



**Remarkable Trends in Aging Interview with Dr.  
Richard Miller**

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**KONDRACKE:** Let me just start out by asking, what exactly is aging? I mean what happens? All of us are going through it: your hair is turning white; my hair is turning gray; we're getting on. What exactly is going on with our bodies and our minds?

**MILLER:** Well, I think it's an important question. You said it's a warm-up question, but I think it's a key issue. The reason is that, although people who are not scientists use the word "aging" more or less in a consistent way, scientists have often used it to mean whatever they're studying that they think they might get funding for.

I think a common sense definition of aging is that it's the process that just takes healthy, young adults progressively into older people who are more and more likely to get sick—who have more and more difficulty in combating whatever threats their body or the environment can produce for them. Older people are more likely to get cancer or to get the flu, or if they break a bone, they're more likely to recover slowly. Aging is the process that creates that kind of person from that healthy young adult that nearly all of us were when we were just about to enter college.

It's important to distinguish that approach from the idea of aging as merely the study of old people. For many people, if you say, "I do aging research," they kind of assume you help to figure out what an old person is like, what's wrong with the old person.

Although I'm certainly in favor of studying elderly people, I think the impact of this kind of research that will count the most is actually work that you have to do on young and middle-aged people to try to figure out why it is that they're getting old. What changes in their body and gene expression and in their hormonal systems to actually turn them into older people? That's what I would consider aging research in its most fundamental and probably its most productive sense.

**KONDRACKE:** How did you get into this? How did you become a gerontologist?

**MILLER:** Well, there are real psychological reasons and then there are ex post facto rationalizations.

**KONDRACKE:** Explore any and all.

**MILLER:** Most kids, when they are growing up, go through a phase where the idea of getting old and dying is really scary and really something they're against, and I did, too. Most people grow out of it, but I didn't. It's important—once you get to the point that you've decided that aging research is something you're interested in and something you want to pursue, you eventually recognize that it's a good thing to be doing. If you're interested in scientific mysteries—things that aren't yet solved—where people really need to use their intuition to discover what the important cracks are, aging is right up there at the top of the list, as cancer biology was fifty years ago or infectious disease was two hundred years ago.

In addition, it has, I think, going for it the advantage that if we are actually able to learn enough about aging to intervene in the human aging process, then that's going to be overwhelming in terms of public health impact, in terms of what it can allow us to do to keep people healthy. It's going to overwhelm all the other sorts of research that are going on anywhere in the world in terms of health prevention and health treatment. I think in terms of both intellectual satisfaction and its potential for doing good for people, there's nothing that can beat it.

**KONDRACKE:** We will explore that—the emphasis that the federal government gives in funding to aging and to diseases—but to follow up on the first question, what is aging? What exactly is the process? Is it cell death? Is it cells incapable of reproducing themselves any longer? What is the mechanism that causes aging? Do we know?

**MILLER:** No, we don't know. We know a good deal now about what causes cells to die, and we know a good deal about what causes cells to stop dividing. A lot of people who think they're doing aging research study those things. They're really exciting and they've made terrific progress and it's really terrific cell biology.

But aging isn't any of that. Aging doesn't happen to cells and it doesn't necessarily cause cells to die. Aging is what takes a healthy young person into an old person who's more and more vulnerable. If someone looks you straight in the eye and tells you they know what the mechanism of aging is, they are trying to kid you. No one really knows what the mechanism of aging is. There are good ideas, things that are worth pursuing, but nothing on which an honest person can state that he or she knows to be the truth.

**KONDRACKE:** Animal models don't tell us anything more than our own experience?

**MILLER:** Animal models tell us a terrific amount more than our own experience because animal models give us all sorts of experimental, as well as observational, power that you don't get just from looking at old people. Nature has done us a terrific favor by producing animals that are like us in many ways. I'm thinking of mice and rats, in particular, whose body plans and chemistry and body mechanics are extremely similar to that of humans, but are really short-lived.

So you have two systems that are very similar to one another, one of which is aging thirty times faster than the other. For scientists that's a gold mine; that really lets you test specific ideas of what might cause aging. You mentioned cell death. There's a popular idea that differences in the degrees to which specific cells in the body are more or less prone to die contribute to the aging process. But now we've got animals like mice that live three years and dogs that live twelve years, and horses that live twenty years, and people that live eighty years or so. You can test that idea to see if your ideas about cell death and how it relates to aging meet the facts on the ground. So far, none of the ideas about what causes aging have actually met those facts. There are some pretty good ones that have not yet been disproved. There is the stress resistance idea, which I hope we'll get to talk about later; I think that is likely to provide an important unifying factor.

In addition to giving us a diversity of things to play with, some of the animal models are easy to manipulate. In mice, worms, and flies we've been able to get specific information about changes that can slow aging down. That has sort of been the major breakthrough in aging research in the last ten years—the thing that really convinced those of us in the field that aging could be modified. We know it can be modified because we can do it.

**KONDRACKE:** We will get into some of that, but do you think aging is a single process or is it a set of multiple different processes? There are those, as I understand it, who believe in the unitary theory and the multiplex theory. Which do you believe in?

**MILLER:** I think it's important to understand that both viewpoints are partly correct. It is a unitary process and it is a highly complex process with multiple avenues. It's like if you ask a political scientist, "Is legislation a process?" Legislation *is* a process. We teach it in civics class. You can bring legislation to a halt by any one of a number of specific changes in who's talking to whom and what the political leadership wants to do.

Yet, to consider it only as a unitary process is clearly a mistake. There are multiple processes having to do with how the system is structured and who's having an impact on it. Studying those individual subprocesses is really important, but to lose sight of the fact that they are coordinated in a central way is also to miss the big picture.

There is a popular theory now in aging research. I think maybe seventy or eighty percent of the pros that do this work would endorse a kind of multiplicity idea—that aging of the brain and aging of the immune system and aging of the arteries, each one of them are different and complicated and interesting and that's certainly true.

But I think the greater truth is that they all take eighty years in people and three years in mice and twenty years in dogs. That's not a coincidence. All of those rates are synchronized, and those rates are very different in different species. That's the key mechanism of aging that scientists need to pay attention to.

**KONDRACKE:** It's clearly genetic in some sense of the word. I mean there is some kind of a program that is at work, which determines that a human being will live so long and a dog will live so long and a rat will live much less.

**MILLER:** You're absolutely right about that, but the question, Is aging genetic? is often a tricky one because it depends on whether you're looking across species or within a species. So clearly, the short life span of a mouse compared to the long life span of a person is because they have different genes. If we lived in a mouse's environment we would still live a lot longer than a mouse and vice versa.

But if you consider the differences among people, how much of the difference between their age range is due to genetic differences? That seems like a similar question, but it's really quite a different question because you get a different answer. The answer there might be five percent or ten percent or twenty percent, but never more than about twenty percent no matter how you slice it.

The genetic differences among people—and also among different mice and rats—that modify aging are really important to learn about because they give us clues to mechanisms and they will eventually give us clues to drugs.

**KONDRACKE:** From a different point of view, we have already extended the human life span by a considerable amount, from probably in the forties somewhere to eighty-something in Swedish and Japanese women, right? How did we do that and what does that tell us about how to extend the life span even further, and furthermore the healthy life span?

**MILLER:** Most of the change in the last couple hundred years in the average age of death and the life expectancy at birth has had nothing to do with aging research in the slightest. I can pretty confidently say that basic aging research has not yet had the slightest impact on our knowledge of disease and how to prevent it and what to do about it. It's come largely because of our ability to detect and to combat diseases of childhood, diseases around the birth period and infectious diseases that used to kill a substantial proportion of kids and young adults.

Those changes have been the major players. Changes in sanitation and health prevention practices have been important. There have also been changes in our ability to help people in their fifties, sixties and seventies who come down with a disease. Surgery and antibiotics and some classes of drugs have helped improve the chances that a sixty- or seventy-year-old is going to make it to eighty years of age.

But those don't really have anything to do with aging research. If what we really want to accomplish in aging research is to make an impact on health, what we need to do is develop a way to slow aging down. We will know that we have done that when people are in their eighties and nineties and maybe even one hundred years old and are just as healthy as today's average fifty- and sixty-year-old. It's not a matter of immortality, it's a matter of slowing down the rate at which major chronic diseases of old age actually get us.

**KONDRACKE:** But just as a layman in all of this, it would seem that just looking at airports, for example, the average eighty-year-old is living a life that is a lot like what the average sixty-year old lived forty years ago. They're healthier. So does the process by which those people live healthier not teach us anything about what it takes to get those people to one hundred in a healthy shape? I don't know whether it's nutrition or it's vitamins or what.

**MILLER:** There are very small changes in the last thirty or forty years, say, in how healthy an average eighty-year-old is. One way to look at it is to ask how long is an average community-dwelling eighty-year-old likely to live and the life expectancy of an eighty-year old in the last thirty or forty years has gone up only slightly, a year or so.

It's a mystery as to why that should be. Demographers have noticed it. They have documented it. They haven't a clue as to what has caused it. I think that it is not likely to

tell us very much about how aging research works or how aging works. We can, in animal models, increase the average life span by forty, fifty, sixty percent and have been able to do so for seventy years.

**KONDRACKE:** Say that again. In animal models...

**MILLER:** We can take a mouse, where an untreated mouse is going to live about two years, and we can get it to live three years. It's been a routine matter to get that in the lab. Those three-year-old mice are extremely healthy. They have intact cognition and they are as strong in terms of their muscles, in terms of their immunology, in terms of their reflexes as your healthy middle-aged mice.

**KONDRACKE:** And how did you get to do that?

**MILLER:** Well, the first discovery of how to do that was by caloric restriction. If you take a mouse or rat and find out how much it wants to eat and you give it only sixty percent of that, you get an extremely thin, very hungry mouse that lives fifty percent longer than a mouse on a normal diet. That was the first discovery.

The second class of discoveries over the last ten years has shown that you can do the same thing by mutating any one of eight different genes. It is now possible through at least one diet—probably two, but at least one diet—and through at eight genes, to increase rodent life span by thirty, forty, fifty percent. That, to my mind, is the very strongest evidence. Although aging is a very complicated process, there are a very small number of controls, sort of rheostats, that can tune the whole system to run slower if you know where to push, which button to twist.

**KONDRACKE:** Well, starting with the caloric intake model, does that apply in any way to humans? I mean, how thin would you have to be to stay alive extra years?

**MILLER:** Well, there are two answers to that question. The easy one doesn't actually have to do with aging research, but it's been extremely well documented that most people in a Western society, where food is extremely abundant and exercise has to be looked for deliberately, become obese. When they become obese, they are more susceptible to all sorts of diseases: diabetes, heart attacks, strokes, and cancer. It's clear that for most of us, unless we are well below the average body weight, losing weight would be a good thing. It would help us avoid those diseases.

That's not something I know much about, but anyone who reads widely knows that that's true. The kind of caloric restriction that slows aging down is substantially more dramatic. Mice and rats that are on a caloric-restricted diet that will extend their life span are exceedingly thin. So, for instance, I'm five foot ten. If I were on the kind of a diet that leads to caloric restriction, I would have a body weight of 140 pounds or something like that to reach life span extension.

**KONDRACKE:** How much do you weigh?

**MILLER:** I'm not at liberty to discuss that.

**KONDRACKE:** You're five foot ten, and you would have to weigh 140 pounds.

**MILLER:** One hundred and forty pounds. So I would have to lose a great deal of weight.

**KONDRACKE:** We're not talking anorexia here. I'm trying to think of this in a way that everyone can sort of picture what it would take to reduce the caloric intake if you were going to really do that. So everybody would be walking around looking like an anorexic or not?

**MILLER:** They'd look exceptionally thin. I mean, to do this properly, you'd have to have a diet that is adequate in protein and micronutrients, and that is not the same diet that starved people in starving countries have, because there they don't get enough good nutrition. But we're talking about restriction of calories.

This is not the kind of diet that people can do voluntarily. It's been shown over and over again that, if people are given even really strong motivation to diet they can lose some weight and only a very few of them keep it off for more than a couple of years. The research on caloric restriction is not designed to prove once again to people that losing weight would be really good for their health—people know that already. What it's designed to do is teach us how aging works because it's one of the very few things that really slow aging down.

**KONDRACKE:** Now this, however, applies not only to rats but it applies to dogs and all other animals in between?

**MILLER:** It's been tried on various creatures, on rats and mice, insects, etc., and works almost all the time. It's been tried in monkeys now in three separate studies; two in Maryland and one in Wisconsin, and so far those studies look very promising. The monkeys that are on the caloric-restrictive diet in many ways, in terms of their biochemistry, resemble those of the caloric-restricted mice and rats.

The studies will have to go on another decade or so before people really know whether the diseases of aging have been slowed down in the monkeys. I'm optimistic that that will work.

**KONDRACKE:** OK, let's go to genetic engineering now. In rats, there are eight or so genes that exist where we understand what each of the genes do and what have we done to them?

**MILLER:** Well, the first publication of this kind was only five years ago, and people look at these mutations in mice and have stumbled over the fact initially that the animals lived a very long time. The reason these models are important is that it now gives us animals that we know from birth are going to be aging slowly. So we can start to ask what is different with these animals in terms of their hormones or what genes they

express or their biology? Then we can ask if they have things that they share in common, because that would give us clues as to what we can try and mimic.

To give you an example, most of these mouse models and, it turns out, flies and worms that are long-lived also share in common changes in a particular hormone pathway. It's not insulin—it's not the hormone involved in diabetes, but it's a pathway like insulin; it's called insulin-like growth factor. If you change the genes that modulate the response to this hormone, then you get extended longevity.

So it opens up a whole new batch of questions: Could we do the same thing in monkeys or eventually in people by pharmacologically changing that hormonal pathway? Would it be good for us to do it, say, only in the kidney or only in the brain or only in the muscles or only in the liver? It gives us a whole series of new things to look at that have the potential for doing far better for cancer than the cancer research or for lung diseases or for heart attacks.

**KONDRACKE:** These changed hormone productions defeat specific diseases, or do they slow down the aging process in general?

**MILLER:** It's the same thing. They slow down the aging process in general and, as a very pleasant side effect, the diseases are slowed down too because aging is the main risk factor for these diseases.

**KONDRACKE:** Aging renders you more susceptible to disease, weakens you so that the disease can be more likely to attack you?

**MILLER:** Yes. In some ways, it also makes the disease stronger and more difficult to deal with in addition to weakening your defenses. For instance, a caloric-restricted mouse doesn't get breast cancer, doesn't get lung cancer, doesn't get liver cancer. But it also doesn't lose cognitive function, it doesn't lose immune function, it doesn't get cataracts, it doesn't go deaf. It does eventually do all those things; it just does them half a life span later.

**KONDRACKE:** It must be very irritable, though.

**MILLER:** Right.

**KONDRACKE:** So what is the implication or what is the transferability of these genetic discoveries to humans and how far away are we from being able to exploit any of that knowledge?

**MILLER:** The transition is that they provide us with research tools. No one is going to say that we should take people and change their genes and make them only live in that way. That's somewhere between science fiction and arrogance, and that's not what we're talking about.

But having these genetic changes available in our laboratories makes us formulate guesses as to what makes us live so much longer than dogs and less long than whales, for instance, so that we can begin to think about how to postpone not just the diseases, but all the problems of aging—the problems that don't kill us necessarily—things like arthritis and cataracts and deafness that may not be a major contribution to the life span statistics, but which make people reluctant to get old.

**KONDRACKE:** We have no idea how many human genes might affect the aging process, do we? If there are eight in mice, does the genome project tell us anything about that?

**MILLER:** Well, it's a complex question because if the question is, does a gene affect the aging process? the answer to that is probably thousands to tens of thousands. You know, some people have genes that are more likely to make them have a heart attack or become deaf or get gray hair or get colon cancer. All of those genes in some sense affect the aging process.

The genes that I'm more interested in learning about are the genetic differences between people and, say, monkeys that make people live to be eighty and monkeys live to be twenty-five or thirty. The number of genetic changes that were necessary to create a long-lived primate like us from shorter-lived primates from which we evolved, that number is not known. But I have a rational instinct to say that it's rather small. The reason that I think you can maintain that it is rather small, is that in mice, single-gene changes or dietary changes by themselves can lead to a fifty percent life span extension. So the number of things you have to do to get life span extension of a really significant kind – the number of changes you have to make—may be as little as one or two or three.

I will bet that nature, having an opportunity and the need to create a longer-lived primate like us, knew which one or two or three changes were most likely to slow maturation down so that people have enough time to teach their kids and to do what it is they need to do. They mature more slowly than other primates, and, as a side effect, the aging process was put off. Because those are probably the same genes, the ones that time maturation and that ones that, later in life, time how long it takes us to get old.

**KONDRACKE:** Now, there are other factors that I have seen referred to at various times. One of them is oxidation, and anti-oxidants presumably would contribute to longevity, as would some amino acid restrictions. Tell us what promises there are.

**MILLER:** Well, many people think that a key player in the aging process is oxidation. The body uses oxygen—we breathe in oxygen all the time—and inside the cells oxygen can be converted into a very dangerous chemical, which can render the cells sick. And that's been an attractive idea.

**KONDRACKE:** Which are free radicals?

**MILLER:** Free radicals, that's right. So it's been an attractive idea to many people that the free radical damage helps cause some of the signs and symptoms of aging. I think that's an attractive idea, although whether free radical damage is more or less important than other kinds of damage is really not understood in a serious way.

But from my perspective there are other sorts of damage to the cells, as well, that need to be explained before we understand why mice age thirty times faster than people and why dogs age five times faster than people. We're all breathing in oxygen, and we're all bathing in glucose, which can cause other kinds of damage. We're all getting mutations from gamma rays and from x-rays that can cause cancer. Why these things take seventy or eighty years to hurt people and only three years to hurt mice is the important question, and not one you solve simply by guessing that it's all to do with oxidation.

The second question you raised had to do with special diets that have low levels of a particular amino acid, and this is, I think, really exciting work. Our lab is working on that, too. We certainly don't think that starving kids or grownups of proteins is going to be an appropriate therapeutic solution. I do think that by understanding how restricting amino acid intake does slow aging down, and whether there are mechanisms there which overlap with caloric restriction, is going to point us in the right direction. In the vast array of things we could be working on, there are probably three or four avenues that we should be looking harder at and which could pay off. Finding out how different kinds of aging laboratory maneuvers come together will tell us where we need to look more intently.

**KONDRACKE:** What about hormone therapy, which is lately getting a bad name because of side effects that weren't anticipated? What is the promise and what are the dangers of hormone therapy as an answer here?

**MILLER:** Well, that's a question that's not actually about aging research very much because it's a question about the extent to which middle age and older people might be helped by giving them specific hormonal changes. It's not an area in which I'm an expert. The seminars that I've attended have suggested that it's been over-hyped to a substantial extent. There may be some older people for whom the benefits of growth hormone therapy outweigh the very substantial risks, but there hasn't really been a sufficiently long-lasting study to answer that. Some people were excited by the early publications, which said that you took some growth hormone shots and suddenly you got muscular again. That made everybody feel great, but the follow-up experiments have been much less exciting and have begun to highlight the substantial dangers.

People are making millions of dollars peddling these notions to middle-aged and older people who would like a miracle drug to make them young again. It's unscrupulous and it is very hard to be proud of.

**KONDRACKE:** Now, it is your contention that the federal government would be best advised to spend more money on aging research to discover what aging is and how we do

affect the aging process rather than devoting money to specific diseases. Explain why you say that.

**MILLER:** Well, that's certainly true. It's a politically tricky thing to discuss because I certainly understand why people would be motivated—and appropriately so—to study Alzheimer's disease, Parkinson's disease, cancer, and heart attacks. These are important diseases that everyone knows about, cares about, and would like to solve. So I'm not against that kind of research in any way.

But I think people dramatically underestimate the likelihood that the solutions to these problems will emerge from studies devoted to the basic biology of aging. To give you an example, Jay Olshansky, who's a demographer in Chicago, has calculated that if there were no cancer at all—we snap our fingers and suddenly no one over the age of fifty ever gets cancer again—that the average white American woman, who now lives about eighty years, would gain only two and one half extra years of life. In fact, Jay has calculated that if there were no cancer, no strokes, no heart disease, and no kidney disease, that this woman would gain more than two and a half years of life; she'd gain eight or ten years of life.

**KONDRACKE:** Then she would die of what?

**MILLER:** She would die of the same thing she would have died of at eighty, but now she'd be ninety.

**KONDRACKE:** But not one of those diseases.

**MILLER:** She would die of the next disease coming up, of one of the four or five next diseases that include Alzheimer's disease, getting hit by a bus and having a hip fracture, and getting an infection. She would die of something else.

**KONDRACKE:** That's true.

**MILLER:** But aging research in the laboratory, not in people but in the laboratory, has been able to do three times better than that and has been able to do that for the last sixty or seventy years. So if we've got something in a laboratory animal that works, and already can accomplish an extension of healthy life span—vigorous both physically and cognitively—that is dramatically better than the best we could hope for by conquering the four major diseases. I think it deserves a lot more attention, and a lot more brainpower, and a lot more money than it's currently getting.

**KONDRACKE:** Part of the politics of this must be that lots of very young people die of cancer, and that young people die of kidney disease and so on. As opposed to extending life span for older people, we want to save people who are younger, right? The whole purpose of medical research should not be simply to extend the life span of older people, but rather to accomplish a healthy life for younger people.

**MILLER:** You know, I don't think I agree with you there. Many of the diseases that are receiving a lot attention in the scientific community, in the public community, and in legislature as well are diseases that are scourges of people who are middle-aged and older. These people are getting Alzheimer's disease, Parkinson's disease, lung cancer, and breast cancer—all of which are diseases that are really pretty rare in the twenty to thirty year age group. They are receiving a great deal of attention, as they deserve to.

I think that people are motivated to do research to increase the likelihood that not just twenty-year-olds will have long, healthy lives but that will help combat the much more common diseases that afflict the majority of us that will make it into our fifties and sixties and seventies.

**KONDRACKE:** Let me just remind the audience that we are eager for your questions; I can't think of them all. So by all means, e-mail in, or those of you who are here in the audience, scribble off a question. We have received a few off the Web, and I will pose them in a couple minutes.

**MILLER:** Let me say one more thing if it's OK.

**KONDRACKE:** Yes, go ahead.

**MILLER:** It's in response to that last question of whether the motivation for aging research is under-funded and under-appreciated. If I were to come before an influential person, a Congressman or someone who is in charge of the National Institute on Aging, and say, "I've got a cure for breast cancer. So far it only works in animals, but I'd really like to pursue it and can reduce the chances by ninety percent that an older individual will get breast cancer." Everyone would say, "Well that's great. Let's work on it."

If I were to say, "It's got a side effect; it also stops people from becoming blind. Is that OK? Can I still work on it?" "Sure. That's a good side effect." And if I were to mention, "It also stops them from getting lung cancer and colon cancer, and they don't lose cognitive function and they don't lose hearing. Is that a good thing to work on?"

People would say yes until they understand that it's aging research that you're talking about. You've tricked them! What you really want to work on is aging research. It's at that point the doors get closed because everybody knows that aging research is not going to be productive.

**KONDRACKE:** Why do they think it's not going to be productive?

**MILLER:** Well, for a variety of reasons. Some people associate aging research with hucksters; people who are pushing growth hormone and DHEA and melatonin. People are so—appropriately—frightened of getting old that they are willing to turn to unproven remedies that are introduced to them by people with a friendly smile and a testimonial or two. The far smaller number of us who are honest and serious students of aging are sort

of drowned in that societal understanding that people talking about aging are quacks or crackpots.

If Nixon goes on TV and says, “We will cure cancer,” he gets applause. You know, everybody thinks that’s a great thing. If a president should be so foolish as to go on TV and say, “I’m going to invest the resources of my administration to slowing the aging process by fifty percent,” he or she is going to be jeered at and laughed at. That’s a matter of public misunderstanding; that’s a matter of society and people who run the press. The intellectual leaders who set the tone for discussion in this country have set up that situation so that’s a laughable statement.

**KONDRACKE:** How would you reverse that? If a politician said, “I intend to extend the human life span and to help people live happier, longer lives or healthier, longer lives,” I would think that that would politically be a winner. Would it not?

**MILLER:** I would think that, too, but you and I are in the minority. As you can imagine, I’m not going to mention any specific presidents, but individuals who say, “We’re going to devote the resources of this administration to slowing the aging process down,” they would be considered weirdos.

How do you reverse it? I think you reverse it by having Webcasts of this sort compulsory in all schools throughout the country for the next 20 years.

**KONDRACKE:** Support your local gerontologist.

**MILLER:** Yeah.

**KONDRACKE:** You would describe something as gerontologiphobia. What’s that?

**MILLER:** My wife is an English professor and we sat down to dinner one day with a distinguished colleague of hers, a professor of philosophy. She was really eager for me to get to know this guy and for us to become friends. He was really going to be an intellectual resource for us in Ann Arbor. I told him I did aging research and he said, “No; that’s not a good thing.” And I said, “Yes it is.” And he said, “No, that’s a terrible thing to do. We don’t want the world to fill up with old people. We’ve got to stop aging research, because if, God forbid, you should get it to work, then everybody will just become old and we don’t want to be surrounded by old folks all the time.”

And I tried, politely at first, before he stormed away from the table, to say that that kind of reasoning doesn’t make any sense as far as I can tell. If you believe that’s the case, then you ought to be against cancer research—and you ought to be against research in cardiovascular diseases. And he was in favor, as most of us are, of cancer and cardiovascular research. He’s against giving away cigarettes in schools. He’s against taking seat belts out of cars because, in general, like all of us, he is in favor of things that will increase the likelihood that we’ll get to be seventy or eighty and be in terrific health. And I said that’s what I was doing and he said, “No, no. You’re doing aging research.

You want us to live forever and the world will fill up with old people.” He wasn’t able to recognize that the good kind of research, the kind that everybody except me is doing, and the bad kind that us gerontologists are doing, were aimed at the same kind of problems and that, if successful, would produce the same kinds of situations and deserve the same kind of moral support.

But the position that this fellow took, before leaving our lives forever, is extremely common.

**KONDRACKE:** Right after dinner, I take it.

**MILLER:** Right after dinner. I was polite over the appetizers but when the main course arrived we were yelling at each other. But it’s extremely common, and if I give a lecture that has an audience that is non-scientists, educated people who work in other professions, this is almost always a question that I get, “Aren’t you doing a bad thing by trying to slow aging down?”

I think that’s simply a mistake, but sometimes it’s a mistake that people are very slow to come around to understanding.

**KONDRACKE:** We have a question from the audience: “What is the most important finding in aging research over the last ten years and what is likely to be the most important over the next ten years?” Good question.

**MILLER:** If you had asked me that question ten years ago I would have said, “Caloric restriction!” Caloric restriction is the breakthrough that proved you could slow aging down.

But now I think the most important finding is actually an observation from the study of mutants in worms, of all things. People have made a lot of different types of mutations in worms to slow life span down, and the really cool thing is that these mutations have a side effect and that is that they make the worms resistant to all sorts of stresses. I don’t mean worry about the next exam. I mean if you irradiate them or if you give them an oxidizing chemical or if you heat them up a little too much—these are really bad things and worms tend to die—but the mutants that would live a long time are resistant to all of these stresses.

And the reason that’s an important finding is that it’s a big clue as to what it takes to expand life span and to slow aging down. It suggests that you’ve got to find ways of increasing the resistance of cells throughout the body to all sorts of things.

So the next step in that, which is just now becoming clear, is to ask whether stress resistance of that kind also applies to mammals. Several labs, mine included, have begun to document that if you have mutations that make mice long-lived, that these cells from these mice are also stress-resistant. So that opens an important therapeutic approach. If you could figure out what it takes to make cells stress-resistant, this might be the same

thing that it takes to slow aging down. We can now study people that are going to be very long-lived and people that, like most of us, are going to die in their seventies and eighties and ask, Do they differ in their cells which are stress-resistant? Are there genetic factors? Can we mimic that with specific hormones or nutrients or behavior modification?

These are the avenues toward prevention that are very likely, if pursued appropriately, to give us ways to prevent not just one disease, but all the diseases of aging together. That's the breakthrough that I think is most exciting and deserves to be focused on the most.

**KONDRACKE:** But what you are doing is studying the consequences of the mutation of genes, as opposed to how to manipulate genes in humans. In previous SAGE Crossroads debates we have discussed germ line engineering and actually reengineering human beings. That's not where you're going. You're going to medicines that people would take to reduce the oxidation or stress or increase stress resistance that you learned from your genetic studies.

**MILLER:** That's exactly right. The genetic changes are changes that give us research tools to ask questions about the physiology and the cell biology so that we can come up with medical strategies—presumably drugs, but who knows—to accomplish the same thing that nature does by genetic changes.

**KONDRACKE:** OK. Another question: “Is your goal to understand the aging process for slight improvements of quality of life, still allowing for a natural course of aging or for drastic extension of the number of years lived?”

**MILLER:** I guess it depends on what you mean by drastic.

**KONDRACKE:** Is there in aging research a thought about whether there is a natural limit to human life span?

**MILLER:** Sure. It used to be when people were asked this question to try to pick a number that was large enough so that they'd be the first person mentioned in the lead article in *LIFE* magazine. There would be a competition to see who would push that limit the furthest.

But I think there's actual data now and there's a good clear answer: Caloric restriction extends life by about fifty percent. Each of these genetic mutations extends life span by about thirty or forty or fifty percent. So we can, without stretching a point, understand that we've got good reason that we can slow down aging and, in that way, get a fifty percent increase in age extension so that the average person who is ninety years old would be roughly as healthy or unhealthy in a variety of ways, productive or unproductive as today's sixty-year-old. I think that would be an important and exciting thing to do.

Whether one considers that a drastic or a small change, that depends on your perspective. From the perspective of a mouse, that would mean getting to live as long as a dog would,

and that would be a dramatic extension of life span. From our perspective, it's not that impressive.

**KONDRACKE:** Doing the math here, you are saying that the average human life span could be extended by forty years.

**MILLER:** Yeah.

**KONDRACKE:** So we could live to be 120.

**MILLER:** If we were able to accomplish in people what is now routine in mice, it would be an extension of about forty percent—about thirty or thirty-five years would be reasonable to expect. More than that is science fiction. It's guesswork. You can't say it could never happen, but there's no reason to expect it either.

**KONDRACKE:** Another question: "Is gestation length somehow related to longevity? Or is there a constant ratio?"

**MILLER:** There are differences among different species that parallel, more or less, the differences among species of life span, and it has to do with evolutionary principles. There are some kinds of animals, like mice, who live in a very risky environment where they're going to freeze to death or they're going to get eaten by a fox. For them it's really important to have a short gestation period, get their babies out there before they themselves get eaten. And that kind of environment doesn't produce slow aging, it produces really fast aging.

Individuals like us and elephants and whales, where we're much less likely to starve to death or get eaten by a fox, have a life span that's a lot longer, and we can also afford to have longer gestational periods. So the two tend to go hand in hand. Whether it's cause and effect, which is, in some sense, an implication of the question, is a much trickier thing to decide.

**KONDRACKE:** OK. Looking at hormones in aging—insulin, IGF1, growth hormones and sex hormones—what are we learning about their impact on aging, both pro and con?

**MILLER:** Well, we're learning very different things. Insulin is a critical player in diabetes and diabetes is a scourge of all Westernized countries. Learning more about diabetes and how to prevent it and the role of insulin is a great thing to do. Whether it has much to do with aging, I think, is less likely. IGF1 is the thing that is going to be more informative than insulin research, and the reason is that nearly all the mutations in the worms that extended life span block IGF1.

**KONDRACKE:** IGF1 is what?

**MILLER:** It stands for Insulin-like Growth Factor 1. It's related to insulin but it has a very different role. Of the mutations in mice that extend life span, five of the eight also interfere with IGF1. And, if that's a coincidence, that's a huge coincidence.

So people have begun to think—and it's very sensible—that IGF1, among its other roles, makes us grow fast, is good for bones and muscles, but also may be that it times the aging process. Maybe, when we are children, it sets our whole life span so that we are more likely or less likely to make it into our eighties in good health.

**KONDRACKE:** So where is IGF1 on the therapeutic process? I mean, is there a pill on the horizon or injections of IGF1?

**MILLER:** There's no reason to think that would be a good thing. There is some reason to think that might be a bad thing, particularly for children. The genes that lower IGF1 levels in early life tend to promote life span—exceptionally good life span. But no one would suggest that you should take a batch of kids, as an experiment, and shoot them up with something that's going to make them really short in the hopes that they would be extremely long-lived.

**KONDRACKE:** That would be the consequence of...?

**MILLER:** That's a plausible guess, but no one really knows.

**KONDRACKE:** I see. Well, are there biomarkers for aging and how would we develop them?

**MILLER:** Well, a biomarker, as I would use the term, is something you can test how old someone is in a biological sense. You might have someone who's fifty years old by her birth certificate, but who you think might have the health of a seventy-year-old or a forty-year-old. You'd want to be able to do a test to see among people who are in middle age who are looking older or looking younger from a variety of perspectives.

Studying aging without biomarkers is like trying to study blood pressure without a blood pressure cuff, or fever without a thermometer, in the sense that biomarkers would provide a scale for aging. And unfortunately we don't have any good ones yet. We have a few that sort of work in mice, but the kinds of research to measure the aging rate in people is very unpopular, very under-funded. It's not exciting science, it just happens to be very important science.

**KONDRACKE:** This next question relates to the phobia of gerontology, and it goes to the question of evolutionary biology. One of the theories on why people age is that evolutionary biologists used to think, as I gather, and no longer do, is that Mother Nature really did want to clear the field for younger, reproductive-age humans or animals and clear out the clutter of old people. Now, I gather that that is no longer accepted among evolutionary biologists. Can you explain why?

**MILLER:** Well, it's a popular thing. Whenever I go to talk to medical students, there's always somebody in the classroom that says, "Yeah, it's got to be just like you said: You have to have a gene to clear out the old folks so that the young folks can inherit the farm," or something. The problem is that it's a misunderstanding of how selection works. If you actually had a gene that caused aging, that gene would go away because aging is bad for you. It doesn't help you leave additional children to get old and die. The genes that are good for you are the ones that slow aging down.

So there may be genes for slowing aging down, but genes whose function is to cause the signs and symptoms of aging are wiped out by ordinary Darwinian pressures. Just like there's no gene for making you run slow or think slow or not know how to talk, there are no genes for causing aging. They're really bad things to have.

**KONDRACKE:** And yet aging is such a constant in life and in biology that you would think that it does serve some sort of evolutionary function, wouldn't you?

**MILLER:** No, you wouldn't. Aging is really common because there's not enough selective pressure to put it off forever. A mouse in the wild lives six months. You don't need to make a mouse that'll live ten years because it's going to get eaten. You don't need to make people that are going to last three hundred years because when we were living in caves and growing up as Neanderthals, most of us didn't make it past thirty, so there was no need to design a person that could last five hundred years. People just didn't make it regardless of whether they aged or not.

Nature has evolutionary pressures to make individuals that last long enough to make a couple of babies, enough to repopulate the species, and not much longer than that. Any additional work done in that area would be wasted effort—waste of effort that could go into reproduction, which is what selection actually pays attention to. There are a lot of things, including aging, that are in nature, but are not the positive product of the selective process.

**KONDRACKE:** We're almost to the end here. If you were to have a message for Congress, you would tell them what as to the kind of funding levels that the aging field could absorb? And what kind of results could you produce for them, do you think, say, over the next decade?

**MILLER:** I think it's rash to make promises; it can lead to overly high expectations.

I think that the promise of aging research is so dramatic that the pittance that it receives is a national shame. And if the amount of funds going into aging research were to increase gradually, but dramatically, over the next five or ten years, it would have the advantage of attracting the best brains in the next generation and giving them the money they need to test out all these exciting theories.

Twenty years ago, aging research was a backwater. The only kind of research people could do was to take some old animals and some young ones and see how they differed.

But now the scientific community has brought out a dozen really exciting ideas about how aging might work. There are actual exciting problems and useful methods that could be brought to bear on testing those ideas.

They won't get tested if the field is under-funded because the money is necessary, and, just as important, smart minds are necessary. Scientists, like all of us, want to have jobs, they want to be able to support their families, and they want to go into areas that are well funded.

So new funding is important to boost the community. And that's a job that scientists by themselves are not going to be able to undertake. It requires, more than anything else, the support of individuals who have the ear of the public and the ear of those who set science policy.

**KONDRACKE:** Dr. Richard Miller, thank you so much for being with us.

End.