Let me know if you should see one…

ALAN ALDA And then your computer goes bong, and says you've got Gmail.

ERIC LANDER You've got Gmail. That's right. The thing you were looking for just showed up last night, here it is.

ALAN ALDA (NARRATION)

JIM WATSON, the first director of the Human Genome Project, was convinced it would revolutionize medicine. So…

ALAN ALDA Tell me about how our lives will be different now, medically. I mean, how revolutionary is this going to be?

ERIC LANDER Well, it's possible to over-hype all this stuff and I think people have outrageous expectations that there are going to be cures next week from all of this. It's certainly not going to be like that. What it is that's really revolutionary is for the first time we're going to be able to understand the mechanism of how cells work, organs work, at a really detailed level. See, we don't actually know what's wrong in most diseases. We can describe that when you have diabetes you have high blood sugar. That's great, but it doesn't tell you what's wrong, what part of the machine is broken. We haven't even had the parts list of the machine. Trying to practice medicine would be like trying to practice auto mechanics when you don't know what the parts are in the car. You'd never take your car into an auto mechanic who didn't know what the parts were and how they are connected.

ALAN ALDA Oh, I have many times.

ERIC LANDER Probably, yeah. And you know the results.

ALAN ALDA Paid through the nose for it too.

ERIC LANDER Well, you take your body in, to medicine, and for the past century we didn't know what the parts were. I mean, the hearts and the lungs were, but not the little molecular machines and how they work, so how could we describe what was wrong in diabetes and what's wrong in asthma and what was wrong in hypertension? The real breakthrough of the Genome Program, the real guarantee, is that we're going to be able to figure out what all those little molecular machines are doing and what goes wrong in disease. It doesn't promise you you'll be able to fix it because of that, but the understanding sure beats the ignorance we've had and it's going to transform medicine because for the first time we are going to have met the enemy in disease.

FISHING FOR BABY GENES

ALAN ALDA (NARRATION) Our next story is also about finding human genes.

NANCY HOPKINS Now I always wash my hands, dip my hands here. If you don't mind doing that.

ALAN ALDA (NARRATION) But

NANCY HOPKINS isn't looking for human genes in humans -- she's looking in fish.

ALAN ALDA These are all your fish here?

NANCY HOPKINS Yes. Yes.

ALAN ALDA How many do you have?

NANCY HOPKINS In this room alone -- I don't know-- we have maybe in here about, I'd say, seventy five thousand?

ALAN ALDA Seventy five thousand?

NANCY HOPKINS A hundred thousand maybe. We have a total of about a hundred and fifty thousand fish.

ALAN ALDA How many did you start with?

NANCY HOPKINS Twenty three.

ALAN ALDA Twenty three?

ALAN ALDA (NARRATION) The fish are zebra fish, originally from the Ganges River. They're a popular choice for home aquariums for at least one of the reasons they're popular with Nancy -- they thrive in tanks -- with the right care and attention.

NANCY HOPKINS There's only about a thousand more to go.

ALAN ALDA (NARRATION) But the main reason Nancy is raising all these zebra fish -- unlikely though it may seem -- is to find the genes that make a baby.

NANCY HOPKINS Of course, we'd like to use humans…

ALAN ALDA Yes, but you can't fit them into the tanks.

NANCY HOPKINS But we haven't had any volunteers.

ALAN ALDA How close are their genes to ours? I mean, how much can we learn about the development of a baby human from the development of a baby fish of this kind?

NANCY HOPKINS A lot, yes. We would be horribly crushed if it didn't turn out that the genes weren't almost identical.

ALAN ALDA This is really hard to understand because if I made a list on a piece o f paper of the features that were identical between that fish right there and me… I mean we have eyes, our tails are different, our gills are different…

NANCY HOPKINS But, they have a head end and a tail end, they have a heart that beats. They have a liver, they have a gut, and at the cellular level their cells have to do all the same things that your cells do. We really believe that the genes we're going to find for making a baby fish will be many many of the same as making a baby human.

ALAN ALDA (NARRATION) A zebra fish egg is mostly yolk. In this speeded up shot, the cells that will become the baby fish are at the top. The cells divide and multiply, and then in just 24 hours form all the many different types of tissues from which the baby fish is made. Under the microscope, the tiny embryos are already wriggling vigorously a day after the eggs were fertilized.

NANCY HOPKINS So that's the tail and it's wrapped around the yolk. There it goes, whoops. There's the brain, the middle of the brain, the hind brain.

ALAN ALDA Look, look. It's like a little frisky anchovy.

NANCY HOPKINS Well thank you for pointing that out. I'd never thought of that.

ALAN ALDA Where's the heart?

NANCY HOPKINS Just sort of under the chin.

ALAN ALDA It's beating fast.

NANCY HOPKINS So you can see why it's a terrific animal to study early development because in one day you have that. And one fish, those little female fish, can lay several hundred eggs like that in a morning.

ALAN ALDA (NARRATION) Nancy estimates that only about 2400 of the tens of thousands of zebra fish genes are actually involved in making a baby fish. Her goal is to find as many of these baby-making genes as she can. She starts by injecting early embryos with a virus that invades the cells and inserts its DNA randomly into the fish's DNA. If a piece of virus happens to land in the middle of a gene, that gene will be destroyed. And if the gene was involved in making a body part, then the descendents of the fish whose gene was damaged will have a problem. But because Nancy can't know in advance what genes the virus will hit, she has to bombard all the genes in thousands of embryos in the hope that occasionally she'll hit something interesting. Then she has to raise and cross-breed thousands of offspring to find out if she did. That's why she needs so many fish. And it's also why much of her lab's time goes into peering at thousands of baby fish, looking for her unfortunate victims.

NANCY HOPKINS It turns out that generally the defects you get in these little babies actually result in death. So you see a very specific thing go wrong and then the fish is doomed, it's going to die.

ALAN ALDA (NARRATION) So far

NANCY HOPKINS and her colleagues have found more than a dozen specific defects in their zebra fish embryos.

NANCY HOPKINS Here's a normal embryo that's two days old. And these two embryos are also two days old but they have a mutation in just one out of maybe 30, 40, 50 thousand genes. And that one defect is causing this embryo to look like this instead of this. So whenever you take away that gene, you get this specific result.

ALAN ALDA (NARRATION) To track down the damaged genes, Nancy makes use of the fact that they were damaged in the first place by having a bit of virus DNA stuck into them. Fishing out the virus also fishes out the gene it disrupted.

ALAN ALDA What do you look forward to as the end result of this work?

NANCY HOPKINS Oh well, I think there's really two things, you know. One is it has tremendous medical potential I think, because you know we're looking for genes with which you really construct the body parts of a vertebrate animal. And so you can imagine that if you have something go wrong with somebody and you wanted to fix it, having the genes that make organs grow, make tissue, specific cell types grow and so forth, could have medical application. So that would be terrific if we found the gene that cured some disease. That would be wonderful. But that's sort of a random shot. But in the meantime you know we're really

collecting a list of genes that are essential to build this animal and we hope that in the end to end up with a set of bottles on the shelf; and there'll be a hundred genes to make a heart and the seventy-five genes to make the blood, over here fifty to make the ear, you know. So it would be all the body parts, in genes.

ALAN ALDA (NARRATION)

NANCY HOPKINS was already in mid career in a different field when she laid everything on the line to invent this way of using fish to look for the genes that make a baby. So perhaps it's no wonder that to her zebra fish are something special.

NANCY HOPKINS As scientists we're not supposed to get attached to our animals as individuals but I do love my fish. I must say I do. When I'm upset I come in the fish room and just…

ALAN ALDA When you're upset you come in and…

NANCY HOPKINS Just look at the fish.

ALAN ALDA That's interesting.

NANCY HOPKINS Hmm. Very calming. You can't help wondering what they're thinking about really.

A GENE YOU WON'T FORGET

ALAN ALDA (NARRATION) These are fruit flies -- about as unlike you and me as it's possible for another living creature to be. Unless you look at their DNA. Then -- as with

NANCY HOPKINS' zebra fish -- the similarity between their genes and ours is downright spooky. For a hundred years, fruit flies have been a favorite with geneticists -- and never more so than today: scores, perhaps hundreds, of human diseases have their genetic counterparts in flies. But of all the insights into ourselves we've gained from these creatures and their genes, few are more dramatic than the discovery made by this man,

TIM TULLY. Tully is fascinated by memory, and he's devised an ingenious machine to test the memory skills of fruit flies. He puts several dozen flies into a chamber lined with an electrical coil. The flies are in for an experience they won't forget -- at least for a few minutes.

TIM TULLY Now I'm attaching the voltage source, where the flies will get a slight little shock to their feet. They're only receiving about five nano-amps of current, which is nothing. Just enough for them to notice, not enough to hurt.

ALAN ALDA (NARRATION) While they're noticing the tingle in their feet, the flies are also noticing something else -- an unusual smell, a chemical scent. The purpose of the experiment is to see how well the flies remember that the tingle and the smell go together. The flies are tapped into a crowded elevator, where they wait while Tim attaches two tubes to the basement level of his machine. One tube is fed the odor the flies experienced while being shocked, the other tube gets a different odor. Now comes the test. Tim gently lowers the elevator to a point between the two tubes. The question is, which tube will the flies choose? If they remember the unpleasant experience upstairs, they'll avoid that smell down here. If they've forgotten, they could choose either tube. With the experience still fresh in their minds, these flies are indeed avoiding the shocking smell. But what Tim really want to know is how well the lesson stays with them a week or so later -- in their long-term memory. It turns out it all depends on how they were trained

TIM TULLY In order for a fly to form a long-term memory of this single little odor-shock presentation, it has to practice repeatedly. And we've shown clearly with our genetic experiments that if you give the fly ten training sessions of odor-shock pairings, and you cram them together, it does not form a long-term memory.

ALAN ALDA You have to give them the right amount of time between sessions, huh?

TIM TULLY They have to be spaced out in between. The spaced training is required. There must be a rest interval in between each of those ten training sessions.

ALAN ALDA But is it true that it mustn't be too long a time?

TIM TULLY Of course. If we were to wait 24 hours between sessions, the flies would not form long-term memory, because obviously the memory from one session is completely gone before the next session and that's not going to help. And for this particular task in this fly, the optimum rest interval appears to be something like 15 minutes.

ALAN ALDA (NARRATION) So like most of us, normal flies can't cram, nor can they learn from a single experience.

TIM TULLY So is your needle sharp enough to penetrate that egg? STUDENT We shall see.

ALAN ALDA (NARRATION) But this fruit fly egg is getting something extra -- a gene called creb. Along with the creb gene, the flies also got a gene that turns their eyes red. So the creb flies -- anesthetized to keep them manageable -- can be easily identified. All flies have a creb gene. It's job is to help convert short-term memories into long-term memories. And when the red-eyed flies with the extra creb gene were tested a week later in Tim's memory machine, most of them crowded away from the shock -associated odor no matter how badly they'd been trained.

TIM TULLY For the creb-on flies, they can form a normal memory after cramming or even after one training session. So they have the functional equivalent of a photographic memory.

ALAN ALDA (NARRATION) As you'll probably not be surprised to learn by now, we too have a creb gene -- a gene that functions like a switch to turn short-term into long-term memories: the phone number you just looked up into the phone number you remember all your life.

TIM TULLY This switch works in both directions. And this is now what we think is occurring normally, not in a genetically engineered fly, but in each of us. The switch is set somewhere between fully on and fully off. Now if we can target that switch with a drug, in principle we can find drugs that set the switch more toward on, and that should facilitate the conversion of short-term to long-term memory. We can think of that as a very therapeutic treatment for those who suffer from Alzheimer's disease and perhaps even for the age associated memory loss that all of us are going to have eventually. Because what we're doing is, we're turning up the gain on how easy it is to convert short- term to long-term memory.

ALAN ALDA Yeah, but you know also, where were you for eleven years when I was trying to learn all those lines on MASH. I could have just taken one of these creb pills and I'd have been fine.

TIM TULLY Exactly. And you know, as we move from considering this kind of drug discovery from clinical applications to lifestyle issues, then even the notion that someone could use a drug like this to memorize lines is not out of the realm of possibility.

GENES FOR YOUTH

ALAN ALDA (NARRATION) This is

CYNTHIA KENYON. And these are her worms.

ALAN ALDA Is that it?

CYNTHIA KENYON There they are. There they are.

ALAN ALDA Wow! Look at them move!

CYNTHIA KENYON Aren't they pretty?

ALAN ALDA (NARRATION) If you thought studying fish and flies was an odd way to find out about ourselves, what about worms smaller than a grain of sand? But worms too may contain human secrets -- in this case, how we age.

ALAN ALDA Most of us would think, How is that possible? How could the way a worm ages be anything like the way we age?

CYNTHIA KENYON They have all the same kinds of tissues in their bodies that we have in our bodies. So for example, they have muscle cells that let them move. They have a whole nervous system that lets them go towards things they like, go away from things they don't like. They have skin. They have an intestine that looks a lot like our intestine. So at the level of individual cells and tissues, these animals are very similar to us.

ALAN ALDA (NARRATION) Normal nematode lifespan is just 2 weeks.

CYNTHIA KENYON This is a brand new adult worm. This will be maybe a college graduate -- about that old.

ALAN ALDA How old is he?

CYNTHIA KENYON He's, in worm days, he's three days old and he would be the equivalent of a twenty year old person. So he's pretty frisky, moves around, has nice muscle tone. You can see.

ALAN ALDA The worm has nice muscle tone.

CYNTHIA KENYON He does! So he's moving through his food. This is bacteria, that he's... a lawn of bacteria.

ALAN ALDA That's a nice sinuous movement. What does an old guy look like?

CYNTHIA KENYON Okay, now I'll get an old worm for you. Here's some nice old worms. Here's a pair of them.

ALAN ALDA Boy, they're just sitting out in the sun!

CYNTHIA KENYON Look at them. Look at them. There are two of them!

ALAN ALDA They're on their lawn chairs.

CYNTHIA KENYON They are -- or maybe even in the nursing home. This worm is still a little bit active but it's nothing like a young worm. And look at its body, you see this big gap here and these little pock marks? So it doesn't look young anymore. It looks very old now. And actually what I think is really interesting is that anyone in the world looking at these worms can see that they look kind of old. So in other words, there is something about the aging process that speaks to you, directly from an animal of any type.

ALAN ALDA (NARRATION) In a series of experiments that became instant classics, Cynthia has made worms that live twice as long as normal. First she gave normal worms a bath, in a rather unpleasant chemical that causes random changes -- or mutations -- in the genetic material inside the worms' cells. Next she laboriously placed thousands of single worms onto their own individual dishes. Now she could follow each worm over time, generation after generation. Most worms died or lived shorter because of their mutations. But in a few there was a single change -- a change in one gene -- that led to longer life. So now living in the incubator in Cynthia's lab is a strain of mutant worm that lives 4 weeks, rather than 2. It's astonishing to see a lively, young-looking worm that's the same age as the old folks we'd seen earlier.

ALAN ALDA Oh my God that really is...

CYNTHIA KENYON …this is a mutant worm. This is the exact same age.

ALAN ALDA The same age!

CYNTHIA KENYON It's the same age -- I'm not kidding you. Look at that. I mean it doesn't look like...

ALAN ALDA I never looked at these worms before but this looks the same. To my eye this looks the same as the three day old...

CYNTHIA KENYON Well it's a little different.

ALAN ALDA How is it different? Show me how it's different.

CYNTHIA KENYON It's a little slower. It's a little bit bigger. But you know, it is much younger in spirit than that one we just saw. That's for sure. Isn't that amazing!

ALAN ALDA It is amazing.

CYNTHIA KENYON I mean it's just unbelievable -- you change one gene and essentially you cure this disease of aging, if you want to put it that way.

ALAN ALDA I'm taking this very personally here for a minute because…

CYNTHIA KENYON Uh-oh.

ALAN ALDA …well I'd like to live to about 106 -- at least that's what I've always thought. But now I may switch. Maybe I'm too modest - maybe I should go for 140 or so.

CYNTHIA KENYON Why not?

ALAN ALDA Yeah, well that is what I want to ask you, why not? Because what I want to know is, this guy is 12 days old, he's still thriving at 12 days -- 12 out of a 14 day usual life span. He's going to go on another 2 weeks, right?

CYNTHIA KENYON Yeah.

ALAN ALDA Now, in those two weeks, how much of those two weeks will be vigorous like this? When is he going to start to act like a 100 year old, or a 110 year old person? What do you observe?

CYNTHIA KENYON I would say that in about one more week this animal will be still not looking as bad as the normal worms that I just showed you, the normal 12 day old worms. But they will be much slower. They'll be walking and not running.

ALAN ALDA (NARRATION) In other words, everything takes twice as long -- youth, middle age and old age. This really could happen with people some day, because Cynthia's rapidly figuring out how the lifespan system works.

CYNTHIA KENYON Here it is.

ALAN ALDA What is this, like a thousand times bigger than it ought to be?

CYNTHIA KENYON Even more than that I think because the normal worm you can hardly see. So this is a zillion times larger.

ALAN ALDA A zillion. Ah, I knew there was a number.

ALAN ALDA (NARRATION) In nematodes, lifespan is regulated by hormone messengers that circulate in the body and land on receptors -- like this blue mushroom.

CYNTHIA KENYON This red thing here is a cell. And the worm is actually full of many cells and this is just one of them.

ALAN ALDA Yeah.

CYNTHIA KENYON The receptor sits in the edge of the cell and its job in the animal is to receive signals from the outside and the signals that it receives are hormones. So this is a hormone…

ALAN ALDA OK.

CYNTHIA KENYON We have lots of hormones in our bodies controlling all aspects of our growth and our physiology. In the normal worm, where the hormone is bound to the receptor, the consequence is that the worms have a short life span.

ALAN ALDA (NARRATION) The mutation that extends life changes the shape of the receptor so the hormone's blocked.

CYNTHIA KENYON And so the hormone can't fit in to its normal spot -- see like that, it can't fit in there. And as the consequence, the animal lives longer.

ALAN ALDA Do you know why?

CYNTHIA KENYON We don't know all the details, but we do know that one thing that is very important are these little orange balls here. These, it turns out, we can call these fountain of youth balls.

ALAN ALDA (NARRATION) With the receptor blocked, the cell makes more youth chemical -- and that's the stuff the worm needs to live. But in normal worms with working receptors, the fountain of youth dries up.

CYNTHIA KENYON So here goes, I'm going to start shooting the laser at it. Now the way I do that is with the little foot pedal here.

ALAN ALDA (NARRATION) Cynthia has discovered a second lifespan regulation system in nematodes, this time by disrupting cells used in reproduction. She delicately knocks out the cells, using a tiny laser.

CYNTHIA KENYON I think I've killed it now, yes. Here's the cell I've been shooting at. When I started off it looked a lot like this cell with a nice dish shaped center, but now you see its gone, there's no round circle.

ALAN ALDA (NARRATION) Worms with reproductive cells destroyed also double their lifespans -- and the mechanism is just like the first system Cynthia discovered. In this case the worms no longer make a second kind of messenger hormone, again resulting in more youth chemical being made inside cells. So what happens when one worm has both lifespan systems blocked?

CYNTHIA KENYON What we found is that it lives twice again as long.

ALAN ALDA You're kidding!

CYNTHIA KENYON Yeah, it's a very amazing result. So it lives now, instead of a human living like not 90 years but 180, its like living 360 years. Do you see what I'm saying? You're doubling the doubling of the life span.

ALAN ALDA (NARRATION) It's too soon to know if an anti-aging pill for humans could one day be based on

CYNTHIA KENYON's old but sprightly worms. But she's hopeful.

ALAN ALDA Before you did this work did you have an age that you thought you might live to, and now have you changed your mind about what that age might be?

CYNTHIA KENYON Ah, yeah, I'm much more, er... Well I have to tell you, I have a retirement account. So that means that at some level I think I might have to retire at some point. So part of me is living in the real world. On the other hand, I have an imagination that I might not have to use it for a very long time. It could get really big!

BYPASS GENES ON TRIAL

ALAN ALDA (NARRATION) So far in our show about genes, we haven't seen many humans -- scientists excepted. And so far, despite the immense promise of the genetic revolution, its impact on most of us has been slight. Mall-walker

LILLIAN COOPER was an exception.

LILLIAN COOPER I started about 7 years ago, and I could walk 5 miles every morning. I don't want to be immodest, but I was a good mall walker. I was usually at the head of the group.

ALAN ALDA (NARRATION) But for the two years before we met her, Lillian had been sidelined by a badly narrowed artery in her left leg.

LILLIAN COOPER If I don't find a way to get it fixed, I'm gonna lose the leg. I've been advised of that by two doctors. And I'm not ready for that.

ALAN ALDA (NARRATION) In 1997, Lillian took part in an experiment conducted by Dr

JEFFREY ISNER to see if a gene could help save her leg. As we'll see, this form of gene therapy would later become engulfed in controversy. But for Lillian, everything went smoothly, as a dye injected through a catheter revealed the extent of the blockage in her artery.

JEFFREY ISNER This is where the problem is. It takes a long time for that dye to wind it's way all the way down to her calf muscle and foot. That's why she's having all the pain. And so the need here is to find a way to somehow deliver a significantly larger volume of blood flow down to the lower leg.

ALAN ALDA (NARRATION) Isner plans to employ a gene that make new blood vessels grow -- in effect to create a bypass around the blockage without the need for a surgeon.

JEFFREY ISNER The idea that people could grow their own bypass is an intriguing one because there is nothing like letting nature do the surgery.

ALAN ALDA (NARRATION) To deliver the gene, Isner employs a narrow balloon that will be slid into Lillian's artery to a point just above the blockage and inflated to squash the gene into the blood vessel's walls. Hundreds of millions of copies of the gene are coated onto the balloon, then dried so that they stick there. As the balloon is inflated, the hope is that at least some of the millions of genes will go to work in the cells lining her artery. Six weeks later, and Lillian at least is convinced that the genes are doing their job.

LILLIAN COOPER Yesterday I walked from the hospital down the main street - over a half a mile - and I kept going. I feel that there have to be new blood vessels forming because what else would cause this? My leg is better, my foot is better, I can walk better. Has to be that. NURSE We'll have to use that cane as kindling.

LILLIAN COOPER Ha, ha.

ALAN ALDA (NARRATION) Another test is done to measure blood flow into Lillian's leg. The result at least partially justifies her optimism. While before it took 15 seconds for blood to reach her calf, now it takes only nine. Since Lillian had her gene therapy, many others have received -- and apparently benefited -- from

JEFFREY ISNER's blood-vessel-growing gene. Isner himself had growing confidence in the technology.

JEFFREY ISNER Whenever you try something like this for the first time, you always wonder: is it science fiction, or is it going to be real therapy? A lot of things we try turn out to be science fiction, make good movies, but they don't help too many patients. I think this has the potential to be great science fiction, but now we are seeing a few indicators that suggest that it actually might be useful.

ALAN ALDA (NARRATION) Our story now jumps ahead to the fall of 1999. Again, Dr

JEFFREY ISNER is preparing to try to grow a new bypass with his gene -- this time not in a leg, but in a heart. The patient is

JOE LENNON.

ALAN ALDA Good morning.

JOE LENNON 'Morning.

ALAN ALDA I hope this isn't too intrusive. I know it's got to be intrusive to some extent. Are you a little groggy?

JOE LENNON Yes I am.

ALAN ALDA How would you describe what shape your heart is in?

JOE LENNON Well it's like a 50-pound block on me that's sitting there. You know, the pressure, the breathing is bad.

ALAN ALDA Yeah. And internally what's happening? What's going on inside your heart?

JOE LENNON Well, I've had seven angioplasties, and three bypasses, and four heart attacks.

ALAN ALDA (NARRATION) And so today, Joe is to get some genes -- millions and millions of them, injected directly into his heart. Or maybe not. Because it is also entirely possible that all Joe will be getting in his heart is a shot of salt water.

ALAN ALDA This is a double blind test, so you don't know what's going in today.

JEFFREY ISNER No we don't.

ALAN ALDA Who does know?

JEFFREY ISNER We don't know, the patient doesn't know. The only person who really knows is this young lady standing right behind us,

CYNTHIA CURRY, who's preparing the DNA, or the saline, the salt water. Cynthia, you almost ready there? OK, great, I'll be ready to go.

ALAN ALDA You have to leave?

JEFFREY ISNER Yes, we'll be ready to start.

ALAN ALDA Well, good luck with it.

JEFFREY ISNER Thank you very much.

ALAN ALDA (NARRATION) When not being filmed for Frontiers, Jeff Isner comes nowhere near this lab. It's off limits to everyone involved in the trial.

CYNTHIA CURRY I have to be very careful about what I say to the nurse coordinators and to the doctors. Just basically I have to keep my mouth shut. And I guess that's OK because I've always been good at keeping a secret.

ALAN ALDA You're part of a double blind trial, is that right?

JOE LENNON That's right.

ALAN ALDA And you don't know if you're getting the real stuff or not.

JOE LENNON True.

ALAN ALDA Is that… was that a hard decision to make?

JOE LENNON I just hope that eventually, if I don't get it this time, I'll get it the next time.

ALAN ALDA Yeah.

JOE LENNON Anything to get rid of the chest pain. I figure it's worth the risk.

ALAN ALDA (NARRATION) It's a risk several patients have taken already -- though Joe will be one of the first to be getting the injection into the inside of his heart. The earlier patients were injected through a surgical incision in their chests. Joe's injection will be via a catheter snaked into his heart from his groin, using a tiny needle that will stab into the heart's inner wall.

ALAN ALDA How do you decide exactly where to put the DNA material?

JEFFREY ISNER Yeah. So the map on the right has a red zone. And that red zone indicates an area where the heart muscle is not contracting normally. And that's we presume because there's not enough blood flow to that site.

ALAN ALDA Is it going in now, the DNA?

JEFFREY ISNER Yeah, this is going to be the first of six injections that we're going to do. If you look carefully you'll be able to see -- right about there -- the needle should come poking out. You see it? It's very thin. And now Dr Vale is going to be injecting the DNA. We don't want to be doing this too quickly because we don't want any of the solution to come squirting back at us. So we'll sort of ease it into the muscle. So now Dr Lasorda has moved the catheter to another site…

ALAN ALDA (NARRATION) It's the catheter injection method that's really on trial here today. The previous tests, in which the DNA was injected a surgical incision, had promising results. The hope is that the more benign catheter method will be as effective. The elaborate double blind trial is to make sure that it isn't simply the injection procedure itself but the DNA being injected, that's working.

JEFFREY ISNER How you doing Joe?

JOE LENNON I feel a little like a warm feeling around my heart. I don't know if that's natural or not but I do feel a little something.

ALAN ALDA (NARRATION) What none of us in the catheter lab that day knew was that the whole concept of gene therapy was about to be put on trial -- and that both doctor and patient would be caught up in the fall out. In September 1999, the news broke that a young man enrolled in a gene therapy experiment at the University of Pennsylvania had died. The case involved a different disease from

JOE LENNON's, a different gene and a very different way of putting the gene into the patient. But the Pennsylvania incident triggered a sweeping governmental review of all gene therapy experiments. While all this was going on, Joe came back for a three-month check up -- concerned much less with the potential risks of gene therapy than he was with its potential benefits.

JOE LENNON I still don't know if I got the DNA yet, but we'll see. I've felt a lot of good days, but then I'm back to where I was again. And them days I'm just, gee, it's working slow, but when the bad days come again, I don't know.

MRS LENNON We were encouraged, and we're a little disappointed that there hasn't been a big change. But there's still time, and as Joe said, even if you didn't get the DNA, you can always get it later. NURSE You're going to go right under this camera. It's going to be really close…

ALAN ALDA (NARRATION) Joe signed on for the clinical trial with the promise that -- should it turn out that he'd not received the DNA -- he'd be eligible to get it later. But as the follow up tests on Joe continued to show little or no improvement, suddenly the rules changed. In the review of all gene therapy trials conducted by the Food and Drug Administration in the wake of the Pennsylvania case, Jeff Isner came in for harsh criticism. A few weeks later, his heart trial was shut down. One year later,

JOE LENNON's condition had worsened.

JOE LENNON If I feel good during the day I try to walk and putter around doing little things, but I seem to get tired out. I get light headed, dizzy, and my heart starts to race, so it's not getting better, it's getting worse. I was upset about the trial being shut down. I figure that was my last resort, so hopefully it'll begin again.

ALAN ALDA (NARRATION) But by the summer of 2001, Jeff Isner's gene therapy trial was still on hold. And

JOE LENNON was still waiting and wondering. Did he get the gene? And if not, would he ever get his second chance? For scientists working on the human genome, this is an exciting -- even heady -- time. But for the man who did so much to start it all, enthusiasm is tempered with the reality that most of us, like

JOE LENNON, are still waiting.

JIM WATSON People say, aren't you very happy that the genome project's almost done? And I say, ah, I'm not depressed. I mean it's going good and it's great, but I'll only be truly happy if we stop cancer or stop schizophrenia. I mean,

there were two motivations for the genome… One you want to understand life and the other that you want to understand disease. And when, you know, when I started out life, science, I wanted to understand life. And you get older you realize that what…

ALAN ALDA You want to understand death too…

JIM WATSON No not death…

ALAN ALDA Or what leads to it.

JIM WATSON Yeah, you don't want to study death. You want to stay away from it!

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