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Turning back the hands of time: ageing gracefully!
Transcript

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TURNING BACK THE HANDS OF TIME:

AGEING GRACEFULLY

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Getting old is the prerogative of very few species on the planet but it is a major bug-bear for many humans:

"I grow old…I grow old….
I shall wear the bottoms of my trousers rolled.
Shall I part my hair behind? Do I dare eat a peach?
I shall wear white flannel trousers, and walk upon the beach"
- T.S. Eliot "The Love Song of J Alfred Prufrock"

"That is no country for old men. The young
In one another's arms, birds in the trees
- Those dying generations – at their song,
The salmon falls, the mackerel crowded seas,
Fish, flesh, or fowl, commend all summer long
Whatever is begotten, born, and dies.
Caught in that sensual music all neglect
Monuments of unageing intellect."
- W.B. Yeats "Sailing to Byzantium "

In this lecture I will outline some of the explanations of why we age, what effects the ageing process has on our mental and physical functions and where we might find some solutions to either ageing less perceptibly or with increased grace!

Is ageing a universal biological process?

W.B. Yeats is quite correct in stating "Whatever, is begotten, born and dies" but if he had added a suggestion that age-related degenerative changes were also part of this inevitable chain of events he would have been quite wrong. Some animal species show very few effects of ageing, continue to grow throughout their lives and seem to exhibit very few obvious signs of degenerative decline. These are mainly aquatic species and include sharks, turtles, alligators, female (but not male!) flounder, lobsters, sturgeon, rainbow trout and a number of other fish. For land-based species only the Galapagos tortoise comes into this category.

So why you might ask are we not overrun by these apparently immortal species? The simple answer to this is that they are not immortal since they can still be killed off by predation, accident and disease. This is of course the same general reason why very few species experience anything other than the very start of age-associated deterioration because as soon as this does begin to happen life-threatening risks escalate significantly.

As we will see later, scientists have also managed to engineer cells in culture that are effectively immortal if one feeds them and generally treats them kindly.

So all in all biological ageing is not a universal rule and this simple fact alone might engender hope in many that age-prevention can be achieved for mankind even if it means drinking several hundred litres of shark fin soup or feasting on caviar! However, in more serious vein, nothing is as simple as it might first appear and this will become clearer once we look at why we do age and what is controlling the process.

The one piece of good news to reveal at this stage is that for humans there is tremendous variability in the degree and time course of ageing and that while some of its effects on our bodies are pretty much universal, others are not. As we will see later, one of the most important functions where ageing may sometimes have relatively minor effects are our mental faculties.

What is research on human ageing hoping to achieve?

Before we consider what we have established about factors that influence ageing and lifespan in humans and other species it is perhaps wise to consider at the outset what science is hoping to achieve. One important principle that needs to be made clear is that finding a way to increase lifespan might not necessarily solve the problem of ageing but might simply delay its onset. Thus, if all we achieved was a way of making us live to 150 but have the same, or even an extended, period of degenerative decline the impact on regulation of human populations and the cost of healthcare would be likely to be punitive – even if we could find a way of colonising other planets.

It is a sobering thought that the idea of increased longevity extending our working lives from 65 to say 100 might not have universal appeal!

The stated aim therefore of most programmes involved with research into ageing is to achieve something akin to the situation described in Aldous Huxley's "Brave New World" where ageing simply does not occur and you are young, fit and beautiful until the moment of your death. This approach has been given the objective title of "increasing health span". However, this assumes that it is possible to achieve a state whereby apparently healthy individuals die suddenly of natural causes when they reach 100, for example, without undergoing any form of degenerative senescence. In reality this would seem to be a pipe dream since unless we adopt some final life-event strategy that makes us die of exhaustion (like the pacific salmon), or deliberately engineer heart failure at a fixed time, or adopt some form of euthanasia policy, it is difficult to see how this could be achieved.

Another social issue that would result from success in this enterprise is that since we use the external signs of ageing in other individuals to determine our attraction, relationships and attitudes towards others, abolishing such cues would be of major social consequence. Perhaps we would all have to wear badges advertising how old we were!

So while strategies to reduce or even abolish the ravages of age are laudable, the consequences of success would herald a whole new set of difficult problems. However, having opened a potential can of worms of what might happen if we could prevent ageing one can at least temporarily put them to one side since there are no imminent effective anti-ageing solutions on the horizon – no matter what some scientists may claim. So in the mean time I will try to summarise what current views are about what makes us age and what we might already be able to do to help ameliorate or even prevent this process.

Evolutionary theories of ageing

If we consider from the outset that all species have a priority to survive for the optimum amount of time to be able to reproduce successfully. The biological imperative is to produce sufficient numbers of offspring to continue this process so that the population is at least maintained and it is clear that there is little adaptive pressure in this scenario to select genes that confer protection against ageing. For females at least age-associated physical deterioration does not kick-in significantly until after reproductive potential is all but passed and while for males this reproductive window of opportunity may theoretically be much longer, each male still inherits half of his genes from his mother. There is also the problem that males will have to compete vigorously to obtain access to females and so for both sexes there could be a trade-off whereby genes selected to confer optimal reproductive competitiveness during early life might actually end up accelerating subsequent decline into senescence and death.

In short, species survival is all about pumping yourself up for the main event with little consideration given to what happens after the race has been won and you need to hang up your running shoes. In this sense all species resemble the pacific salmon with the exception that such so called "big bang" species only get to race once whereas most others get to do it a number of times at a number of different locations with a number of different partners!

To extend this analogy further it is clear that for all species reproduction is of necessity a short-distance sprint race rather than a slower paced marathon. Just as we all appreciate that sprinters are incapable of adapting to be competitive at running

marathons so genes selected for peak early reproductive fitness are unlikely to be that effective for helping maintain a sub-optimal reproductive longevity. Indeed, the cost of successful reproduction is a reduced longevity and this has been shown systematically in species like the fruit-fly, drosophila, where individuals that breed late or not at all, live longer than those that breed early.

This reproduction/longevity trade-off seems to occur in humans as well. A major study looking at married women from the British aristocracy between 740 and 1876 has confirmed that the earlier women produced children, and the more they had, shortened their life-expectancy (Westendorp and Kirkwood, 1998). Not surprisingly the highest longevities were seen in individuals who did not have children at all. Just in case you were wondering, the husbands of these ladies did not show a similar correlation between longevity and having children, so it has nothing to do with the marital environment *per se,* and for men having lots of kids is not going to shorten your life unless, that is, they cause you significant additional amounts of stress!

This general idea that longevity and reproduction act in competition with one another is called the disposable soma theory – i.e. as soon as your body cells have done their job in getting you to reproduce successfully they are no longer worth maintaining, putting you on the downward slope towards degenerative ageing and death.

While it might be tempting to put forward an evolutionary theory that ageing is part of a programmed biological death clock aimed to provide both population control and reduced competition for resources, this seems unlikely. In the first place it is difficult to see how such a mechanism could have evolved and in the second place members of most species in the wild do not actually survive to reach their maximum life span anyway and so to date there has been no need to evolve some kind of genetically programmed control over death.

Thus ageing and death are unlikely to have been subjects for genetic selection and are probably the indirect consequences of having to burn the candle at both ends to survive long enough to reproduce successfully.

So why do some species live longer than others?

From what I have just said about evolutionary theories of ageing it is clear that in principle longevity in any particular species should be dependent upon the optimum time it needs for individuals to reproduce successfully. This will be dependent upon a number of factors including predation, injury and disease risks, availability of food resources and mates, developmental time courses, responsibility for parental care, metabolic rate, social structures etc.

While one could imagine circumstances where time-pressures on reproducing early could be reduced (as in many modern human societies) this is still unlikely to dramatically increase selection pressures that would significantly enhance longevity. This is because ideally all biological organisms need to be prepared to adapt to the unexpected and the best way to do this is to ensure a fast-breeding strategy to promote rapid gene turnover and thereby allow faster uptake of appropriate adaptive mutations.

Size, metabolic rate and flight

With the majority of mammalian species there is a close relationship between size and longevity – the smaller you are the shorter you live. This is not so much about size per se however but the fact that the smaller you are the higher your basal metabolic rate tends to be. This means that investment in cell maintenance during the early period of life where reproduction can occur is very high and the cost of this is rapid ageing and an early death. Larger animals with lower metabolic rates can afford to invest less in early cell maintenance and both reproduce later and live longer.

However, this tight relationship between size, metabolic rate and life expectancy goes out of the window when we consider birds. Many avian species are small, have very high metabolic rates but live much longer than similar sized mammals. The reason for this seems to be the ability to fly. For example, flightless birds such as ostriches do not have the same longevity as a canary or budgerigar. Even in mammals this association between flight and longevity seems to hold true if one looks at bats for example which live much longer than similar sized flightless mammals.

The evolutionary argument that is put forward to explain this is that if you can fly the likelihood of predation is reduced (even with man’s efforts on August 12 th and after – the start of the game shooting season!). These species can therefore afford to reproduce later and invest less in early cell maintenance – the result being that longevity is increased.

So perhaps if we could develop wings and fly this would increase the chances that we could live for longer! – flying in a plane at 30,000 feet is unlikely to qualify in this respect.

The "grandmother" effect

There are a number of species where longevity is significantly beyond the end of the maximum period where females exhibit ovarian cycles and have the potential to reproduce. Humans are most notable in this respect, although other highly social species such as elephants and some of the great apes fall into this general category as well. This only seems to happen when young need long periods of care after birth and where non-reproductive individuals can contribute in some way to enhancing the survival of the young produced by others.

As I have already discussed in one of my previous lectures on parental care ("Are good parents more important than good genes" – December 2002) dads in the vast majority of animal species don't get directly involved with raising kids. The same would seem to be true of most early human cultures. This means that for any species to evolve a longevity strategy associated with offspring care the key sex must be females and because of the general evolutionary strategy of fighting hardest to promote your own genes this would mean that the key individual would be the one most closely related to the one still producing kids. This individual is of course the grandmother!

Human babies need large amounts of care after weaning and recent work has shown that success of maternal rearing is improved by the presence of help from grandmothers (Lahdenpera et al, 2004). One of our nearest relatives, the chimpanzee, is similar to us in terms of a peak in female reproduction at around 30 which falls of to virtually zero by 45. However, whereas chimpanzee females are only likely to survive until 50 or so even in captivity, human females are currently expected to live until around 85. Grandmothers are not that important for baby chimpanzee survival however whereas it is argued that they are for human babies. If we assume that maximum average reproductive span for human females is around 45 before menopause then if individuals continue to live for another 40 years or so they will see out the total reproductive span of most, if not all of, their offspring.

If this theory is correct both sexes in humans owe their current enhanced longevity to the importance of care assistance to babies by their grandmothers. So perhaps the view that Grandparents have all of the fun of playing with their grandchildren without the having to deal with the more onerous responsibilities they had previously as parents is not quite correct. Perhaps this theory is also something hassled parents can use to help persuade their children's grandparents to give them the occasional night off!

So what determines how long we and other animals can live?

This is one of the key big questions that we would like answers to and there are indeed some credible answers to consider. One of the most influential ideas originally put forward by Professor Leonard Hayflick at the University of California in 1961 is that your cells are designed so that they are only capable of dividing a finite number of times (about a maximum of 50 times for human cells in terms of population doublings in cultures). In many body tissues the result of cells stopping this division process is that nothing is renewed and the remaining cells can subsequently gradually senesce and die.

In general it seems that when cells are cultured from different species with different life spans then the number of divisions they are capable of showing are correlated with them. The relationship between number of divisions and longevity is by no means a linear one and there are anomalies. One should also be careful in taking home the message that ageing is all about the cells in our body hitting the buffers at the end of life's track and this leads to death. The connective tissue cells (fibroblasts) typically used in these studies can actually survive long after they have stopped dividing and many important cells in the body – notably in the brain and heart - do not normally divide in this way even when we are young.

The ability to use tissue culture methods to make detailed studies of cellular senescence revolutionised the field of biogerontology (the study of ageing) and Haflick's observations on dividing cells and those of many others in the field finally answered a key question as to whether organism ageing was due to changes going on within cells or to damage caused to them by external factors. Initial claims that all cells were capable of infinite numbers of divisions were proved by Hayflick's experiments to be incorrect, most cells are mortal. Old and young cells co-cultured also do not influence one another

suggesting that the ageing control mechanism is within cells. Ageing and lifespan are therefore primarily the result of changes going on within the cells in our bodies. How is this achieved?

Telomeres and telomerase

The answer to why dividing cells can only undergo a limited number of divisions was discovered when it was found that chromosomes have tail-like nucleoprotein structures at each end called “telomeres” These consist of TTAGGG tandem repeats and telomere binding proteins which by capping the chromosomes protect them from DNA-damage repair pathways. The telomeres shorten with each division until they reach a critical stage whereby the chromosomes can no longer replicate. This process can be reversed by enzymes called telomerases which are present to varying degrees in different cells and different species. Scientists can effectively make cells immortal in a culture dish by engineering them to express high levels of telomerases and it seems that the species I mentioned earlier on which show minimal signs of ageing also tend to have high levels of them. Cancer cells also have high telomerase concentrations and these are capable of an infinite number of replications. Indeed, measurement of telomerase activity in cells is a key diagnostic for determining whether they are cancerous.

There are a number of human genetic disorders that are associated with accelerated ageing and reduced life expectancy (so called progeroid conditions). These include Werner’s, Bloom’s, Hutchinson-Gilford’s and Down’s syndromes. Many of these syndromes are associated with shortened telomeres and cells that are consequently less resistant to stress and subsequent damage. It would be wrong to conclude from all of this that the secret of long-life is simply a matter of either preventing your telomeres from getting shorter or trying to start off life with longer ones. There are many other factors that are important and there are likely to be species specific and tissue specific variations to complicate matters. The mouse, for example, which only has a life expectancy of a few years has longer telomeres than humans and most cells show signs of senescence (accumulated mutations, damage and impaired repair machinery) well before they are shortened to the point where they stop dividing.

What does seem to be true is that telomeres provide an intracellular counting mechanism whereby cells can be controlled in terms of how many times they can divide. Hayflick has reported that cultured human fibroblast cells have an accurate memory of how many times they have divided and even if he froze a line of them for over 40 years when they were reconstituted they clearly retained a memory for how many times they had divided already and continued on from this. It seems likely that the telomere shortening counting mechanism in cells reflects a measurement both of the maximum lifespan of cells and of the organs that they comprise. In this sense they may have more to do with regulating longevity rather than ageing per se.

However, a recent study reported in The Lancet has found that people with shorter telomeres at the age of 60 are nearly twice as likely to die of age-related diseases over the next 15 years or so. On average those individuals with telomere lengths in the top half of the population measured (i.e. the longest telomeres) lived 4-5 years longer than those in the bottom half (shortest telomeres) (Cawthon et al, 2003).

While it might seem strange to have evolved a counting mechanism of this kind it is important for an animal to regulate the number of times its cells can divide. Every times cells divide this causes small, cumulative replication errors and mutations and therefore each new cycle increases the risk of the cell developing a cancer phenotype or some other functional problem. So even if increasing telomere length or telomerase activity in our cells might help extend our theoretical lifespan it would also increase the likelihood of developing cancer. We would therefore have to have found a cure for cancer first before attempting this step.

One of the big debates that have been sparked by the idea that aged cells are likely to be capable of fewer divisions than young cells due to telomere shortening is in relation to cloning. Here the issue is whether cloning using adult cells is likely to produce identical offspring but with a reduced life-expectancy. With Dolly the sheep’s early demise this spectre over the whole issue of the efficacy and ethics of cloning has increased controversy. However, any conclusions based on a single case must be extremely tenuous and observations from a range of other animal and cell cloning experiments have not really produced consistent results. Certainly, in many cases, older cells do have shorter telomeres and perhaps this will result in cells in key body tissues of individuals cloned from them degenerating earlier. Whether this outcome will decrease life expectancy or disease resistance in the animal concerned is less easy to predict.

Are there ageing genes that we could control to reduce age-associated degeneration and/or increase longevity?

The current general belief is that the ageing process may only have a 25% genetic contribution. The main reason for this that compared to developmental processes which have a major genetic contribution and which therefore occur in an highly ordered fashion and like clockwork, ageing processes are highly variable both in terms of when they happen, how long they take and even whether they happen at all. Also, the fact that ageing seems to be an indirect consequence of the price of living at the most appropriate pace to reproduce successfully suggests that few genes are actually directly responsible for promoting it.

The majority of work attempting to identify key genes and proteins associated with age-related degeneration and longevity have focussed on simple short-lived organisms or have used cell culture preparations. The upshot of this is that we know a lot more about genes associated with longevity in worms (*c. elegans*) and flies (*drosophila*) – which only live for a few weeks or so - than we do in mammals. There seems to be some form of appropriate irony here in that the kinds of species we associate with capitalising on diseased or dead tissue are the ones we have turned to to understand what causes these processes in the first place! Indeed, if you think about it, progress when carrying out work on the science of ageing is not going to be very fast if the species you are studying lives for many years. Studying long-lied species can also be highly costly in terms of resources for keeping your experimental subjects.

So is there anything we can learn from studies on worms, flies and cell cultures that is relevant to ageing and longevity in humans and other mammals? The answer to this would appear to be yes although some care has to taken in extrapolating too far. We have reached a stage now that mutational analysis and gene targeting studies in flies and worms have turned up a number of different genes whose activity impacts on longevity. Manipulating the expression of these genes can increase longevity by up to 40-60% in some cases, although it would seem that some form of age-related degeneration must still be taking place, albeit delayed.

What makes cells senesce and ultimately die is a combination of arrest of growth and repair mechanisms, DNA damage and increased susceptibility to metabolic and activity-dependent stresses. One would therefore anticipate that genes associated with cell growth, replication, protection, metabolism and activity should be involved in some way. This does indeed seem to be the case.

Genes associated with growth and repair

A key hormonal pathway which is important for regulating lifespan is that involving growth hormone. If we follow this pathway from the cells in the hypothalamus of the brain which produce the substance which releases growth hormone from the pituitary (growth hormone releasing hormone) we find any major dysfunctions in this part of the system lead both to reduced size, impaired fertility and increased longevity. If dysfunctions are too severe of course growth arrest may be sufficient to cause embryonic death.

When growth hormone activates its receptors it releases other growth factors. In relation to longevity a key important target is insulin growth factor-1 (IGF-1) which both acts on its receptor to promote growth, development and fertility and also acts to regulate cellular signalling molecules such as p66 Shc which influence resistance to oxidative stress. Reducing levels of the IGF-1 receptor can increase mouse lifespan by around 30% without having a major influence on body size or fertility (Holzenberger et al, 2003). Complete removal of the receptor leads to embryonic lethality due to arrested growth. Mutating the downstream p66 Shc intracellular signalling protein has the same general affect and increases mouse longevity by 40% (Migliaccio et al, 1999). The importance of this IGF-1 signalling pathway in determining longevity in the mouse was first demonstrated in worms and flies so it would appear to be a highly conserved mechanism.

Recent research with mice has identified another longevity gene which is responsible for producing a protein that helps body tissues heal and replenish themselves. The FoxM1B gene seems to play an important role in preventing build up of another protein within cells (p21Cip1) which increases with age and not only blocks DNA division, but may also trigger other genes associated with cancer and Alzheimer's. Expression of the FoxM1B gene is progressively reduced in our cells as we age.

While gene therapy options are a long way off the importance of growth hormone for helping to improve ageing and longevity has been considered in humans. One of the most robust changes observed during ageing is the reduction in growth hormone production due mainly because of reduced time in stages 3 and 4 of sleep when it shows peak release. This reduces metabolic efficiency and progressive organ failure. Giving growth hormone to ageing individuals under these conditions is associated with restoration of organ function and rejuvenations of skin and muscle tone (Rudman et al, 1990). There are also a number of claims that it increases longevity. In theory this seems to contradict animal research showing that inhibition of growth hormone

signalling pathways can prolong life. However, it probably reflects the fact that it is hard for older organisms to deal with decreased metabolic function when growth hormone and IGF-1 hormone levels decline and this outweighs the potential benefits of increased protection against oxidative stress and still ends up accelerating the ageing process. Giving growth hormone back can therefore potentially reverse this process even though it will also restore susceptibility to oxidative stress.

Genes that prevent cell damage

One of the major causes of cell damage is oxidative stress through exposure to free-radicals and this is very much at the heart of the ageing process since the older you get the more susceptible your cells become to this process. One of the trademarks of any genetic manipulation that increases longevity is that it is associated with increased resistance to these kinds of stresses. Manipulating expression of genes that either promote free-radical production (such as nitric oxide synthases) or reduce it (superoxide dismutase) have been associated with increased lifespan as well as reducing cell damage at all stages of life as a result of toxic or ischaemic insult.

Immunity and inflammation

Ageing organisms all have reduced immunocompetance and are therefore more susceptible to disease. In general, neurodegenerative disorders such as Alzheimer's disease involve a strong inflammatory component and there is wide interest in the involvement of cytokines in this and ageing in general. There is ongoing research into whether possession of genes for inflammatory cytokines correlates with longevity and if routine administration of anti-inflammatory drugs, such as aspirin, can help reduce ageing effects on susceptibility to disease.

The adrenal hormone dihydroepiandosterone (DHEA) which appears to play an important role in, among other things, enhancing immune resistance to infection and disease falls by the time you are 75 to 10-20% of the level when you were 20. As a consequence it is one of the most popular putative anti-ageing substances on the market. However while taking DHEA supplements reportedly increase a sense of well being there is no clear evidence to date for improvement in human longevity.

Cholesterol

Most of us are aware about the potential dangers of our bodies containing too much cholesterol. The two major forms of cholesterol measured in blood are either called high-density lipoproteins (HDL) (so called "good cholesterol" because they protect against disease, ageing and diabetes) or low-density proteins (LDL) (so called "bad cholesterol" because it gets deposited in blood vessels and contributes to cardiovascular disease. It has been found that individuals who live to be over 100 are more likely to have variants of a gene which protects against damaging effects of LDL cholesterol. In particular there is a strong correlation with variants for the gene for apolipoprotein E (ApoE) which is a central component for cholesterol-carrying lipoprotein complexes. Individuals with at least one copy of the ApoE4 form of this gene have a higher risk of earlier onset cardiovascular disease and Alzheimer's disease. Those who live over 100 are half as likely to carry this form of the gene and are instead much more likely to carry the ApoE2 form which may help protect against these diseases.

Recently studies on Ashkenazi Jews who have a remarkably similar genetic make up and longevity have also identified the importance of genes that control cholesterol (Barzilai et al, 2003). A total of 213 parents and 216 of their children were sampled. The average age of the parents was 98 with almost half being over 100. They turned out that they a 3-times more likely to have a DNA alteration in the cholesterol ester transfer protein (CETP) gene which helps to regulate blood levels and size of HDL and LDL cholesterol. This results in their having higher levels of good cholesterol (HDL) and larger LDL molecules which are less likely to clog up blood vessels.

Will we live longer if major human diseases are controlled?

While cancer, stroke and cardiovascular diseases are sources of both worry and suffering to many and cause many to die before achieving a normal lifespan it has been calculated that even if we were to find cures for them all it would only increase the average lifespan by around 15 years. Curing major diseases such as Alzheimer's, which usually only affect older individuals, would apparently only increase average lifespan by 19 days! (see Hayflick, 2000).

So the opportunities for increasing lifespan by eradicating major human diseases which tend to have a late onset in life will not have a big impact on average lifespan. Indeed, most of the large increases we have seen in average lifespan in the last 100

years have been contributed by medical and nutritional advances reducing infant mortality.

Why do females live longer than males?

Current estimates of life expectancy for human males in developed countries is 4-6 years less than for females and this reduced lifespan in males seems to be true of many other species. The oldest documented human is also a woman (Jeanne Calment who died in 1997 at 122 years and 164 days) although there are claims that there is a woman still alive in Chechnya whose passport reveals her to be 124. The oldest males are Yukichi Chuganji from Japan (114 – died September 2003) and Antonio Todde from Italy (112 – died January 2002). The most likely reason for males not living as long as females is probably the presence of the male sex hormone, testosterone and the behavioural and physiological effects it has. If you like, it is another example of something that is used to pump us up to compete more vigorously for reproductive success which also has the down side of shortening life expectancy. Castrated male animals and humans tend to live longer than gonadally intact ones but it seems unlikely that this rather drastic step would appeal to men wanting to live longer.

Effects of lifestyle and nutrition on ageing

With at least 75% of the influence on the ageing process being of non-genetic origin it is immediately clear that the way we live our lives plays a big part in determining when and how we die. From this we can all appreciate the fact that economic factors can impact both positively and negatively on this process. This is why survival curves in the majority of developed countries in the world are showing a steady upward trend but not in those, such as Russia , where the recent decline in its economy has completely stopped this upward trend.

Our desire to invest large amounts of money on pills and potions that claim to prolong life shows that this message that ageing and longevity is not hardwired has got through. It is not my intention to provide a systematic trawl through all of the candidate substances claimed to help you avoid the ravages of age. Instead, I will simply focus on some more general themes that have some scientific support.

It goes without saying of course that excesses of alcohol, smoking, addictive drugs (including caffeine), high fat foods, sugar and inadequate exercise are all bad news and it is not therefore worth spending time on them.

Restricting calories

We know that excessive calorie intake leading to obesity will in general shorten life but what about the effects of eating very little? In animals such as mice and rats it is possible to almost double lifespan by reducing calorie intake (50-75% of normal levels). This seems to act by reducing IGF-1 activity and expression of genes associated with DNA damage and oxidative stress and increasing that of genes promoting protein and energy metabolism and biosynthesis (Lee et al, 1999).

It is not fully established whether this would work in humans as well and we know that taking things too far, as in anorexia nervosa, can lead to a considerably shortened lifespan. Thus while it may prove to be a useful research tool for studying pro-longevity and anti-ageing mechanisms it is unlikely to catch on as a way for improving lifespan in humans. A life on a near-starvation diet would for most of us not seem to be worth a pay-off of living an extra twenty or thirty years! Nevertheless, the general idea that eating more than our bodies need to function is likely to reduce our life expectancy seems to have some support.

Anti-oxidants

Since a major cause of cell death is oxidative stress it has long been proposed that controlled use of anti-oxidant substances should be beneficial for prolonging life by reducing the effects of ageing. The double Nobel Laureate Linus Pauling has been a huge advocate of the anti-ageing, anti-cancer properties of Vitamin C. The other main anti-oxidant vitamins are A,E and selenium.

While there is recent evidence that low Vitamin C levels in the blood of older people are strongly predictive of mortality (Fletcher et al, 2003), claimed efficacious effects of taking mega-dose vitamin C supplements remain controversial. While there is some sense in the idea that deriving additional vitamin C naturally from foods may be more beneficial than taking artificial supplements

the route problem may simply be that no matter where you get your vitamin C from it needs to get into your cells and mimic what normal endogenous anti-oxidant processes do. This may not happen that effectively in complex whole organisms.

Recent studies in birds (zebra finches) have shown that feeding them a low quality diet for the first two weeks of life (low in anti-oxidant vitamins) significantly reduced their overall lifespan. This restriction period is equivalent to the first 10 years of life in humans! So perhaps an important factor in boosting your anti-oxidant fight against the ageing process may be down to having a high quality diet rich in these factors when you are young!

A recent study has also just reported that taking combined vitamin E and C supplements reduced the prevalence and incidence of Alzheimer's disease (Zandi et al, 2004).

Phenols present in a number of foods can also act as antioxidants and have been claimed to have anti-ageing effects. Perhaps the most well known of these is the proverbial glass of red wine although less well known may be that a study on 7,841 male graduates from Harvard published in the British Medical Journal has claimed enhanced longevity from eating chocolate (in moderation!) (Lee, 1998). Effects on longevity were modest however (an increase of 0.92 years) so don't get too enthusiastic about this. Nevertheless, chocolate does also contain anti-oxidant phenols.

Stress

One of the major common features of individuals who live well into their 100s is that they have led relatively stress-free lives. It is well documented that experience of extreme chronic stress such as can occur in soldiers exposed for long periods to traumatic war zones, can physically age as much as 20 years in a very short period. If you are constantly feeling stressed one of the wisest steps you can take for both improving the quality of your life, and ultimately how long you are going to live, is to take a stress management course and/or get out of the situation that is causing you to be stressed.

Stress releases a cascade of hormones in the body the most important of which, from a damage point of view, seems to be cortisol. The stress hormone produced by the adrenal gland is geared up to make you avoid problems as quickly as possible (by changing your blood pressure and boosting muscle energy) and learn to avoid similar circumstances in future (at low levels it can actually enhance memory). However, what is an essential defence mechanism in the short term is potentially lethal in the long-term. For example, chronic exposure to high cortisol levels promotes cell death in the brain, notably in the hippocampus which is very important for normal learning and memory functions.

Environmental toxins and food additives

I will be spending more time talking about these subjects in a lecture on Diet and obesity at the end of this year. It goes without saying however that pumping your body full of environmental toxins from fertilisers to pesticides to heavy metals, and even substances leaching out of plastics, is not likely to help you live a longer healthy life. It is a misnoma to consider that substances which preserve food will help preserve us. They may help preserve our body tissues for longer after death but they will shorten the period in which our cells are alive! At the risk of appearing macabre it appears that a problem being reported in Italy is that bodies buried in family burial plots over many generations are no longer decomposing fast enough to accommodate requirements!

The ageing brain and peripheral nervous system

The majority of adult brain cells, like those is heart muscle, do not divide and so there is a progressive cell loss from an early age which is not directly associated with arrest in replication machinery. This progressive cell loss is associated with a wide range of changes in our sensory, memory and muscle control systems. The most common neurological problems in elderly humans are:

- Slowed reaction time
- Slowness and narrowed range of perception
- Small pupils with restricted pupillary reflexes
- Reduced range of upward gaze

- Presbyopia (problems with focussing on nearby objects)
- Presbycusis (loss of hearing sensitivity)
- Reduced sense of smell
- Reduced motor activity
- Reduced muscular power
- Flexed posture of trunk and limbs
- Reduced vibration sense in toes and feet
- Impairment of fine co-ordination and agility
- Thinness of leg muscles
- Reduced or absent Achilles Reflexes

Brain structural changes as we age

With only small amounts of new brain cells being produced after early development our lives are associated with a progressive loss of them. In some parts of the brain, particularly those involved in motor control, cell loss may amount to nearly 35% in old age. However, as worrying as this may sound, the brain has billions of cells and current views are that where age-related decline in brain function occurs it is more to do with the impaired connectivity and efficiency in the way the remaining cells are working that are responsible.

So what kinds of mental functions are affected?

Unfortunately there is a long list of potential problems. These include:

- Slowed reaction and decision times
- Increased propensity to forget new information
- Greater difficulty in active (working memory) rather than passive processing of information
- Decline in ability to solve difficult problems
- Decline in spatial learning and memory
- Decline in both global and selective attention
- Increased incidence of depression

Are there any mental advantages to getting older?

Elderly are often better at creative thinking due to wider knowledge base

How to help prevent age-associated cognitive decline – “Use it of lose it!”

One central conclusion arising from both human and animal work is the importance of keeping your brain active throughout your life. Evidence from work on experimental rodents has shown that if they practice a particular type of learning task a number of times during their lives they show almost no decline in performance with age. However if the task is not practiced then ageing

can cause a profound impairment.

Work on humans has confirmed this general idea that you do not lose the ability to apply well learned strategies with age. Researchers have distinguished between so called crystallised (Gc) and fluid (Gf) mental abilities. In general Gc (knowledge of past events) does not decline with normal ageing whereas Gf (ability to apply novel strategies for learning new information) does. However, if your brain has been constantly challenged during your life to produce a wide range of well practiced and effective learning strategies then these will still be available to you as you age and will reduce the likelihood that you will have to learn completely new strategies to deal with new sets of information (i.e. even though you may have some impairment in learning new strategies it will not be that noticeable since you already have well practiced and preserved routines to help you out of most situations where new information has to be assimilated).

Genes associated with cognitive decline

Long-term studies of both laboratory animals and humans over the next few years where longitudinal assessments of changes in cognitive functioning have been carried out will hopefully allow us to use powerful new gene and protein expression profiling screens to identify both which are the key molecules for helping preserve out mental abilities as we age. Work in my own laboratory at Babraham by Dr Lawrence Wilkinson and his colleagues has already used this approach to isolate around 15 novel genes associated with age or practice effects. In the next few years we may therefore have identified a number of new therapeutic targets for helping us reduce age-associated cognitive decline.

Other studies in my own laboratory and elsewhere in transgenic mice have also identified several genes associated with holding on to your mental prowess during ageing. Animals that have reduced expression of a gene responsible for binding calcium in cells (calbindin D28K) while showing impaired speed in learning spatial memory tasks when they are young (unlike normal animals) do not get worse as they age. By contrast mice that do not express neuronal nitric oxide synthase (responsible for producing nitric oxide in the brain) can actually have normal performance on some olfactory memory tasks and this also does not worsen with age. Both studies illustrate that to some extent what may be important when you are young for helping cognitive function may not be so beneficial when you get older.

Changes in the way the ageing brain processes information

Advances in brain imaging techniques have revealed striking differences in the way young and old brains process new learning tasks (see Reuter-Lorenz, 2002). Two general findings are that old brains seem to process new information both using more of the brain and with a reduced amount of specialised use of one brain hemisphere as opposed to the other (so called brain lateralisation effects). For example, initial work found that for matching faces and locations young adults showed a restricted activation of ventral parts of the temporal lobe for faces and the dorsal parietal lobe for locations. Older individuals showed equivalent activation of both brain regions in both tasks.

With verbal working memory tasks (short-term memory for lists of words) other studies have shown that young adults only activate a subset of brain regions within the left hemisphere whereas older ones activated the same regions on both sides of the brain and also involved additional parts of the prefrontal cortex that were less activated in the younger group.

So old brains do things differently from young ones: why? Two general possibilities are that either old brains have to compensate for loss of power by engaging more systems to help out, or that ageing breaks down the brain’s ability to use its optimal specialisation strategies of lateralised processing. These two possibilities are not entirely mutually exclusive and probably both are going on. However, a recent study has provided some support for the compensation hypothesis.

Cabeza et al (2002) found that in similar word-based memory tasks, older people who were assessed to be low-performers on most cognitive tasks (i.e. had undergone some age-associated cognitive decline) showed similar lateralised and restricted patterns of activation within the frontal cortex as found in younger individuals and their memory performance was worse. On the other hand, high performing older individuals showed a bilateral and wider activation pattern within the frontal cortex but had a similar memory performance to the young ones.

This may also go some way to explain why older individuals are generally slower in performing these cognitive tasks than younger ones because one of the advantages of using restricted and lateralised brain systems for information processing is that they allow you to do things faster.

So perhaps the bottom line is that if you want to hang on to your cognitive powers when you get older you will need to use

more of your brain and this may slow you down a little!

Why some individuals retain youthful restricted patterns of brain activation and may as a result become cognitively impaired as they get older is an important question. The most likely explanation is that your ability to compensate for the effects of age by using your brain in a different way comes back to the “use it our lose it” scenario. It you constantly challenge your brain to deal with demanding problems then it will become more flexible and able therefore to adapt to age-related changes.

Perception of time

In my last lecture on “Biological Clocks” (February 2004), I discussed how our perception of time is influenced by a wide variety of factors and particularly by our emotional state. It is commonly asserted that time seems to pass faster as we get older although it is difficult to establish this with some form of objective measures. Based on more subjective reports some have assessed that our perception of time undergoes a form of exponential progression whereby the passage of time from say 10-20 is equivalent to that from 20-40 or from 40-80. If this were true then we would have to extend life expectancy from 80 to 160 to experience the same amount of time subjectively as we did between 10 and 20! Definitely a law of diminishing returns.

Whatever the correct algorhythm may turn out to be we know that age brings about reductions in metabolic rate; interest is sex; attentional mechanisms; ability to assimilate complex novel information and remember new information, and that unerring sense that there is nothing new in the world and that you have seen it all before. All these things can act to speed up our subjective perception of the passage of time since the events going on around us appear to shoot by without making a lasting impression! In theory therefore exercise and finding ways to make life events have a bigger and lasting impression on you should do the trick in helping to reverse this trend.

The consequences of ageing in societies where beauty is only skin deep.

The huge increase in cosmetic surgery in the developed world over the last 10 years or so is testament to the fact that the human race is particularly concerned with disguising the external physical signs of ageing. Of all the degenerative signs of ageing skin, connective tissue and muscle changes are inevitable although they can of course be quite variable in degree and time course.

Pills and potions to reverse the external signs of ageing are big business and the subject of claims that are often outrageous and with very little basis in scientific fact. Most experts will normally make the key recommendation of avoiding prolonged exposure to the sun and making sure you have a healthy diet and drink large amounts of water.

It is a sad fact that obsessive concern with maintaining the appearance of youth can be linked with a fear or inability to adjust to different phases of life where some advantages are lost while others can be gained. Such inflexibility may, arguably, help to prevent compensatory changes from occurring beneath the surface, notably in the brain, which will minimise the impact of ageing on our personality, mental faculties and perhaps even on other vital internal organs. While our increasing knowledge of the physiological mechanisms which govern ageing will undoubtedly provide us over the next few decades with surgery-free alternatives to retaining youthful looks, the problem of needing to be able to adjust positively to the changing phases of our lives will not diminish as a result.

Similarly, it is unlikely that the general positive lifestyle features (healthy diet, exercise, low stress, using your brain etc) which we already know can help us combat ageing will be any less important even with the advent of new pharmaceutical or gene based therapies.

Some general conclusions:

- Not all species age, but most do
- Ageing may be a consequence of investment in reproduction
- Baby-sitting grandmothers may have increased human lifespan

- Ageing is mainly about changes occurring within cells
- They can count the years as accurately as we can!
- 25% of ageing is down to genes, 75% to lifestyle and other factors
- Growth and repair mechanisms are of key importance
- Genes promoting HDL cholesterol are strongly associated with longevity
- Extending lifespan may be easier than preventing ageing
- Finding cures to major adult human diseases will not greatly increase average life expectancy.
- Reducing stress, healthy diet and exercise are important
- Vitamins C and E, red wine and chocolate can be beneficial
- Mental dysfunction due to ageing is not inevitable if you continue to use you brain
- Ageing brains can be more creative
- The key to ageing gracefully is accepting and maintaining a positive attitude to change

Keith Kendrick, March 2004

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