Why we get old and die, and what to do about it

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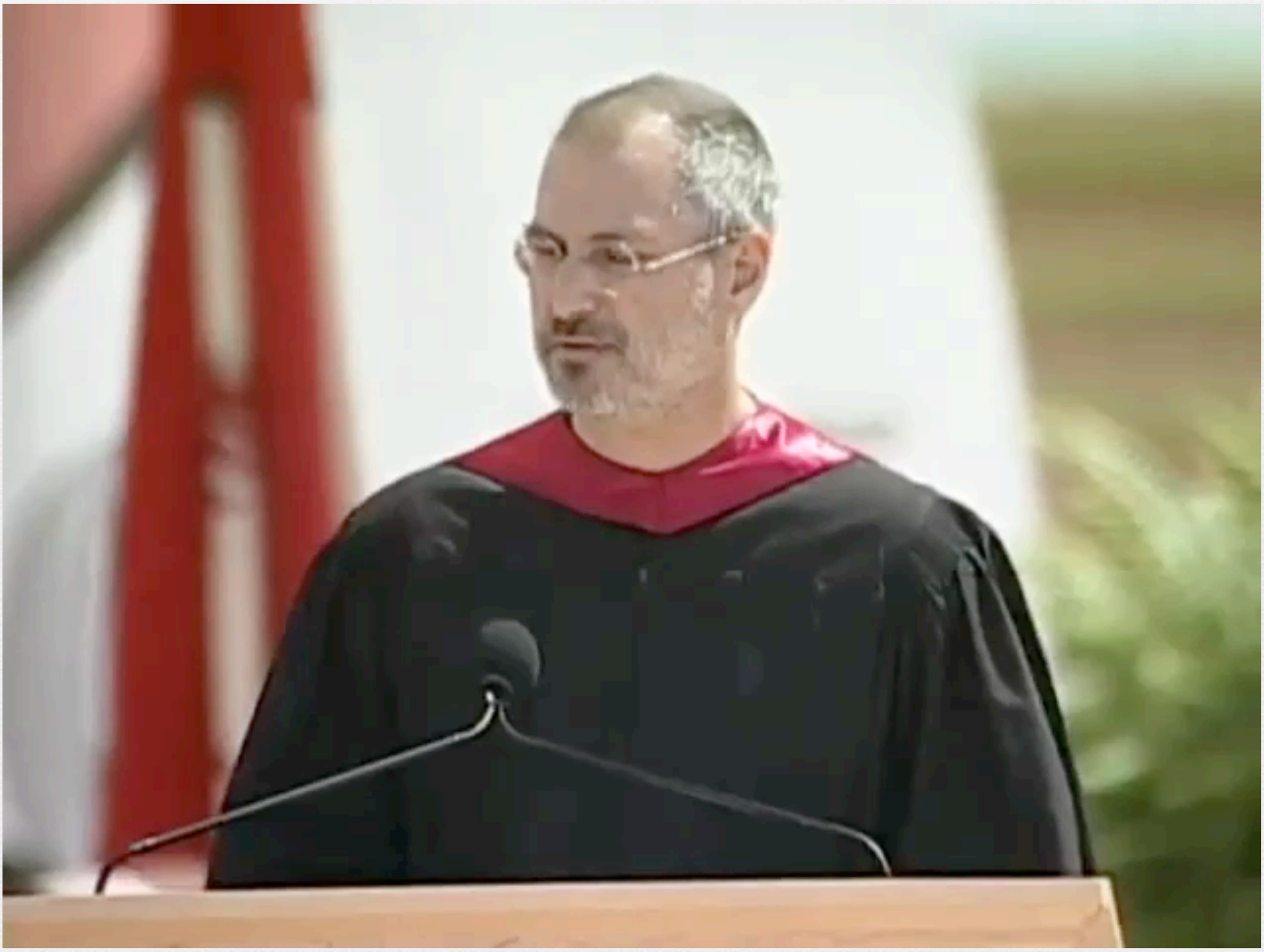
To scroll the notes: U for up, D for down

X switches displays

B goes to black screen

I would like to start by paying homage to a visionary who died not so long ago of pancreatic cancer. Steve Jobs, CEO of Apple, was 56 when he passed away in October 2011.
Here is a short video clip, part of a speech he gave to the graduating class at Stanford University in 2005. He talked about being confronted with his own mortality when told he had cancer, and his subsequent relief when he learned that it was curable.



“No one wants to die. Even people who want to go to heaven don't want to die to get there. And yet death is the destination we all share. No one has ever escaped it. And that is as it should be, because Death is very likely the single best invention of Life. It is Life's change agent. It clears out the old to make way for the new. Right now the new is you, but someday not too long from now, you will gradually become the old and be cleared away. Sorry to be so dramatic, but it is quite true.”

Steve Jobs (1955-2011), CEO of Apple, Inc.
Commencement Address, Stanford University,
2005-6-12

Here is what he said.

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The highlighted words are, “Death is very likely the single best invention of life.”

I understand this to mean that Jobs believed that death has been built in by evolution. I think so, too.

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And these words, “It clears out the old to make way for the new”. This is my understanding of the why, why evolution designed us to die.

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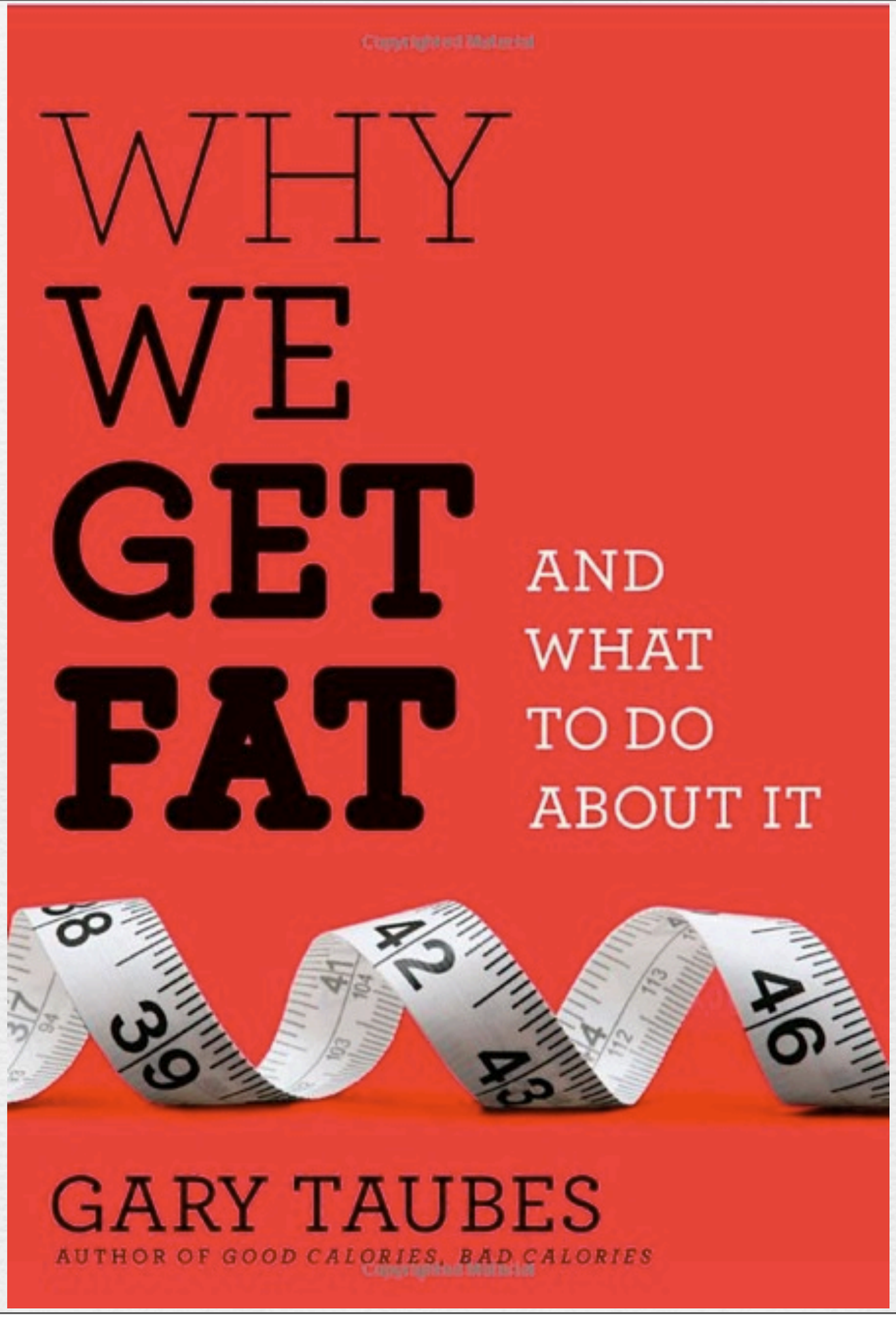
And finally this bit, “You will gradually become the old and be cleared away”. This is the answer to how, how evolution arranged for us to die. We die through aging, assuming that accident, infection, or starvation haven’t knocked us off first.

Why we get old and die, and what to do about it

Why did I choose this particular title for my talk?



I borrowed it from this book, “Why we get fat, and what to do about it”, with the permission of its author, Gary Taubes. I’ll get back to this book later.

Learning Objectives

- to look at why our genes want us to age and die quickly;
- explore some of the ways in which aging can be postponed and lifespan increased;
- consider the surprising consequences in terms of stress, diet, and behaviour.

The management wanted me to write down the learning objectives for my talk today, so here they are.

They're also keen about disclosing any conflicts of interest. Unfortunately, nobody wants to give me any money, so I have no conflicts of interest to declare.

At the end, I'll put up a slide with my email address, and also with a link so you can download a pdf of these slides along with my notes.

Evolution arranges for members of a species to do the work of reproduction and then to get out of the way, that is, die, in order to not compete for resources with their offspring. Aging is the mechanism used by evolution to ensure a rapid death in the wild, once the reproductive phase is over, for sexually reproducing species. However, when food is scarce, longevity increases and reproduction slows down, awaiting the return of good times. Insulin is a signal that early in life promotes growth and reproduction but later on promotes aging, by its action of suppressing those repair and replacement mechanisms in each cell which counteract the wear and tear that is aging.

Here is a summary of what I'm going to be talking about today.

Evolution arranges for members of a species to do the work of reproduction and then to get out of the way, that is, die, in order to not compete for resources with their offspring. Aging is the mechanism used by evolution to ensure a rapid death in the wild, once the reproductive phase is over, for sexually reproducing species. However, when food is scarce, longevity increases and reproduction slows down, awaiting the return of good times. Insulin is a signal that early in life promotes growth and reproduction but later on promotes aging, by its action of suppressing those repair and replacement mechanisms in each cell which counteract the wear and tear that is aging.

When food is plentiful, so is circulating insulin, and individual members age and die as programmed by evolution. When dietary carbohydrates are high, insulin levels go above normal, and aging proceeds more rapidly, with higher rates of type 2 diabetes, cancer, cardiovascular disease, and dementia. Eating less, i.e. caloric restriction, extends longevity in many species, and suppresses insulin levels. Substances which lower insulin levels, such as metformin, aspirin, and coffee, and other compounds which interfere with the insulin signalling pathway, such as rapamycin (an immune suppressant) and resveratrol (found in red wine), have also been found to decrease mortality. Restricting dietary methionine, an essential amino acid, may also increase longevity, again perhaps through insulin signalling.

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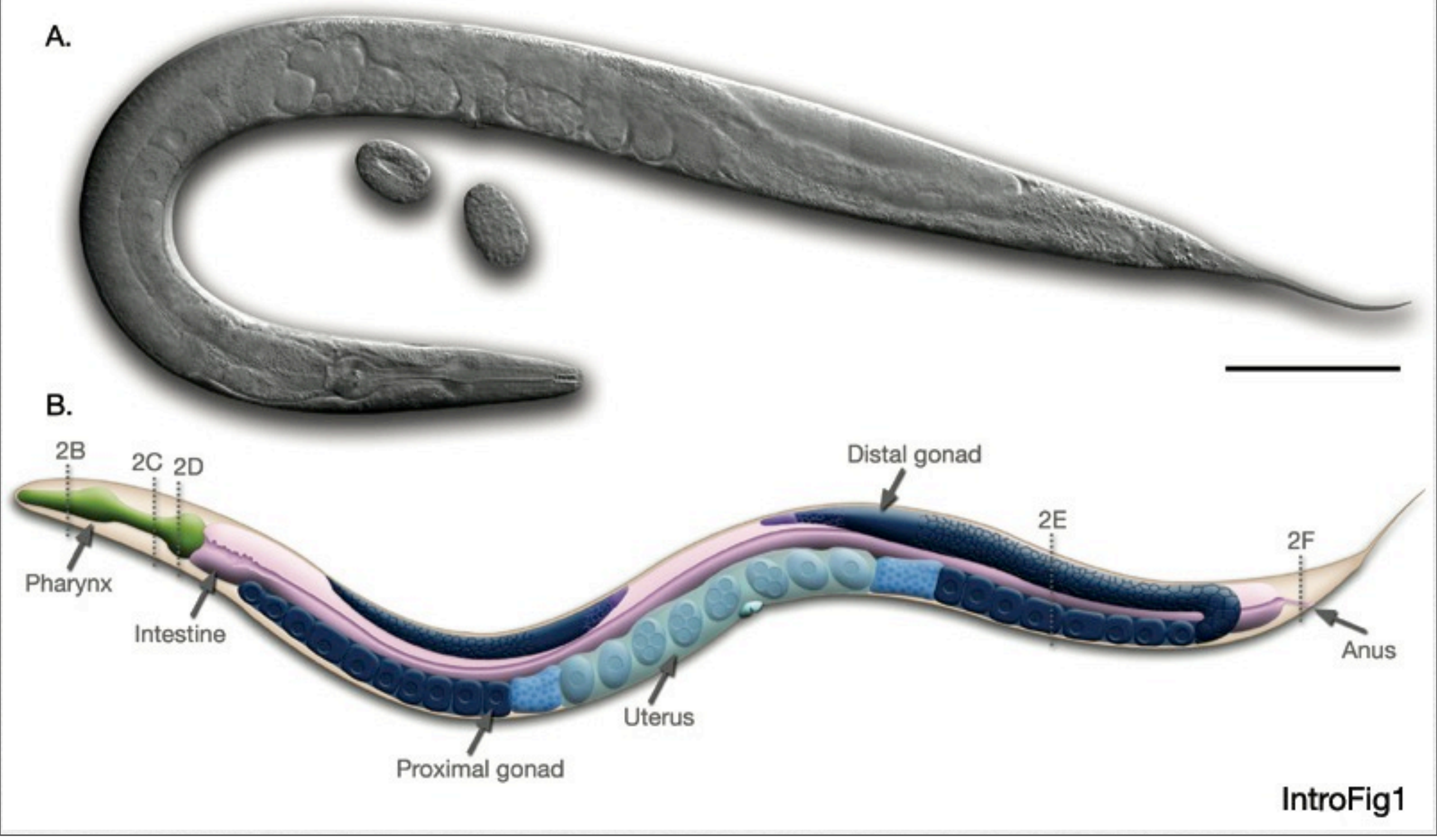
So, let’s get started.

Drosophila Melanogaster

To start, let me introduce you to some of the animals commonly used in aging and longevity studies. This is a photo of a fruit fly, scientific name Drosophila Melanogaster, which is Greek for dark-bellied dew lover.

This species is a favourite of researchers since about 1910, because it lays lots of eggs, breeds a new generation every ten days or so, takes little room in the lab, and it’s easy to separate males from females visually.

Caenorhabditis Elegans



And here is another animal, C. Elegans for short.

It's a tiny roundworm, only about 1 mm long. It's been a favourite of researchers since the 1970s because it's simple, easy to grow in bulk, and easy to study. It has only 959 cells altogether, of which 302 are neurons. And it's transparent!

Aging research, though, benefits from two properties: one, it can have offspring every 4 days, and it only lives for two or three weeks; second, under conditions of stress, like not enough food or overcrowding or too hot or too cold, it can morph into a type of larva stage called the dauer state. In this state, the worm is resistant to these stresses and can live up to 10 times its usual lifespan. However, in this state it is infertile, it cannot reproduce.

What researchers think is that, when times are tough, the organism should just wait it out, stop reproducing and conserve its energy, until the good times return.

Relatively new on the scene in aging research are these wrinkly things called African naked mole-rats. About 3-4 inches long, they live in colonies of 100 to 300 animals, and live up to 28 years in the lab, making it the longest-living rodent. They seem to be immune to cancer and show very little aging. Interestingly, only one female in the entire colony, the queen, can reproduce; she lives up to 17 years in the wild, having one litter per year. Other than 1 to 3 males who are also fertile and long-lived, the other animals in the colony are infertile and typically live only 2 to 3 years in the wild. When the queen dies, the other females fight, even to the death, and the winner becomes the new queen. She adapts over a period of 6 months or so, becoming bigger and fertile, and of course longer-lived.

Take-away message:

- Lifespan is likely under genetic and epigenetic control
- Lifespan and reproduction are tied together

This slide has builds!

There are two messages I would like you to retain from the example of the worm which has a long-lived but infertile dauer stage, and the naked mole-rat where females who become queen become fertile and increase their lifespan by 5 to 8 times:

♥

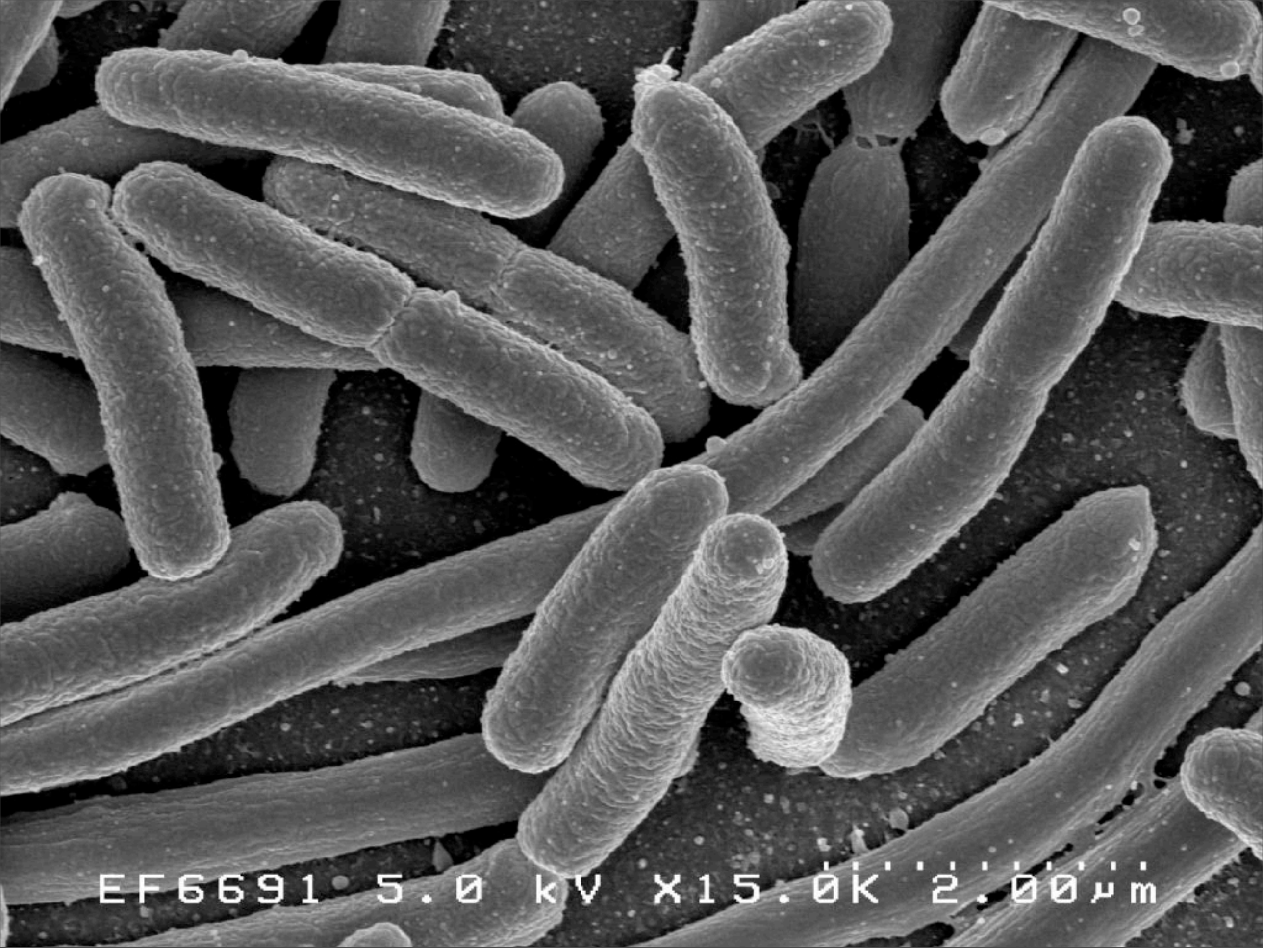
the first is that lifespan can be adjusted during the lifetime of an individual, which suggests it's under some kind of epigenetic and genetic control;

♥

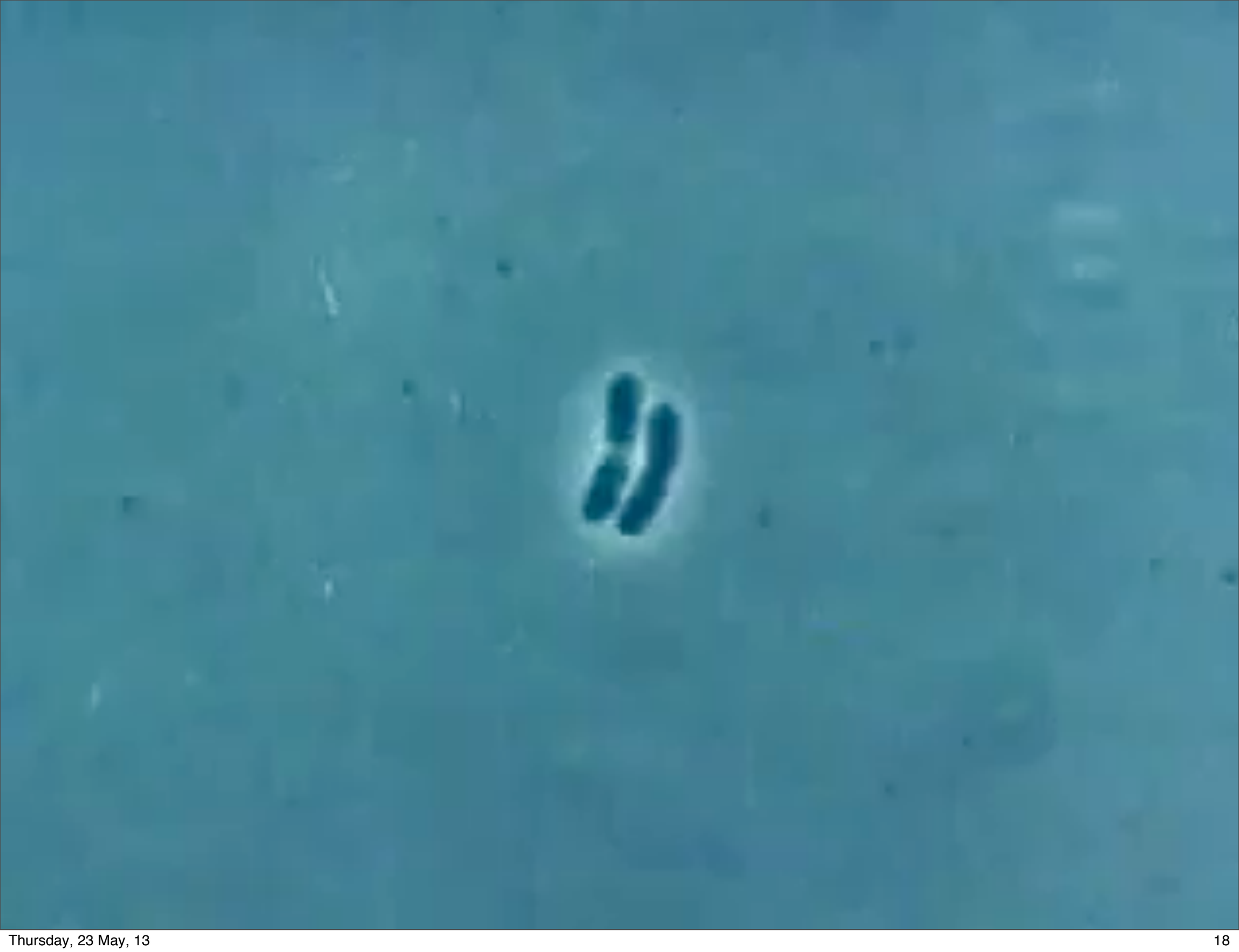
the second is that reproduction and lifespan are linked somehow.

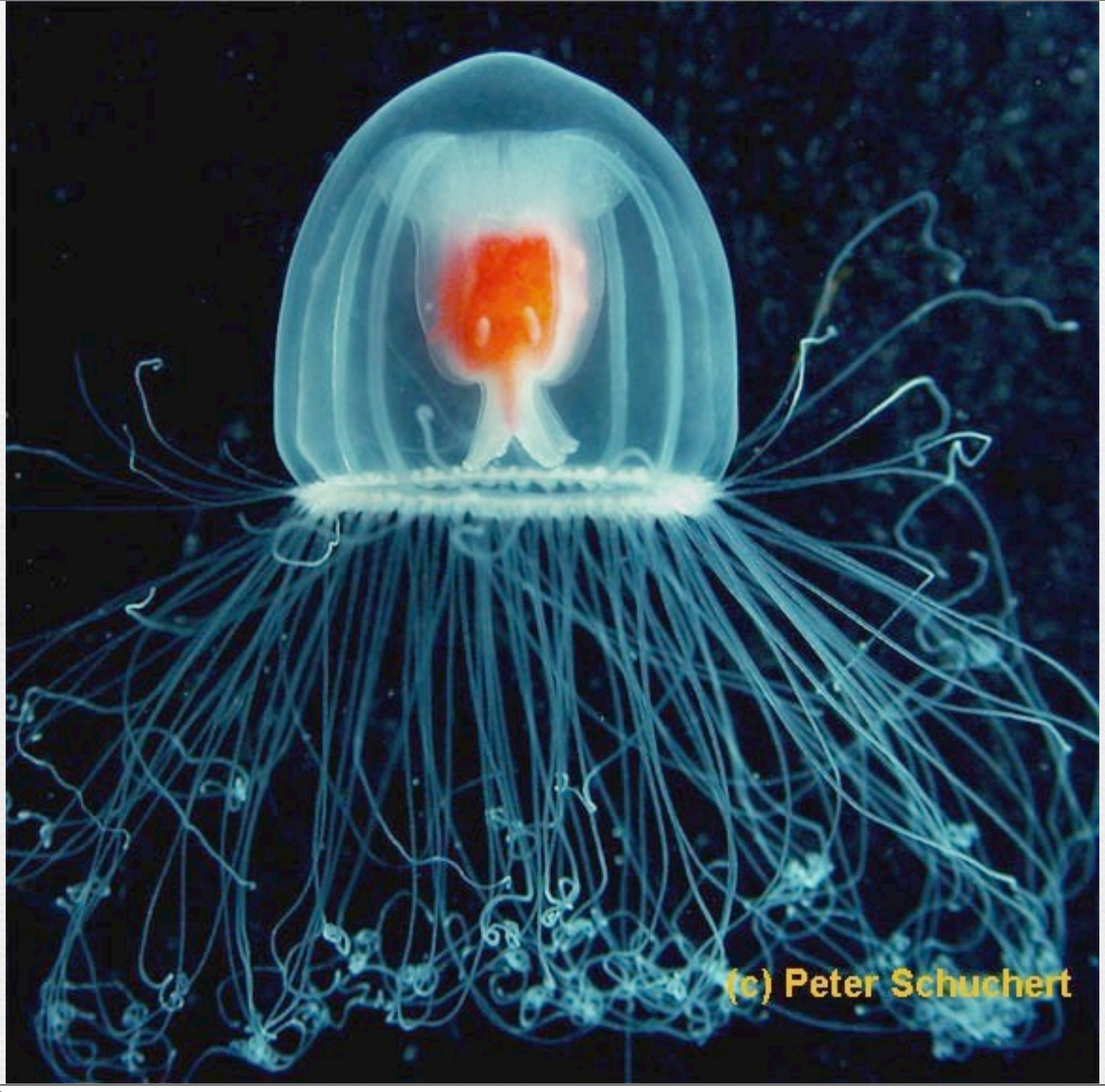
As Steve Jobs pointed out, no one wants to die. Here's the poster for a recent movie in the Pirates of the Caribbean series. "On Stranger Tides" is about a quest for the fountain of youth. This theme, of regaining lost youth and health, or becoming immortal, has inspired countless books, comic strips, computer games, and movies.

Benjamin Franklin wrote "The only two certainties in life are death and taxes." But is this really true?



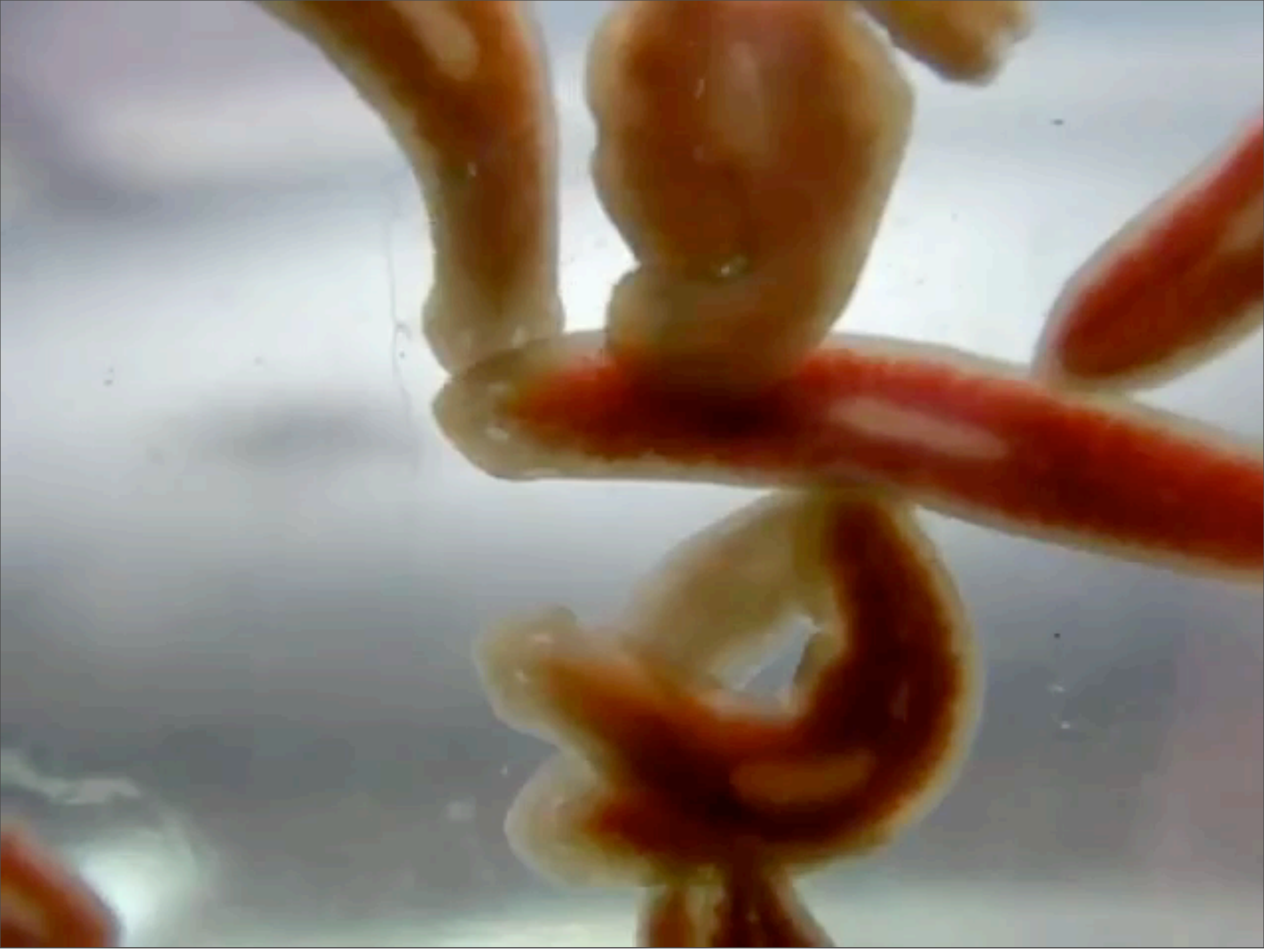
Here is a scanning electron microscope image of E. Coli bacteria. Bacteria are immortal. A single bacterium splits into two identical daughter cells, each of which further splits. You can see several in various stages of division. ☞ This process, also called fission, continues indefinitely, which means that the bacterial colony is essentially immortal, although of course individual cells and even the whole colony can be killed or starved or poisoned. But under the right conditions, bacteria don't die. They don't even age.





Are there other immortal species? The Turritopsis Nutricula is known as the “immortal jellyfish” because even once sexually mature,

it can revert back to a polyp, its first life stage, and it can repeat this process over and over, which makes it immortal for all intents and purposes.



Then there are flatworms, which are able to regenerate every part of their body except the head, from a relatively small number of cells. In the laboratory, it has been possible to regenerate a complete worm from a single cell! Clearly, this is a subject of intense study, with the goal of learning how humans might be able to regenerate limbs or other organs.

Some species, although not immortal, can get extremely old, like the Bristlecone pine. Individual trees have been found which are over 4800 years old, based on counting growth rings. However, bristlecone pines do appear to age.

Aging: what is it? There seems to be general agreement, dating back to the 19th century, that aging is the result of accumulated wear and tear.

Thomas Kirkwood

- "Ageing is not programmed but results from accumulation of somatic damage, owing to limited investments in maintenance and repair."

Tom Kirkwood is an English biologist who made his contribution to the biology of aging by proposing the concept of the Disposable soma. He believes that somatic damage causes aging.

Leonard Hayflick

- "There is a huge body of knowledge indicating that age changes are characterized by the loss of molecular fidelity."

Leonard Hayflick is known for discovering that human cells divide for a limited number of times in culture, typically only 40 to 60 divisions. This is known as the Hayflick limit, and it is believed to be due to telomeres, which are regions of DNA on the ends of chromosomes. These telomeres get shorter with each cell division, and when they have been shortened to some critical size, no more cell division is possible.

Hayflick writes that the loss of molecular fidelity results in aging. In other words, wear and tear.

Wear and tear

- injuries, infections
- DNA damage
- RNA damage
- accumulation of breakdown products, eg lipofuscin
- cross-linking of proteins
- free radicals

What kinds of wear and tear?

For multicelled organisms, injury and infection take their toll.

At the level of individual cells, there are processes such as DNA and RNA damage, which can be caused by ionizing radiation, viruses, or chemicals; accumulation of breakdown products which then uselessly take up space in cells; cross-linking of proteins which make up enzymes, receptors, and structural components, thus impairing their normal functioning and possibly inhibiting their breakdown. Free radicals are molecules possessing an extra electron, which causes that molecule to react with other molecules in highly volatile and destructive ways.

What about immortal organisms?

- repair and replacement mechanisms undo damage caused by wear and tear

This slide has a build!

So if wear and tear at the level of the whole organism as well as at the cellular level causes aging, does that mean that immortal organisms do not have wear and tear?

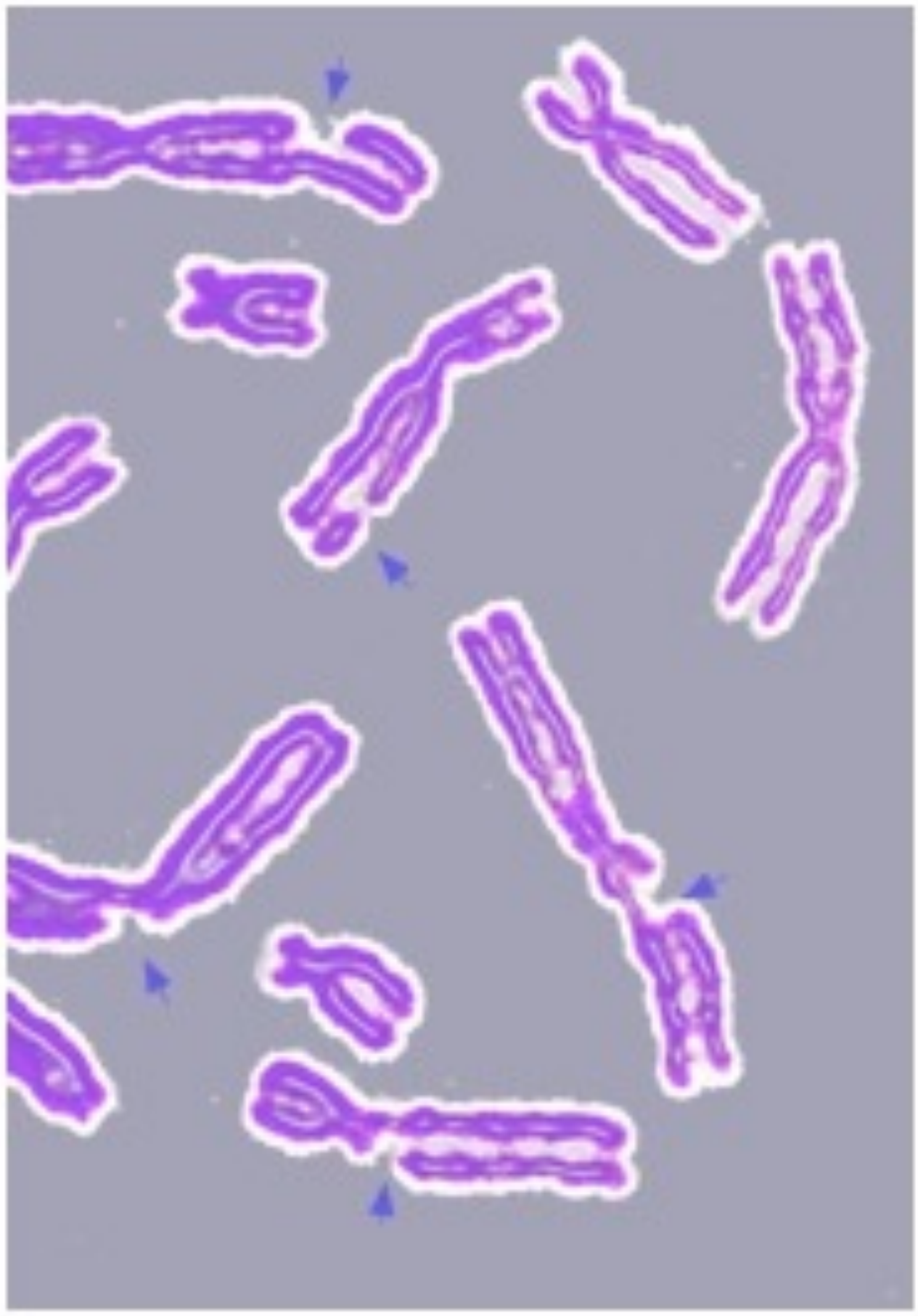
♥

No, not at all. What immortal organisms such as bacteria have are very effective repair and replacement mechanisms which can undo many kinds of damage caused by wear and tear.

Does this imply that organisms which age do not have these repair and replacement mechanisms?

There is every reason to believe that the repair and replacement mechanisms found in bacteria have been conserved in more complex organisms, and are potentially as effective at undoing damage.

DNA damage resulting in multiple broken chromosomes (blue arrows)



As an illustration, let's look at one of the wear and tear mechanisms. Here is a slide illustrating DNA damage affecting chromosomes. DNA can be damaged by ultraviolet light and by other forms of radiation, as well as by viruses and certain chemicals.

In the case of human cells, it has been estimated that this type of DNA damage can happen as much as a million times daily, for each individual cell. Fortunately, most of this DNA damage gets repaired. If the damage can't be repaired, the cell can no longer function properly, or in some cases can become cancerous.

Repair and replacement

- tumour suppression
- cell cycle arrest
- detoxification of reactive oxygen species
- apoptosis
- autophagy

Besides DNA repair, there are other repair and replacement mechanisms operating inside cells. Here's a list, almost certainly partial because new discoveries are being made all the time in this field.

When some or all of these repair and replacement processes are working at reduced efficiency, when they've been turned down or even turned off, cells show signs of aging, and so does the whole organism.

But, when these processes are working well, aging is slowed down, and the organism lives longer.

Regeneration

- liver lobes
- finger tips

And there is also every reason to believe that the regeneration capabilities of flatworms and salamanders, continue to exist in species which evolved more recently. After all, liver lobes in humans regenerate, and there are documented cases of finger tips growing back after accidental amputation.

If cells and organisms can repair damage, why does aging happen?

This leads to the question: if the mechanisms to undo damage in cells and organisms are potentially so effective that aging can be prevented, why does aging take place at all? Clearly, these repair and replacement mechanisms are under genetic and epigenetic control, and these mechanisms, for some reason, have been more or less disabled or crippled in species which show aging. Why?

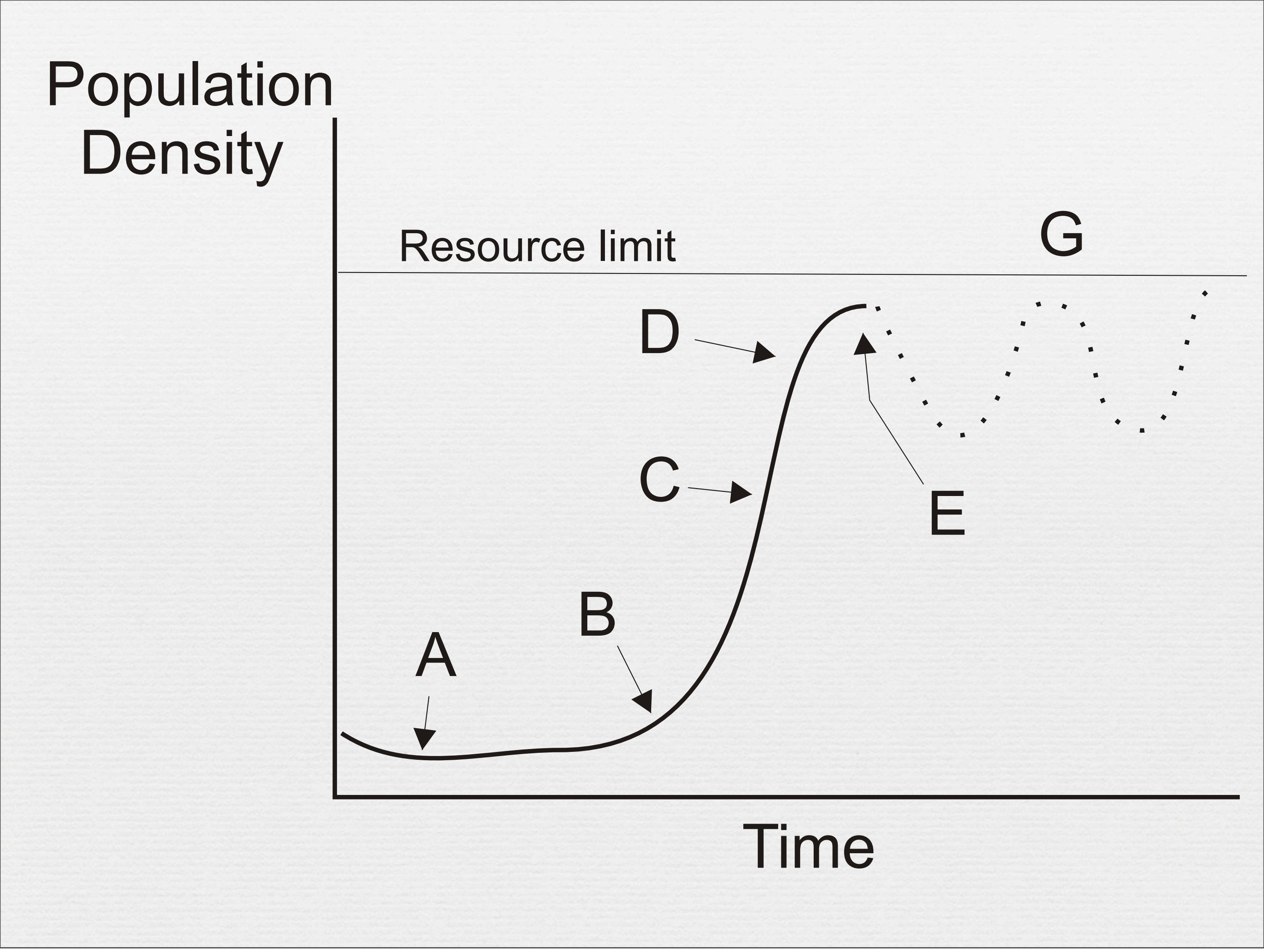
If cells and organisms can repair damage, why does aging happen?

Why shouldn't we be immortal?

Why not keep these repair and replacement mechanisms humming along, so that we could be immortal, or at least live a very long time? After all, as Steve Jobs pointed out, no one wants to die.

The sad reality is, that if we lived forever, we'd run out of room on the planet for all the people, we'd run out of food, and we would probably poison ourselves with all the wastes we produce. So there is a rationale for dying.

In general, a particular territory has an upper limit on the number of individuals of a species that it can support.

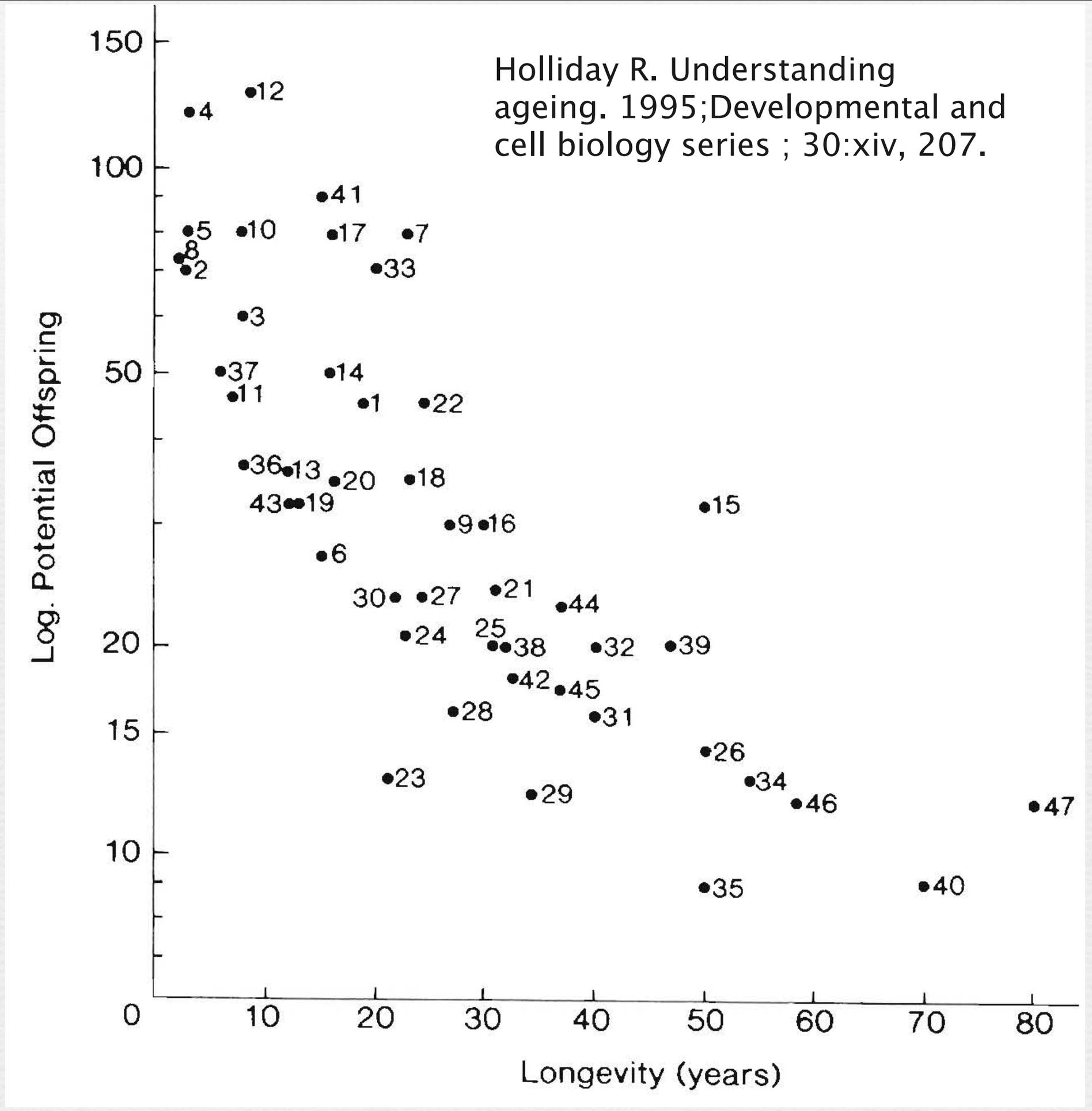


The principle is shown here in this typical population curve. Populations of organisms typically increase as much as they can in their environment, until some form of resistance from the environment, such as lack of food, stops the growth. Letter A points to the lag phase, when the number of organisms is very small and so the reproduction rate is low. As the young grow up and start to reproduce, we enter the acceleration phase, letter B. Soon, the population begins to grow very quickly, in the exponential phase, letter C. Eventually, growth slows as environmental resistance is encountered, in the deceleration phase, letter D. Eventually, the equilibrium phase, letter E, is reached, where the population is stable, meaning that the number of births equals the number of deaths. Commonly, the population fluctuates around the carrying capacity of the environment, shown as letter G.

births = # deaths

Just to repeat myself, at equilibrium, the number of births equals the number of deaths. Now this has a very practical consequence: if the birth rate increases, then the death rate must also go up, which means that the average lifespan must go down. And vice versa, if life span increases, then the birth rate has to decrease.

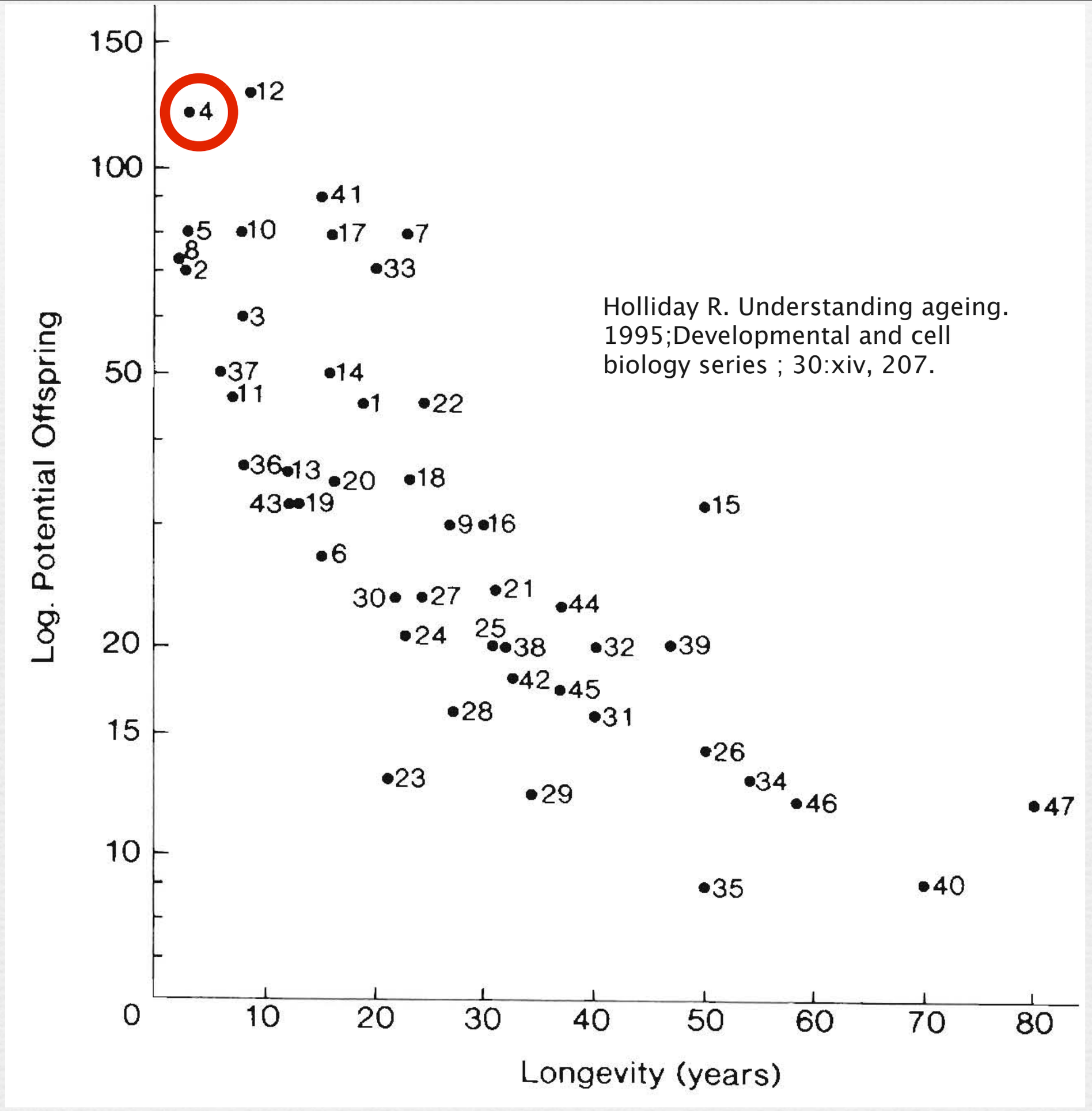
Remember one of the take-away messages from the naked mole-rat and the dauer stage of C. Elegans: reproduction and lifespan are linked?



This is a plot of reproductive potential vs longevity for placental mammals.

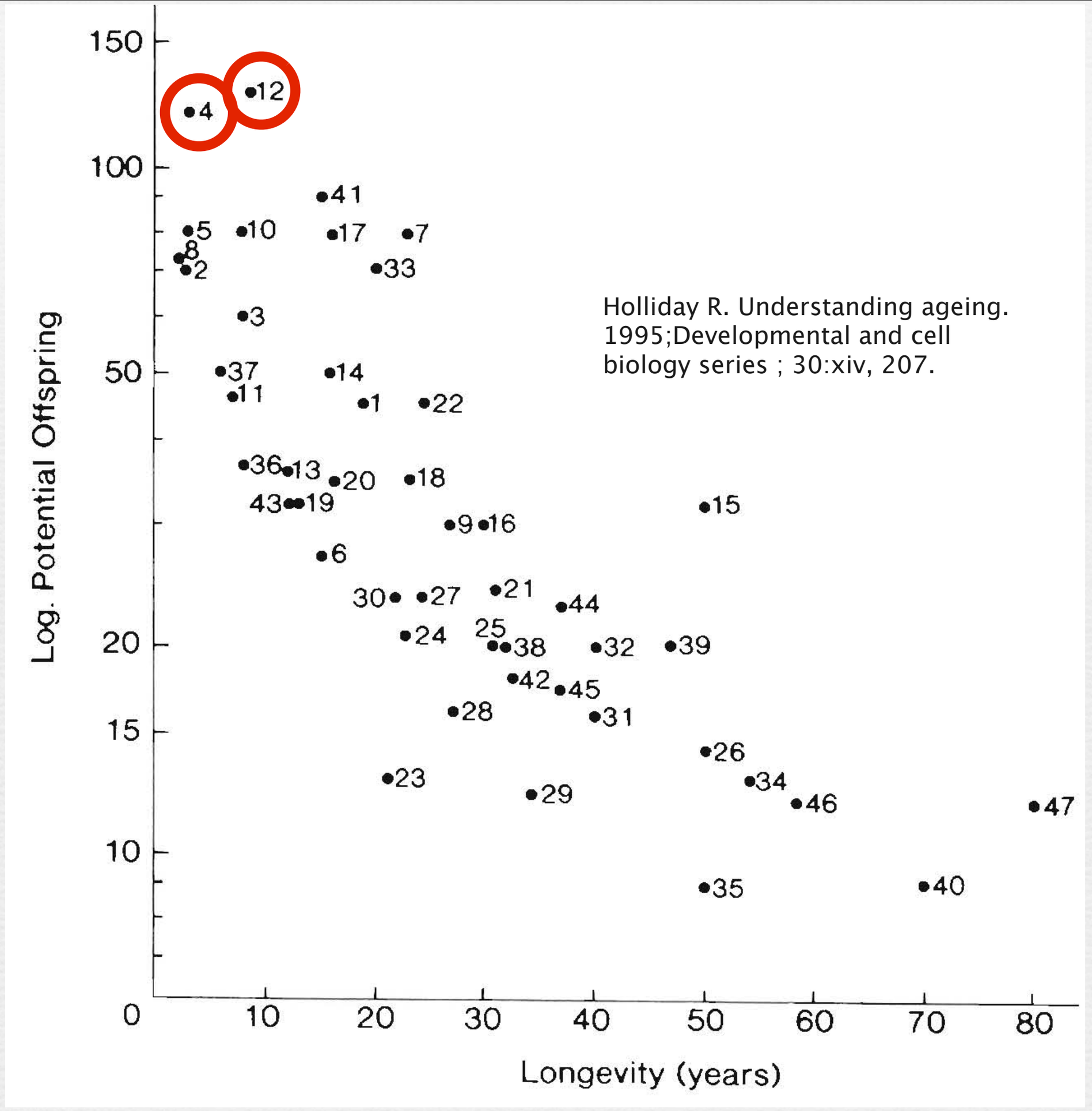
Reproductive potential is the maximum number of offspring that might be produced under ideal conditions and assumes there is no infant mortality.

Longevity is based primarily on the maximum lifespans of limited numbers of individuals kept in captivity.



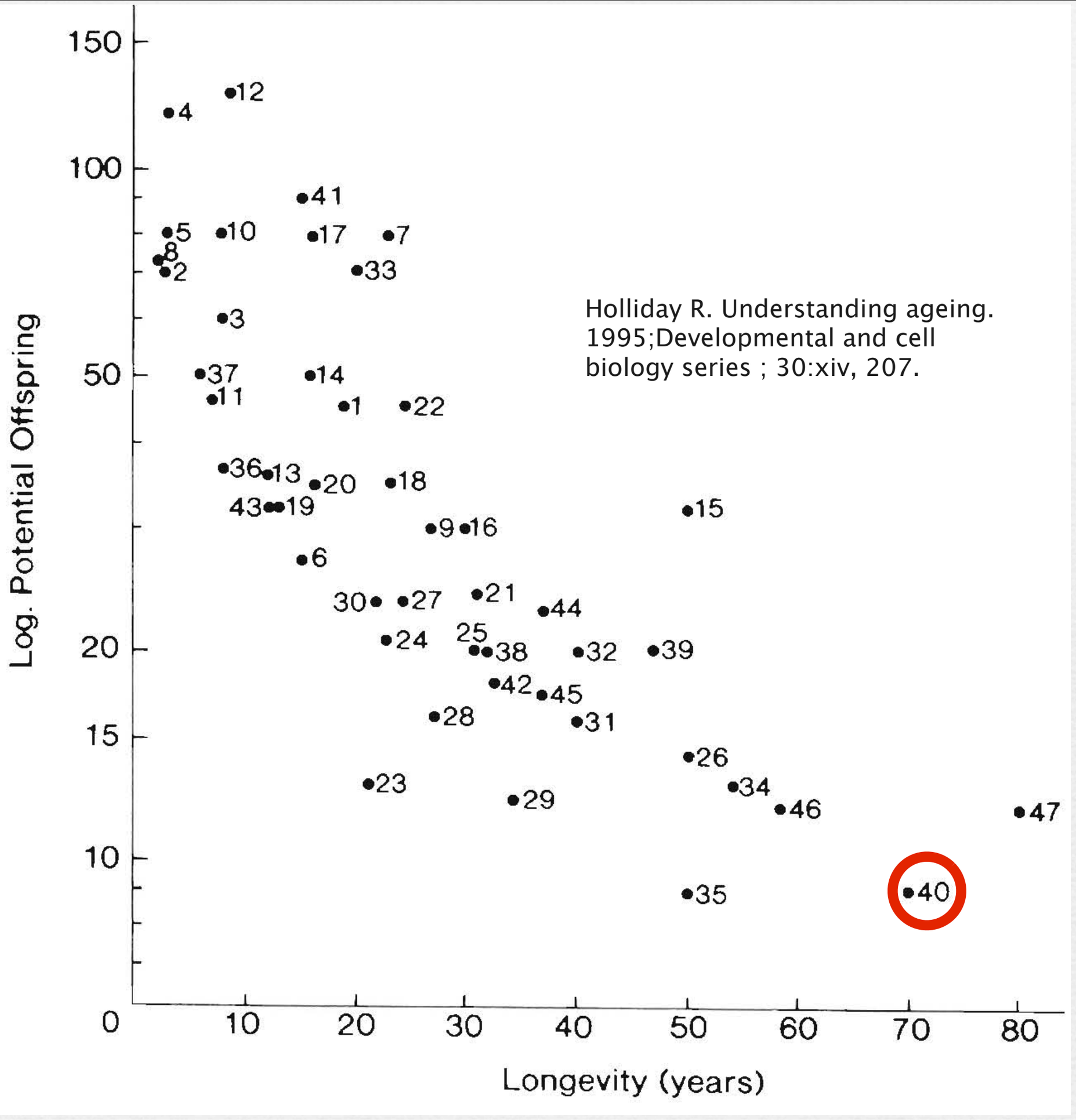
Holliday R. Understanding ageing. 1995;Developmental and cell biology series ; 30:xiv, 207.

Up near the top for number of offspring, but with the shortest lifespan, is number 4, the lab mouse,



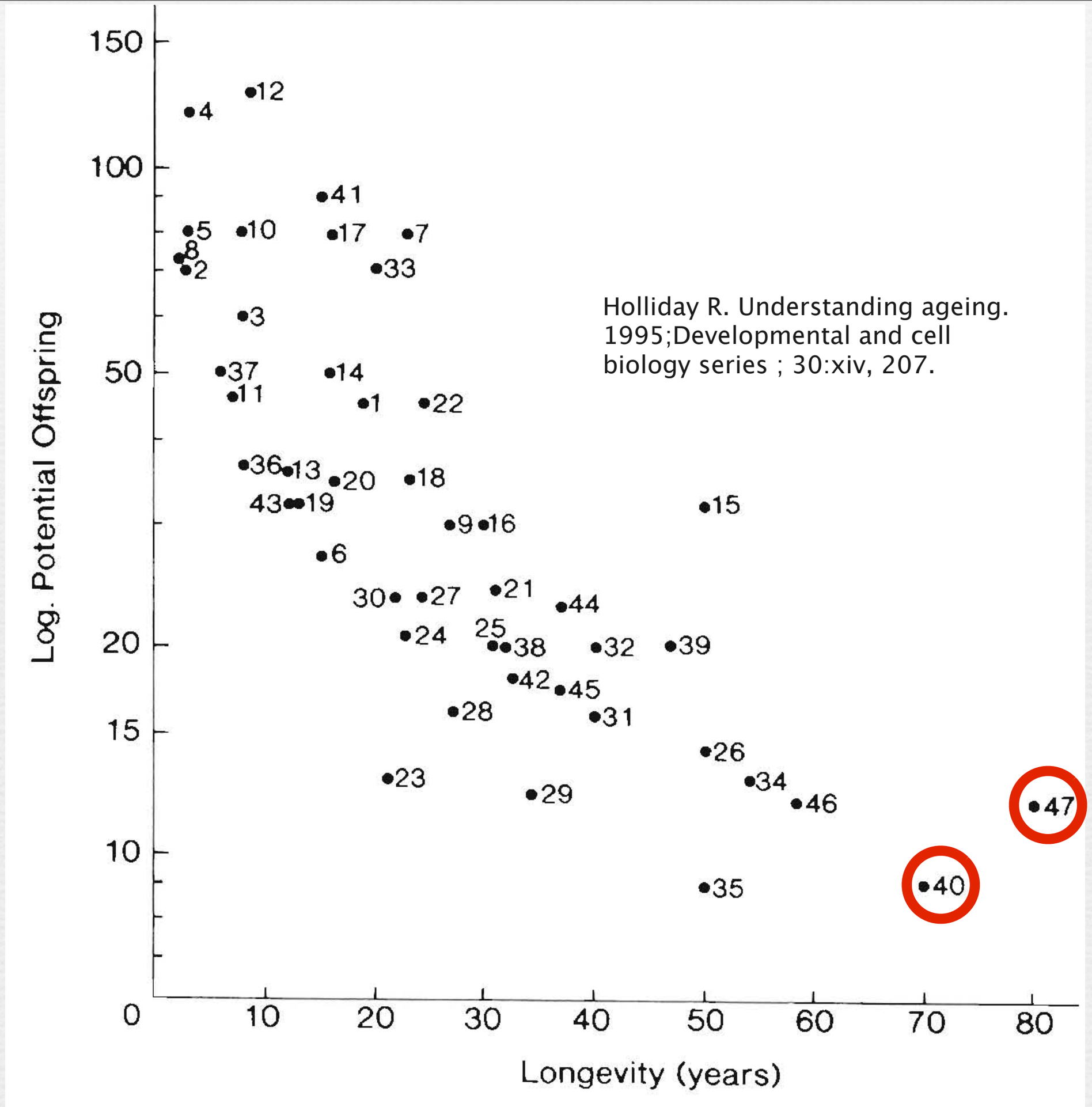
Holliday R. Understanding ageing. 1995;Developmental and cell biology series ; 30:xiv, 207.

and right next to it is #12, the rabbit.



Holliday R. Understanding ageing. 1995;Developmental and cell biology series ; 30:xiv, 207.

At the other extreme, we have the longlived elephant at #40. Elephants have very few babies.

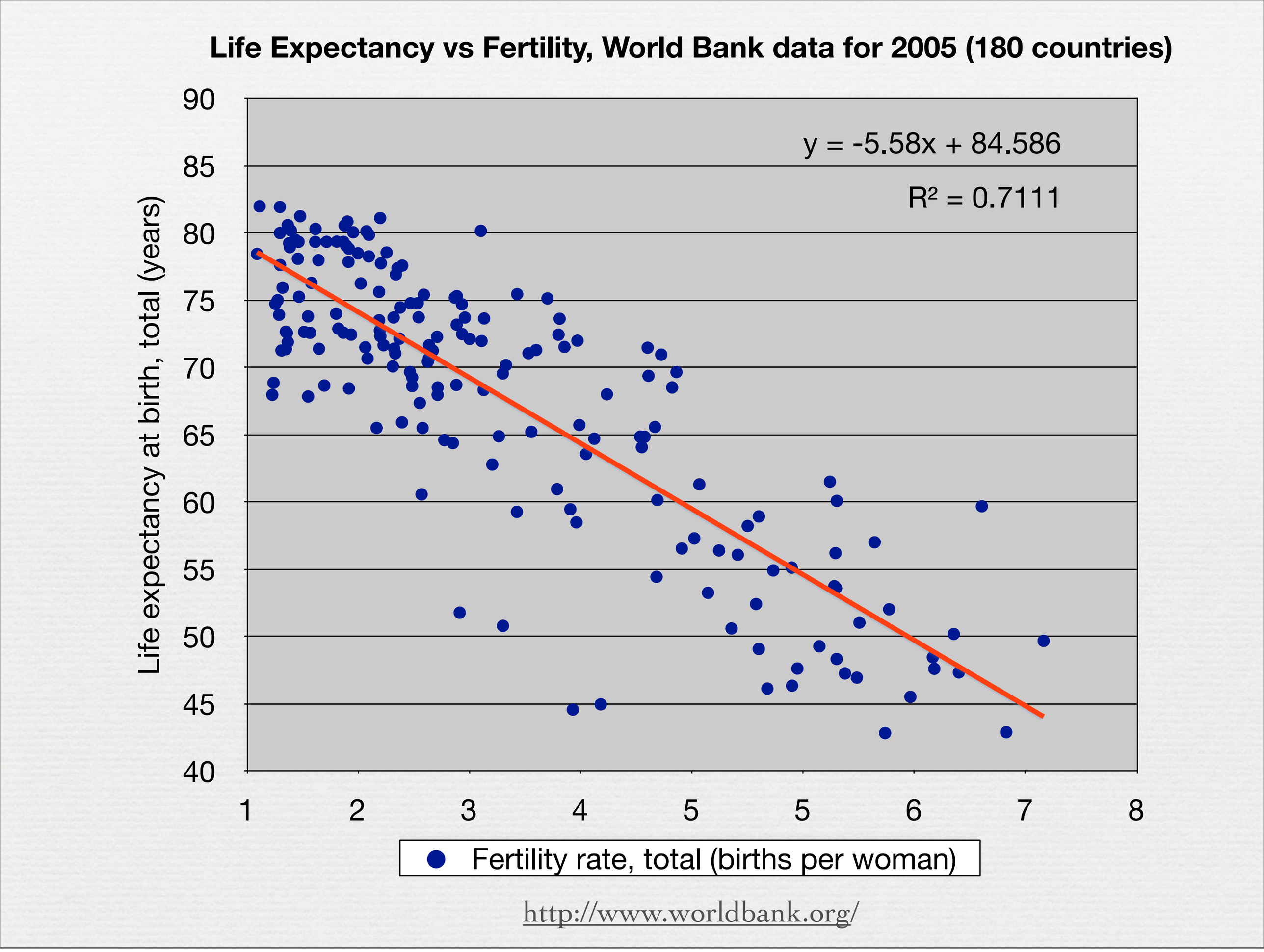


Holliday R. Understanding ageing. 1995;Developmental and cell biology series ; 30:xiv, 207.

and homo sapiens (that's us!) is pretty close, at #47.

A regression line would be somewhere along here.
(use pointer)

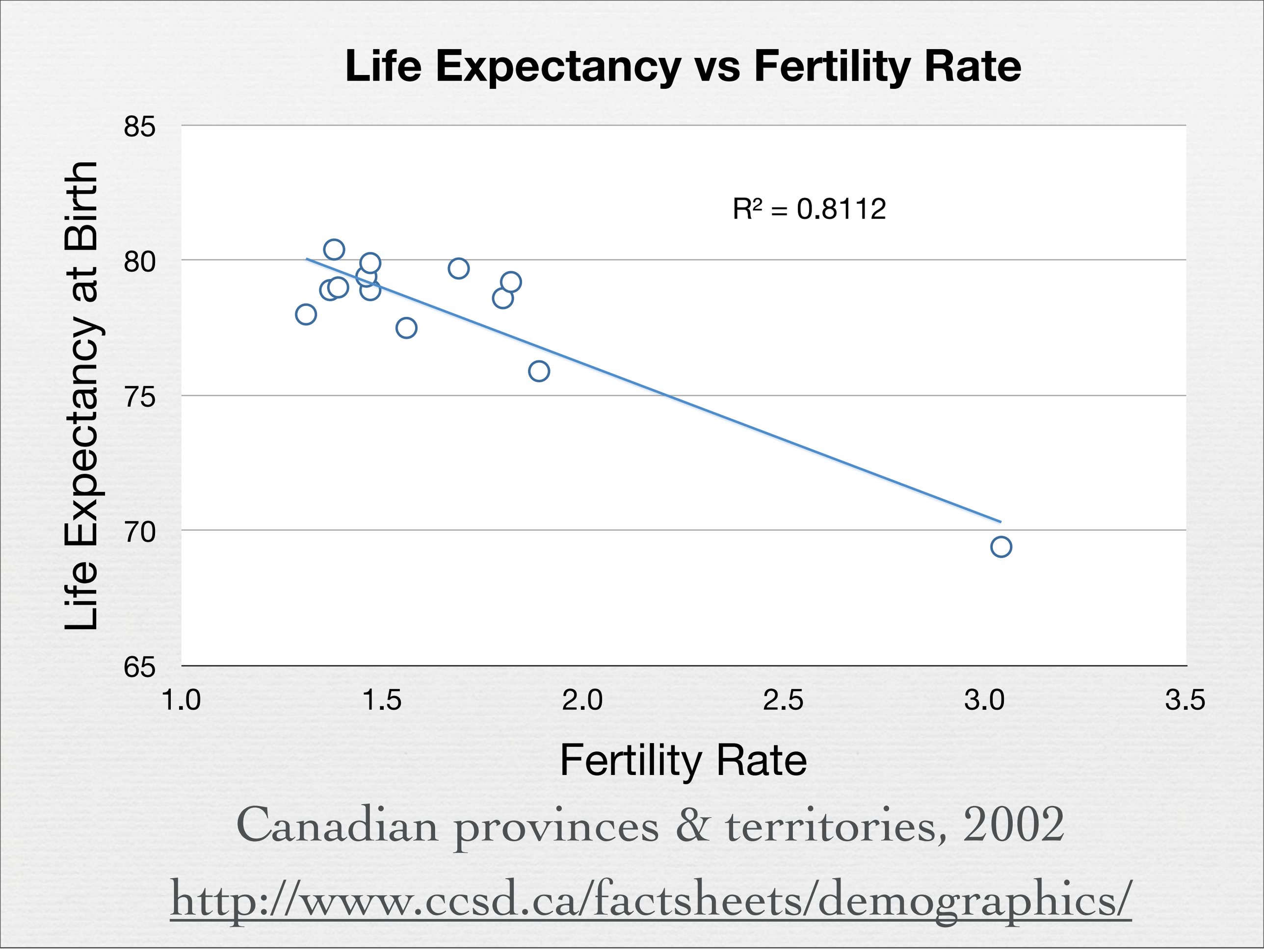
The point is, longevity is inversely related to the number of offspring.



This relationship between lifespan and reproductive rate appears to hold true for humans also. Using data from the world bank for 180 countries, I made this plot of life expectancy at birth vs fertility rate. The strength of this association is quite high, with an R squared value of 0.7111.

Now, most people would say that this is not cause and effect, it's simply an artifact. They believe that the improvement in life expectancy in the developed world, and the lower life expectancy in third world countries, is because richer countries spend more on health care which leads to improved health and thus people live longer. That may be true.

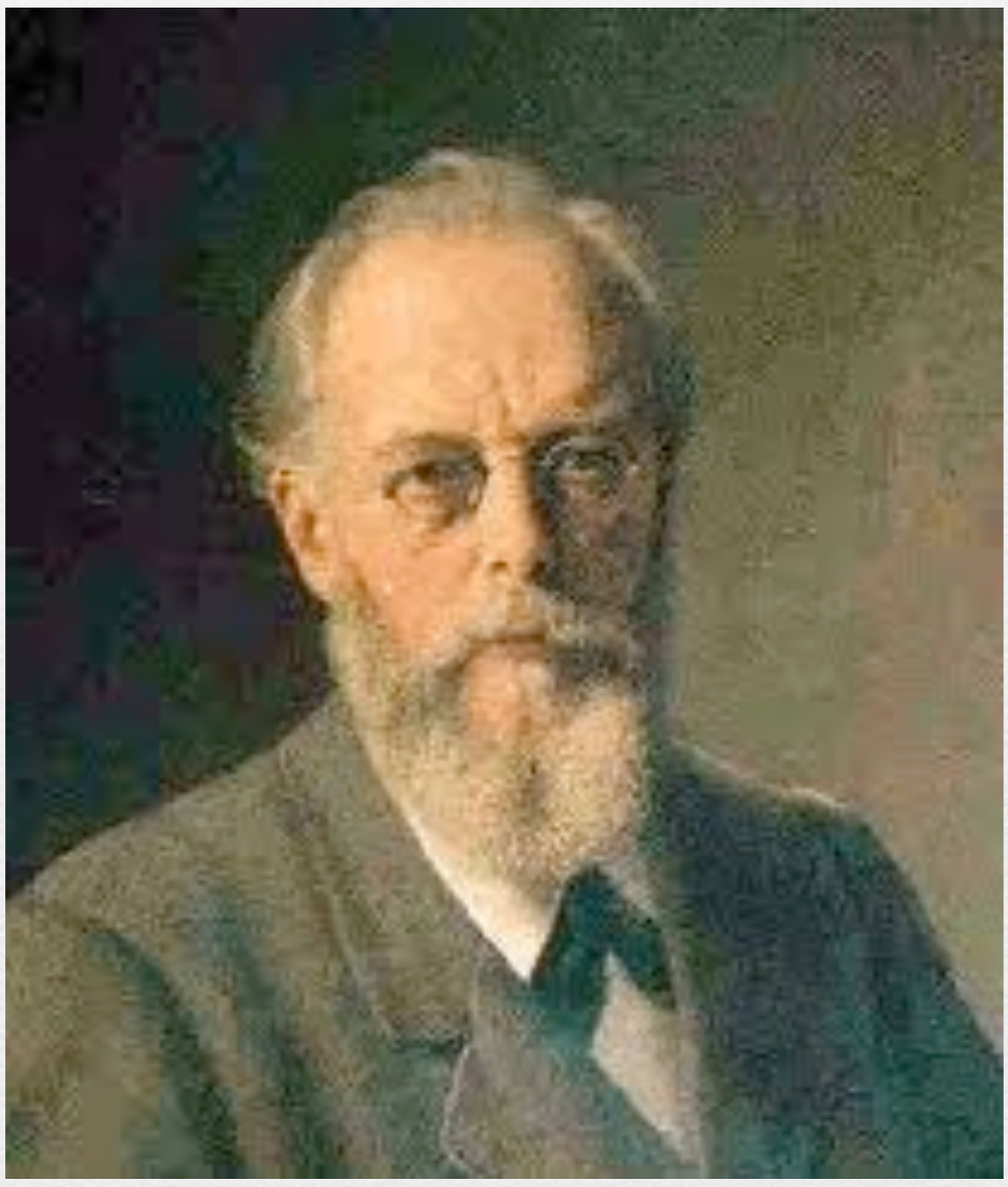
But there are other explanations. When health care, sanitation, and nutrition improve in developing nations, infant and child mortality plummets. As a consequence, people have fewer children. And as we saw for a whole bunch of different mammalian species, having fewer offspring means longer lifespan.



Canadian provinces & territories, 2002

http://www.ccsd.ca/factsheets/demographics/

This is data for Canadian provinces and territories from 2002. Again, note the high degree of correlation between life expectancy and fertility rate.



ESSAYS UPON HEREDITY

AND KINDRED

BIOLOGICAL PROBLEMS

BY

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Oxford

AT THE CLARENDON PRESS

1889

Now, this is really quite old stuff. It was clearly stated by August Weismann, ranked the second most notable evolutionary theorist of the 19th century.

"...thus we have the origin of *old age, decay,* and *death;* for it is evident that when one or more individuals have provided a sufficient number of successors they themselves, as consumers of nourishment in a constantly increasing degree, are an injury to those successors. Natural selection therefore weeds them out."

Inserted into: Weismann, 1889, Essays upon heredity and kindred biological problems, 1-66 (p23) by the editor, E. B. Poulton.

Even earlier than Dr. Weismann, there was Dr. Alfred Russel Wallace, a British naturalist.

Dr. Wallace provided a clear explanation of why death was necessary; if an animal did not die, then it would consume resources such as food and living space needed by its offspring. So evolution arranged for animals to get old, wear out, and die.

“in regulating duration of life, the advantage to the species, and not to the individual, is alone of any importance....It is of no importance to the species whether the individual lives longer or shorter, but it is of importance that the individual should be enabled to do its work towards the maintenance of the species. This work is reproduction, or the formation of a sufficient number of new individuals to compensate the species for those which die. As soon as the individual has performed its share in this work of compensation, it ceases to be of any value to the species, it has fulfilled its duty and may die.”

Weismann A. The duration of life (Chapter 1). Essays upon heredity and kindred biological problems. Oxford: Clarendon Press; 1889. p. 1-66.

Both Wallace and Weismann believed that evolution was responsible for individuals aging and then dying. Of course, they had no idea how that happened, as Watson and Crick’s DNA helix was not discovered until many years later.

Weismann’s ideas held sway for a long time, but in 1952, Sir Peter Medawar, who later won the Nobel prize in medicine, delivered a lecture at University College London. In his talk, Dr. Medawar pointed out what he felt was a serious flaw: aged animals are pretty rare in the wild.

Effects of aging

- cataracts impair vision
- arthritis slows down running
- cognitive changes impair judgment and reaction times
- worn / missing teeth cause starvation
- obesity, diabetes, cancer impair survival

It's true; aging is quite rare for animals in the wild. But is this because the theory is bad?

I think there is a different explanation: in the wild, as soon as an animal develops any of the many possible manifestations of aging, it will very quickly die. A mouse with arthritic joints won't be able to run fast enough to escape a swooping hawk. A monkey swinging from vine to vine in the jungle will miss and fall to its death when cataracts develop. An elephant whose teeth wear out will starve to death. A fox whose brains, sense of smell, and taste has been impaired by dementia, may eat spoiled food and die of poisoning.

Thus, in the wild, aging quickly leads to death. So if the biological imperative for an animal is to do its work of reproduction and then get out of the way, aging would certainly do the job.

However:
there are other ways to
“cull the herd”;

so why aging?

Of course, that still leaves a big, unanswered question: if individuals of a given species have to die so as to keep the numbers relatively constant, why use aging to bring about those deaths? Why not some other mechanism, for example, just let a lack of food, or overcrowding, or poisoning from accumulated waste, kill off the excess members of the species, as happens for bacteria? Why would evolution choose aging?

It’s because aging is a better method of culling the herd. It’s not random; aging selects the oldest members of the species as the first to die.

To understand why it’s better to have the oldest individuals die first, rather than just at random, let’s look at what differentiates aging from non-aging species.

Sexual organisms: show aging

Asexual organisms: ± immortal

This slide has builds!

The mode of reproduction, sexual vs asexual reproduction, seems to differentiate aging from non-aging species.

♥

Aging seems to occur only in species which reproduce sexually, or perhaps more generally, species which share genetic material horizontally or laterally, between members of the same generation.

♥

On the other hand, asexually reproducing organisms are immortal, or at least potentially very long-lived.

Asexual Modes of Reproduction

- fission (eg, bacteria)
- budding (eg, yeast)
- vegetative reproduction (eg, tulips make bulbs)
- spore formation
- fragmentation

Here is a list of asexual modes of reproduction.

Some species can reproduce both sexually and asexually. Again, aging seems to happen only when these organisms are in sexual reproduction mode.

Nature prefers sexual reproduction.

Why?

It turns out that sexual reproduction is vastly preferred by nature over asexual modes of reproduction. There are many theories about why this might be. A theory that is widely accepted has to do with the advantage that organisms which share genetic material between individuals have when it comes to adapting to changes in the environment, ie evolving. Simply put, sexual modes of reproduction allow for a wider choice of adaptive outcomes, and also provide for rapid dissemination of advantageous adaptations.

Let's first look at how sexual modes of reproduction allow for a wider choice of adaptations.

Mechanisms of adaptation

- mutations to the genome
- sharing of genetic information between organisms
- epigenetic mechanisms

In DNA-based organisms, adaptation occurs through mutations to the genome, sharing of genetic information between organisms, and epigenetic mechanisms.

Most of these adaptations, however, are a reworking or recombining of existing traits in the species.

Brand new traits, or the evolution of new species, requires mutations to DNA. And for sexually reproducing organisms, these DNA mutations have to occur in the germ cells, that is, in eggs or in sperm.

New traits:
require DNA mutations

- radiation
- viruses
- chemical exposure
- errors during DNA replication
- errors during genetic recombination in meiosis

These occur because of radiation, viruses, and chemical exposure, as well as errors occurring during DNA replication or genetic recombination as part of meiosis.

Most mutations are deleterious, and only a small number are beneficial.

Beneficial DNA mutations

- enhance survival and reproduction of offspring
- will propagate through the species
- may create new species

Beneficial DNA mutations will enhance the survival and reproduction of offspring. Thus these changes will, over time, propagate through the species, or possibly even create new species.

Mutation Rate

- Too high: extinction of the species
- Too low: extinction of the species

The rate at which evolutionary change takes place is therefore dependent on the rate of mutations. Because most mutations are detrimental, too high a rate of mutations leads to extinction of the species.
On the other hand, too low a rate means that the organism may not be able to respond to changes in its environment, and can therefore also lead to extinction. Remember that its environment includes its predators, parasites, infectious agents, as well as its food sources, all of which are undergoing evolutionary changes also.

Mutation rate

- can be adjusted when the environment changes
- by adjusting the effectiveness of DNA repair mechanisms

The implication is that the rate of mutation can be adjusted by the organism to account for changes in its environment. It adjusts the mutation rate by making the DNA repair mechanisms that I mentioned earlier, either more effective or less effective.

DNA repair

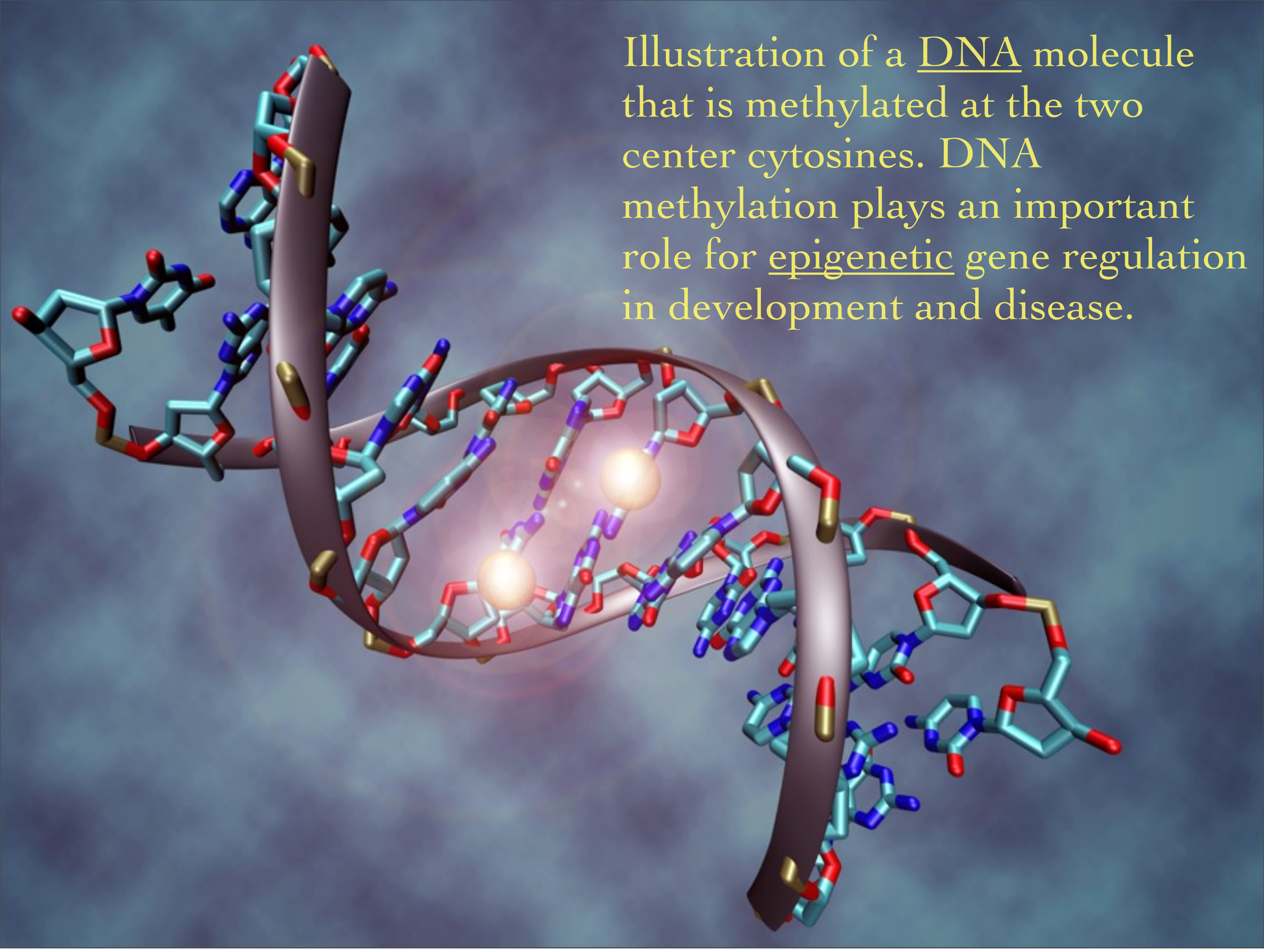
- under genetic control
- these genes can be turned on or off

Since these DNA repair mechanisms are themselves under genetic control, cells have mechanisms for turning genes on or off, that is, controlling whether genes are expressed or not.

Epigenetics

- changes in gene expression not due to changes in the underlying DNA sequence
- examples:
  - DNA methylation
  - histone deacetylation
  - RNA methylation

The science of the mechanisms which control gene expression is called epigenetics, and is one of the hottest fields in science currently.



Here is a graphic representation of DNA methylation.

So we can make a case that a cell's DNA repair machinery is adjustable, via epigenetic mechanisms, and that this adjustment controls the mutation rate.

For germ cells, this control determines whether a species becomes extinct, or develops brand-new traits.

For somatic cells, mutations to the DNA usually cause a deterioration in cell functioning, or may cause the cell to become cancerous. Both of these are seen with aging. And as for germ cells, the rate at which these DNA mutations occur is under epigenetic control.

DNA mutation laboratory

- each individual is like a DNA mutation laboratory, weeding out deleterious mutations
- sharing of genetic material between individuals: pooling of results from many DNA mutation laboratories

Looked at in this sense, each individual member of a species is its own little laboratory, where DNA mutations are tested to see if they are good for that individual or not. But this process is slow when limited to individuals.

Suppose, however, that you could join a number of these little laboratories up, so that any one individual could have access to the beneficial mutations of a whole community of individuals. This can occur when genetic material is shared between individuals.

For example, suppose there are 1000 fertile animals in your group. That means you have a choice of about 500 breeding partners. And in general, out of the 500 you will choose partners with the most advantageous mutations. This is what I mean by pooling the results of individual mutation laboratories.

Competition

- Meiosis (production of germ cells)
- Germ cell quality
- Competition for sexual partners
- Choice of sexual partner

But there's more. Not only do you get pooling of the results from each individual's testing of DNA mutations, sexual reproduction adds more ways, more types of competition, to separate good from bad mutations.

First is the process of meiosis which produces germ cells (gametes). Faulty genetic material can result in faulty meiosis, which weeds out some bad phenotypes. The quality of the gametes, that is, the eggs and the sperm, themselves can vary, in the same individual; thus, gametes compete with each other. In order for male and female gametes to get together, a sexual act has to take place. Males compete with males, and females with other females, to have access to sexual partners. For example, male animals with antlers, such as bull moose, will battle each other.

Finally, sexual partners tend to be choosy in picking mates.

Once mating has occurred, the millions of sperm compete with each other to be first to reach the oocyte. In species in which females mate in rapid succession with a variety of males, the sperm race helps select between individuals. Here is a video of that process in the fruit fly. The sperm of one male have been labelled with a green fluorescence, and the sperm of a second male labelled with red, which unfortunately is barely visible.

Fluorescent sperm in the female sperm-storage organ of Drosophila melanogaster

Sperm competition occurs after females mate with multiple males whose sperm compete for fertilizations within the female reproductive tract. Our understanding of events during sperm competition has been constrained by the challenge of directly observing sperm behavior and fate inside the female and the inability to differentiate sperm from multiple males. This image shows the primary sperm-storage organ (seminal receptacle) of a female Drosophila melanogaster that has mated to transgenic males with green (first male) or red (second male) fluorescently-labeled sperm heads. Sperm competition mechanisms elucidated by these novel transgenics include active sperm motility, sperm displacement and female ejection.

Mollie K. Manier, John M. Belote, Kirstin S. Berben, David Novikov, Will T. Stuart, and Scott Pitnick.
Resolving mechanisms of competitive fertilization success in Drosophila melanogaster.
Science 328, 354-357 (2010).

Nurturing the fetus and infant

- good maternal diet
- nurturing skills
- intelligence
- good relationships with kin

Once an egg has been successfully fertilized, more factors come into competitive play. Nurturing the fetus, and later the infant, requires a good diet in terms of nutrition and safety, thus more intelligent mothers (or those with kin who are more likely to share) will enjoy greater reproductive success.

Speed of dissemination

- Alpha males
- Egg-laying females
- contrast with asexual reproduction

When a particular mutation has successfully run the gauntlet of this series of competitions, it will often become disseminated quickly through the community. For example, in some species, the alpha male in a group is the only one who can legitimately mate with the majority of the females; his genes (including successful mutations) may therefore dominate even within a single generation. Similar effects may be seen in colonies of social insects such as bees. In contrast, individuals in asexually reproducing species have a far smaller pool of potentially beneficial mutations to play with, and many generations may be required before those genes have significant penetration within the species.

Sexual reproduction

- High rates of evolutionary change are possible
- Much higher than current estimates
  - existing mathematical models and computer simulations are inadequate

(This slide has builds)

The upshot of all this is, for species which reproduce sexually,

♥

evolutionary change can be very fast, probably much faster than any estimates currently out there. Species can evolve very quickly, and new species can emerge quickly, and new features such as vision can arise within reasonable time intervals.

♥

Current thinking that evolutionary change happens slowly is based on mathematical models or computer simulations that are inadequate, because they fail to account for all the forms of competition that I've just outlined. For example, the most elaborate simulation that I could find, has sexual pairing happening randomly. I mean, seriously, who picks sexual partners at random?

Who should die?

- The youngest generation is likely to be the best adapted to its environment
- If culling is required, the oldest generation should go first
- Aging knocks off the oldest generation

(This slide has builds)

The consequence of this high rate of genetic variation for sexually reproducing species means that in general,

♥

the youngest generation is likely to be the best adapted to its environment, and the oldest generation the least. For this reason, if culling of individuals is required to ensure that resources continue to be available,

♥

the culling should be of the oldest generations first. This kind of culling is achieved by

♥

aging, which works quickly to to reduce numbers in the oldest generation for animals in the wild.

Thus, for human beings, the consequences are that, if we manage to survive infections and accidents, a genetically built-in aging program will arrange to do us in eventually. But we recognize that this encompasses a great deal of variation; some of us live longer than others while hanging on to good health. Why is this? Why do the ravages of aging come earlier and more severely in some individuals than in others? And can we exert any control over the processes of aging?

Who should live longer?

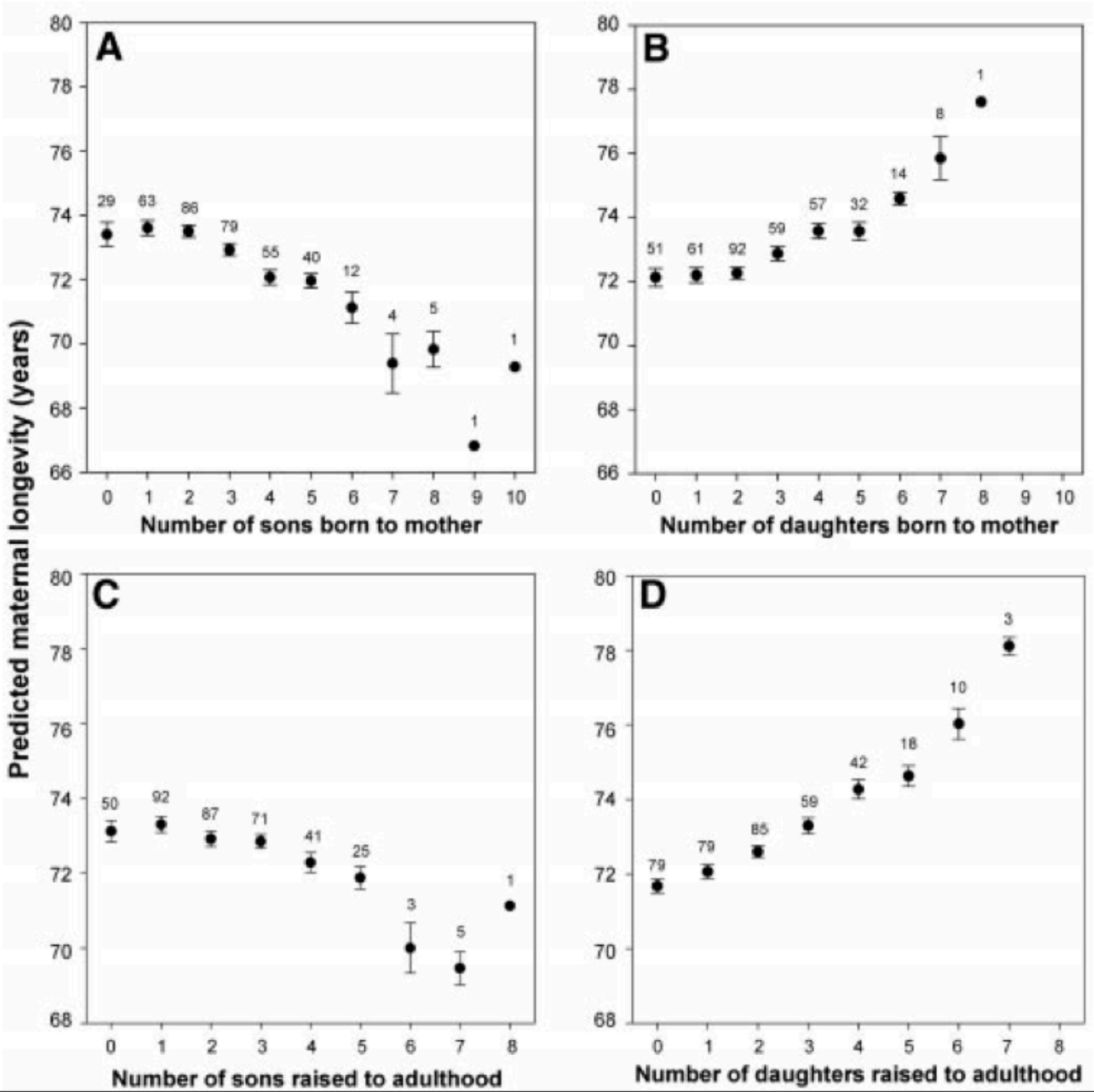
- the “Grandmother hypothesis”

Hawkes K, O’Connell JF, Jones NG, Alvarez H, Charnov EL. Grandmothering, menopause, and the evolution of human life histories. Proc Natl Acad Sci U S A. 1998;95:1336-1339.

In the previous slide, I asked, “Who should die?” But not everyone dies young. Many people live long, happy, and healthy lives. What determines a longer than average lifespan?

Human beings are unique among primates in that women have an extended period of life following menopause, that is, following their reproductive phase. To explain this, researchers coined the phrase, “grandmother hypothesis”. What is the grandmother hypothesis, and how might it influence lifespan? Well, humans are unique among primates in yet another way, which is connected. Human mothers share food with their offspring.

In a hunter-gatherer society, where women do the gathering of roots, berries, grubs and so on, which keeps everyone alive while the men are off playing at their hunting games, older women are likely to be more effective gatherers than younger women. For one thing, the older ones are more experienced; also, they are not likely to be encumbered by having to carry around infants. Thus older women can gather more food than they need for themselves, and can share the extra with their daughters and grand-children. In this way, grandmothers can have a direct influence on the reproductive success of their offspring, and this would then be selected for by evolution.



Helle S, Lummaa V, Jokela J. Sons reduced maternal longevity in preindustrial humans. Science. 2002;296:1085.

In many human societies, sons often move away to start families of their own, whereas daughters often stick close to their mothers, even after they have their own children. So we might expect this “grandmother hypothesis” to work differently for women with female offspring compared to those with male offspring. And that is exactly what this study found: having more sons shortened a woman’s lifespan, while more daughters extended it.

The study also found that the lifespan of fathers was not affected either by the number or by the gender of their children.

Helping / influencing others

- doing healthy things which are imitated
- having a large sphere of influence
- being good communicators

In general, though, any trait you have which positively influences the reproductive success of your genome and that of your descendants or your community, may be valued enough by evolution to the point of contributing to your own health and longevity. You might speculate that someone who helps others, for example by doing volunteer work, might enjoy better health and a longer lifespan. Because humans, just like many animals, learn by imitating others, individuals who do healthy things for themselves, such as being careful about food choices or avoiding accidental injury, and who in addition have the charisma or social skills that leads to them being imitated by many individuals, that is, having a large social circle, might live longer, not only because of doing those healthy things, but also because they have a positive influence on younger generations.

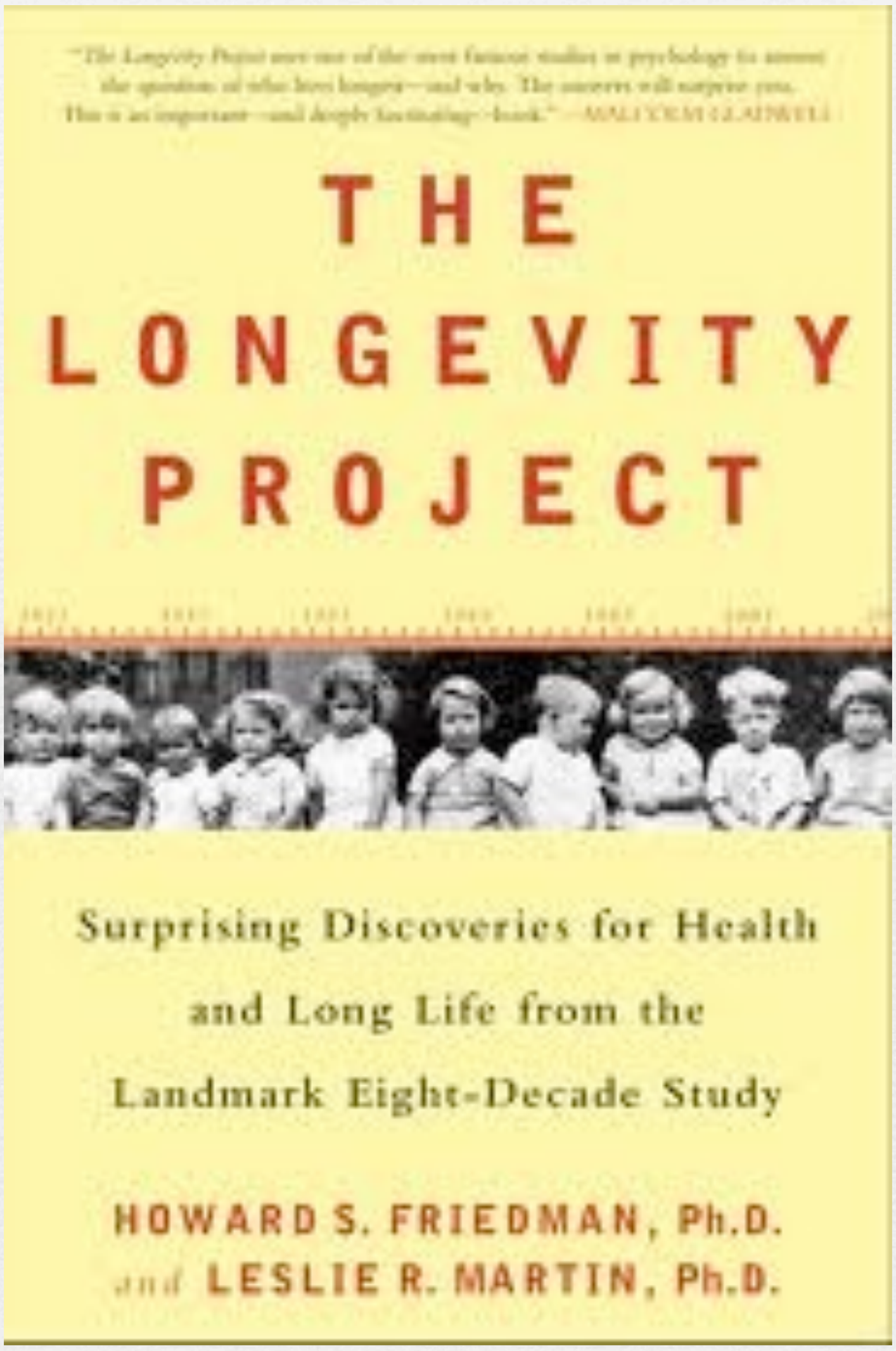
Longevity examples

- orchestra conductors
- Oscar winners
- Nun study: nuns who wrote better essays

Snowdon DA, Greiner LH, Kemper SJ, Nanayakkara N, Mortimer JA. Linguistic ability in early life and longevity: findings from the Nun Study. In: Robine J-M, Forette B, Francheschi C, Allard M, editors. The Paradoxes of Longevity. Berlin; New York: Springer-Verlag; 1999. p. 103-113.

Being good communicators and having a large sphere of influence, may be the reason why orchestra conductors and Oscar winners have been found to have longer lifespans than average. Although it must be pointed out that the statistical approach used in these studies has been questioned.

Less controversial are the findings from the Nun study. An analysis of autobiographical essays written by these nuns when they were between 18 and 32 years old, showed that idea density, that is, the number of ideas or propositions for every ten words in their essays, was correlated with all cause mortality. Those with high idea density died at a median age of 88.5 years, compared to 81.7 years for those with low idea density.



This book, as the subtitle indicates, tells about the discoveries for health and long life from a study over 80 years of about 1500 people who were about 11 years old at the start of the study.

In September 1921, a Stanford University psychologist, Lewis Terman, went to a number of schools and asked teachers to pick out the brightest kids in the class. Dr. Terman was interested in the sources of intellectual leadership and wondered if he could identify early glimmers of high potential. He selected about 1500 boys and girls, all born around 1910.

He collected all sorts of information about their families, schooling, and activities. How many books in their houses, how active in their playtime, how happy their parents' marriages were. He measured their personalities. He then followed them as they grew up, made career choices, and had families of their own.

Dr. Terman died in 1956, but his project continued, carried on by others. It was picked up in 1990 by the two authors of this book, who spent a lot of time and energy tracking death certificates. Quite a few papers have now been published on their findings with respect to health and longevity. Here are some of the findings.

The Longevity Project

- The best childhood personality predictor of longevity was conscientiousness
- other predictors of of health and longevity:
  - having a large social network
  - engaging in physical activities
  - giving back to your community
  - enjoying and thriving in your career
  - nurturing a healthy marriage or close friendships

(This slide has builds)

The best childhood personality predictor of longevity was

♥

conscientiousness – the qualities of a prudent, persistent, well-organized person. In following people through the years,

♥

other characteristics emerged. It was not good cheer or being popular and outgoing that contributed to good health and longevity. It was also not those who took life easy, played it safe, or avoided stress. Rather, the paths to long life reflected an active pursuit of goals, a deep satisfaction with life, and a strong sense of accomplishment.

When I look at this list of predictors, I am struck by the fact that someone who has these characteristics makes a good role model for others to imitate.

Of course, the research did not answer the question: can we modify our health and longevity by purposefully doing these things that are associated, or is it necessary to already possess the qualities, to be born with traits, that cause you to follow these paths?

Can we control aging?

- Caloric restriction

Smith DLJ, Nagy TR, Allison DB. Calorie restriction: what recent results suggest for the future of ageing research. Eur J Clin Invest. 2010;40:440–450.

Koubova J, Guarente L. How does calorie restriction work? Genes Dev. 2003;17:313–321.

(This slide has builds)

Can we control aging? In other words, can we extend the healthy lifespan of a species?

The answer is yes. Let's look at some of the research.

Probably the earliest and the most-studied finding is that ♥ caloric restriction increases lifespan. This was first studied in rats, about 75 years ago, but it's been found in many other short-lived species, including yeast, worms, spiders, flies, fish, mice, hamsters, and dogs. Ironically, the first study in rats was done during the Depression years, in an attempt to prove that not getting enough to eat would be bad for your health. Thus, finding the exact opposite was truly a surprise for these researchers.

In rodents, the lifespan extension can approach 50%, when calories are restricted to a level 25 to 60% of what they would normally eat.

Caloric Restriction (CR)

In rhesus monkeys:

- lower body fat
- slower rate of muscle loss with age
- lower incidence of:
  - neoplasia
  - cardiovascular disease
  - type 2 diabetes mellitus
  - endometriosis
- improved insulin sensitivity and glucose tolerance
- no apparent adverse effect on bone health
- reduction in total energy expenditure

(This slide has builds)

I mentioned the caloric restriction experiments done on various short-lived animals including fruit flies and roundworms. What about animals closer to humans? There are two ongoing studies which started about 25 years ago, in primates. One of these so far has shown that caloric restriction in rhesus monkeys leads to

♥

lower body fat, compared to control monkeys on standard rations;

♥

slower rate of muscle loss with age;

♥

lower incidence of neoplasia, cardiovascular disease, type 2 diabetes mellitus, and endometriosis;

♥

improved insulin sensitivity and glucose tolerance; and

♥

no apparent adverse effect on bone health, as well as

♥

a reduction in total energy expenditure. In addition, there are no reports of deleterious effects of CR on reproductive endpoints, and brain morphology is preserved by CR.

“With food shortage, reproduction becomes dangerous for the parent and offspring survive poorly; nutrients are hence reallocated to somatic maintenance, thus increasing the chances of the organism surviving to reproduce success- fully when the food supply returns.”

Grandison RC, Piper MD, Partridge L. Amino-acid imbalance explains extension of lifespan by dietary restriction in Drosophila. Nature. 2009;462:1061-1064.

This slide has a build!

You would think that going hungry all the time is a big enough price to pay to extend your lifespan, but there’s more. In general, caloric restriction impairs fertility. In humans, for example, significant weight loss in women results in amenorrhea.

You remember the infertile but long-lived dauer stage which happens to C. Elegans when there is not enough food? Researchers believe that this is how the organism is able to wait out the bad times until the good times return, when it again becomes fertile and short-lived. ♥

Caloric restriction in other species may be just a less radical manifestation of the same principle.

Longevity intervention trials

- Aspirin
- Nitroflurbiprofen
- Nordihydroguaiaretic acid
- 4-OH-a-phenyl-tert-butylnitrone
- Caffeic acid phenethyl ester
- Enalapril maleate
- Rapamycin
- Simvastatin
- Resveratrol
- Oxaloacetic acid
- Green tea extract
- Curcumin
- Medium chain triglyceride oil
- 17a-Estradiol
- Methylene blue
- Acarbose

Smith DLJ, Nagy TR, Allison DB. Calorie restriction: what recent results suggest for the future of ageing research. Eur J Clin Invest. 2010;40:440–450.

In addition to caloric restriction, a number of other medications or dietary modifications seem to be able to affect lifespan.

This is a recent listing of some of the compounds being studied. The ones in red I will discuss in a little more detail later.

Gut bacteria, as influenced by probiotics such as yoghurt, may also have an influence.

other compounds

- konjac root (glucomannan)
- a. nilotica extract
- berberine
- scia
- rosemary extract
- hibiscus extract
- harmane
- low-dose arsenite
- n-butanol extract from seed of Platycladus orientalis (BSPO)
- malate, fumarate
- Dimethyl sulfoxide (DMSO)
-

Stress and longevity

- overcrowding
- low environmental temperature
- heat stress

(This slide has builds)

Now, you've all heard that stress is bad for your health, right? We're told to avoid too much stress, don't be a type A personality, you'll have a heart attack, and so on.

But it turns out that stress may actually improve your health and increase your lifespan!

The studies on caloric restriction demonstrated that a particular kind of stress, that of food deprivation, increases longevity and improves health. But there are other kinds of stresses.
♥
Overcrowding, low environmental temperature, and also heat stress can extend lifespan, if they're not so severe that they kill you first. Findings for these other stressors are less consistent than for caloric restriction, however.
That reminds of the story about the man who went to see his doctor. The doctor told him that he had to give up "wine, women, and song."

The man asked, "If I give up wine, women, and song, doc, will I live longer?"

The doctor replied, "No. But it will seem like it!"

Stress and longevity

- Hormesis:
  - generally favorable biological responses to low exposures to toxins and other stressors
  - A pollutant or toxin showing hormesis thus has the opposite effect in small doses as in large doses

Why would stress increase lifespan? One hypothesis is the idea of hormesis.

The idea is, that something that is usually bad for you, can be good for you at low doses. Physical exercise and alcohol are two examples. One is a stressor, the other a toxin. Both do damage at high doses, and can be beneficial at low doses.

Of course, the whole idea of homeopathy is based on hormesis.

Stress and longevity

- Stress impairs reproduction
- Wait out the bad times

(This slide has builds)

I think a more likely explanation than hormesis, is that the improvement in health and longevity with certain stresses can be accounted for by the effect of those stresses on reproduction. ♥ When the organism is stressed, survival takes priority over reproduction, ♥ so the organism just “waits it out” until the stress is gone, the same as for caloric restriction.

How does stress increase longevity?

- stress cranks up repair and replacement mechanisms
- this slows down aging
- also interferes with reproduction

(This slide has builds)

Whatever the explanation for why stress can improve health and help us live longer, if we can figure out the how, we may be able to apply what we learn to ourselves.

Earlier on, I made the point that cells have repair and replacement mechanisms which can effectively deal with wear and tear, even to the point of making some species immortal. But evolution does not want us to live forever, or even long enough to impede the reproductive success of the youngest generation, so it cranks down those repair and replacement mechanisms which then brings on aging, and eventually death.

And as we've seen, stresses such as insufficient food,

♥

crank up these repair and replacement mechanisms, which

♥

slows down this aging process, but they also

♥

interfere with reproduction.

Now this led me to a conclusion which greatly surprised me at first.

Evolution: reproduce, then die

Unhealthy for reproduction

=

healthy for longer life

Healthy for reproduction

=

unhealthy for longer life

(This slide has builds)

Evolution wants us to reproduce, and then get out of the way by aging and dying.

♥

If stresses like lack of food interfere with reproduction as well as with getting out of the way, in other words, extend our lifespan, then it would make sense that

♥

things which are good for reproductive success, should also speed up aging and dying once we've finished with reproduction. In other words, what's healthy for us when we're young, may become unhealthy when we are older.

As far as I can tell, no research is being done to explore this possibility. But there are some recent research findings which become understandable if we look at them in this way.

Dietary supplements and mortality

- The Iowa Women's Health Study: supplement use
  - vitamin B6 and folic acid: increased mortality
  - iron, zinc, magnesium, copper: increased mortality
  - calcium: decreased mortality

Mursu J, Robien K, Harnack L, Park K, Jacobs DR. Dietary Supplements and Mortality Rate in Older Women: The Iowa Women's Health Study. Arch Intern Med. 2011;171:1625-1633.

A very recent paper in the Archives of Internal Medicine looked at the self-reported use of dietary supplements and mortality in over 38,000 older women, part of the ongoing Iowa Women's Health Study. Here are their findings (read). Iron, in particular, showed a strong dose-response relationship to mortality.

Now, we all know about how important folic acid is for reproductive success. Folic acid is so effective at preventing certain birth defects when taken by pregnant women, that starting in 1998 flour manufacturers have been required to add folic acid to flour to prevent these neural tube defects. Of course, this means that we might be getting more folic acid than is good for us when we're older.

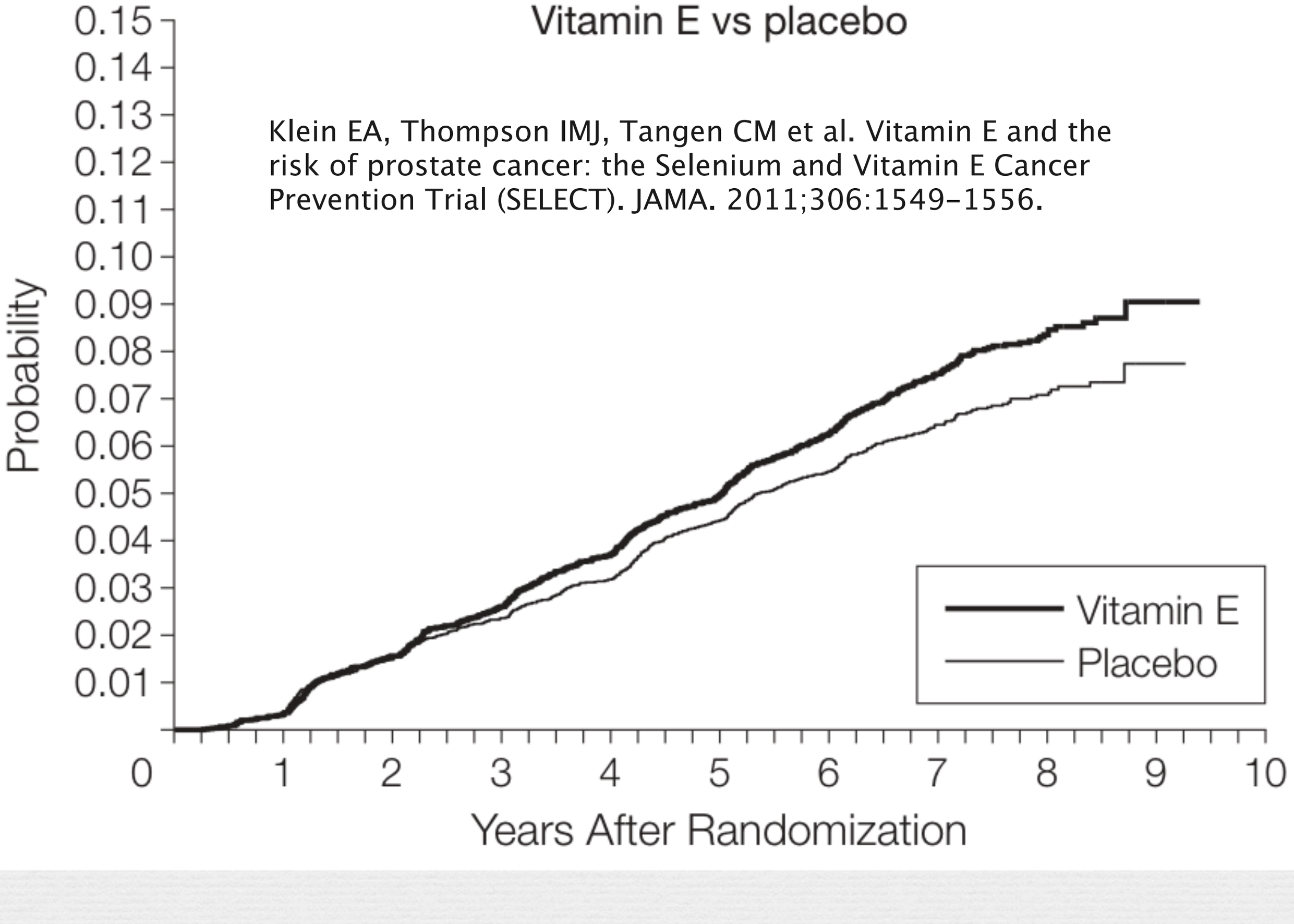
Calcium supplements

- meta-analysis of randomized trials: increased MI risk
- observational study: 24% increased risk of CHD
- increased prostate cancer risk

Bjelakovic G, Gluud C. Vitamin and Mineral Supplement Use in Relation to All-Cause Mortality in the Iowa Women's Health Study: Comment on "Dietary Supplements and Mortality Rate in Older Women". Arch Intern Med. 2011;171:1633-1634.

The decreased mortality in older women taking calcium supplements is interesting. The commentary which followed this article, pointed out that other studies had shown risks from calcium.

The commentary also made reference to meta-analyses of anti-oxidant studies, showing that vitamins A and E as well as beta-carotene increased cardiovascular and all-cause mortality.



Klein EA, Thompson IMJ, Tangen CM et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011;306:1549-1556.

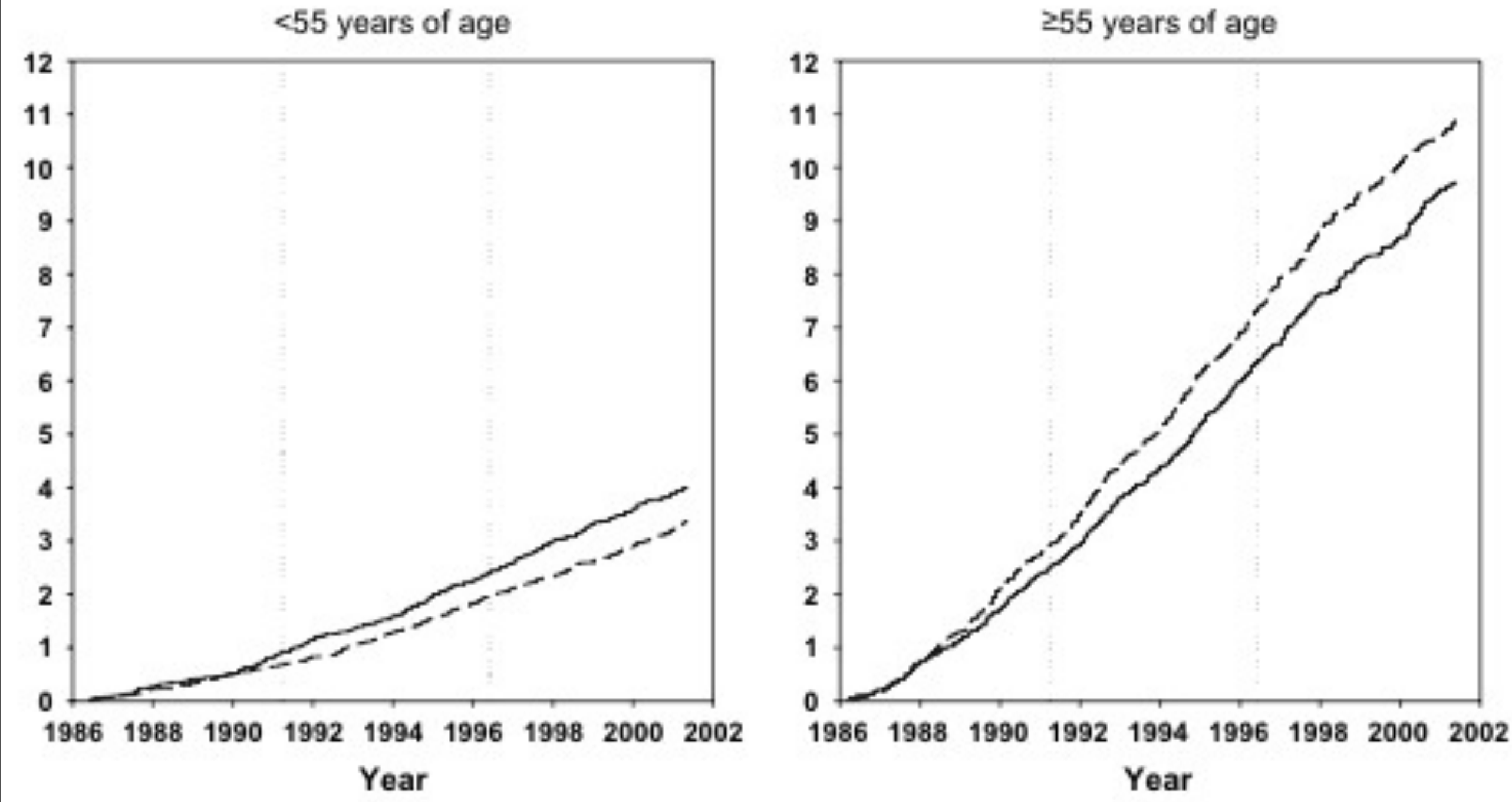
Here is a study involving a total of more than 35,000 men from 427 study sites in the United States, Canada, and Puerto Rico, all over 50 years of age. The men were randomized into one of 4 different groups: selenium supplement, vitamin E supplement, both selenium and vitamin E, or placebo. Over 10 years, the vitamin E group had a significantly elevated risk of developing prostate cancer, compared to placebo.

Dietary supplements and mortality

- the Linxian General Population Nutrition Intervention Trial
  - vitamin A and zinc: increased total and stroke mortality
  - vitamin C and molybdenum: decreased stroke mortality
  - selenium, vitamin E, and beta-carotene: decreased mortality (all causes, cancer overall, and gastric cancer)

Qiao YL, Dawsey SM, Kamangar F et al. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. J Natl Cancer Inst. 2009;101:507-518.

Here is an intervention study involving over 29,000 people in China who received one of four different combinations of daily supplements over a period of 6 years. The intention was to prevent gastric and esophageal cancer. Linxian is a province with high baseline rates of esophageal cancer. This paper reported on outcomes 10 years later. What they found was (read).



An interesting finding showed up when results were separated by age. In the group who received factor D, that is, selenium, vitamin E, and beta-carotene, there was 17% less death from esophageal cancer in the under-55 group, but 14% increased deaths in the over-55 group, as shown by the dotted line in the graphs above.

So we've seen that some dietary supplements seem to follow the principle that I hypothesized earlier: things which are good for you during your reproductive years may lead to an earlier death in later years.

Metformin

- Beneficial effects of metformin:
  - reduces risk of certain cancers, dementia, cardiovascular disease
  - increases longevity
- Probably acts through reducing insulin levels
- In C. elegans, excess dietary sugar eliminates lifespan increase

Gallagher EJ, Leroith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. Ann N Y Acad Sci. 2011;1243:54-68.

Algire C, Amrein L, Zakikhani M, Panasci L, Pollak M. Metformin blocks the stimulative effect of a high-energy diet on colon carcinoma growth in vivo and is associated with reduced expression of fatty acid synthase. Endocr Relat Cancer. 2010;17:351-360.

Cabreiro F, Au C, Leung K-Y et al. Metformin Retards Aging in C. elegans by Altering Microbial Folate and Methionine Metabolism. Cell. 2013;153:228-239.

What about the other half of that hypothesis: do interventions that increase longevity have a deleterious effect on health or fertility during our reproductive years?

Let's look at some of the things that have been found beneficial for health and increased lifespan when we're older.

First up is metformin, a drug of the biguanide class considered a first line treatment for type 2 diabetes. Metformin increases longevity, through its beneficial effects on cancer, dementia, and cardiovascular disease. Some of this work is being done nearby, by Drs. Pollak and Panasci at the Jewish General Hospital. It is thought that metformin may exert these beneficial effects by decreasing levels of insulin.

Metformin increases lifespan of C. elegans by up to a third, probably by altering the metabolism of bacteria in its gut, according to a recent study. Interestingly, when excess sugar was added to the worm diet, the life-extending effect of metformin was completely cancelled out.

On the other hand, this medication may have deleterious effects on reproduction. For example, it reduces testosterone levels, and it impairs vitamin B12 absorption.

Metformin

- Metformin decreases testosterone in normal men

Shegem NS, Nasir AM, Jbour AK, Batieha AM, El-Khateeb MS, Ajlouni KM. Effects of short term metformin administration on androgens in normal men. Saudi Med J. 2002;23:934-937.

- Reduces absorption of Vit B12

de Jager J, Kooy A, Lehert P et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010;340:c2181.

On the other hand, this medication may have deleterious effects on reproduction. For example, it reduces testosterone levels, and it impairs vitamin B12 absorption.

Rapamycin (sirolimus)

- Used clinically:
  - immunosuppression to prevent graft rejection
  - cancer treatment
- directly inhibits the TOR protein complex
- TOR: regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription

Mouchiroud L, Molin L, Dalliere N, Solari F. Life span extension by resveratrol, rapamycin, and metformin: The promise of dietary restriction mimetics for an healthy aging. Biofactors. 2010;36:377-382.

Rapamycin was initially identified as a new antibiotic with strong antifungal activity. It gave its name to the TOR protein complex, where TOR stands for Target of Rapamycin. TOR is part of the pathway by which calorie restriction increases longevity. TOR inhibition by rapamycin or by other compounds increases lifespan in a variety of animal models, including in mice at 20 months of age which corresponds to a human age of 60.

Rapamycin has also been shown to reduce decline in a mouse model of Alzheimer's. However, as an immunosuppressant, it can increase the risk of serious infections and of some cancers.

Resveratrol

- resveratrol increases longevity:
  - in yeast and C. Elegans
  - in obese, but not normal, mice
  - in female fruit flies on a low-sugar or a high-fat diet
- Phytoestrogen with mixed agonist/antagonist effects
  - may reduce male reproduction

Gruber J, Tang SY, Halliwell B. Evidence for a trade-off between survival and fitness caused by resveratrol treatment of Caenorhabditis elegans. Ann N Y Acad Sci. 2007;1100:530-542.

Wang C, Wheeler CT, Alberico T et al. The effect of resveratrol on lifespan depends on both gender and dietary nutrient composition in Drosophila melanogaster. Age (Dordr). 2011

Henry LA, Witt DM. Effects of neonatal resveratrol exposure on adult male and female reproductive physiology and behavior. Dev Neurosci. 2006;28:186-195.

Resveratrol, a substance found in grape skins, is believed to be responsible for the beneficial effects on health of drinking red wine. It's a polyphenol which has antioxidant, anti-inflammatory, and anti-carcinogenic effects. It increases longevity, and possibly with fewer negative effects when we're younger than some of the other interventions.

Aspirin and cancer mortality

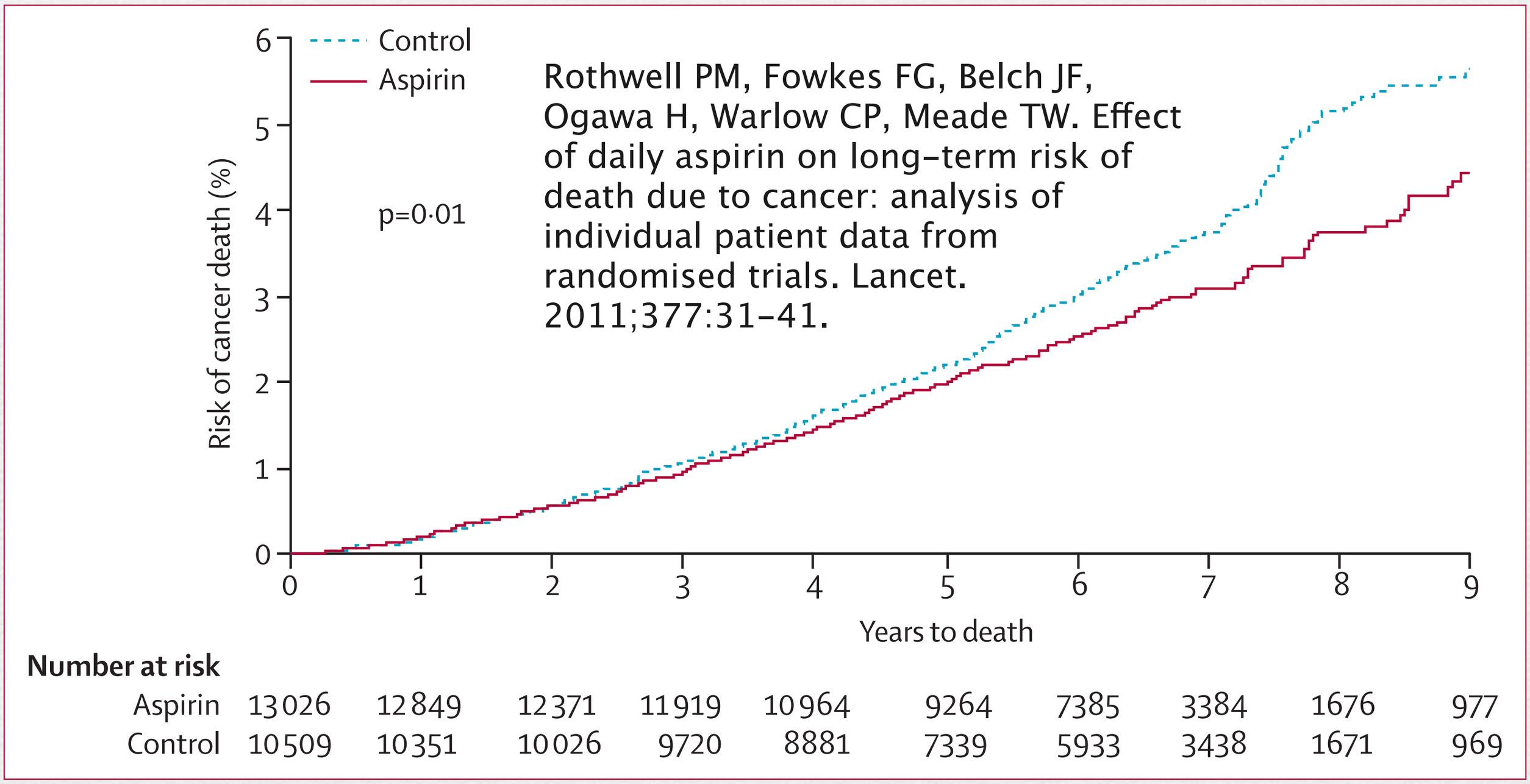


Figure 2: **Effect of allocation to aspirin versus control on risk of death due to cancer during the trial treatment periods in a pooled analysis of the 23 535 patients in seven trials**[17–21,23,24]

Turning to another substance, we all know that aspirin is useful in patients with cardiovascular disease – it reduces the risk of cardiovascular events by about 25%.

Less well known is the finding that daily aspirin use for 5 years or longer reduced cancer mortality by 20%, in this meta-analysis. Benefit increased with longer duration of treatment, and was pretty well restricted to adenocarcinomas.

It's not known how aspirin has this effect on cancer.

Aspirin

- aspirin reduces mortality:
  - from adenocarcinomas
  - from cardiovascular events
- possibly related to its effect on glucose absorption and reduction of insulin levels
- aspirin resistance is associated with prematurity, fetal distress, preeclampsia

Antonoff MB, D'Cunha J. Killing two birds with one salicylate: aspirin's dual roles in preventative health. Semin Thorac Cardiovasc Surg. 2011;23:96-98.

Arvanitakis C, Chen GH, Folscroft J, Greenberger NJ. Effect of aspirin on intestinal absorption of glucose, sodium, and water in man. Gut. 1977;18:187-190.

Wojtowicz A, Undas A, Huras H et al. Aspirin resistance may be associated with adverse pregnancy outcomes. Neuro Endocrinol Lett. 2011;32:334-339.

But actually, there is a pretty good explanation. It's been known since the 1950s that aspirin and other salicylates lower blood glucose levels both in type 2 diabetics and in normals, and experimental studies suggest that this effect is due to a decrease in glucose absorption by the small intestine. Lower glucose means less insulin secretion, and therefore less stimulation of cell division and cell growth, as I will discuss later.

While aspirin may extend longevity, it may also impair reproduction.

Coffee

- Beneficial effects of coffee:
  - reduced risk of type 2 diabetes, certain cancers, dementia, cardiovascular disease

Salazar-Martinez E, Willett WC, Ascherio A et al. Coffee consumption and risk for type 2 diabetes mellitus. Ann Intern Med. 2004;140:1-8.

  - reduced mortality risk
- Possibly acts through reducing insulin (by decreasing intestinal glucose absorption)

Johnston KL, Clifford MN, Morgan LM. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. Am J Clin Nutr. 2003;78:728-733.

Finally, coffee. Coffee is drunk all over the world, and because it contains a number of substances with important physiological effects, people have researched it for years. Both regular and decaf coffee appear to have the same kinds of beneficial effects as metformin. And as for metformin, these effects may be due to a reduction in insulin levels.

Coffee

- Maternal caffeine consumption:
  - increases fetal death risk
  - associated with lower birth weights

Bech BH, Nohr EA, Vaeth M, Henriksen TB, Olsen J. Coffee and fetal death: a cohort study with prospective data. Am J Epidemiol. 2005;162:983-990.

Sengpiel V, Elind E, Bacelis J et al. Maternal caffeine intake during pregnancy is associated with birth weight but not with gestational length: results from a large prospective observational cohort study. BMC Med. 2013;11:42.

During the reproductive years, however, coffee consumption by pregnant women has been shown to produce smaller babies and to increase the risk for stillbirth.

And many of you probably remember your parents telling you when you were young and were asking them why you couldn't have coffee like they were drinking: "Coffee will stunt your growth." This idea is so pervasive, there is likely some truth to it.

So both sides of the hypothesis seem to be borne out for these substances. I want to draw your attention to the fact that resveratrol and coffee are often parts of our regular diet.

And clearly the most studied longevity intervention, caloric restriction, also involves diet.

Effect of diet

- Caloric restriction seems most effective
- Certain dietary components have an influence
- Can we modify our diet to get benefits with less hardship?

(This slide has builds)

So what can we say about diet and longevity? Clearly,

♥

caloric restriction is an important mechanism, as it can extend life by 30 to 50% in some cases. And caloric restriction manifests the tradeoff between reproduction and longevity that I hypothesized. We know that weight loss impairs fertility – witness the cessation of menses in women who lose weight rapidly. We have also seen that

♥

certain substances in our diet, such as vitamins, minerals, resveratrol, and coffee, have an effect on longevity and probably on reproduction.

The problem is that caloric restriction, while effective, is extremely difficult for most people to do voluntarily. The question then becomes:

♥

can we modify our diet in such a way as to get the benefits of caloric restriction without the hardships?

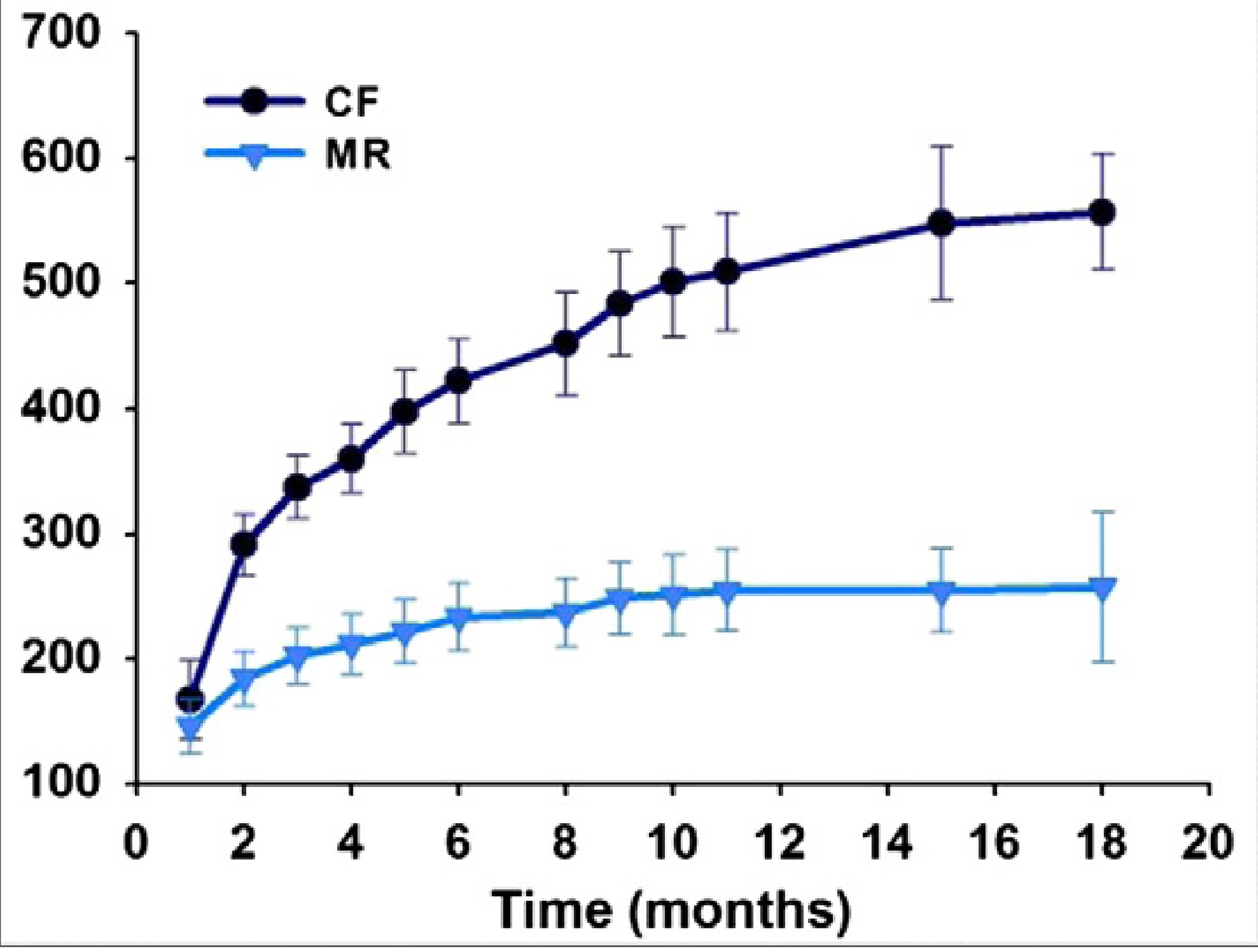
Methionine restriction

- essential amino acid
- leads to lower weight gain, increased lifespan in mice and rats
- found especially in eggs, sesame seeds, Brazil nuts, fish, meats and some other plant seeds, including some cereal grains
- most fruits and vegetables contain very little
- has been found to reduce insulin levels

One way might be through methionine restriction. Methionine is an essential amino acid, and reducing the amount in the diet fed to mice and rats results in increases in healthy lifespan, even though energy intake may increase.

Methionine is found in high concentrations in eggs, sesame seeds, Brazil nuts, fish, meats and some other plant seeds, including cereal grains. Interesting that this list includes so many things we really like to eat. On the other hand, the health-promoting effects of a strict vegetarian diet may be due to methionine restriction!

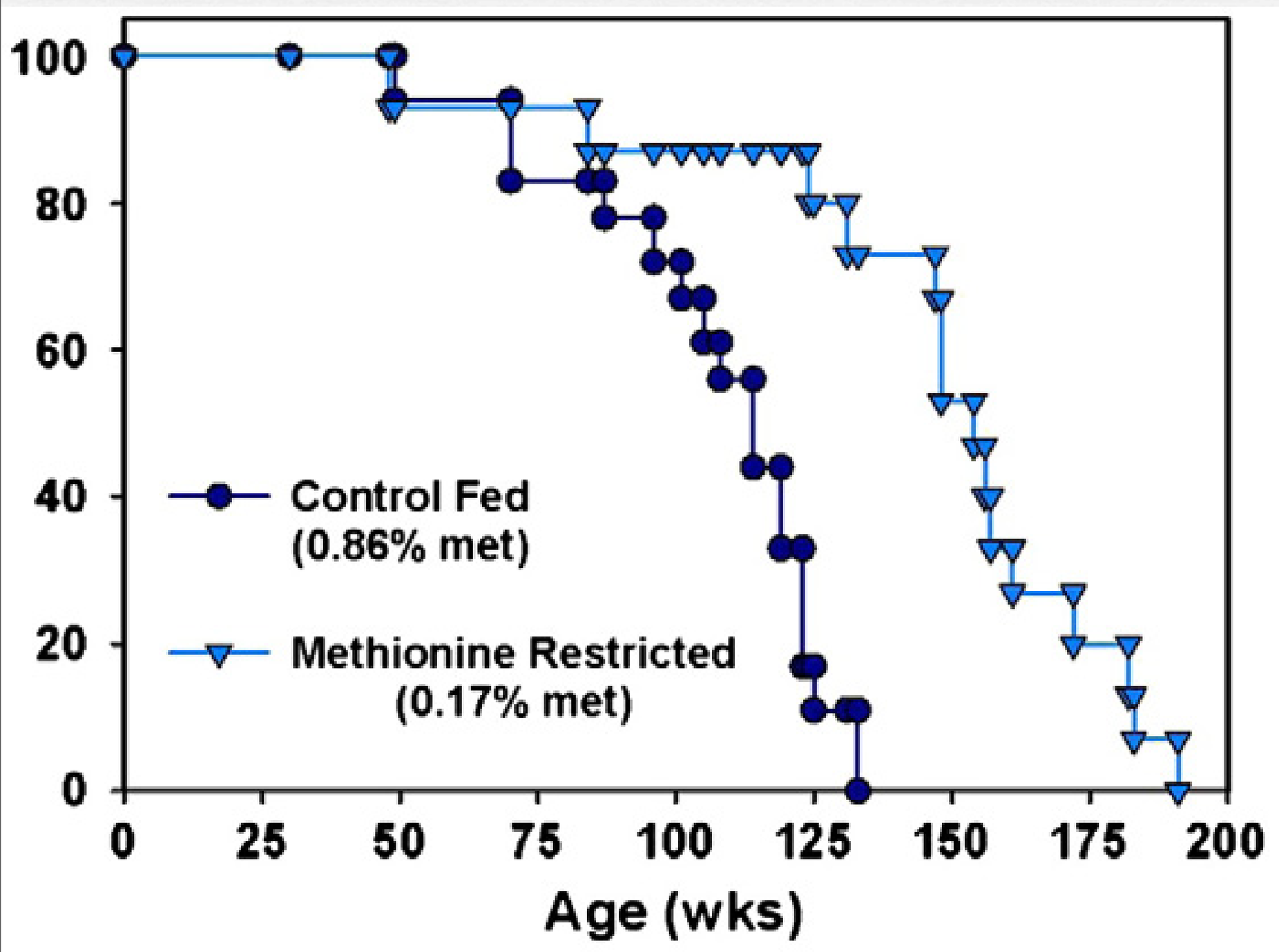
Methionine restriction



Perrone CE, Malloy VL, Orentreich DS, Orentreich N. Metabolic adaptations to methionine restriction that benefit health and lifespan in rodents. Exp Gerontol. 2012

Methionine is an essential amino acid, and when rats are fed on a methionine-restricted diet, they fail to gain weight. Total lack of methionine causes fatty liver disease and anemia in rats, in addition to the failure to gain weight.

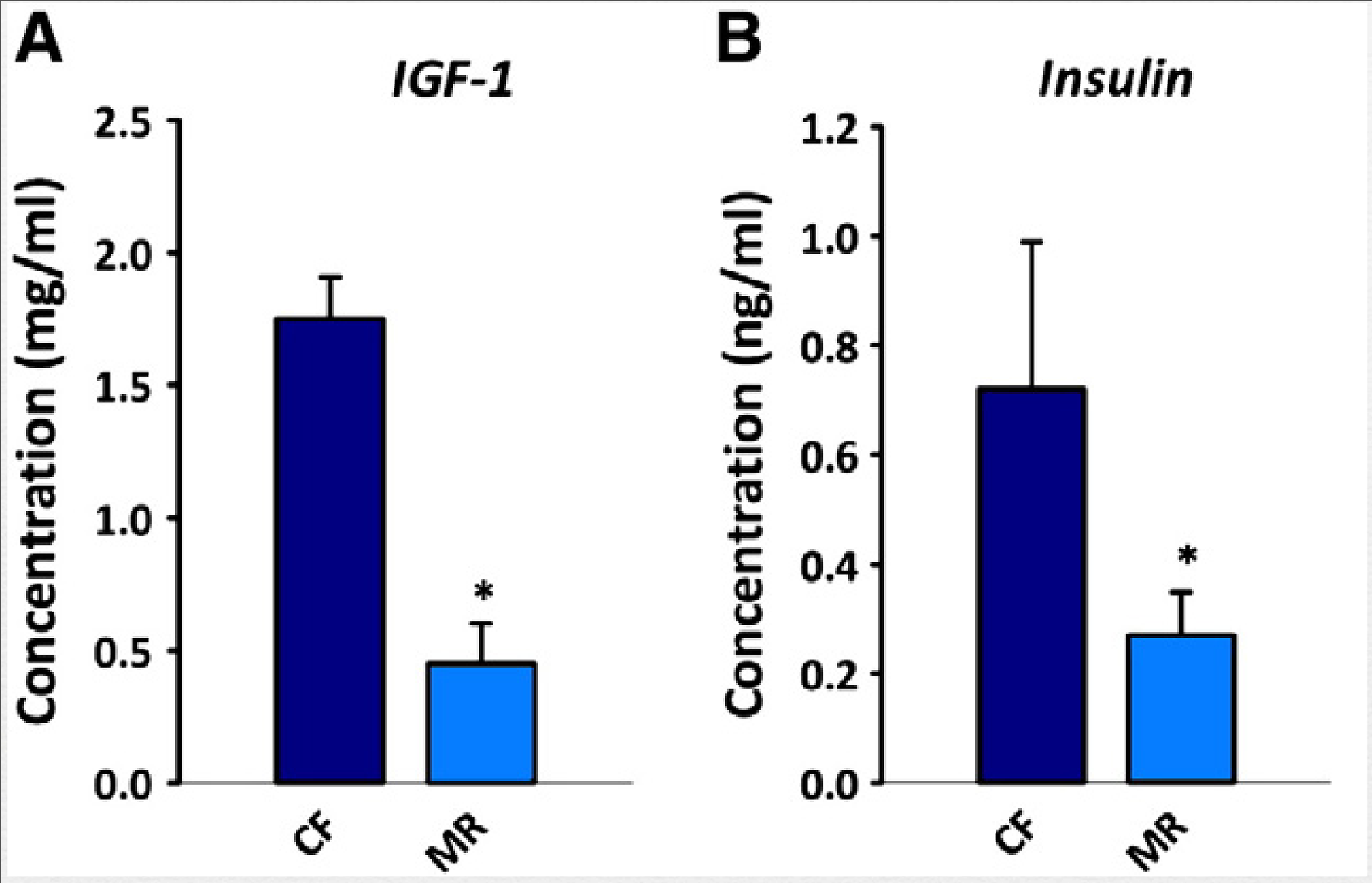
Methionine restriction



Perrone CE, Malloy VL, Orentreich DS, Orentreich N. Metabolic adaptations to methionine restriction that benefit health and lifespan in rodents. Exp Gerontol. 2012

But methionine restriction at 80% of the usual intake does confer health land longevity benefits to rats and mice, as these survival curves show.

Methionine is thus, very clearly, a substance that is good for young rats but bad for older rats, from the point of view of contributing to aging.



Perrone CE, Malloy VL, Orentreich DS, Orentreich N. Metabolic adaptations to methionine restriction that benefit health and lifespan in rodents. Exp Gerontol. 2012

In rats, methionine restriction causes marked reductions in the levels of both insulin and insulin-like growth factor.

IIS pathway

- IIS: Insulin and Insulin-like growth factor Signalling
  - controls autophagy, tumor suppression, cell cycle arrest, repair of damaged DNA, detoxification of reactive oxygen species, apoptosis (through FOXO3)
  - controls innate immunity
  - regulates energy metabolism
  - controls development of some tissues (eg, prostate)

Amrit FR, May RC. Younger for longer: insulin signalling, immunity and ageing. Curr Aging Sci. 2010;3:166-176.

To go back to what I said earlier: repair and replacement mechanisms which are coded for in our genes, act against the aging effects of wear and tear. A normal diet in terms of calories allows aging to take place by suppressing the repair and replacement mechanisms, typically by methylation of DNA.

When these mechanisms are studied in detail, for example in genetically modified animals, it appears that most if not all of these repair and replacement systems include insulin and insulin-like growth factor signalling pathways. These IIS pathways work through a variety of intermediates to modify the expression of a family of transcription factors, which in mammals are labelled as FOXO1 through 4.

"DAF-16/FOXO is a forkhead transcription factor that serves as a central regulator of longevity (Kenyon, 2010). DAF-16/FOXO is best known as a transducer of IIS. Molecular genetic studies have led to a model whereby stimulation of the insulin/IGF receptor results in activation of a PI3K/PDK/AKT kinase cascade, which phosphorylates DAF-16/FOXO, resulting in its nuclear exclusion in most tissues and inhibition of its transcriptional activity (Kenyon, 2010). A reduction of IIS results in FOXO accumulation in the nucleus, where it turns on genes involved in stress resistance, quality control, immunity, and longevity. In particular, mild loss-of-function mutations in daf-2, the insulin/IGF receptor ortholog, provoke a remarkable extension of lifespan by 2–3 fold, in a manner wholly dependent on DAF-16/FOXO (Kenyon et al., 1993)."

Antebi A. Regulation of longevity by the reproductive system. Exp Gerontol. 2012

This is from a recent article looking at mechanisms of lifespan extension in C. elegans.

Higher levels of insulin or insulin-like growth factor (IGF)

suppress repair and replacement mechanisms

(ie, increase aging)

(This slide has builds)

In general, higher levels of insulin or insulin-like growth factor (IGF for short) act through IGF receptors to suppress the functioning of repair and replacement mechanisms.

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Higher insulin, then, means more aging.

Suppression of IIS Pathway

- mice: IGF-1 receptor heterozygous (+/-) knockout mice live 33% longer
- Drosophila: mutations that attenuate insulin/ IGF signaling extend adult life span 80%
- C. Elegans: mutations in the insulin/IGF receptor produce a 2 - 3 fold increase in adult longevity

Tatar M, Bartke A, Antebi A. The endocrine regulation of aging by insulin-like signals. Science. 2003;299:1346-1351.

Conversely, various genetic manipulations which decrease the effect of the IIS signalling pathway, result in lifespan increases, ranging from 33% in mice, 80% in fruit flies, to 200 or 300% in the C. Elegans roundworm.

So, higher levels of insulin contribute to aging in a wide variety of species, ranging from yeast to mammals. The genes involved are said to be highly conserved from an evolutionary point of view.

High insulin levels

- May promote cancer (prostate, breast, pancreatic, and colorectal)

Call R, Grimsley M, Cadwallader L et al. Insulin--carcinogen or mitogen? Preclinical and clinical evidence from prostate, breast, pancreatic, and colorectal cancer research. Postgrad Med. 2010;122:158-165.

Of course, that's not all that insulin does. People with type 2 diabetes, who typically have high insulin levels, have double the risk for cancers of the liver, pancreas, and endometrium, and are also more likely to have several other kinds of cancers. And once these diabetes patients are put on insulin treatment, the cancer risk increases even more.

There are several mechanisms potentially at work. For example, insulin stimulates cells to divide, and thus may promote the growth of certain cancers. Most cancer cells have abnormally high numbers of receptors for both insulin and for insulin-like growth factor. Insulin can also increase levels of estrogen and IGF.

But as you know, people with type 2 diabetes, who have those high insulin levels, are at risk for many other conditions which can shorten lifespan, including heart disease, kidney disease, visual problems, and so on.

Dietary control of insulin

- stimulus to insulin secretion: glucose in the blood
- source of glucose in blood: dietary carbohydrates

Eat less carbs

Eat low-GI or low-GL carbs

(This slide has builds)

Although we may not have much control over how much insulin-like growth factor is circulating in our bodies, we do have some control over how much insulin is secreted by our pancreases. We exert that control by what we eat, and how much.

♥

The major stimulus to the secretion of insulin is an elevated level of glucose in our bloodstream.

♥

And the most important source of glucose in our bloodstream, for most people, is the carbohydrate in their diets. Carbohydrates are sugars and starches.

♥

Bottom line: in order to live longer, we may need to eat less carbs. ♥

Or eat carbs which are less likely to stimulate insulin secretion.

Insulin Resistance

- High levels of dietary carbs
  - high levels of circulating insulin
    - down-regulation of insulin receptors
      - fewer receptors = insulin resistance

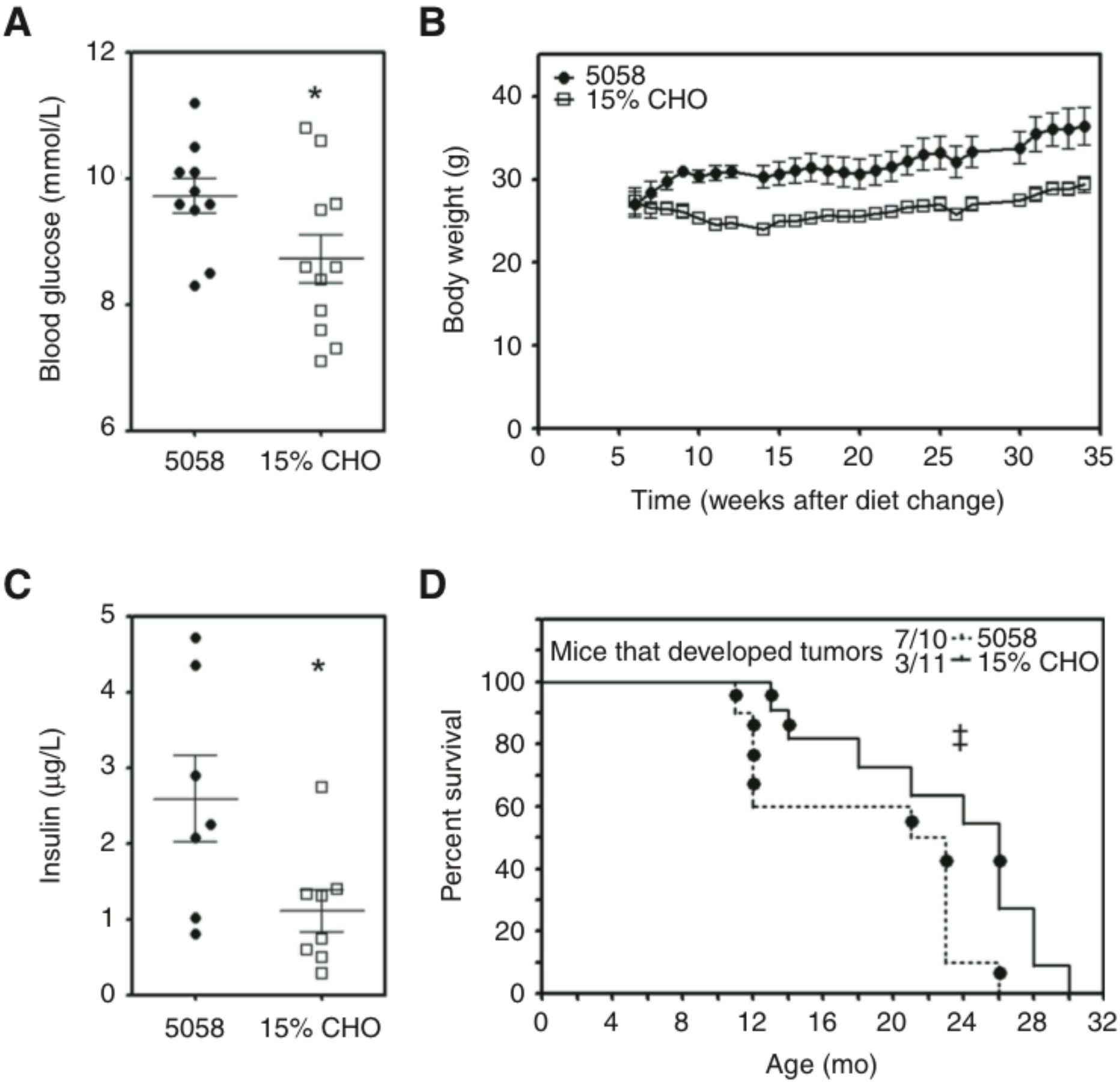
Garvey WT, Olefsky JM, Marshall S. Insulin induces progressive insulin resistance in cultured rat adipocytes. Sequential effects at receptor and multiple postreceptor sites. Diabetes. 1986;35:258-267.

We know that type 2 diabetes is characterized by insulin resistance. What causes insulin resistance? I remember from my medical school physiology classes that insulin resistance is a manifestation of receptor downregulation. Receptor downregulation occurs when the receptor substrate concentrations are high. In the case of type 2 diabetes, then, high levels of dietary carbs cause high levels of circulating insulin, which in turn causes insulin receptor downregulation, or insulin resistance. This is the same principle that I as a psychiatrist see often: it explains why people on opiate painkillers often need to escalate the dose, or why the effects of benzodiazepines wear off over time.

- when we're young:
  - dietary carbohydrates and proteins stimulate insulin production
  - insulin leads to high growth rates and fecundity
- after we finish reproducing:
  - the same diet still stimulates insulin
  - now, the insulin promotes aging and early death

...as designed by evolution

(This slide has builds)
When we're young,
♥
a diet rich in carbohydrates and protein stimulates insulin production, which leads to high growth rates and improved fecundity.
♥
After our reproductive phase is over, the same diet will still stimulate insulin production. Only now, this insulin promotes aging and early death.
♥
Exactly as planned by evolution.
What's the evidence for this?



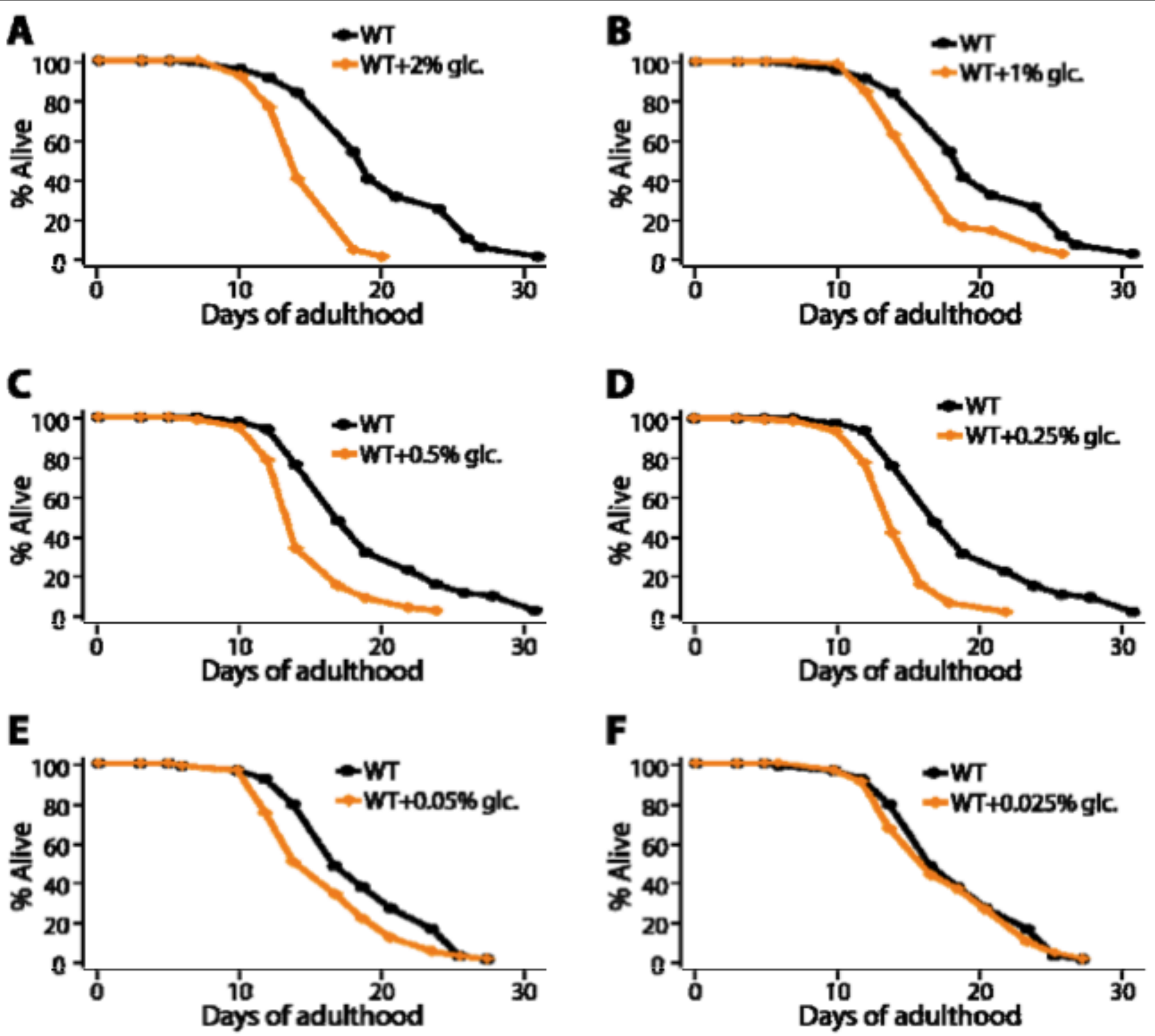
Ho VW, Leung K, Hsu A et al. A low carbohydrate, high protein diet slows tumor growth and prevents cancer initiation. Cancer Res. 2011;71:4484–4493.

I won't bore you with the details, but this is a study using mice which have been genetically engineered to spontaneously develop breast cancer. It showed that on a low-carb diet, not only did these mice develop fewer breast cancers, but they also lived longer.

This is a study on mice which have been genetically engineered to spontaneously develop breast cancer. Female mice were put on a regular "Western" diet with 55% carbs, or on a low-carb diet with only 15% carbs. Total calories were the same.

As the bottom right-hand graph shows, tumor penetrance in mice on the Western diet was nearly 50% by the age of 1 year whereas no tumors were detected in mice on the low carb diet. Each dot represents a tumor occurrence. This difference was associated with weight gains in mice on the Western diet not observed in mice on the low CHO diet, as shown in the top right-hand graph. Moreover, whereas only 1 mouse on the Western diet achieved a normal life span, due to cancer-associated deaths, more than 50% of the mice on the low CHO diet reached or exceeded the normal life span.

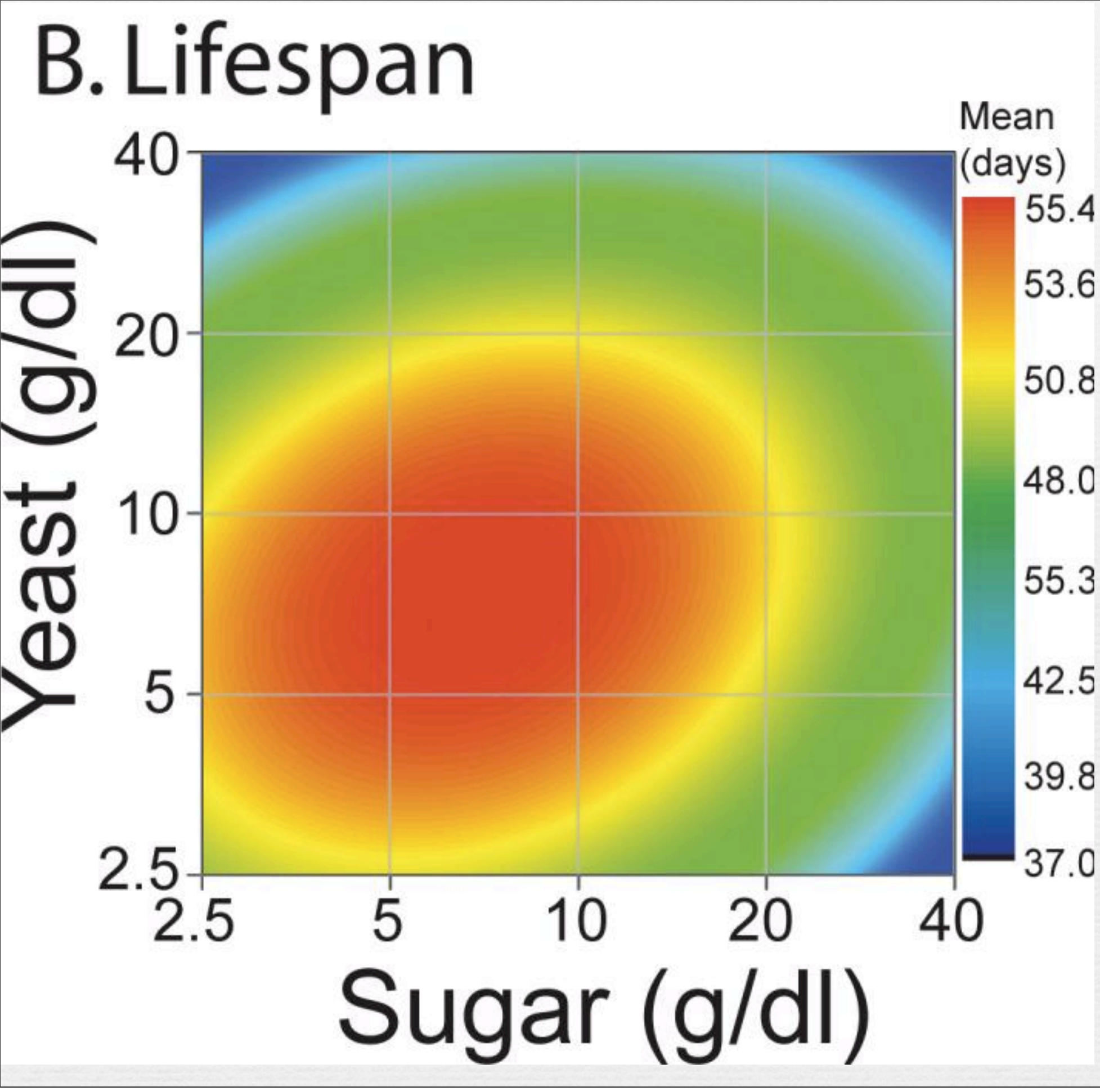
The left-hand graphs show that the low-carb diet mice had significantly lower levels not only of blood glucose, but importantly for the point I want to make, lower levels of insulin.



Lee SJ, Murphy CT, Kenyon C. Glucose shortens the life span of C. elegans by down-regulating DAF-16/ FOXO activity and aquaporin gene expression. Cell Metab. 2009;10:379-391.

Again, without going into detail, this study with the C. Elegans roundworms demonstrated that the more sugar they were given, the shorter their lifespan.

Conversely, adding sugar to the medium used for breeding the C. Elegans roundworm, decreases lifespan in a dose-dependent way. These 6 graphs show the survival curves for worms, with the black lines for the usual medium, and the orange lines for the worms with added glucose. The 2% glucose solution produced the greatest decrease in lifespan, as shown in curve A, with progressively decreasing effects with smaller percentages of sugar. Curve F shows that when you get down to 0.025% glucose, there is no longer an effect on lifespan.



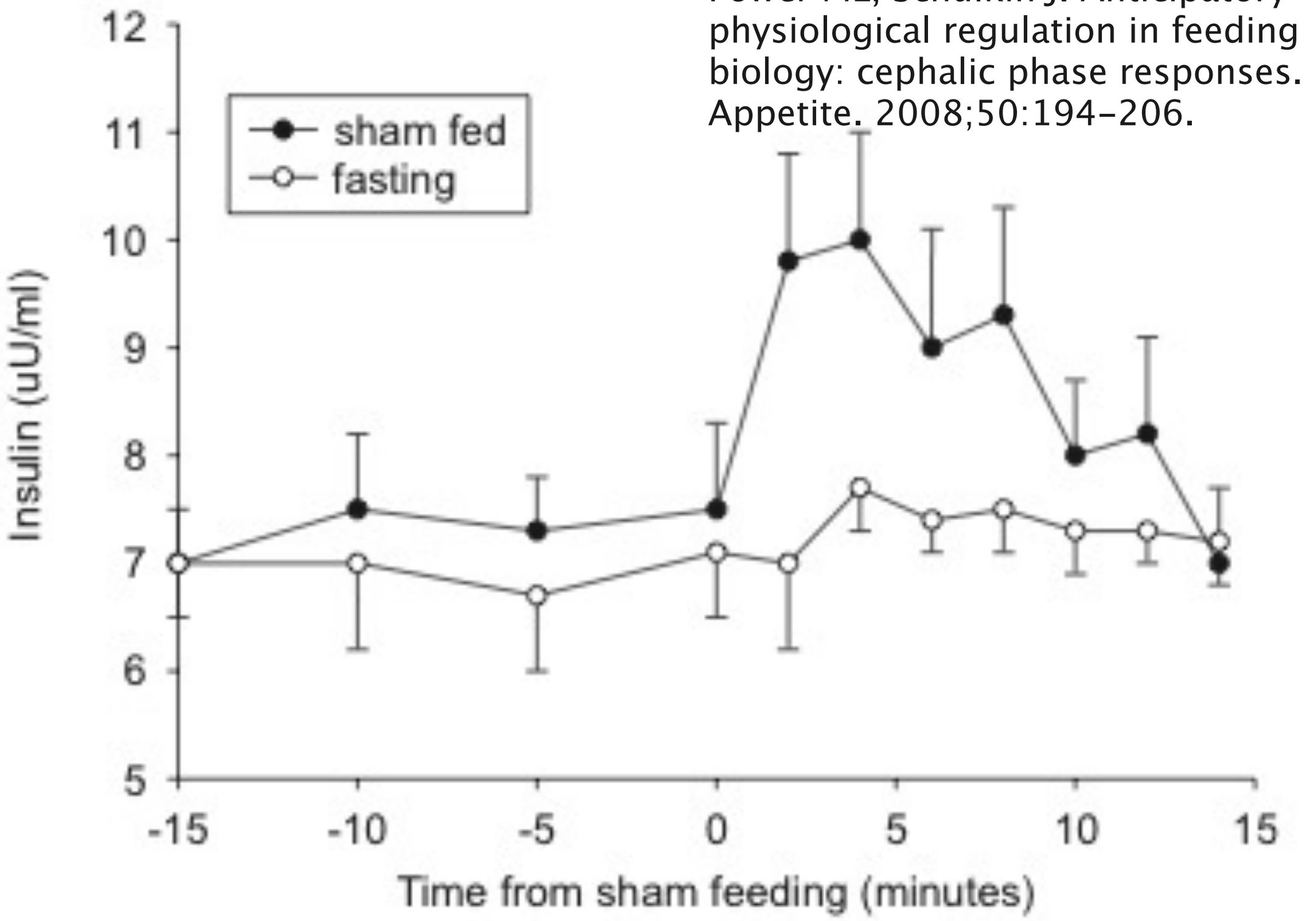
Skorupa DA, Dervisefendic A, Zwiener J, Pletcher SD. Dietary composition specifies consumption, obesity, and lifespan in Drosophila melanogaster. Aging Cell. 2008;7:478–490.

With fruit flies also, the longest lifespan, at the center of this red oval, was obtained with a diet balanced in yeast and sugar. Giving more sugar, or more yeast, shortened lifespan.

Similar results have been obtained with fruit flies. In this experiment, fruit flies were fed one of 25 different diets which varied in the amounts and proportion of yeast and sugar. This contour plot shows that maximum lifespan occurs with a diet having about 8 grams per deciliter of both yeast and sugar. As the sugar content or the yeast content increases, lifespan goes down.

Cephalic phase response

Power ML, Schulkin J. Anticipatory physiological regulation in feeding biology: cephalic phase responses. Appetite. 2008;50:194–206.



Interestingly, it isn't only the eating of those carbs that stimulates insulin. Just tasting sweet on the tongue, and even the smell of the food can do it. In humans, seeing the food even in sealed containers can stimulate gastric secretions. These anticipatory changes are called cephalic phase responses, and were first described by Pavlov (you remember the dog who was trained to salivate upon hearing a bell?).

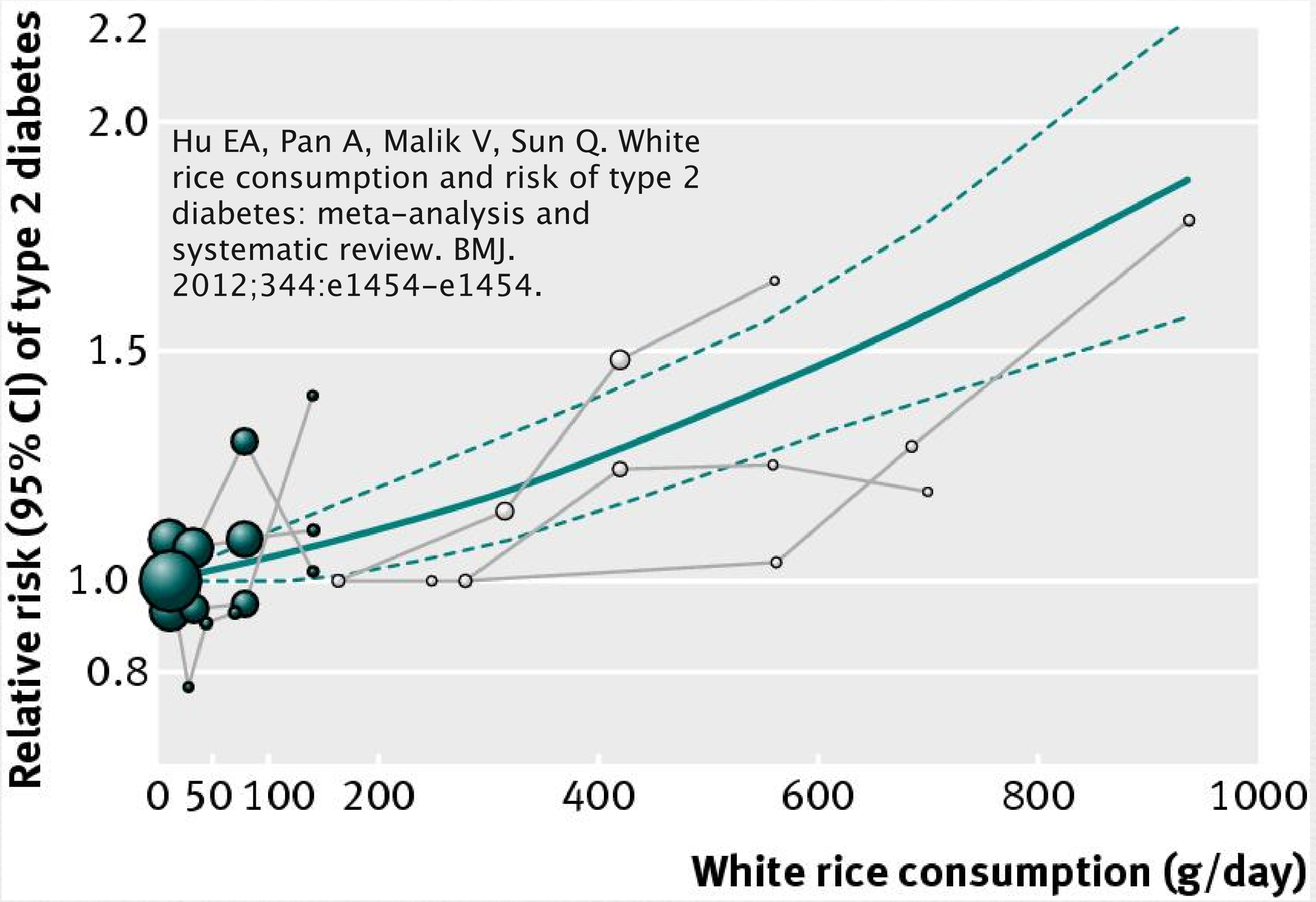
The upper set of points shows the insulin response in human subjects to a sham feeding (the subject chews the food but then spits it out without swallowing).

Human Evidence

Kassi E, Papavassiliou AG. Could glucose be a proaging factor? J Cell Mol Med. 2008;12:1194-1198.

What is the evidence implicating dietary carbohydrates in humans? So far, people have just barely started to even ask the question.

You've all seen the reports implicating soft drinks, particularly those sweetened with high-fructose corn syrup, as a cause of obesity.



Hu EA, Pan A, Malik V, Sun Q. White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review. BMJ. 2012;344:e1454-e1454.

Here is a meta-analysis of studies which looked at the risk of developing type 2 diabetes for different levels of consumption of white rice, which is almost entirely starch. They found a dose-response relationship, suggesting that high starch consumption causes diabetes.

Dose-response relation between white rice intake and risk of type 2 diabetes. Solid line represents point estimates of association between white rice intake and diabetes risk; dashed lines are 95% CIs. Filled circles are relative risks corresponding to comparison categories in studies in Western populations; open circles are for studies in Asian populations. Size of circle is in proportion to sample size for each comparison group.

Low-carb diets

- for weight loss
- treatment of epilepsy
- treatment of type 2 diabetes

Westman EC, Yancy WSJ, Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr Metab (Lond). 2008;5:36.

But there is lots of evidence that low-carb diets are effective for weight loss, treatment of type 2 diabetes, even for the treatment of epilepsy.

For example, this study compared a low-carbohydrate, ketogenic diet to a low glycemic index diet. In the low-carb arm, 20 out of 21 patients were taking medication for their diabetes. All 20 were able to reduce or eliminate their medication while on the low-carb diet.

Who here has heard of type 3 diabetes? Show of hands.

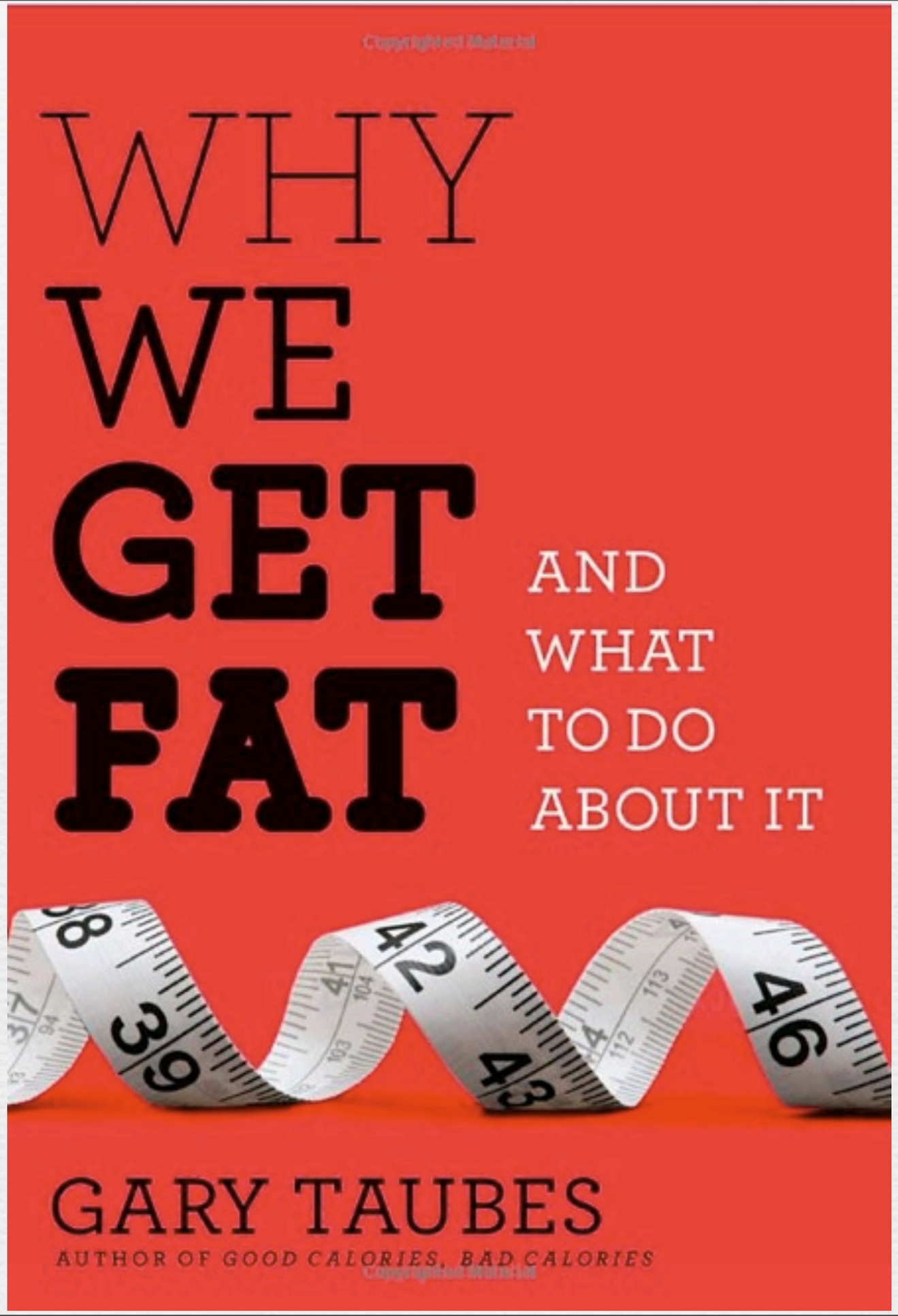
Type 3 diabetes

- Type 2 diabetics have 2-3x risk for Alzheimer's
- AD brains show insulin resistance
- intranasal insulin improves cognition
- hyperinsulinemia by itself is a risk factor for AD

de la Monte SM. Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. Curr Alzheimer Res. 2012;9:35-66.

It's known that patients with type 2 diabetes have 2 to 3 times greater risk for developing Alzheimer's Disease. It's also known that the brains of AD patients have substantial downregulation of several components of the insulin and insulin-like growth factor signalling pathway. Finally, administration of intranasal insulin improved cognitive function in patients with AD.

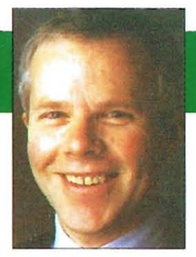
These and other findings have led to the hypothesis that AD is primarily a metabolic illness characterized by insulin resistance in the brain, or type 3 diabetes. Again, it is likely that high insulin levels are responsible for the insulin resistance.



I showed you this book cover earlier. For the past 40 years of so, doctors, dieticians, and other experts have been telling us to eat less fat in order to prevent heart disease. Unfortunately, their suggestion was to replace the fat with carbohydrates. The result is that we are now seeing a pandemic of obesity and type 2 diabetes.

The author of this book, Gary Taubes, is a science journalist who has published extensively on the bad science and the politics behind the low fat advice. Both in this book and in an earlier work, entitled “Good Calories, Bad Calories”, Taubes explores in detail the science that supports low-carb as the life-style of choice for good health. The key is insulin, which as we learned in med school physiology, is what causes fat cells to store fat, and also prevents the use of that stored fat as fuel.

SECOND OPINION/ *by Dr. Henry Olders*



Sue Truman

METABOLIC MAYHEM

Hunter-gatherers trapped in an agrarian age

What disease affects 33% of Canada's population and costs the health-care system $6 billion per year? Obesity. Spreading rapidly around the world, this scourge doubles in prevalence every five years. But not everyone becomes obese. So is it entirely a question of how many calories you eat, or how much exercise you get? Highly unlikely. These factors are probably less important than genetic makeup interacting with the specific foods a person eats.

The so-called thrifty gene is found in about 25% of the North American population and an even greater proportion of aboriginals. On a typical North American diet, carriers of this gene often become obese and develop adult-onset diabetes, along with cardiovascular disease and high blood pressure. In aboriginal peoples on traditional diets, these illnesses were essentially unknown. What changed?

One hypothesis is that thrifty-geners (TGs) have a metabolism genetically programmed for a low-carbohydrate hunter-gatherer (HG) diet in which game, fish and insects providing fat and protein were supplemented by edible leaves, fruits, flowers, roots and tubers. Without cooking and processing, much of the carbohydrate in the latter could not be absorbed and selective breeding had not yet increased sugar and starch content.

Every autumn, however, the availability of high-carb items increased dramatically, as wild fruits, nuts, vegetables and grains became ripe. HGs who feasted on the plenty accumulated body fat and better survived the winters of scarcity. Those most able to fatten up were more likely to reproduce and pass on their thrifty gene.

Enter the agrarian era, with the cultivation of foods for storage and consumption. With grains, vegetables and fruits providing a rich and continuous source of carbohydrates, the feast-famine HG metabolism became obsolete. Those responding to the high-carb regimen with quick weight gain remained obese when

experience as a hunter-gatherer trapped in the postagrarian age. Overweight and unathletic from childhood, I stopped smoking after the birth of my first child and immediately gained 10 lb. Chancing upon the Atkins diet, I easily lost 20 lbs., dropping down to 150 lbs. on my frame of 5' 9". When I stopped the diet, I rapidly gained 5 lbs. Over the next 25 years, my weight crept up to 175 pounds, in spite of running, cross-country skiing, roller-blading and triathlons.

With a family history of diabetes and heart disease, I restarted on the Atkins diet in October 1996, losing 12 lbs. in six weeks. I have kept my weight steady by avoiding potatoes, rice, bread, pasta and sugar—except for special occasions. I eat a lot of meat, cheese, fish and eggs, and high-fibre vegetables daily, particularly lettuce, celery, raw spinach, peas, green beans or broccoli. Glucose-raising fruit juices are out, although I occasionally have raw fruit. Large dollops of mayonnaise accompany meats, foods are fried in canola oil, butter is added to cooked vegetables. A typical breakfast is five strips of bacon and three fried eggs, complete with pan drippings.

A heaping daily tablespoon of psyllium husks in a large glass of water prevents constipation. The diet is also supplemented with a multivitamin, 1,000mg of slow-release vitamin C, 800IU of vitamin E, plus a garlic capsule and β-carotene, calcium and magnesium.

Reading food labels is essential to avoid items containing any form of sugar (glucose, sucrose, dextrose, maltodextrin, corn syrup or solids, fructose). I look for items with a gram or less per serving.

At a weight of 170 lbs., I have put on lean muscle, thanks to weight training and cross-country skiing. My endurance when running, cycling or skiing has improved. Because I burn fats instead of glycogen when exercising, I no longer "run into the wall" or "bonk" when my muscles run out of glycogen. Gone are

I've been eating low-carb, more or less, for the past 16 years. Even before that, I had been aware of the negative effects of a high-carb diet. I'd even written about it. This article, entitled "Metabolic mayhem: hunter-gatherers trapped in an agrarian age" was published in 1998 in a monthly newspaper distributed to Canadian doctors called "The Nutrition Post".

Dietary carbohydrates

- Causes obesity and type 2 diabetes in some people (metabolic syndrome)
- obesity & diabetes contribute to cardiovascular disease and depression
- cardiovascular disease & depression are risk factors for dementia

May contribute directly to aging

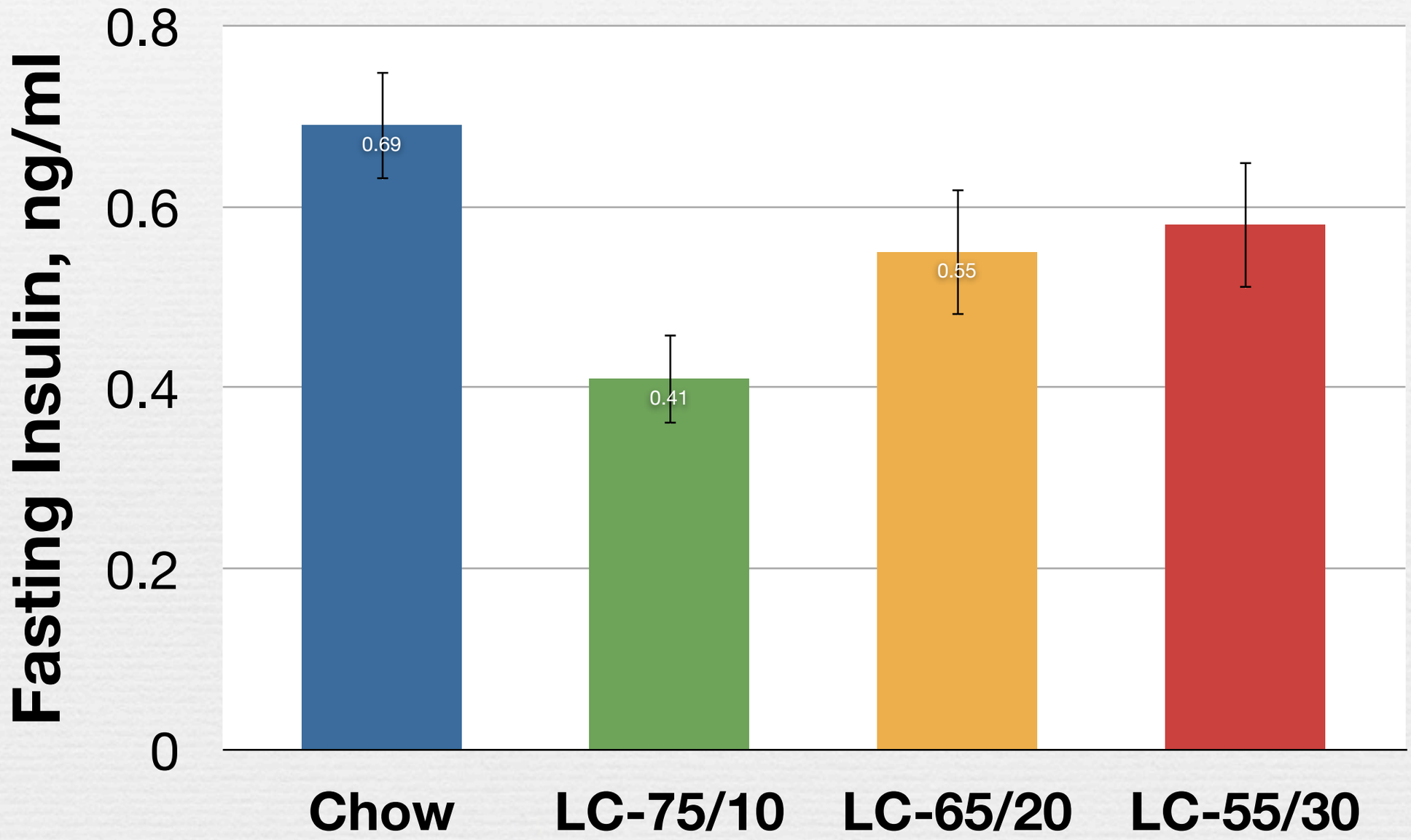
(This slide has builds)

What I knew then was that some people are genetically susceptible to gain weight quickly on a typical high-carb diet. This obesity then contributes to metabolic syndrome and type 2 diabetes; both of these contribute to heart disease. Obesity seems to contribute also to depression, and depression and heart disease are risk factors for dementia. Not to forget that too much sugar rots your teeth!

So a high-carb diet in many people contributes to ill-health and increased mortality. What I didn't know then, and what my recent researches in aging are now telling me, is that ♥

high-carb diets may contribute directly to aging, via the insulin and insulin-like growth factor signalling pathways. Who knew?

Dietary Fat



Bielohuby M, Menhofer D, Kirchner H et al. Induction of ketosis in rats fed low-carbohydrate, high-fat diets depends on the relative abundance of dietary fat and protein. Am J Physiol Endocrinol Metab. 2011;300:E65-76.

I said earlier that both dietary carbohydrates AND dietary protein stimulate insulin secretion. Carbs lead to an increase in blood glucose, while dietary proteins are broken down into amino acids, two of which, arginine and leucine, stimulate insulin secretion. Thus, replacing carbs in the diet with protein is likely to be only a half-measure. However, replacing carbs with fats may reduce the amount of insulin secreted.

In this experiment using rats, the group on the low-carb diet with 75% of dry weight as fat and 10% as protein (LC-75/10) had significantly lower levels of fasting insulin compared to the group fed rat chow, or to the groups with lower percentages of fat content and more protein.

I mentioned methionine restriction earlier. I've just started this as a diet, and the challenge is to find low-methionine foods which are also low glycemic load.

Conclusions

- Aging and a reduced lifespan when times are good, are programmed in by evolution
- Vitamins and dietary supplements may be beneficial when we're young, but may contribute to aging and mortality when we're older
- Other dietary components and certain drugs may increase longevity, but may also impair reproduction
- Having a large social circle and helping others is associated with longevity
- Because aging is partially controlled by insulin, low-carb or low-GI dieting may help keep us young longer

So to conclude, here are the principal points that I hope I've communicated today. (read)

Implications for Policy-Makers

- Increases in longevity are more strongly related to decreases in fecundity than to health care spending
- Health decisions affecting the population (eg, fortifying flour with folic acid) should take into account that effects may differ between younger and older people

For policy-makers, throwing money at health care is less likely to improve longevity than people having fewer children; and be careful when making treatment decisions affecting large segments of the population, such as mandatory fortification of flour with folic acid.

Implications for Researchers

- Studies should be designed with the expectation that outcomes will depend not only on age but also on gender

- Aging-associated deterioration should be considered as built in by evolution, rather than as "diseases" with external causes

- Focus on finding out what makes the exceptions (those who have good health and longevity) different from the rest

Break down study results by age and gender; deterioration with age is the norm, not a disease; look for the exceptions

Implications for Clinicians

- You now have a rationale for recommending coffee and red wine to your older clients while discouraging them for those seeking to have children
- Re hyperinsulinemia / insulin resistance in metabolic syndrome and type 2 diabetes:
  - Reconsider the role of diet composition vs calories consumed/expended

The good news is that us older folks can now feel good about drinking coffee and red wine.

And, a special appeal to those of you who treat people with metabolic syndrome and type 2 diabetes: please be open to the possibility that diet composition may play a greater role than the number of calories consumed or expended.

To do so means no longer having to blame the victims of this pandemic for their lack of willpower in eating too much and not exercising enough.

Implications for geriatric psychiatrists

- Consider the possibility that Alzheimer's Disease may be a metabolic disease characterised by insulin resistance in the brain

- Interventions which lower insulin levels may help prevent and/or treat AD

Luchsinger JA. Type 2 diabetes and related conditions in relation to dementia: an opportunity for prevention? J Alzheimers Dis. 2010;20:723–736.

For those of us working in geriatrics or geriatric psychiatry, we may need to start considering the possibility that some cases of Alzheimer's Disease are really a type of diabetes affecting the brain. This raises the fascinating possibility that preventive interventions or treatments for type 2 diabetes may also have a role in Alzheimer's. This includes medications such as metformin, acarbose, and insulin sensitizers, but especially low-carb diets.

Words of wisdom

- Old age isn't so bad when you consider the alternative.
  ~Maurice Chevalier, *New York Times*, 9 October 1960

- If I knew I was going to live so long, I would have taken better care of myself. ~George Burns, on turning 100

- Everything slows down with age, except the time it takes cake and ice cream to reach your hips. ~Attributed to John Wagner

- Middle age is when a narrow waist and a broad mind begin to change places. ~Author Unknown

- You are only young once, but you can stay immature indefinitely. ~Ogden Nash

Finally, here are some words of wisdom on aging. The one at the bottom is my favourite.

Thank you very much. You've been a great audience!

Link to pdf of talk:

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