

"NEVER SAY DIE"

- SHOW 1003

Episode Open

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EPISODE OPEN

ALAN ALDA: This laboratory mouse has lived much longer than normal, and it won't be long before humans can do the same. On this edition of Scientific American Frontiers, science begins to explore how we get old, and how we can avoid it.

ALAN ALDA: (Narration): We'll see how we could keep our bodies' cells young forever. We'll discover how nature governs lifespans, in worms and maybe people, too. We'll find out how to grow spare parts for aging bodies. And we'll see how eating less makes a long life, while doing more makes a happy one.

ALAN ALDA: I'm Alan Alda. Join me now for Never Say Die.

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EAT LESS - LIVE LONGER

ALAN ALDA: We may not like it, but this is where we all end up after our allotted span. This is Albertine -- she lived 62 years; Sarah -- 45 years; Joseph -- 74

years. Many different ages, but you won't find any past about 120, and the average right now is in the seventies. But what if I told you, you wouldn't have to check in here until you were 150 years old? 200? 250? Right now a lot of serious, smart Scientists are beginning to say that's what's possible. They're starting to understand the details of what makes us age, right down to the level of our DNA. It's becoming realistic to think about intervening in the aging process. Already there are astonishing results with lab animals, with some living 4 times as long as normal. In this program, we'll be meeting Scientists whose work may help us live longer -- a lot longer. And we'll also be asking what it would be like to live a lot longer -- would life be worth living? But how do we get there? How do we get to a longer life? This first way may surprise you...

ALAN ALDA: Hello... Hi Dr. Walford? Glad to meet you. How are you? I brought my lunch.

ROY WALFORD: Oh you did, great.

ALAN ALDA: (Narration): I've come to see Roy Walford, in Venice, California. For 30 years, Dr. Walford has been studying the relationship between food and long life.

ROY WALFORD: I think it would be better if it were like whole wheat bread. I would say that's two slices of white bread.

ALAN ALDA: Let's see what else I have. You probably don't like this. Sometimes I like something crunchy while I have a sandwich.

ROY WALFORD: Well pretzels are empty calories so, I don't like that.

ALAN ALDA: How about pickles?

ROY WALFORD: OK. That's all right.

ALAN ALDA: Well this is all just for taste. How do you feel about mustard?

ROY WALFORD: It doesn't add much in the way of calories unless you use a huge amount.

ALAN ALDA: (Narration): For Walford, watching calories is only one of the keys. He believes if you eat less, you'll live longer -- so long as you make sure that what you do eat has high nutritional value. I'm aiming to make a pretty lo-cal lunch -- no more than 500 calories.

ALAN ALDA: You use a lot of calories getting the pickle jar open you know.

ROY WALFORD: Yes, that's the whole point. That's your exercise.

ALAN ALDA: This is about it. This is what I could...now, now, let's see that wouldn't be enough though. I'd still be interested in more. I'd probably eat five or six of these pretzels. I would take the salt off the pretzels. I don't like to eat a lot of salt. Then I would have probably, to make myself feel better, I'd either have about four ounces frozen yogurt or ah, if I was feeling really healthy, health minded, I'd have an apple. Let's say an apple.

ROY WALFORD: Okay.

ALAN ALDA: I would give myself the benefit of the doubt.

ROY WALFORD: Okay.

ALAN ALDA: (Narration): Now let's see what kind of nutrition my lo-cal lunch delivers.

ROY WALFORD: Let's see, turkey breast-no skin, roasted is about as close, and you didn't have half a breast but maybe a quarter of a breast. You added a piece of tomato in that.

ALAN ALDA: Yeah, two little slices of tomato.

ALAN ALDA: (Narration): When you add it all up, I did fine on the calories -- but that's about all.

ROY WALFORD: What you had is deficient in A, B12, C, E, folic acid and panithinic acid. Among minerals it is deficient in calcium, copper, magnesium, manganese and zinc.

ALAN ALDA: And what's that big tall yellow one? What's that?

ROY WALFORD: Well that means it has a great deal of sodium.

ALAN ALDA: Oh, I'm doing fine with the sodium. OK.

ROY WALFORD: And you have too much cholesterol

ALAN ALDA: Where'd I get that from? The turkey?

ROY WALFORD: From the turkey probably, yeah.

ALAN ALDA: (Narration): But here's what goes into Walford's lunch. Every one of his 500 calories packs a high nutritional punch.

ALAN ALDA: How did you first get interested in this?

ROY WALFORD: I got interested in this kind of nutrition because it's been known since 1935 that if you keep animals on a very low calorie diet but one that is not deficient in vitamins and so forth, you extend their maximum lifespan and their average lifespan.

ALAN ALDA: (Narration): In the 1960's Walford, who's a

RESEARCHER at UCLA medical school, set out to refine the low-calorie studies. He confirmed that laboratory mice live up to twice the normal age if calorie intake is reduced by up to half. At the same time he detected intriguing signs of improved health -- lower blood pressure, lower insulin and cholesterol; and stronger immune systems. Then in 1991 Walford joined Biosphere 2 as the project doctor. He was part of the team which sealed itself inside a 3-acre greenhouse. The aim was to be self-supporting -- to subsist entirely on the miniature ecosystems growing inside. Things didn't turn out as expected. Food production was about 40% short, but for Walford it was a lucky accident. Like it or not, the team found itself on a low-calorie, high-nutrition diet. The team members went hungry. But in regular medical exams, Walford discovered they were developing the same good health patterns as the lab animals. Biosphere 2 confirmed for Walford that a low-calorie, high nutrition diet is likely to benefit humans, and he has been following it ever since. It sounded pretty good to me. How do you get started?

ROY WALFORD: What you wanna do is lower the calorie content so that you lose weight gradually until you're 10-20% below your set point - where your set point is defined as what you would weight normally if you ate just kind of a normal diet.

ALAN ALDA: That sounds like, ah, a lot of weight loss. I mean I'd be a bean pole without the beans, I think. I mean, that sounds severe to me.

ALAN ALDA: (Narration): These lively rhesus monkeys are on just such a severe regimen. I'm visiting Rick Weindruch at the University of Wisconsin.

ALAN ALDA: Is this for my protection, or for the monkeys'?

RICK WEINDRUCH: I think its mutual for both, yes.

ALAN ALDA: Okay.

ALAN ALDA: (Narration): Weindruch has about 80 monkeys -- half on restricted calories, half normal. The study has been running for a decade, and the animals are now 20 years old -- middle age for rhesus monkeys -- so there won't be any results on life span for a while.

ALAN ALDA: Which kind? What does he get?

RESEARCHER: This guy up above.

ALAN ALDA: (Narration): The restricted diet is exactly like Walford's. In fact Rick Weindruch was his student at UCLA.

ALAN ALDA: Here you go, pal.

ALAN ALDA: (Narration): The monkeys' calories are reduced, but their nutrition is excellent -- it's not in any way a starvation diet. So within the next few years, as old age should be approaching, the expectation is that the normally-fed group will begin to lose its health, while the calorie-restricted group will stay healthy.

RICK WEINDRUCH: We're starting to see signs of better health in our restricted animals. It's going to really be, shall we say, show time for these diets over the next five years.

ALAN ALDA: (Narration): Just like Walford's Biosphere team, the monkeys get regular checkups, although they're sedated for some procedures. This is a scan for bone mass, which tends to become reduced with age. They also examine tiny samples of muscle from the monkeys, looking for signs of cellular damage which normally develops with age.

ALAN ALDA: Is this part of a cell?

RICK WEINDRUCH: This is a component of a cell and this is the stuff that makes your muscles contract, basically.

ALAN ALDA: (Narration): This black dot in the muscle of a 4 year-old monkey is damage caused by things called free radicals. Free radicals could explain why eating less helps you stay healthier and live longer. Nutrients from the food we eat get absorbed by every cell of our body. These nutrients normally combine with oxygen to make essential energy-storing chemicals. But an unavoidable by-product is the production of free radicals -- reactive oxygen compounds that damage whatever they hit. The body makes chemicals, called anti-oxidants, which defend against free radicals. But damage still accumulates over the years, leading to all kinds of old-age diseases. The exciting thing about Weindruch's

study is that while 20-year-old monkeys on normal diets show extensive free radical damage, calorie-restricted monkeys -- who are the same age -- look like young kids.

ALAN ALDA: So this is a 17-year-old monkey with about the same amount of free radical damage as, how old a monkey?

RICK WEINDRUCH: A four-year-old.

ALAN ALDA: A 17-year-old as healthy as a 4-year-old.

ALAN ALDA: (Narration): Weindruch is also pursuing the free radical theory with a large-scale mouse study.

ALAN ALDA: So one bunch is on a restricted diet and one... ah, I'll tell you something that I see right away. These are really active and these are just sitting around.

ALAN ALDA: (Narration): These are senior-citizen mice -- about 2 years old -- and they're on a normal diet. And these are on calorie restriction. But Weindruch also has four other groups being fed normal diets plus some special extra ingredients. He's adding combinations of the anti-oxidant supplements, like vitamins C, E, and beta-carotene, that so many of us are taking now. The result so far -- not very encouraging. Anti-oxidant dietary supplements are no substitute for calorie restriction. They don't seem to affect life span one way or the other.

RICK WEINDRUCH: The best survival at this point in time is group 5 - our calorically restricted animals.

ALAN ALDA: Who aren't taking any supplements.

RICK WEINDRUCH: No, no their not.

ALAN ALDA: So, so far taking supplements, if you have a normal diet, or any kind of diet, it doesn't make you live longer, so far and you have a lot of time to go on this, but so far you are living the longest...

RICK WEINDRUCH: ...just plain old caloric restriction...

ALAN ALDA: ...with high nutrition.

RICK WEINDRUCH: Right, but again it's early so come back in a year, please.

ALAN ALDA: Yeah, yeah. Well meanwhile I'm taking the pills.

RICK WEINDRUCH: Me too!

ROY WALFORD: So Alan, I made 4 servings in the wooden bowl. This is one serving and it's about 500, 550 calories.

ALAN ALDA: This is one serving? This is a lot of food!

ROY WALFORD: That would be one serving, yes.

ALAN ALDA: And this is equal to that sandwich I made? ROY WALFORD: More or less. It's about equal in calorie content to your turkey sandwich.

ALAN ALDA: It's very good. How old do you think you're going to be, eventually?

ROY WALFORD: Well, older than I would be. I've just been on this diet for about 10 years or so, maybe a little more so, I certainly didn't start when I was young. If my destiny on a normal diet had been to live to be 90, then on the diet I should add another 15 or 20 years. So that would put me out to be 110, starting at 60.

ALAN ALDA: That's where it would put me, if I started around now. 110. See I always thought it'd be nice to live to 106. 110 is even better! This doesn't look so appetizing anymore. I got plenty of crunch. I didn't need the pretzels. And this wouldn't be bad for dessert, or am I denied dessert now?

ROY WALFORD: No, that would be fine. Sure. An apple is good dessert.

ALAN ALDA: Your heart would sink if I took out the frozen yogurt probably.

ROY WALFORD: Well no, yours would.

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THE CLOCK OF LIFE

ALAN ALDA: (Narration): From infancy to oblivion - it's the natural and mysterious trajectory of our lives, and it's been that way for the several 100,000 years we've been on this Earth. Now suddenly we've begun to glimpse nature's

machinery of aging inside our cells. Throughout life, cells constantly rejuvenate, through division, to keep our bodies healthy. In the sixties it was discovered there's a lifetime limit of about 50 divisions - and then cells die or start causing trouble. But what if we could avoid this limit and let cells divide forever? That's the extraordinary idea we'll explore in this story. We start with a highly magnified picture of human chromosomes -- the structures inside cells made of DNA. On the ends of each chromosome are things called telomeres -- highlighted here with a special dye. In the 1980s it was discovered that telomeres get shorter every time a cell divides, until the telomeres disappear almost entirely. I'm visiting Geron Corporation, a small biotech company in Menlo Park, California. Their chief Scientist, Cal Harley, is the man who made this discovery about telomeres.

CAL HARLEY: The little plastic tip at the end of a shoe lace is like the telomere. It functions to sort of protect the end of the chromosome or in this case the end of the shoelace from fraying and not being able to function.

ALAN ALDA: It seems to me that this thing that's acting like a telomere would be useful for eliminating or holding off fraying. For a long time it can get very, very, very short and it will still do the job. Is the telomere like that?

CAL HARLEY: There is actually a critical point when the telomere gets down to maybe less than 5% of its length at birth where at that point there is a very strong signal that this cell is in danger because there is some damaged DNA now being exposed.

ALAN ALDA: (Narration): Cal found that cells stop dividing when telomeres run out. They're like the clock of life. Another breakthrough came when Geron located the exact section of DNA -- or the gene -- that governs the manufacture of telomeres in cells. It's called the telomerase gene. At a Boston hospital, Ronald Depinho is working with this gene to explore what happens when telomeres finally run out.

RONALD DEPINHO: Let's take a look.

ALAN ALDA: (Narration): They've bred a special strain of mouse which has no telomerase gene. Because mice normally have much longer telomeres than people, it has taken a few generations of the lab mice to get down to short telomeres. Now it's getting interesting.

RONALD DEPINHO: What we see are some obvious external manifestations of short telomeres. We have a normal mouse here with a quite normal looking coat color that has a nice black sheen to it. And this is a mouse of equivalent age that has short telomeres. And what we see are some obvious hair graying compared to the normal coat color of this mouse here -- short telomeres, normal telomeres.

And still others have the additional problems where they have accelerated hair loss.

ALAN ALDA: (Narration): Since hair never stops growing, hair cells would be among the first whose telomere clock runs out. This is some of the first solid evidence that telomeres can affect at least the symptoms of aging. For the first time we can shed some light on the tragic disease of progeria -- premature aging. These are children, all under 12 years old, attending an annual get-together of the 40 or so progeria kids in the world.

MICHAEL FOSSEL: Bonjour. Ca va?

ALAN ALDA: (Narration): Pediatrician Michael Fossel studies the disease.

MICHAEL FOSSEL: These kids are born old. They have normal childhood minds. They're bright. They're funny. They're typical of any other child, but they also get angina, and they also get heart attacks in the playground and they get arthritis. They have old skin. They don't move well. They're shrimpy, you know. But otherwise they're normal kids.

ALAN ALDA: (Narration): Progeria kids have the diseases of old age, and we now know they have something else -- short telomeres. Short telomeres mean cells can't divide and repair damage, so disease starts. Now at least the door is open to a genetic cure for these kids. You can get an idea how such a cure might work back at Geron. Cal Harley showed me under the microscope what human eye cells look like when they're young, healthy and still able to divide.

MICHAEL FOSSEL: So Alan, here's an example of a young cell within that population that is going through the process of division.

ALAN ALDA: (Narration): These are the cells dividing, using up their telomeres. Now take a look at old cells, with no telomeres left. They're literally bloated -- they've lost their youthful lines. Abnormal cells like these cause the symptoms of old age - cataracts, gray hair, wrinkled skin, arthritis, even cancer.

ALAN ALDA: What if you took telomerase and got it in there, could you built up the ends, the tips of the shoe laces?

CAL HARLEY: That's the million dollar question, is can we prevent this process from happening or in part, reverse it?

ALAN ALDA: (Narration): Cal invited me to answer the million dollar question for myself. Using the normal procedures of the genetic engineering lab, I set about

inserting the telomerase gene into old human eye cells. This is an experiment first done at Geron just 18 months earlier.

CAL HARLEY: I'll just take that one for you

ALAN ALDA: See when I had chemistry, I didn't have a personal coach like this. I would have done much better.

ALAN ALDA (Narration): The final step is to force the new genes into the old cells with a Frankenstein-like electric shock. And... bingo! It works. You get new, youthful cells.

ALAN ALDA: I'm kind of surprised at how vivid this is.

CAL HARLEY: Yeah. The first time we saw it, we were very much surprised. Even though this is what we were predicting and hoping for, the impact of this is dramatic. Some of these cells have been going now for 300 doublings, where the normal cells age at 50.

ALAN ALDA: They are still ready for more.

CAL HARLEY: Yeah. We sometimes call them immortal, but a more accurate term would be indefinite division capacity.

ALAN ALDA: So if this were happening, let's say, in the skin on my face...

CAL HARLEY: What do you mean?

ALAN ALDA: You have to understand I'm an actor, during most of the week. So if this is happening to the skin on my face, the bags under my eyes would tend to go away by themselves, apparently.

ALAN ALDA (Narration): Right now we don't know the answer to my question. We can rejuvenate cells in a dish, but that's not the same as repairing tissue damage on a large scale. Here at UCLA, Rita Effros is working on one of the first applications of large scale cell repair. The goal is to rejuvenate the cells of the body's immune system, in the same way I did at Geron with eye cells, by adding the telomerase gene. If old folks had young and vigorous immune systems, they'd obviously be able to fight off diseases more effectively.

RITA EFFROS: What we're hoping to do is extend the life of elderly people to the maximum limit that we now know is the human limit, which is approximately 120 years. So we're hoping that a person who is 100 or 105 would respond better to an infection, and therefore not die from that infection and continue living.

ALAN ALDA: (Narration): This work is now looking very promising. For example, this is the response of a rejuvenated immune system to a virus. The dark patches are dense swarms of immune cells attacking the intruder. Compare that to the weak response of a normal 80-year-old's immune system. Sometime in the next few years, getting an immune system boost could become routine for people over say 60. Many more people might conquer disease and reach the 120-year limit. But can we go further?

ALAN ALDA: Will we be able to live 150 or 200 years? Is that possible?

CAL HARLEY: There is no reason why genetically we can't have a lifespan that could be 100, 200, 300 years. There is just no theoretical reason that that is impossible.

ALAN ALDA: (Narration): To double or triple human lifespan is an astonishing idea -- but don't dismiss it before you see our next story.

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WISDOM OF THE WORMS

ALAN ALDA: (Narration): This is Cynthia Kenyon, a biologist at the University of California, San Francisco.

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): Cynthia's crazy about nematodes -- tiny worms, smaller than a grain of sand, that live in soil just about everywhere. She's figuring out how nematodes age, and she's pretty sure humans work the same way.

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.

ALAN ALDA: Why would nature arrange it that way if it's going to lead to an early death? Is there some advantage to this nematode, this individual nematode, dying in two weeks instead of what you can arrange -- four weeks?

CYNTHIA KENYON: We don't know. We don't know why the worm has its own Grim Reaper inside of it. This is essentially the Grim Reaper - it's cutting the life span short of the worm. We don't know why that is. Evolution must have selected for it and I don't really know why.

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 likely that all living things use these same hormone messengers to regulate life span. The fascinating thing is that the hormones are related to insulin, which is made by the body when we eat food. So maybe that's why restricting calorie intake lengthens life. Something like a long life pill could be possible, once we fully understand these systems. And some day we surely will, thanks to Cynthia Kenyon.

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!

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HOW TO MAKE A NOSE

ALAN ALDA (Narration): It has never been hard to put together body parts -- in the movies.

MAD SCIENTIST: It's alive. It's alive. It's alive. It's alive. It's alive.

ALAN ALDA (Narration): But Hollywood better look out because MIT scientists are getting in on the act.

ALAN ALDA: Does he have the nose?

BOB LANGER: Yeah, its coming.

ALAN ALDA: You got it? That's the nose?

RESEARCHER: It's right in the dish here.

ALAN ALDA (Narration): OK now, we are not, repeat not, on a movie set.

ALAN ALDA: Wait, what is this?

RESEARCHER: This is cartilage. It is a scaffold of...

BOB LANGER: You see the nostrils?

ALAN ALDA: Yuck! Wait a minute! Look, with nostrils and everything...

BOB LANGER: We made a scaffold and there's the little nostrils there -- and that's pure cartilage.

ALAN ALDA: You could make it in big blocks and carve whatever shape you want.

RESEARCHER: Exactly, exactly, that's the whole idea.

ALAN ALDA: Would you mind taking this back. I really don't wanna...I mean it's alive, it's sort of alive.

BOB LANGER: Yeah, sort of alive. We just wanted to give you a flavor for it.

ALAN ALDA: Unbelievable! You bring in a nose! I can't get over that

ALAN ALDA (Narration): In this MIT lab they're actually figuring out how to make body parts.

RESEARCHER: First we make what we call a polymer scaffold, and that's a piece of synthetic material that we can make into the form of a sheet, or other three dimensional forms.

ALAN ALDA (Narration): Now we're making heart muscle, starting with little clumps of synthetic fibers -- the polymer scaffold, as they call it. Then the scaffold is bathed in living heart cells. Bob Langer has pioneered this new field of tissue engineering.

BOB LANGER: She's trying to mimic, outside the body, what actually happens inside the body. She's giving it the kind of food it needs, the kind of structure it needs, and even the kind of mixing, you know, that it may get inside the body.

ALAN ALDA: (Narration): If you get the conditions just right, you can grow pieces of living heart tissue.

ALAN ALDA: I'm looking at something that's making heart. Does that sort of strike you, every once in a while, that you're making these things that used to be that if you lost it, that would be the end.

BOB LANGER: Well that is what we want to do, you know. It does strike us. What we hope is that some day we'll be able to have a whole series of replacement parts for people so that if they find a problem, we'll be able to help them.

ALAN ALDA: It's like an auto part shop, you know. I need a new carburetor and you just go in and you drive out again. I mean, this is... how many years away are we from having a part shop for bodies, I mean where you can really just get what you need. Is it ten years? Fifty years? A hundred years? Must be hard to guess.

BOB LANGER: Right I think it may depend on the part, you know. Some of the easier parts like skin or cartilage, I think you know that's probably five or ten years. Some of the harder parts like heart, that may be many, many years away, fifty or, you know, it's hard to know.

ALAN ALDA (Narration): Here, after about two weeks of growth, are the pieces of new heart.

ALAN ALDA: They're under a microscope and then you can see it on that monitor?

BOB LANGER: That's right, we have a microscope here and then basically they're on the monitor and you can see them beating

ALAN ALDA: That's not the dish shaking, those are separate cells beating.

BOB LANGER: Right. Say, take a look right down here, for example, or here. And these are individual heart muscle cells, and they're just beating.

ALAN ALDA: Is there any way you could make use of that right now, in a heart?

BOB LANGER: It's too early to do that now, but some day what I expect is that we could make a sheet of this, you know, and make cardiac muscle. And some

day, if we have the right type of cells to actually transplant that onto a patient. You know if they have, er, if some of their heart muscle's damaged.

ALAN ALDA (Narration): Right now they're working with animal cells, but Bob Langer's hope is not at all far-fetched. Take a look at one of those pieces of heart as they give it an EKG, like a regular heart checkup you might get from your doctor. The new tissue transmits heart beats exactly as it should. With tissue engineering advancing rapidly, the search is on for a reliable source of human cells to grow parts from. I'm visiting Michael West at his company, Advanced Cell Technology. He's aiming to make any kind of cell required -- heart, liver, skin, you name it -- starting from the kind of cell we all came from. They're called stem cells. Stem cells are the first cells that grow as an embryo develops. All body parts are derived from them, so the idea is to grow human stem cells, inside cow eggs.

ALAN ALDA: Go straight in?

SCIENTIST: Yeah straight in.

ALAN ALDA (Narration): The technique is just like the one used to clone Dolly the sheep. First I have to pierce the cow egg and suck out the nucleus, containing the cow's genetic material.

SCIENTIST: There's a syringe next to your hand now. Turn it.

ALAN ALDA: There it is. Here it comes. Watch this, watch this guys. This is good. This is good. Have I got it?

SCIENTIST: Go back a little bit more

ALAN ALDA: OK. Got it. Got it.

SCIENTIST: Perfect. Right there is perfect.

ALAN ALDA (Narration): Next I pick up a human cell -- this one's a skin cell. Now I slide the human cell into the cow egg. This is startling research -- producing human cells inside animal eggs is an unprecedented idea.

ALAN ALDA: It's amazing that you can get these human cells to grow inside the cow egg. It's amazing to me. Why don't you use a human egg to do this?

MICHAEL WEST: This is potentially a technology that could be used to treat upwards of half of all healthcare problems. You'd make beta cells for diabetes, or cartilage cells for arthritis, and so on. There's literally millions of people that

would need the technology, and so you'd need millions of human egg cells. And they're simply not available.

ALAN ALDA (Narration): At the end there's a little electric shock, which stimulates the human nucleus to start dividing inside the shelter of the cow egg. And the human stem cells multiply. The next step has to be signaling the stem cells to make particular cells, like heart or cartilage. Scientists are beginning to do that, but isn't this all a bit scary?

ALAN ALDA: Is there anything in the cow egg that makes... that gives a cow any of its characteristics that could get into the human cells, or mix with them in some way, so that you'd wind up with some cow characteristics of any kind, with human characteristics in these cells? Do you know that can't happen?

MICHAEL WEST: There's the possibility that the mitochondria could live on. They're little what we call organelles within the egg.

ALAN ALDA: Yeah. That's what we get the energy from.

MICHAEL WEST: Yes. Little batteries. They have their own DNA. But all of our information that we have in our hands today would suggest that those cannot survive, so that the cow mitochondria will die, and that the human mitochondria then will live on. And so, our belief is that the cells eventually will become entirely human.

ALAN ALDA (Narration): Fully expecting that one day engineered human cells and body parts will be available,

JAY VACANTI: a pediatric transplant surgeon at Mass General in Boston, is developing medical technologies to use the new materials. They're working, for example, on a way to implant replacement cells in a damaged heart, using a special gel.

JAY VACANTI: It's an interesting plastic material that turns into, on specific signaling, it'll turn into something that sort of feels like jello

ALAN ALDA: So it starts out one way, and then it turns into jello?

JAY VACANTI: Exactly.

ALAN ALDA: Is there something about this gel that's allowing you to do something that you never did before?

JAY VACANTI: Yes, the reason we use a gel is because it allows the cells to align very closely to one another and talk to each other. And once they can start talking to each other, they actually then start forming new tissue.

ALAN ALDA (Narration): Right now they're using the gel to implant new mouse heart cells, under the same conditions they'd use for people.

JAY VACANTI: So here what we're going to do is actually take this preparation that we've made and put it in the heart muscle.

ALAN ALDA: So you want to see if you can get these cells that you're injecting to actually merge with the existing heart cells? J

AY VACANTI: Exactly right.

ALAN ALDA (Narration): This is the kind of technique that Dr. Vacanti hopes will eventually relieve the widespread and tragic shortage of transplant organs that exists right now. So far it's looking promising,

ALAN ALDA: Now is this an intestine that you've allowed to grow in here?

JAY VACANTI: Yeah, actually what we're gonna see here is a piece of new intestine that's been tissue engineered, and has been back in the animal now for three weeks.

ALAN ALDA (Narration): Replacement intestine, liver, cartilage, heart valves, even heart muscle. One day we're going to have spare parts grown just for you, starting with your own stem cells, so there'll be no rejection problems. And no doubt as a result, we're going to live longer.

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USE IT OR LOSE IT

ALAN ALDA: Now you walk like this every day?

ALAN ALDA (Narration): Our final segment is about how to be successful at being old. Before long, many of us really could find ourselves living to 150, 200, who knows? But can we get there without losing our mental abilities, so that we can enjoy our longer lives?

TOMMY RAWSON:, Harvard's boxing coach, is not quite there yet - he's 92. But what a 92.

TOMMY RAWSON: And this is what they have to do. One, two. One, two, bom.

ALAN ALDA (Narration): Throughout his life, boxing has always kept Tommy on his toes.

TOMMY RAWSON: You get something in your mind. You want to take and try to hit a man with a left hook. And if he's got a good guard, keeps his hands up, then you don't use that. Then you got to take and try the right hand.

ALAN ALDA: The combination of your mind working quickly and your hands and feet working quickly. That's. Most people don't do that. They don't coordinate those things the way you do.

TOMMY RAWSON: That's what you have to do to be successful, I'd say. The feet have to be working with the hands.

ALAN ALDA (Narration): As we'll see, keeping active is the key to keeping the mind going strong.

TOMMY RAWSON: One, two, three.

MARYLIN ALBERT: Just look and try to remember.

ALAN ALDA (Narration): Mass General psychologist, Marilyn Albert, has been investigating what happens to people's thinking abilities as they get older.

ALAN ALDA: Get up on here?

ALAN ALDA (Narration): One of the most common problems in the elderly is memory loss - and lately Marilyn's group has been looking for changes in the brain which might account for this loss. They're testing people of different ages, and today it's my turn. A slide projector will beam photographs onto a screen that I have to watch, while I'm inside an MRI machine. As I stare at the pictures and try to form a memory of them, the machine will detect which areas of the brain I'm using. While I'm presented with these pictures, cross-section/..../images of my brain instantly show up in the control room. The light areas correspond to brain tissue, and dark areas to fluid surrounding the brain.

ALAN ALDA: How is my brain?

MARYLIN ALBERT: Actually it looks very young.

ALAN ALDA: Yes? What could you see?

MARYLIN ALBERT: We were admiring it.

ALAN ALDA: Yeah, what could you see?

MARYLIN ALBERT: We could see that there isn't too much fluid. As you get older, the brain tends to shrink a little bit and gets a little bit more fluid, and yours looks very tightly packed.

ALAN ALDA (Narration): Now we'll compare my brain to those of other subjects. On average, Marilyn finds that people in their 20s and 30s show intense activity right here, while they're forming a memory of a picture. In contrast, people in their 80s tend not to have that activity. I was happy to see that my brain activity still looks pretty young.

ALAN ALDA: Now what is that activity, what is that associated with?

MARYLIN ALBERT: We think the neurons are firing. We're measuring the activity of nerve cells in the brain.

ALAN ALDA: What does that mean? Does that mean that older people have a harder time actually registering what they're trying to remember? It's not just that they don't recall something. They haven't got it in there in the first place?

MARYLIN ALBERT: That's right. We think what happens as you get older is that it takes you longer to learn something new. If you work hard and you remember it, and you learn it really well, you remember it as well as somebody much, much younger than yourself.

ALAN ALDA (Narration): Hard work seems to be the key to all kinds of mental activity in old age, not just memory, as Marilyn found out in a large study she helped organize.

RESEARCHER: Hi, Mrs. Ryan. How are you?

MRS. RYAN: Good, dear.

RESEARCHER: I'm Jennifer.

ALAN ALDA (Narration): The 10-year study followed 1200 people as they made the transition from middle to old age. Every two years, participants got a battery

of tests - like this memory challenge, where the object is to pick out the chip that has just been placed on the board. The study tried to identify factors which might explain why people like Mrs. Ryan remain sharp even in their 80s, while others decline.

RESEARCHER: Great. How often do you read books, magazines or newspapers? Do you do that 3 or more times a week? Once to twice a week?

MRS. RYAN: Three or more.

RESEARCHER: Three or more times. Do you do arts, crafts or other hobbies?

MRS. RYAN: Knitting

ALAN ALDA (Narration): They looked at thinking activity, and physical activity.

RESEARCHER: And how many city blocks or their equivalent do you walk each day?

MRS. RYAN: Oh, about 30 I guess. Because I walk three hours every day.

RESEARCHER: Ready, stand.

ALAN ALDA (Narration): The results were unequivocal. If you maintain good physical health, get moderate exercise and keep your brain reasonably stimulated, you can stay mentally sharp. If you don't do those things, you go down hill.

RESEARCHER: ...five. Great.

ALAN ALDA (Narration): Bill Greenough, at the University of Illinois, has done a landmark experiment with rats which reveals what mental and physical stimulation actually does for the brain. Aging animals were let loose for one hour a day in a rat wonderland. The toys were changed daily so every day, when the rats explored, they got not just a physical workout, but an opportunity to learn something new, as well. When compared to the brains of elderly, unstimulated rats, the stimulated ones had much denser neuron fibers, without the dying off usually seen in older animals. And all these light shapes showed the stimulated rats also had many more blood vessels nourishing their brains. In effect, the stimulated elderly rats had brains that looked young.

BILL GREENOUGH: We used to believe that the brain developed, then it got done developing and the brain was stable, and then eventually the brain began to get old and declined and would deteriorate. We've found really that both those

things are wrong. If the brain is constantly challenged - both mentally in terms of demanding problem solving tasks, and physically in terms of physical exercise, then that brain seems to remain remarkably stable. Not to show very much in the way of the kind of declines that we often thought of as inevitable.

ALAN ALDA (Narration): The lives of real people back up this idea. Take Catherine McCaig. Throughout her 103 years, she's been reading, dancing, learning languages -- and making jokes.

ALAN ALDA: How long have you been playing piano?

CATHERINE McCAIG: I've never played the piano.

ALAN ALDA: How long have you been sitting at one of these and working on it?

CATHERINE McCAIG: A hundred years.

ALAN ALDA: A hundred years? You started when you were...

CATHERINE McCAIG: And I still can't play.

ALAN ALDA: Did you drive a car?

CATHERINE McCAIG: I did.

ALAN ALDA: When did you start driving a car?

CATHERINE McCAIG: 79.

ALAN ALDA: The age of 79. And how long did you drive?

CATHERINE McCAIG: Ten years.

ALAN ALDA: Ten years. CATHERINE McCAIG: Yeah. And when I finished driving, as I say, after going through the plate glass window.

ALAN ALDA: Tell me about that.

CATHERINE McCAIG: Have I got to?

ALAN ALDA: If you don't mind... What kind of a building was this?

CATHERINE McCAIG: Pardon?

ALAN ALDA: What kind of a building was it that you went into?

CATHERINE McCAIG: The bank.

ALAN ALDA: The bank?

CATHERINE McCAIG: Yes, and they thought it was an explosion.

ALAN ALDA: I can imagine.

CATHERINE McCAIG: They ran for their lives.

ALAN ALDA: So, you invented the drive-through window.

MARILYN ALBERT: So now we know that the old saying "use it or lose it" really is true.

ALAN ALDA: And it's like literally true. Your brain starts to go away if you don't use it every day. And every day is important.

MARILYN ALBERT: I think so.

ALAN ALDA: You can't go away for a renaissance weekend once a year. It's got to be every day.

MARILYN ALBERT: Yes. And it's the things you do day to day. Not complicated, you know, unusual things, but to make it part of your life.

ALAN ALDA (Narration): Nobody knows what would actually happen to the brains of people who lived until 150 or 200 -- because nobody has yet lived that long. But so far, there doesn't seem to be any limit. As long as we keep stimulating our brains with challenging hobbies and jobs, and remain physically active, we can probably retain our mental capabilities, no matter how old we get. We've seen in this program that science is closing in on the secrets of aging. For the first time in human history, we may be able to deliberately extend our lifespans. Maybe we'll do it by restricting our calorie intake... Or by renewing the telomeres that limit how many times our cells can divide... By manipulating the genes which govern lifespan... Or by growing spare parts for our bodies. However we do it, it looks like it's really going to happen- and soon too.

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