



How Soon Until We Control Aging?

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KONDRACKE: On my left is Dr. Aubrey de Grey, who has achieved an enormous amount of publicity lately for predictions that I will let him make in detail, but who basically claims that we can live forever. And soon. He is at Cambridge University's Department of Genetics in England. His opponent in this debate is Dr. Richard Sprott, who is the executive director of the Ellison Medical Foundation.

DE GREY: Thank you. Should I go to the podium?

KONDRACKE: No. You can stay here.

DE GREY: OK. So, I'm going to give a very specific numerical statement about my feelings about the time scales for serious progress in doing something about human aging. I am going to suggest that by 2030, twenty-seven years from now, we will probably have the technology to take middle-aged people, people aged fifty, shall we say, who are typical fifty-year-olds, in reasonable health, and give them fifty extra years of healthy life expectancy over and above what they have today.

So today, a fifty-year-old might be expecting to live until they are eighty. I'm saying that by 2030 we will have the technology to get them to live to about 130. And those extra years will be healthy years. That's very important not to forget—that this will not be an extension of frail life.

OK. That's the case I'm going to make, and I am going to make it in the most direct way possible. I'm going to tell you how we can do it.

I'm going to set out a panel of interventions, which I believe we can implement in that timeframe, and I am going to set them out in sufficient detail to justify my confidence that we can do it in that time frame.

I want to start by defining aging in a way that helps me explain what we need to do in order to affect aging. There are, of course, many ways to define aging and living long, good years.

Aging is a side effect of being alive in the first place. So being alive—the whole myriad of molecular and cellular processes that keep us more or less the same from one year to the next. It is an incredibly complicated network of interacting processes. I am going to just use the word metabolism to cover that whole thing.

Now, if metabolism were perfect, in other words, if it really kept just completely unchanging from one year to the next, then we wouldn't have aging, because, obviously, the remaining life expectancy of an organism as a result of intrinsic mortality is a consequence of something that's actually different in an older person relative to a younger person.

So something must go wrong. And indeed, what goes wrong is that metabolism has side effects. And those side effects accumulate. At the molecular level and the cellular level, there are microscopic changes that accumulate in our bodies over time.

At first those changes are harmless. They do not have an effect on the function of our tissues and on our susceptibility to age-related diseases and so on. But eventually they reach a level of abundance that is bad for us. It's pathogenic. So it causes aging-related diseases and eventually it kills us.

But the critical thing to point out here is that that only happens once these types of damage have reached a certain level of abundance. So a thirty-year-old, for example, is more or less in as good condition in terms of how they work, as a twenty-year-old. But we know there is something subtly different about the thirty-year-old because the thirty-year-old has a shorter remaining life expectancy.

OK. Now, why do I want to define aging that way? First of all, I should point out that what I've said so far isn't really at all controversial. I very much doubt that Dick will have any difficulty with that definition of aging for the purposes of today.

The reason it is useful is because it tells us what we can do that we might not have thought of. When most biologists are pessimistic about the likelihood of doing anything serious about aging any time soon, the reason they are pessimistic, in my view, is that they overlook the alternatives that are available to us.

Biologists tend to look at evolution as a good example of how to fix aging, because evolution has very successfully taken a short-lived organism and turned it into a long-lived organism on many occasions.

But evolution has very, very different tools than we have. Evolution can only work with the products of spontaneous mutation and such that occur in organisms that can be selected. We have the tools of molecular biology and cell biology in addition.

If we only had the same tools as evolution, and if all that we could do to aging was to follow the same sorts of strategy that evolution has followed, then I would completely agree with all of the pessimists in this building, including Dick, that it would be many, many decades before we could do anything half as much as I am saying we can do by 2030.

The reason we can do better, in my view, is because we have an alternative. Evolution works basically by making metabolism cleaner. So I've defined aging as, essentially, metabolism causes damage and damage eventually causes pathology, which kills us. Evolution slows down the rate at which metabolism causes damage, so it delays the point at which damage gets to a level that caused pathology.

Fine.

We have the alternative of focusing not only on metabolism, but on the damage itself. We can let metabolism do the stuff it does, lay down its damage, at the rate that it naturally lays it down, but we can also go in periodically and repair that damage—actually fix it so that it's never allowed to get to a level of abundance that causes pathology. And by that means we can unlink metabolism, or being alive, from pathology, being dead.

Why is this easier? Well, basically, the reason why it is easier is because of complexity. Metabolism is unbelievably complex. It's a real mess. We have to understand it well in order to mess with it, and that's why it's very hard to mess with it and we won't be able to do so effectively for a long time.

The pathology that we eventually die of is also very complicated and messy, certainly. No question. But the linkage, the damage, the microscopic damage that links the two, and without which there would be no pathology from age-related causes, is simple. There are really only seven major types of damage that actually accumulate during time, and if we could fix them all we simply wouldn't age.

These seven types are as follows. I am going to go through them very quickly, and I am going to suggest to you the essence of how we can fix each of them.

First of all, there is cell loss. Certain tissues of ours lose cells with time, and those cells are not naturally replaced, so certain areas of the brain, of course, and also the heart, are examples. This is what stem cell therapy is for. Stem cell therapy is an area which is proceeding really quite nicely at the moment, despite the regulatory obstacles that it faces in some countries, and it's working pretty well to augment our natural regenerative capacity in those tissues that don't have enough to start with.

So it's not particularly outrageous to suggest that by 2030, twenty-seven years from now, we will have cell loss pretty much licked.

Second is mutations in our chromosomes. Mutations in our chromosomes cause cancer, and there is very good reason to believe that that's all they cause that matters to us in anything like a normal life span. It is so important not to die young of cancer that we have really, really good DNA repair that gives all the other genes that have nothing to do with cancer a sort of free ride.

Therefore, all we have to do in order to eliminate mutations in our chromosomes, as relevant to aging, is to cure cancer. Now, that of course, is easier said than done. We've been trying for a while with only modest success. But stem cell therapy gives us a massive new opportunity that we have never had before.

The gist of this new therapy is to replace stem cells progressively and repeatedly in all our tissues with ones that do not have a gene for a special enzyme called telomerase that maintains the ends of chromosomes and allows cells to divide indefinitely.

So again, the hard part of this is stem cell therapy, which is going pretty well already.

The third thing we have to fix is what are called mitochondrial mutations. Mitochondria are special machines in the cell that have their own DNA. They only encode thirteen proteins of their own. All the other proteins that make up the very complicated mitochondria come from the nucleus. So the way to obviate, rather than eliminate, mitochondrial mutations with respect to aging is to make copies of these genes and put them in the nucleus, suitably modified so that they still work.

That sounds pretty damned ambitious, just said boldly like that. Right up until you hear that it was actually done successfully fifteen years ago—only for one of those thirteen genes, and only in yeast, but it was done and there has been more progress in mammalian cells with two more of those proteins in the past couple of years. So we are moving fast here.

Number four is cells that we have too many of and that don't do any good. We should have gotten rid of them, but they hang out even though we don't want them to. Senescent cells are an example of this. Senescent cells are normally studied in the cell culture dish, but they also occur in the body and we really ought to just get rid of them.

And then the major example is fat cells, especially in the abdomen, which cause insulin resistance and diabetes. These are cells that we need to get rid of, and work is proceeding very successfully in model organisms to make those cells commit suicide or, alternatively, to activate the immune system against them so they are destroyed.

This is work going on in the labs of senior, respected gerontologists, so it's proper work.

Number five is extracellular cross-linking. This is the thing that causes hardening of the arteries. Basically, it's a chemical reaction between sugar in the circulation and long-lived proteins that make up the artery wall and other tissues that are long lived.

We are lucky here because it turns out that the chemical structure of these cross links is different from anything that we make naturally. So it's been possible to design drugs that can break the cross links without serious side effects. One of these drugs is already in clinical trials, which is a measure of how far along we are.

Number six is extra cellular junk, or garbage. This is most important in Alzheimer's disease, where you have big aggregates of a special protein called amyloid beta that accumulates between cells, and again, we have a therapy that is already in clinical trials, not simply to slow down the accumulation of this stuff, but actually to get rid of it after it's been laid down by activating the immune system against it.

That's worked because once this junk gets inside cells, the cells can apply more machinery. They have special machines called lysosomes, which do this.

That brings me to number seven, the last one, which is the breaking down of junk that accumulates inside cells. Junk accumulates because there are some things that even the lysosome can't break down. There the most promising work is actually going on in my

department in Cambridge, in England, where we are identifying enzymes and genes for enzymes from the soil from microbes, bacteria and fungi in the soil, which can break down the things that we can't.

These turn out to be easy to find. No surprise, because, of course, when we are buried, these things are degraded even though we couldn't degrade them ourselves when we were alive.

So those are the seven things, and that gives you a feel for how hard and how fast the science to fix these things is already going. That makes me feel that we ought to be able to develop all of these technologies in mice within ten years and, with the impact on expectations for biomedical progress that that will cause, it seems very plausible to me, not remotely outrageous, to suggest that within another seventeen years, by 2030, we'll be done. We'll have transferred those technologies to humans.

Now I want to stress, before I close, that the ideas I just described are not just my ideas. They have been extensively scrutinized by senior experimental scientists and have not been found glaringly wanting. The first publication of all this stuff that I made was about eighteen months ago now in conjunction with a bunch of very famous gerontologists, people like Bruce Ames, Judy Campisi, Roger McCarter. They signed up to this because they felt that this was not sufficiently implausible. And it's been published and it's still there. So it's not science fiction.

So, to conclude, I'll just say that in summary I have given eight separate ways to show that my optimism is misguided. I've give the possibility to identify one of my seven areas of aging that is actually much harder to fix than I say, and therefore we won't get anywhere to speak of with it by 2030. Or, you can identify an additional component of aging, which would still continue, and still kill us, even if we did fix all the seven things I mentioned.

So I'll stop there and I'll let him do his worst. Thank you very much.

KONDRACKE: Well, before we get to Dr. Sprott, and as a kick-off to Dr. Sprott, I would say that you sort of understated your optimism here. I've seen you quoted as saying that people who are alive now will live to be one thousand years old, and you've also been quoted as saying that by the year 2100, people will be living four thousand to five thousand years. Do you stand by those predictions?

DE GREY: Sure. Can I answer that numerically?

KONDRACKE: Yeah. Sure.

DE GREY: OK. So actually your mistake there is to suggest that the predictions you just mentioned are more optimistic than the prediction I've just mentioned. In fact, if my prediction actually comes to pass it's more or less a given that we will have people

already alive that will live to a thousand years and people born in 2100 will live even longer, because of the bootstrapping.

If you think about it, what I am talking about here is rejuvenation. Not slowing down aging, but actually fixing people up who have already aged somewhat. So supposing we are at a point where we can take, let's say, a fifty-year-old and make them live fifty years longer than normal.

Now, fifty years is an eternity in science, so that person is going to be around for the next generation of anti-aging treatments that are cleverer and can fix up someone who is even older, right?

So really, we will have reached easily escape velocity by that point, you might think of it that way, whereby it gets progressively easier to keep people going, even though they are older, because we are finding out and fixing the things that go wrong with us faster than we are encountering them.

KONDRACKE: Later we will get into the philosophical discussion of why anyone would want to live five thousand years, but let's go to Dr. Sprott.

SPROTT: And I didn't pay Morton to ask that question!

I apparently got myself into this debate as a result of my comments after the Greg Stock-Bill McKibben debate, "Do We Want Science to Reinvent Human Aging?"

Much of that debate was devoted to the promise and premise, both technical and ethical, of germ line engineering, which includes gene therapy and related technologies that could be used as interventions that would retard or even reverse aspects of aging.

My comment at the end of that debate was essentially that I am not convinced that aging is a disease or genetically programmed in ways that would allow us to attack it in the same way that we attack diseases.

Given that conviction, I think that one of the real dangers of the push to control aging by scientists who are interacting with the media and seeking specific kinds of legislation to enable or prevent such developments is that we risk wasting very precious fiscal, intellectual, and political resources on what I think is a highly unlikely goal, at the possible cost of not pursuing research on the diseases of aging, which would in fact improve the lives of nearly everyone on the planet.

The title of this debate, which Aubrey and I agreed on, was "How Soon Will We Be Able to Control Aging?" I think it makes the rather astounding assumption that control of aging is a given, and that the only question is how long it will take us to get there.

As Aubrey's already stated, he and I agreed that for the purposes of this debate we would assume the control of aging means that by the year 2030 we will be able to take people

aged fifty, in generally good health and hence, with about a thirty year remaining life expectancy, and extend their healthy life span by fifty years, on average, even without using any therapies not yet invented by 2030—that's bootstrapping.

DE GREY: Yes.

SPROTT: Thank you. And that would produce human beings with a healthy life span of 130 years.

Since the longest lived human so far, Madame Jeanne Calment lived only the age of 122, raising average life expectancy to 130 years would be quite a feat. But it only begins to approach the sort of promises that are being bandied about in the media, and by a few of our scientific colleagues. One hundred and fifty years is a commonly used figure, and it's a lot less than 5,000. And I think it's even more unlikely that we get there.

However, let's stick to the 130 years that Aubrey and I agreed we would stick with for this debate.

Aubrey's argument, as I understand it, both from his comments here this morning and his written exposition of his views in other places, rest on, I think, a few main assumptions.

He enumerated eight assumptions, and I am not going to deal with all eight because I don't think we need to. They rest on a few assumptions, and the logical consequences of those assumptions as he sees them.

Assumption one is that the originating cause of aging is clear. It results from our being alive in the first place. I can't argue with that.

The idea that if we could not age, we would not exist is cute, but I don't think it's terribly useful for this particular discussion.

More to the point, and Aubrey does make this point, being alive requires maintenance of the organism. Damage to the system results from the processes needed to keep the organism alive and functioning, and from the slings and arrows hurled by the environment. Even in the absence of an aging process, we wouldn't last forever because there are those trucks out there aimed at us, or what have you.

In fact, most definitions of aging start with these simple facts and assume that aging is the loss of the ability to repair that damage.

The definitions vary in sophistication and complexity, and I don't think they need to be debated here. But most gerontologists, I think, do subscribe to some version of that definition.

The other possibility is, I think, that aging is programmed in our genes just like early developmental events. At the species level this must be true. It's not an accident. I think

that guppies live to be about a year, maybe; dogs, 7 to 15 years; chimps, 30 to 50 years; and humans up to, so far, 122 years.

The longevity program, however, is likely the unintended consequence of selection for early life reproductive factors, not selection for greater age.

The variance that we are really most concerned about here today is not that species variance, but the variance within a species. We want to understand and control the factors that make it possible for some human beings to live somewhere between eighty and a hundred years in relatively good health, and others get only half of that amount.

What Aubrey wants to do is to add another fifty years to that expectation. I think that's a whole different kettle of fish.

His second assumption, as I understand it, is that the best approach—and this is the key assumption of his point of view—is that the best approach to achieving this increased life expectancy is to prevent damage from overwhelming the organism—that's you and me—by repairing the damage periodically, rather than by preventing it in the first place.

I would certainly agree that preventing the damage is not possible, but I'm not even vaguely convinced that we could repair the damage periodically with any real success.

Len Hayflick, who is well known for his views on this topic, uses the auto repair analogy, pointing out that we are not able to keep an organism as simple as an automobile, which is simple compared to us, functioning for a life span of anything like a hundred years without shoving it in a museum, thus removing it from life. And this is with an endless possible number of replacement parts that can be plugged into that organism.

The notion that we know or will know enough to control an organism as complex as a human being well enough to accomplish this seems to me to be arrogant in the extreme. Granting that molecular biologists don't lack for intellectual arrogance does not grant that they know enough to accomplish that task.

Now, before I get shot by all my molecular biologists friends, I have to point out that they are mostly very, very nice people. They are engaged in very worthwhile research that will surely have impact on the human condition.

What many of those investigators are attempting is to alter the human genome in ways that will prevent the damage from occurring, or that will improve the efficiency of innate repair mechanisms.

I simply don't think that's going to happen any time soon, and I don't think Aubrey thinks that's going to happen any time soon, either, since he's chosen another route to go down.

Indeed, I don't really think it's going to happen at all, but that's the subject and part of this debate.

The example of hormone replacement therapy, I think, is very instructive at this point. We've been pursuing this approach to preventing or repairing the damage caused by age-related hormonal decline for nearly fifty years, and we clearly don't have it right yet.

I think this is an eloquent demonstration that the human organism is enormously complex, and we don't know enough to override our genetic heritage. To assume that we do know enough is, at the very least, overreaching our demonstrated ability and, at the worst, possibly quite dangerous.

Aubrey obviously disagrees. He has stated elsewhere, although not this morning, that the endocrine system is a relatively straightforward system to repair if such repair is needed.

The endocrine system, however, I think, is just one example of the systems that decline with advancing age. The immune system, the cardiovascular system, the central nervous system, and so on, all decline, and each would need to be successfully repaired.

This would require repair capacity that boggles my mind, and probably most of yours. Unless you've been extraordinarily lucky, your experience in the auto repair shop for humans—otherwise known as the HMO, or, if I want to be a little more fair, some of the nation's finest hospitals—probably doesn't give you much hope that this is a doable thing.

The other approach would be to find the master gene or genes—what we will call “gerontogenes”—that control all age-related changes that lead to our demise and to re-engineer those genes.

That way, the “gerontogenes” would take care of all of the difficult work, coordinating the very complex tasks that need to be accomplished to produce significant life span extension.

It's not the approach that Aubrey favors, as he stated elsewhere, that the complexities involved are not likely to be overcome any time soon.

What he does advocate was summed up in his January SAGE article; first using gene therapy—and he did it again, by the way, this morning, the same points. First, using gene therapy, we would need to enable cells to break down intracellular aggregates, what he calls junk, by giving those cells extra enzymes that can degrade the junk.

These enzymes are not yet identified, but Aubrey is hopeful that they will be by the time we have the gene therapy techniques in hand that will allow their insertion into every cell in the human body.

Next, again, using not yet developed gene therapy techniques, we would need to make, and I quote, “Fairly obvious changes in DNA sequences that encode important mitochondrial proteins, and then put that DNA into the nucleus of cells.” And he told us more about that a few minutes ago.

As Aubrey has pointed out, these proteins are very important. Damage to mitochondrial DNA may well be a key part of aging decline, and Aubrey’s approach would be to make mitochondrial DNA superfluous. The fairly obvious changes in DNA sequences would accomplish that task.

Here, too, the changes would need to be engineered in such a way as to affect every important cell in the body. Then, because of the very major role that cancer plays in aging decline, we would need to eliminate it in all of its forms.

This would be accomplished by “total elimination of the genes for maintaining telomere length from all mitotic cells.” I think that even if this were technologically feasible it rests on an oversimplified view of the role of telomeres and telomerase in cell function in cancer. It also assumes that telomeres serve no useful purpose in a mature organism, and I think that’s an iffy proposition, as well.

In order, then, to produce the life span extension that Aubrey asserts is possible by 2030, we would need to achieve not just one, but every one of these redesigns of the human genome and repairs, and I submit that that’s simply not going to happen.

While I recognize that my assertion is every bit as much a statement of belief as Aubrey’s, I think that probability is on my side. So, if there is a little time here, what do I think is possible and desirable?

I’m not proposing any great change in the research that we are conducting. The biology of aging research currently funded by the NIA, by the Ellison Medical Foundation, by the American Federation for Aging Research, by the Alliance for Aging Research, can have enormous impact on the health and well-being of humans world wide. It doesn’t really matter why an investigator is motivated to seek greater understanding of the basics of biological aging, so long as that research is honest and honestly reported.

What does matter a great deal, however, I think is how that research is presented—read “sold”—to the public and to Congress. In both instances, hype about producing significant increases in human life span produces unreasonable expectations that are bound to be disappointed.

We have all seen the growing disenchantment of the public, the Congress, the media, ourselves, with the continual release of recommendations and warnings about health effects, good and bad, of substances from common foods like coffee, to treatments like hormone replacement therapy.

A great deal of public good will and energy is wasted on false hopes created by well-meaning scientists. The fact that the quacks and the hucksters trade on those hopes and the ammunition that we hand them just makes the situation, I think, all the more difficult.

What we can do is take the high road and refuse to hype great increases in life span for fun and profit. I'm not really naïve enough to believe that those biogerontologists with fiscal interests in the private sector, that are based on the promise of increasing life span, will suddenly quit saying this stuff in public. But I think the rest of us can provide a tempering voice whenever we are given an opportunity to do so.

In the long run, I think the dividend will be greater support from the public and from Congress and from our fellow scientists. I really do believe, as well, that most people over the age of sixty-five or so aren't really all that interested in adding another fifty years of decline to their lives.

What they are interested in is making the last third of their lives healthy and productive. Producing that outcome would be a fine achievement, and I think a fitting payoff from the new biology that was paid for by that same public.

KONDRACKE: Thank you, Dr. Sprott.

Clearly there have been advances in longevity and life span over the last decades. What do you think is possible in terms of lengthening average life span over the period from now until 2030? That's only twenty-seven years.

SPROTT: OK. And there are two parts to what you just asked, and that's average life span versus maximum life span. Madame Jeanne Calment is an illustration of the known maximum human life span. Average life span is considerably less than that, and what we've seen throughout most of the last century is increases in that life span that resulted from eliminating infectious diseases, better hygiene and better maintenance of the organism.

One of the interesting questions is whether the kinds of changes that we see in mice and rats with caloric restriction, which by the way, took place also in the context of very, very different husbandry, would be repeated in the human situation where we have pretty much already maximized the environment.

So those are interesting kinds of questions.

What do I really think is possible? I think we might see average human life span approach the mid-nineties, another decade beyond where we are now.

KONDRACKE: And that's fundamentally by curing the diseases of aging?

SPROTT: Yes. I think everybody here is probably seeing the basic thing: if we eliminate cancer, heart disease, diabetes, obesity and most of the things that kill people now, we

would add about seventeen years to human life expectancy, which would get us a little beyond what I just said.

KONDRACKE: OK. Now, do you see in any of the seven areas that Dr. de Grey mentioned sufficient progress that major advances could be made in any of them in the timeframe that he is talking about?

SPROTT: I think it's possible that we might see some genetic reengineering that will have a major impact on our susceptibility to some diseases. It could have an impact on our ability to repair some kinds of damage. Where I disagree is I think you have to do that whole list that Aubrey presented or the vast majority of it to get there, and that's what I don't think is terribly likely to happen in the near future.

KONDRACKE: Your chance to rebut.

DE GREY: OK. Well, the first thing I want to mention that Dick said, which I would like to dispute, is his assertion that his view is a statement of belief almost as much as mine is. I would say that it's a statement of belief much more than mine is, because what Dick hasn't done is shown me the miracle.

Those of you who know what I am talking about will remember a very famous cartoon that was produced where two professors are discussing some particular problem by a blackboard, and one of them has claimed to have solved some important problem.

And he's written a large amount of algebra on the left and a large amount of algebra on the right, with arrows between them. And in the middle it says, "Then a miracle occurs." And the other professor says, "I think you need more detail here in step two."

Dick hasn't taken on any of my eight challenges to him. He has not identified a specific molecular or cellular mechanism that might contribute to aging, let alone does contribute to aging, that is independent of the ones I mentioned. He also has gone only a very small way to identifying any difficulties that exceed the ones I suggested in implementing my proposed solutions to each of those seven strands.

One thing he said about cars was interesting. It's actually perfectly possible these days to keep a car on the road that's a hundred years old. And what's rather interesting to observe in vintage car races and so on is that it's not actually all that much more difficult to keep a car on the road for a hundred years than for fifty years. You are more or less fixing everything by the time you get a car out to fifty years. It's hard work to do it. I'm not saying it isn't hard work, but it's not beyond us.

The point that Dick made about hormone replacement therapy is an important one with regard to the science of all this.

Hormone replacement therapy indeed is something we are not terribly good at yet, which we ought to be better at. But the reason it is so difficult is precisely the reason I gave.

Hormone replacement therapy is an attempt to mess with metabolism. It's an attempt to mess with short-lived, bioactive molecules that are circulating in our bodies. Short-lived molecules, by definition, cannot be components of what I have called "damage" because they cannot accumulate. They are broken down or excreted or whatever. And there may be a higher abundance of those damaged, short-lived molecules in an older person than in a younger person, but logically that has to be a consequence of the accumulation of damage in a long-lived way, either in long-lived molecules or in long-lived tissues that are not replacing their cells, for example. It cannot be the primary cause of anything.

So what I am saying is that you wouldn't need hormone replacement therapy if we fixed all seven things that I described earlier.

Now, another thing Dick mentioned was the research agenda. I think it is indeed correct that it will be a very long time before it becomes superfluous to carry on doing research to understand aging better. That's obvious. That's not where we differ.

But historically, there is a strong tendency, when a field with technological or biomedical relevance moves forward enough, for those scientists who actually made the critical progress in our understanding that made the solutions possible actually not to realize how close they were to solutions.

And you can think of cases, like, for example, the Wright brothers going ahead and building planes just three weeks after some professor at Case Western published a proof that heavier-than-air flight wasn't possible. And this is just one example of many people who had said flight wasn't possible right up until it was done.

It's important to remember that people have specializations. People have different ways of thinking. The engineering type of creativity is in many ways very different from the basic science type of creativity.

The last thing I want to mention is that the attitude of the public to perhaps less than predicted rate of progress in an important field that costs a lot of money is definitely important to consider, but we have a much better precedent for that than any that have been mentioned so far, which is the war on cancer.

Cancer research has progressed well over the last thirty years, but it has progressed far less well than Nixon thought it would in 1971 when he announced the war on cancer and announced this big hike in the budget of the National Cancer Institute and so on. Has that turned into disillusionment from the public or a diminution of funding? You bet it hasn't. The NCI is still funded in an increasing amount every year. When the public gets its teeth into wanting to fix something, the public will accept that science is not predictable, but that we have to try our best.

KONDRACK: Now, what about his point that you have got to succeed not just in one of these areas but all seven? You've got to run the gauntlet here and do it all.

DE GREY: Sure. I didn't mention that because I absolutely agree. It may be we can get away with five of them. I think mitochondrial mutations and senescent cells are two areas in which the jury is still out as to whether they really matter in anything like a normal life span.

But they might matter, and all the others more or less definitely do matter. So I am basically with Dick on that one.

KONDRACKE: OK. I want to remind the Web audience that they have about twenty-five minutes to send in questions. The instructions are on the screen.

Now, you yourself acknowledge that this is really complex and really messy. And yet you think that all this can be done in seventeen years?

DE GREY: That's not quite what I said. I said that metabolism is really complex and messy and the pathology is really complex and messy, but the damage that links them together is not complicated and messy—it's still fairly complicated, but the degree of complexity is massively, massively less and that's why it's within range.

KONDRACKE: Oh. OK. So now just considering brain disease itself. I mean, here you have this enormously complex structure called the brain. And I happen to know something about—

[BREAK IN TAPE]

—of any of them because we are going to cure it in fifteen years. That was fifteen years ago and we are still working on endless numbers of therapies to try to do that. Stem cells offer a hope of possibility of that. But it's not at all clear that that's going to happen.

So why are you so confident that in just twenty-seven years we will be able to replace neurons of any kind with stem cells?

DE GREY: OK. First of all, I'm not saying we're definitely going to be able to do this. I am only saying we are probably going to be able to do this, OK?

So clearly these things might take a hundred years. We just don't know until we've done it. But I said the probability is better than fifty percent.

The second thing is, I mean, stem cell therapy is moving really fast. It's something that wasn't moving so fast fifteen years ago. Maybe that fifteen-year prediction was over-optimistic. Maybe my prediction is a bit overoptimistic. Maybe it's a lot overoptimistic. We are definitely not at a position where we can carry on not even trying.

KONDRACKE: Well, there's no question that we should be trying. But what is your forecast on what stem cells can do to solve this part of the problem?

SPROTT: I think what stem cell research can offer us is the opportunity to repair and replace cells in a very different way than we currently do. The possibility that we could, in fact, provide replacement body parts through stem cell replacement—I think that's a reasonable possibility. Whether I'd say we could do it in twenty-five years or fifty years, I don't really know. I don't think we are going to do it next year.

DE GREY: One down, six to go.

SPROTT: If the UN has its way, we are not going to do it ever, but—

KONDRACKE: What's happening at the United Nations is that the Bush administration is trying to get the United Nations to discourage cloning of embryos for stem cell research. But even if it succeeded, the UN can't stop Israel or England or anywhere else from doing that, just to be clear on that.

OK. Go ahead. Continue.

SPROTT: Well, I had mostly gotten through that.

KONDRACKE: Now, as to replacing cells that produce telomeres, your second area of success. Various aging experts that have been here say that what we want to do is produce telomeres in order to prevent the shortening of telomeres in chromosomes. If I understand this correctly, it sounds like you are suggesting the exact opposite as the answer to the aging problem. Would you explain that please?

DE GREY: Sure, and this is actually not terribly controversial within gerontology. It's actually extremely rare to find anyone who knows really anything about this biology who thinks that giving yourself telomeres will be good for us.

Telomerase is an enzyme that's in all our cells, and in most of our cells it's very, very robustly turned off. The general consensus in the field is that this is precisely because telomerase allows cancers to kill us. OK. So telomere suppression has evolved as an anticancer mechanism that makes us live longer because we don't die of cancer.

The idea of turning off telomeres is not just by turning the gene off, but by removing it so that even the very hyperactive mutability that exists in cancer cells will not be sufficient to restore the ability of the cell to divide indefinitely its telomere shortening.

And, of course, some cells in all of our tissues that are rapidly renewing actually need telomeres in order to divide often enough so they would cease to function as stem cells after a while, but we've good reason to believe that we would only need to replace them with new cells that again lack telomeres, but had nicely refreshed long telomeres that were refreshed outside the body every ten years or so. Going in for a ten year service is a small price to pay for an indefinite avoidance of cancer.

KONDRACKE: —body wide that you have to eliminate telomeres.

DE GREY: Body wide, but with different types of treatment in the details for different tissues. So, for example, in the blood it's relatively straightforward—a bone marrow transplant is all we are talking about here, and that's a relatively routine therapy already.

In the skin, for example, we are talking about replacing the stem cells that keep the epidermis going, the outer layer of the skin, and that sounds—pow! Until you remember it's basically what we do already for burns victims. It's what burn therapy is basically about.

The gut is another area which definitely needs to be addressed in this, and it looks again like a pretty ambitious thing until you get to the right literature and you find that ten years ago, in mice, an experiment was done that found the gut wall is capable of rebuilding a perfectly functional intestine with all the villi and crypts and so on just from totally disaggregated cells plated onto a denuded intestinal wall. This is something, which, of course, you wouldn't do by opening up a person. You would do it by some sort of endoscopy technique.

But the proof of principle is ten years old. You know, it's something that you can only really dismiss as science fiction until you've read the right experimental literature.

KONDRACKE: Dr. Sprott, what do you think about those ideas?

SPROTT: I think those are very interesting notions. I think, however, the belief that we are all going to sign up for getting rid of all of our tumors and our telomeres and then check in for a stem cell replacement refill once every ten years—

DE GREY: If your choice is dying of cancer, would you make it?

SPROTT: It doesn't matter whether—I mean, in one sense would I make it were it possible? I suppose I might.

DE GREY: You suppose you might.

SPROTT: Do I think it's possible? No. Do I think we are going to do this society-wide?

KONDRACKE: Why do you think it's not possible?

SPROTT: At this point, while Aubrey said there is proof in principle in a mouse gut, we're a long, long way from a mouse gut to doing all human beings.

DE GREY: Twenty-seven years is a long, long time.

SPROTT: So we finally disagree about how much time twenty-seven years is.

KONDRACKE: OK. Let's see. We can prevent a cancer in a mouse gut. Can we eliminate telomeres from the cells of a—

SPROTT: We could repopulate the mouse gut—

DE GREY: That's right. That's the idea.

KONDRACKE: All right, now what about the differences between mice and humans?

DE GREY: Very important. Very, very important. So I am saying that these things that we need to do in humans in order to eliminate all of the aspects of aging that exist in a normal human lifetime can all be developed in mice within the next ten years.

KONDRACKE: Leaves you only seven years left.

DE GREY: Seventeen years.

KONDRACKE: Seventeen years.

DE GREY: That is not the same as saying that in mice we can make mice, we can do the same proportional life extension. We can take, for example, a two-year-old mouse that would normally live to three years and take it to fifty.

If they can only live to five years, it's not the same as that. It's a lot stronger than that. It's probably going to be relatively easy to turn a mouse that appears old into a mouse that lives for five years rather than three, precisely because mice are simpler than us. Mice are still rather bad at aging, and so fixing them up so that they are better at not aging and can live longer is easier than fixing a human up.

But that means simply that getting mice to live a long time has partly a biological or biotechnological value and partly a publicity value. But of course, the more we do with mice, the more people will acknowledge the plausibility of corresponding progress in the foreseeable future in humans.

KONDRACKE: Now, of these seven categories of things, how many of them have been done in mice?

DE GREY: None of them have been done, but I am saying all of them could be done in ten years.

KONDRACKE: OK. And you've got this prize that you are involved with for the first person to produce a five-year-old mouse, right?

DE GREY: That's not quite how the prize works. It first works incrementally like a world record. So if you produce a mouse that's older than any mouse that we've heard of before, then you get some money. The amount of money you get depends, of course, on how big the prize fund is at the time.

You can go to our Web site, methuselahmouse.org, and put some money on the prize with a credit card. If you want to give us a lot of money, you can talk to us privately.

So it depends on the amount of money—

KONDRACKE: How old is the oldest mouse? What is the longevity of mice now?

DE GREY: So if I could just finish the last question, it also depends on the margin by which you beat the previous record. So that's why it could go on indefinitely.

SPROTT: The answer to your question, Morton, is in excess of five years.

DE GREY: The life expectancy—

SPROTT: Already.

DE GREY: The life expectancy of mice at the moment is about three years depending on the strain. But we are talking about a single mouse here, so we are talking about the maximum life span. The best record that we know of the species that we are interested in, which is the one that most laboratory mice work on, the Methuselah mouse, is just one week short of five years. We gave the inaugural prize in June to Andrzej Bartke who published research in Illinois for this mouse, which was a growth hormone receptor knockout that lived to one week short of five years.

KONDRACKE: Now, as I understand it, though, in order to maintain mouse longevity, what you have to do is you have to calorically deprive them, and you have to genetically alter them so that they are dwarf mice.

Now, as I asked in the last debate that we had, who wants to live his life without hamburgers and in a dwarf status?

DE GREY: You are absolutely right. It wouldn't do at all.

KONDRACKE: In order to achieve long life, OK.

DE GREY: And for this reason we are starting a second prize next year. This prize is simple: it's just that your mouse has to live longer than any other mouse before.

The new prize will be called the reversal prize, and the way in which it will be determined whether you win and how much you get if you do, will take into account the age at which you started treating the mouse. The people who want to take part in this competition will get their mice from some registered place like Jackson Labs, for example. The Jackson Labs will certify the age of the mouse at the time that it was delivered to the investigator, and will also notify us at the prize. And that will be defined to be the age of onset of treatment. So the structure of the prize will be such that the later you start, the more credit you get.

KONDRACKE: OK. But is caloric deprivation not still the way to keep mice alive?

DE GREY: Not really, no. Basically, the thing is with starting later on, not much work is done on trying to extend life span of mice that have had nothing done to them until they are age two or so, precisely because nobody has the faintest idea how to do it.

If you start caloric restriction at age two, you get virtually nothing. If you do any of the things we know how to do at the moment at age two, you get virtually nothing in terms of life extension.

KONDRACKE: OK. Go ahead.

SPROTT: I was just going to comment that I was at a meeting last night listening to David Sinclair talk about his ability to increase mouse life span with late-onset caloric restriction.

DE GREY: How late?

SPROTT: As late as two years, so maybe that's a red herring in the whole thing. One of my concerns about where you go with the caloric restriction—

KONDRACKE: Caloric restriction, by the way, is not on your list.

DE GREY: That's right. I don't really think there's much scope for increasing human life by more than a year or two with caloric restriction.

SPROTT: The only thing we are going to get out of caloric restriction that is of any use to humans is to understand how it works.

DE GREY: Yes!

SPROTT: And then use that for some other sort of therapy.

KONDRACKE: And what do we know about what caloric restriction does?

SPROTT: This was my career.

KONDRACKE: OK, proceed.

SPROTT: What caloric restriction does, in part, is to shift metabolism and produce less of that metabolic damage. It may do a number of other things; it may have significant effects on mitochondrial DNA, for example. It may shift certain kinds of enzymes into a more favorable state.

But clearly, one of the things that concerns me right now is that virtually all of the caloric restriction demonstrations we have are in organisms that live in a very artificial *ad libitum* environment which probably is overfeeding.

Now, that may be the equivalent of the human couch potato myself, obviously, included.

Caloric restriction then isn't going to be of much use directly for us. And whether it's a good model for what changes in humans would be is a very open question, too. I doubt Aubrey disagrees with that.

DE GREY: You are quite right; I don't disagree.

KONDRACKE: Do we have any questions from the audience? Go ahead. There's a microphone up there.

AUDIENCE MEMBER: It seems to me that your arguments are actually not too far apart. I'm kind of surprised about that. You may not agree with me, but it seems like you are in violent agreement except on the amount of time that you would get in maybe ten or twenty years' worth of research.

So the question I have is, or it's a statement at first and then a question, is that when AIDS first became recognized it was a disease that only pariahs in society at that time could have. It seemed to me that was the mental state of the country. And then the people who saw their friends dying started a grass roots effort and got Hollywood involved, and a tremendous amount of money was spent shortly thereafter due to convincing Congress that this was a serious problem, not just among unfortunate communities that few people seemed to care about.

So to make a long question short, why wouldn't the war on aging galvanize the same kind of activity and force cures, because AIDS, which was considered to be inevitably fatal, is now becoming tractable? It's coming into hand as far as treatments.

SPROTT: I'd like to respond to that. I think your questions are reasonable, if one assumes that aging is a disease, and I don't think it is. I think aging is a reflection of a number of basic processes. And I, by the way, did not agree that significant life span extension was possible. I didn't disagree about the amount. I disagreed about the possibility. Aubrey?

DE GREY: Yeah. I think that whether aging is or is not a disease is a red herring. Aging is, first of all, undesirable. And it's a biological phenomenon, so if you want to define disease that way you are done.

But also the main thing is that aging is a process that makes some people more likely to die in a given period of time, starting now, than other people. And that seems like a fine definition of disease to me, you know.

If the only definition of what is a disease and what isn't is terminological, then it's not useful to tell us whether we can fix it or not.

KONDRACKE: Well, what kind of investment would it take, do you think, to achieve your goal?

DE GREY: Well, I normally talk about the ten-year goal. In other words, fixing all these things in mice as a proof of concept, so to speak. And I reckon that Dick's got the money he needs. Twenty million dollars a year is a pretty damn good start.

If I had \$100 million a year I'd probably think of ways to spend it, but I think with \$10-20 million a year, it would probably take only ten years with a good probability.

KONDRACKE: And then how much longer to translate that?

DE GREY: Of course, then we don't know because we don't know how far the science will have progressed for humans in those ten years. It may be that we will be able to leverage off stuff that's gone in parallel, or it may not. We may have made little progress because, until that time, there may continue to be skepticism in society with regard to whether this is ever going to be possible.

So it may be only at that ten-year point that we start putting serious money into things like getting gene therapy to work well in humans.

KONDRACKE: Let me ask the philosophical question: why does anybody want to live to be 5,000 years old? Assuming that you could live to be 130 and be reasonably healthy, presumably you would have to work until you were 100 or maybe you would have to work until you were 80. Do you think that people really want to do that?

DE GREY: Yeah. I think this is another big red herring. We only talk about the desirability of fixing aging because we have the luxury of it being something that most of us feel is a long way away.

People don't want to die when they are healthy. People who get the most of their life might want to retire. They might want to change jobs. They might want to do different things.

KONDRACKE: They want to retire, is what they want to do?

DE GREY: They want to retire because they are getting tired.

KONDRACKE: Um-hmm.

DE GREY: They haven't got the vivacity that they used to have, by and large.

When people have the vitality that they had when they were twenty-five, they are not going to want to sit in front of the television or play golf twenty-four hours a day. They are just not going to.

KONDRACKE: Um-hmm. OK. I'll allow you to start the finish and then Dr. de Grey to finish. We've got about three minutes left.

SPROTT: One of the things I thought was rather interesting, Aubrey, in the very beginning of his presentation, made reference to Jay Olshansky and his point of view. And I think it's rather interesting, Aubrey and I both were among the fifty some scientists who signed a position paper authored largely by Jay, and I thought I might quickly sum up by mentioning some of the key points that we both agreed to when we signed on as co-authors.

KONDRACKE: Quickly.

SPROTT: Yeah, there are about twenty of them, so let me pull out a couple of them that are particularly interesting. "Past and anticipated advances in geriatric medicine will continue to save lives and help to manage degenerative diseases associated with growing older, but these interventions only influence the manifestations of aging, not aging itself."

"Medical interventions for age-related diseases do result in increased life expectancy, but none have been proven to modify the underlying processes of aging."

And finally let me just speak to the last one, which we did both sign. "Although it is likely that advances in molecular genetics will soon lead to effective treatments for inherited and age-related diseases, it is unlikely that scientists will be able to influence aging directly through genetic engineering."

DE GREY: OK. I think that's a good place for us to end because I have an important answer to give to that.

First of all, there is a slight inaccuracy in what Dick said. We did not sign up as co-authors. We signed up as endorsers. And when I was asked to sign up, I took that to mean, "Do you agree with the general thrust of the article?" not "Do you agree with every word or every phrase?" in the way that I would have thought if I were going to be a co-author.

This is an important distinction because certainly the things that Dick has just read out are things with which I do not agree, and which I tried to get changed before publication.

And I wasn't the only one who signed up despite not being able to agree with everything.

What I did agree with was the main thrust of the paper, which has to do with the inability with current technology to do very much about aging, despite the protestations to the contrary from those who make money out of things that don't work.

And I think it's very important for the public to have a good sense of proportion about the efficacy of things we already have, or rather, the lack of efficacy.

So that's why I signed up. But I have taken the trouble to make my views very clear in papers that I have been the author of. For example, I had a paper out two months ago in *Experimental Gerontology* in which I started off by pointing out that it is extremely unfortunate that those who wish to voice legitimate claims that current anti-aging medicine, as it's called, doesn't work, tend to spoil their argument by talking about what we might be able to do in the future in the same breath. I think these things are separate. I have very different opinions about both of them, but that didn't stop me from endorsing rather than co-authoring this paper.

KONDRACKE: Thank you both very much, and I am sort of sorry that we are not going to be around to 2030 to find out whether you are right.

DE GREY: Or maybe we will be. Perhaps we will.

KONDRACKE: Thank you very much.

End.