EMBO reports

interview

Curing ageing and the consequences

An interview with Aubrey de Grey, biomedical gerontologist at the University of Cambridge, UK

EMBO reports (ER): You have proposed serious life extension therapies to overcome the ageing process, to the point where we could live indefinitely. What is your definition of ageing?

Aubrey de Grey (AD): Ageing has a reputation of being terribly difficult to define, but that's only if you want a definition that suits all purposes. If you want a definition that is useful for evolutionary biology, then you would say one thing. A definition that's useful for biomedical purposes would be different. I like to think about it in a mechanistic way that helps one consider how to cure it, so my definition is 'the accumulation of side effects of normal metabolism that eventually become pathogenic'.

ER: You define seven things that need to be fixed in order to circumvent ageing: chromosomal and mitochondrial mutations, lysosomal and extracellular aggregates, extracellular protein crosslinking, cancer and cell senescence.

AD: These seven things are rather categories. There are many metabolic side effects that accumulate during life. For some of them, we have good reason to believe that they are never bad for us during a normal lifetime. So those ones don't count. Of the ones that we have reason to believe may eventually be pathogenic, I've put them into these seven categories. One can argue about how the partitioning should be done. In my partitioning, the plausible approach to doing something about each thing varies for different tissues in the body, but only slightly. So, for example, I regard mutations in the nucleus and mutations in the mitochondria as two separate things because the way to fix them is different.

ER: Are all categories equally important to fix?

AD: I take the view that there is a realistic probability that if we don't fix each of them, we won't achieve very much. In practice, it could be that one or two of them don't turn out to be that important. But I think it's very important to recognize that we have a choice whether to focus on first establishing some sort of pecking order of importance and then moving on to fixing the ones that count, or alternatively to fix everything that might matter. I'm very much in favour of the latter. We've spent far too long navel-gazing and trying to work out this pecking order.

ER: So if all these things can be fixed, then—theoretically—there is indefinite life?

AD: It's indefinite in terms of what I describe with the phrase 'escape velocity'. For each of these seven categories, different interventions must be applied. Each of these interventions is ambitious and you will never be able to do them perfectly. But because each of the interventions constitutes a reversal of the accumulation of damage, as opposed to slowing it down, that means that it's OK to do only a partial job as long as you're doing a sufficiently comprehensive job on all of them together. This then gives you more time to improve the technology. 'Escape velocity' is the concept that one gets to the point where the therapies are improving faster than damage is accumulating. Once we get to the first generation of therapies that will, for example, give us an

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extra 20 or 30 years of healthy life, then that will be beyond this escape velocity transition, such that we will not have much trouble progressing the science faster than time is passing. So, the practical upshot will be that we live indefinitely.

ER: But is it not more important to focus on preventing rather than repairing damage?

AD: Basically, prevention is impossible in this scenario, because the things that we're trying to prevent from reaching a threshold level of abundance are intrinsic side effects of metabolism. Messing with them means improving on what evolution does in regard to metabolism. That's impractical.

ER: You describe your approach to solving the problem of ageing as an engineering approach. How is that different from classical biomedical science?

AD: It's not different from the biomedical approach. It's different from the basic science approach. There is a consensus within society that ageing is not a disease and therefore not an appropriate target for the biomedical approach. That's the problem.

ER: Is that going to change by defining ageing as a disease?

AD: We define ageing as undesirable, that is what it comes down to. I consider myself a biomedical gerontologist—someone who is interested in developing technologies that do something about ageing. I distinguish myself from biogerontologists, who are mainly interested in understanding ageing but not necessarily in doing anything about it. There is a subtle but clear difference between the creativity involved in an engineering or biomedical way of thinking and in the basic science way of thinking. If you're trying to solve a problem in a very complex system, then your ideas of how to manipulate the system may depend on a particular item of knowledge that you don't have. If you can identify that item of knowledge, that's great. But suppose you can't. From the engineering point of view, it's just as good to figure out a way of manipulating the system that sidesteps this unknown. From a basic science point of view, that doesn't make sense, because the knowledge is an end in itself. That's really the main difference I've put my finger on.

ER: Cancer is one of the categories in your list. Cancer research has now seen more than 30 years of intense efforts that combine the engineering approach and the basic science approach, but despite enormous investments, we still don't have a cure.

AD: Unlike ageing, cancer is recognized by society as a disease. So cancer has been approached by people who are thinking the way I think about ageing. The reason I'm confident that more can be done about cancer is because I've got a new idea for how to address cancer by a much more ambitious high-tech approach than anyone would dream of at the moment. It's important to remember that age-related diseases are competing to kill people. In other words, if you delay the average age of death from one particular age-related disease by even a decade, then that's equivalent to curing it, because most people are going to die of something else in that time. Even if one has an ambitious and far-sighted idea for curing cancer properly, there's no reason to do it in the current world when everything else is still not cured. But when you're thinking in terms of curing ageing, you can't cut that corner. I describe cancer as the hardest part of ageing to cure. If we cure everything else but cancer, we'll get 20 years extra lifespan if we're lucky.

ER: How will it change medicine as we know it, if we all live to be 5,000?

AD: The main thing is we won't have any frail people around. That's important when you look at the money being spent on healthcare. It's well known that on average in the western world, people consume more medical resources in their last year of life than throughout the rest of their life. We work hard to keep people alive an extra couple of years when they are already suffering advanced ageing. What a cure for ageing will mean for the provision of medicine is that it will be more effective because it will be used on people who are robust and able to withstand treatments. Most of the medicine will be rejuvenation treatment.

ER: Will these advances mean that infectious diseases will kill more people than cancer and heart disease?

AD: My view, which is rather optimistic, is that we will become more risk averse in general, not just at the personal level, but globally, and we'll spend more on vaccine development and anticipating new infectious diseases. It's a complete outrage that so little effort is being put into developing vaccines. It's not happening because vaccines aren't profitable. That argument won't apply in a world of longer lifespans.

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ER: But a human is a complicated machine. Your approach is to fix things without fully understanding the system as a whole, which might lead to other unexpected side effects.

AD: That's true if you fix things too late, because then it is about staving off disaster when you've already got accumulation of age-related problems. It's a losing battle. The underlying cellular damage is still accumulating, so the problem gets harder and harder to stave off. My approach is more practical, simply because it's intervening as early as possible without being so early as to manipulate metabolism itself. It's reversing the accumulating damage that starts being laid down before birth, rather than waiting for these things to reach the threshold at which they start to be bad in terms of dysfunction. It is still complex, but it's not nearly as complex as later on. That's why it's practical.

ER: Would this approach involve research and trials on healthy young human subjects? That would mean rewriting the whole code of medical ethics.

AD: Young people are not suitable subjects for this sort of therapy, because the whole point is to repair accumulated molecular damage. If you're 30, you haven't got much of this damage, so you are not really a suitable subject. People in their 50s or 60s

would be the ideal subjects. People in their 80s are so close to the edge that the first-generation therapies may not be able to pull them back from the brink. Would it be contrary to current medical ethics? This is an extremely interesting question. I don't have much time for the Hippocratic Oath myself. I think it's something that made a lot of sense when the understanding of medicine was primitive and when people could spontaneously recover from illnesses for reasons that the doctor couldn't identify. That's where the 'do no harm' idea comes from. That becomes less reasonable as we become more knowledgeable about how to intervene in the body's metabolism. One also has to remember that around the world there are very different versions of medical ethics. There's good reason to believe that many of these therapies will first be developed in countries where they are more forward-looking about the cost–benefit ratio.

ER: Given the potential market interest in anti-ageing products, why don't we see more interest from pharmaceutical companies?

AD: Because within the commercial sector it's much more important to make money with high probability in a short timeframe than to make a lot of money. If a company can make a million dollars with 99% probability in 2 years' time, that is preferable to making a billion dollars with 50% probability in 20 years' time, even though the actual net gain would be much higher. That's why the pharmaceutical market is not interested.

ER: But they do invest a lot in ageing research.

AD: All these therapies relate to age-related diseases rather than to ageing itself. In the biomedical sector, there's this triangular logjam. Specialists in ageing are on the television all the time, but they work on what the government will fund. And the government disburses funds in a way that is extremely biased in favour of low-risk, low-gain projects. The reason it does that is because if it funded pipe dreams, then it wouldn't be the government for very long, because voters wouldn't like it. The reason that voters think curing ageing is a pipe dream is because television only shows my colleagues talking about what they can get funded. It's a complete fiasco.

ER: Some critics say that it is wrong to discuss the possibility of preventing ageing because you give people hope.

AD: The idea that one engenders unwarranted optimism by talking about serious life extension is disgraceful. We now have comprehensive and reasonable ideas for how to cure ageing. That turns the irresponsibility the other way around. It means one is irresponsible to remain silent, because that simply perpetuates the pessimism in the public. That in turn means that research doesn't get funded and lives are lost. I'm very strongly of the view that it's irresponsible to remain silent now.

ER: It seems like a lot of nonscientists are very willing to accept the possibility of anti-ageing. Do you find it easier to convince nonscientists?

AD: No, the people I find easiest to convince are hard scientists: physicists, mathematicians, computer scientists. This is not surprising because these people have been trained to take things to their logical conclusions and think in a more abstract manner. If this life business is fun, then there's no reason to suppose it's going to stop being fun as a result of anything other than getting frail. So not getting frail seems like a pretty obvious goal. This is something that computer scientists, mathematicians, physicists and philosophers, of course, have no trouble with, whereas nonscientists, and also biologists in general, seem to have a bit of a hang-up about it.

ER: Curing ageing leads to the idea of enhancing the natural abilities of mankind, something that has been discussed by transhumanists. Why is this still considered a fringe area of research?

AD: It's largely because the types of enhancement that the community discusses are rather extreme, relative to the degrees to which we have been able to enhance ourselves so far. That's why computer scientists don't have any difficulty with thinking about these things. But it's also why most people regard them in the same way that they regard teleportation. It's entertainment but it's not something they need to fight for

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because it's not going to happen in their lifetimes. Life extension is really at the boundary between futurist ideas and what you might call 'mainstream science' in the sense that it's something most people can see to be possible in principle. In other words, something that can be progressive, whereas many other transhumanist concepts are often described in terms of the end product rather than how we might get there. That's certainly the main reason why the transhumanist community regards life extension as the most practical component of what they are interested in.

ER: Why don't we see a broader debate on life extension?

AD: You can tell it makes me miserable thinking about why we don't. It comes down to two things that are linked to each other. One is that people still don't think that serious life extension is going to be possible in the foreseeable future, during their lifetimes or their children's lifetimes. The second thing is that they are highly ambivalent about whether it's actually desirable to have seriously extended lifespans. We have this ghastly thing—ageing—that makes us miserable and we can't do anything about it, so we put it out of our minds and get on with our lives. We try to convince ourselves with arguments of arbitrary ridiculousness that ageing is actually a good thing. But of course this feeds back on itself when the feasibility of doing something about ageing becomes at least worthy of debate. Opponents are tied into the opinion that "It might not be a good thing", and it's hard to break that cycle.

ER: When we have the first steps towards life extension, we will have to face the complications, such as the social implications.

AD: It's going to be even more mayhem than you might think, because the problems are going to start not when these therapies arrive, but when they begin to be widely anticipated. There's going to be a point, maybe 10 years from now, when biologists demonstrate to the world in a sufficiently persuasive manner that human ageing may soon be properly treatable. That's when the real pandemonium is going to hit. It's going to be very difficult to keep people in risky jobs. They will want to maximize their chances of staying around long enough to benefit from these therapies. Much more will be spent on traditional medical care. It will cease to be possible to get elected except on a commitment to have a Manhattan Project to cure ageing as soon as possible. All manner of things will change overnight. It's going to be absolute pandemonium.

ER: That's not a good way of selling it.

AD: I think it's important to be realistic about it. For each problem one has to think about the options. For example, pensions. The fact that we've got laws at the moment that say everyone gets a pension over 65 doesn't mean we can't change the law. Pensions exist for frail people, and there won't be any frail people. Retirement will still exist but it will be a periodic voluntary thing. Adult education will become much more important. You'll have retraining—you could have a completely different life every 50 years and become a rock star, or whatever. People ask, 'Wouldn't it be boring?' What do you do today when you're bored? Do you top yourself? No. We're not forcing this on anybody. People don't have to get rejuvenation therapy if they don't want it.

ER: Would we still have religion? Every major religion centres on the concept of death.

AD: There's still going to be death. There are still going to be buses to walk under. If you look at the major religions, they are not keen on hastening death. They say that suicide is bad; murder is bad. However much better the afterlife may be, it's not something you ought to hasten. That means the major religions are telling us to cure ageing.

ER: You believe there would be much less violence and more risk aversion in a population with greater life expectancy. What do you base this on?

AD: It's the extrapolation of what we see at the moment at a global or national level. Where there is a low life expectancy, people tend to engage in more life-threatening activities. In Europe it's more pronounced than in the USA. We've got rid of the death penalty in the past 50 years. We don't even extradite people to places where they might be subject to capital punishment. Why did this happen? Because we have a greater value for life now. Similarly, we've had no war between western European nations for the past 60 years. That hasn't happened since Roman times. It bodes well.

ER: What sense of urgency will we have to drive us forward to achievement if we live for thousands of years? Critics suggest we'll have no reason to do today what we could put off to the next millennium.

AD: I'm almost as speechless at this notion as I am at the boredom question. Young people now, in their teens or 20s, aren't driven by death or the fact that they are going to die 50 years from now.

ER: There's going to be a much slower turnover of new people. That means fewer new Da Vincis and Einsteins, but also fewer new Hitlers and Bin Ladens. How will that affect human progress?

AD: This is a complete unknown. We don't know how malleable the brain is. But I am firmly of the belief that there is a high probability that appropriate access to higher education and to adult education, combined with complete rejuvenation at the biological level and maintenance of the flexibility of the adult brain, has huge potential to give rise to new Da Vincis from people who were previously plumbers, for example. They don't have to be born Da Vincis. So the turnover is still there.

ER: Dr de Grey, thank you very much for the interview.

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