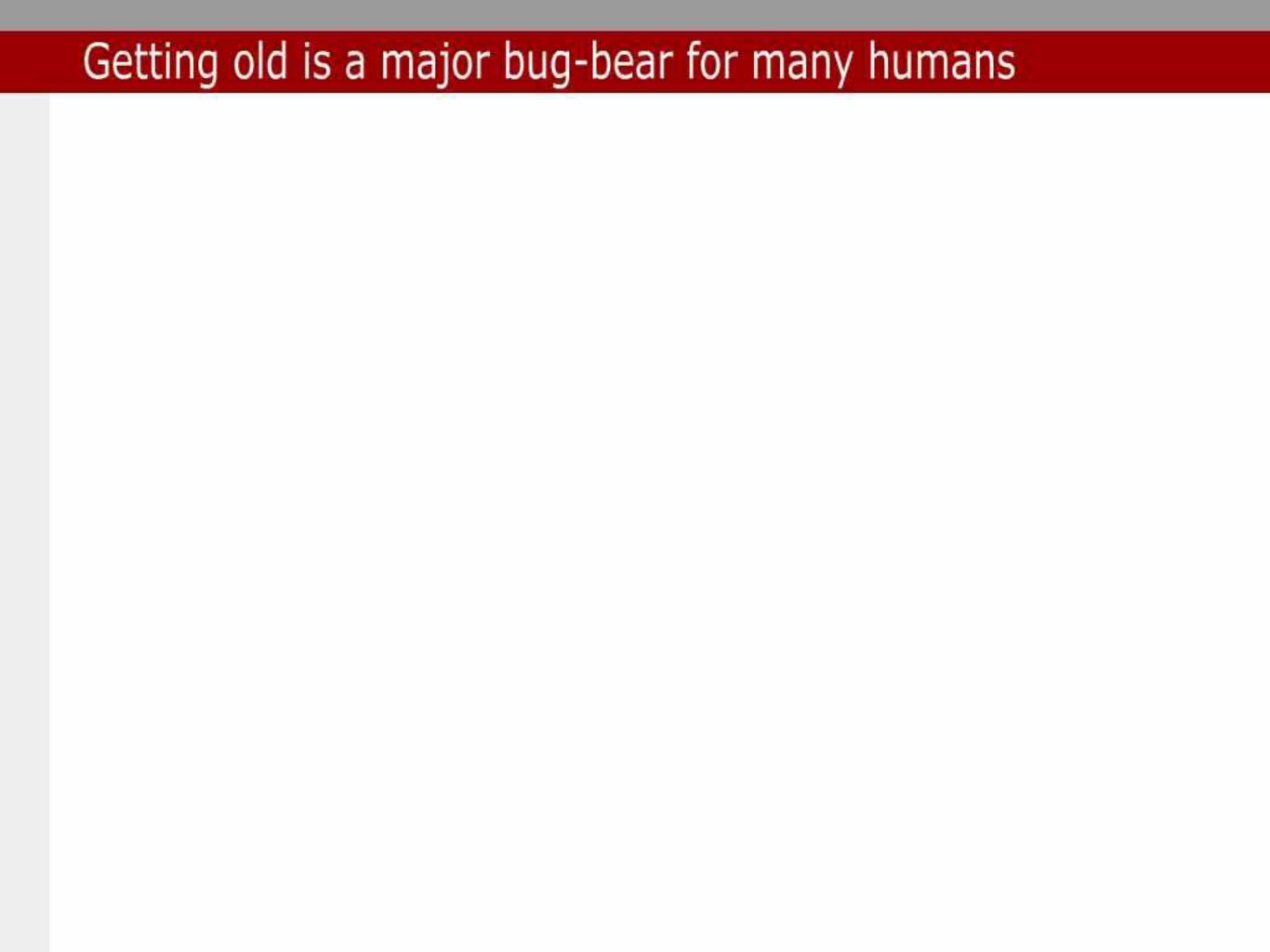
# Turning back the hands of time: Ageing gracefully!











#### Getting old 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'





# Main questions:

Why do we age?



#### Main questions:

Why do we age?

What effects does ageing have on mental and physical functions?



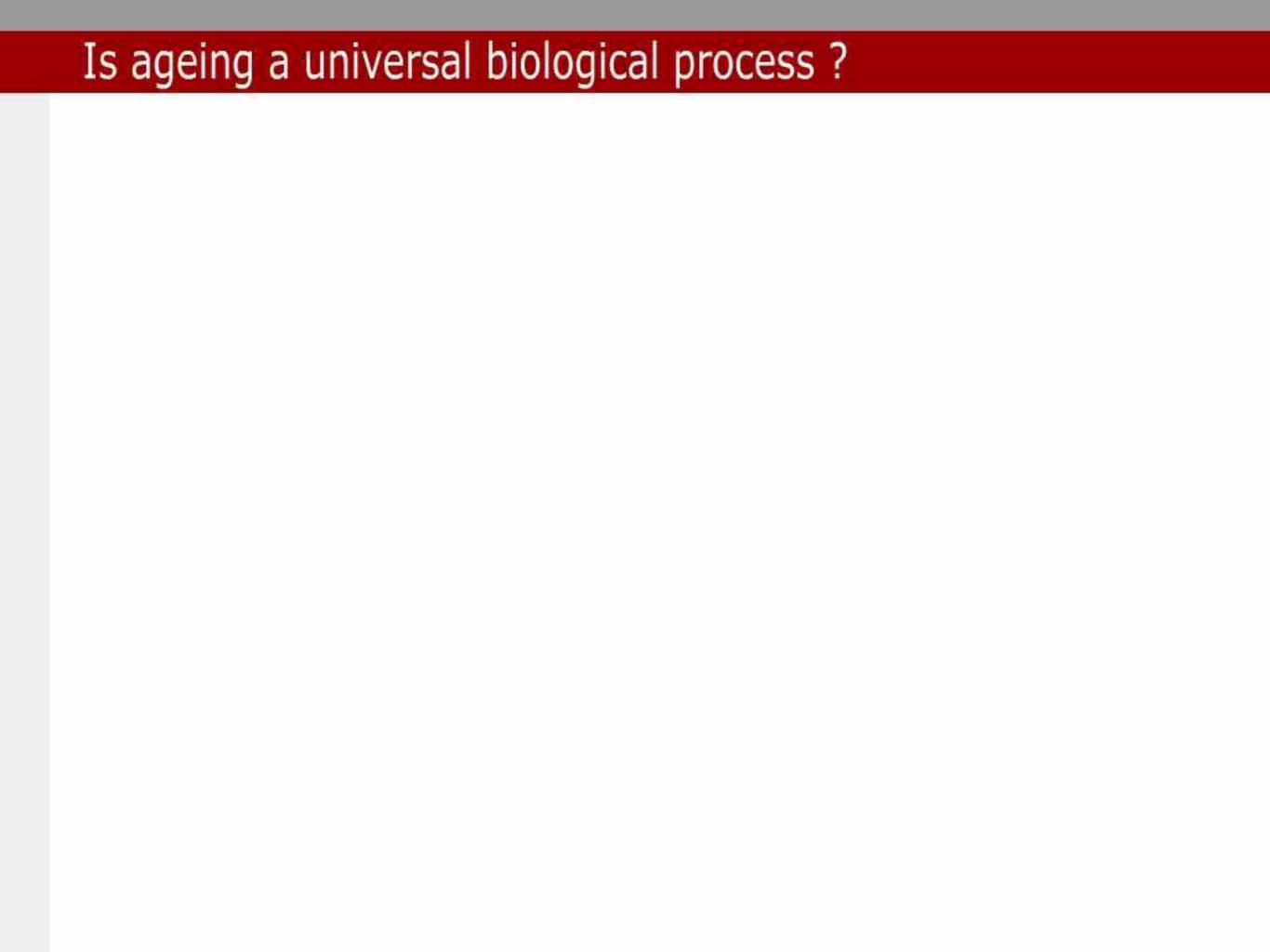
#### Main questions:

Why do we age?

What effects does ageing have on mental and physical functions?

What, if anything, can we do about it?





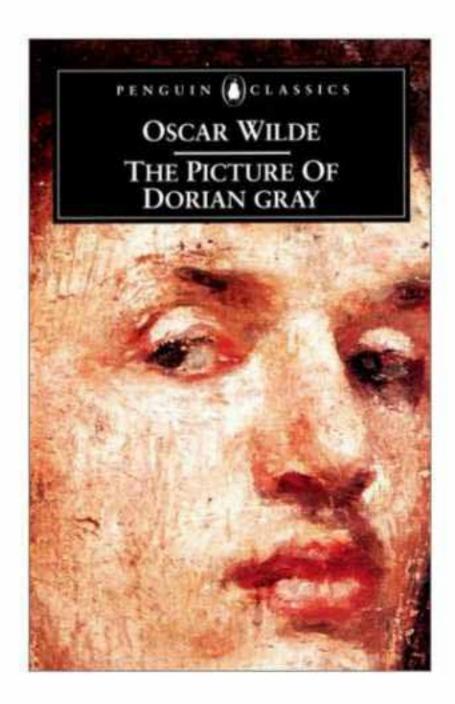
'Whatever, is begotten, born and dies'



MacGregor family bible

'Whatever, is begotten, born and dies'

But not all species appear to age



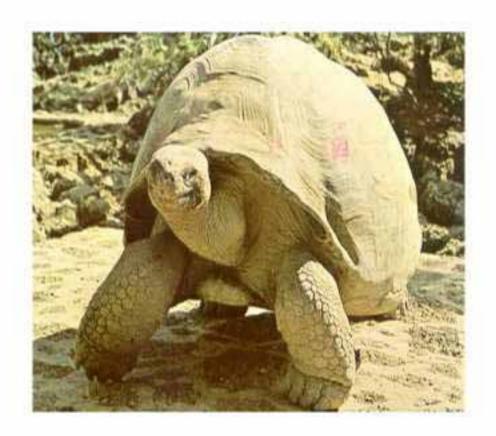
#### Aquatic species:

Sharks, turtles, alligators, female (but not male!) flounder, lobsters, sturgeon, rainbow trout and a number of other fish

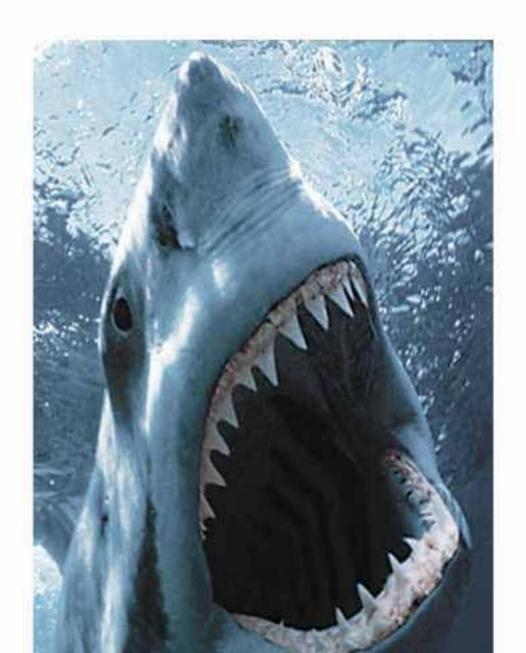


Land-based species:

Galapagos tortoise



So why aren't we overpopulated by sharks the size of Jaws?



So why aren't we overpopulated by sharks the size of Jaws?

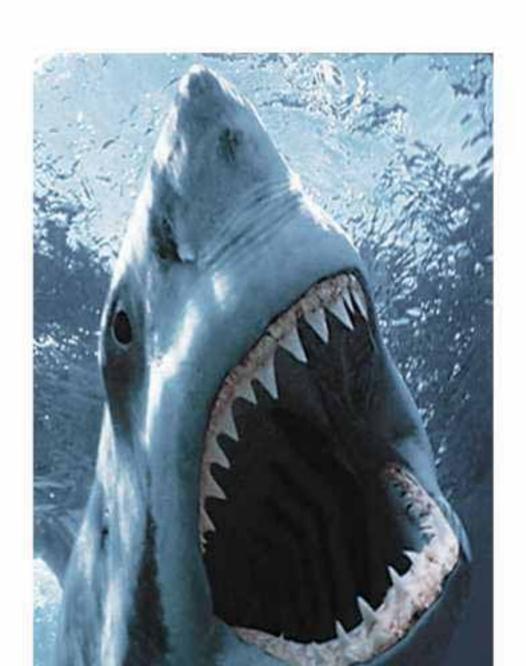
Answer - they all get killed off by man, predators, injury or disease



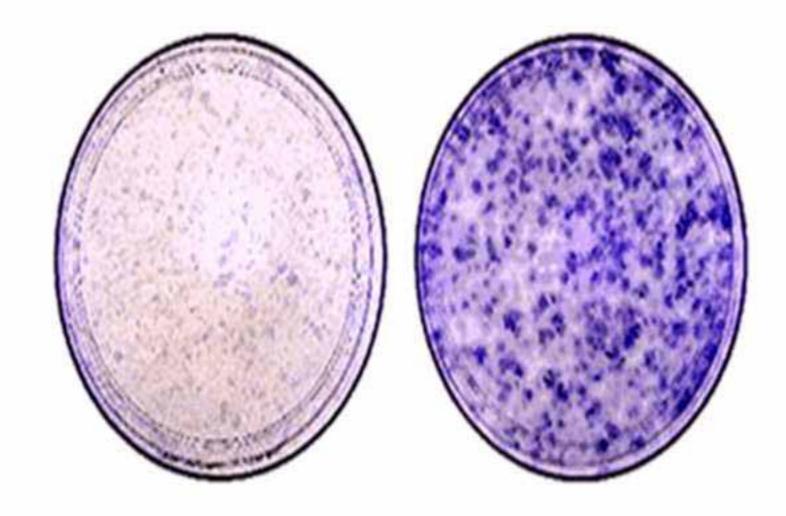
So why aren't we overpopulated by sharks the size of Jaws?

Answer - they all get killed off by man, predators, injury or disease

- and film makers!



Immortal cells can be engineered in culture



Immortal cells can be engineered in culture

So, in theory at least, something approaching immortality is possible

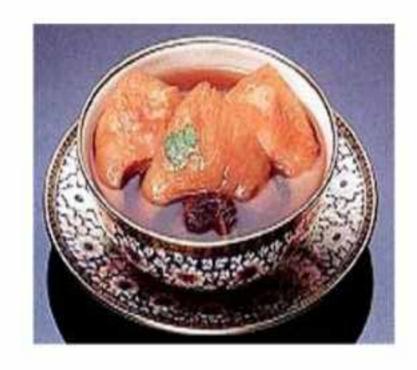


8 Taoist immortals

Immortal cells can be engineered in culture

So, in theory at least, something approaching immortality is possible

Sharks fin soup and caviar?



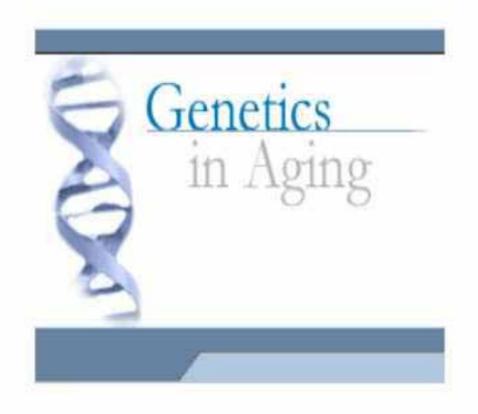






The difference between ageing and longevity





The difference between ageing and longevity

Increasing longevity without preventing ageing would just delay the problem

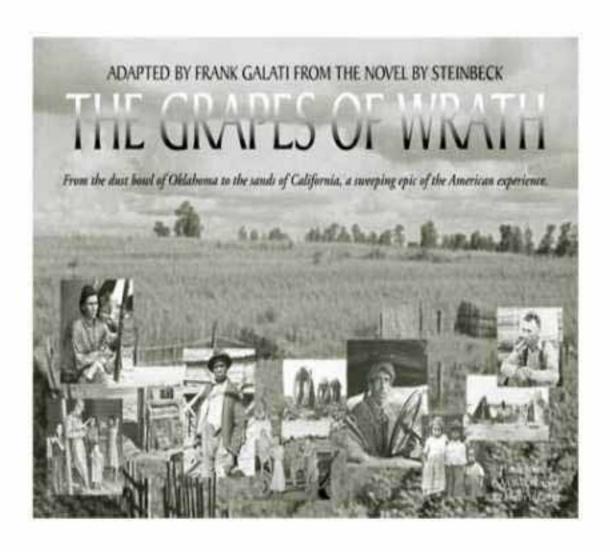




The difference between ageing and longevity

Increasing longevity without preventing ageing would just delay the problem

Potential economic or population disaster

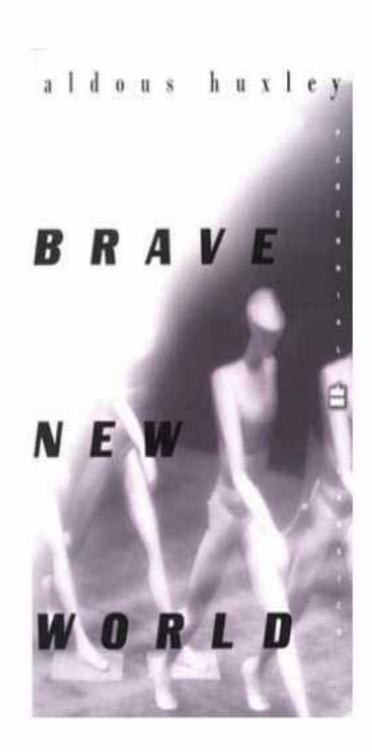


The difference between ageing and longevity

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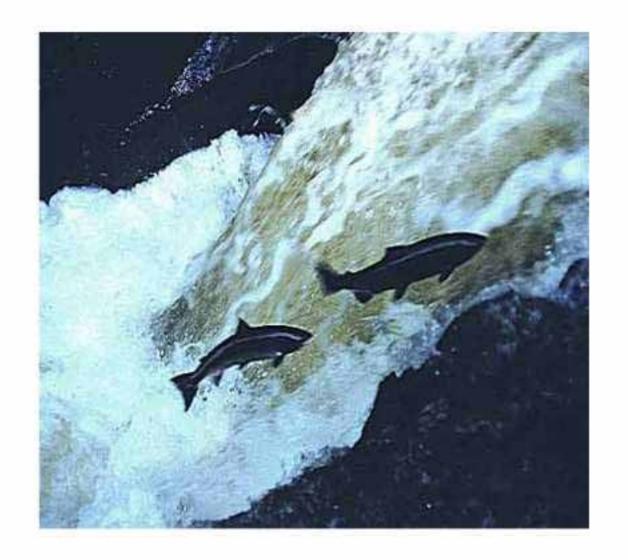
The 'Brave New World' of increasing healthspan



Problem: What makes you die if predation/injury/disease risks are minimal?

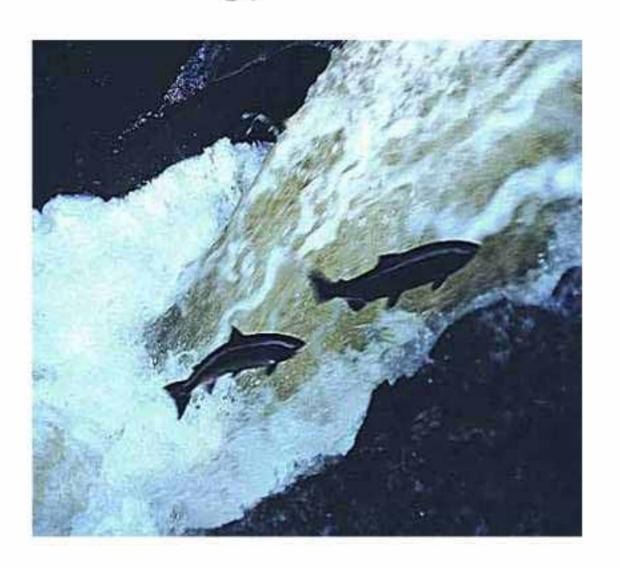
Problem: What makes you die if predation/injury/disease risks are minimal?

Final life event strategy?



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Final life event strategy?

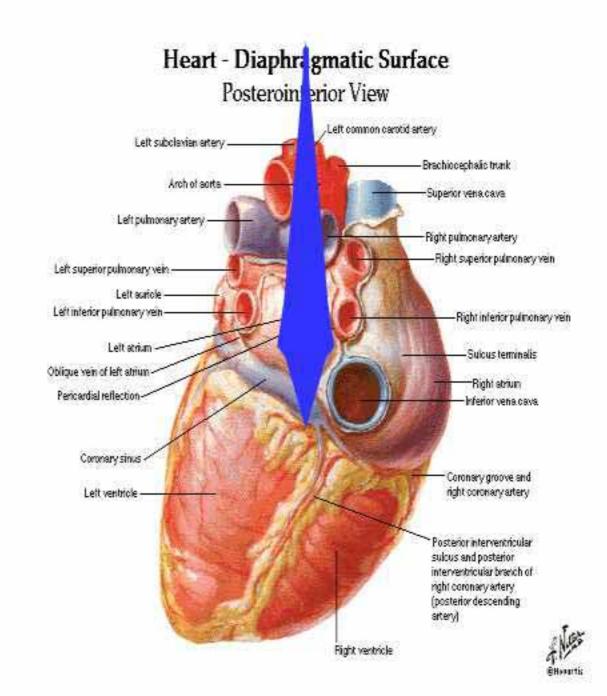




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Programmed heart failure?



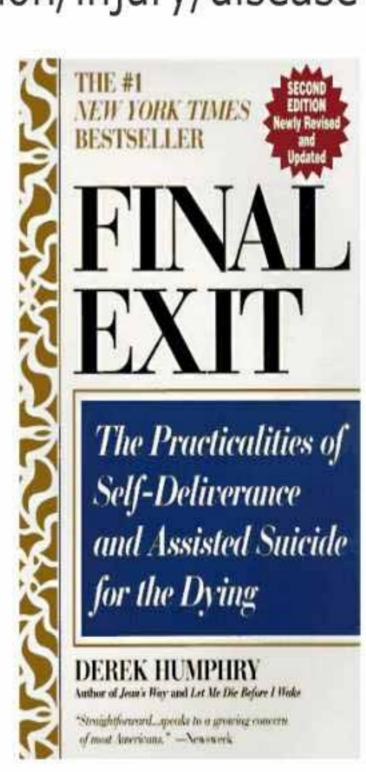
Problem: What makes you die if predation/injury/disease

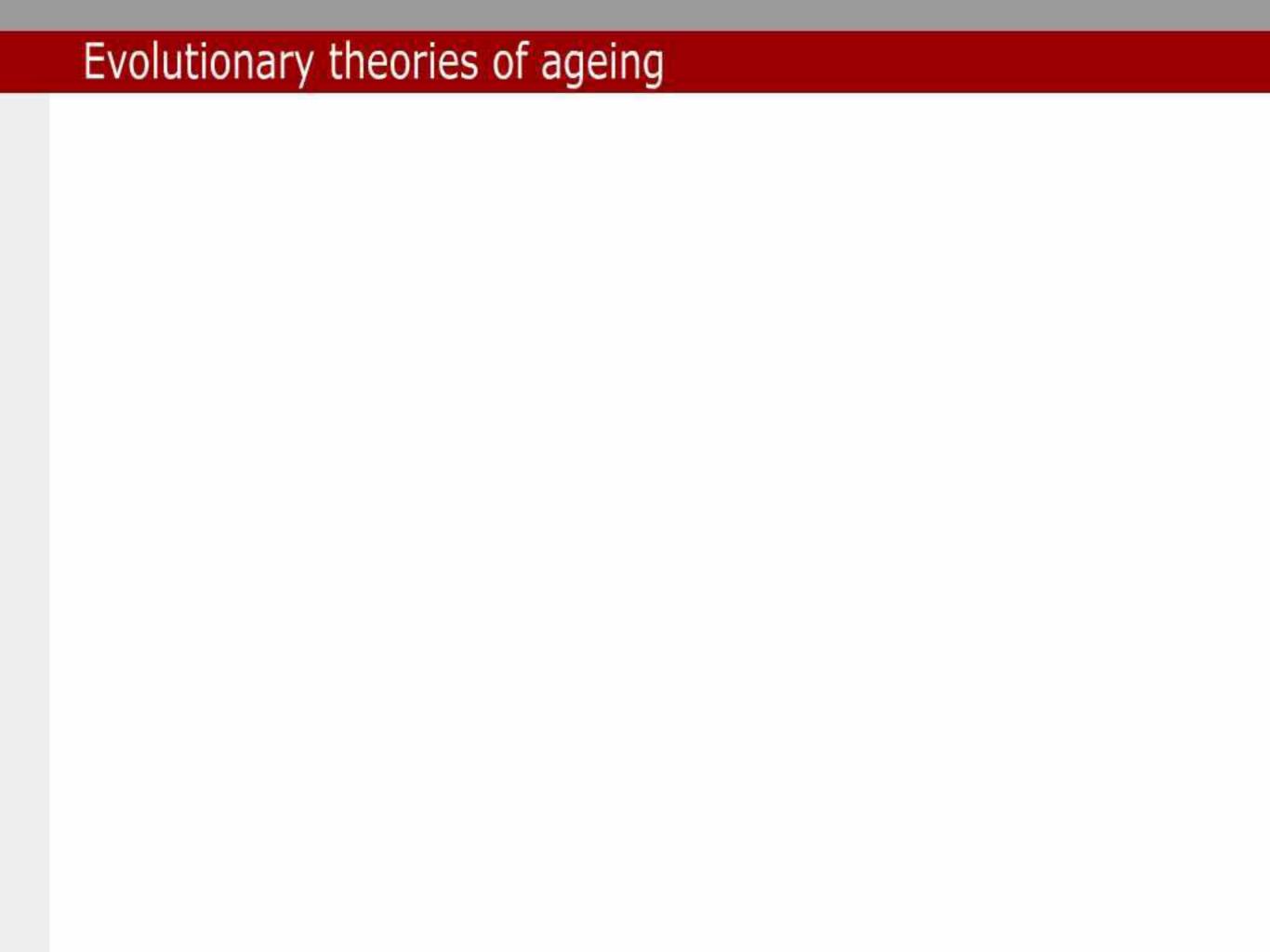
risks are minimal?

Final life event strategy?

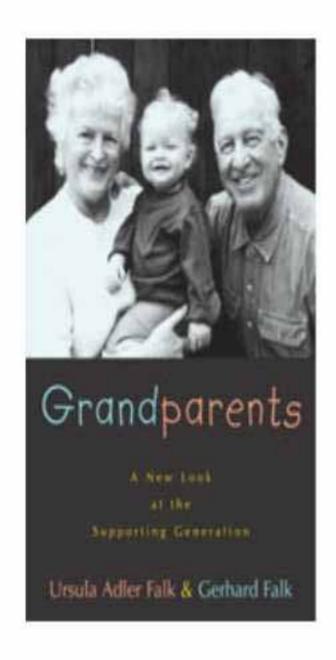
Programmed heart failure?

Euthanasia policy?



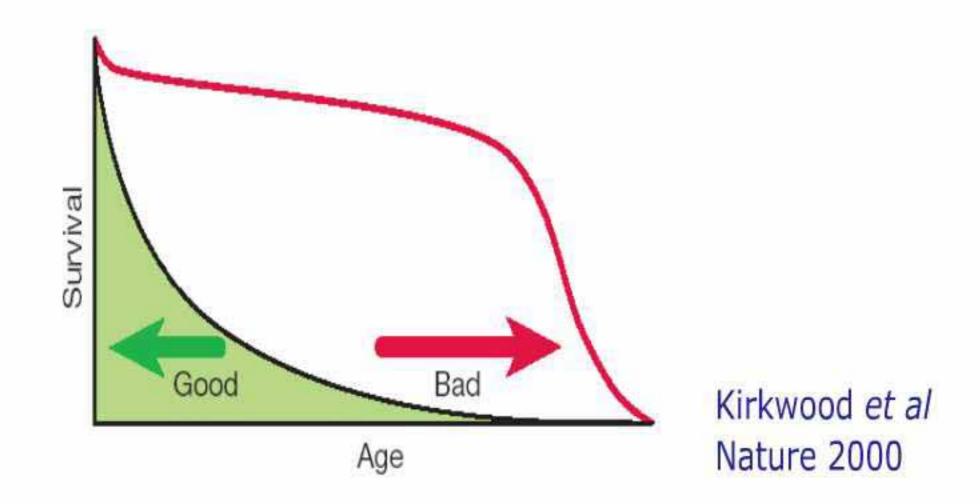


Minimal adaptive pressure to select genes that protect against ageing



Minimal adaptive pressure to select genes that protect against ageing

Disposable soma hypothesis



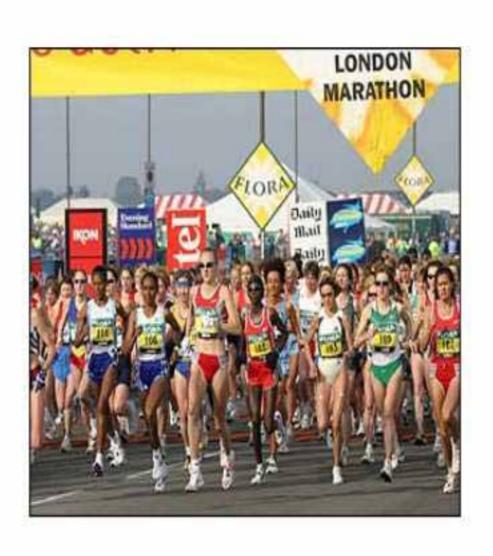
Minimal adaptive pressure to select genes that protect against ageing

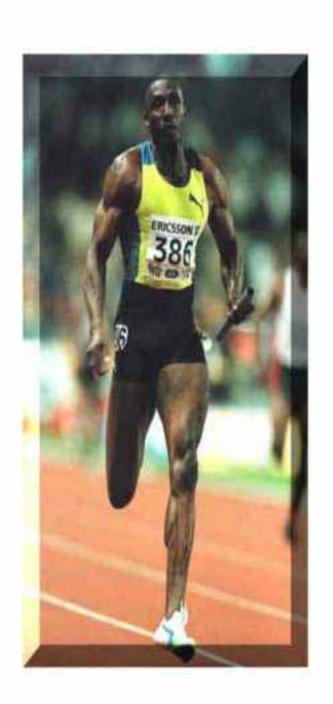
Disposable soma hypothesis

Ageing is an indirect consequence of selecting genes for early reproduction



## Sprinters and marathon runners





Sprinters and marathon runners

Most species run lots of races in different places and with different partners!



Sprinters and marathon runners

Most species run lots of races in different places and with different partners!

Big bang species only get to run once!

If this is correct there should be a reproduction-longevity trade-off



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If flies breed early they die early



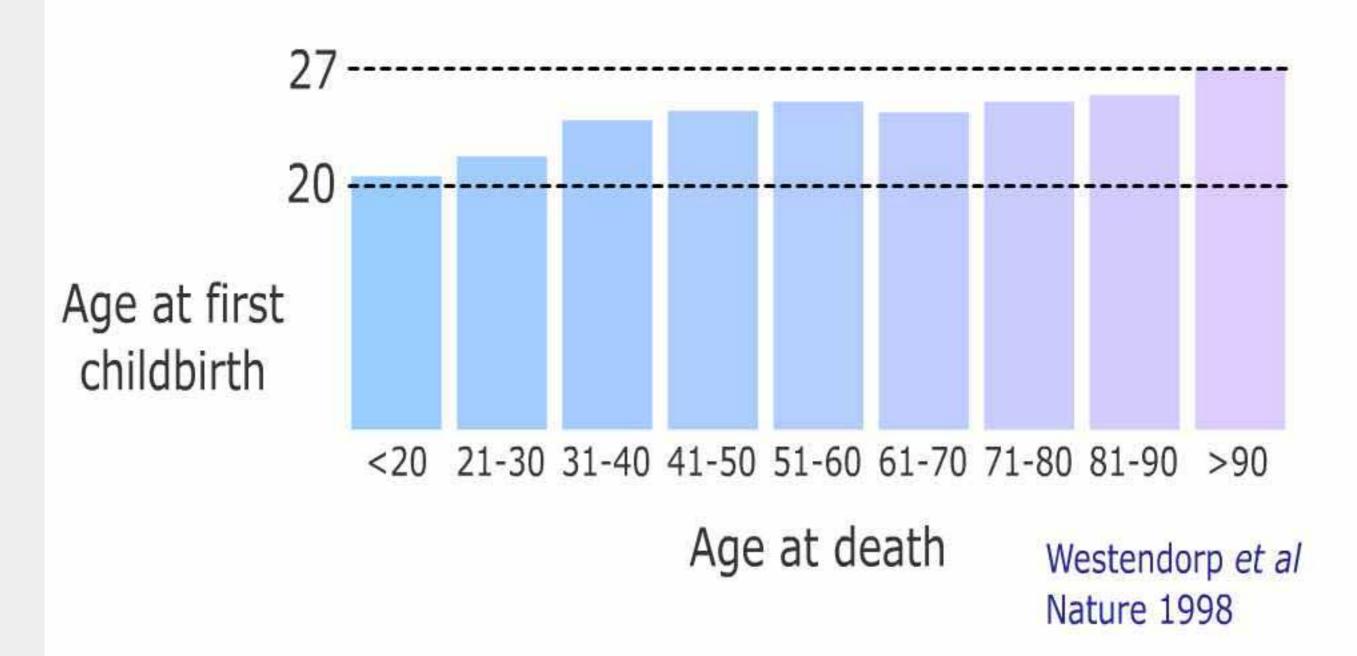
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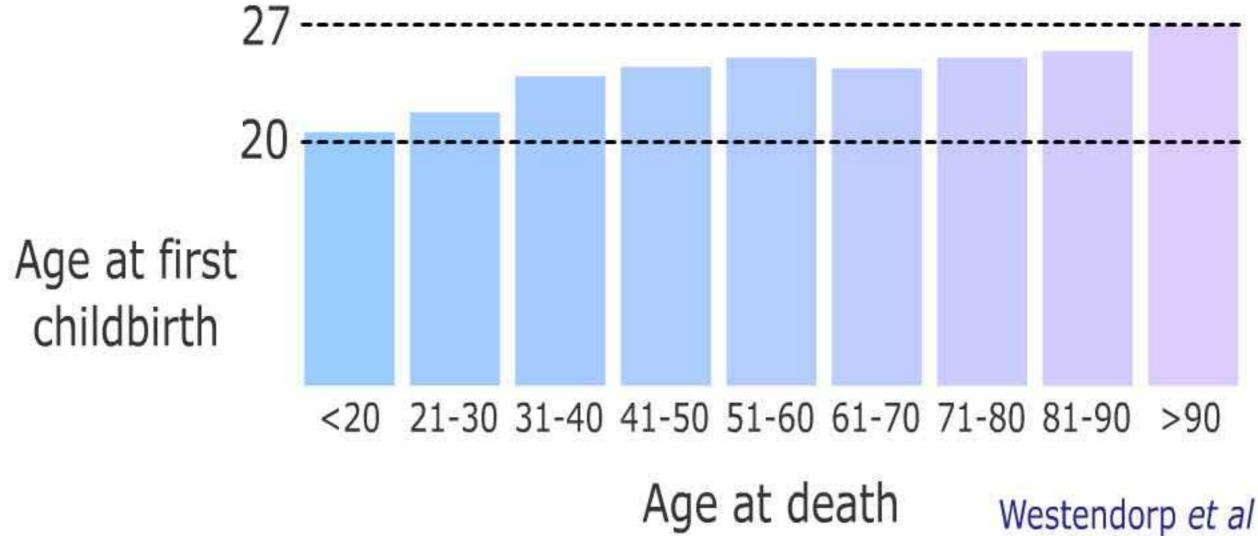


The same is true of married female British aristocrats from 740-1876

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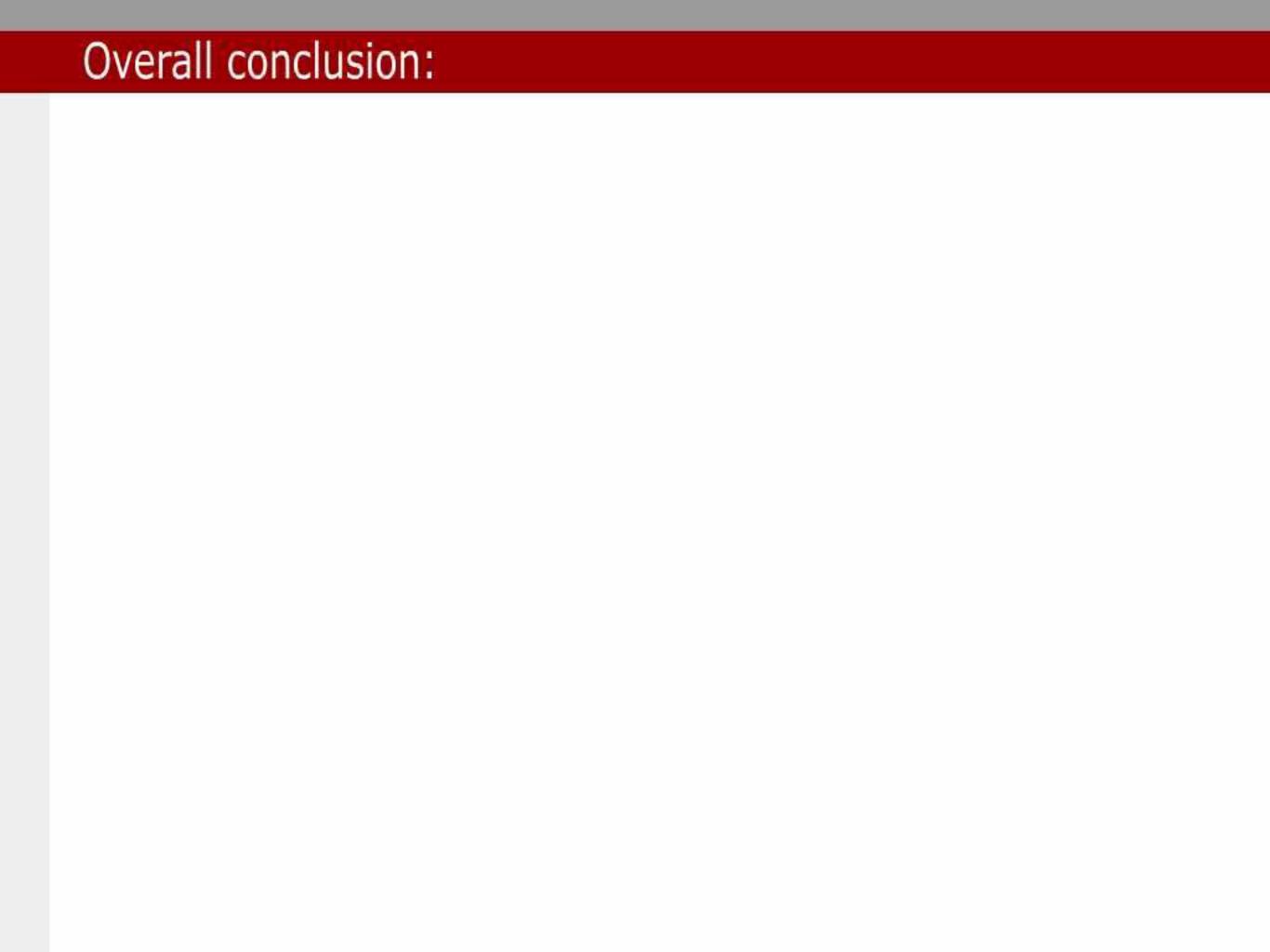


The same is true of married female British aristocrats from 740-1876



But not for their male partners!

Westendorp et al Nature 1998



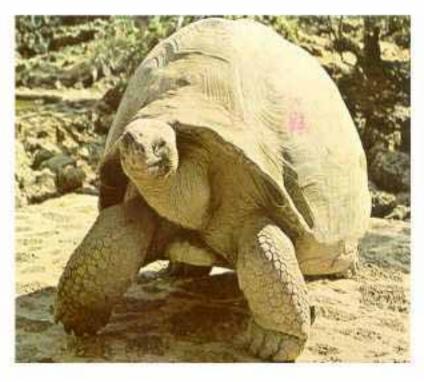
#### Overall conclusion:

Ageing and death are the indirect result of needing to burn

the candle at both ends





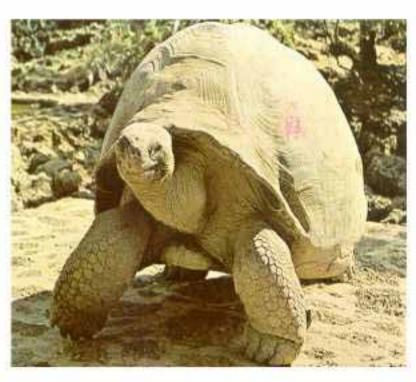


### Surviving long enough to reproduce









Surviving long enough to reproduce

Dependent upon:





Surviving long enough to reproduce

Dependent upon: predation, injury and disease risks





Surviving long enough to reproduce

Dependent upon: predation, injury and disease risks availability of food resources and mates

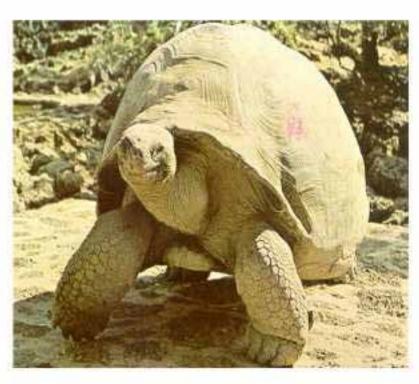




Surviving long enough to reproduce

Dependent upon: predation, injury and disease risks availability of food resources and mates developmental time courses and size

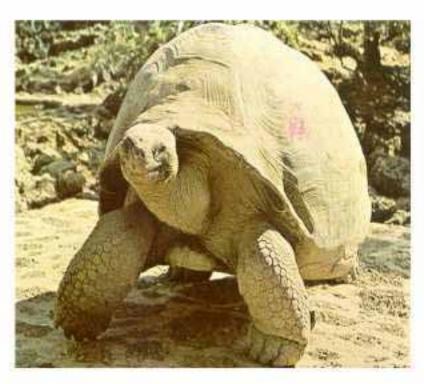




Surviving long enough to reproduce

Dependent upon:
predation, injury and disease risks
availability of food resources and mates
developmental time courses and size
responsibility for parental care

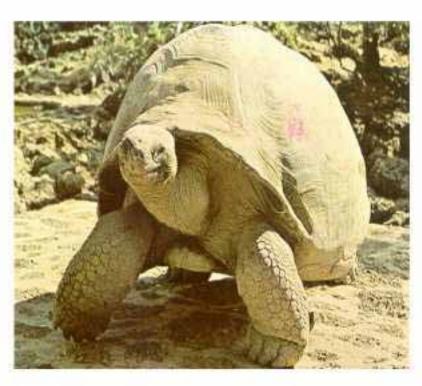




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Surviving long enough to reproduce

Dependent upon:
predation, injury and disease risks
availability of food resources and mates
developmental time courses and size
responsibility for parental care
metabolic rate
social structures



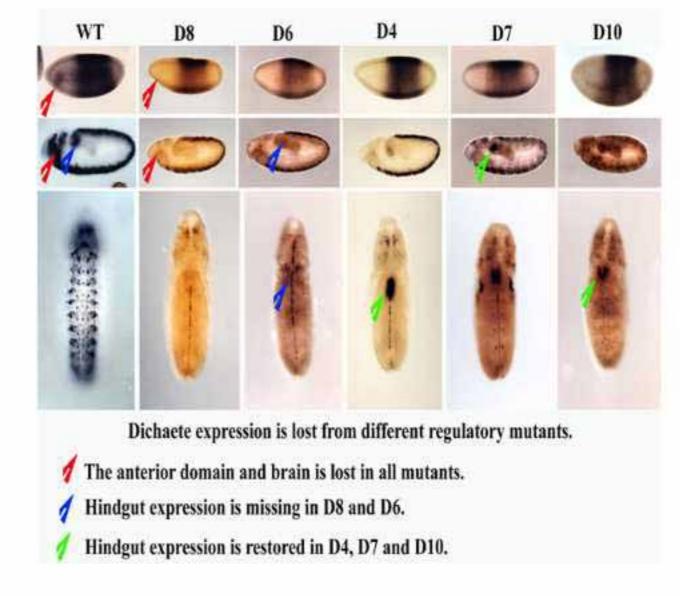


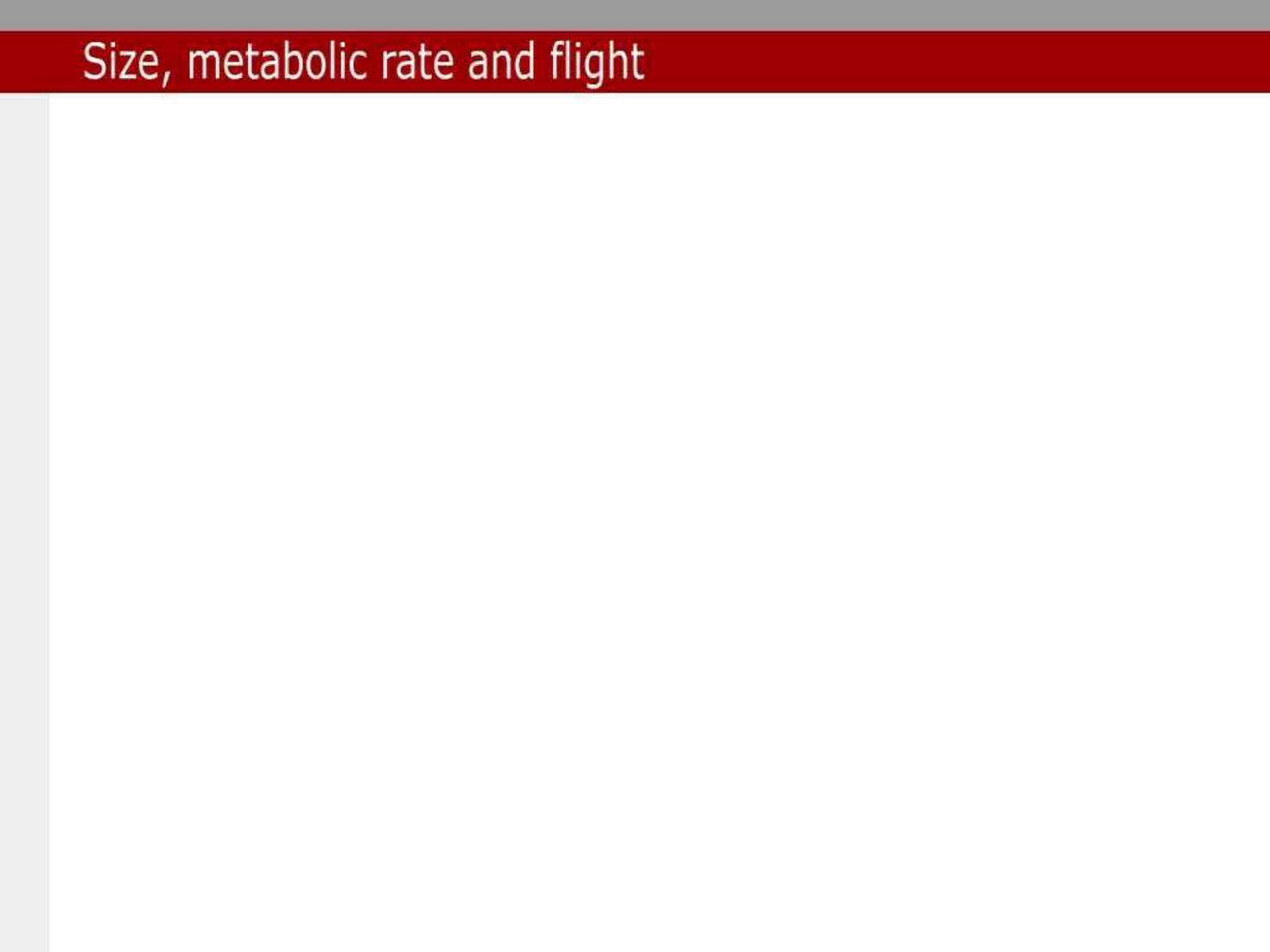
All species need to be prepared to adapt to the unexpected



All species need to be prepared to adapt to the unexpected

A fast-breeding strategy promotes higher rate of adaptive beneficial mutations





Longevity is positively correlated with size





Longevity is positively correlated with size

Negatively correlated with metabolic rate

Longevity is positively correlated with size

Negatively correlated with metabolic rate

Birds seem to contradict this



I believe I can fly!











I believe I can fly!

Being able to fly reduces predation risk so you can breed slower and live longer



I believe I can fly!

Being able to fly reduces predation risk so you can breed slower and live longer

So perhaps if we could develop wings and fly we could do the same!



Why do humans live longer than chimpanzees?





Why do humans live longer than chimpanzees?

Mothers helping to raise their daughters' children



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Improves survival and production rates



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Lifespan = max = 45 + 40 = 85 years



Why do humans live longer than chimpanzees?

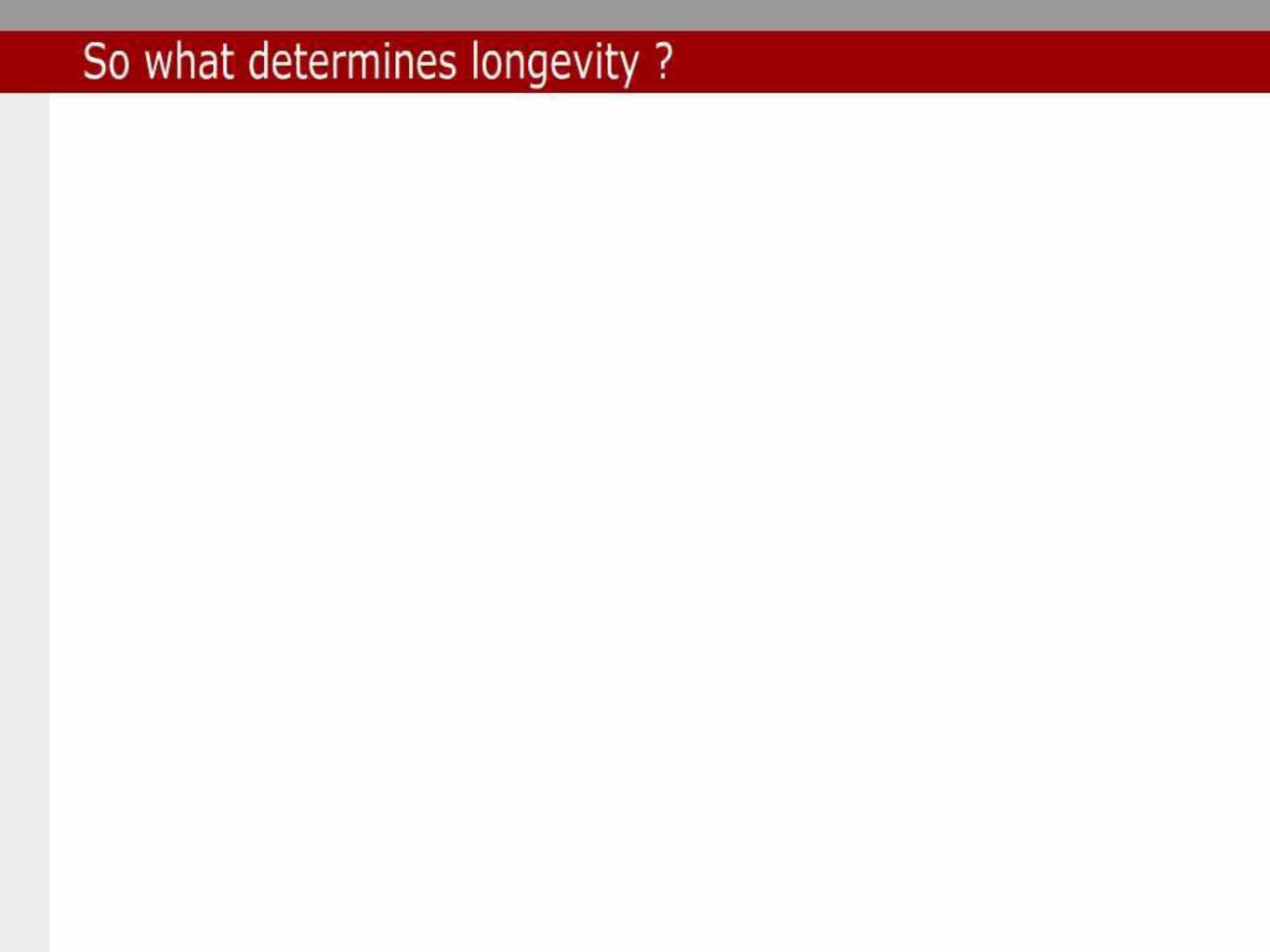
Mothers helping to raise their daughters' children

Improves survival and production rates

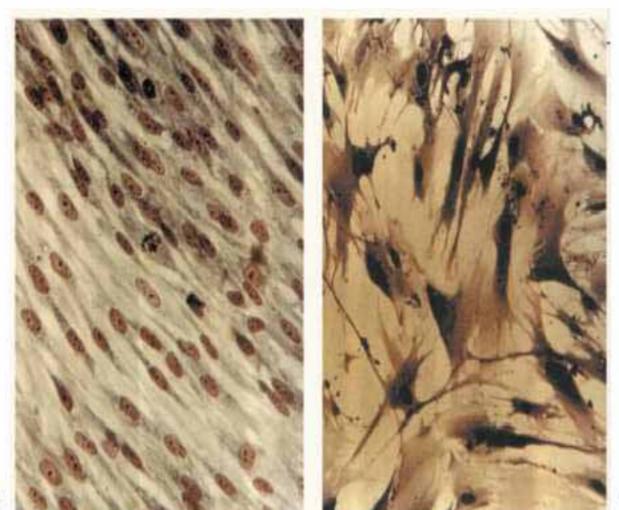
Lifespan = max = 45 + 40 = 85 years

Perhaps we all owe our current extended lifespan to Grandmothers





Cells are mortal in culture so ageing must reflect what goes on inside them

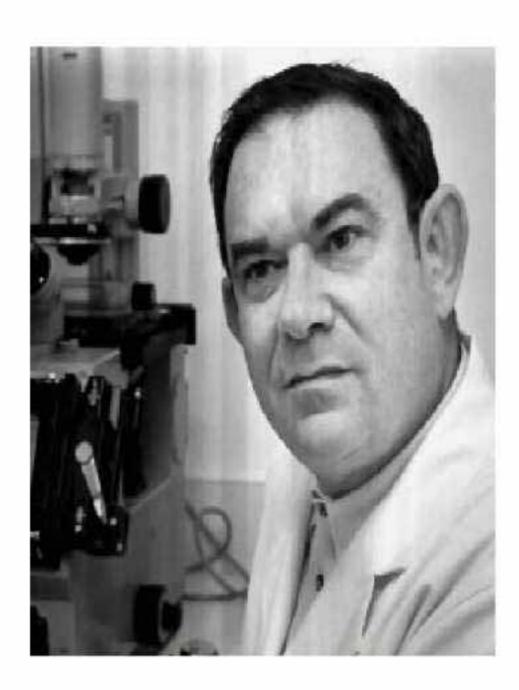


Young cells

Old cells

Cells are mortal in culture so ageing must reflect what goes on inside them

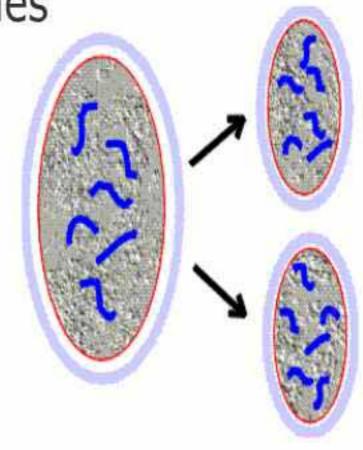
The Hayflick Hypothesis:



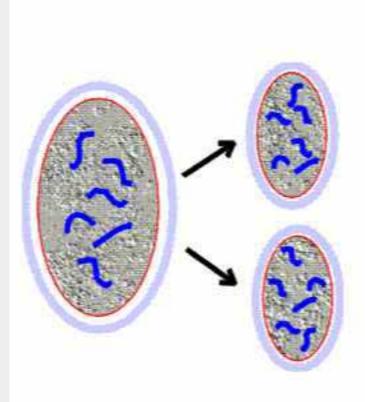
Cells are mortal in culture so ageing must reflect what goes on inside them

The Hayflick Hypothesis:

Cells can only divide a finite number of times (around 50 for many human cells)



Cells have an on-board counter for how many times they have already divided





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Number of divisions is correlated with species longevity

### So what determines longevity?

Cells have an on-board counter for how many times they have already divided

Number of divisions is correlated with species longevity

This does not mean that cells hit the buffers

of their division maximum and die



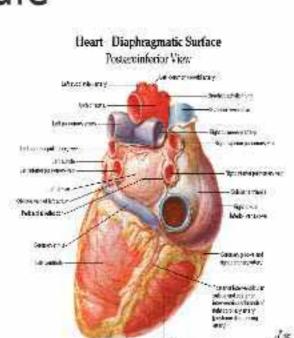
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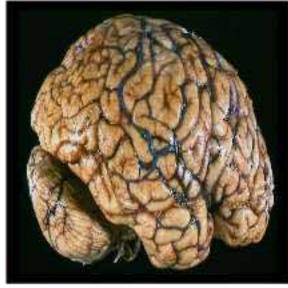
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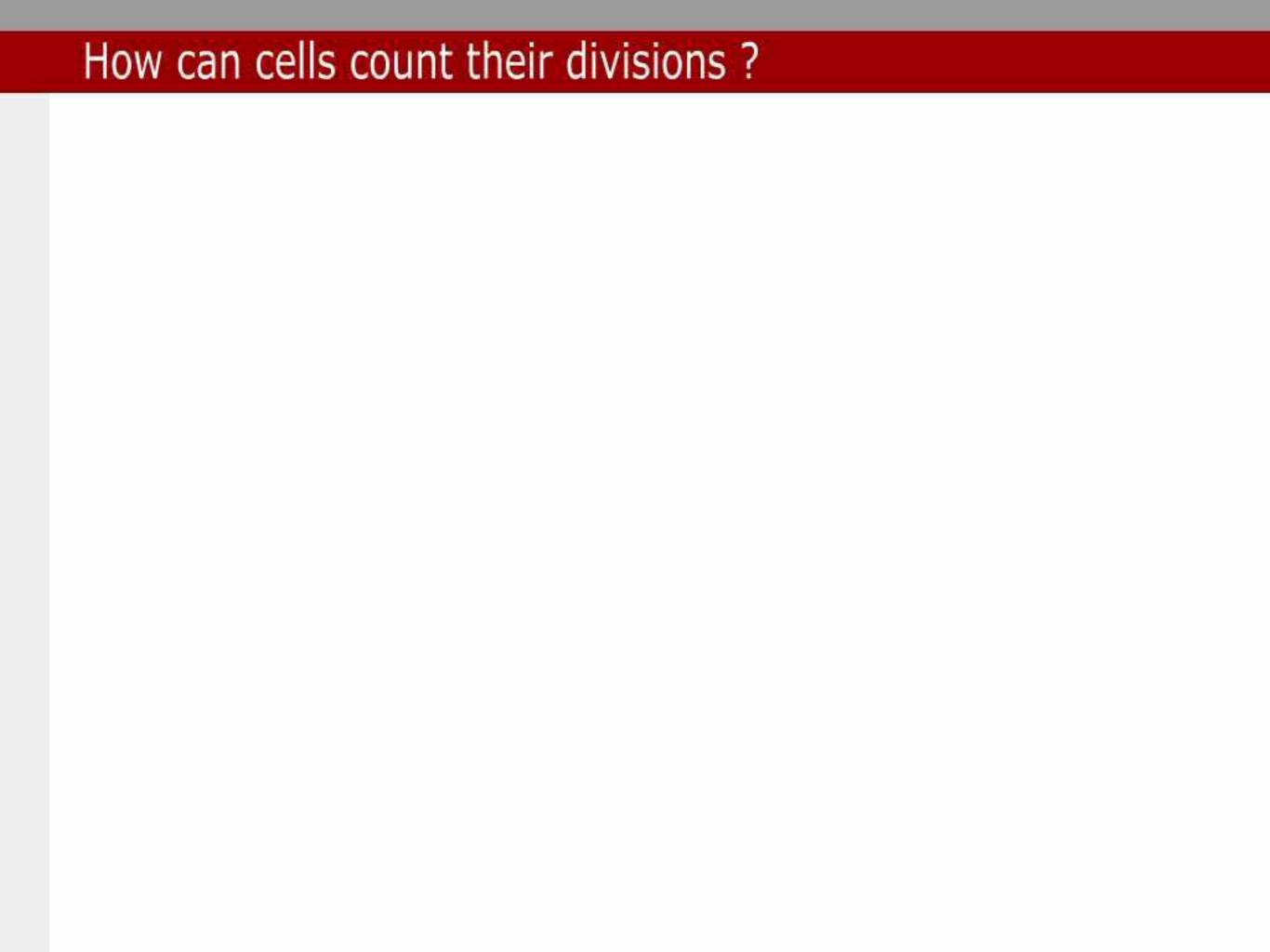
Number of divisions is correlated with species longevity

This does not mean that cells hit the buffers of their division maximum and die

In brain and heart the majority of cells do not divide

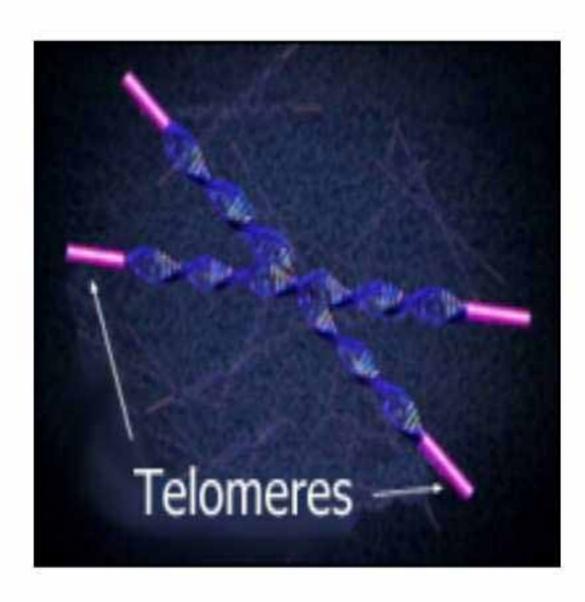






#### Telomeres

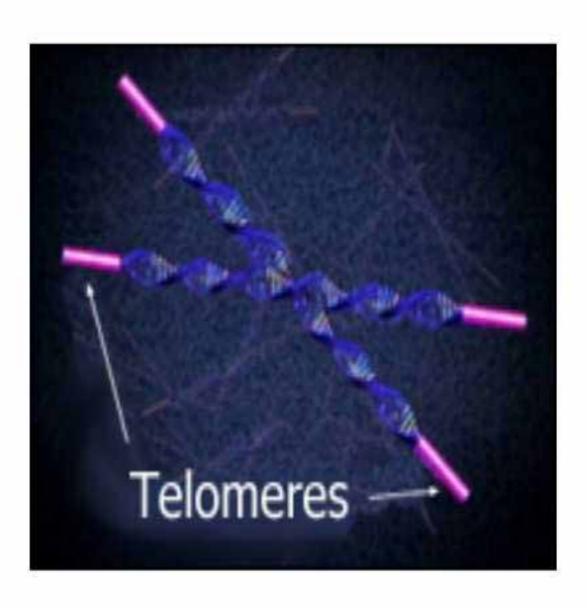
- the TTAGGGs on the ends of your chromosomes



#### Telomeres

- the TTAGGGs on the ends of your chromosomes

Telomerase and immortality

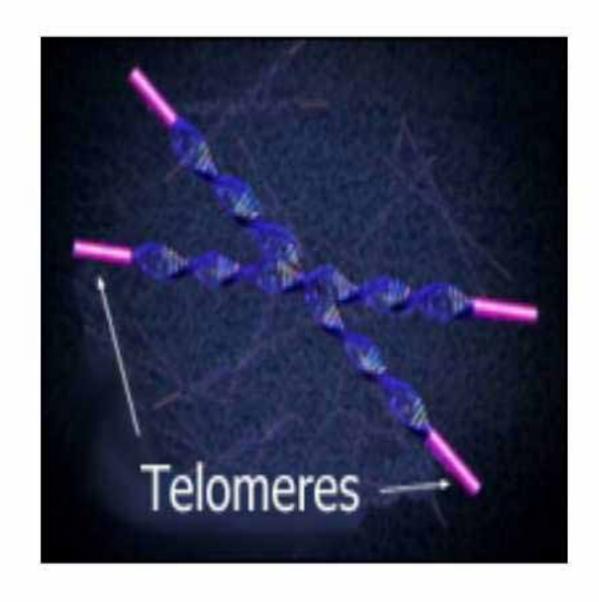


#### Telomeres

- the TTAGGGs on the ends of your chromosomes

Telomerase and immortality

- Species that don't age (high levels)



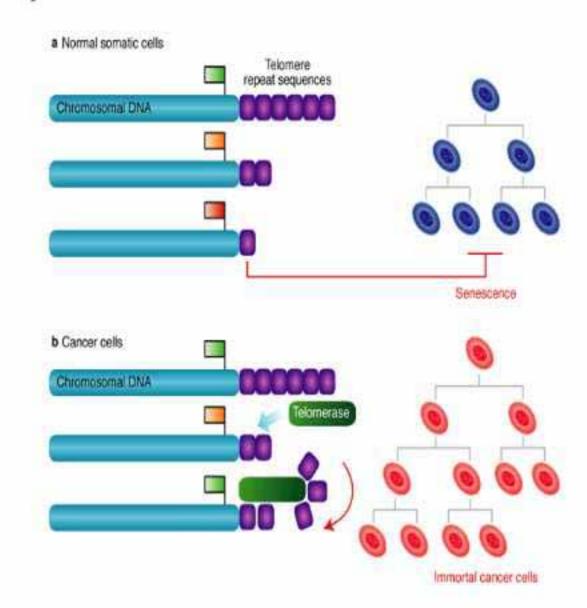
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#### Telomerase and immortality

- Species that don't age (high levels)

 Cancer cells (high)



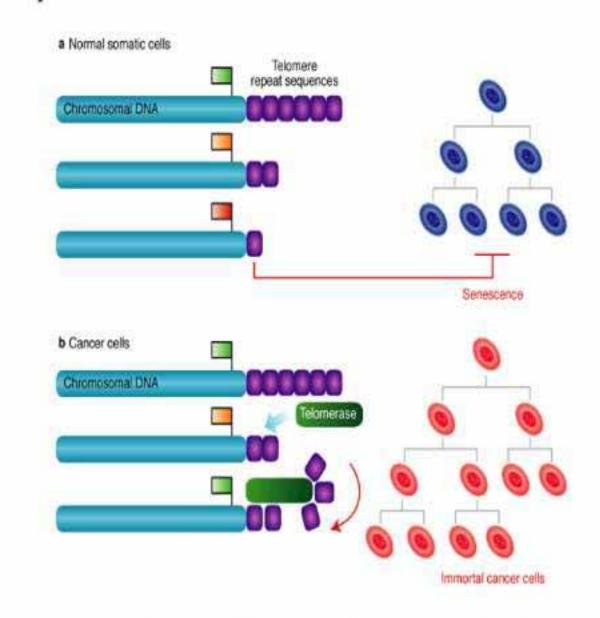
#### Telomeres

the TTAGGGs on the ends of your chromosomes

Telomerase and immortality

 Species that don't age (high levels)

 Cancer cells (high)



- Engineered into cells in culture makes them immortal

Accelerated ageing (Progeroid conditions) is associated with shortened telomeres

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Werner's, Bloom's, Hutchinson-Gilford's and Down's syndromes



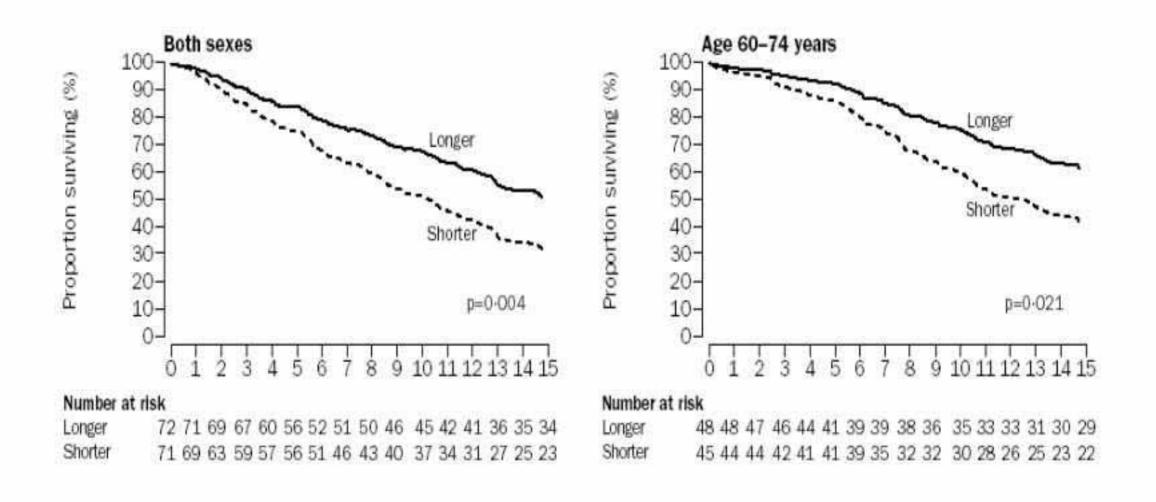






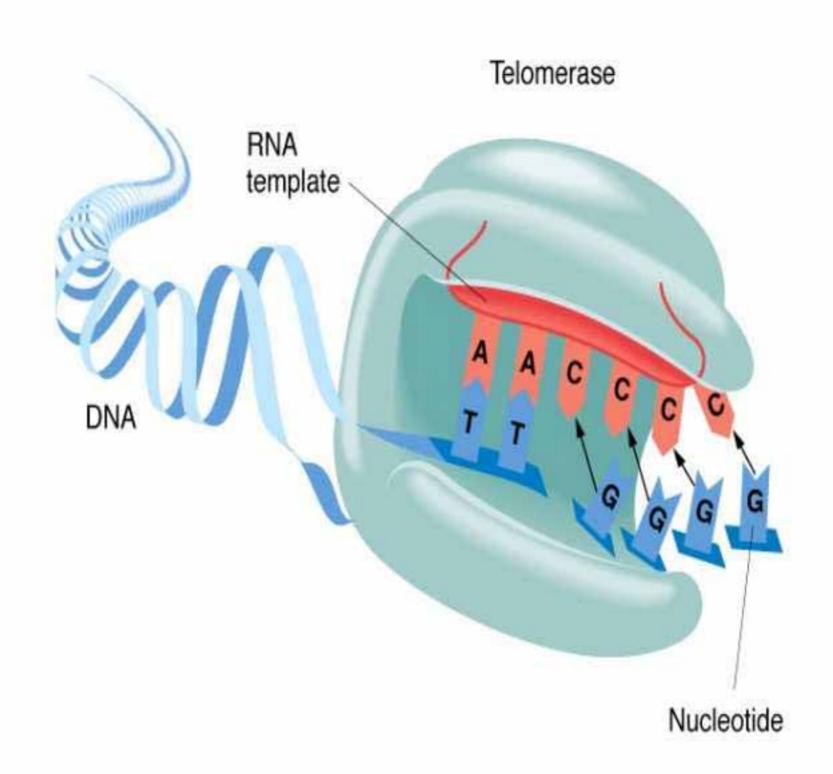
Telomere length may predict life expectancy

Telomere length may predict life expectancy



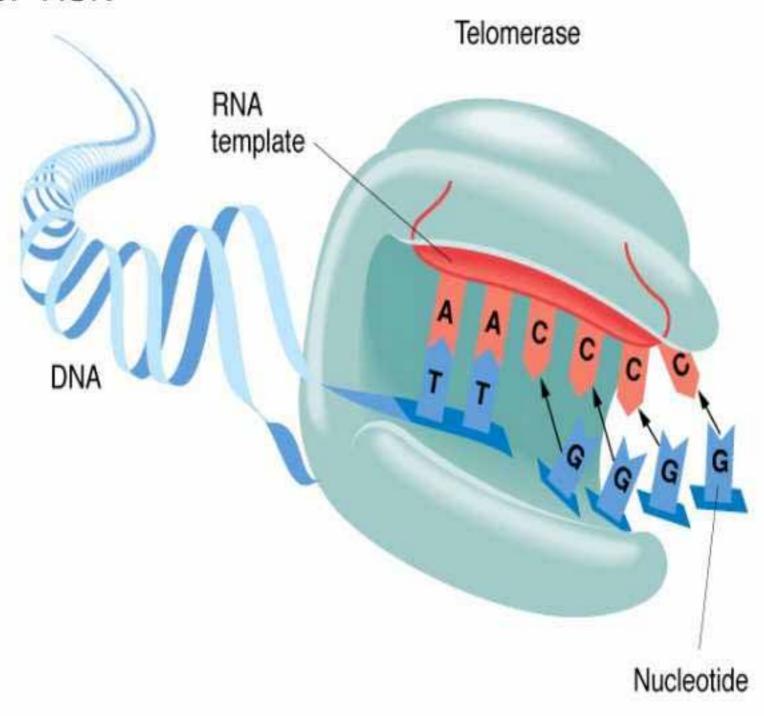
Over 60s with longest telomeres live 4-5 years longer than those with shortest ones Cawthon et al 2003 Lancet

# So is taking telomerase the answer?



## So is taking telomerase the answer?

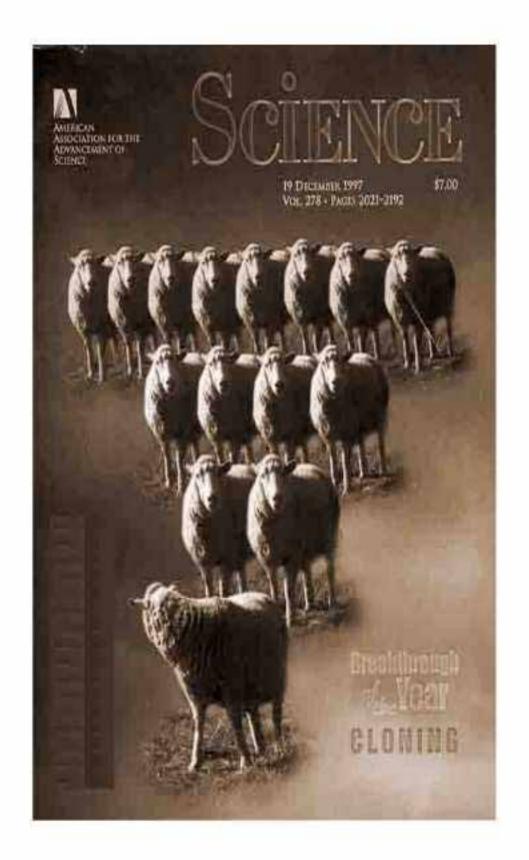
In theory it might help but could increase cancer risk

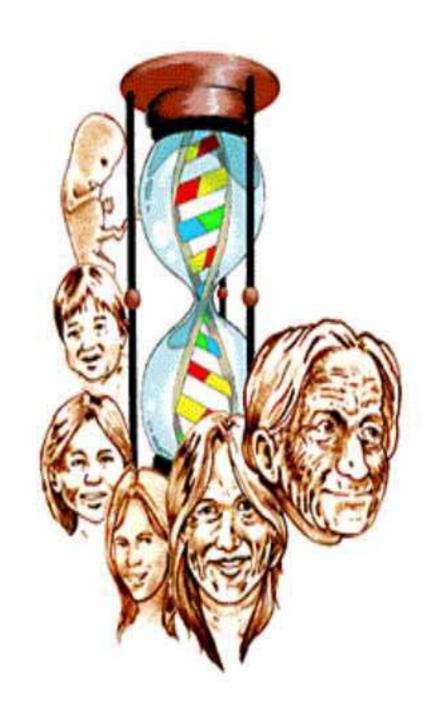


#### So is taking telomerase the answer?

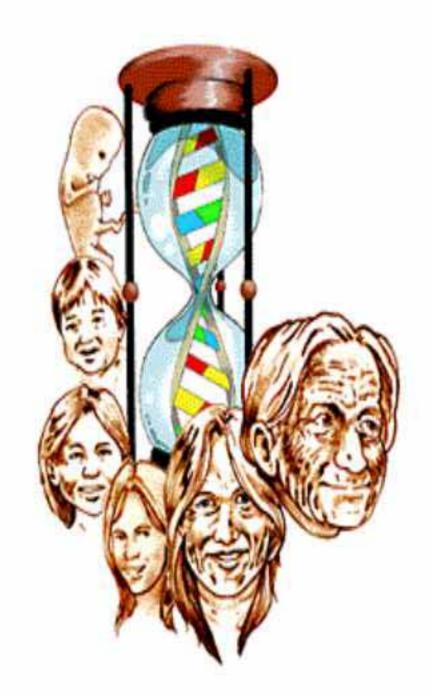
In theory it might help but could increase cancer risk

Does cloning from older cells reduce life expectancy of offspring?



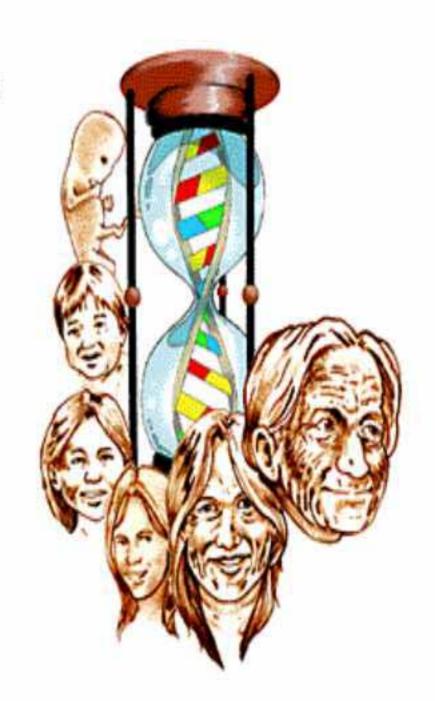


Current estimates from twin studies - 25% genetic contribution to ageing



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Large individual variability in age effects suggests low contribution



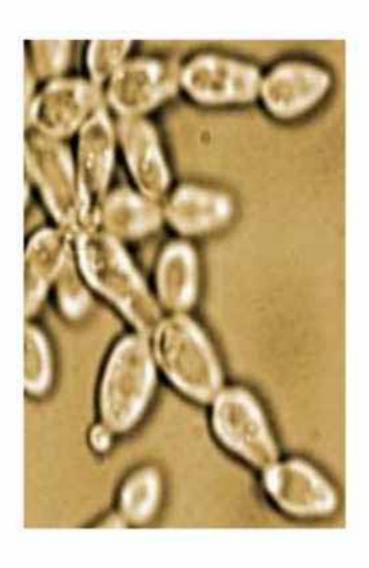
Current estimates from twin studies - 25% genetic contribution to ageing

Large individual variability in age effects suggests low contribution

Difficult to select for good ageing genes!



Yeast, worms and flies - model systems

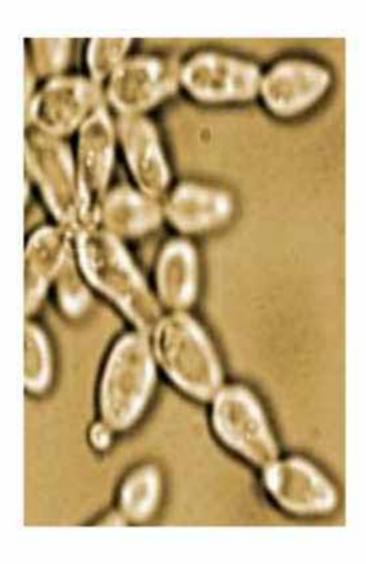






Yeast, worms and flies - model systems

Long-lived species are costly and time-consuming models



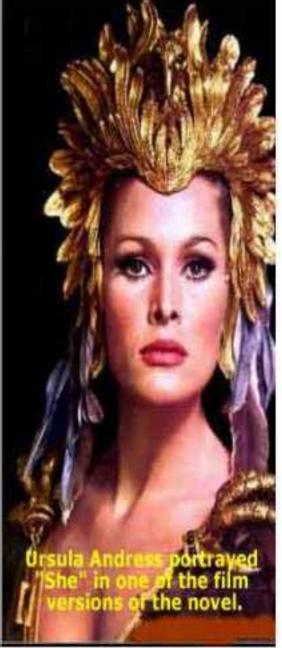




Genetic manipulations can increase longevity by up to 60%







The Methuselah Mouse Prize

\$49,713.78

Genetic manipulations can increase longevity by up to 60%

However does not mean that ageing is eliminated

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Cells age and die because of:



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Cells age and die because of:

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Genetic manipulations can increase longevity by up to 60%

However does not mean that ageing is eliminated

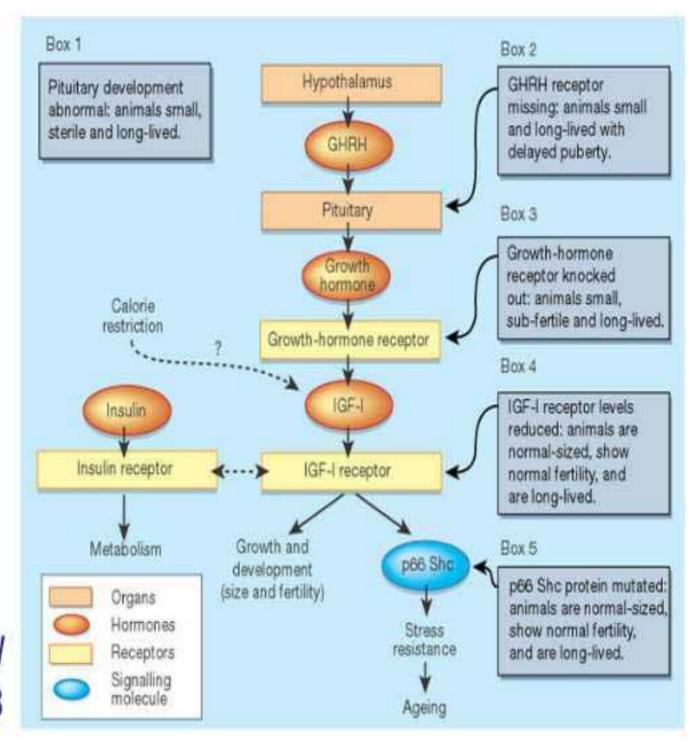
Cells age and die because of:

- Arrested growth and repair
- Mutation and DNA damage
- Increased susceptibility to stress





#### Growth hormone signalling pathways of key importance

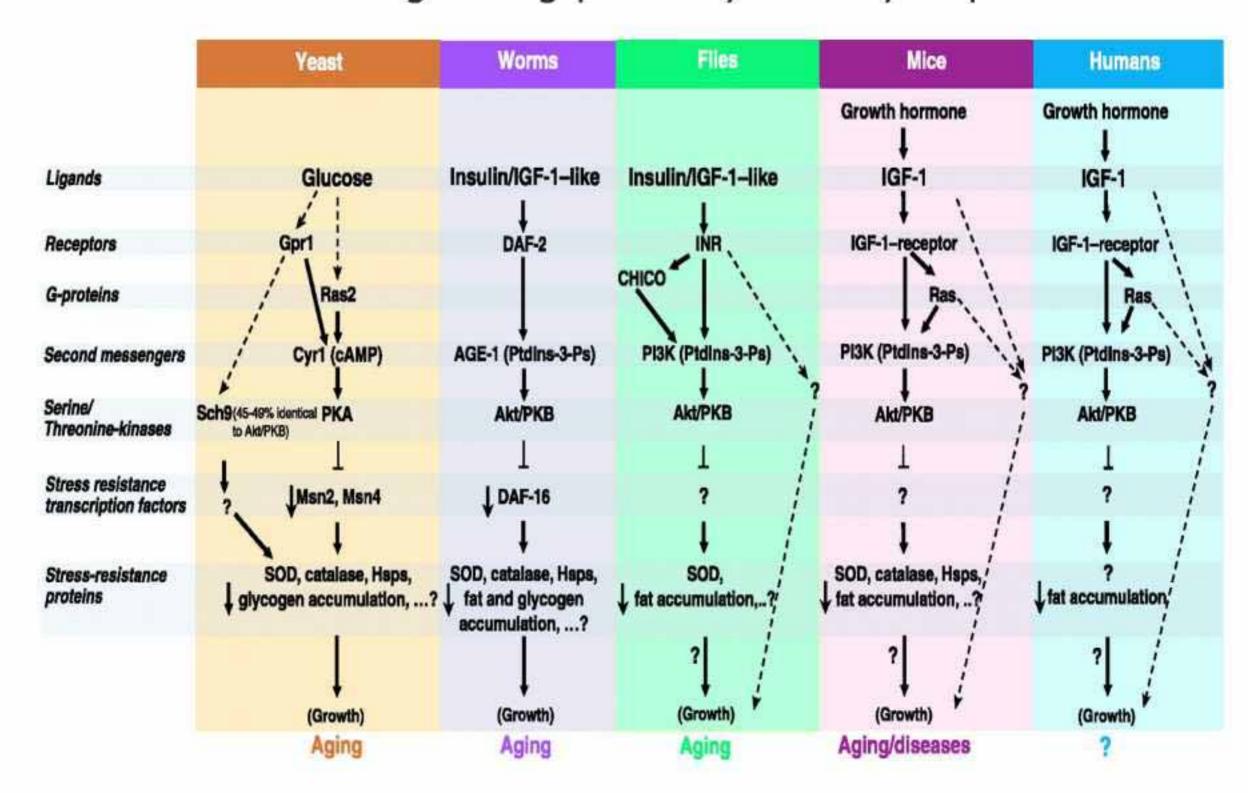


Lithgow et al Nature 2003

Growth hormone signalling pathways of key importance



#### Growth hormone signalling pathways of key importance



Growth hormone signalling pathways of key importance

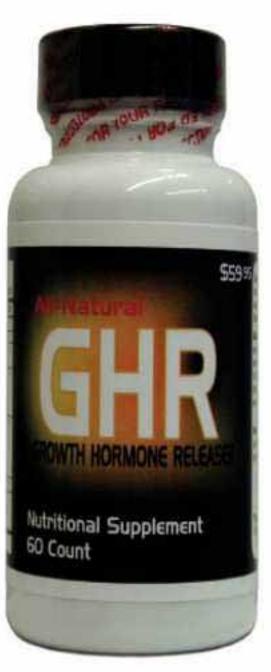
However growth hormone levels decline as we get older

This reduces metabolic efficiency, wound repair and promotes organ failure

This reduces metabolic efficiency, wound repair and promotes organ failure

Growth hormone supplements reverse these effects and may increase longevity

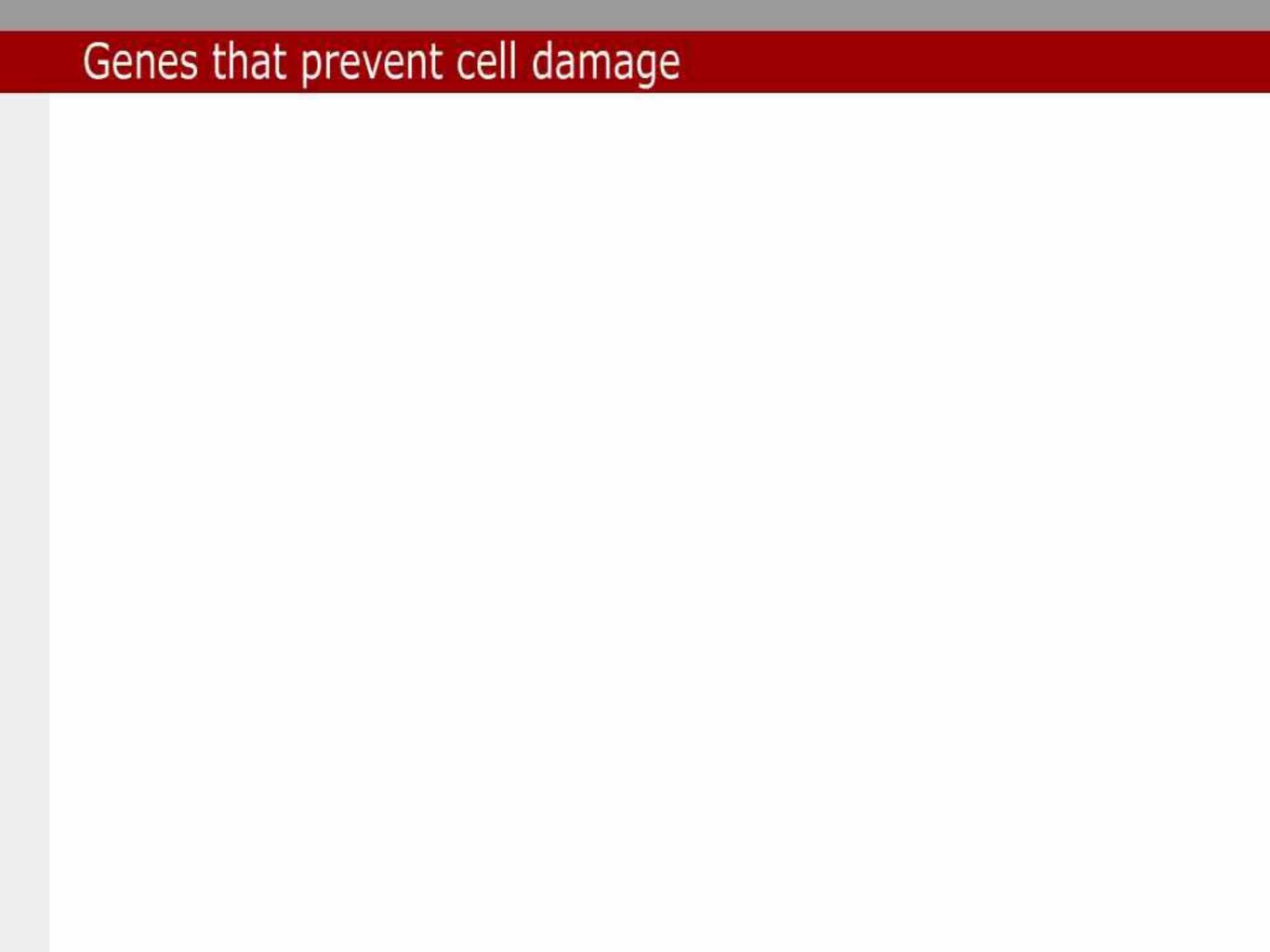




So while reducing growth hormone signalling throughout life may increase longevity...

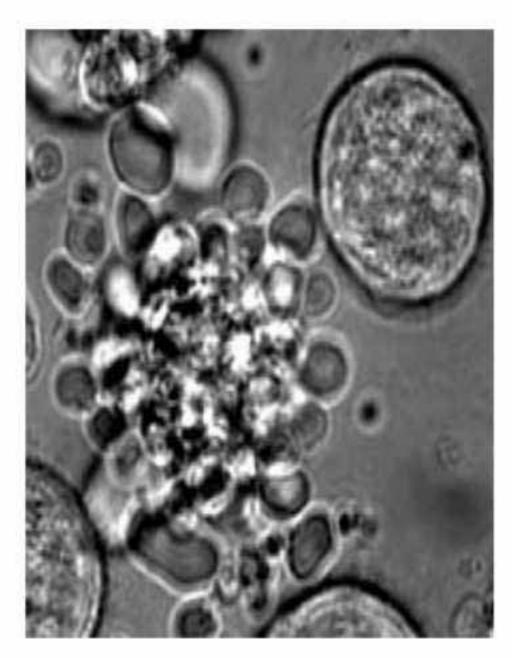
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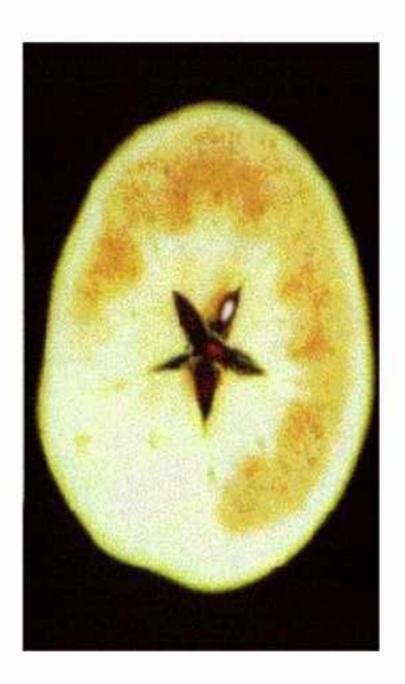
...when it is reduced normally as a result of ageing it may do the opposite



A major cause of cell damage is oxidative stress by exposure to free-radicals



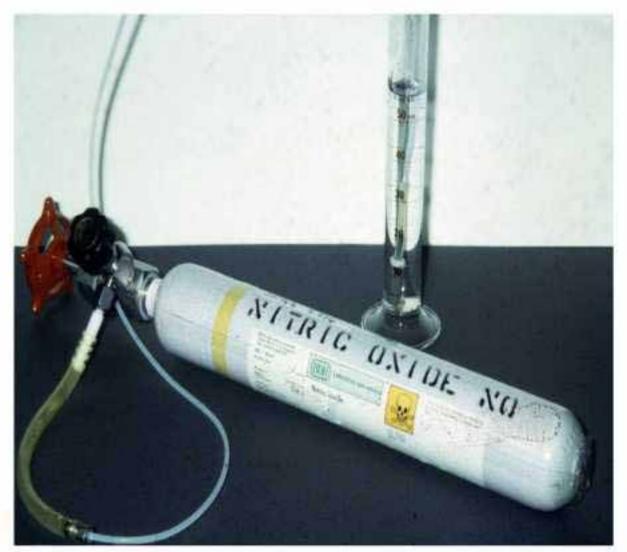




Ageing and/or longevity can be improved by:

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Reducing expression of genes triggering free-radical production....



Nitric oxide

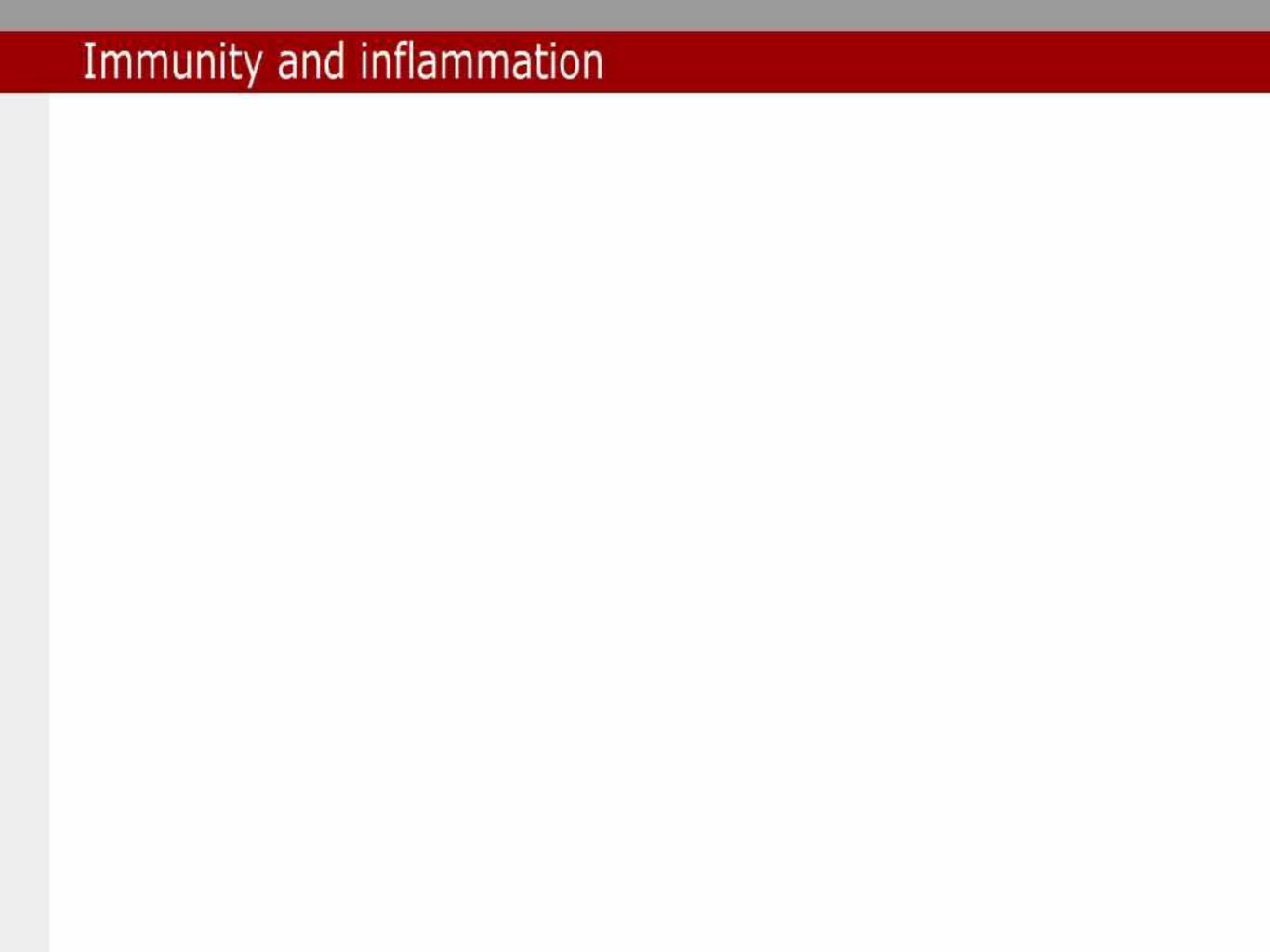
Ageing and/or longevity can be improved by:

Reducing expression of genes triggering free-radical production....

....or increasing expression of genes preventing it



Superoxide dismutase

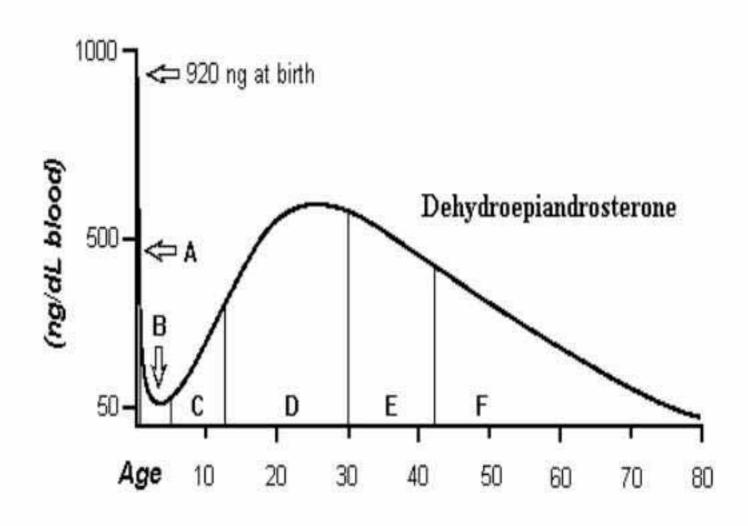


Ageing organisms all have reduced immunocompetance

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The adrenal hormone dehydroepiandrosterone (DHEA) reduced to 10-20% by age 75

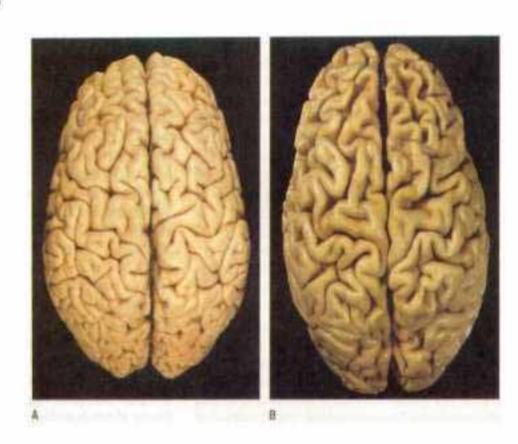




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Neurodegenerative diseases involve a strong inflammatory component

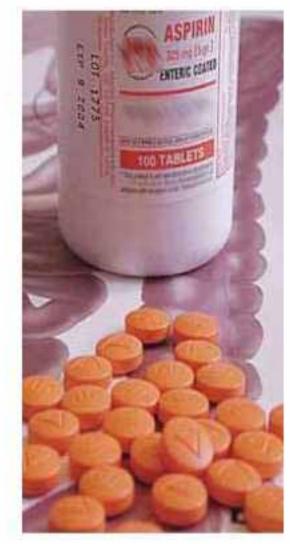


Ageing organisms all have reduced immunocompetance

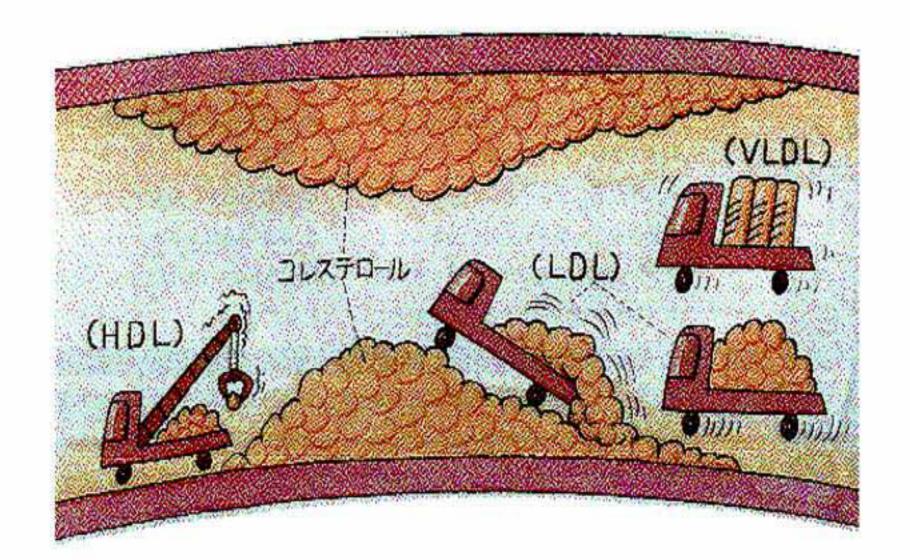
The adrenal hormone dehydroepiandrosterone (DHEA) reduced to 10-20% by age 75

Neurodegenerative diseases involve a strong inflammatory component

Much interest in potential benefits of anti-inflammatory drugs - aspirin etc

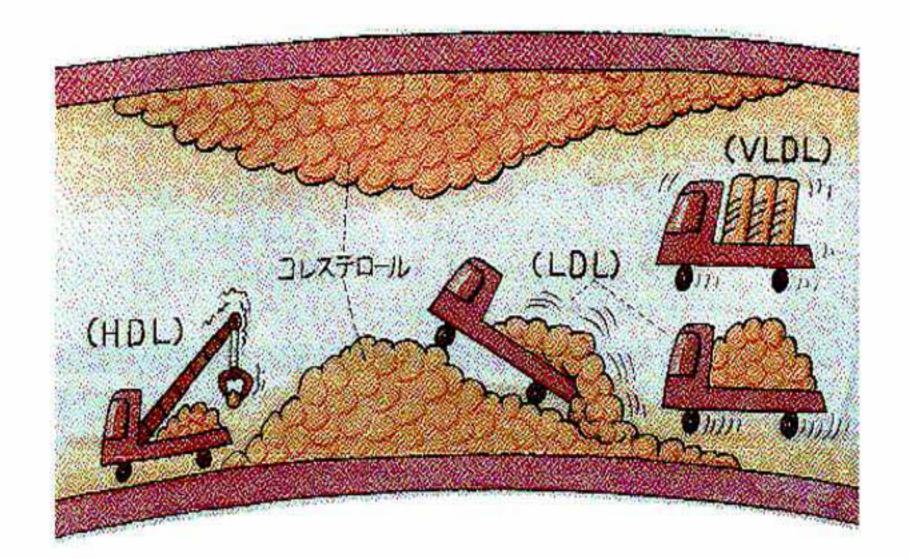


Two major forms of cholesterol measured in blood:



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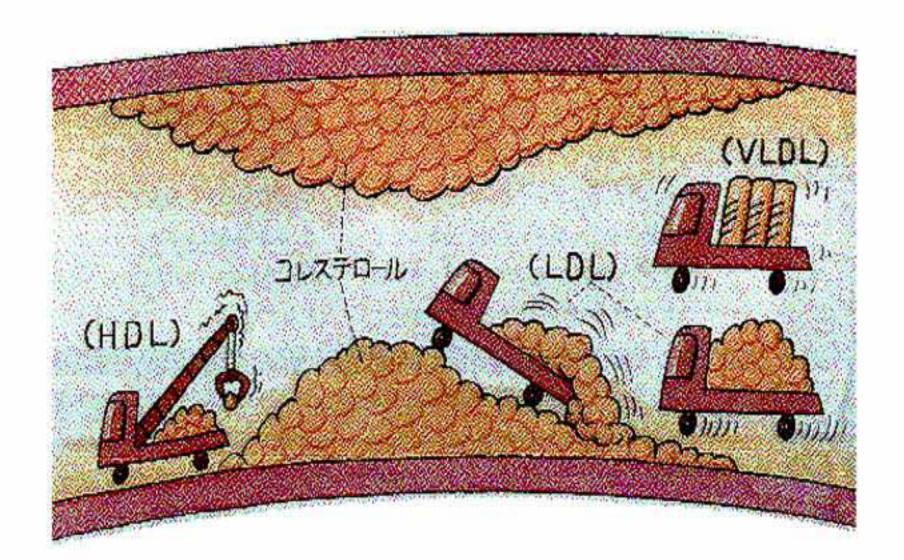
High-density lipoproteins (HDL) 'good'



Two major forms of cholesterol measured in blood:

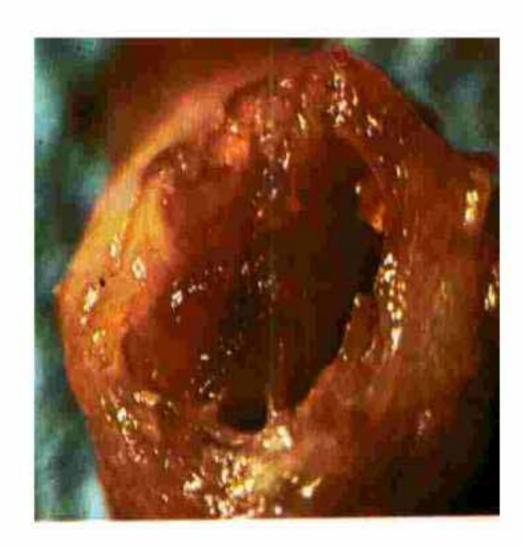
High-density lipoproteins (HDL) 'good'

Low-density lipoproteins (LDL) 'bad'



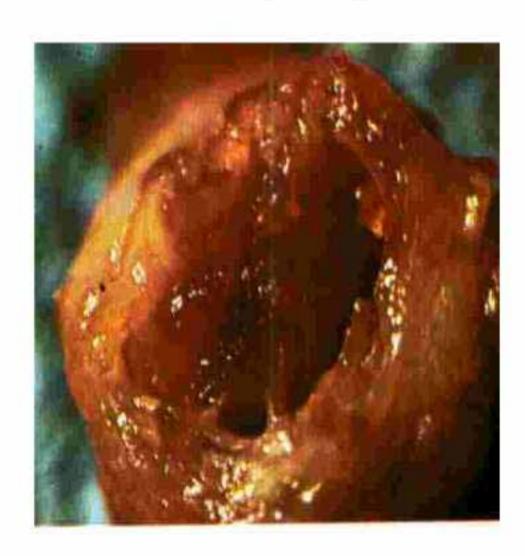
Living to >100 years is associated with having genes that protect against LDL and boost HDL

LDL (bad)

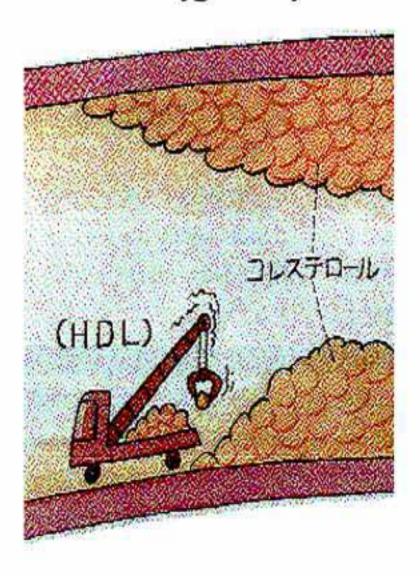


Living to >100 years is associated with having genes that protect against LDL and boost HDL

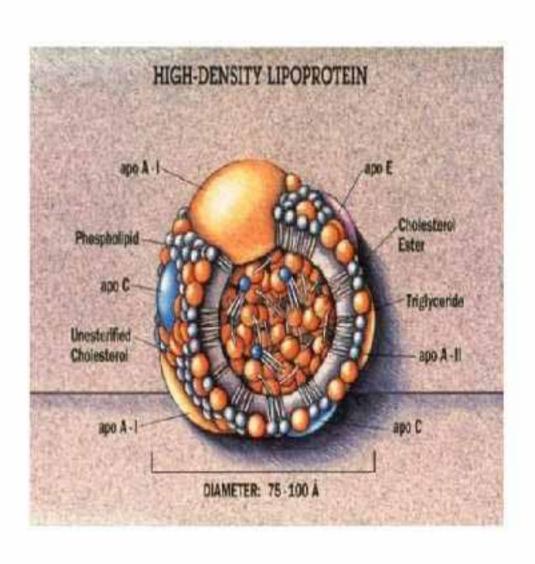
LDL (bad)



HDL (good)

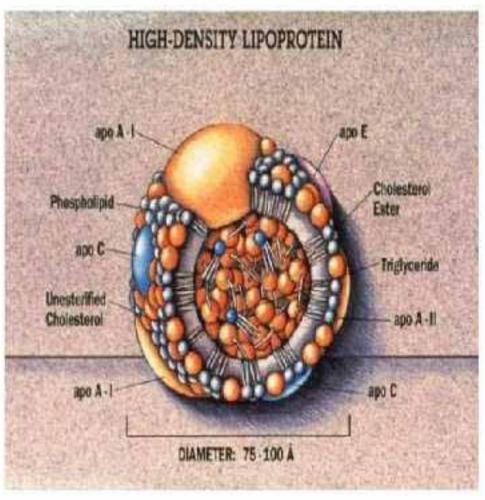


Apolipoprotein E (ApoE) is a central component for cholesterol-carrying lipoprotein complexes



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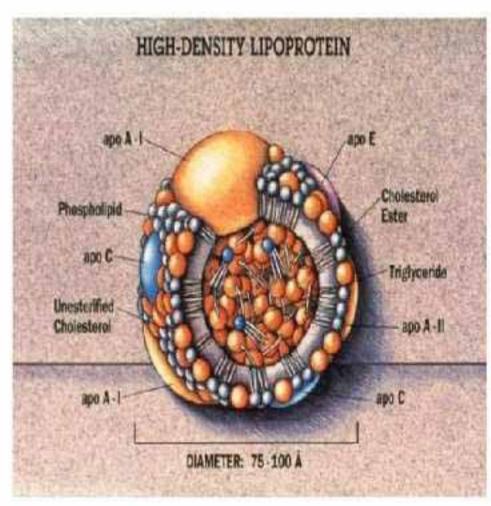
ApoE4 - higher risk of cardiovascular and Alzheimers disease



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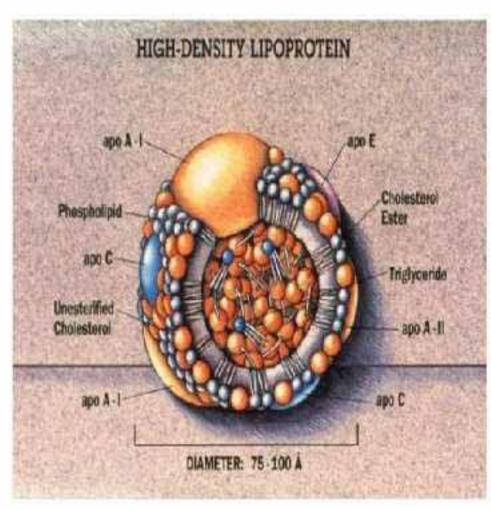


Apolipoprotein E (ApoE) is a central component for cholesterol-carrying lipoprotein complexes

ApoE4 - higher risk of cardiovascular and Alzheimers disease

Those who live over 100 are half as likely to carry this form of the gene

And have the ApoE2 form which is more protective



The 1405v variant of cholesterol ester transfer protein in Ashkenazi Jews

(Barzilai et al JAMA 2003)

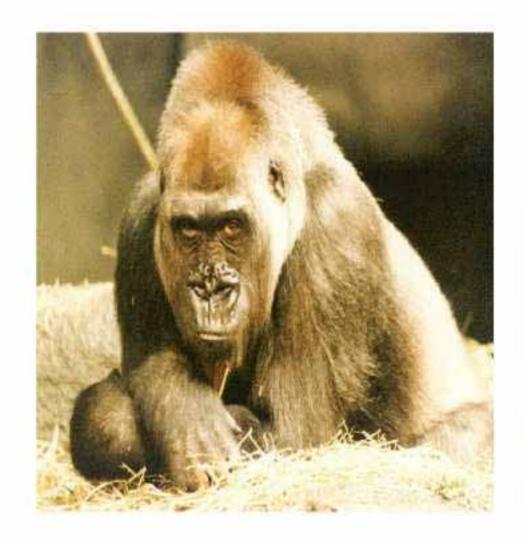




Life expectancy for human males in developed countries is 4-6 years less than for females

Life expectancy for human males in developed countries is 4-6 years less than for females

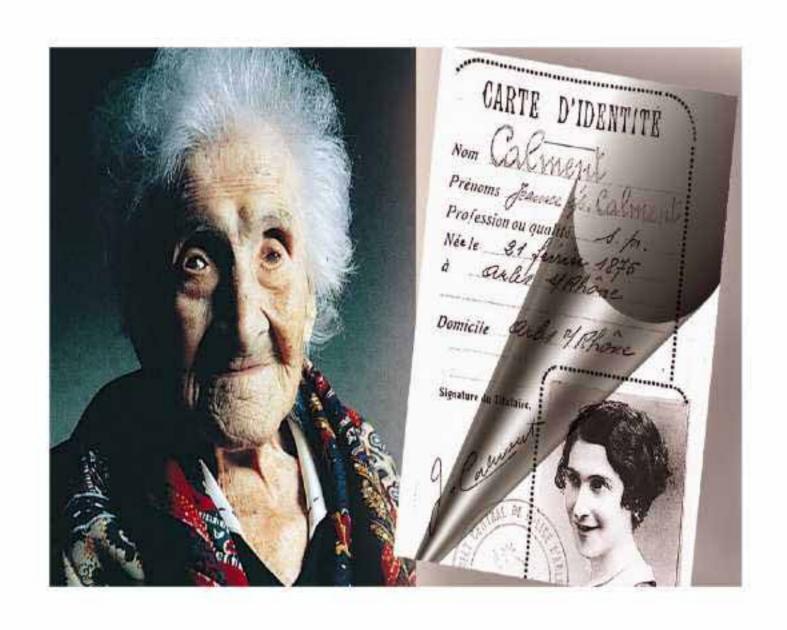
#### Not specific to humans





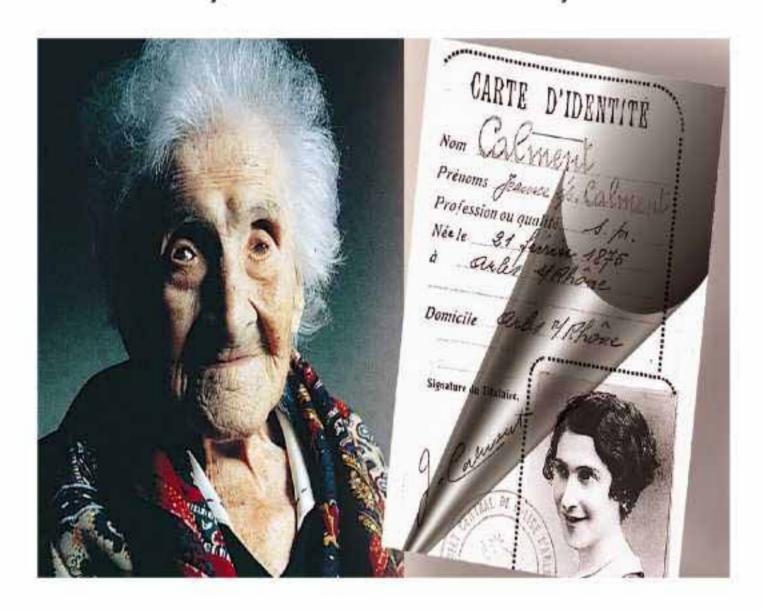


The oldest documented woman is Jeanne Calment

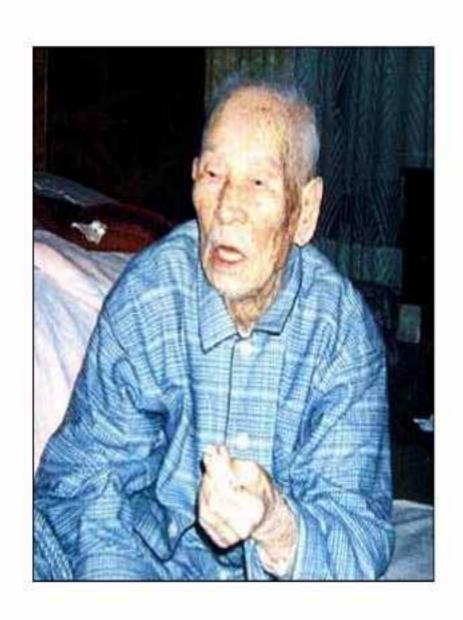


The oldest documented woman is Jeanne Calment

- died in 1997 at 122 years and 164 days

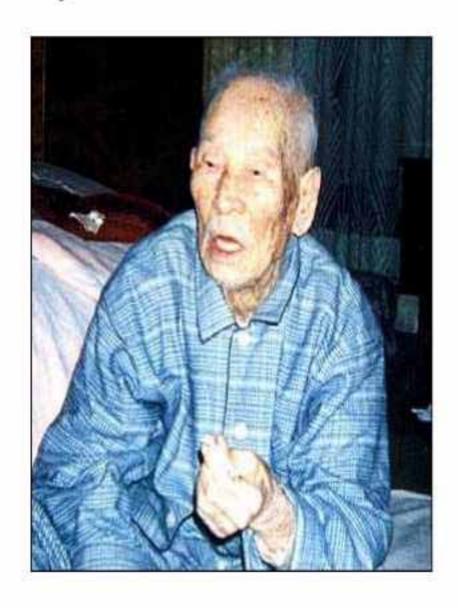


The oldest documented man is Yukichi Chuganji

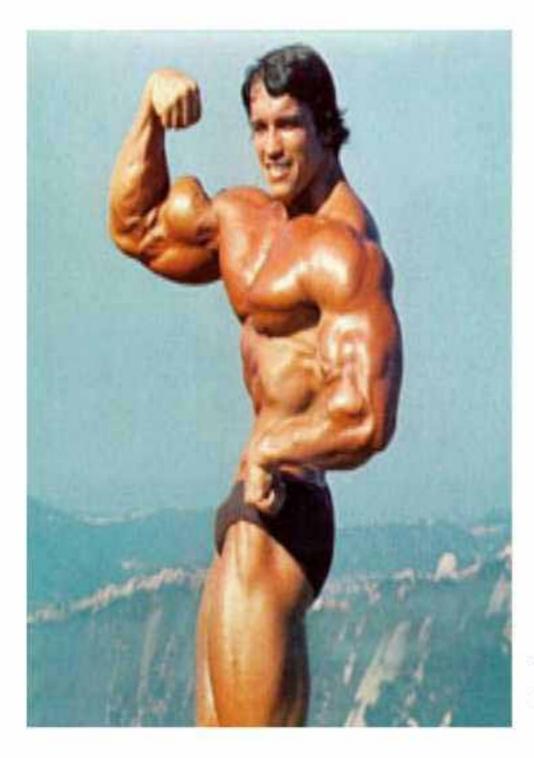


The oldest documented man is Yukichi Chuganji

- died in 2003 at 114 years



#### One key factor may be testosterone



Arnold Schwarzenegger Governor of California

One key factor may be testosterone

In both humans and other species castration is associated

with increased longevity

Shabnam Mausi (First eunuch elected to India's Legislative Assembly)

One key factor may be testosterone

In both humans and other species castration is associated with increased longevity

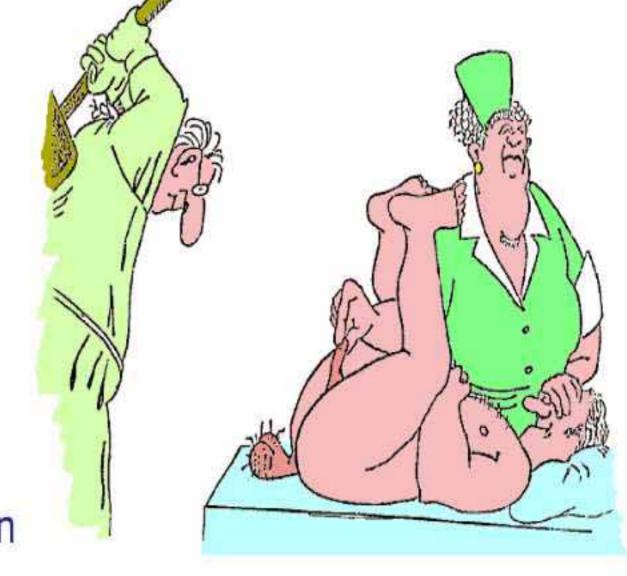
Unlikely to prove a popular means of living longer

One key factor may be testosterone

In both humans and other species castration is associated

with increased longevity

Unlikely to prove a popular means of living longer



Economy castration



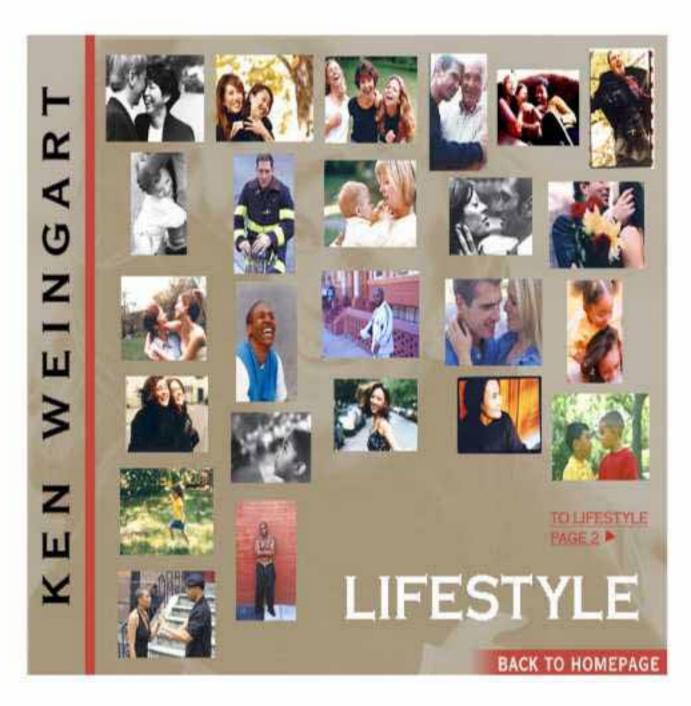
#### Effects of lifestyle and nutrition on ageing

75% of the influence on the ageing process is of a non-genetic origin

#### Effects of lifestyle and nutrition on ageing

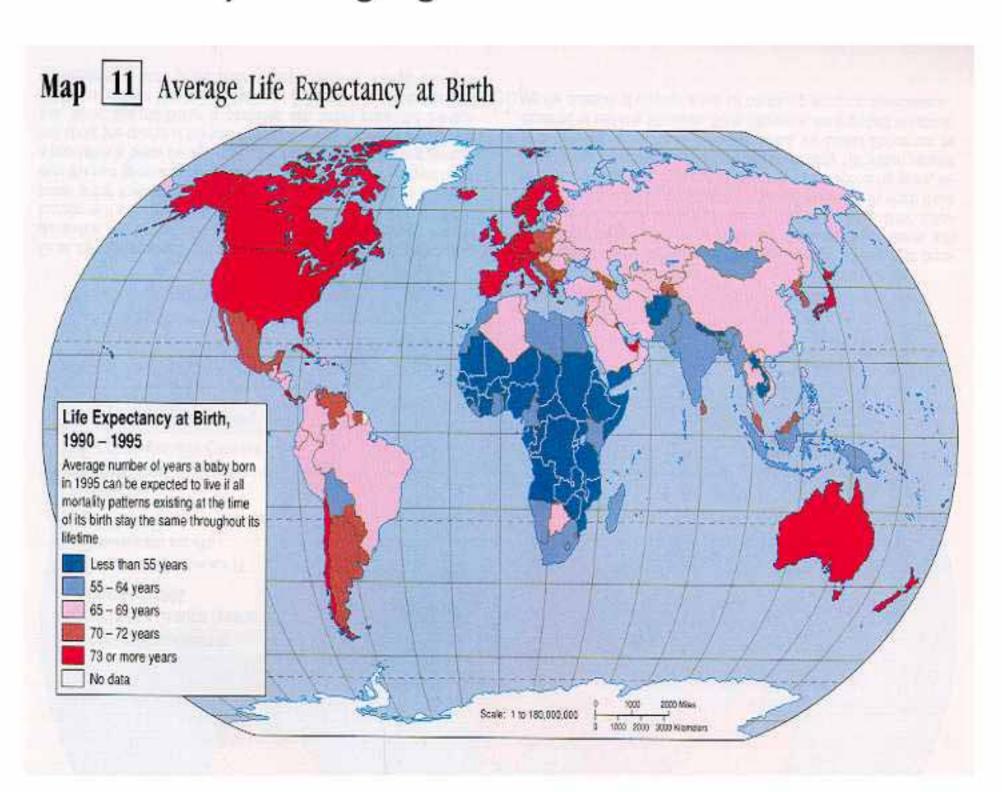
75% of the influence on the ageing process is of a non-genetic origin

Lifestyle factors are likely to play a major part



# Effects of lifestyle and nutrition on ageing

# This is reflected by changing national economies



# Effects of lifestyle and nutrition on ageing

We invest large amounts of money on pills and potions to help prolong healthy life!



# Effects of lifestyle and nutrition on ageing

We invest large amounts of money on pills and potions to help prolong healthy life!

Alcohol, smoking, addictive drugs, high fat foods and sugar and lack of exercise are all bad news





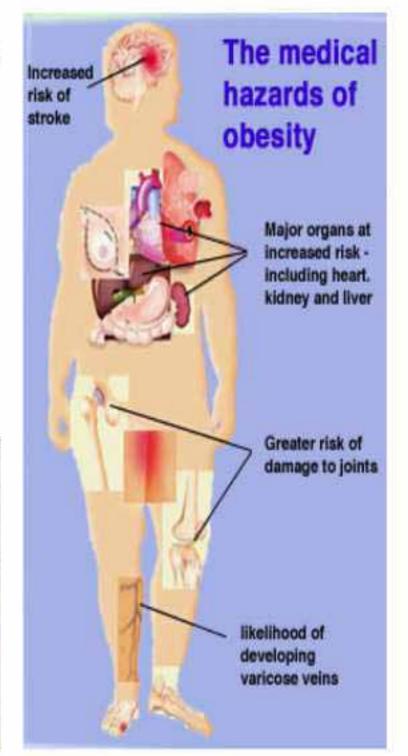








Excessive calorie intake leading to obesity will in general shorten life





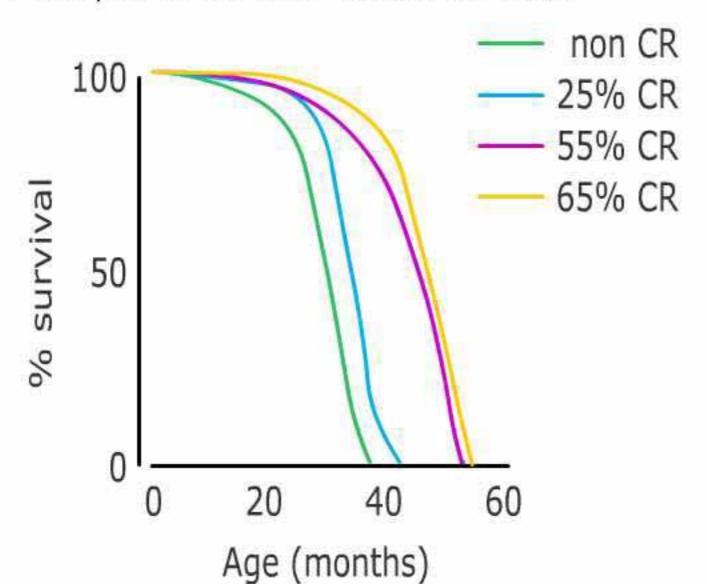






In animals lifespan can be doubled by reducing calorie intake (40-75%)

Life span of CR mice vs non-CR mice





In animals lifespan can be doubled by reducing calorie intake (40-75%)

It reduces IGF-1 levels and expression of genes associated with DNA damage and oxidative stress

In animals lifespan can be doubled by reducing calorie intake (40-75%)

It reduces IGF-1 levels and expression of genes associated with DNA damage and oxidative stress

It increases that of genes promoting protein and energy metabolism and biosynthesis (Lee et al 1999)

Humans? - problem of getting it wrong: anorexia







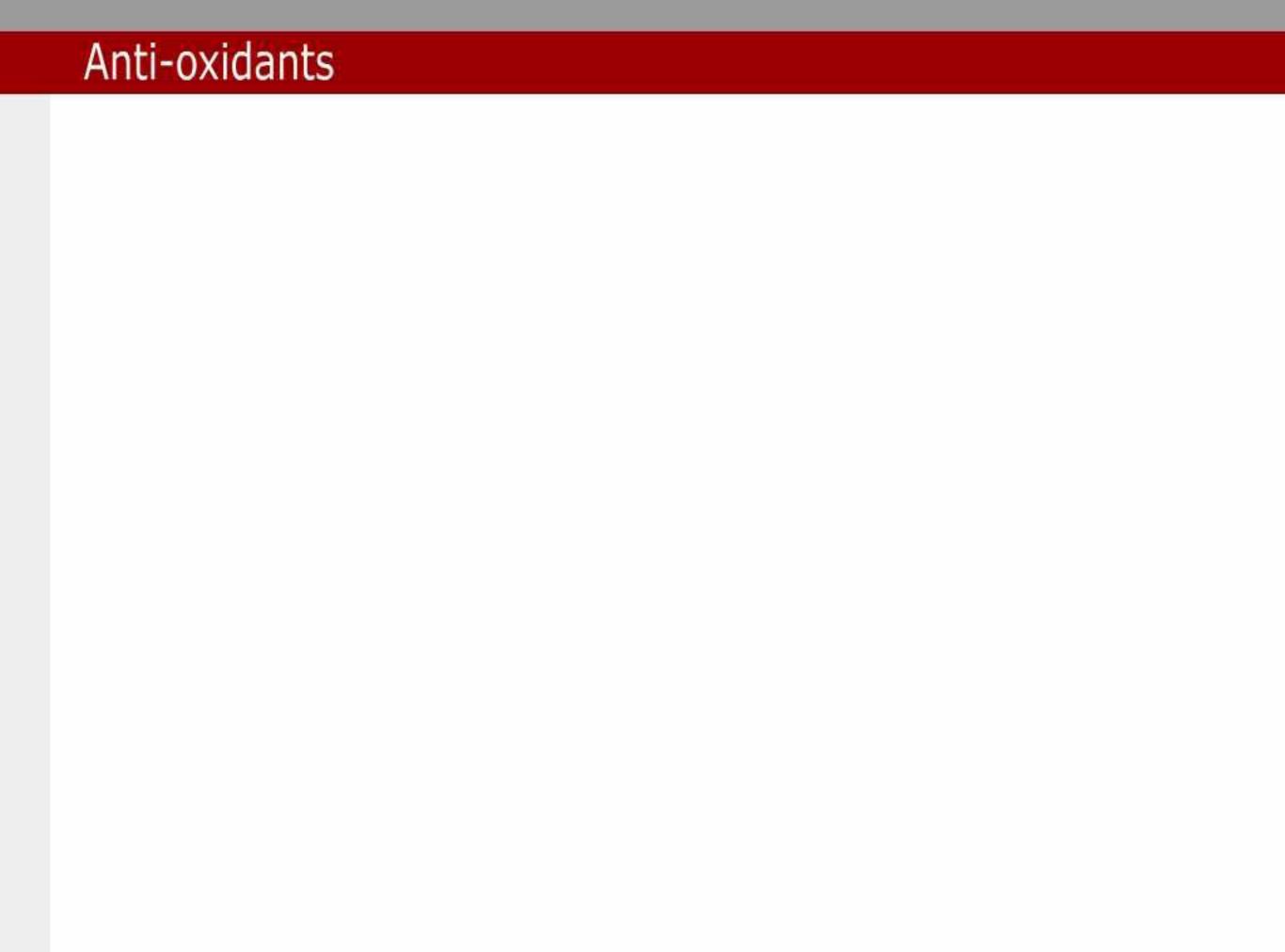




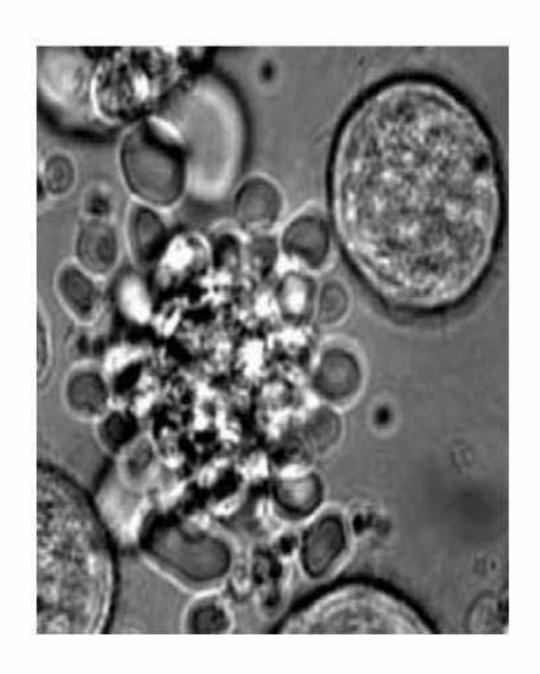
Humans? - problem of getting it wrong: anorexia

Near starvation diet is unlikely to prove a popular panacea for ageing





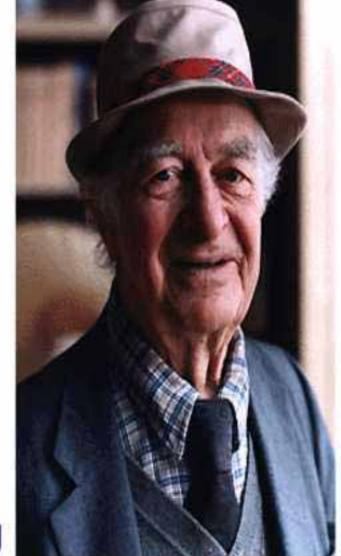
A major cause of cell death is oxidative stress



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Anti-oxidant substances should be beneficial for prolonging

life



Linus Pauling

A major cause of cell death is oxidative stress

Anti-oxidant substances should be beneficial for prolonging life

- vitamin C



A major cause of cell death is oxidative stress

Anti-oxidant substances should be beneficial for prolonging life

- vitamin C
- vitamins A, E and selenium









Low blood Vitamin C levels are strongly predictive of mortality



Low blood Vitamin C levels are strongly predictive of mortality

Efficacious effects of taking mega-dose vitamin C supplements remain controversial



Poor quality early diet low in anti-oxidants reduces longevity in zebra finches





Poor quality early diet low in anti-oxidants reduces longevity in zebra finches

Taking combined vitamin
E and C supplements reduces
chances of Alzheimer's disease
(Zandi et al, 2004)

#### B B C NEWS WORLD EDITION

Last Updated: Tuesday, 20 January, 2004, 02:07 GMT

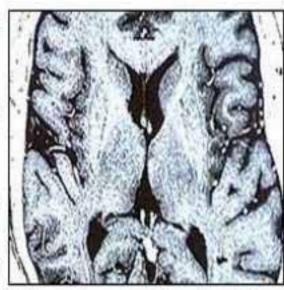
E-mail this to a friend

#### Printable version

#### Vitamins 'cut Alzheimer's effect'

It may be possible to reduce the effects of Alzheimer's disease by taking the right combination of vitamins, US research suggests.

Scientists have found vitamins E and C may protect the ageing brain - but only if taken together.



Alzheimer's causes damage to the brain

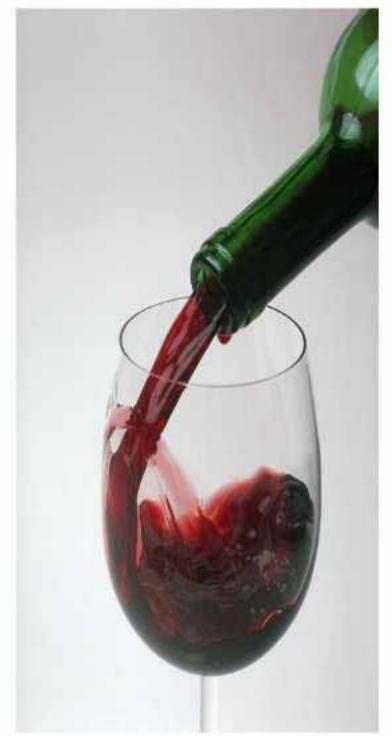
Phenols present in a number of foods can also act as antioxidants



Phenols present in a number of foods can also act as antioxidants

Chocolate taken in moderation can increase longevity





Phenols present in a number of foods can also act as antioxidants

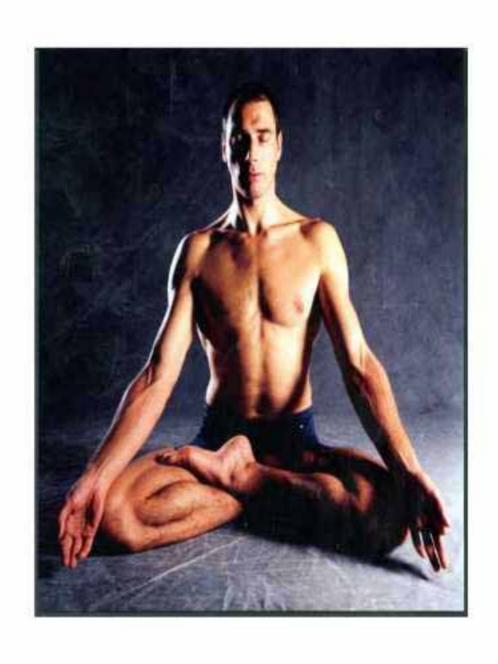
Chocolate taken in moderation can increase longevity

But only by 0.92 years in 7,841 Harvard graduates (Lee, British Medical Journal, 1998)





Most common feature of those who live longest is low stress



Most common feature of those who live longest is low stress

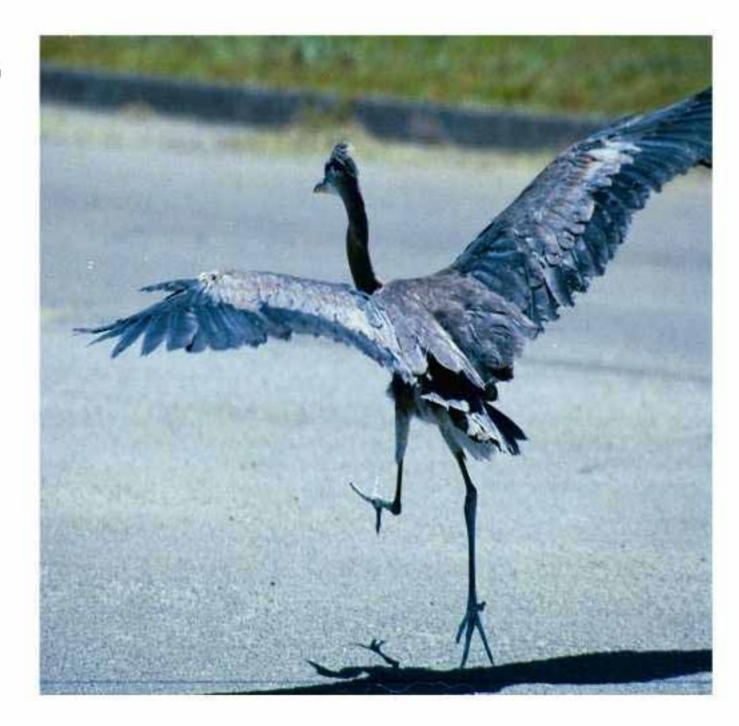
Soldiers in prolonged combat can age as much as 20 years in a few years



Best advice if exposed to constant stress:

Best advice if exposed to constant stress:

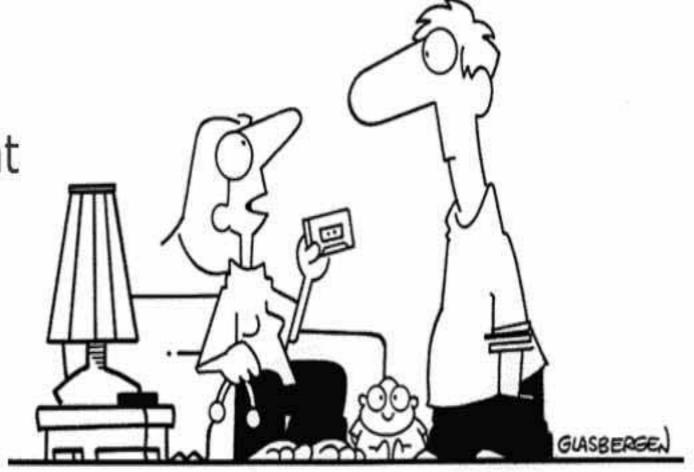
Get out of the situation...



Best advice if exposed to constant stress:

Get out of the situation...

... or try stress management

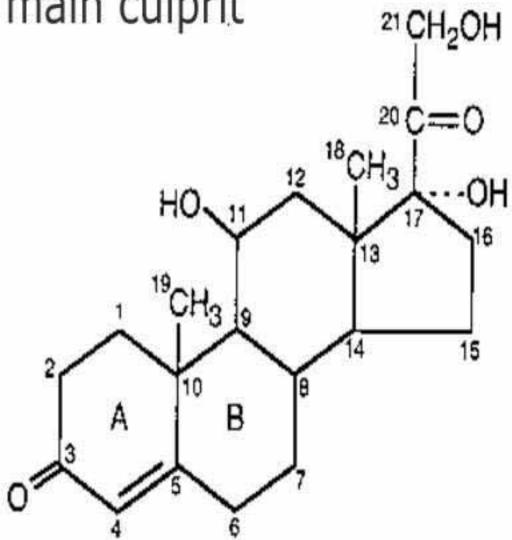


"This is my relaxation tape—
it's the sound of ocean waves crashing
onto the shore, snatching my boss's body off
his beach chair and carrying him out to sea."

Adrenal cortisol release is the main culprit <sup>21</sup> CH<sub>2</sub>OH

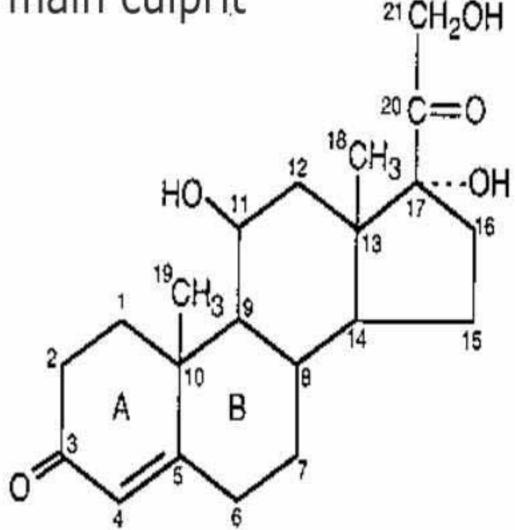
Adrenal cortisol release is the main culprit

It is good in the short term for preparing you for appropriate action...



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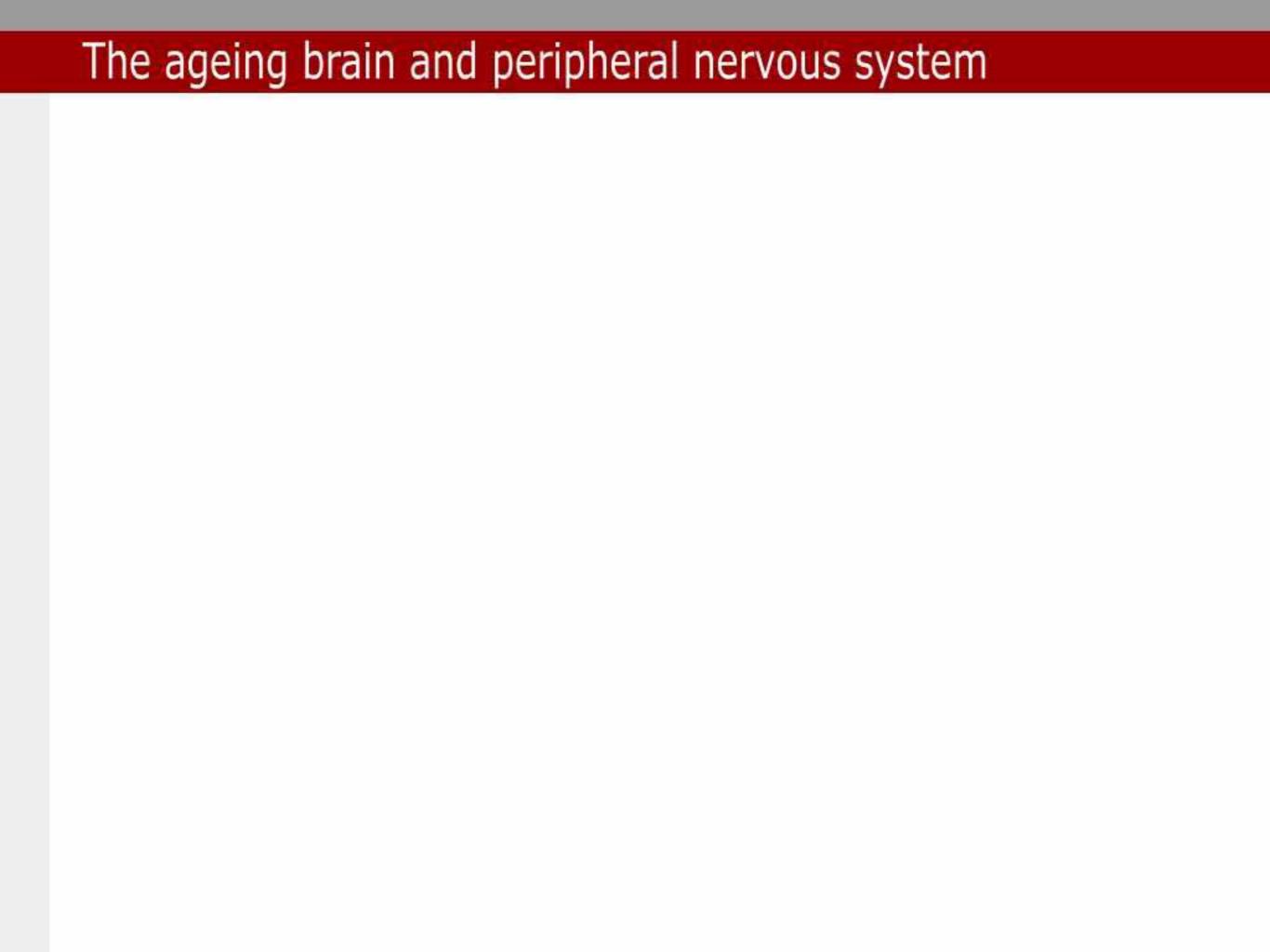
...but bad in long-term because it promotes cell death



## Environmental toxins and food additives

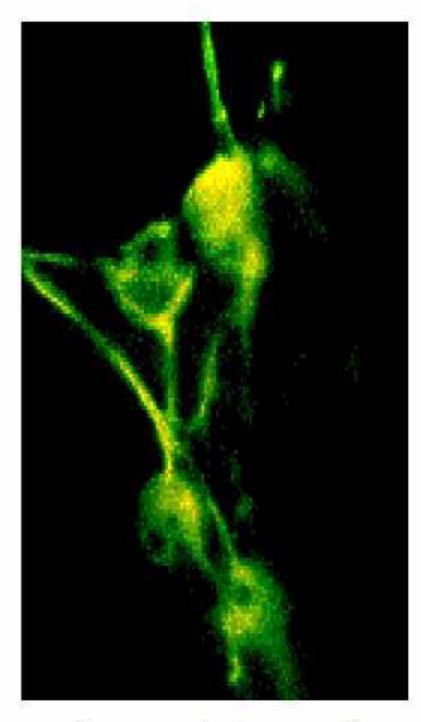
May preserve your body in death but not in life!





# The ageing brain and peripheral nervous system

Most adult brain cells, like those of heart muscle, do not divide

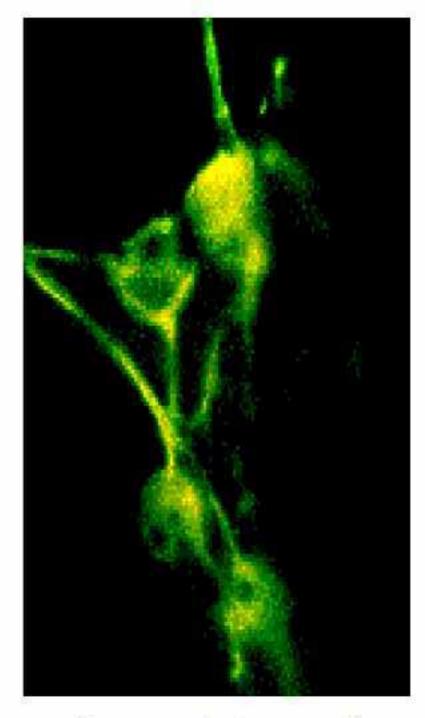


Neuronal stem cell

# The ageing brain and peripheral nervous system

Most adult brain cells, like those of heart muscle, do not divide

Progressive cell loss occurs as we age (up to 35% in some regions)



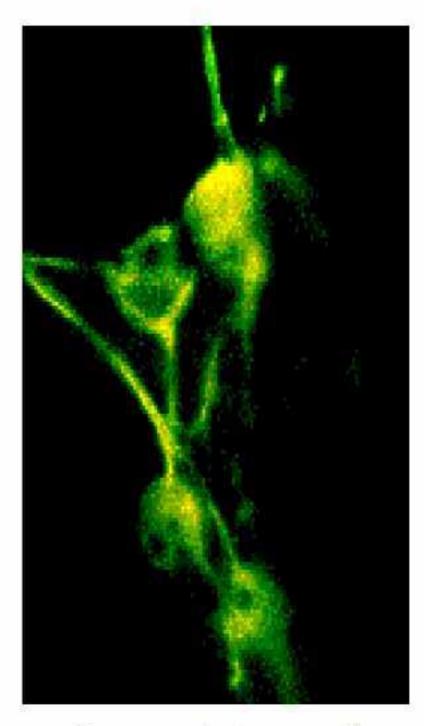
Neuronal stem cell

# The ageing brain and peripheral nervous system

Most adult brain cells, like those of heart muscle, do not divide

Progressive cell loss occurs as we age (up to 35% in some regions)

Altered connectivity and cell function are more important



Neuronal stem cell

Common neurological problems in elderly humans are:



Common neurological problems in elderly humans are:

Slowed reaction time



Common neurological problems in elderly humans are:

Slowed reaction time Slowness and narrowed range of perception



Common neurological problems in elderly humans are:

Slowed reaction time Slowness and narrowed range of perception Reduced sense of smell



Common neurological problems in elderly humans are:

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Impairment of fine co-ordination and agility



Common neurological problems in elderly humans are:

Slowed reaction time
Slowness and narrowed range of perception
Reduced sense of smell
Reduced motor activity
Reduced muscular power
Impairment of fine co-ordination and agility
Thinness of leg muscles



#### So what kinds of mental functions are affected?

On the down side:

Slowed reaction and decision times

Forgetting new information

Difficulty in active memory but not passive processing

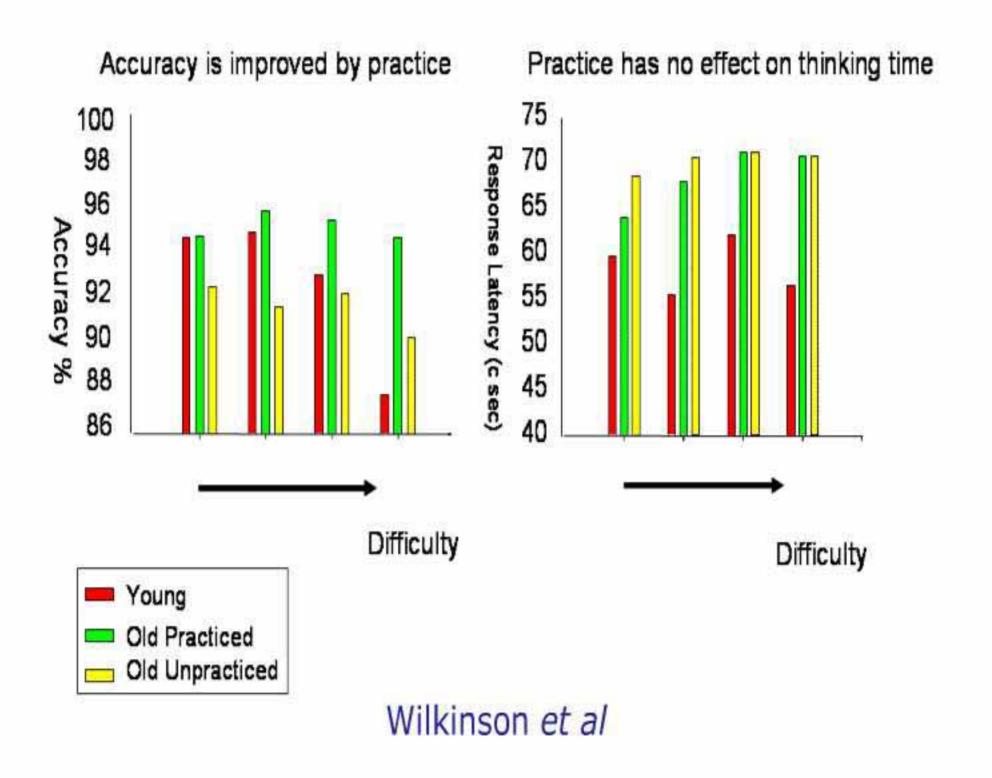
Decline in ability to solve difficult problems

Decline in spatial learning and memory

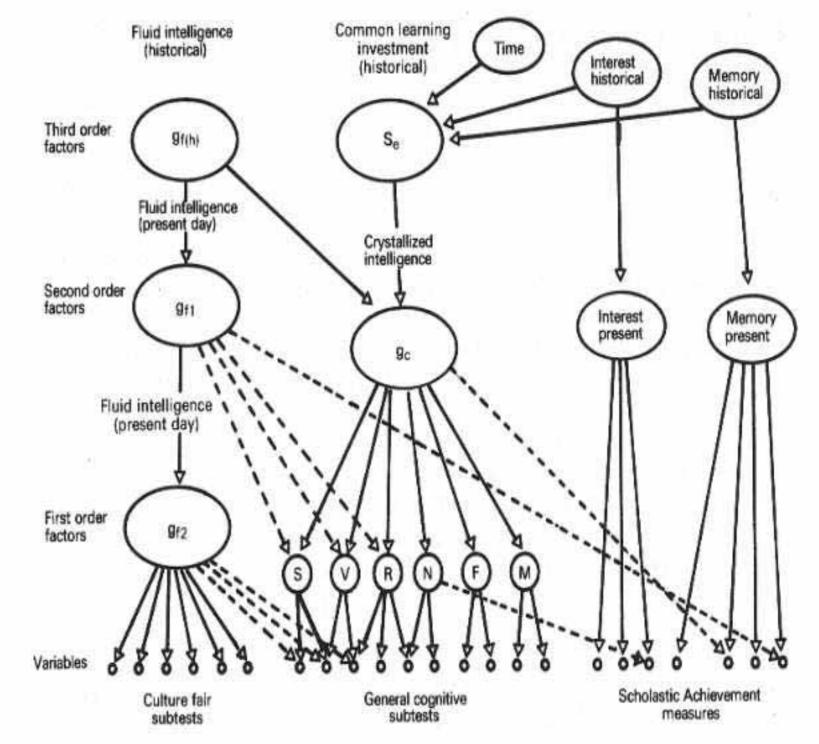
Decline in both global and selective attention

Increased incidence of depression

## There is considerable support for this principle



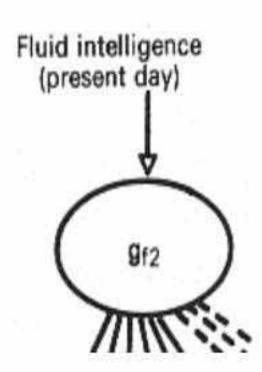
Difference between crystallised (Gc) and fluid (Gf) mental abilities



Difference between crystallised (Gc) and fluid (Gf) mental abilities

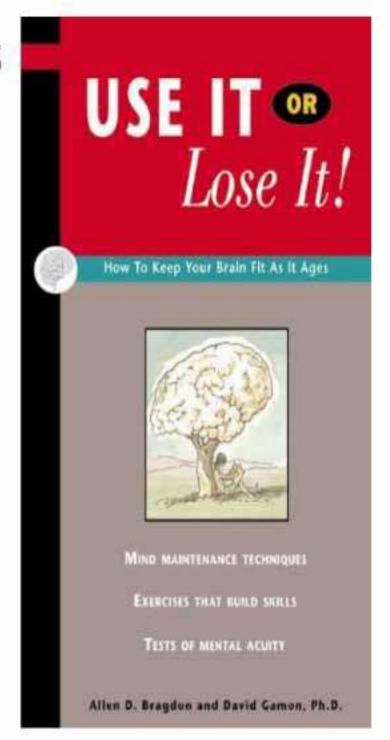
Gc (knowledge of past events) does not decline with normal ageing

Gf (ability to apply novel strategies for learning new information) does decline



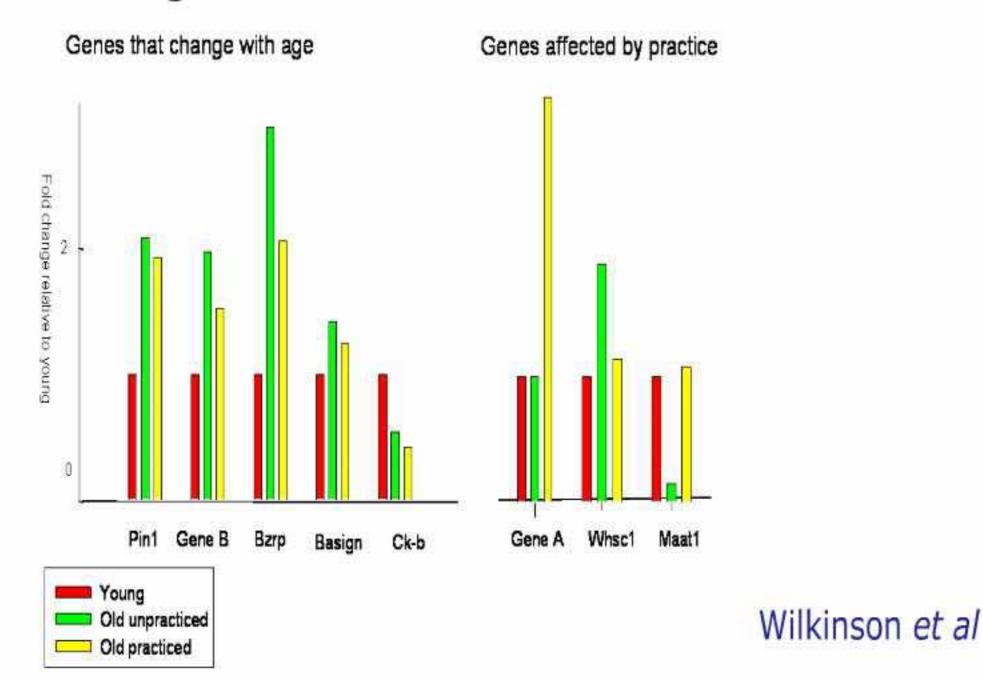
However, if you practice building strategies during early life you retain them

You are likely to be able to use these for most new information



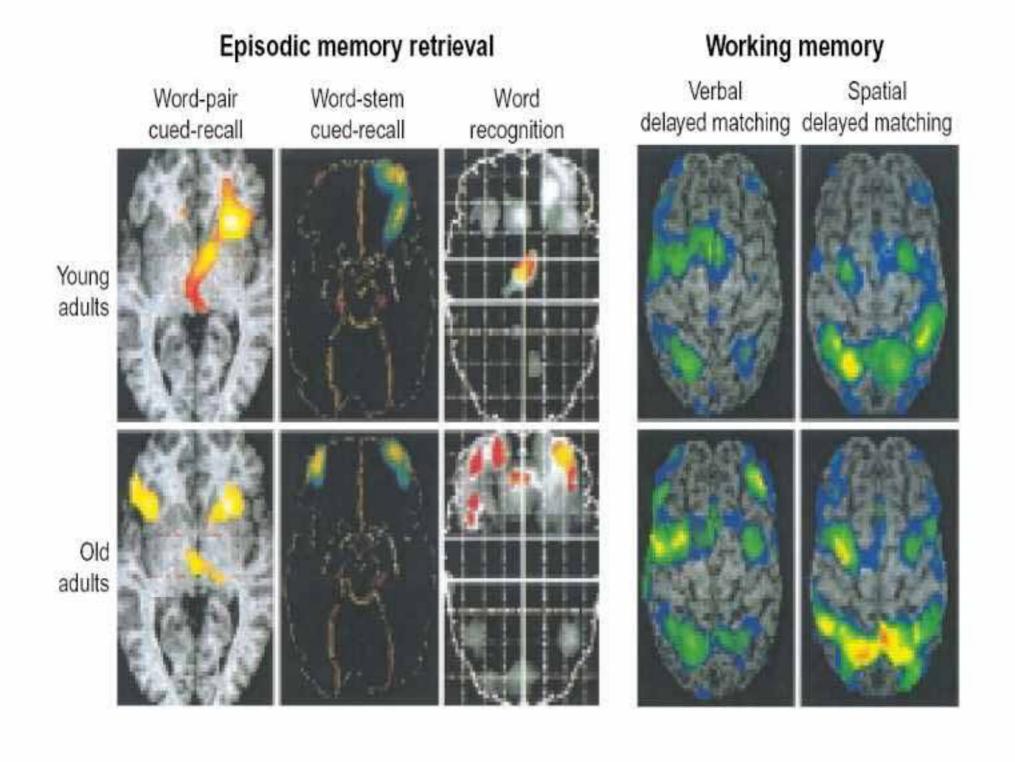
#### Genes associated with cognitive decline

Gene and protein screening studies have been successful in identifying new targets



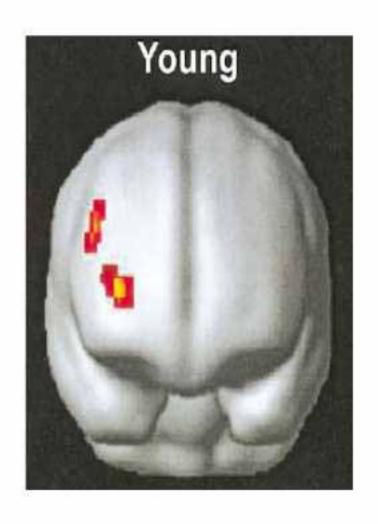
## Changes in the way the ageing brain processes information

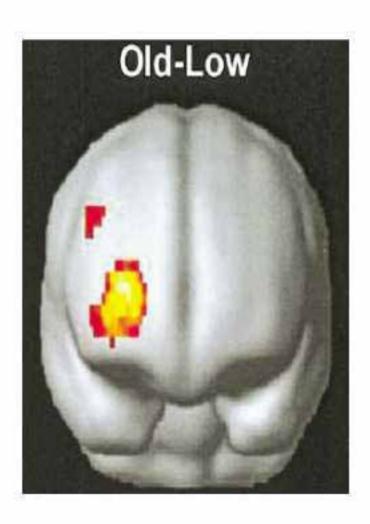
## Good old brains do it differently from young ones

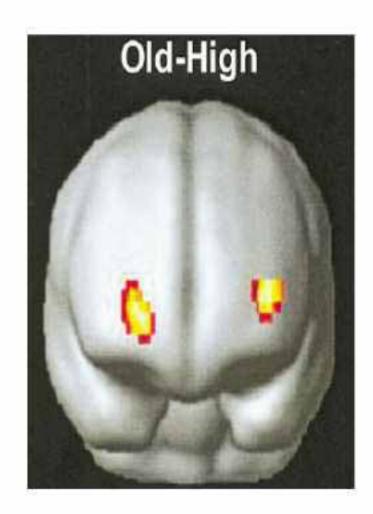


# Changes in the way the ageing brain processes information

#### Good old brains do it differently from young ones





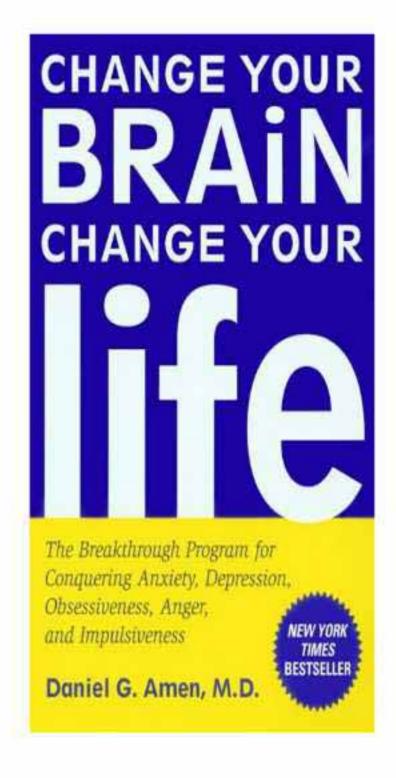


## Changes in the way the ageing brain processes information

Having to use more of the brain may explain:

Why age slows down processing information...

... and increases creativity



Time can subjectively pass more quickly as we age

Exponential progression of time perception equivalents ? 10-20 = 20-40 = 40-80



Time can subjectively pass more quickly as we age

Exponential progression of time perception equivalents ? 10-20 = 20-40 = 40-80

Perception of an extended life from 80-160 same as 10-20?

Age decline in registering routine events may make things appear to happen faster

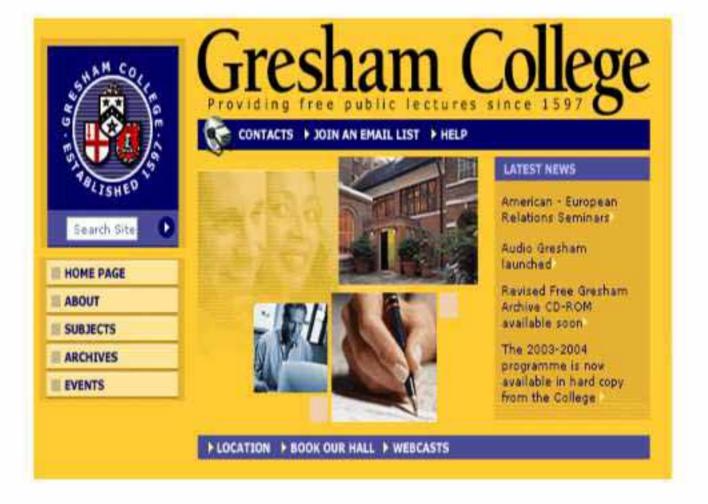
Each day's events flash by in a blur of inattention!



#### Solutions:

Make sure you try to attend to and remember more daily

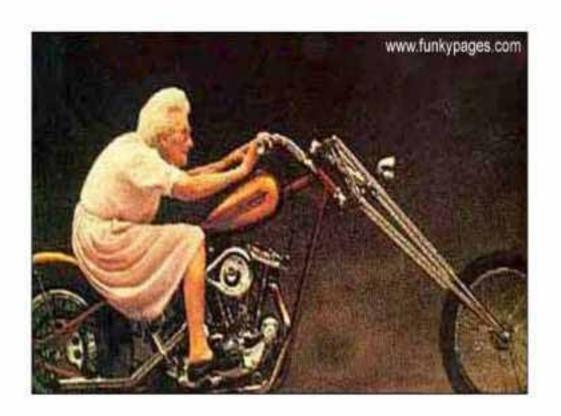
events



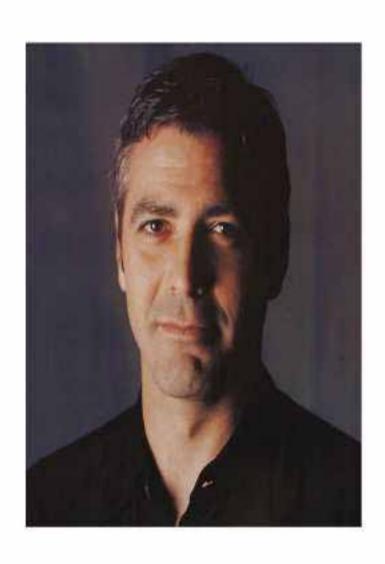
#### Solutions:

Make sure you try to attend to and remember more daily events

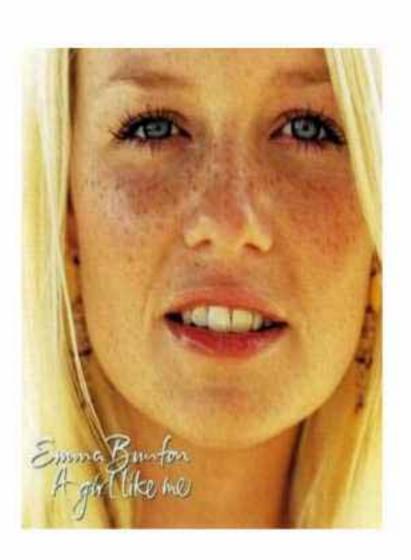
Get more involved in stimulating life events!



# Beauty is only skin deep







Beauty is only skin deep

Increasing concern with disguising the external physical signs of ageing



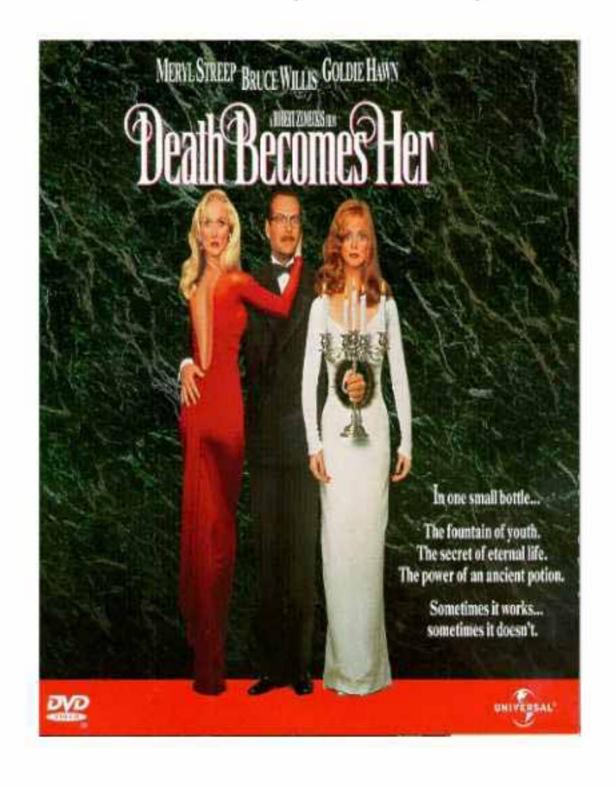


Beauty is only skin deep

Increasing concern with disguising the external physical signs of ageing

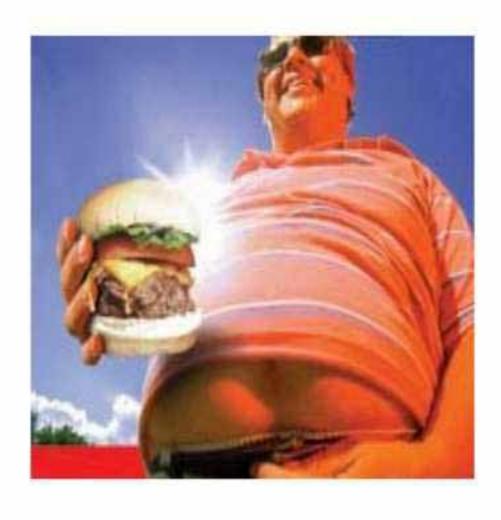
Ageing skin, connective tissue and muscle changes are inevitable although variable in degree and time course

Outrageous claims made for pills and potions



Outrageous claims made for pills and potions

Experts: diet, exercise and avoid too much sun







Outrageous claims made for pills and potions

Experts: diet, exercise and avoid too much sun

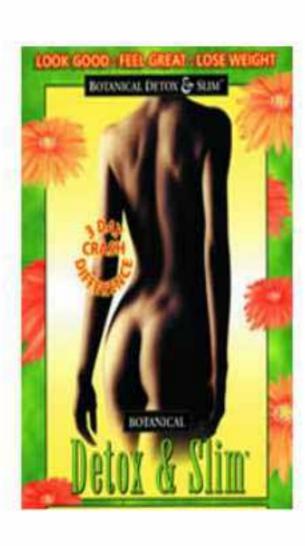
Obsessive concern with youthful looks often linked with difficulty in adjusting to different phases of life

With each phase some advantages are lost while others can be gained

Such inflexibility may prevent us from adapting beneath the surface

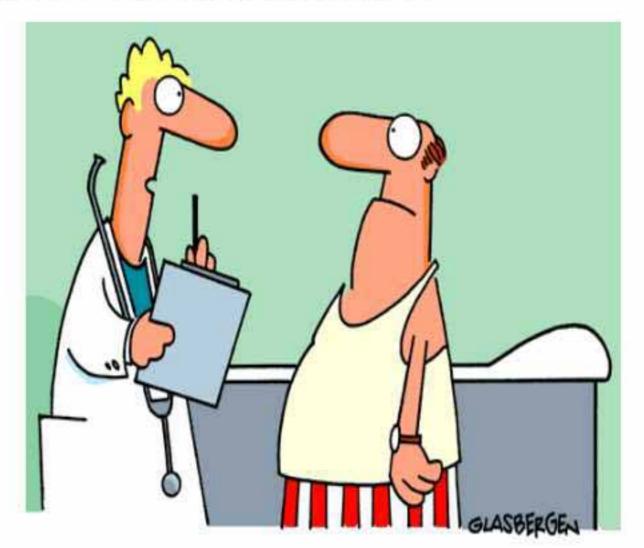
Even if we can invent effective surgery free methods of maintaining the exterior...







... the importance of adjusting positively to the changing phases of our lives will not diminish

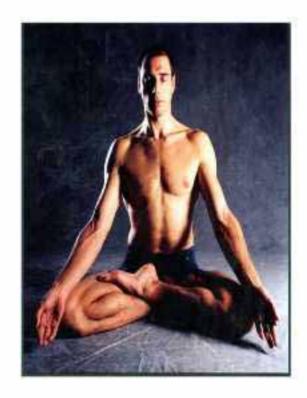


"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"

General positive lifestyle features will also still be essential









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

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 your brain

Ageing brains can be more creative

The key to ageing gracefully is accepting and maintaining a positive attitude to change

