



**Transcript – Diving into the Fountain of Youth with
Aubrey de Grey - #326**



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Speaker 1: Bulletproof Radio, a state of high performance.

Dave Asprey: You're listening to Bulletproof Radio with Dave Asprey. Today's cool fact of the day is that getting older may be the key to happiness. A recent study at the University of Chicago found that happiness increases incrementally from 65- 80 years old, and some studies show that people are happier in their eighties than they were in their twenties. The scientists who do these studies believe that our toolbox of social, and emotional instincts that are built on experience, are the key to being happy later in life, which is a cool perspective on it. If you're twenty, and miserable, just think, it won't suck nearly as bad when you're eighty. I'll tell you when I'm eighty, all right?

Before we get into the show, if you're not familiar with Bulletproof Upgraded Aging Formula, you should check this stuff out. This has quietly become one of our most popular supplements, because it really, really works. It works on some of the problems with aging- particularly in the brain via four different pathways- including things that optimize your daily brain function. It regulates genetic expression similar to the way fasting does, which is really, really cool. If you want to live longer, one thing you can do is fast regularly. You can also take things that mimic the genetic changes. It also protects neurons in the brain from excessive glutamate, and it helps people to maintain healthy blood sugar levels. All those things happen to you as you age. It's one of my favorite supplements, and something that works on those mitochondrial pathways. It primes the mitochondrial pump, in that it's the last step in energy production in the Krebs cycle right before additional keytones, or additional sugar enter the cycle. It's a very interesting supplement, and one that I value. It's called Bulletproof Upgraded Aging Formula.

Now, today's guest is a friend; a guy I first met six, or seven years ago over breakfast. I think we had some omelettes in Mountain View, California, and this is none other than Aubrey de Grey. He is probably the most famous anti-aging guy out there. A Biomedical Gerontologist focused on regenerative medicine. He's the editor-in-chief of Rejuvenation Research, and a fellow of the Gerontological Society of America, the American Aging Association, and the Institute for Ethics, and Emerging Technologies; definitely qualifies as a biohacker by any measure, and the owner of the single coolest beard I've ever seen. Aubrey, welcome to the show.

Aubrey de Grey: Thank you very much. It's great to be here.

Dave Asprey: Your work on aging has been some of the most seminal work out there, where you talked about these five big causes of aging, and what we could potentially do about them. What's your definition of aging, today, for listeners?

Aubrey de Grey: First of all, let me correct you, it's actually seven causes.

Dave Asprey: Seven? Forgetfulness was one of those things. I have a ...

- Aubrey de Grey: What's the definition of aging? It's actually a really simple definition. Aging is simply the accumulation of damage in the body that occurred; is created as a side effect, or the consequence of the body's normal operation. The reason I like that definition is not just that it's mechanistic, but also that it emphasizes that aging is not really a phenomenon of biology. It's a phenomenon of physics. It's something that happens to any machine with moving parts, irrespective of whether that machine is alive. It demystifies aging. Aging is not a mystery. Aging is a simple thing. It's just the same in the human body- in essence- as it is in a car, or an airplane.
- Dave Asprey: I absolutely love that definition, but you said something. You said, "In the normal course of living." What about damage that comes from things that are abnormal?
- Aubrey de Grey: Of course, the real question is- it's a very important question- which of those two actually contributes more to the rate at which damage accumulates. Many people would like to believe that we can very substantially reduce the rate at which damage accumulates by doing a particular thing in terms of lifestyle, whether it's yoga, or meditation, or supplements, or exercise, or more sex, or less sex, or whatever. Unfortunately, the evidence seems to be that these things only play a relatively minor role when compared to the things that we all have to do. The single biggest problem; the single thing that drives the greatest amount of accumulation of damage is breathing. Breathing is not negotiable, really. The next one is probably the transport of sugar. Of course, that controls things like diabetes, and so on. Again, you've got to have sugar. You can have less sugar, or more sugar, but you're still going to have a certain amount, and your blood sugar levels are going to fluctuate a certain amount, and you're going to have the consequences of that.
- This is the kind of reason why we've decided to sidestep this question entirely, and not focus on which are the major contributors to the creation of damage, but rather intervene one step later down the road, and try to repair that damage after it's been created so that it doesn't really matter where it came from.
- Dave Asprey: That is an incredibly elegant answer that says, "I don't care where it comes from, let's just fix it, and help the body repair itself." If you're looking at maintaining your race car, or let's just say, your commuting car, you can change your oil, and do your careful servicing intervals, and drive it carefully, and put the brakes on slowly. It'll go an extra fifty-thousand miles, or you could just replace the engine when it goes out, right?
- Aubrey de Grey: I wouldn't quite like to say that it's an either/or.
- Dave Asprey: Yes.
- Aubrey de Grey: I think that preventive maintenance comes in many forms even for a relatively simple machine like a car, but we certainly do see, of course, by the existence of cars that are more than a hundred years old, that with sufficient work; with sufficiently comprehensive preventative maintenance, the healthy longevity of the machine can be extended arbitrarily long. These cars, obviously, they were not designed to last a hundred years. They were

designed to last maybe ten, or fifteen years.

Dave Asprey: We share that perspective, and I probably am a little more biased towards, "Well, let me see what I can do to extend the useful service life before I need to replace parts."

Aubrey de Grey: Before you go on, don't get me wrong, I absolutely think that lifestyle optimization is a good thing, simply because if apart from anything else, we just don't have these therapies, yet.

Dave Asprey: We're in full agreement on that one. I'd rather just eat cake all the time, and just replace bad mitochondria that come as a result of that. I just don't know how yet, so I'm not going to eat the cake. Right? Okay.

Let's talk about those seven things, because that is- and, I say this having run the Silicon Valley Health Institute. You came, and spoke there many years ago. In fact, that was where I first met you now that I think about it, before we had breakfast, but I look at what impact that's had on the world; that perspective, and I think it's been very far-reaching in the American Academy of Anti-Age Medicine. Walk me through the seven things that are happening that are messing us up.

Aubrey de Grey: First of all, I want to start that answer by emphasizing that there are actually far more than seven things. There are many, many, many things. The seven comes from the classification of those things. First of all, I want to describe what the motivation for having a classification at all is. Motivation is to simplify the development of the specification of the fixes. The idea of this classification is that for each of the categories, there is one generic approach to repair of that type of damage. It's something that may be differing in details from one example within the category, but only in the details. If we go through the categories, then the first one is, loss of cells. Simply, cells dying, and not being automatically replaced by the division of other cells. That sounds like a very broad category, and it is, but the fact is, it's got a generic fix, and you all know what that fix is; it's stem-cell therapy; putting cells in that will be able to divide, and differentiate to replace the cells that the body is not replacing on its own.

Dave Asprey: Have you had stem-cells?

Aubrey de Grey: Oh, certainly not yet. Most stem-cell therapies are at a relatively early stage of development at this point, and moreover, I'm only 53, and I'm doing pretty well. I'm not in danger of needing that kind of thing, yet.

Dave Asprey: Have you banked your stem-cells?

Aubrey de Grey: Okay, let me finish the first answer.

Dave Asprey: Okay, got it, sorry.

Aubrey de Grey: It's important to understand that there's always a trade-off between doing preventative

maintenance early, and doing it later, but still early enough, and benefiting in the latter case from the fact that the therapies have been improved in their comprehensiveness; their quality, or whatever. At the moment, I believe that I'm on that side of the curve; that I should not, because I'm doing pretty well for my age to be actually engaging in these therapies, yet.

The separate question you asked about banking your stem-cells is a very interesting one. Of course, the idea of banking is that our stem-cells deteriorate over time, and that therefore, if we were to try to do some kind of autologous stem-cell therapy; in other words, therapy that involves taking our own cells, and manipulating them in some way, and then putting them back, then we wouldn't have starting cells to work from that were as good as the ones that we might have had at an earlier age; but, we've got a couple of reasons why that has become less important, especially in regards to treatments for things about aging.

The main reason is the development of induced pluripotent stem cells. The idea here, of course, is that we can now take cells that are not even stem cells at all, let alone primitive stem cells, and we can de-differentiate them back into a much more primitive state; and then, we differentiate them back out into whatever kind of state we would like so that they will be programmed into the appropriate form. They will then be our own, so they will not immunorejection, or anything like that, but they will also be in a state that might not exist, or at least to very high frequency, in the body before we start. Yet, we still have them without having had to bank them.

Dave Asprey: I am so intrigued at that line of things. I have done some cell therapy. I'm going to talk about it my conference. I just did a whole bunch of it, but I'm looking to only be thirty for the rest of my life, so we'll see how well that works.

Aubrey de Grey: [Laughs]

Dave Asprey: I'm not thirty, I'm forty-three.

I'm really intrigued at your comments though on where it will be in ten years. I have no idea, and hopefully what I'm doing now is beneficial, and not damaging. It is a coin toss. I totally acknowledge that. Cell loss; we can deal with that with stem cells, and what was next on your list of seven?

Aubrey de Grey: I can deal with the next two jointly, because they're both the opposite of cell loss; having too many cells rather than too few. The reason there is two categories is because there are two different ways in which we end up having too many cells, and depending on which way, the therapy is different. It could lead back again to the reason for the classification. One way is, cells dividing when they're not supposed to, and that of course is, more or less, the definition of cancer. People have had plenty of ideas about how to deal with cancer, and I think they're going pretty well at the moment, I guess, especially over the past few years, there's been huge breakthroughs in cancer immunotherapy, which are looking very promising. We, at SENS Research Foundation are pursuing a rather more ambitious, and rather more innovative approach that involves controlling the ability of cells to extend their

telomeres; the ends of the chromosomes.

This is not a new idea exactly. It's something that has been pursued by other groups, especially by a company named, Jaron, but we are proposing to do it in a much more comprehensive, and hard-hitting kind of way, which we believe is necessary in order to really defeat cancer. It's very elaborate, the approach that we're taking, and we hope to goodness that we're not actually going to need to do it, because something else that's simpler will work well enough; but, we're not betting on that, and that's why we are pursuing this very much more aggressive approach.

The second type of way in which you can have too many cells is when, instead of cells dividing when they're not supposed to, they don't die when they are supposed. That's a little more counter intuitive. Most people don't think in terms of cells being supposed to die in any circumstance, but actually there are circumstances in the body where that is the case. The most important one; the most high profile one, so to speak, is the immune system, where you get an infection, have a very tiny proportion of our white blood cells expand like crazy; they divide like crazy for a while in order to be populous enough to eliminate the infection, and when the infection is eliminated, they almost all die, and just a small residual population of what are called, "Memory cells" remain, so as to be able to respond much more rapidly if you get the same infection again; and, that's all very nice.

Unfortunately, there are certain infections that hang around in the body, rather than being completely eliminated, they become latent, and they re-activate every so often. When that happens, you get the rather unfortunate cycling of the same cells expanding, and dying, and expanding, and dying. Eventually, probably for anti-cancer reasons, the cells stop refusing to go through that cycle. The problem is that they refuse at the expanded end. In other words, you end up with cells that should be responding to signals telling them to die, and they no longer do respond, so you have too many of them, and that inhibits the ability of other cells to divide to respond to new infections. That's an example of where we need to get rid of cells. There are other examples of what I call, "Death resistant cells," and the way to get rid of these things ... There are various people around, and it's quite high profile now; trying to use small molecules from a pharmacological approaches to kill these cells. There are some tentatively promising results. I'm certainly following that work very closely.

We're not sure that that's going to pan out to a sufficient extent to really solve the problem, and so we're pursuing a rather more rationally-designed, shall we say, involving genetics; involving suicide gene therapy. There's something that's a relatively routine tool in the lab, but it's not really yet used in the clinic. It's called suicide gene therapy, and what that is, is you use engineered viruses, just like in any other gene therapy, to deliver DNA to cells, but weirdly, what you deliver is a gene that kills the cells. The reason that this makes sense is because you arrange so that they will not be expressed; the protein that's toxic will not be constructed, unless the cell gets into a particular state where you want it to die. This is a way of essentially overriding the death resistance of these cells.

Dave Asprey: Are they death resistant to high amounts of oxidative stress?

- Aubrey de Grey: They are resistant to that. Most are resistant to that; fairly resistant anyway. The real problem is that these cells are resistant to signaling; to actually the signals that would normally get them to turn on a cell suicide process of their own. It no longer works.
- Dave Asprey: Okay.
- Aubrey de Grey: That's three types of damage so far.
- Dave Asprey: Three, right.
- Aubrey de Grey: The three I've mentioned so far are all about cell number; having too few, or too many. The rest is at the molecular level, rather than the cellular level. Two of the remaining four are inside the cell. The first one is mitochondrial mutation. The mitochondria, of course- as they call the power plant of the cell, the place that does the chemistry of breathing. The mitochondria have their own DNA, which they are the only part of the cell that does that's outside the nucleus. That DNA, for various reasons, accumulates mutations much faster; far faster than the nuclear DNA. It's generally believed; there's plenty of- albeit somewhat circumstantial evidence- and, we don't really know the mechanism, yet, but there's plenty of good evidence that the accumulation of mitochondrial mutation contributes to various aspects of aging. We'd like to fix that.
- There are various approaches that people have proposed, but nothing's really panned out. Again, we're taking a very aggressive approach that's difficult to implement. If we can, then it would really solve the problem. In this case, that approach is what is called allotopic expression. What that means is we take a copies of the mitochondrial DNA, and we modify them, and we put them into the nuclear DNA. We're using gene therapy, again. The idea here is that if we implement the correct modification, then those genes will express proteins that will be imported back into the mitochondria even those the genes are in the nucleus. The reason that's not completely out of the realm of plausibility, is that mitochondria already do this, naturally, with 99% of their proteins. There's only thirteen proteins that the mitochondrial DNA. The idea is simply to co-opt the same mechanism that already exists for these thousand, or more other proteins. It's going well. This is an idea that's been going around for thirty odd years, and progress has been rather fitful. We're a lot closer to getting it to work than anyone else has ever been. We've still got a little way to go, though.
- Dave Asprey: Are you a little concerned about those extra proteins made by nuclear DNA floating around in the cytoplasm, because there's too many of them for the mitochondria to use?
- Aubrey de Grey: Sometimes, it's important to implement some kind of copy control of these things in any kind of genetic therapy. However, in general that turns out to be not much of a problem, because the cell already has really good ways of implementing copy control itself, or getting rid of superfluous proteins automatically. We don't have to worry about that too much.
- Dave Asprey: Cool.

Aubrey de Grey: All right. The other type of damage inside the cell is much simpler to describe; it's just waste products. The cell constantly makes stuff that it doesn't actually use as side product of things that it does need, and in general, those things are eliminated either by being destroyed, or by being excreted, so that's all great. Unfortunately, some things that are by products that are very slowly accumulating; the relatively rare by products. Those things; simply, the body doesn't care. Evolution doesn't care about these things, because even if they're not destroyed, or excreted, they still don't accumulate to a sufficient amount to cause problems until old age, and as we all know, evolution doesn't care about old people. It only cares about people in terms of their reproduction.

We need to get rid of these various types of waste product that cause things like atherosclerosis, and macular degeneration. The way that we've approached that problem is by stealing some technology from an area of biology that isn't even biomedical. An area called bioremediation, which is used for environmental decontamination. Basically, what happens is that we find bacteria in the soil that are able to destroy a particular target compound, and then in bioremediation, what happens is they just grow a lot of those bacteria, and shuck them into the environment, and the environment is de-contaminated. In our case, we don't want to do that. What we do instead is we identify the genes that these bacteria have that give them the ability to break down the target compound. Then, we incorporate those genes modification so that they still work into human cells, so that those cells are able to destroy the stuff that's accumulating.

For example, one thing we published a few years ago is that we could identify a gene that we could put into white blood cells, and those cells would then be able to break down oxidized cholesterol. Normal cholesterol is a perfectly essential molecule, and we'd better not destroy it too much, and that's why statins are not a very good drug against atherosclerosis. They work by reducing the amount of cholesterol that we make, but the real enemy in atherosclerosis is oxidized cholesterol, so if we can directly eliminate that, rather than going after the normal cholesterol, we've got a much better chance; and, that's what we have shown- only at proof of concept level so far, but still- that might be possible to do.

All right, so I've got two types of damage left, and they are both molecular again, but in this case, rather than being inside the cell, they are outside the cell. They are in the spaces between cells. The first one is, again, waste products. They accumulate outside the cell, too. The reason why it's a separate category is the usual reason, namely, that we're going to go after it in a different way than inside the cell. Molecular waste products inside the cell. What we'll do in this case is we actually only need to re-locate the stuff.

Outside the cell, the natural machinery that exists for getting rid of stuff; for breaking it down, and so on, is very primitive; very much more restricted, and less powerful than anything that exists inside the cell, which means that stuff accumulates there- outside the cell- which would not accumulate- it would be naturally destroyed if it were just inside the cell. All we have to do is make that happen, and it turns out that that's not so hard. You can vaccinate against stuff that you want to get rid of, and the immune system will engulf. It will get it inside the cell, and after that, it's pretty much toast. That's actually a very

promising approach, and indeed in the late nineties, it was first demonstrated to work in the cases of one particular type of extra cellular garbage; namely the amyloid that we see in Alzheimer's in the brain. It was demonstrated in mice, and that went through to clinical trials, and it's been shown it really works. It doesn't give much in the way of cognitive benefit; at least not to most patients, but that's simply because the amyloid is only one component of Alzheimer's disease. You need additional therapies, too, that have not developed.

It looks like it works. We've been pursuing the same idea in the context of other types of garbage; also types of amyloid, but made of different types of protein, and occurring in different parts of the body. We've specifically been going after something called, transfer amyloid, which accumulates in the heart, among other places, and causes a disease called senile cardiac amyloidosis. That's a disease that has come very strongly to the attention of gerontologists recently, because it's been determined that this disease is responsible for a huge proportion- maybe as much as half- of the death of really, really old people; people over 105, 110. We definitely need to fix that. We have duly indeed been able to develop antibodies that seem to work, and we are hoping that these are going to go through the usual process, and become therapy.

The final type of damage is not waste products, but rather a change in the structure of something in the space between cells. There's this lattice of proteins called the extracellular matrix, which holds our cells together, and gives our tissues their physical properties; their elasticity, especially. Elasticity is really important in certain places in the body, such as the major arteries. The main reason why we get high blood pressure in old age is because our major arteries get stiffer. They get less elastic, and that results in the need to push the blood harder, and it results in damage to the more fragile minor components of the circulatory system.

What we'd like to do is restore that elasticity, and that sounds like it shouldn't be too hard, because we have a good understanding at this point at the molecular level. We understand that it's mainly caused by the reaction of amino acids in the extracellular matrix with sugar in the circulation; and, sometimes, those reactions cause new chemical bonds to be laid down that link between the proteins that make up the extracellular matrix. That's what, essentially, causes the stiffening that we see; the loss of elasticity. If we could have drugs that would break those unwanted cross links, then we'd be golden. It turns out that the structure of these cross links- the molecular nature of them- is very different from anything that the body lays down on purpose. That means that in principal, a small molecule that attracts these things- even if it's not particularly specific- it will be specific enough not to have particular side effects, and that's the kind of thing we're looking for right now.

Dave Asprey: Now, you said amino acids. I'm mostly familiar with advanced glycation end-products.

Aubrey de Grey: That's what I'm talking about.

Dave Asprey: Okay, cool. Those, though, require relatively high levels of glucose, so is it an amino acid problem, or is it a sugar problem? Are there specific amino acids that you're more worried

about than others?

Aubrey de Grey: First of all, yes there are certainly specific amino acids. The links that we're talking about only form between lycene, and argenine, but the amount of those amino acids in the extracellular matrix is non-negotiable, because they are one of the proteins that are involved in actually constructing extracellular matrix are what they are. You're not going to be able to change those. You can, of course, change the other side of the equation, as you mentioned, the level of sugar; but, what's really important to understand is you can't change it all that much. If we have too little glucose; too little sugar in the circulation, that's hypoglycemia, and it's bad for you. We can't change it all that much.

One thing we can change is the amount of fluctuation in the amount of sugar we have. Certainly, the big problem with insulin resistance, and Type II diabetes is exactly that; that our system for regulating sugar, and getting rid of those spikes after eating as quickly as possible, that machinery starts to work progressively less well. However, the point is that even in early life; even when there is perfect glycemic control, you've still got a respectable amount of sugar in the circulation, because you need it, and so glycation is going to happen; and, advanced glycation end-products, including these cross links I'm talking about, are going to accumulate.

Dave Asprey: There are lifestyle factors in that one that seem to have a pretty big ... Alcohol, when it breaks down in the liver aldehydes; giant cross link forming things. If someone drinks less, they're going to have less of this stuff until these small molecules come out that can break down the links. That seems like a pretty valid way of preventing one of the seven problems.

Aubrey de Grey: Again, it's a matter of the contribution of these different mechanisms. Yes, certain types of components, depending on the specifics of how good your enzymes of particular types are—certain ones may make a difference to the level of certain drivers of glycation in the circulation. If you are, for example, particularly poorly equipped to eliminate alcohol from your bloodstream, so that you have aldehydes, especially, in the circulation, because you have good alcohol dehydrogenates, but you don't have good aldehyde dehydrogenates, then not only will you be prone to getting hangovers, you'll also be prone to also having somewhat accelerated accumulation of glycation end-products. As I say, we've got to always have a sense of proportion about this, and understand that the essential amount of glucose that you have in the circulation is actually the major contributor to the accumulation.

Dave Asprey: Sugar, and oxygen are toxic, unquestionably, and we use them every day, so let's repair that. I'm in full agreement on that one.

Are there things we can do now that turn up our body's natural mechanisms for repairing these types of damage?

Aubrey de Grey: There doesn't seem to be all that much that we can do now. Certain things we know we can do that are the wrong things to do. We know that smoking is bad for you. We know that getting seriously overweight is bad for you. Probably, meditation is good for you, insofar as

it reduces stress hormones like cortisol, and those things definitely contribute to the rate of accumulation of various types of damage. Everything I'm saying here is what your mother told you. The question you're really asking is, "Is there any new news? Is there any big discovery that helps us to do things that we couldn't do before?" The answer is, no, there is not. At the moment, the best thing that you can do to have a higher probability of living a longer amount of time in a healthy state is a very boring thing. It is, give me large amounts of money so that we can get this research done faster, and develop medicines.

Dave Asprey: Do you hear that everyone? Send your money to Aubrey. No joke, if you are in a position to make non profit donations, and you like this aggressive hacking of aging, Aubrey is the man. Seriously, SENS Foundation is worthy of your support.

Aubrey de Grey: It sounds like a joke, but-

Dave Asprey: No, it's not.

Aubrey de Grey: It's the actual truth.

Dave Asprey: Anyone who has listened to this much of the interview understands; I think the technical term is, "You know your shit." I don't know another way to put it.

Dave Asprey: Let's talk about cancer. I've been talking with Dominic Agostino, looking at the mitochondrial parts of cancer. I'm working on a book on mitochondria right now; not a cancer specific book. We're seeing huge changes when you use hyperbaric oxygen, and you change the mitochondrial biogenesis, and all these crazy things. What's your take on cancer? It seems like one of those things that's bad for aging. Give me Aubrey de Grey cancer story.

Aubrey de Grey: Okay, so first of all, I think that the appropriate way to classify cancer is to say that it is part of aging. It's a part of aging that is essentially antagonistic to the rest of aging in the sense that it is a phenomenon of excessive regeneration, if you like, of too much cell division whereas many other parts of aging are alleviated by more cell division; by more stem-cells, things like that. A lot of the way that the body allows us to live as long as we do is, because of finding a good trade off between those two things; perhaps, dampening down our ability to have good regeneration, especially late in life, as a way of also dampening down the ability of cancer cells to divide rapidly, and kill us that way instead.

Then, I guess the real question is- I suppose it's in two parts- there are various theories about how we might prevent cancer from getting going, things like that. Then, there are various theories about how we might eliminate cancer, or control cancer after it's got going; after it's been diagnosed, and so on. We at SENS Research Foundation as with all the other aspects of age related ill health, we tend to be focused on the latter; on rejuvenation, and repair. Our approach to combating cancer is a little bit off the beaten track of most of what we do. Rather than simple repair- simple restoration of the structure of how the body was at an earlier age- we want instead to effectively put a time bomb into cells to eliminate

their ability to divide indefinitely by eliminating the genetic capacity that they have to extend the ends of their chromosomes.

The idea here is based on a discovery made way back in the early 1970's, or rather an insight that was made, which is that the way in which DNA replicates is, it's only been evolved once, or DNA polymerases have a lot in common; and, it works in a way that is unable to replicate the ends of a linear DNA molecule completely. Whenever a cell divides, it's DNA is replicated, and the ends of the chromosome get shorter, and that can't go on indefinitely. Eventually, things start going wrong. Of course, the obvious thing is, you eventually start losing important genetic information. Actually, things go wrong much sooner than that. They go wrong when you've just lost a little bit of DNA, because that impedes the ability of the cell to recognize the difference between- on the one hand, the end of the chromosome, and on the other hand, a broken chromosome, which happens all the time. Chromosomes have to be repaired after being broken constantly, and it'd be very bad if that same machinery recognized the ends of two chromosomes, and thought they were a broken chromosome, and joined them together, end to end. That's why the special sequence, called telomeres exists at the end of the chromosome.

We are interested in insuring that cells in cancer can't do what I just said; can't extend the ends of the chromosomes, and maintain their telomeres. If they can't, then eventually after dividing quite a bit- but, way before the cancer has grown big enough to kill us- then the things like joining chromosomes end to end will start happening, and the cells will just divide themselves into oblivion. We're trying to stop that from happening.

Dave Asprey: That's such an elegant way of hacking the problem. I'm a computer science guy, and you look at how you disrupt systems, and that is very different than the typical thing you hear. I am still intrigued by looking at the mitochondrial affects of cancer, and I believe there's probably some hacks you could do to your mitochondrial function, which ought to have profound anti-cancer effects, but-

Aubrey de Grey: Oh yeah, people have been definitely pretty excited about for example, stimulating mitochondrial activity as a way to eliminate what's called the Warburg effect- the deliberate suppression of mitochondrial activity in cancer- but, it's not yet clear that that would be a really decisive therapy. The thing is, that cancers are awfully clever at figuring out how to evade what we do, and in order to really get rid of a cancer, you have to do something that's so hard hitting that even the trillion cells in a clinically relevant cancer can't find a way out of it.

If you look at the mitochondrial thing, for example, suppose you have some drug that stimulates mitochondrial function; if the cancer can figure out how to break down the drug, or to stop the drug from getting into the cell in the first place, or even just suppress mitochondrial activity harder so that the drug is essentially outrun. All of these things are possible.

Dave Asprey: Definitely cancer will fight back. I suspect that the final answer will be many different therapies all at once, rather than just one. Although, the one you're talking about- if that

works- that seems very decisive. I like that thought. That's really cool.

What are the other things besides cancer that are really big threats to longevity? If you're sitting down to do an analysis, what would you think about?

Aubrey de Grey: The reason we have these seven categories is because they're all big threats. All of these types of damage accumulate semi-independently of each other, and therefore, they are all controlled by selective pressure- by evolution- in the same way. They all have the same essential deadline; the ill health, and decline in performance, and death, the results. In other words- put it like this- they have different genes that are involved in combating them, and slowing down the rate at which they accumulate, which means of course that if you have different sets of genes combating different types of damage, and one particular set of genes for one type of damage is unnecessarily effective, so that the type of damage that it is protecting against would not kill us until we were age 500, whereas everything else is going to kill us at age 100. Then, the genes in question- the genes that are controlling that type of damage- will not be selected for. They will accumulate spontaneous mutations- I'm talking here in the germ line, not in the body- and, they will become- these will be mild mutations, so the genes will still be there, and they'll still somewhat work, but they won't work as well as they used to, and eventually they will work only just well enough to defend against that type of damage for 100 years; same as all the other types of damaged genes. That's why all these seven types of damage are equally important.

Dave Asprey: I love the way your mind works. You also talk about something called, "Compression of morbidity," which is kind of a technical term, but explain that for listeners. It's a cool idea.

Aubrey de Grey: Okay, so first of all, I certainly don't talk about it, because I don't think it's a cool idea.

Dave Asprey: Oh, okay, I do, so tell me all about it.

Aubrey de Grey: Let me tell you why it's not a cool idea.

Dave Asprey: Okay.

Aubrey de Grey: First of all, let me tell you what it is. The concept of compression of morbidity, as a goal, for biomedical gerontology- for doing something about aging- is that we've got this lifespan, and the last end years of the lifespan is unhealthy. Of course, exactly what end is depends on how you define unhealthy; how severe your ill health has to be. Still, the idea is we have this certain amount of time. Way back in about 1980, a very prominent gerontologist said, "Okay, maybe the goal of gerontology needs to be to postpone the decline into ill health," in other words, extend the healthy longevity, and then we will have less time in the unhealthy stage. Sounds great, but of course, that concept relies, first of all, in terms of its actual plausibility, on the idea that there is something that kills us on schedule irrespective of how long we've been unhealthy. That somehow, if you delay the onset of ill health, then the ill health will become more severe at a more rapid rate than it would if you didn't delay it. There's absolutely no reason whatsoever to think that that's the case. If you can delay the beginning the of ill health, then it's probably going to proceed at the normal rate.

Secondly, we have to ask ourselves, do we really want compression of morbidity? If you think about it, the ultimate limit of compressing mobility is that you live to 100 in the same kind of mental, and physical state that you were when you were thirty, and then suddenly one day, you don't wake up. Now, the thing is that in general, if you ask people whether they want to die anytime really soon, then their answer may depend substantially on how healthy they are, but it won't depend in the slightest on how long ago they were born. If we want to be non-agist about this- if we don't want to discriminate against people who were born a long time ago- then, really we shouldn't be thinking in terms of compression of morbidity much at all. We should only be thinking in terms of postponement of morbidity.

The final thing I want to say on this is the really good news, which is that when we postpone morbidity, we're giving people an extra amount of life, but then they're going to fall into ill health anyway, except if before they fall into ill health, we postpone their morbidity again; a little bit more. If we can find therapies that, let's say, keep people healthy for an extra five years, we've got five years to figure out what to do next. Five years isn't very long, so we might not figure it out, but supposing we have a bunch of therapies which we can apply that extend people's healthy life by 30 years? Thirty years is a long time to figure out what to do next. 30 years is the kind of amount of time that I believe the panel of therapies I've outlined to you earlier on in the interview are likely to give us, which means that I think that once we get them, we will have solved all the problems that we need to solve. We will have 30 years to figure out SENS 2.0 so to speak; and, I don't know what SENS 2.0 is going to look like. I don't know exactly, anyway. I'm fairly sure that we won't end up needing additional categories, but we may certainly end up needing additional examples within the categories, so there will be complications.

The thing is, 30 years is such a long time in any technology, including medicine, that we're very, very likely to get there in time. Of course, after that, we may have got someone out to being 150 before they get sick. That means we've got another 50 years, or whatever, to figure it out. This is the thing that I've called, "Longevity escape velocity." It's the thing that gets me into the most trouble with scientists, because of course, it's not science, this is technology I'm talking about. When you're talking science, you can have a sensible discussion about SENS 1.0; about the feasibility of these various things that we're already working on, but you can't have a discussion about SENS 2.0, because we don't know what it's going to look like. We don't even have a proposal, yet. From a scientific point-of-view that means we shouldn't even talk about it. From a technological point-of-view on the other hand, it means we should talk about it. We should be asking ourselves questions about the likelihood of delivering this rate of improvement, and we should answer those questions by looking at the kinds of rates at which other technologies have improved following the decisive initial breakthrough.

Dave Asprey:

I spend a good amount of time with Peter Diamindis, and looking at exponential technologies- I think you do, too, or at least you're connected through the university- Singular University- and, unquestionably, I look back. I'm the first person to have done e-commerce. The first product sold over the internet was actually the version 1.0 of the T-shirt I'm wearing now, with a trimethylxanthine, ie. caffeine molecule on it. You look at

how the world has changed in 30 years; of course, stuff is going happen, but the reason I was laughing so much about your brutal takedown of the compression of morbidity is that I love to talk about the compression of morbidity, because people still think they're going to die; and, getting them to go beyond that is just too much work. I'm like look, "Why don't you live really, really well, and of course you'll die." The whole point is, if you're still 30 when you're 80, you're probably not going to just drop dead. Just like you said, but I find that the mental leap that it takes to get someone to think about that is just too much work that I'm happy to talk, "Of course you'll die;" but, shouldn't you just be young, and ass-kicking till then?

Aubrey de Grey: To be honest, Dave, I think you're right. I think that it's vital to convince people to support this work, and I'm perfectly fine convincing them by arguments that I don't believe. The thing is, that I'm not very good at delivering arguments that I don't believe in. I'd rather you did it instead.

Dave Asprey: I appreciate the way you think, because you're exactly right, if you're really 30 when you're 80, why would you die? It's so obvious. Okay, we actually do agree there, and it's actually really humorous to me.

Aubrey de Grey: From a rhetorical point-of-view, I think it's vital. I am very good at what I do, but I only do what I do, and so I think we need a wide variety of voices out there explaining this concept, and the importance of doing something about aging to a wide audience so that one of us which actually communicate effectively to these people.

Dave Asprey: I think you should keep doing what you're doing, because it's working pretty well from where I sit. Let's talk about the other big question that comes up, and I've been public saying, "I think 180 is a reasonable age for me to live." That's because I started out with crappy mitochondria. I used to be obese. I have all sorts of risk factors, but I think I can pull off 180, and maybe I'm wrong, in which case, I'll be dead, and it's okay. People say that either that's unnatural, or it's an ethical thing; like I'm somehow stealing from someone else. What's your take on the ethics of immortality.

Aubrey de Grey: I think that people's concern about the ethical ambiguity of this kind of work arises entirely from the clinging to a completely obvious misconception about the relationship between aging, on the one hand, and the diseases of aging on the other hand. Basically, people have this idea in their heads that is extraordinarily entrenched that there is a difference. That there's aging itself, which is not a disease, or not like a disease; and then, there are the diseases. This is the underpinning of a huge amount of problem.

First of all, it's a huge amount of medical problem, because people go about trying to fix the diseases of old age, like Alzheimer's, as if they were infections; as if they could be eliminated from the body without eliminating aging itself, which is nonsense. Billions, and billions of dollars is spent in geriatric medicine, and medical research trying to do that, which is never going to work.

The second problem is that people are so confused about whether aging is a medical

problem at all that they are confused about whether it would be a good idea to fix it. You don't get people asking whether there is any kind of ethical ambiguity about whether we should do anything about Alzheimer's disease. People are pretty unanimous that Alzheimer's disease is a uniformly bad thing. If people understood that it's all part, and parcel of the same phenomenon, then you wouldn't get this bullshit thing being spouted about whether it would be a good idea.

Ultimately, it all comes down to remembering that longevity is not what we work on. Longevity is purely a side effect of what we work on. What we work on is a completely ethically unambiguous phenomenon, namely, ill health. We want to get rid of ill health, and there will be this side effect of extra longevity on average, because let's face it, what most people die of is being sick. We're not working on stopping people from being hit by trucks, though I guess we are pretty happy that some people are working on that.

Dave Asprey: That is so well said. Assuming that worse comes to worse, and you actually do die, are you going to freeze your body?

Aubrey de Grey: I am signed up. I believe that cryonics is an extremely feasible concept, and furthermore, that the quality of cryopreservation is improving rapidly. I keep my finger very much on the pulse of research in that area, and I think that there's a high probability that by the time I get old enough to have a high risk of death, even in the absence of any advances in the kind of work that SENS Research Foundation does, that cryopreservation will be really good. The damage done by the cryopreservation process will be very minimal, which means that the likelihood of someone who is cryopreserved very shortly after their heart stops is quite high.

Dave Asprey: I'm not sold on that theory, yet, but I'm open to it. I have lots of friends who have the bracelet, and are planning to freeze their head, or freeze their body.

Aubrey de Grey: The only reason to be sold on it is if you understand the details of technology. Certainly, it's very straightforward to say, "This sounds far too difficult," but one just has to look at what's possible, and what's looking like it will be possible soon, and that's how to make that decision.

Dave Asprey: I'm not worried about the technology at all, I'm just not certain that restarting the hardware after it stops; that the operating system, and the things will still be there.

Aubrey de Grey: I can help you there very quickly. When, for example, falls through ice on a frozen lake, and their heart stops, and their brain stops as well for maybe an hour- this has happened many times- that they get revived, and they don't even have any ill effects. These are the kinds of-

Dave Asprey: There is evidence, yeah.

Aubrey de Grey: Yeah.

- Dave Asprey: I hear you there, and I just wonder what the time limit on that is; if there's a wavering in the power supply in your computer, your hard drive is fine, but man, what was stored in memory; gone. It feels like there are some core assumptions about the session state that I'm not sure we can restore a session state after a long freeze. I don't have evidence either way, I'm just, "That's a big assumption you have to make before you go to all the rigmarole of deciding to freeze yourself."
- Aubrey de Grey: Even there; even there. I'm not going to let you get away with this.
- Dave Asprey: I'm interested, yeah.
- Aubrey de Grey: We do, for an absolute fact, that once you are down at -196 C, nothing happens. Absolutely nothing happens. If you can take someone down there, and get them back immediately, and they still work, then for absolute sure, and certain, you can take them back down there, and leave them there for 1000 years, and they will still work just as well. The time spent at the low temperature is absolutely time that doesn't count. We know that for a fact.
- Dave Asprey: I definitely understand that part of it. What I'm concerned about there is the fact that you died before they took you down to that temperature. If I was going to do it, I would want to be alive when they took me down there. That would be the interesting thing.
- Aubrey de Grey: Right, of course, you're not the only one who thinks that way. People have been trying to make that happen for quite some time. At the moment, there's a number of cryopreserved people who somewhat hastened their own death by essentially starving, and essentially refusing food, and water, and it doesn't take very long. That's a way, for example, to make sure that if you have some progressive neurodegenerative disease then that doesn't destroy your brain before your heart stopped.
- You've always got to remember that death is not what most people think it is. Most people think of death as an instantaneous phenomenon that happens at a particular point, but of course, the medical definition of that point has changed over the years, because of a rather embarrassing frequency of cases where people have been declared dead, and they've woken up again. Of course, the reason for this is we actually know, as biologists, and medics, that death is not an instantaneous process. The definition of it as an instantaneous process is purely a sociological convenience, because we don't like to have people to be half dead. We prefer people to be alive, or dead, and nothing in between, but that's actually not biologically sensible.
- Dave Asprey: Full agreement. Death is not a binary thing. There's a curve to it, I absolutely agree.
- I may be convinced one way, or the other, I'd say. I'm on the fence about that one, and your arguments have a lot of merit, unquestionably.
- We're coming up on the end of the show. I could talk with you for days just for fun, obviously. I'm looking at all the things I want to ask you. Let's talk about specific goals that

you have with SENS in the next five to ten year time frame. What are we going to see pretty soon here?

Aubrey de Grey: On a five, or ten year time frame, our key goal is something that I've always called, "Robust mouse rejuvenation." We are not so much focused on getting things into human clinical trials, though of course anything that did get that far would be a bonus. Really, our focus is on getting everything working together in mice. We believe that it's a realistic goal to be able to do that within 6, or 8 years at this point.

Dave Asprey: Wow.

Aubrey de Grey: It might take longer. If we can do that, what we will expect is to be able to take mice that are already in middle age, and maybe double, or triple their remaining lifespan. Take that remaining lifespan up from one year, when the mouse is two years old, to maybe three years. The reason we're so focused on that is twofold. Number one, of course, from a purely biological perspective, from a technological perspective, it's a proof of concept. It shows that we have not actually overlooked some key type of damage that makes the mice die on schedule even though we've done everything. The other thing it is, is PR. It shows the work that this is for real. We believe- I've always believed- that that kind of dramatic result is what's going to be necessary to overcome this thing that I've always called, "The pro-aging triumph;" this irrational clinging to questions like whether there are ethical ambiguities about doing anything about aging, and so on.

Dave Asprey: When you get the mouse to live three times its normal lifespan, and you can do it three, or four times, and you're like, "This is a cracked code. We know how to do this," that's when the discussion about compression of morbidity can stop. We can just stop saying, "Wouldn't you like to be 30 when you're 80," and we can start saying, "Wouldn't you like to be 30 when you're 180?" The conversation will change, but you have to crack that first.

What's it going to take in the next five to ten years in terms of funding, in terms of regulatory change? What do you need to do this?

Aubrey de Grey: Okay, so you can certainly forget about regulatory change, because we're only talking about mice, and the FDA doesn't regulate what can be done on mice.

Dave Asprey: Not yet, give them time.

Aubrey de Grey: You may be right. What else do we need? We definitely need more money. At the moment, SENS Research Foundation is struggling along on a budget of only 4, or 5 million dollars per year, which is absolutely pitiful. It is so insane that as a leading organization working on rejuvenation biotechnology, we find it so difficult to pull in funds. There are explanations for that, in terms of short term-ism of people; in terms of the fact that this is high risk/high reward research, which is always hard to fund through peer review, and so on; but, the fact is, it's a tragedy, and we need to fix it, and we need to fix it fast.

If we don't fix it fast, then those 6, or 8 years that I just mentioned could easily be 15 years.

We could be set back by a decade, in terms of how soon we actually start saving lives. Ten years is half a billion lives that we'd be talking about, because you've got more than 100,000 people every day dying of aging, one way, or another. That's the most astronomical amount of suffering. I think we could probably speed up the research by a factor of two, or three if we had, let's say, ten times more money; just one more digit on the end of our budget. That is not very much to ask. 40, 50 million dollars a year; that is a tiny fraction still of the medical research budget of the USA for example.

Dave Asprey: Did the ice bucket challenge piss you off?

Aubrey de Grey: I think that there is room for every kind of promotion of fundraising for this work. I don't care how the money is gained- up to a point, I don't care where the money comes from- I just want it to be spent on the research.

Dave Asprey: The reason I'm asking that is not just because it was a funny thing, but it raised an enormous amount of money for ALS, which is a really important neurodegenerative disease that's tied back to mitochondrial function. In fact, it's tied back to probably four, or five of the seven things that you talk about?

Aubrey de Grey: Most of the complex diseases that we know of are indeed tied back to two, or three at least, of those things.

Dave Asprey: Exactly, but all the money went to this disease, instead of the causes of these diseases, and that has to be frustrating at some level, isn't it?

Aubrey de Grey: It's kind of frustrating, yes. Of course, it depends. The problem is not necessarily that the research is focused on a particular disease. The problem is that when the money comes in, the way that it's distributed- the particular research directions that it tends to be directed at- there the problem happens, because the overwhelming majority of research that gets funded is focused on the symptoms, not on the earlier stages; the damage that's accumulating that is causing the symptoms, and that's why it's not going to work.

Dave Asprey: I hope that being on Bulletproof Radio this time gets a few people with nice checkbooks to write some relatively small checks to the SENS Research Foundation. It's a worthwhile cause. Going back to my favorite ice bucket challenge video, which was Patrick Stewart-Captain Pickard- and, he said, "Here's my ice bucket challenge." He has an ice bucket, and he takes two ice cubes out, puts them in a glass of whiskey, and then writes a check. Done; handled like a boss. For people listening who are interested in this kind of stuff, and there's a lot of transhumanists, and a lot of people who are just deeply interested in controlling their biology. That includes feeling amazing when you're old. In fact, feeling so amazing you don't know you're old, and neither does anyone else. That's the win.

Aubrey de Grey: That's the win.

Dave Asprey: For that, if you're one of those people, and you're looking for your charitable donation around tax time, or whatever else, I would say think about what Aubrey is working on with

the SENS Foundation; it's cool.

Aubrey de Grey: At the moment, we actually have a challenge going on that has just launched yesterday.

Dave Asprey: Okay. I didn't even know.

Aubrey de Grey: If you go to SENS.org, right now, you'll see it. It's called, "Control, alt, delete." It's all about part of our anti-cancer approach that I was discussing earlier.

Dave Asprey: Okay, approaching cancer is an awesome idea, because there is a lot of funding for that, and a lot of public support for it. If you can solve some parts of cancer at the same time, many other parts of aging, it's a double win, and everyone is good there.

Aubrey, we're coming up on the end of the interview, but I have a question for you that I ask every guest on the show. If someone came to you tomorrow, and said, "Aubrey, I want to perform better at everything I do as a human being, what are the three most important pieces of advice you have for me?" What would you say?

Aubrey de Grey: Okay, I'm going to cheat. I'm going to answer a different. I'm going to answer the question that says, "Why am I good at what I do?" I'm afraid the answer is not really something that people can acquire on purpose, at least not quickly. I think that why I'm good at what I do is a combination of charisma, and determination, and confidence. Of course, it helps to be smart, but I think that lots of people can be very smart, and still get very little done in their lives, and make very little difference. I occasionally give a talk on this kind of thing called, "How to be a successful heretic." That actually has more than three; it has ten different pieces of advice.

Dave Asprey: I will link to that in here. The other thing you didn't say, though, is you're relatively fearless. I've hung out with you personally enough times that you just don't give into that stuff. You're willing to say, "I just don't care about that," and you live your personal life in a way that's without fear, and full of love, and passion for what you do. I think that's got to be a part of your success formula?

Aubrey de Grey: I would say that it's another symptom of who I am, rather than-

Dave Asprey: A symptom, I love it. All right, I could see that.

Aubrey, as always, it is a pleasure to chat with you, and it's an honor to have you on Bulletproof Radio. Have an awesome day; and, for everyone listening, I'm not kidding, and neither is Aubrey about what's possible with anti-aging, and if you're in the mood to make a donation, think about this. This is seriously one of the biggest things that we as a species can be working on. Thanks Aubrey.

Aubrey de Grey: Thank you.

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