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# Biomarkers of Aging: Do They Hold the Key in the Search for the Fountain of Youth?

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**KONDRACE**: Thanks very much. Our guests are David Harrison, who is a senior staff scientist at the Jackson Laboratory at Bar Harbor, Maine, and Rod Bronson, who is a pathologist in the Rodent HistoPathology Core at the Dana Farber Cancer Center at Harvard.

The basic question today is whether there is a way of tracking aging. That is to say, whether we can find a marker that will predict how long an organism is going to stay alive. This leads to the question, are there one or two processes of aging that we can put our finger on and watch over time? and will this have some predictive capacity?

That's the subject of today's debate, and it gets into the question of whether one is optimistic or pessimistic, and whether we'll ever get to the bottom of what aging really is.

So I'm going to let David Harrison, who is the optimist, start off with five minutes, and then Rod Bronson will answer back. Then we'll have an exchange. We welcome audience participation. Just write your question down on a piece of paper or e-mail it in, and we will be glad to put it to the guests.

Go ahead.

**HARRISON**: OK. I'm Dave Harrison from Bar Harbor. Thank you, Mort.

The purpose of the discussion here is to focus on biomarkers. Now, the information I was sent suggests that there are people who feel the NIA initiative on biomarkers was a failure. I find that hard to believe because the fact is that they did a lot of good, solid, basic research through that initiative.

The fact is, we do not have biomarkers that accurately predict life span in any creatures, except, of course, for measuring disease when we know that you are going to die soon.

What we would like to find are measures of different biological systems whereby measuring these changes and the rates of change in these systems with age, we can get an idea of the underlying processes and mechanisms that are aging, and get an idea to simplify things—whether your aging clock is running faster or slower. We could use that to not so much predict life span, although that would be the first step, but to actually evaluate treatments that are supposed to do something about aging—either retard the rate of aging, or possibly even reverse it for some types of systems.

We haven't been successful in that, but it's a big order and it is a serious question as to whether we will be successful in it.

In order to make the measurements, initially one has to make measurements that don't kill the animals, because in order to study the types of biomarkers that have a possibility of predicting life expectancy, in a mouse, say, we obviously have to keep the mouse alive. In fact, we can't even hurt it. We can't even stress it. We can't even annoy it. We want our mice to be happy and healthy and enjoy having the measurements made.

That puts some limitations on the kinds of measurements that we can make. By making a wide range of measurements we can get a pretty good idea of how systems, like the immune system, extra-cellular macromolecules, wound healing, kidney function, liver function, and to some extent the brain, function, and we can measure a lot of important things.

Brain function, in terms of intellectual function, is hard to measure in mice because their level of intellectual function is so different from ours. But we can measure a lot of important things, and we can follow whether or not specific treatments have beneficial effects on those different biological systems.

That has, I think, a reasonable importance all by itself, even if we don't get to the basic mechanisms of aging. I suspect, Rod or Mort, I don't think there is going to be any disagreement in that we should measure things, and we should try to find treatments that retard or reverse deleterious changes with age.

In some ways, that's what I see as the fundamental use of biomarkers. The more fundamental question is, can we use biomarkers? Can we use total maximum life spans? Can we use species comparisons in order to get at basic clocks underlying all the different changes in the physiological systems and in the pathology resulting, so that we can actually retard, or even reverse, some aspects of aging and increase the healthy period of life span for people?

But first of all, it will have to be for mice.

**KONDRACKE**: So far, in mouse research, do we have some predictive markers or semi-predictive markers, or what?

**HARRISON**: We have markers that predict what's going to happen for a population. We don't have markers that predict what's going to happen for an individual.

So, for example, food restriction starting very early in life, and very, very severe food restriction, retards a wide range of aging markers and increases maximum life span.

Dwarf mutations affect the function of the anterior pituitary, so about half the things the pituitary does don't get done and there are little tiny creatures. Those animals have about the same beneficial effects, in terms of life span, as food restriction. Other less severe conditions also have some beneficial effects on maximum life span.

In every one of those cases we have a whole bunch of measures that actually will show that food-restricted animals or dwarf animals or animals with little mutation are aging more slowly. Those are interesting. It's also interesting to ask which ones are consistent with the predictions of the increased maximum life spans and which ones are not.

But within those populations, to have a real predictor —it’s not enough to go between these groups because there’s a lot of things that happen when you have one of these important mutations, when you have food restriction. Those animals are different in a lot of ways.

So we don’t know which of the many ways that we are measuring are actually the ones that are important in causing them to be healthier as they get older.

**KONDRACKE**: Before we began this, I said if you have to be calorie restricted and you have a mutant gene, and which makes you sterile, the question is whether longevity is worth having!

*(Laughter)*

—at least in mice. OK, Rod Bronson.

**BRONSON**: OK. I think that people expect about six things of biomarkers. First of all, it is assumed that whatever change there is, it is going to be linear. So if something changes from the age of twenty to thirty, the same order of change will happen from thirty to forty, and from forty to fifty.

So you can measure any time you want. You can do a five-year study from twenty to twenty-five, or from fifty-five to sixty, and you will be measuring the same thing because the change is linear.

Well, I think that isn’t right, because I don’t think that aging is linear. I would argue that not much important changes up until about the age of forty in people, and nothing much important changes in mice up until they are about fifteen months.

After the age of forty, that’s when everything starts to go to hell, right? You go gray. You become deaf for high tones. Your pulmonary function decreases. Women go through menopause. That’s when cancer starts up. Don’t worry about cancer before age forty. It’s very rare. After forty, the risk goes up exponentially.

So aging is not linear. Therefore, biomarkers are not going to be linear.

Secondly, following that, biomarkers are supposed to sensitive for the short term, as I said. So you are supposed to be able to do a study for five years. You take one group, put them on the fountain of youth extract, and you take the other group and put them on something else, and you run the study for five years, and you get your results. No. In people, aging doesn’t happen over a five-year period. It probably happens over ten-year periods, maybe twenty-year periods. So if you are going to create some sort of aging intervention drug or something, you are going to have to run the study for probably ten years, not three or four years. So they are not sensitive in the short term.

Now, it’s always assumed that biomarkers are going to be somehow universal, so if you find a biomarker in mice, it will be the same as in rats, same as in cats, dogs, humans, and elephants. I don't think that's true at all. I think that rats and mice age in very different ways.

If you look at their diseases, they are entirely different. For that matter, if you look at the diseases, even within inbred strains of mice, they are quite different. Then you go from mice to cats and there are big changes. If you go from dogs to cats, there are also big differences. If you go from any of those species to people—big differences. So the assumption that you can extrapolate from mice to rats probably isn't true. The idea that you can extrapolate from rats or mice to people may not be true either.

So we may learn nothing about biomarkers. Even if we did find a wonderful biomarker or a series of biomarkers in mice, you still wouldn't know for sure whether they are going to work in people. You still have to do a ten-year study in people looking at the same biomarkers. You are still going to be stuck with a very long study.

Now, there's the assumption that because aging runs by some kind of a clock, or maybe a series of clocks, that all biomarkers are going to go in the same direction and at the same rate. Well, I don't think that's true. If you count gray hairs, the increase in gray hairs such that fifty percent of the people have fifty percent gray hairs by fifty years of age. OK. But the increase in grayness is not necessarily going to be linked at all to bunions. Bunions are also an age-related trait, you know. Young people don't have bunions. You get bunions when you are old. And so on and so forth. So I don't think the biomarkers are going to be linked.

Cancer isn't linked to osteoporosis. Asthma, age-onset asthma, which I happen to have, is not linked to prostate cancer. They are not linked. So therefore, biomarkers shouldn't necessarily be considered to be linked, either. I don't believe they are linked.

As for the non-invasive thing, if you can't be invasive, you are really limited at what you can look at. You can look at body fluids, but not spinal fluid, because no one is going to sign up to get a spinal tap. So it has to be blood. It has to be a limited number of cells. It is unlikely that people will sign up to get a skin biopsy. So if you are going to be noninvasive, you are going to be in big trouble.

Now, in the biomarker study that I was involved in where we studied rats and mice, most everything anybody did was invasive, because you have to be invasive to find inborn changes in cells and so forth. So I don't think we are going to find much unless we can accept a lot of invasiveness.

Then there's the predictive thing. It cannot be true. The ability of the kidney to concentrate urine is well known. Say, for example, you put the person or the mouse on a twenty-four-hour period where they don't drink anything, or a twelve-hour period, and then you collect urine and you look at the specific gravity. A young person will concentrate urine and will be producing very little urine. As you get older, you can't help yourself by dumping urine, because you can't concentrate urine.

Urine concentrating ability can have nothing to do with pulmonary capacity. As you get older, your pulmonary capacity goes down. Your urine concentrating ability can have nothing to do with pulmonary capacity. Your ability to remember ten words, ten minutes later, goes from very good to really bad when you get old. That ability can have nothing to do with pulmonary capacity.

The development of osteoarthritis, which we all get—here it is—there's a little bit of osteoarthritis right there! Here's another little bit right there, right? Everybody gets it. That can have nothing to do with prostate cancer. Nothing. Zero.

So predictiveness is, I think, impossible, unless you are talking about a biomarker of disease. So, sure, cholesterol levels have pretty good, but not too good, predictive value to determine whether you are going to die of heart attack or stroke or something. Even with that example though, there are a lot of people running around with high cholesterol and they never get any disease in their blood vessels. There are other people with low cholesterol who get heart attacks. So even there the predictive value isn't too great. But I am not going to deny that there are disease markers that are predictive for that particular disease, but a biomarker for pulmonary function can have nothing to do with what's going to happen in terms of your brain function or in terms of whether you will get Alzheimer's disease or cancer.

So I don't think that there is any hope of ever finding any useful biomarker.

**KONDRACKE**: Well, you said that—

**BRONSON**: Except on a population basis.

**KONDRACKE**: But gray hairs can have nothing to do with bunions; and urine concentration can have nothing to do with pulmonary function. But are you saying that it is utterly impossible that there could be some sort of common process that goes on where all of these things have various consequences?

In other words, it is some sort of cell breakdown—telomere length or some process that is inherent in genes—that makes you susceptible to disease, slows you down, grays your hair, all of these kinds of things? Are you saying that we will never find one thing or ten things maybe, but there will be an infinite number of things?

**BRONSON**: Well, that's the basis of the debate here. It actually isn't just about biomarkers. It's about one's view of aging or the theory of aging, which we can come to.

**KONDRACKE**: No, let's go right there right now.

**BRONSON**: Hmm?

**KONDRACKE**: Go ahead.

**BRONSON**: OK. So there's no question that there are biomarkers of aging. I don't deny it. The test is—look around the room. I can tell that in that corner over there, all those people are young. I never asked them their age.

Now, I don't want to point to anybody else and say that they are, should we say, not young. But it's a piece of cake. Obviously, we all age. For most people, just showing them a picture or having them look around the room, they could peg anybody to within plus or minus ten years. So sure, there are biomarkers.

But are they predictive of anything? Where do they come from? Where does aging come from? That's the real question. Why is it that mice get cancer beginning at about fifteen to eighteen months? People begin to get cancer somewhere between forty and fifty years. What's the difference? How come people live so much longer and how come their biomarkers are delayed compared to mice?

By the way, mice get lots of kinds of cancer. They also get osteoarthritis, and they get all kinds of nasty things, and they always die. They die somewhere between two and two-and-a-half years, depending on the genotype. Same thing with rats. Why is that? Well, you have to go back to this wonderful statement, which nobody understands, but it's the key to the whole thing.

**KONDRACKE**: It comes from where?

**BRONSON**: I believe Williams was the one who first said it, and he said that the force of natural selection declines with increasing age. Now, what does that mean? It says that here you are—you're a mouse. You're a studly young guy. You've been producing a bunch of babies and you've been passing on your genes. And you're only, let's say, three months old. So you go out tonight to forage and an owl gets you.

Now, let's say that you are another mouse, and you are nine months old. You go out. You have the same chance as the young mouse of being killed by that hawk or whatever.

Every species is susceptible to accidental death. That is, non-natural causes. Things like drought, fire, flood, murder, predation, and accidents are very important, especially for small animals.

If a male horse decides to mount a female horse and she is not ready for it, she kicks him in the jaw, his jaw cracks, and no matter how studly he was, he is now dead. If you have a broken jaw and you're a horse, you're dead.

So something's going to kill you. If you are a sheep and you are grazing on sandy soil, your teeth will be worn down by the time you are five or six years old, and you will die.

Every species has an upward limit beyond which nobody ever lived, right? For mice it was probably about fifteen to eighteen months. For people, it was probably forty to fifty years. Even now, in the developing countries, very few people live beyond forty or fifty years. Even in Russia, since so much nasty stuff is going on over there, the life span is now about fifty-five—going right back to where it was.

So the reason why the force of natural selection decreases with age is that in any age population there are a few older than younger, because the longer you live, the more chance you have of dying from one of these unnatural causes. In any population there are a lot of studly young guys, but each time they go out and do anything, especially chasing mates while they are not paying a lot of attention to those hawks up there—boom! They're gone!

So as things go on, they disappear. In other words, the young are always going to contribute more genes to the population because they have a better chance of being alive.

**KONDRACKE**: So this definition doesn't work, obviously. This definition of natural selection decreases with time, basically.

**BRONSON**: Yes, but the point is that if you get bigger and smarter and wiser, the way people have, you can forage better. You can prevent yourself from being eaten by cave bears. You can maybe get a more orderly life where you are not killing everybody. And now, older people will be living longer and reproducing longer.

So now there is a force of selection of genes to be better buffed up to get you to age forty. As long as you can stave off these unnatural causes of death, there will be strong selective pressure on all your genes to live longer. It's a subtle argument, but it is the key to the whole thing.

**KONDRACKE**: David? I want to let David respond.

**HARRISON**: Well, the basic idea that Rod's talking about is the explanation for a very fundamental question that is, why do you age at all? In the simplistic evolutionary theory there's some possibility of living to very, very old age. If you could reproduce at those very old ages, that should give some slight selective advantage. So there should always be an increasing life span, increasing healthy life span, and of course, that doesn't happen. Since we know that's not true, we have to find some way of rationalizing that. When Medawar first thought of the idea—that the ability of natural selection to remove deleterious genes gets lower and lower as the chances of being removed from the population increase, as Rod said.

Williams went one step further and pointed out that not only is it hard to remove the deleterious gene the older you are and the smaller the chance that you have survived, but, suppose that deleterious gene does something good for you early in life—that's the pleiotropic effect. Suppose it actually helps you reproduce when you are very young, or helps you reach the age of reproduction faster and more efficiently, then even though it may have deleterious hard consequences late in life when you are most likely going to be dead anyway, it is not going to be removed. It's going to be selected for.

So those pictures are very, very influential now in explaining why aging occurs. And I think Rod explained very dramatically why there are differences between species.

**KONDRACKE**: OK.

**HARRISON**: But there is one other thing that happens that is important to remember, and that is, not only do we all age at rates that are roughly proportional to life spans and life expectancies of our ancestors in the wild, but aging can be changed by natural selection fairly quickly.

There are some studies with fish which suggest that in just a few generations, life spans and natural history rates of development, rates of reproduction, and natural history can change over twenty or thirty-year periods.

**KONDRACKE**: How does it happen?

**HARRISON**: Well that's the point. Those creatures must be carrying genes for slower aging.

Now, if aging is caused by an accumulation of thousands and thousands of late-acting deleterious mutations, which is what is predicted by the Williams and Medawar hypotheses, in order to slow down aging perhaps the best experiments were done by Steve Austad with opossums.

**KONDRACKE**: Tell us about how this illustrated the theory.

**HARRISON**: Right.

**KONDRACE**: Because the theory is very abstruse.

**HARRISON**: Well, the opossums lived on what are now the Georgia Sea Islands. Ten thousand years ago they were part of the mainland. Then when the glacier melted—and we have a pretty good idea of when this happened—the islands were cut off from the mainland.

By chance, the predators disappeared from these islands. So the opossums had much lower predation rates on the Sea Islands than they had on the mainland. That happened maybe five or six thousand years ago. Austad predicted that creatures who are living in a situation with very low predation are going to develop slower, reproduce slower and live longer, and indeed that does seem to be true of the Georgia Sea Island opossums compared to those on the mainland.

That suggests that there are ways of adapting really quickly to conditions that favor increased life span—this is within a species, now.

**KONDRACKE**: Could be stress!

*(Laughter)*

Less stress.

**HARRISON**: Fewer hawks chasing you?

**KONDRACKE**: Exactly.

**HARRISON**: Well, probably, if there are fewer hawks chasing you, you wouldn't reproduce more slowly and you wouldn't develop more slowly. You probably would develop, if anything, better with lower levels of stress. So it's probably actually not stress, although that is an innovative suggestion.

It is probably some kind of underlying timing mechanism or mechanisms. Now, why couldn't it simply be reverse mutations of all those hundreds or thousands of deleterious genes? Well, it could. But if you think about what it takes to increase the life span, that requires not just one, but hundreds of things that could have killed you have to not kill you. Right? Because you die of the first thing that kills you. That means that all the things that could have killed you have to not kill you, if you are going to increase the maximum life spans as happened with those opossums.

**KONDRACKE**: OK. I think we should get off of this philosophical theory. I want to get a little bit more practical.

The National Institute on Aging sponsored an attempt to find biomarkers. Is it now over? How much money was spent on it? Is more investment meritorious or not?

**BRONSON**: It's supposed to be $20 million that we spent on it. I help spend some of that money.

**KONDRACKE**: Over how long?

**BRONSON**: A ten-year period.

**KONDRACKE**: Ten-year period.

**BRONSON**: There were anywhere from fifteen to twenty groups over that period of time that looked at all kinds of different parameters—behavior, cellocites, all kinds of things. We found plenty of biomarkers, as defined by things that change with age, but with a lot of animal-to-animal variability. We certainly found that those things that would change with age changed more slowly in caloric-restricted animals, as we looked at caloric-restricted animals along with full-fat animals.

So in that sense we found plenty of biomarkers. It's just that they are not going to do what people want them to do. That is, they are not going to predict in the single individual. They are only going to work on a population basis.

So I think we were successful. Now, as I said before, they were always invasive and that's not going to work for people. But sure, sure biomarkers exist. It's just that all the things that people want of them are just not going to happen.

**KONDRACKE**: So, should we keep looking?

**BRONSON**: —particularly the predictive idea.

**KONDRACKE**: We should keep looking and spending the money on it?

**HARRISON**: If you think of one of the critical biomarkers as the age when the female—at least in a mammal—loses the ability to reproduce, that happens relatively early in terms of the total life span in both mice and people. It's roughly half way through the life span that you lose the ability to reproduce.

If you find things that will extend female reproductive life span, for example, what's the chance that that's going to extend total life span? Well, actually, we don't know. But it's probably pretty good.

**KONDRACKE**: That's the whole hormone replacement therapy question.

**HARRISON**: Well …

**KONDRACKE**: No?

**HARRISON**: Well, hormone replacement therapy isn't extending female reproductive life span. Hormone replacement therapy is trying to prevent osteoporosis after the menopause is over. I'm talking about aging more slowly as far as the female reproductive life span goes. Now, at least in mice, there are genes and there are treatments. One of them is food restriction, which postpones reproductive senescence in females. It also increases maximum life span and seems to slow down a whole bunch of markers of aging.

**KONDRACKE**: This has come up again and again and again—the idea of food restriction as a way of perpetuating life. Now, what happens when calories are restricted? What does that do to the system, or to the organism as a whole that allows that organism to stay alive longer?

**BRONSON**: Nobody knows.

**KONDRACKE**: I see.

**HARRISON**: Well, it does so many things. Basically, when you are comparing the severely food-restricted animal at, say, eighteen months, with a normal control, it's like comparing a twelve-month-old normal control with a nineteen-month-old. There are so many differences. Probably ninety percent of the things that change with age slow down with age in the food-restricted animal. So it really doesn't help much to answer the fundamental question, "what is the mechanism that does it?" The value of biomarkers, I think we'd all agree, is in trying to understand mechanisms of aging.

**KONDRACKE**: OK. You know that if a female goes into menopause early that her life span is shorter. But you don't know how much shorter, and it's not a measurable thing?

**HARRISON**: I'm not sure …

**BRONSON**: Within a species.

**HARRISON**: Within a species.

**BRONSON**: When you go through menopause, that's not predictive.

**KONDRACKE**: Oh. OK.

**HARRISON**: I think that that's—

**BRONSON**: Now, if you breed for increased reproductive life, that might theoretically have an effect on increasing the total length of life. That's what David was saying. But the idea that a woman who goes through menopause at forty is going to die at sixty is just complete baloney. I mean, one hundred percent baloney.

**HARRISON**: That actually illustrates one of the things I think we all agree on about biomarkers. They are useful in a population basis—we know the food restriction greatly retards female reproductive senescence, or the little mutation which cuts out growth hormone, these things retard female reproductive senescence. But that's on a population basis.

In terms of individuals, there are so many different things involved, especially in a population like humans where you have genetically diverse individuals living in different environments; you really couldn't use a single biomarker, even as evolutionarily powerful a marker as female reproductive senescence, and expect that to make predictions for individuals. That's probably unrealistic. It may well be, however, that if you can make changes, and if you can develop treatment that retard senescence in a variety of biological systems, they will cause the populations in which it's retarded to be healthier later in life.

**KONDRACKE**: Go ahead.

**BRONSON**: You could design a very simple experiment. You could take your fountain-of-youth drug, and I would say you should start giving it during that time of life when things really begin to go bad, around age forty. Now, you just take a picture of the person at forty. Then you take a picture of the person at fifty. You do this for a hundred people in the control group and a hundred people in the fountain-of-youth group, and then you take these pictures and you shuffle them up and you give them to a ten-year-old and you say, “Put them in a pile, from older to younger.” And they put them in a pile; and we’ll find out.

Do you do well during that ten-year period or not? It would work, because just the facial features between forty and fifty are enough of a biomarker. You would know at the end of that period.

Well, let’s look at another biomarker—the number of times you go to the doctor for anything other than the normal check-up. If the fountain-of-youth drug is working, you could prove that it is working with that simple experiment. No fancy invasiveness, just take a picture and give them to the ten-year-old and say, “Put them in a pile.”

For some people on the fountain-of-youth drug, the forty-year picture and fifty-year picture will be identical. For the people in the control group, the fifty-year-old picture will look older than the forty-year picture. It would work on a population basis. Now, it is not going to say anything about predictors or subsequent longevity.

Maybe the people on the fountain-of-youth drug will all drop dead at sixty. But at least you know that you are delaying aging. You could do it. You’re never going to get FDA approval to give anybody a drug for ten years, but you could do it and it would work.

**KONDRACKE**: Well, there are some products that we had a debate about before that the FDA has no ability to touch that are being sold by the gazillions of pills.

**BRONSON**: Well, I know. I know, but…

**KONDRACKE**: But they’re utterly untested by the FDA or anybody else.

**BRONSON**: Yes, exactly. And suckers are buying these ridiculous things all day long. The most important thing that’s happened in all of medicine, in all of aging research in the last year or two years, is that female replacement hormones turned out to be bogus. Now, that was approved stuff. This is what all doctors believed was good. Now, there is not a single advantage, except maybe in the short term, if you don’t want to have night sweats and all that kind of stuff. But if you take hormone replacement, you are going to die earlier, you are going to get everything earlier. So even that didn’t work. It was bogus. So don’t take anything.

By the way, there is another paper showing that vitamin E and vitamin C or supplementation also is not good for you. Don’t take anything. Take nothing. Buckle up. Quit smoking.

**KONDRACKE**: Linus Pauling is rolling in his grave. OK.

**BRONSON**: Oh, Linus.

**HARRISON**: I think, if we are going to be giving advice to human beings, you have to remember one thing, and that is that the placebo effect is really strong in us. So if you are taking vitamin C and vitamin E, or probably even something as strong as hormone replacement therapy, although that is a little disturbing, but if you truly believe that it's good for you, if you truly believe it, it will be good for you. It will have some beneficial effects.

**BRONSON**: In the short term.

**HARRISON**: It may do nothing physiologically, but the fact is the placebo effect is really strong, and that is of course why there is so much junk out there. Because if you believe, if your snake oil salesman is really effective, and you believe in that snake oil, it actually will do some good—not because the snake oil is doing any good but because your belief is doing good, as a placebo effect.

**KONDRACKE**: OK.

**HARRISON**: That's one of the things you do have to watch out for, and that's why in aging studies you have to do them double-blind with human beings.

**KONDRACKE**: OK. Now, what about telomere length? That has been written about as a predictor that as cells reproduce the telomeres—which is the end of a chromosome, if I've got my biology right, shortens and it keeps shortening and shortening and shortening and when it gets to a certain length, the cells die.

**BRONSON**: There are two things wrong with it: (A) mice have telomerase and they can—

**KONDRACKE**: Which is—

**BRONSON**: They don't lose telomeres.

**KONDRACKE**: Telomerase is what?

**BRONSON**: It is an enzyme which will stick telomeres back on. People don't have that. So every time a cell divides you lose a telomere.

**KONDRACKE**: Aging has nothing to do with telomeres?

**BRONSON**: The second objection, which is a really important one, is that nobody thinks that human beings run out of cell cycles. Nobody believes that. In other words, you have gut cells which are always turning over. Nobody thinks that when you reach seventy suddenly you have no more intestinal cells because they have all lost their telomeres. You don’t reach that telomere-absent state where you’ve lost all your telomeres until there have been more cell cycles than you could ever possibly want.

So I don’t know how we got off on the telomere thing. It is just complete foolishness. Don’t say anything about telomeres ever again!

*(Laughter)*

Now, it is true if you knock out telomerase in mice, they do get cancer earlier. It is said that they go gray. Therefore, they are aging like people, because mice don’t usually go gray. I mean, who knows? Those studies have to be reproduced in some manner. It may be that there is something there, but boy, oh, boy, their whole company is at the base of the telomere theory. And it’s just foolishness. It really is just foolishness.

**HARRISON**: Well, let’s give the audience a bit of an introduction to it. One of the models for aging human beings is fiberglass, OK? Skin fiberglass. Skin fiberglass proliferates in tissue culture and then eventually stops. This was a fundamental discovery made by many people, but actually Len Hayflick was the first one who had the guts to go against the scientific establishment and say that this is what really happens to non-transformed cells.

For a long time people didn’t understand why human fiberglass, and sometimes epithelial cells in tissue culture, had limited proliferative capacities. This was used as a model for aging, to try to understand why this happened. And it turns out, although everybody in this field is not completely convinced that it’s telomeres, it does seem to be that telomere length best predicts the subsequent proliferative life span of the fiberglass and epithelial cells. That’s one piece of evidence.

Another very strong piece of evidence is, if one puts into the cells the essential element for the enzyme to make bigger telomeres—or telomerase—this is, interestingly enough, a reverse transcriptase which came from the AIDS virus. That is how it was recognized.

If one puts that reverse transcriptase, the limiting feature of the telomerase enzyme, into these cells they seem to go on for a very long time, although whether they stay normal for that very long number of proliferations is still argued. Now, the telomerase enzyme uses RNA as a template, so in order to make more telomeres, it matches up the RNA, which is why it needs a reverse transcriptase.

For the mice in which the knock-out was done, they simply removed the DNA, which made the RNA for the template for the telomerase. So the telomeres could not be made any longer. And they bred the mice. The first generation of offspring were fine. I’m talking now just about literature, because I have not been able to get hold of those mice. I tried to get hold of those mice for years and years after those papers were published in top-notch journals, and they never return my calls.

In any case, the literature says, and I believe it, that the mice were fine. They were fine the first three generations. They were fine right up to the fifth generation. Then at that fifth generation the telomeres, incidentally, were getting shorter and shorter. Mice start with very big telomeres. Mice have way bigger telomeres than we have, which is sort of counter-intuitive if you think that telomeres are causing aging, but let's put that aside!

So the mice are actually healthy and, I believe, had pretty normal life spans—at least through three generations—without any telomeres whatsoever. But at that fifth generation both males and females became sterile. That's a little funny, because the number of generations it takes on the sperm line is much more than the number of generations on the egg line. One would have expected the males to have become sterile two or three generations before the females. But, in any case, then all the bad things that Rod was talking about happened.

So that's the history of the telomerase/telomeres. I'd be more hesitant about saying that it's absolutely without merit. It's true that few, if any, people die because they run out of proliferative capacity of epithelial cells and fiberglass. But on the other hand, a lot of the aging phenotypes, you know, with skin being wrinkled and so forth—one could argue that the fiberglass is not turning over the collagen properly, and of course, there are other types—

**KONDRACKE**: But the telomere theory was the holy grail, or the gold standard?

**HARRISON**: Yes.

**KONDRACKE**: And it applied to cells all over the body.

**HARRISON**: Right.

**KONDRACKE**: And if you could keep telomeres from shortening, you could prevent cancer and heart disease and so on.

**HARRISON**: Well, actually, by adding the time ratio, you increase the risk of cancer.

**KONDRACKE**: Ah.

**HARRISON**: Judy Campisi wrote a neat review a while ago where she talked about sort of a knife-edged balance between cancer and aging. You want to avoid cancer. You also want to minimize aging, so you need a certain amount of proliferative capacity, but if you have too much proliferative capacity it's too easy to transform or fall off into the tumor class.

Just because something doesn't explain everything doesn't mean that we should confine it to the outer darkness. Also, incidentally, I think when people come up with hypotheses, it probably would be wise to exercise a little bit of humility and admit that it's unlikely that all of aging is going to be explained by a single mechanism. Even an optimist like myself.

**BRONSON**: Well, how about twelve genes, though, right? Three genes? Four genes?

**HARRISON**: Well, I have no idea.

**BRONSON**: How about twelve? How about thirty thousand?

You see, when I talk about how people are living beyond the length of time that their ancestors ever lived, my point of view is that it's all just junk. It's not that you are getting new mutations in the genes. Your genes were buffed up to get you through forty, whereas a mouse's genes are buffed up to get them only to about eighteen months.

**KONDRACKE**: By buffed up, you mean naturally?

**BRONSON**: Buffed up so they are functioning better.

**KONDRACKE**: Yeah.

**BRONSON**: Now, I want somebody to look at obvious issues like cancer, for example. We know that cancer is due to mutations in single body cells and mutations in tumor suppressor genes. We know that there is a lot of DNA repair going on, so if you get a mutation in the gene there are also many other molecules in the cell which will fix mutations in DNA.

Since mice get cancer beginning at fifteen to eighteen months, and people get cancer beginning at forty years, you must have to assume that somehow the tumor suppressor genes in people work better than in mice. By definition they must.

So how about somebody trying to define how it is that we have better tumor suppressor genes than mice? What does it mean to say? If you could figure that out for cancer, because a lot is known about cancer, then maybe you could address the question of why is it that mice, for example, get osteoarthritis beginning at about a year of age? People get osteoarthritis beginning about forty or fifty years old. What's the difference? Well, we don't know the genes of osteoarthritis. But as we learn more about each of these diseases, and if we could ascertain that they happen later in people than in mice, then go after the genes.

**KONDRACKE**: For specific things.

**BRONSON**: Yeah.

**KONDRACKE**: In other words, your theory overall is that aging consists of thousands and thousands of little things.

**BRONSON**: Yes.

**KONDRACKE**: Each of which, as we discover them, and if we could fix them for cancer or for arthritis, would contribute to longevity, although it would take an infinite amount of time—so there is no magic key that we're ever going to find to the aging process, or even the ability to measure the aging process.

**BRONSON**: Well, I would like to start with the first one and answer the cancer riddle that makes mice different from people. Or, if you don't want to do that, I want to know why hair turns gray. I mean, nobody wants to study hair turning gray. You can make a lot of money out of it. Right?

But just take anything and figure out why it doesn't happen until late.

**HARRISON**: Mice don't get gray.

**BRONSON**: Why should hair go gray?

**KONDRACKE**: Well, some people get gray at different rates.

**BRONSON**: Sure.

**KONDRACKE**: What is there that is different about people who don't go gray?

**BRONSON**: Well, it wouldn't hurt to find a gene and clone the genes for early grayness. It may not be the same genes as are involved in all the rest of us, but you could go after it that way.

But even early onset of Alzheimer's, Parkinson's, any disease, just doesn't happen before forty years of age. So what is it? What's the difference? It's not that you have a million mutations beginning at forty. You have the same genes in the same cells, so something happens.

What happens is the genes were not selected to be collectively good enough to keep them from going to pot beginning at forty. In mice that secret age is fifteen to eighteen months. Why are the ages different? Because mice are always eaten up by fifteen to eighteen months, and in the old days people were all eaten up or killed each other off or bopped each other on the head by the age of forty.

**KONDRACKE**: Well, if you now take the United States of America, or any Western country where the chances of bopping are significantly reduced, the age of the life span is being extended. But it is being extended partly because we've got better medicine. It's partly because we have a healthier life style. It's partly because we are not getting bopped and so on. But there is still a finite limit to the life span for the species.

**HARRISON**: And a fairly precise one.

**KONDRACKE**: Yes. The question is, can you either extend the total life span of the species, or at least somehow figure out what it takes to get more of the population to live later into the life span in a healthy way?

**BRONSON**: Well, if we're lucky there will be maybe a few genes that are responsible for keeping all the other genes buffed up to the age of forty. There may be a few genes. David talked about the opossums on those islands. If it is true that natural selection can increase the life span in just a few thousand years, that would mean that there can't be too many genes.

So maybe there are reproductive age-assurance health genes, and they may be dominant master genes. Now, that's entirely different from saying that there are genes that switch on that make them get old. That is certainly not true.

**KONDRACKE**: You think there are not.

**BRONSON**: Zero.

**KONDRACKE**: Zero.

**BRONSON**: Aging is not programmed. Aging is the lack of a program. It's the failure of genes to maintain normal homeostasis, to maintain the normal function of—

**KONDRACKE**: Why does it happen?

**BRONSON**: The reason why it happens is because there was no natural selection past the age of forty.

**HARRISON**: No, but that doesn't explain the answer.

**BRONSON**: Nobody survived.

**HARRISON**: What the people want to know is why does it happen in a physiological and biological way, not what the evolutionary reason is. I think, actually, we are agreeing that it's possible that there are a small number of genes which tell all these late-acting deleterious genes when it is late. And if that's true, by being able to alter the genes that tell them when it is late, or in Rod's terms, by being able to increase the activity or delay the inactivity of genes that maintain reproductive performance and maintain health, it might be possible to have major beneficial effects on the health span.

**KONDRACKE**: OK. Questions from the audience: "Many people over one hundred cite positive mental attitude as one of the key factors in longevity. Can you possibly measure mental attitude as you develop biomarkers?

**HARRISON**: Well, probably just being healthy enough to reach one hundred gets you a real boost. But I suspect there is an intimate feedback between a positive attitude and good health. I suspect that as you get sick, it's harder and harder as you get older and as you have more and more chances of something knocking you down physically—and as you get older and older, this increases. It's harder and harder to maintain a good mental attitude, but there is certainly good reason to maintain it.

As far as a biomarker of aging being a healthy mental attitude—

**BRONSON**: Sure, you can measure it. There are psychological tests.

**HARRISON**: There are psychological tests.

**KONDRACKE**: But is there any correlation?

**HARRISON**: I don't know.

**KONDRACKE**: OK.

**HARRISON**: We both work with mice. And the fact is that mice all have healthy mental attitudes!

**KONDRACKE**: Not if you starve them, they don't.

**HARRISON**: Oh, they actually run around and get all excited when you bring them food. They are not starving; you just reduce the amount of food a little bit.

**KONDRACKE**: I see.

**HARRISON**: They actually don't have the intelligence, I think, to have the existential questions that cause people to have a really severe depression sometimes. I've never seen a mouse that evidenced the slightest sign of depression.

**BRONSON**: But do you talk to them very much?

**HARRISON**: Oh. Of course.

**KONDRACKE**: OK. "What is the greatest obstacle to effectively discovering a clear biomarker to gauge human longevity?"

**HARRISON**: That there won't be a single one. I think we can all agree on that. But obviously we need to have a bunch of biomarkers at the very least. The obstacle would be finding the right systems to make the measurements.

**BRONSON**: And the fact that it would have to be non-invasive, which is a big problem.

**HARRISON**: Yeah. Although there are clever ways—

**BRONSON**: There are clever ways, like the ten-year-old girl I was talking about. That would work.

**HARRISON**: Well, it wouldn't work once they've had the makeovers that they've been offering on TV recently.

*(Laughter)*

They go from forty to about twenty-five in the picture for the ten-year-old girl. But inside, of course, they are just as rotten as ever.

**KONDRACKE**: Somebody asked, regarding diet restriction, why is it that people who have anorexia die early?

**HARRISON**: Well, that's because they don't eat at all! Diet restriction, and I should have said this, diet restriction is not something that you would do with your children. It is severe enough to actually stunt the growth, but also must not be malnutrition. If you get malnutrition, of course, mice will be vulnerable to it and die just like anyone else will.

**KONDRACKE**: So what percent of their normal calorie intake are you talking about?

**BRONSON**: Up to forty percent.

**HARRISON**: Yeah.

**BRONSON**: And the anorexics will weigh like sixty pounds when they die.

**HARRISON**: Right.

**BRONSON**: That's not caloric restriction.

**HARRISON**: That's starvation.

**BRONSON**: That's starvation.

**HARRISON**: There really is a difference.

**KONDRACKE**: OK. "How will researchers be able to overcome genetic variation among individuals?"

**HARRISON**: Well, that's a very interesting question, and I think that rather than overcome it, we are going to have to use it. We are going to have to take advantage of genetic variation in the human population and use it to give us hints as to who has the good genes and recognize them.

**KONDRACKE**: But you can't overcome it.

**HARRISON**: No. It can't be overcome. It's going to have to be used.

**KONDDRACKE**: I mean if you have bad genes, gene therapy is never going to work.

**BRONSON**: Because you can't get genes into all the cells that you need to get them into.

**KONDRACKE**: You mean you can't use a virus?

**HARRISON**: Yeah, one can use a virus. Already we have viruses that will target specific tissues.

**BRONSON**: That will target a few of them. But you've got to get enough virus into enough cells to reverse the genetic problem that you have.

**KONDRACKE**: Of aging across the board, you could—

**HARRISON**: You could see the time when we could actually cure something of yours that way.

**BRONSON**: Well, you could try. OK. Fine.

**KONDRACKE**: But theoretically—

**HARRISON**: If you are not too—don't get bopped over the head!

**KONDRACKE**: But theoretically you could do gene therapies on loads of diseases. Forgetting about the aging processes as a whole, there are specific diseases that researchers are very hopeful about gene therapies for.

**BRONSON**: Yes. I'm not as hopeful, but yes. And it's worth trying.

Maybe if there are two or three master genes that control aging, which I certainly don't believe, but if there were, then you could measure a person's gene, and if it turns out that the person has a weakness for that particular master gene, you give it some virus or something, and it makes all the genes and all the cells better.

**KONDRACKE**: Well, that's the golden key theory.

**BRONSON**: Right.

**KONDRACKE**: The other theory is that there would be fifty or a hundred principal smaller golden keys and that you could cure Parkinson's, cancer, and heart disease possibly by genetic therapies. But you don't think that's even possible?

**BRONSON**: Well, people are still going to look a hundred years old when they reach a hundred, even if they haven't had heart disease or cancer. So a lot of the change that you see in people is not going to be reversed by stopping all these diseases.

**KONDRACKE**: But you would lengthen their life span?

**BRONSON**: Yes.

**HARRISON**: A healthy life span.

**BRONSON**: And that might be worthwhile.

**HARRISON**: It might be that appearance might be changed, too, although that wouldn't be changed by curing the specific diseases. There's a lot that we don't know about how many critical timing mechanisms there are that cause aging to be thirty times faster in mice or seven times faster in dogs than in humans.

But there are methods already developing to begin to look for those genes, and species comparisons, massive species comparisons. There are some neat critters—bats, for example, bull rats, colonial organisms, that live way longer than other creatures of their size and metabolic rate.

**KONDRACKE**: Why?

**HARRISON**: It would be interesting to find out why.

**BRONSON**: Why do zebra fish that are this long live for three years? —a lot longer than mice. There must be a lot of predation for a little guy like that.

**KONDRACKE**: "Does something need to be discovered before a defined biomarker can be established or, are biomarkers necessary to define what aging is and what researchers should be looking for?"

**HARRISON**: I'd vote for the latter.

**BRONSON**: Yeah.

**HARRISON**: I mean, we have accepted the definition of biomarkers, now we are talking about measures of aging rates in a wide variety of biological systems in individuals. I think we agree that it's necessary to follow those as much as you can when you are studying aging, whether your focus is on carrying specific diseases or whether your focus is on trying to do something more basic—or, what is really logical, to go after both.

**BRONSON**: I think probably if we found real biomarkers, we would know a lot more about mechanisms of aging.

**HARRISON**: Because they would be following the specific mechanisms.

**BRONSON**: Yes.

**HARRISON**: It would be nice if, as we define specific mechanisms of aging, we could also define their biomarkers. But something like the telomere, that illustrates the problems that can happen. You find one thing that seems really good in one particular model system and you say, “Ah, it’s going to cure everything.” Then it turns out not to. And then, of course, people say, “Well, it’s no good at all.”

We are probably going to need a number of different measures. I’m not absolutely certain that telomeres aren’t going to prove to be important.

**BRONSON**: A little bit, sure.

**KONDRACKE**: “If you were advising Congress of where to put its money, would you advise Congress to spend the money on curing specific diseases or for trying to discover what the aging process is all about?”

**BRONSON**: Well, they’ve got to cure the diseases, for sure.

**HARRISON**: Politically, you couldn’t advise the other.

**KONDRACKE**: Well, forget about the politics.

**HARRISON**: We can beg them to spend a little bit of money on trying to find basic mechanisms.

**BRONSON**: That’s right.

**HARRISON**: That’s the best we can do.

**BRONSON**: And it’s got to be mechanism, mechanism, mechanism. The problem with the biomarkers thing is we weren’t even asked to go after mechanism. I had no idea what the mechanism was. I still don’t.

But it must be mechanism, mechanism, mechanism. What is the mechanism of aging? So for sure, the government should not fund pure biomarker research. Forget it. Fund research where you find biomarkers that are reflecting a mechanism that you’re studying, that’s fine—justified biomarkers that reflect the black box of aging. We shouldn’t do that again. We’ve got to get mechanism.

**KONDRACKE**: I’ll give you the final word. Is that right?

**HARRISON**: It’s necessary to use biomarkers to find mechanism, we agree. It certainly doesn’t hurt to have one person studying biomarkers and finding out what the best biomarkers are so that the rest of us can use those to find mechanisms.

**KONDRACKE**: OK. With that we will thank everybody for being here, and I think we’ve had a great discussion. Thanks a lot.

End.