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Reith Lectures 2001: The End of Age

Lecture 2: Thread of Life

We sometimes say, in extremis, that a person's life hangs by a thread. In fact, all our lives hang by a thread all the time. The thread in question is DNA, the medium through which we inherit our genetic destiny. DNA directs our growth and all of the vital processes on which we depend for survival. DNA is the thread of life, but is it also the thread of death? Does DNA control our end as it controls our beginning?

In my first lecture, I described the revolution in human longevity that has taken place over the last few generations. Tonight, I shall look at the companion revolution in the life sciences - a revolution that has unfolded with breathtaking speed over the last half century and which has accelerated greatly of late. It is this revolution that will allow us to understand the role of DNA in the ageing process.

When the first draft of the human genome was announced on 26 June last year, the world's press rejoiced in the prospect of continuing, even accelerating, the postponement of death that had been the great success story of the 20th century. This enthusiasm was reflected in reports of a telephone call between President Clinton and Prime Minister Blair, in which the President congratulated the Prime Minister that his baby son Leo had, at a stroke, gained 25 years in life expectancy. Politicians' promises are not always the best arbiters of future reality, but the personal nature of the President's message suggests he was sincere. Was he right? And what are we to make of claims that even longer life spans are just around the corner?

DNA plays a dual role in our lives. Like Theseus of old, it combines power and vulnerability - it is both master and servant of fate. On the one hand, DNA is the medium in which our genetic endowment is written. It is the information coded in our personal DNA sequence which we can probe for the presence or absence of particular gene variants - or polymorphisms - that might affect our future. Seen in this light, DNA plays a fixed role in each of our lives.

Our interest is in the differences between one person's DNA and another's and in what these tell us about biological individuality. But our personal DNA is by no means as constant as we might wish. DNA is a working molecule to which our cells refer continually. It is not some dusty tome tucked away in the reference section of the cell but a hive of activity, more akin to a busy internet web site. Just like a web site, it experiences a continual stream of hits.

Most of these hits are harmless requests for data, involving simply a readout out of a genetic string of A's, C's, G's and T's, like the bit strings of zeroes and ones that are downloaded from web sites. But some are real hits by agents of damage which result in lasting harm. It is these latter hits that cause the information coded in our DNA to become corrupted with the passage of time, and it may be these hits that cause us to age.

If we look first at the vulnerable side of DNA, the bad news, I am afraid, is that even as I speak your DNA is in trouble. As I spoke the last sentence, the DNA in your body experienced literally billions of damaging hits. The attack rate on DNA has been estimated at 10,000 damaging hits per cell per day. Your body comprises about one hundred thousand billion cells, so the carnage is considerable.

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Lest you worry unduly, let me assure you at once that even as each hit lands, your cellular emergency services are on the lookout for trouble and putting it right. But, good as these systems are, they are not perfect and some of the damage will persist. During the lecture tonight you will use up about one ten thousandth part of one per cent of your life expectancy. It is not a lot, and you will not feel it, but another grain of sand will have passed through the hourglass of your life.

The villain that is doing most of this damage to your DNA is oxygen. We tend to think of oxygen as friend rather than foe, but it is dangerous stuff. When I light my fire on a cold winter evening, it is the chemical reaction of oxygen with carbon that makes the coals glow hot. But if a spark were to escape from the fire, the same oxygen might burn the house down. Inside the cells of our bodies thousands of minute structures called mitochondria use oxygen to produce energy, and the same oxygen also produces a kind of spark. The inside of the cell is wet, of course, so the burning is, in reality, a damp kind of affair, but the sparks, called "free radicals", are no less destructive for being surrounded by water. Free radicals damage whatever they touch, including our DNA. We have growing reason to believe that it is the oxidative damage caused by free radicals which plays an important role in ageing.

Not all of the damage to DNA is caused by oxygen, of course. There are other factors that regularly damage DNA, like sunlight or tobacco smoke. Nor is DNA the only target for free radicals - our membranes and proteins get hit too. But hits to our DNA are liable to have a lasting effect, because the occasional hit that fails to get repaired correctly can lead to a permanent alteration in the DNA sequence. In this respect, the very zeal with which the DNA repair systems guard against change can be our undoing, since once the sequence is changed, it is the new but erroneous sequence that becomes the object of protection.

When I was a child, the game of Chinese whispers was popular at parties. I expect you know it. The first player makes up a story and whispers it into the second player's ear. The second player whispers it in the third player's ear, and so on. By the time the message has gone around, the original tale of how Lucy's cat got shut in the coal shed might well be an account of a blue hat that got stuck on a goat's head. DNA plays its own version of Chinese whispers all the time. It is quite possible that there is no longer a single cell in your body that has exactly the same DNA sequence as that which was in you when you began your life as a fertilised egg.

Thus goes the story of vulnerability - of how the slings and arrows of outrageous fortune beat relentlessly at our DNA. But DNA is also master of its destiny. A few moments ago I assured you that most of the DNA damage currently causing mayhem in your cells will be put right. It will be put right because encoded in your genome are

instructions for extremely sophisticated DNA repair. You might reasonably ask why, if your DNA is so smart, it does not keep you going for ever. The humbling answer is, it just can't be bothered.

As we saw in my previous lecture, our evolutionary ancestors lived at a time when life was typically brutish and short. In such circumstances, the body was likely to die soon from an accidental cause, rendering any idea of potential immortality somewhat hypothetical. Maintenance does not come cheap and reproduction was more important, so your DNA, in its role as master of your fate, skimped on the maintenance and treated your body as disposable. It is galling to think that we age because our ancestral genes attached limited importance to our individual survival, but we can at least take comfort from the fact that we live a good deal longer than most of our companion species on this planet. Those of us who keep pets soon grow used to a succession of hamsters, budgies, cats or dogs in our lives. It is only the giant tortoises in our zoos that get the chance to feel the same way about their keepers.

The disparity in the life spans of species is scientifically very valuable for we can test ideas about genetic factors that control the rate of ageing by comparing species that age fast with species that age more slowly. Pioneering work in the mid-1970's found that cells from long-lived species are better at DNA repair than cells from short-lived animals. It has since been confirmed in many laboratories, including my own, that cells from the long-lived animals are generally better at maintaining and protecting themselves.

There are strong indications that a search for genetic determinants of human longevity will not be fruitless.

During the last decade we have seen exciting work being done with simple organisms like fruitflies and roundworms, which has shown that long-lived mutants in these species generally gain their extended longevity from genetic alterations that increase the capacity to resist or repair damage. It is attractive to think that what a mutant roundworm can do, we might be able to do for ourselves. But before we let our imaginations run away with the possibilities of boundless extension of life, it is worth thinking about just how we might go about it. One place to start will be by trying to identify the genetic determinants of human longevity from among the vast array of data now emerging from the human genome project.

We have convincing evidence that life expectancy can be inherited. Twin research - that favourite tool of the human geneticist - has shown that monozygotic twins, with all of their genes in common, have life spans that are more similar than those of dizygotic twins, who share just 50% of their genes. Other kinds of study, like a recent report based on analysis of the entire population of Iceland, have come to similar conclusions. But these studies also reveal that life span is not inherited in as clear-cut a manner as blood groups or the colours of Gregor Mendel's famous peas. The genetic studies show that the inheritance of human life span is not that strong. It appears that our genes account for about a quarter of what determines the lengths of our lives.

There is a common misconception that as soon we begin to trawl the gene pool for genes that affect the ageing process, we will fish out genes for ageing, genes for Alzheimer's disease, genes for osteoarthritis, and so on. The reality is that we are most

unlikely to discover genes for any of these traits. The idea that there exist genes for ageing was knocked on the head half a century ago by the Nobel laureate, Peter Medawar, but it is taking a long time to die. Or rather, like Count Dracula, it keeps rising from the dead. The reality is that the vast majority of wild animals die young. Therefore, there is neither need to evolve genes for ageing, for example to control population size, nor is there opportunity to do so.

To understand the real, underlying causes of conditions like Alzheimer's and osteoarthritis we must probe for the weak links in gene networks that probably evolved to do us good and not harm.

Far from evolving genes for ageing, animals evolved genes for longevity. As animals became better adapted to their environments and thus able to avoid some of the dangers therein, it became worthwhile to invest in things like better DNA repair. Once we recognise that the genes we must seek are genes for longevity, not ageing, our task becomes more realistic but at the same time more complicated. We can expect tens, or even hundreds, of genes to be involved in the networks of maintenance systems that keep us alive. Working them out is going to require the very newest gene technologies and some highly sophisticated computation.

What is true for ageing is also true for the diseases of later life. It makes no sense to think in terms of genes for Alzheimer's disease, except in rare families where particular mutations produce unusually early onset. Even in these cases, the genes which are mutated probably do not cause the disease but merely accelerate its progression. To understand the real, underlying causes of conditions like Alzheimer's and osteoarthritis we must probe for the weak links in gene networks that probably evolved to do us good and not harm.

Whether a gene is good or bad depends on the circumstances. This is strikingly illustrated by the gene that codes for the sickle cell variant of haemoglobin. In malarial West Africa, the sickle cell gene conferred protection against fever on those who inherited just one copy, but at the cost of imposing a crippling blood disorder on those who inherited two. In circumstances where the risk of infection with malaria was high, the scales of natural selection were tipped in favour of maintaining a relatively high frequency of the sickle cell gene within the population.

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But times change and people of West African origin who live now in non-malarial regions, run the risk of sickle cell disease as an unfortunate legacy of past evolutionary advantage. Much the same may be true of genes which predispose us to late-life diseases. A prime example can be found if we turn our attention to the very tips of the thread of life.

One of the processes that we believe may have a role to play in ageing is the gradual loss of DNA sequence from the ends of our chromosomes - our telomeres - as cells divide. We know in principle how to arrest this decline by the throw of a genetic switch, but we also know that throwing this particular switch is one of the things that

a deranged cell does when it becomes malignant. There is a growing belief among those who study cellular ageing that the gradual loss of DNA from our telomeres - and whatever this may do to age us - is a price that our genome agreed to pay in order to protect us better from cancer. In past times, when life expectancy was short we reaped the benefits without paying the price. In the future, we may have to choose. But before we can make an informed choice we need to discover the rules of the game.

I said at the beginning of this lecture that there are two sides to the character of DNA - its power and its vulnerability. But, as the Greek storytellers knew full well, a key ingredient of any tale is the interplay between the strengths and weaknesses of its hero.

It is clear that an important facet of the genetics of ageing is the interaction between DNA damage and the genetic control of DNA repair. Nowhere is this more starkly illustrated than in the rare genetic disorder known as Werner's syndrome, where mutation in a gene that controls a part of the DNA repair machinery leads to a two-fold acceleration of many features of the ageing process and a drastic shortening of life span.

The cells in a person with Werner's syndrome show abnormally heavy burdens of DNA damage. But the vulnerability of the genetic message in all of us extends beyond mere damage to the DNA sequence. Not only are there errors in how DNA is copied and repaired, but there are all kinds of hiccups and random variations in how the genetic instructions are translated into proteins, in how proteins are transported around the cells, in how genes get turned on and off, in how cells interpret signals from other cells, and so on. The system works because evolutionary pressure has ensured that that the ensuing muddle is well enough contained that it does not interfere with our vital functions during the all-important early years. This is what mattered in our ancestral past. But variations that do not affect us until middle and later life are relatively unconstrained.

As we look deeper, we find that our genetic blueprint is not so deterministic after all. Genes do not specify the end of our lives with any precision. They do not shepherd us towards some preordained goal like the guidance system of a cruise missile. They merely point us in a certain direction and do their best to keep us ticking along until muddle gains the upper hand. What determines where we each end up is a threefold blend of nature, nurture and chance.

In these heady days of rapid scientific advance, it is perhaps natural that our imaginations should run wild with the new possibilities unfolding before us. Designer babies with the brains of Einstein, the looks of Bridget Bardot, and the longevity of Methusaleh? But the hard realities of life have a habit of reasserting themselves. We can conceive, in principle, of gene therapy that could alter human ageing. But as yet we have neither a clear picture of the genes we would wish to change, nor do we know if changing them would do more harm than good. We have not even cracked the much simpler problem of delivering effective gene therapy for single gene disorders like cystic fibrosis. In the case of cystic fibrosis, we have long known what we want to do. Would that we could do it.

Another approach that holds great promise to intervene in the ageing process is to unlock the regenerative potential of the DNA contained in our cells. Stem cell research - the subject of the conference here now at the Cold Spring Harbor Laboratory- may enable us to replace cells that have been damaged by the degenerative processes that lie at the heart of ageing. But we must be careful not to raise false expectations. A bitter blow was dealt recently to those hoping for a cure for Parkinson's disease. Transplanted foetal cells, which had shown great early promise, were found to produce excessive amounts of the neurochemical dopamine, leaving recipients in a worse state than before.

The difficulties of stem cell research lie in taming the power of DNA and in controlling its vulnerability to damage. It is too simplistic just to say that stem cells contain the genetic blueprint to become any kind of specialized cell within the body.

Embryo stem cells proceed through a complex series of developmental stages to form the cells of the adult. These stages involve sequential alterations in gene expression, modulated by interactions with neighbouring cells. If we want to put early stem cells into mature tissue we need to discover whether they can sufficiently recapitulate the normal developmental process, or if some key step might inadvertently be left out.

On the other hand, if we use adult stem cells we should recognize that these cells may be damaged by age. In recent research on the stem cells of the lining of the gut, my colleagues and I have shown that these cells are altered by ageing in ways that significantly compromise their function, probably because their DNA is damaged.

President Clinton promised Leo Blair an extra 25 years of life. Given the time that it takes to translate groundbreaking new research into effective application, it's a tough challenge for science. Nevertheless, the President's prediction might just be right. Science is on track to discover the deep secrets of ageing. From these insights will assuredly come new strategies to attack the underlying causes of age-related diseases like Alzheimer's, osteoporosis and macular degeneration. If we can assure greater quality of life in old age, it may be that we can slip in some extra years as well.