

How Long Can We Live and What Do We Know About the Aging Process?: An Interview with Longevity Expert S. Mitchell Harman, M.D., Ph.D.

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Dr. S. Mitchell Harman is an internationally recognized expert regarding the effects of aging on hormone regulation and the use of hormone therapy in older men and women. In 1999, Dr. Harman became the first Director of the Kronos Longevity Research Institute in Phoenix, Arizona. Established to conduct and foster translational research, the Institute provides a critical link between findings from the basic research laboratory and corresponding improvements in clinical care and human health. In the following interview, Dr. Harman draws from his rich professional experience to provide a revealing perspective on gerontology and related issues of aging.

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Dr. S. Mitchell Harman, Director of the Kronos Longevity Research Institute, is an internationally recognized expert on the effects of aging on hormone regulation and the use of hormone therapy in older men and women. Dr. Harman received both his Ph.D. and M.D. in 1970, graduating with honors from the 6-year combined Medical/Graduate School program at the State University of New York Downstate Medical Center.

Dr. Harman has trained in Internal Medicine at the Yale New Haven Medical Center, in endocrinology at the Reproduction Research Branch of the National Institute of Child Health and Human Development (NICHD) of the NIH, and in gerontology at the NICHD Gerontology Research Center in Baltimore. In 1976, he founded the NIA laboratory for the study of aging of the reproductive hormone system in males and females within the Endocrinology Section. While in Baltimore, Dr. Harman joined the faculty of the Johns Hopkins University and became a member of the attending physician staff of what is now the Johns Hopkins Bayview Medical Center (at that time, known as Baltimore City Hospital). From 1974 to 1999, when he retired as a Captain in the U.S. Public Health Service, Dr. Harman rose to become the Chief of the Endocrinology Section in the Laboratory of Clinical Physiology, IRP, NIA. He also served as acting Chief of the LCP and acting Clinical Director of the NIA for nearly two years.

Dr. Harman was promoted to Associate Professor of Medicine at the Johns Hopkins University in 1984. He is board certified in both Internal Medicine and Endocrinology. He is the author or co-author of one book and nineteen book chapters, many in major textbooks of Medicine, Geriatric Medicine, and Endocrinology. He has published 58 peer-reviewed papers and presented numerous research reports at scientific meetings. Dr. Harman is also the holder of 5 patents in the area of controlled release drug administration. In 1995 he received the Louis M. Hellman Master Teacher Award from the Downstate Medical Center.

In 1999, Dr. Harman became the first Director of the Kronos Longevity Research Institute. The Kronos Longevity Research Institute was established to conduct and foster translational research—the critical link between findings from the basic research laboratory and corresponding improvements in clinical care and human health. With

aims of preventing the common diseases associated with aging, slowing the aging process, and prolonging a vital, healthy human lifespan, the Kronos Institute disseminates accurate scientific information (regarding novel strategies for reducing the deleterious impact of the aging process and age-related illnesses) to both the professional and lay communities via publication, scientific meetings and symposia, and the media.

How important are hormone changes in producing some of the things that we attribute to aging—some of the things that are responsible for a loss of function?

I have spent my research career up until now first documenting which hormones change and how much they change as people get older. This involves investigating the mechanisms responsible for those changes in some experimental systems in animals, and then, most recently, looking at the effects of replacement hormones in older people to see if some of the documented losses in function that occur with age are really due to the hormonal changes. It is clear that altered hormone balance does explain some of the changes in body composition and function that occur with age, but this is far from the whole story. Since I have taken on the Directorship of the Kronos Institute, I have not been nearly as specialized because I now have a much broader mission. I can't just limit myself to hormones. I have had to start to think about aging as a whole and its effect on all of the important systems that maintain health and life. So my time here has involved a very steep learning curve. I have learned a lot about many things that I really didn't know very much about before, like oxidative stress, cardiovascular disease, cognitive changes, and other issues that really weren't on my plate at the National Institute on Aging.

You may have already started answering this question, but how did you get interested in studying aging?

I came to Gerontology, the study of aging, the way most people in science get interested in one thing or another. In 1964, when I graduated from Emory University with a Biology major, I was actually interested in what is now called genomics, but at the time there

wasn't any science of genomics. There was cytogenetics; people were counting chromosomes and beginning to figure out which known genetic traits were carried on which chromosomes. The methods were primitive, involving examining stained spreads of chromosomes under the microscope—to subdivide them by visible bands and try to figure which traits segregated with which bands. I went to the Downstate Medical Center of the State University of New York at Brooklyn to begin an MD, PhD program, thinking that I would do work in genetics and cytogenetics. If I had done that, I would probably have been a full professor at Harvard or Yale by now. Because, as you know, this has turned into a very hot field. But when I got to Downstate there wasn't anybody there working in cytogenetics, so I couldn't find a major professor for my thesis in that area. I wound up doing a reproductive physiology project in the Anatomy Department because reproduction was about as close to genetics as I could get. The Anatomy department, at that time, was very interested in aging as it affected the reproductive system. My major professor, George Talbert, had done some really groundbreaking work in terms of understanding how the aging process affects ovarian function. And what you do when you are a graduate student is what your major professor is interested in. So I got into aging.

I have known you for a while and you seem to know what the real questions are. The important questions.

Boy, I wish that were true. I would like to think that I know what some of them are, anyway.

What do you think are the important questions right now in the field?

In aging?

Yes, issues and questions.

The really important questions have to do with the mechanisms underlying the aging process and what leads to the progressive, cumulative damage to cell components which we call aging. A related question is why our stem cells, which are present in many tissues, fail to efficiently replace age-damaged, senescent cells with new functional cells over time. The manifestations which we can see, the aging phenotype, has been well known for centuries—gray hair, sagging weakened muscles, wrinkled skin, increased body fat. But, the processes underlying these changes are just beginning to become clear. We are starting to learn to measure the rate of damage, distinguish the different kind of damage, as well as which organs are being damaged most. We now have some clues to where the chemicals that cause this damage are coming from and how the repair systems work to ameliorate, prevent, and minimize the damage. When we fully understand those processes we'll (1) know what aging really is and (2) have some very good clues concerning what to do about it.

Is there anything on the horizon that supports these indications?

Oh, absolutely. There are a number of very exciting developments in aging. First of all, evidence continues to accumulate that oxidative damage to cell components (that is, to proteins, to the lipid in the cell's membranes, and—importantly—to both nuclear and mitochondrial DNA) is really at the heart of the aging process. I think the evidence is so good now that many alternative hypotheses are falling by the wayside. So, that line of research is very, very important. The most exciting single finding is that the life span has actually been extended by as much as 50% in a variety of organisms, by what is called caloric restriction. What these experimenters do is to make sure that the animals get all of the nutrients that they need to survive—enough protein, enough vitamins, enough minerals—but the absolute number of calories is cut to 35-40% below what they would consume if allowed to eat all they wanted (*ad libitum* feeding). What happens in these animal models, whether it is fruit flies, or round worms—those little *Caenorhabditis elegans*, that the worm runners love so much, or mice and rats which, compared to the first two species are very close relatives of ours—is that all of the changes that would be associated with aging in those animals (and, of course, the manifestations differ in different species) are delayed. For example, in the mice—one of the things that happens with age, just as it does in humans, is that the cancer rate goes up. Mice only live about two and a half years. In mice that are 15 to 18 months old, you see a big increase in cancer. Well, if you calorie restrict those animals, the cancer rate goes up but it goes up much later. They die at over 3 years of age. The whole aging process gets stretched out. At 2 years those animals still look young. They are vigorous, whereas the *ad lib* fed animals look old and sick—they are dying. So, what this suggests is that the aging process is modifiable. That it is not inevitable. That there is not a limit to the life span that can't be moved.

What is really exciting about this work (because, obviously, most people are not going to restrict their calories by 40% from the age of 15 or 16 years) is that there are some agents which seem to imitate some aspects of what caloric restriction does and also reduce oxidative damage. I think that in the near future there may be candidate drugs which can be tested, that will act like caloric restriction at least partially, and reduce the rates of aging damage.

One theory as to why caloric restriction reduces the rate of damage is that if you have less energy to burn—that is, less available fuel to burn—the mitochondria (the little energy factories in our cells that provide the cell with energy in the form of adenosine triphosphate—ATP) become more efficient. Mitochondria combine carbon fragments from fats and sugars with oxygen, in order to produce ATP. However, mitochondria leak what are called oxygen free radicals, such as superoxide, which combines with water to form another toxic compound, hydrogen peroxide, and other very reactive molecules. These highly reactive compounds

damage a variety of cell components. Mitochondria that are on a restricted diet may become more efficient. This may be because certain mitochondrial genes become more, or less, active. The mitochondria don't leak as much oxygen free radical and therefore the whole aging process gets slowed down. Also, defense mechanisms that detoxify oxygen radicals may be up-regulated. In fact there are new agents which act like the enzymes that intercept and detoxify the oxygen free radicals. These enzymes are called SOD (superoxide dismutase) and catalase. There are now drugs that act like SOD and catalase. They get into the cell and break down superoxide into harmless oxygen and water.

That is one of the questions I wanted to ask you and you have gotten into it. What do you think about the anti-aging drugs and herbs, including anti-oxidants, that are on the market? Do you believe that they are effective?

I'll come back to that, but first, I do want to mention that there is another really important development in understanding aging that is different from oxidative stress, and that is the telomere hypothesis. This interesting mechanism of aging that still needs to be worked out has to do with what is called the Hayflick phenomenon. Dr. Leonard Hayflick discovered that if you culture normal cells—not cancer cells, but just normal healthy fibroblasts from skin—they will divide a certain number of times in the culture dish and then stop. These cells are said to undergo replicative senescence because they won't divide anymore. It turns out that the likely reason for this is that every time cells divide, some little structures called telomeres at the end of their chromosomes get shorter. When they shorten beyond some critical limit, the cell gets a message to stop dividing. Most normal somatic cells—that is, body cells—lack an enzyme called telomerase that extends the length of the telomeres. Germ cells, which are immortal (if you think about it, we're descended endlessly from a chain of immortal—so far—living cells, back to the dawn of life), extend their telomeres whenever they divide. Other cells that do this are most kinds of cancer cells. So, they are immortal too. The telomerase story, I think, is going to be very important in understanding aging. How we put oxidative stress and the telomere/Hayflick phenomenon story together will probably give us the key to how aging really works. I would say that the caloric restriction experiments, the understanding of oxidative stress, and the telomere story are probably the most important developments in aging right now.

Do those relate to antioxidants?

What most antioxidants do is to act as substitutes for cell components that might otherwise be damaged. They "sacrifice" themselves by becoming oxidized and they use up the oxygen free radicals. Therefore the oxygen free radicals don't damage the cell components because they run into vitamin E or vitamin C, or whatever antioxidant they encounter first. They expend their fury on

the antioxidant, after which they are harmless. In fact, we have a lot of natural antioxidants in our cells, including these vitamins, as well as systems for reducing and regenerating our natural antioxidant molecules, such as glutathione. Without these natural antioxidants, we would probably age a lot faster. We also have several different enzyme systems that can detoxify oxygen free radicals and repair oxidative damage. The problem is that none of these mechanisms is perfect. None of them are 100% effective. So, some of the oxygen free radicals get through and damage the cell components and some of this damage goes unrepaired. So, it accumulates over time.

Is this what aging does? Is this what is meant when we read about research on "slowing down aging" or "reversing" the aging process?

Well, that is what we think. That is the theory. And I think the evidence is pretty good for that now.

What I am hearing—and I'm not sure that I am understanding the level of what you are saying—is that maybe we can retard some of the aging process. Diet, caloric intake, and the antioxidants may help, and I have heard that researchers may be developing drug enzymes that will extend life.

The problem is that the antioxidants we have examined to date—things like vitamin E, CoQ-10, and others—are not very effective. They don't seem to diminish the rate of damage very much. The reason, probably, is that our cells are already pretty good at detoxifying free radicals. There is a very delicately regulated system in place to do that. So, if you add a lot of vitamin E and you reduce the amount of free radical, the enzyme systems—such as SOD and catalase, which are responsible for going after free radicals—get the message that there is not much free radical around and, therefore, down-regulate, resulting in no net gain in oxidative protection. So, we need more effective interventions.

We need ways to up-regulate those enzymes or imitate those enzymes. We need antioxidants that are much more powerful than the ones we have. Basically, all the things that are being sold right now with claims that they extend life span, don't...There is not a bit of evidence that any of them extend life span. In humans or in any animal model.

I read something just recently about vitamin E that goes along with what is being said, that one should not take more than 800 units of vitamin E and that it actually decreases its anti-oxidant qualities.

That is right, it makes things worse, and vitamin C is even worse in this regard. Vitamin C in high doses actually becomes a pro-oxidant. Low levels of vitamin C act as an antioxidant, high levels may become toxic. They have the exact opposite effect from the one desired, increasing the rate of oxidation. A normal vitamin

C dose is somewhere around 100 mg. More than that is probably not helpful. I think that at over 400 mg/day, adverse and unintended consequences may occur.

One of the things in the literature that is confusing to me is the difference between slowing down aging and reversing aging. Are we really ever reversing aging or are we just slowing it down?

Actually, there is one intervention, which I haven't mentioned yet, that may "reverse" aging changes. This other intervention affects what is called glycation cross-linking, which is probably another important mechanism of aging. It is a process different from, but related to, oxidative stress. It is due to glucose molecules which, like oxygen free radicals, are also very reactive, sticking to proteins and linking them together. This process of cross-linking is thought to cause stiffening of tissues and membranes, etc. The cross-links accumulate with age and this process alters or impairs protein function. You can't easily get rid of cross-links either, because they can't be broken by protease enzymes that would normally clean up the damaged protein. So, you are stuck with them. The cross-linked molecules are called advanced glycation end products, or AGE's. These AGE's may play crucial roles in some of the clinical manifestations of the complications of diabetes mellitus, a disease which in some ways has been described as an acceleration of aging. There is a new family of drugs that actually break the AGE cross-links. They are called AGE breaker compounds. This is another very exciting development.

I think when we really understand this whole business, some combination of antioxidant compounds will either stimulate or emulate the enzymes that break down the oxygen free radicals, perhaps some agent that stimulates repair processes, and the AGE breakers will be used to promote longevity. It will be a cocktail of different strategies that, put together in the right proportions, will slow the aging process. But, to truly reverse the process, no, I would be very surprised. That would require a different order of intervention, something on the order of genetic engineering, replacement of stem cells, replacing the damaged tissues, essentially cell by cell. That kind of intervention is not out of the question, but not on the near horizon either, in my opinion.

By definition then, one could believe the AGE breakers may be reversing aging at some level.

Yes, reversing a small part of the aging process.

You may have answered this already, but what do you think is the most significant achievement in aging research, you indicated...

I've already mentioned the Hayflick phenomenon and the discovery of telomeres and telomerase and the experiments with caloric restriction. I think those are probably the most significant things going on. And actually there is an experiment going on at the NIA

right now, and one other center, looking at caloric restriction (CR) in primates. We know CR works in mice and fruit flies and a number of other animals, but it has never been tried up until now in a really close relative of ours. And it looks as if (although it is too early to say for sure), it looks as if it is going to work in monkeys. The indication we have is that the monkeys have now reached the age where the cancer rate should go up and in the *ad lib* fed monkeys it is going up. But, in the caloric restricted monkeys there are many fewer cancers. So, we don't know yet if CR is going to work, based on mortality rate. But, the cancer rate looks very suggestive.

Do you think that would hold in humans?

It probably will, but I can't imagine most people—there actually are people out there doing CR on themselves. There are fanatics who are out there restricting their calories. But, the problem is whether they are getting adequate nutrition. I suspect that a lot of them aren't doing a very good job of it. They are trying to live on lettuce and their immune system may be subnormal or malnourished. They could become more vulnerable to infectious diseases, among other problems.

They may not die of cancer, they may die...

They may die of infectious disease, or something else, instead. It is very hard to get adequate nutrition, enough protein, and enough vitamins and minerals and certain other nutrients, while trying to live on cabbage and string beans.

You may have answered this. Is there a biological or genetic upper limit to how long we can expect to live? What are the significant factors that contribute to life expectancy, and if you could, name them and maybe rank order them?

You know that life expectancy is a funny business. It depends on what you mean by life expectancy. Every species has what is called a maximum lifespan potential, or MLP, which is species specific and, hence, must be genetically determined. There has never been a 90 year old dog and there probably never will be, because dogs have a maximum life span of 25 years or so. Actually, that varies also with the breed of dog. So we know that genes determine maximum life span because it is species specific and varies predictably, even within different strains of the same species. That last animal in any birth cohort, no matter how well you treat it, dies at a certain age. For mice (for most strains of mice), MLP is 2 to 3 years. For Chihuahuas it's up to 25 years. For horses, maybe 30 years. For man it is something, just a little over 100 years. There are few outliers that get to 110 or so, but absolutely nobody gets much past that. So we humans have a genetically determined MLP and right now we have absolutely no intervention, except for caloric restriction, which hasn't been tried in humans—which can extend the maximum life span. But when you talk about life expectancy, that is

a separate issue. What we really mean is how many years an individual can expect to live. And the average life expectancy has been increasing over the centuries.

But if you want to know how to extend your life expectancy, the answer is better nutrition, wearing your seatbelt, keeping your blood pressure under control, and a whole bunch of other common-sense things that we know will reduce the risk of chronic diseases that are the major causes of death in western society. It is clear that eating lots of fruits and vegetables, and especially cruciferous vegetables—the cabbage-related vegetables—decreases your risk of getting cancer. If you think about it, most people die prematurely of heart disease or cancer. If you exercise regularly, eat correctly, don't take risks like jumping out of airplanes, etc., you are going to extend your life expectancy. Control your lipids, control your blood pressure... These are all things that we know work. But, you haven't extended the maximum life span potential by doing these things. What you have done is improve the probability that you will get closer to that maximum potential. Genetic factors also affect life expectancy. Centenarians tend to run in families, so it would seem that there are people who just have "good genes." They probably have better DNA repair processes, better antioxidants, better whatever it is that slows the aging process. Because, after all, if you think about it, we evolved from shorter-lived ancestors, truly shorter-lived ancestors. Our line diverged from the common ancestor we share with the chimpanzee about 4 million years ago. Chimps live to be, on average, 48 or 50 years old—substantially less than humans. Evolution has changed our genes over the last 4 million years and we have increased the chimpanzee lifespan. So, it isn't surprising, given the variation in genetic complements in the population, that some people probably have genes that are better at improving life spans than others. This is part of the explanation why some people die of old age at 80 and some people die of old age at 110. If you don't get any of the age-related diseases you are still going to get old. The question of how old you will get before you wear out is probably settled by genes.

One of the things I think you implied just now relates to my next question. I want to get an estimate of what you think is most important, or least important, in helping one reach their maximum. But I think you are saying...

I'm saying that if you can avoid heart disease and cancer, you have a much better chance. The way to avoid heart disease is to stay lean, to exercise, to eat a diet which is low in saturated fat which eliminates trans fats, eat lots of fish which contains plenty of omega-3 fatty acids, and eat lots of fruits and vegetables, which also help reduce cancer. Then, of course, there are other standard things that you can do to reduce your risk of cancer. The big killers are lung cancer (so, don't smoke), breast cancer (so, women should get mammograms every year, because if you catch breast cancer early, you probably won't die of it), and prostate cancer in men (so,

again, getting a PSA every year after the age of 50 is a good idea). Then there is colon cancer—a lot of that can be prevented by getting a colonoscopy over age 50. There are other medical things that you can do to improve your chances, such as controlling blood pressure. And if your lipids are high, we have these wonderful statin drugs now. A statin and Niacin can get almost anybody's lipids into the normal range, unless they have a serious genetic disorder.

Don't they affect things like the liver?

No, the new ones have almost no effect on the liver. Liver toxicity is the big bugaboo that everyone is worried about. We just don't see it much.

That is interesting.

Millions of people are on statins now and I don't know when the last case of hepatic toxicity that I have heard about or read about occurred.

One of the other things I think about is exercise. Can you do too much exercise? How do you know when too much is too much?

When you start hurting yourself, when you start tearing your tendons and muscles, you are doing too much exercise.

The hardest thing for me to do is maintain anything.

Yes.

I could lose weight, but I can't maintain. I could exercise if I am continually competing with myself.

You know, it seems like the maximum benefit that you can get from exercise in terms of health and life span extension, etc., is 4-6 hours a week of moderately vigorous exercise. Beyond that you may get stronger, you may become more competitive, but there is no evidence that you are improving your risk of avoiding heart disease or dying.

What does moderate mean?

Well, I can't really give it to you in mets or calories, but what it means is swimming at a reasonable pace or jogging. Not running so hard that you get a stitch in your side, but jogging 2-3 miles over a period of 45 minutes or 50 minutes. That is moderate. Once you try to do more than a 10-minute mile you are probably pushing it, and there are of course people who are talented athletes that can do that easily. But a ten-minute mile, that is 6 miles an hour. If you go beyond that you are probably beyond "moderate."

But if you do one mile would you want to do two or three miles?

Yes. I am 58. I can run four 10-minute miles.

I can't.

If I try to get beyond that...

And that is probably more than you would need to do. You answered my question, regarding the word moderate. People say moderate but it means different things. Therefore moderate may be idiosyncratic to the individual. Like the 10-minute mile for some people may be really...

Well, moderate performance goes down as you get older. I don't expect to be able to do that 10-minute mile easily 10 years from now. It would be nice, but I'd be surprised. You really need to work with a trainer—an exercise physiologist—to get a sense of what is appropriate for you. And there are tables, etc. I am not an exercise specialist. In fact, we just hired a really good young scientist with a Ph.D. in exercise physiology to help us with our exercise program.

Exercise has really become a science in the last few years. Our body ages at different rates. Would there be differential effects on different organs, such as the brain?

Yes, well, there is no evidence, for example, that diet or exercise will help prevent Alzheimer's disease. We can talk about some of the things that do seem to help with that disease, but that is a nut that we are really going to have to crack, because it is a serious problem. And the incidence tends to go up very steeply as people get into extreme old age. The incidence of Alzheimer's degeneration gets very high, affecting perhaps 20-30% of the population over 85. And we still don't know how to prevent that. Estrogens seem to help and there are some drugs out there which may also help a little, but Alzheimer's is a big problem and we still don't completely understand it.

There are some drugs on the market or in development that will supposedly help either reverse or slow Alzheimer's down.

Slow it down, yes.

They also use the word reverse.

I don't see any evidence yet.

Do the scientists researching Alzheimer's Disease know anything about how to slow down the aging process?

Well no, Alzheimer's Disease is not a natural aging in the sense that it happens to everyone. It is a disease. If you don't have the tendency to get it you probably won't. There probably are—in fact we know there are—important genes that increase your risk of A.D. We are identifying some of them. If you don't have any of those genes, you probably won't get Alzheimer's. There are people that have lived to 120 and didn't get Alzheimer's. They are aging, but they don't get Alzheimer's.

In other words, the percentage of people that get Alzheimer's is different for different age groups. Of course, we can get A.D. while young, but it is really a function of age. As we get older we are more likely to get it. There seems to be an order to that.

Yes, the age-related diseases all look like that though. If you look at overall rates of cancer or heart disease, etc. you'd see the same phenomenon. The difference between aging and age-related disease is confusing to people. Aging is a background process which is going on all the time, which makes us increasingly vulnerable to whatever age-related diseases we happen to have a propensity for. If you have the genes that lead to a high risk for heart disease, you probably are not going to get it at 25 or 30, but you may get it at 45 or 50. So, it is an age-related disease. If you have somewhat better genes or dietary habits, or a combination thereof, you might not get your heart disease until you are 75 or 80. If you are really careful about diet and exercise and you have just the right genes, you may never get coronary disease at all. So heart disease is an age-related disease in the sense that aging, or age, is one of the vulnerability factors that determines when the disease will express itself clinically. That is also true for Alzheimer's disease. It is also true for cancers, etc. But they are all diseases. Type II diabetes is another example. There are a whole variety of factors which affect vulnerability to age-related disease and age itself is just one of them. Your particular genetics, your body weight, how much you exercise—all will affect the likelihood that you will get diabetes at any particular age. But age itself is also a factor. Very few people get Type II diabetes in their 20s. Lots of people get it in their 50s. But diabetes isn't aging, it is diabetes.

So, what we talked about earlier—caloric intake, antioxidants—may be slowing down the aging process, but also slowing down the disease process?

It won't slow down the disease process. But if you slow down the aging process—if you set your biology to the point where at 60 you are really more like a 40 year old—then your probability of getting an age-related disease would be the probability of a 40 year old and not the probability of a 60 year old. Think of aging as the background—the field—upon which the events are occurring.

There seems to be an increase in Alzheimer's and senile dementia...If the life span is extended, can we expect to see more of this? You extend life, but these are diseases. Would this necessarily be the case?

Right. If we extend the life span so that a 100-year-old person has the physiology (this would be the amount of accumulative damage of all kinds) of a 50-year-old person, then they would have the probability of a 50-year-old person getting Alzheimer's disease.

I have been confused about age-related diseases but you just clarified it.

Almost everybody does. Lots of scientists and doctors do. I read articles all the time in learned medical journals that make the same error. So you are in good company.

I should have known better. Since body parts and organs do not seem to age at the same rate, what are the implications of increased longevity for society? The basic one is ...

Standing room only.

The medical costs?

Well, the medical costs shouldn't go up, because if you actually extend the life span and decrease the rate at which age-related diseases are occurring (chronic diseases of aging, etc.), the medical costs should go down.

If people live longer, other things will go... Their parts wear out, their joints...

I think that is all part of the aging process. It isn't just wear and tear. Cartilage is not like the material on this table—dead and incapable of repairing itself. Cartilage has the capacity to repair itself. And the reason that not everybody gets osteoarthritis as they get older is that some people repair it better than others. Young cartilage repairs itself quite well. The ability to repair the little damage that we do to our joints every day by walking, running, falling, decreases with age. So, eventually, some people—even a lot of people—get osteoarthritis. The cartilage gradually loses its capacity to repair itself and begins to wear out. It gets bare spots where bone meets bone. But that is not just wear and tear. Osteoarthritis is a disease. It isn't just aging.

They are talking about now building cartilage and other things. They are doing that.

They are starting that. I was at a really interesting meeting a couple of weeks ago in San Francisco. I got invited to give a talk at the American Academy of Orthopedic Surgery and I went to a couple of their meetings on this exact subject, which is using stem cells to grow new cartilage. I could say that within ten years we will be able to grow a new joint surface.

Are there any theories of aging that you think are most valuable? Is there a particular biological theory that you support? I think you indicated some biological theories...

The major theories are the oxidative damage theory (the oxidative stress which we talked about) and the telomere hypothesis, which explains the Hayflick phenomenon. There has been a genetic hypothesis. That is, your rate of aging is simply determined by your genes—genes somehow are timekeepers that set the aging process. Our genes kill us, so to speak. I think that you have to turn that one on its head. It would be more accurate to say that we have genes which help us to

resist the aging process and, depending on how good or bad they are, we age at different rates. The question you might well ask is, "Why don't we have genes that are much better than they are, so that we would live to be 250?" The answer appears to be because there has never been an evolutionary reason why human beings needed to live to 250. The evolutionary process has not selected such genes for us. If survival of our species over the next million years depended on having some 250-year-old people, we would probably develop those genes.

I am going to change the focus on you and try to get more personal. What do you believe is the important contribution that you have made?

I don't think that I have made any really important contributions.

Moreover, when it comes to contributions of any kind, I also think that I shouldn't say "I" because I have always worked with a team. Marc Blackman and I have had a wonderful long-term relationship. Dr. Blackman was a Professor of Endocrinology and Medicine at Johns Hopkins and has just become the Director of the NIH Center for Complementary and Alternative Medicine. Also, I have had good mentors. Dr. Blackman and I have had great postdoctoral fellows work with us and the research has always been a team effort. So, what I should say is, we—my group, my section...people I have worked with—I think we have helped elucidate some of the hormonal changes that occur with aging. We have shown that replacing hormones in older people who are hormone deficient due to the aging process has some potential benefits, which may be worth exploring further. There is also potential for adverse effects. We need to better understand how to reduce the adverse effects and improve the beneficial effects. But our work has shown that there are potential benefits and that it would be worth the effort to try and optimize the risk/benefit ratio. This is probably the limit of our contribution to date.

It sounds as though a greater understanding of hormonal changes associated with the aging process has become a research priority.

I think that is part of it. We'd like to understand this better and I am actually involved in some experiments right now with some wonderful collaborators, to start looking at this issue with regard to testosterone. I hope to get back and look at growth hormone again, once we have some better ways of dealing with growth hormones. But my responsibility now as director of the Kronos Institute is much broader. I have to look at a wider variety of issues than just hormones and so we are looking at how to get a better measure of oxidative stress so that we can start looking at these new interventions to reduce oxidative stress. We believe that this is one of the major and important factors that underlies aging.

How does the Kronos Institute support these efforts?

The Kronos Institute—our mission is to do what is called translational research. That is, we are not trying to

do basic research to understand the aging process. We don't work with cells, we don't work with animals. We are doing human studies and (because these are things that are doable in humans at this point) we are trying to explore better ways of detecting the risks and of preventing age-related disease. So, I think we have to first detect the risks for age-related disease. Second, prevent age-related disease. Then, our third mission is to test (when they become available) novel measures for extending the maximum human life span potential. So far there are no such measures (in my opinion) that are ready for human testing. But, I think that there will be within the next five years.

Previously, you mentioned possible tests for use in the detection of age-related disease.

We want to detect and we want to prevent age-related disease. That is it. Not everyone has the same risks. One person's big risk may be osteoporosis, while another person's may be cancer. We'd like to know what your particular vulnerabilities are and we need better algorithms to do that. We need things we can measure, which will give us a better indication (whether you are 40 years old or 50 years old) of which track you are on, so we can change that track to a healthier one.

If you were to give me the goals of the Kronos Institute, would they be what you just said?

Yes. Translational research. Translational means getting stuff from the basic lab into the clinical arena—translating new information that is learned in cells, animals, genes, whatever, into something that we can use in people. So, our goals are to take new interventions that are suggested by data coming out of the basic research lab, that look like they are ready for human application, and getting them quickly into clinical trials to find out if they work. Our goal is within that paradigm—there are better detection methods, better preventions, and (finally) true life span extension studies, which I think are blue sky at the moment.

Is it unique that the Kronos Institute is pursuing these goals?

I don't know about unique, but I think that there aren't very many people that are taking on this kind of research. It hasn't been well supported. Frankly, I feel that the National Institute on Aging is not doing the job that Congress put it together to do. They are concentrating on age-related disease and they have also gotten a lot of good basic research done, but they are not doing a very good job of moving the information from the research lab into the clinical arena. What I see the Kronos Institute doing is moving faster, because our funding is in place and our people will be in place, our laboratory facilities are in place and our clinical facilities will be in place...So, we can jump on something new and do small studies, with 30 or 40 people, to test whether a particular intervention looks really promising. Then, if

it does pan out, this will leverage major support, NIA funds, drug company funds, big foundation funds, to do the larger studies needed for final proof or rejection of a new intervention.

Okay, you just answered another question I have, and that is, can you be moving too fast? One of the criticisms for and against this type of research is the federal regulation of drugs. It takes too long to get them on the market so people go to foreign countries to pick up drugs. And the other argument is that when we do put something on the market that has a negative effect ten years down the line, maybe they will say, "Why didn't you detect it?"

I think it is possible to do things prematurely. Certainly you don't want to start testing something on people until you show that it is really non-toxic in animals. And you don't want to approve something that you are testing in people until you have really shown that it doesn't hurt people in the long run.

But some of these things cause genetic damage. Well, not genetic...DNA, but...

And that's always a risk. Some drugs have failed even after being marketed. There are screens for things that damage DNA, though...There are ways of measuring DNA damage in vitro where you can learn if a drug is really something that causes mutations. There are systems for detecting that. The toxicology screen that all new drugs go through now includes testing for mutagenicity. But, you are right in the larger sense and that is that the long-term outcomes sometimes require what are called Phase IV studies. That is, they have approved the drug and then they watch large populations who are treated for long periods of time and things emerge that you simply didn't expect.

In this country, we have a huge number of people who have been diagnosed with multiple personality disorder. In other countries there is no such diagnosis or illness. Some psychiatrists would say the behaviors exist only because we have the diagnosis. In this country we have a diagnosis, we have a theory for it, and some of the diagnoses and detections of this seem to contain the very nature of what we are looking for.

You are talking about detection bias. The same thing is true of diabetes. We can create an epidemic of diabetes by improving our public relations and publicizing the fact that people should come in and get their blood sugars measured. So, you suddenly see a huge number of new diabetics, because you have gotten people to come in to get their blood sugars measured. Otherwise, they would not be diagnosed.

And there is also a change in the acceptable blood sugar level. It was 120, now it is 110. That has created some additional confusion.

That's right.

Where is the leading edge of aging research now? Do we have adequate research leadership?

There are a lot of good people doing gerontology. There is some very interesting stuff going on. It is hard to name them all. There are probably 10-15 real leaders in understanding the mechanisms of the aging process. There is nobody that I can think of right now doing clinical research on the prevention of aging. I think the big advances will come from better antioxidants, ways of mobilizing the repair mechanisms, and better understanding of mitochondrial processes (which may lead to ways of stabilizing the mitochondria or getting rid of old mitochondria so that the rate of oxidative damage will be reduced). There is a lot of potential there and I think the next five years is going to be very exciting.

I am not sure if it is even meaningful to ask this last question...But if you were in charge of funding certain areas, what research areas would you fund? What would hold the most promise for understanding the process of aging and understanding the quality of life?

Mitochondrial research, oxidative stress research, DNA repair research, and understanding which genes are turned on and off in various systems during the aging process and caloric restriction. Genetic research, too...

Everything that you have said dealt with the biology of aging.

Yes.

And never dealt with quality of life. In fact, ...

I have no expertise in quality of life issues. I think staying interested in things, exercising regularly and eating a nutritious diet and loving people is going to produce a good quality of life.

Are there any data ...?

Yes, there is associative data, but you don't know what's the cart and what's the horse. If people are old and hurting because of biological changes it is hard to have a good quality of life. I think the psychological research in aging shows that people as they get older tend to become "more themselves." People don't really change as they get older but display whatever characteristics they had—if they are kind, they get kinder; if they are mean, they get meaner...

That's the truth. Recently, a physician wrote a book entitled Doctor's Prescription: Go Fishing. The author practices medicine at a cancer institute, where he has trained patients to relax. He feels that this has helped patients with their cancer. I don't know if they've survived any longer, but they may have had a nicer life during the time they did survive...

Thank you Mitch. It was a pleasure.