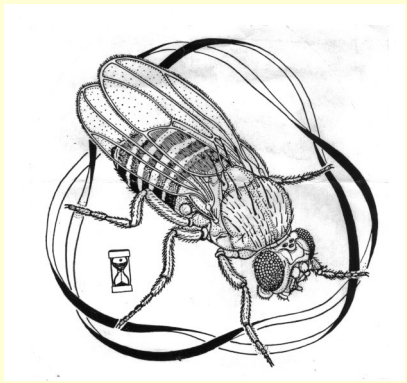
Yukawa International Symposium:

What is Life? The Next 100 Years of Yukawa's Dream

WHY AND HOW WE AGE….. AND IS THAT PROCESS MODIFIABLE?



Robert Arking

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Detroit, MI USA

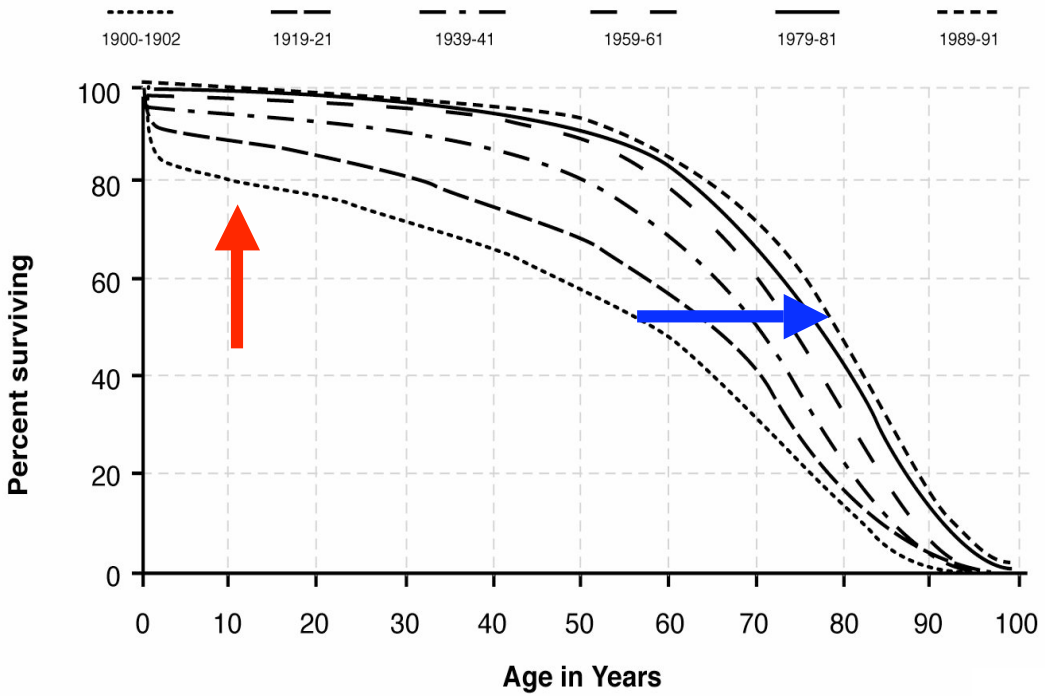
Aging has been a central concern of human beings for at least 50,000 years

Aging has long been accepted as an immutable fact of life

This is no longer true

Today we know how to manipulate aging in the lab, & that technology is poised to move into human society.

Goal of talk: integrated conceptual overview of aging over the life span

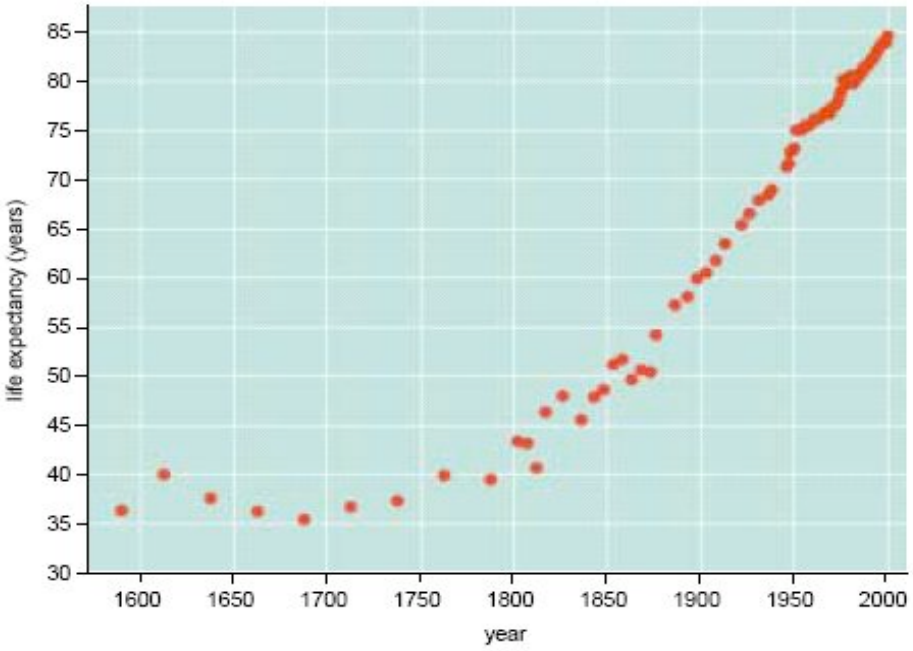


Longevity has increased due to decreases in extrinsic factors of mortality.

Greatest Success of the 20th Century!

Increasing longevity is a long-term trend. We have gained 1 month of life every ~4 months!

Is it reasonable to believe this gain can continue in future?



Two Conceptual Models of Aging

Medical Model:

- ***All deaths are due to disease***

Assumes existence of an aging program

Biological Model:

- ***Disease & aging are different processes.***
- ***Aging has an evolutionary basis***

Rules out existence of an aging program: Aging is a stochastic affair

"It is truly amazing that a complex organism, formed through an extraordinarily intricate process of morphogenesis, should be unable to perform the much simpler task of merely maintaining what already exists"

Francois Jacob, 1982

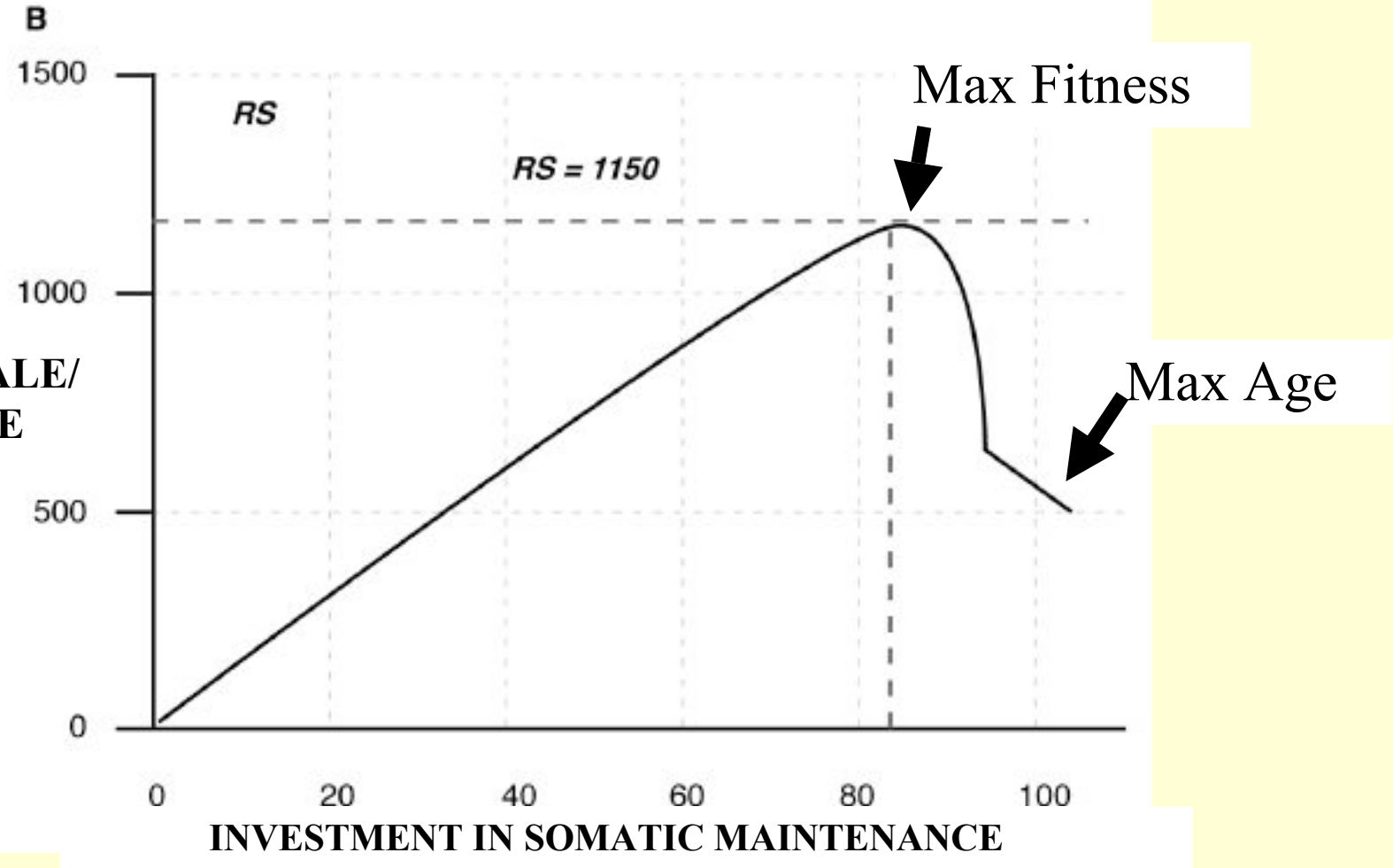
What answer can we give him, based on today's understanding of the aging process?

The Answer?

We age not because we must age, but because there is no biological reason <u>not</u> to age.

Disposable Soma Theory:

It Costs Less Energy to Reproduce While Young Than It Does to Live A Long Life



from Kirkwood, 1977 & Arking et al., 2002

Nothing in biology makes sense except in the light of evolution.

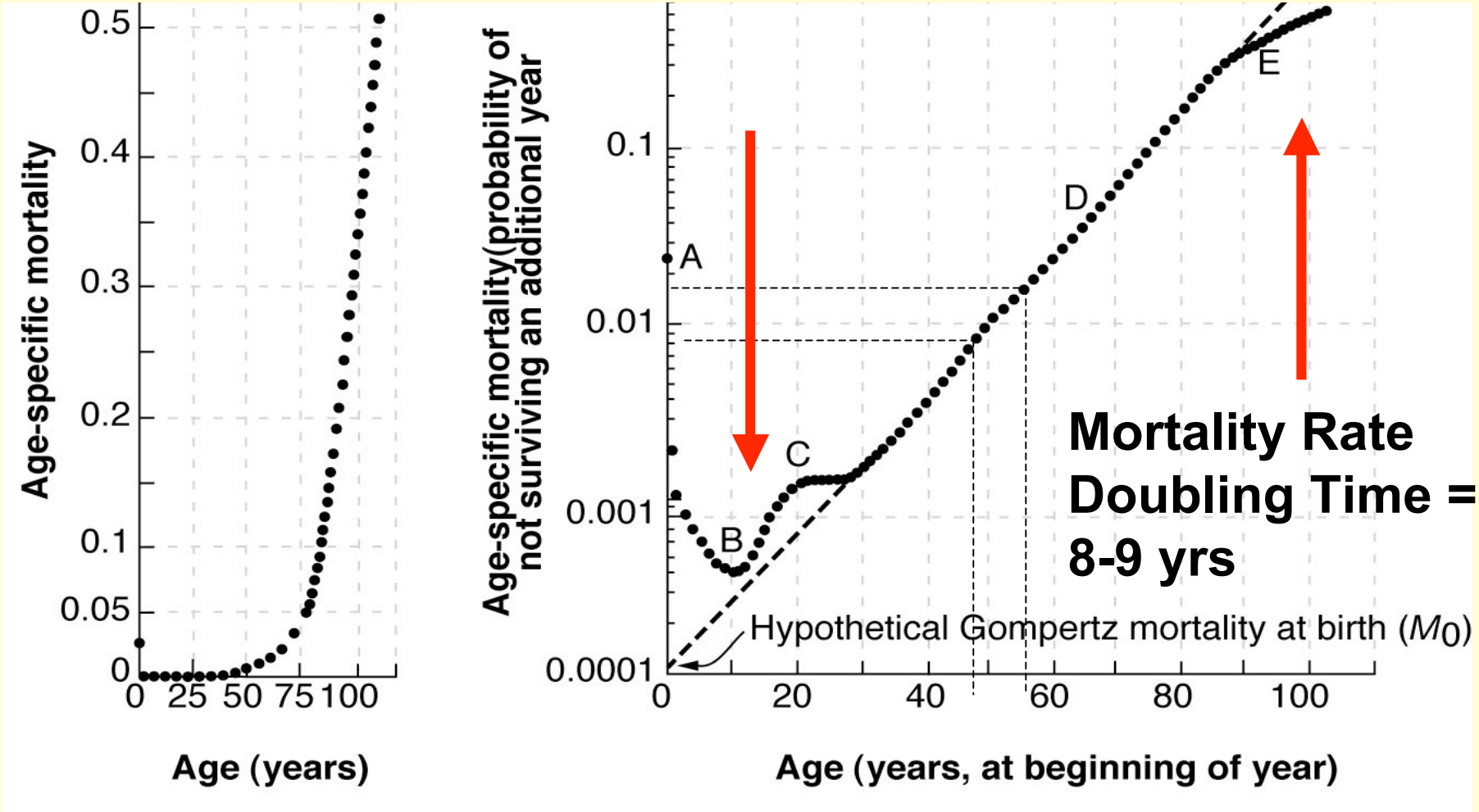
Th. Dobshansky, 1973

- **The name of the game is to get copies of your genes into the next generation.**

- **You are an active player and affected by natural selection only so long as you play the game; once you fold your hand, you are a kibbitizer and are invisible to natural selection. It doesn't matter if you live or not.**

- **Your Darwinian fitness is more important than your longevity!**

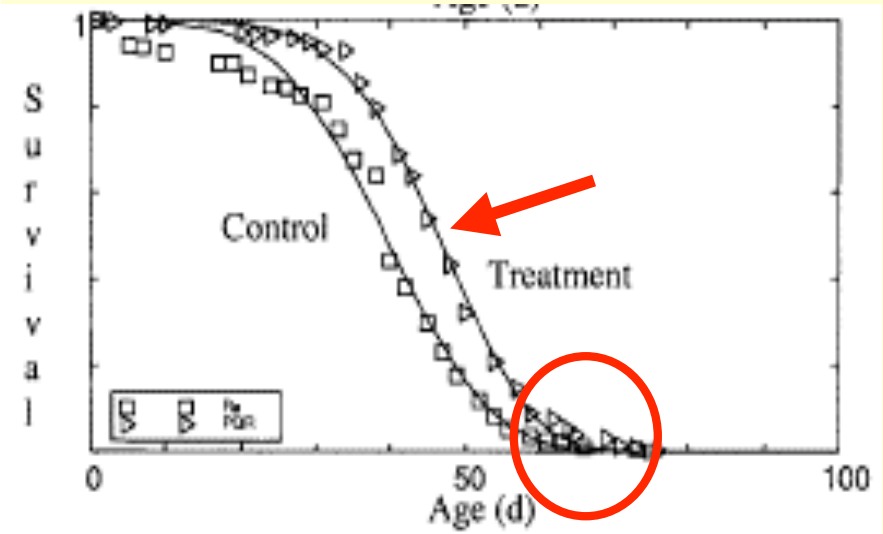
If an Aging Program exists, then it will be impossible to significantly alter the mortality kinetics



How Many Ways Are There to Alter Normal Aging in the Lab?

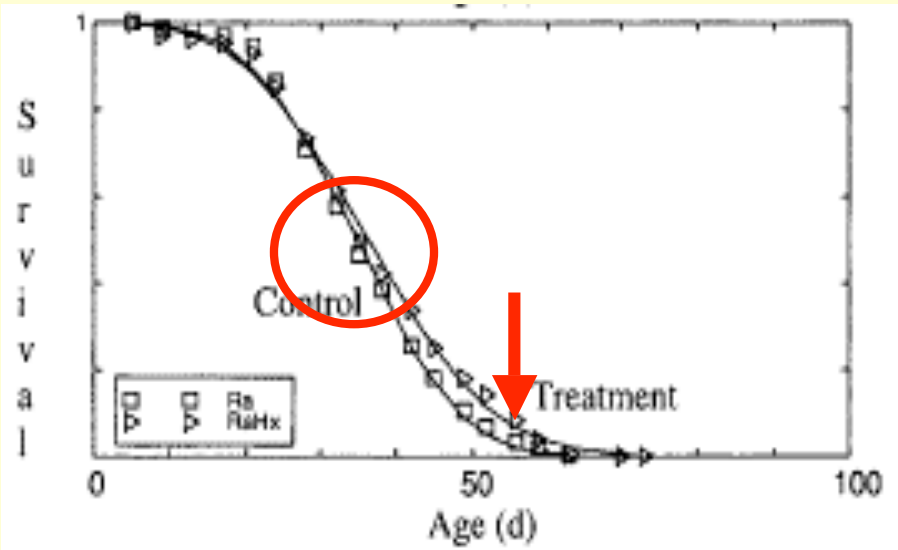
THREE…

1. Increase Mean Longevity



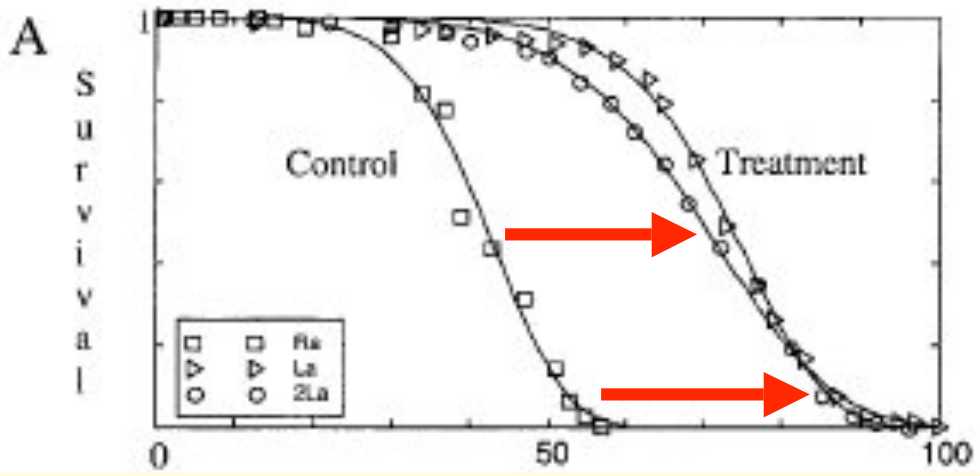
after Vettraino et al, 2001 ;

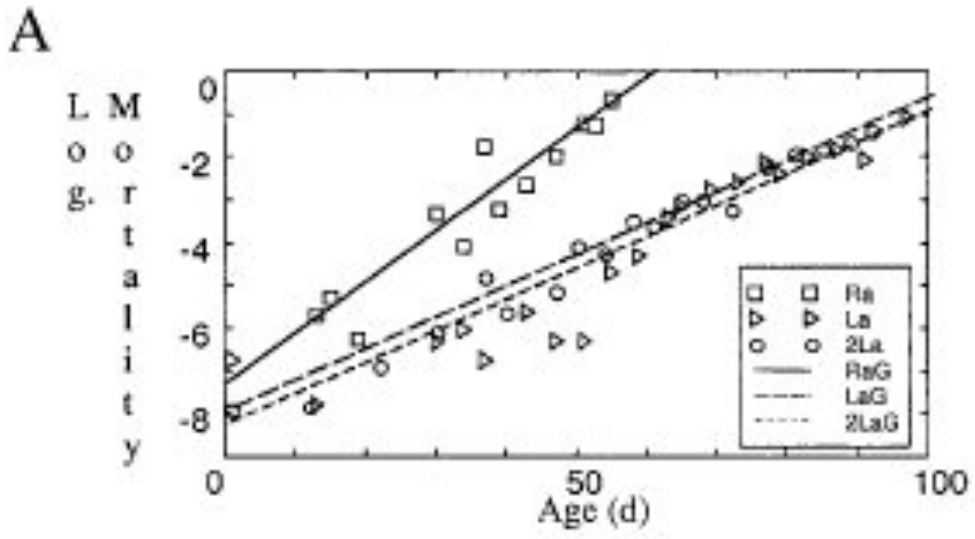
2. Increase Maximum Longevity



after Keuther & Arking, 1999

...and the Third Way: Delayed Onset of Senescence





Selection for longevity yields an increase in the 'health span' but no effect on the 'senescent span'.

after Arking, 1987;

DR mice, **no human example**

The life span changes are due to delayed onset of the midlife increase in the age specific mortality probability, giving rise to an extended 'health span'

MRDT = ~9 days vs ~6 days

after Arking et al., 2004

The fact that we can easily alter the 'normal' mortality kinetics simply shows that there is no aging program.

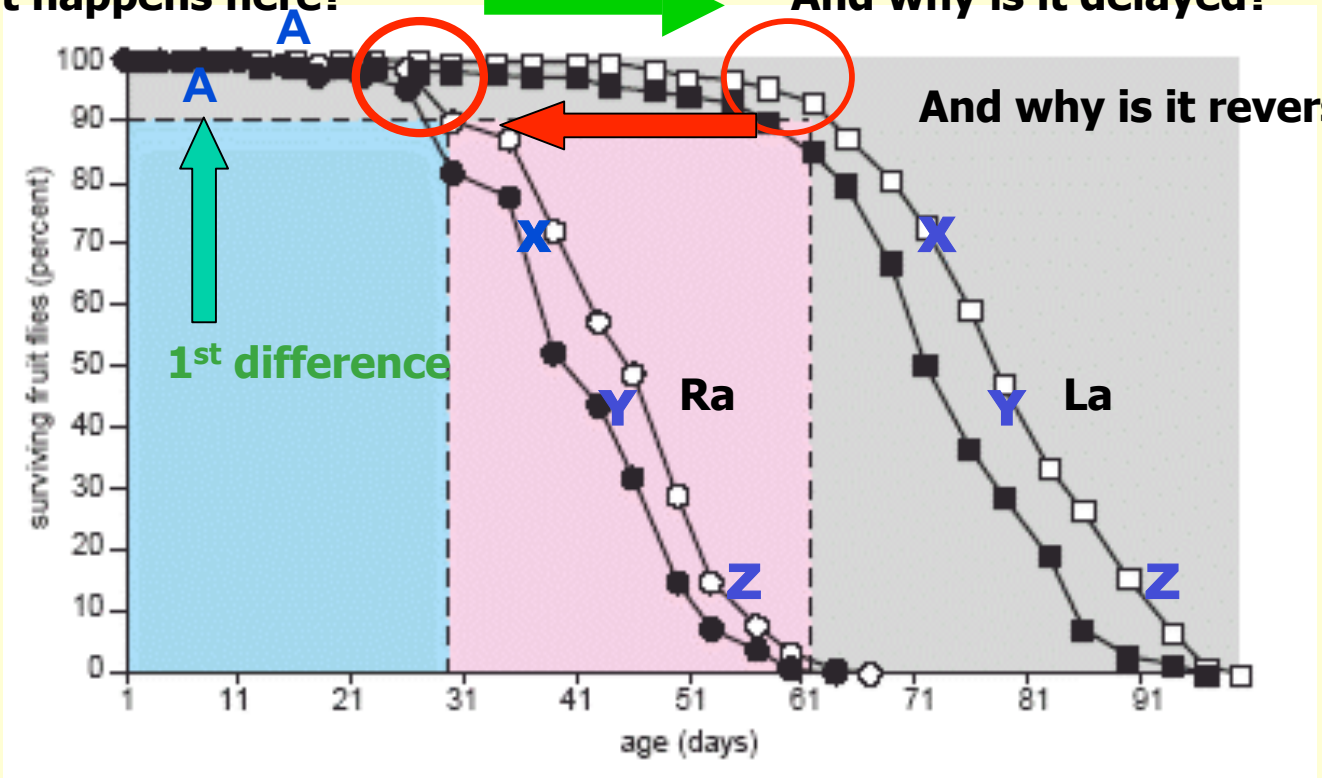
In fact, it demonstrates that the processes which control our longevity are plastic.

How plastic?

How does normal longevity differ from extended longevity in lab animals?

Delayed Onset of Senescence (DOS)Phenotype

What happens here? **And why is it delayed?** ***shomme***



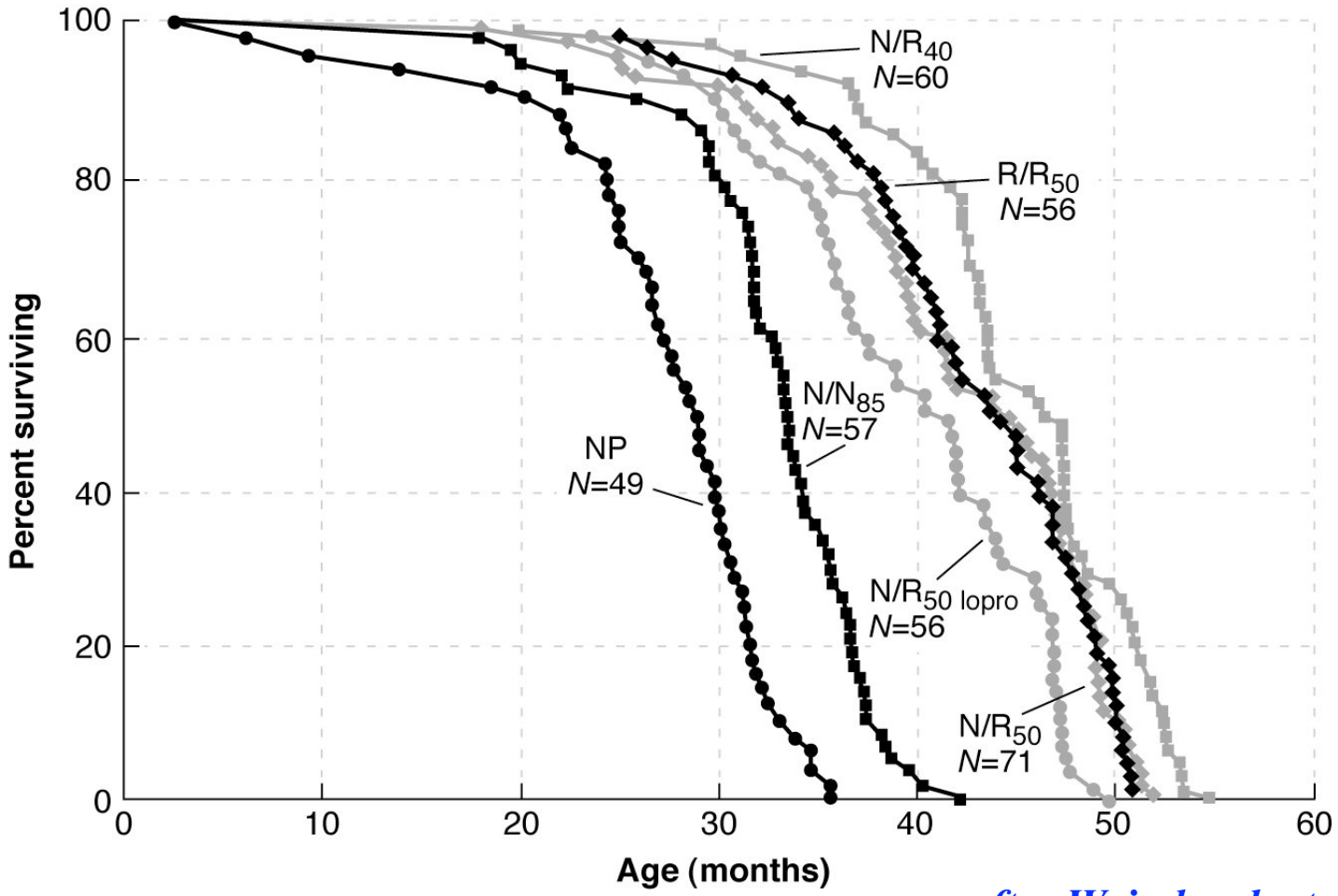
The "HEALTH SPAN" and the "SENESCENT SPAN"

After Arking, 1987 Wells & Arking, 1990; Arking et al., 2000, 2002

What Stimuli Induce the DOS Phenotype?

- Dietary Restriction (DR)
- Lifestyle
- Innate Genetic Differences
- Altered Cell Signaling Pathways
  - Mutants
  - Drugs
  - Change in Signals

Dietary Restriction Effects on Mice



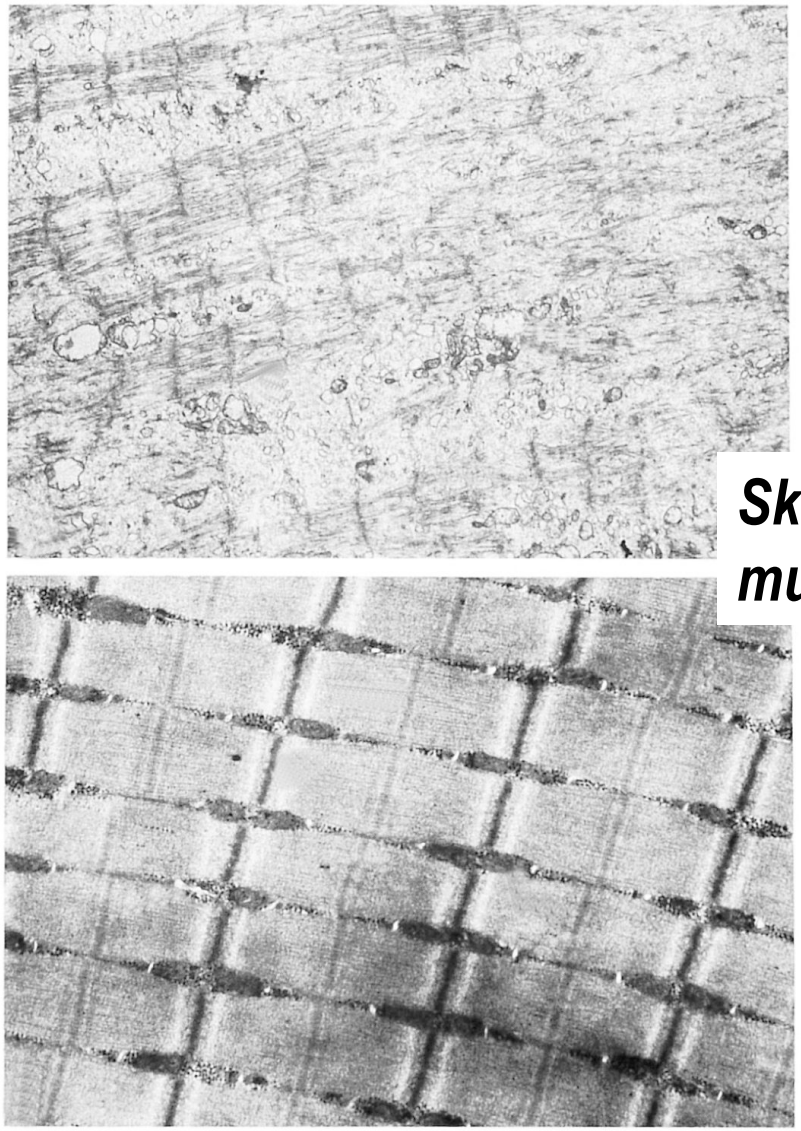
after Weindruch et al., 1986

DR Maintains Cell Structure

Wistar male rat, AL diet, 1010 days old

energy?

Wistar male rat, DR diet, 1248 days old



Skeletal muscle

Effects of Caloric Restriction on a Human

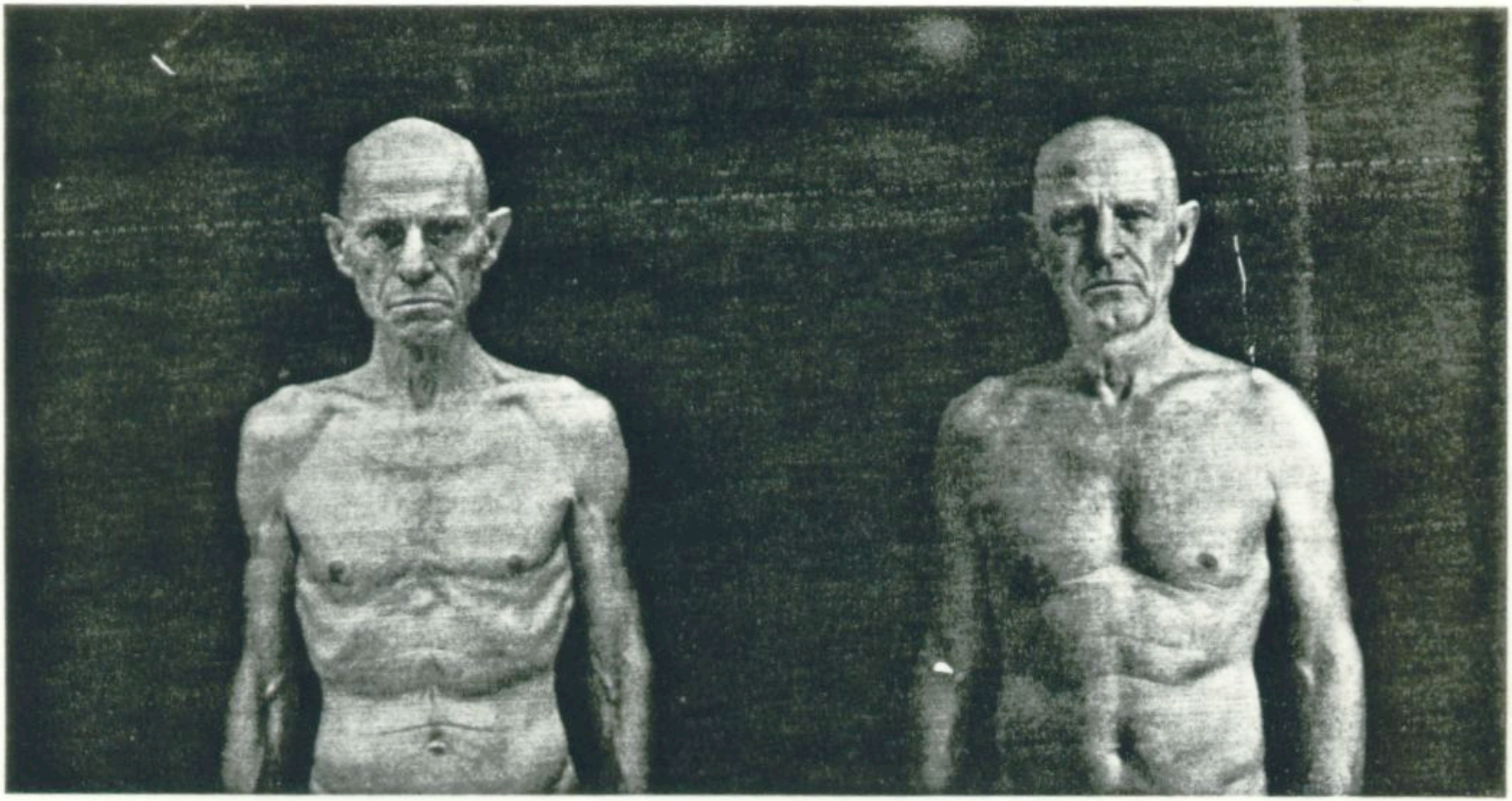


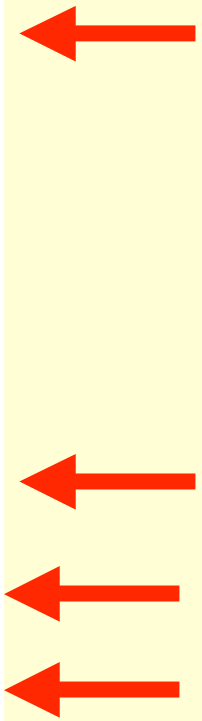
Figure 5. Composite photograph of the senior author (R. Walford) after 15 months residence inside Biosphere 2 (on the left: weight 119 lb or ~54 kg), and 18 months after exiting Biosphere 2 (on the right: weight 150 lb, or ~68 kg; normal weight when on an ad libitum diet).

Why Are Our Concepts of Beauty Based on Plumpness?

Effect of CR on Humans

	Western diet	Calorie restricted
Age (years) (33)	52.3 ± 10	51.4 ± 12
Male:female	29:4	29:4
Body mass index (kg/m^2) (33)	24.8 ± 3.2	19.6 ± 1.6†
Total body fat (%) (33)	23.1 ± 7	8.4 ± 7†
Truncal fat (%) (33)	23.4 ± 9.7	4.6 ± 5.7†
Systolic blood pressure (mm Hg) (33)	130 ± 13	103 ± 12†
Diastolic blood pressure (mm Hg) (33)	81 ± 9	63 ± 7†
Total cholesterol (mg/dl) (33)	202 ± 33	162 ± 34†
LDL-cholesterol (mg/dl) (33)	122 ± 30	86 ± 24†
HDL-cholesterol (mg/dl) (33)	52 ± 15	64 ± 18*
Total cholesterol:HDL-cholesterol ratio	4.2 ± 1.2	2.5 ± 0.5†
Triglycerides (mg/dl) (33)	143 ± 93	58 ± 18†
Glucose (mg/dl) (33)	95 ± 9	84 ± 8†
Insulin (μU/ml) (33)	7.4 ± 6	1.5 ± 0.9†
TNFα (pg/ml) (28)	1.5 ± 0.9	0.7 ± 0.5*
C-reactive protein (mg/L) (31)	1.1 ± 1.2	0.2 ± 0.3†
TGFβ1 (ng/ml) (31)	22.1 ± 6.6	14.9 ± 3.1†
Triiodothyronine (ng/dl) (28)	91 ± 13	74 ± 22†

Values are means ± SD for the number of subjects given in parentheses.
* $P < 0.01$; $^\dagger P < 0.001$ CR versus Western diet.



from Holloszy & Fontana, EG 42:709, 2007

Observed Changes in Gene Expression of Post-mitotic Tissues of the Mouse During Normal and Delayed Aging**

Experiment	*Normal Aging*	*CR* Delayed Aging*
Effect of CR* on mouse muscle	↑Stress Response ↑Neuronal Injury ↓Energy Metabolism	↑Biosynthesis ↑Protein Turnover ↑Energy Metabolism ↓Macromolecular Damage
Effect of CR* on mouse brain	↑Stress Response ↑Inflammatory Response ↓Protein Turnover ↓Growth Factors	↓Stress Response Better Immune modulation ↓Protein Synthesis ↑Growth Factors ↑DNA Synthesis

* *caloric restriction*

** data for top panel taken from C-K. Lee et al. Science 285:1390-1393, 1999.
data for the bottom panel taken from C-K. Lee et al. Nature Genetics 25:294-297, 2000

What Stimuli Induce the DOS Phenotype?

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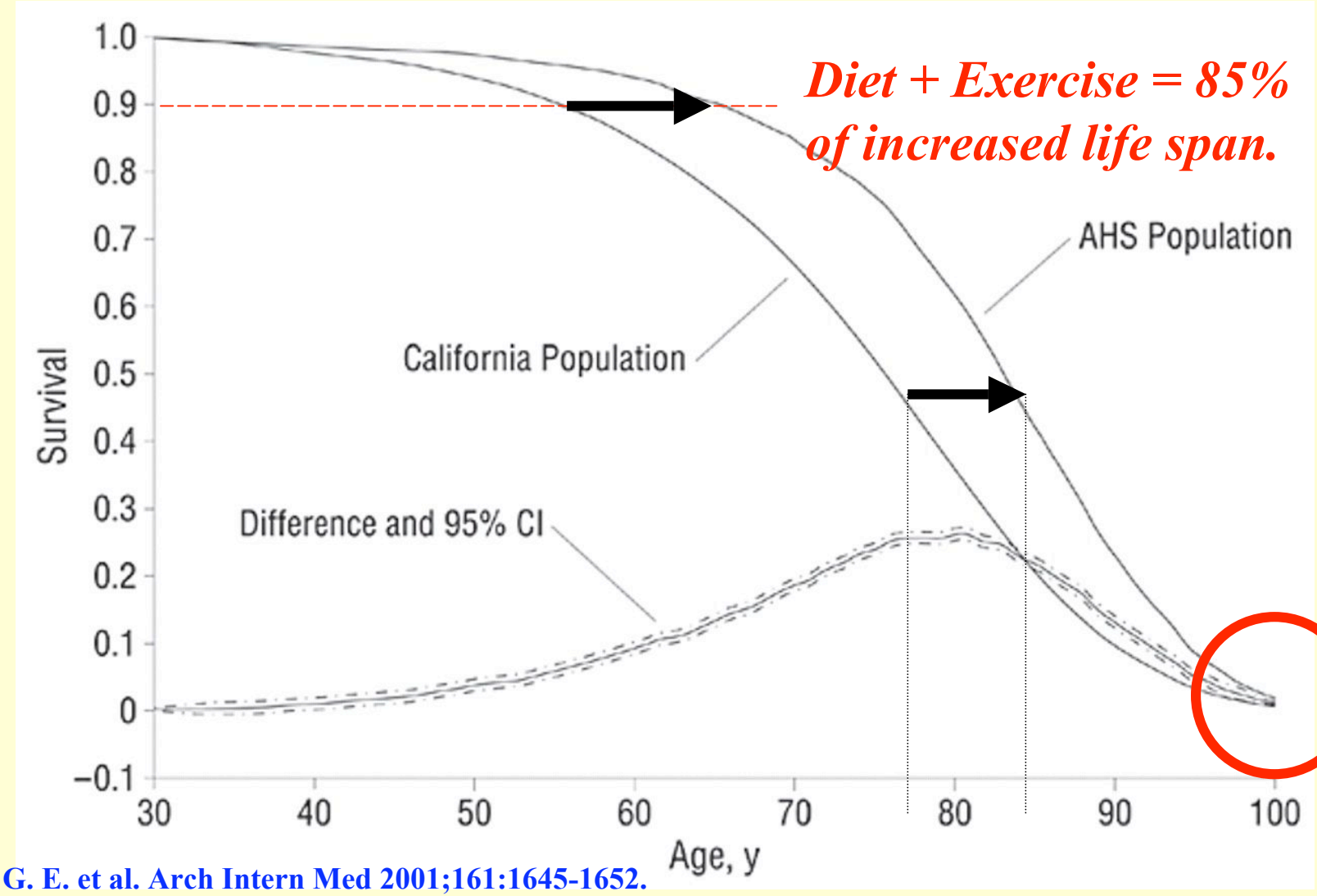
  - Change in Signals

A Vegetarian – Exercise- Non smoking Lifestyle Significantly Increased Mean Longevity and LE_{65} .



Fraser, G. E. et al. Arch Intern Med 2001;161:1645-1652.

What Stimuli Induce the DOS Phenotype?

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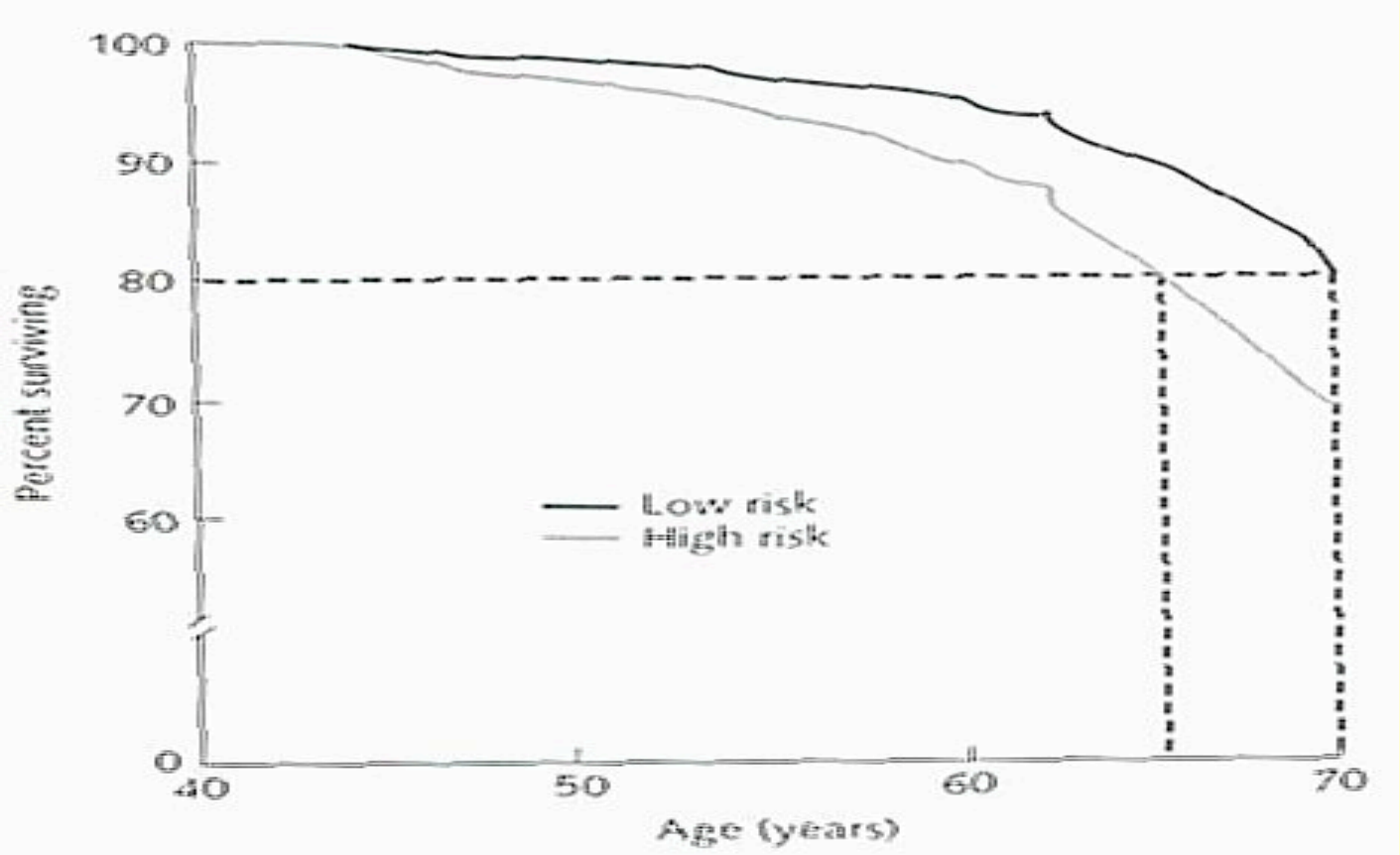
There are Fast- & Slow-Aging Humans



Centenarians & their relatives have a strong genetic component =>DOS.

From Baltimore Longitudinal Study on Aging; Perls & Terry, Exp Geron 38:725, 2003

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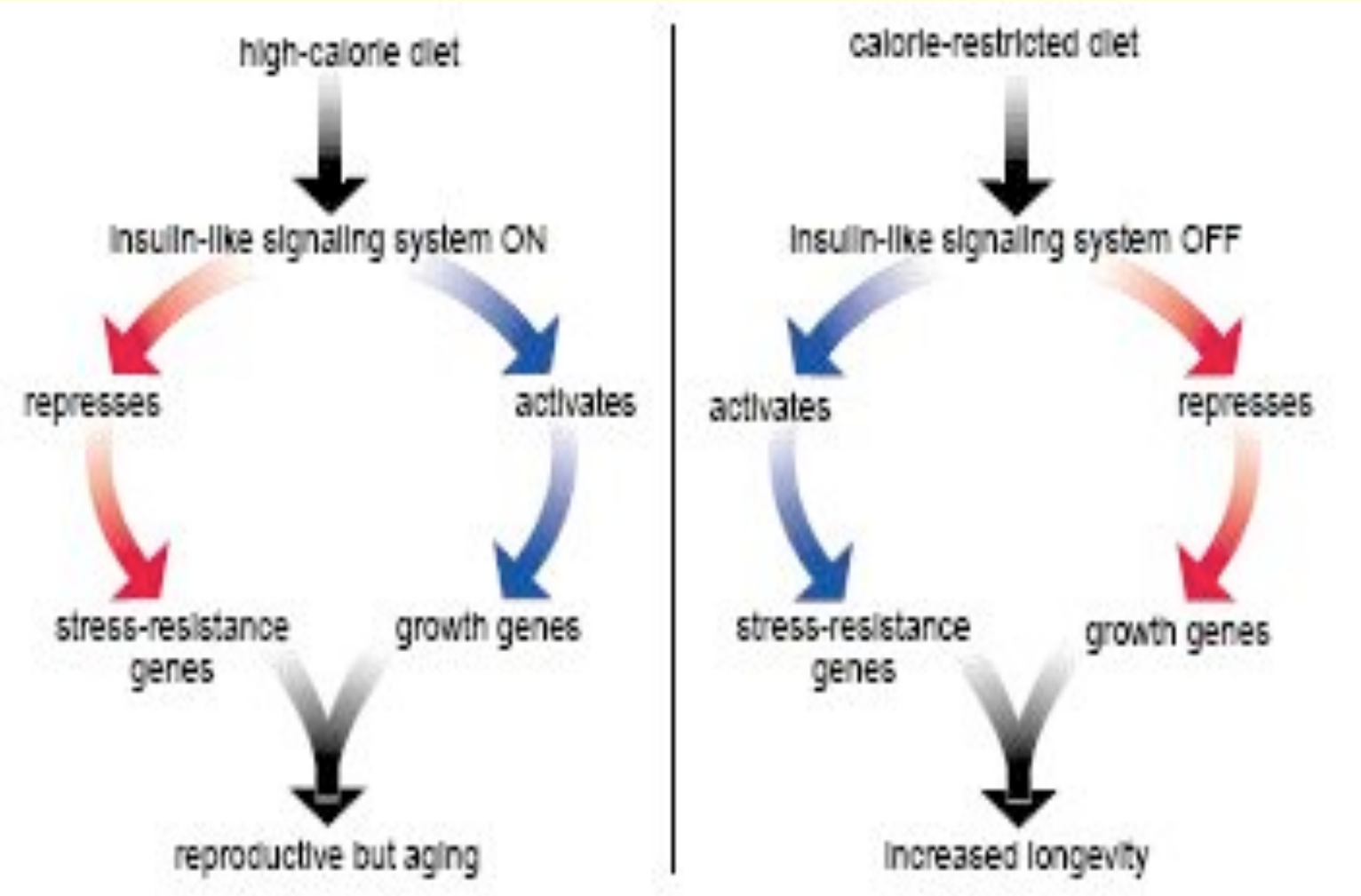
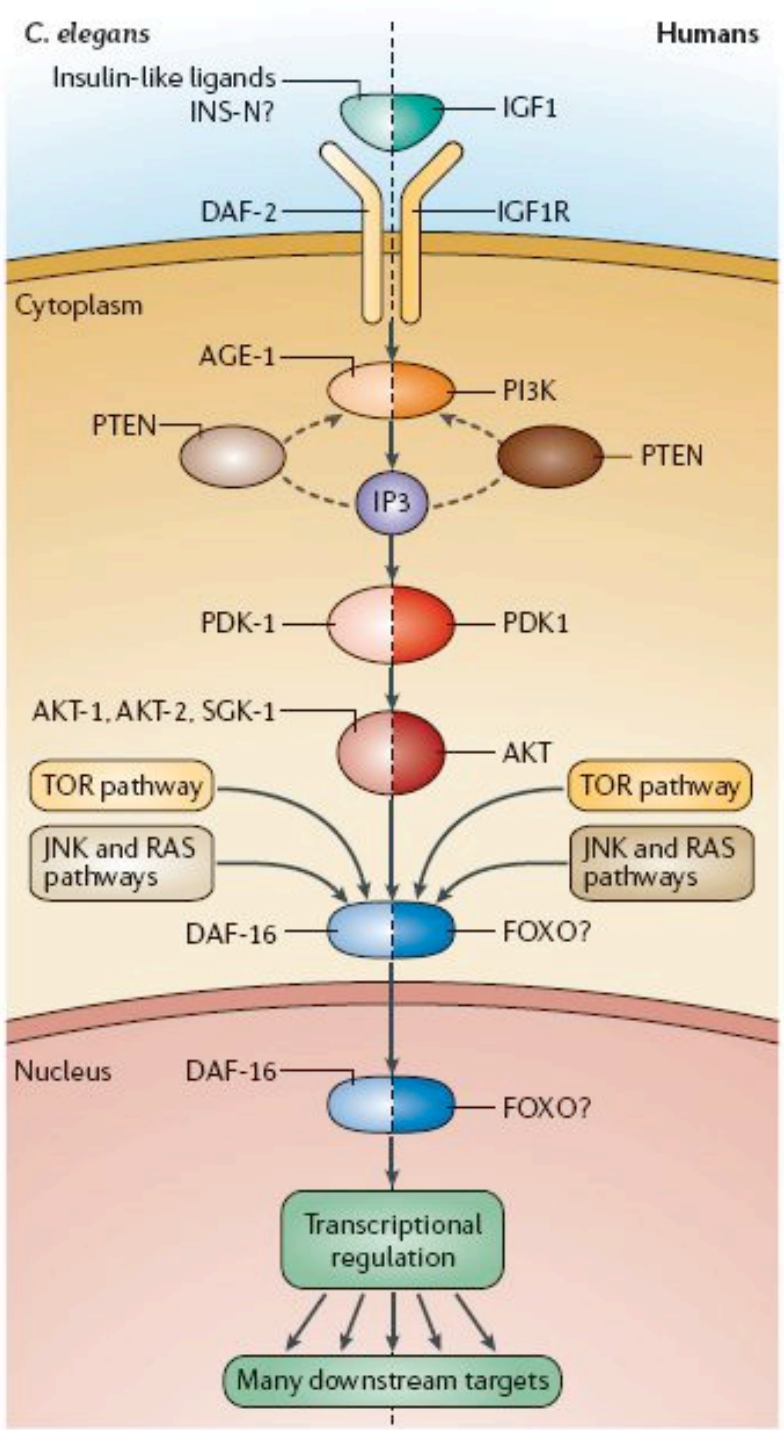
Environmentally Modified Gene Expression Controls this Transition at the Cell Level



Nutrition => Neurosecretory Signal => Altered Cell Signaling => Maintained or Decreased Functioning.

Arking,. 2004

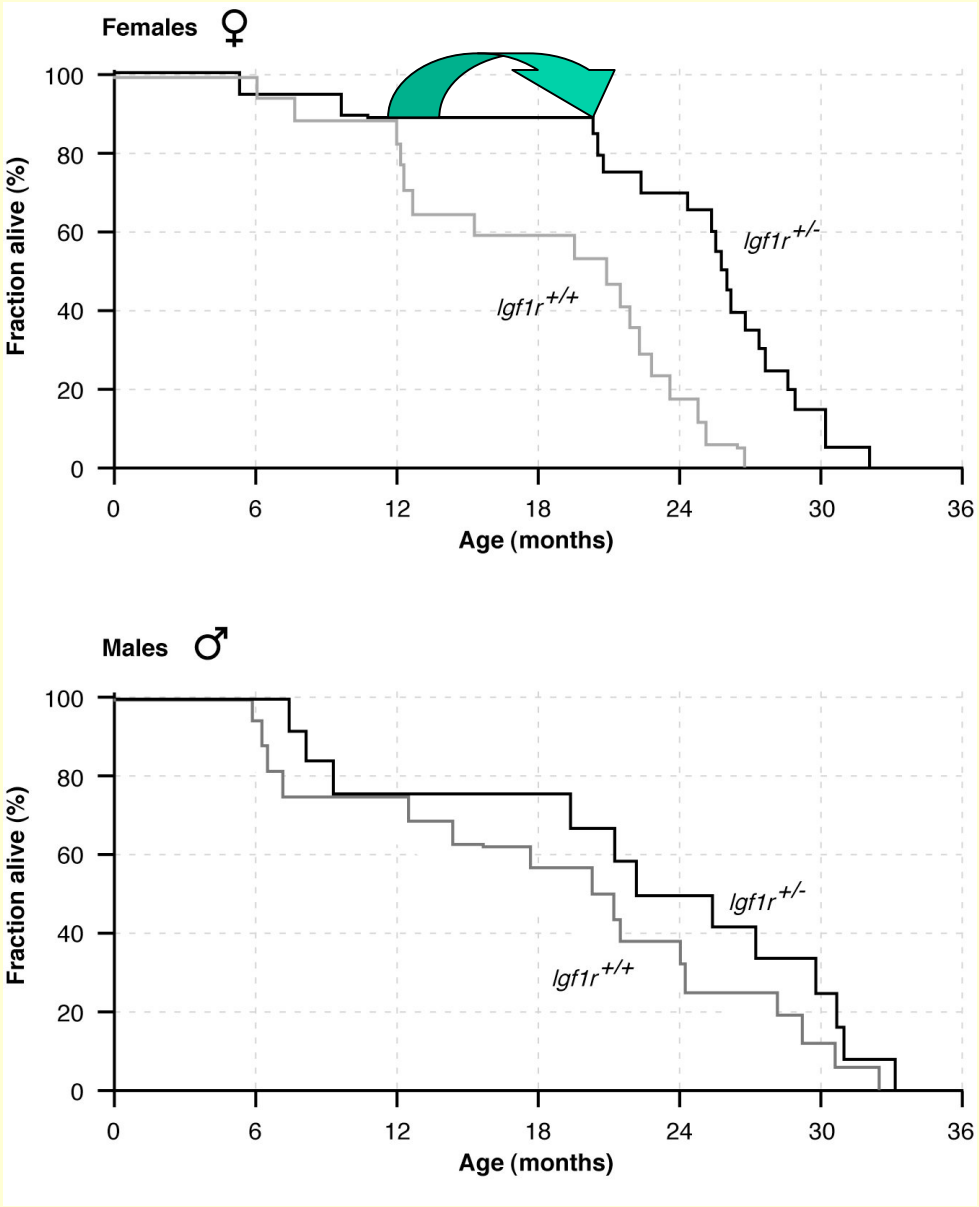


The molecular signaling pathways are conserved in yeast, worms, flies, mice, & humans.

But complexity increases.

From Christensen et al., Nature Gen. Rev. 7:436, 2006

Genetic Reduction of IGF-1 Activity Delays Senescence in Mice



Both Long-lived humans and humans on a CR regime have low levels of IGF-1.

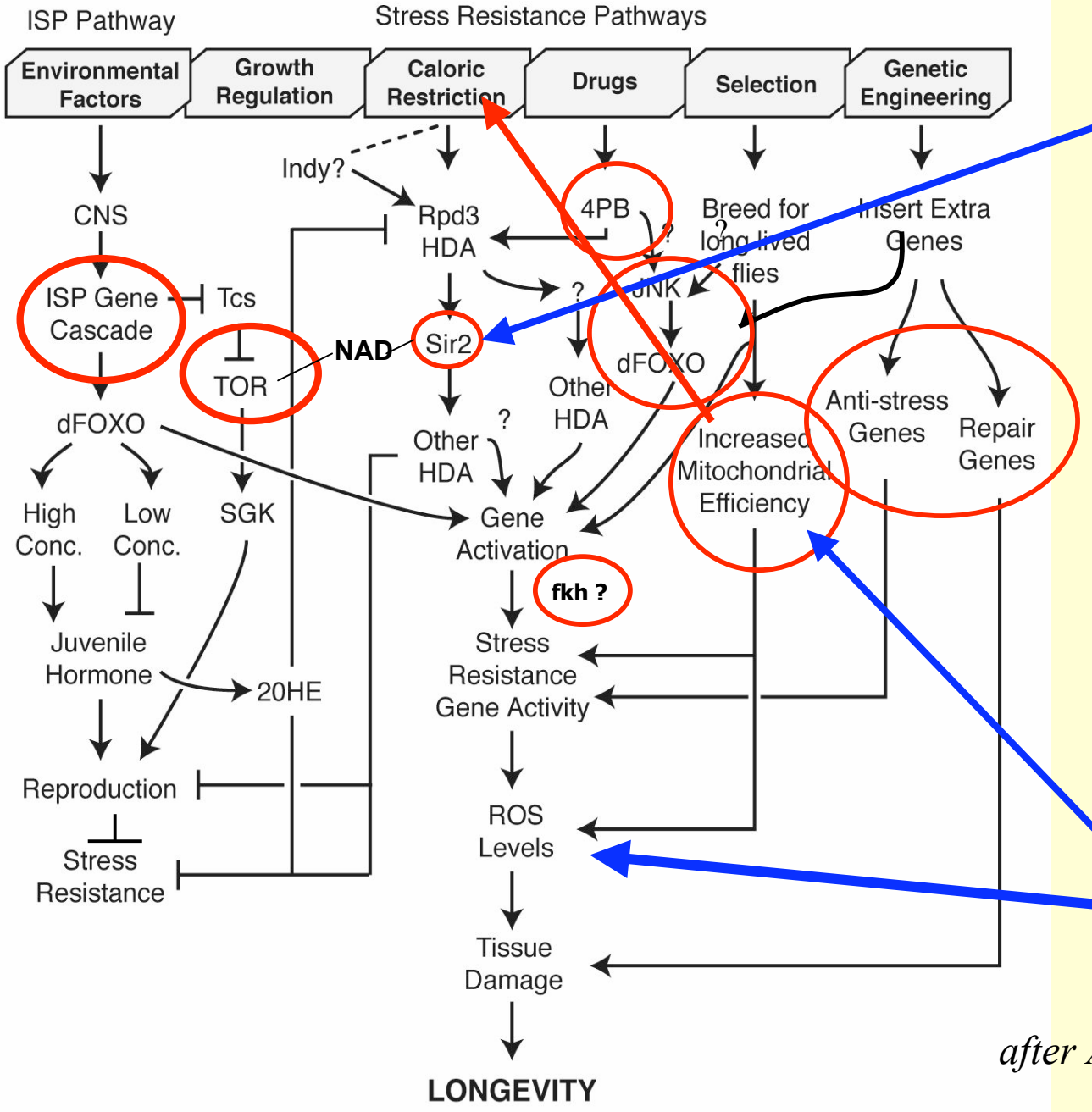
It is a signal.

The perception of a low signal is as good as really being low.

It is possible to fool the cell!

after Holzenberger et al., 2004

Longevity Pathways in Drosophilia



Nature Reviews: Drug Discovery 5:493, 2006

after Arking, 2006

If there is no aging program, and if Darwinian fitness is the most important single variable in evolution, then why should animals have within them cell signaling pathways that increase longevity?

Because there is no point in reproducing at times of low food availability.

The better strategy is to delay reproduction until food supplies increase again.

But in order to reproduce tomorrow, you must be able to survive today. Hence the present activation of costly survival mechanisms is in the service of future reproduction, and so would be selected for.

What Stimuli Induce the DOS Phenotype?

- Dietary Restriction (DR)
- Lifestyle
- Innate Genetic Differences
- Altered Cell Signaling Pathways
  - Mutants
  - Drugs *(pro-longevity biotech companies are hot)*
  - Change in Signals

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Old Animals Have Lower Levels of Signals Than Do Young Animals...But Their Cells Are Still Responsive

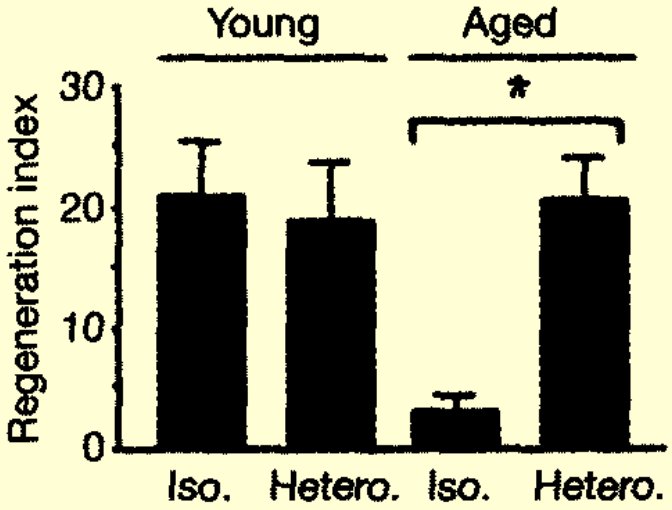
Pair Old or Young Animals via Common Circulatory System….. Measure Their Ability to Regenerate Damaged Muscle.

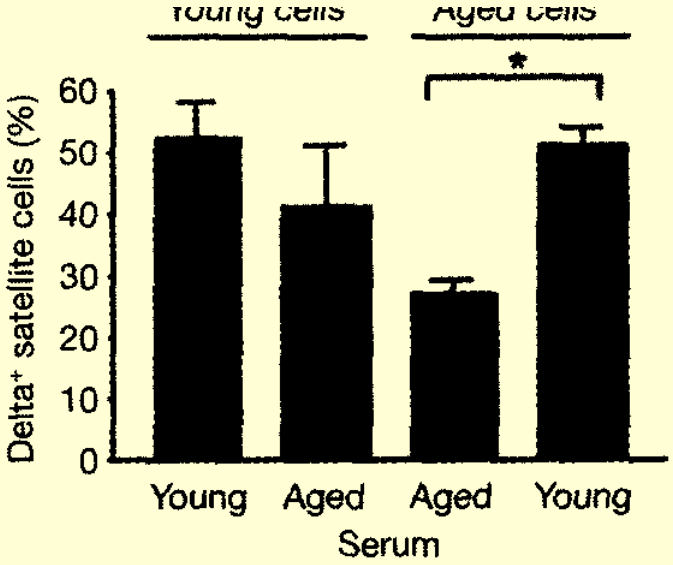
Old Animals Regenerate Better When They Have Young Blood Circulating!

Cells from Old Animals Put in Culture and Bathed with Sera from Young Animals Have Higher Incidence of Activated Regenerating Cells Than Do Old Cells in Old Sera.

Old Cells Are Activated to Regenerate By Sera From Young Animals!

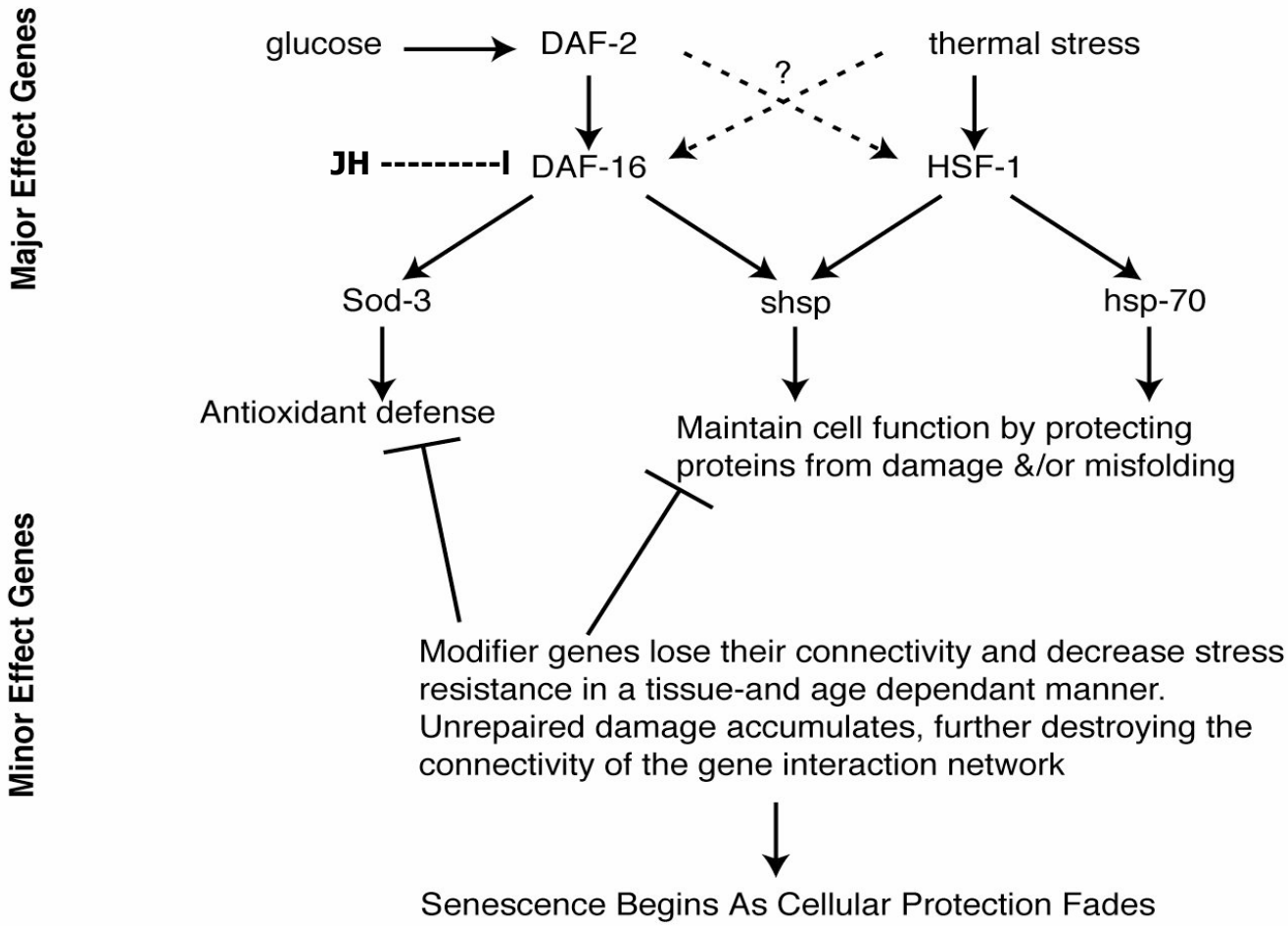
Aging Is Partly A Signals Problem & Not A Hardware Problem!





from Conboy et al., Nature 433:760, 2005

The Transition from Health to Senescence is Regulated by Major & Minor Genes Acting at the Cell Level



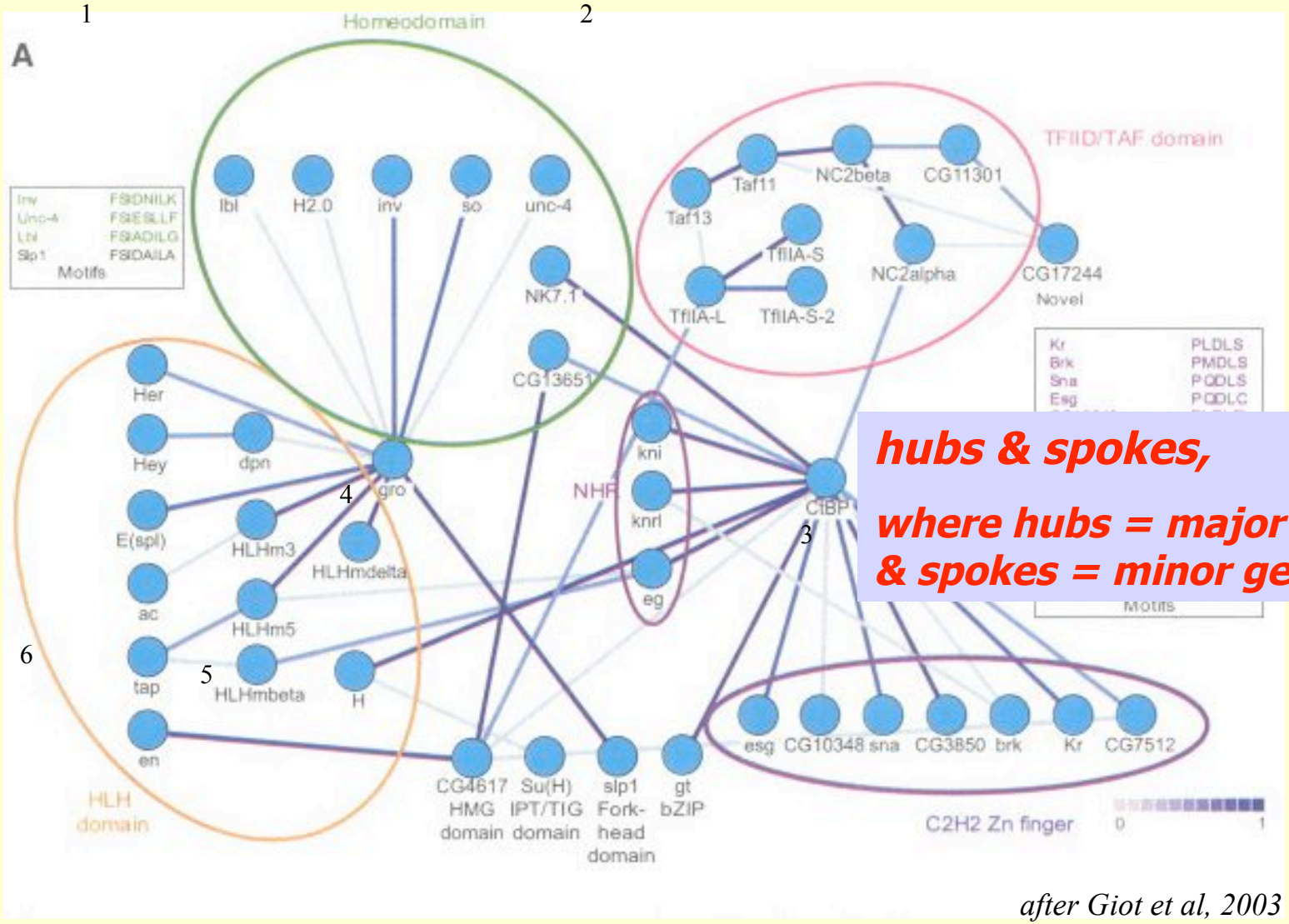
DR activates these same genes.

Senescence not likely to start here.

Senescent Changes likely start here.

from Arking, 2006, based on work from the Morimoto lab

Senescence May Start With the Degradation of the Gene Interaction Network



after Giot et al, 2003

Most essential human genes are expressed in all or most tissues, and are predominantly hub genes, which are highly stable.

Most human disease genes are non-essential, are not expressed in all or most tissues, and are predominantly spoke genes, which are not stable.

The only exception to this rule is cancer, which involves essential hub genes.

Goh et al., PNAS 104:8685,2007

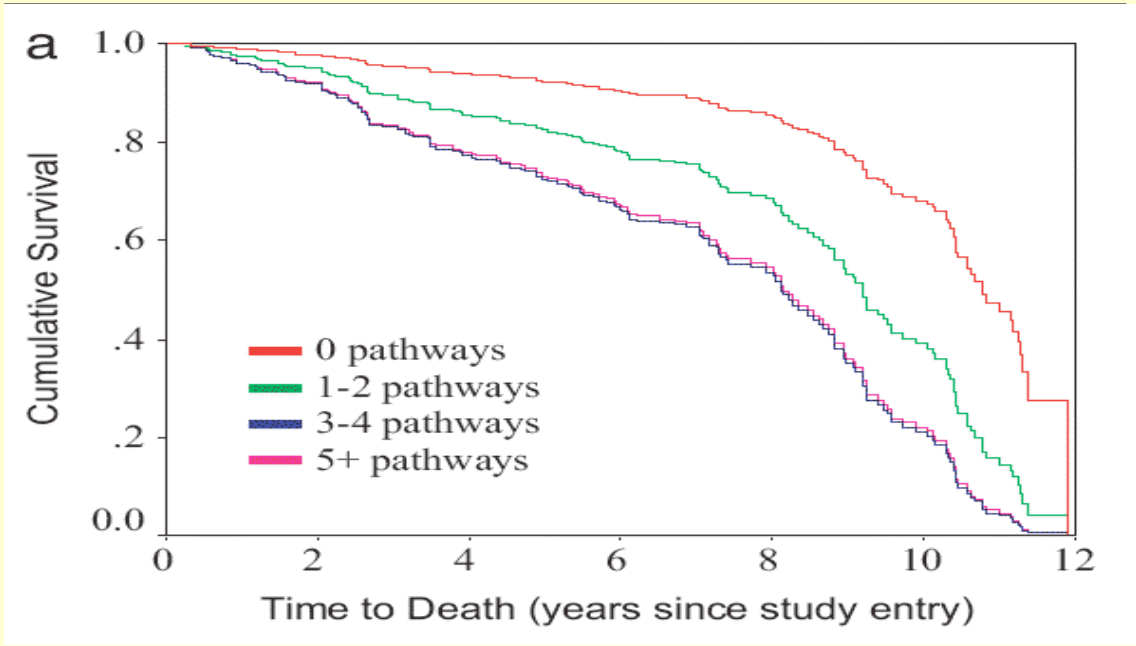
These human data are consistent with the animal data suggesting that spoke modifier genes gradually lose their connectivity in a stochastic tissue- and age-specific manner.

This somatic mutation process underlies the stochastic & individual nature of human senescence.

Onset of Senescence

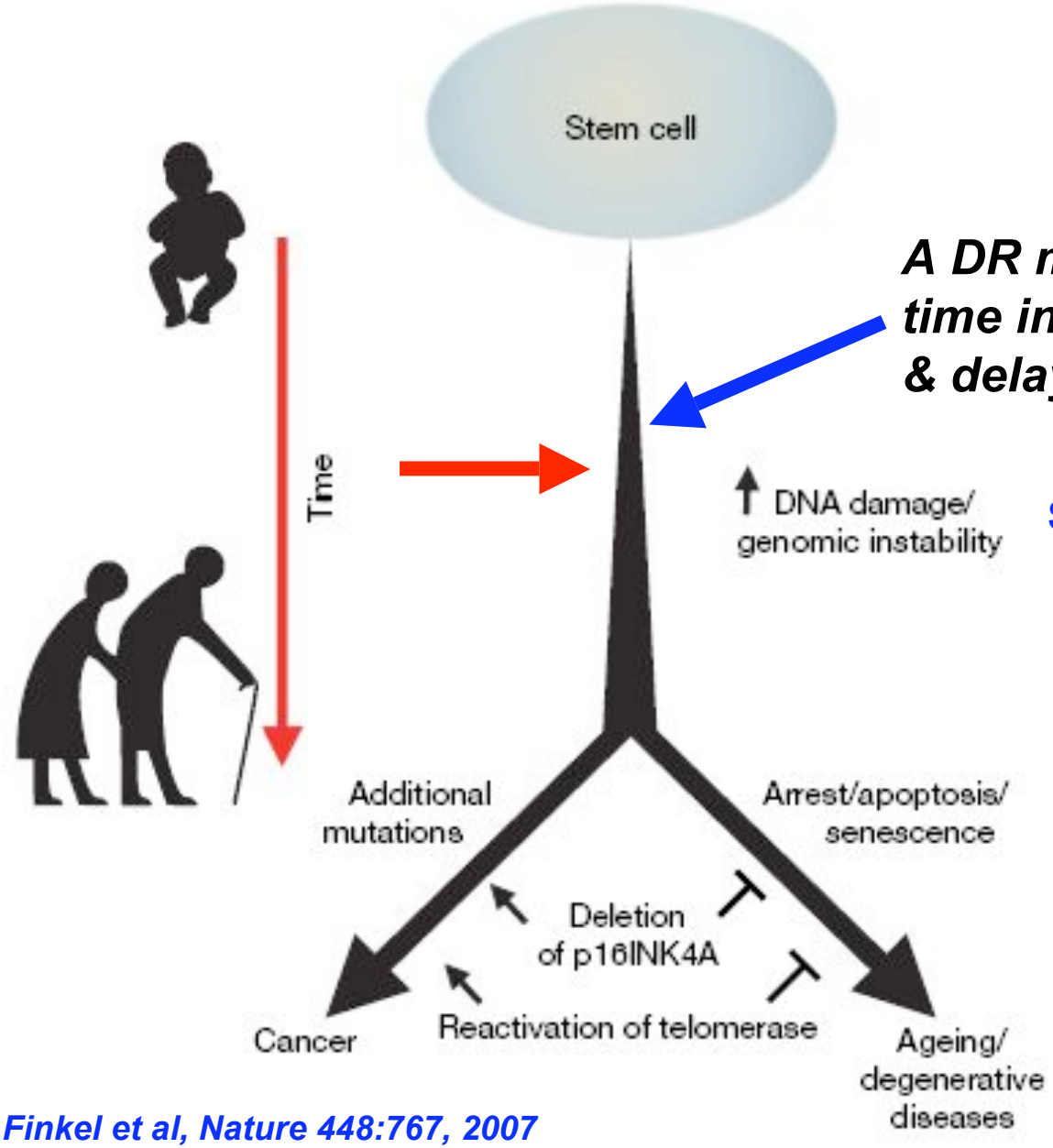
State of High Function → Stochastic Change in Physiological Function → Loss of Function in Various Pathways → Increased # of Clinical Deficits → Increased Probability of Dysfunction & Death

Survival is a function of the number of pathways which are dysfunctional in any one individual.



from Grunewald et al., PNAS 103:14158, 2006 & Mitnitski et al, JAGS 53:2184, 2005

Cellular Processes Involved in Senescence



A DR mimetic inserts extra time into the health span & delays senescence

Somatic mutations (hub)

Short Telomeres & Cell Arrest, Apoptosis & Autophagy
=>Anti-Cancer Defenses

Loss of signal (spoke)

↓ Tissue Function (spoke)

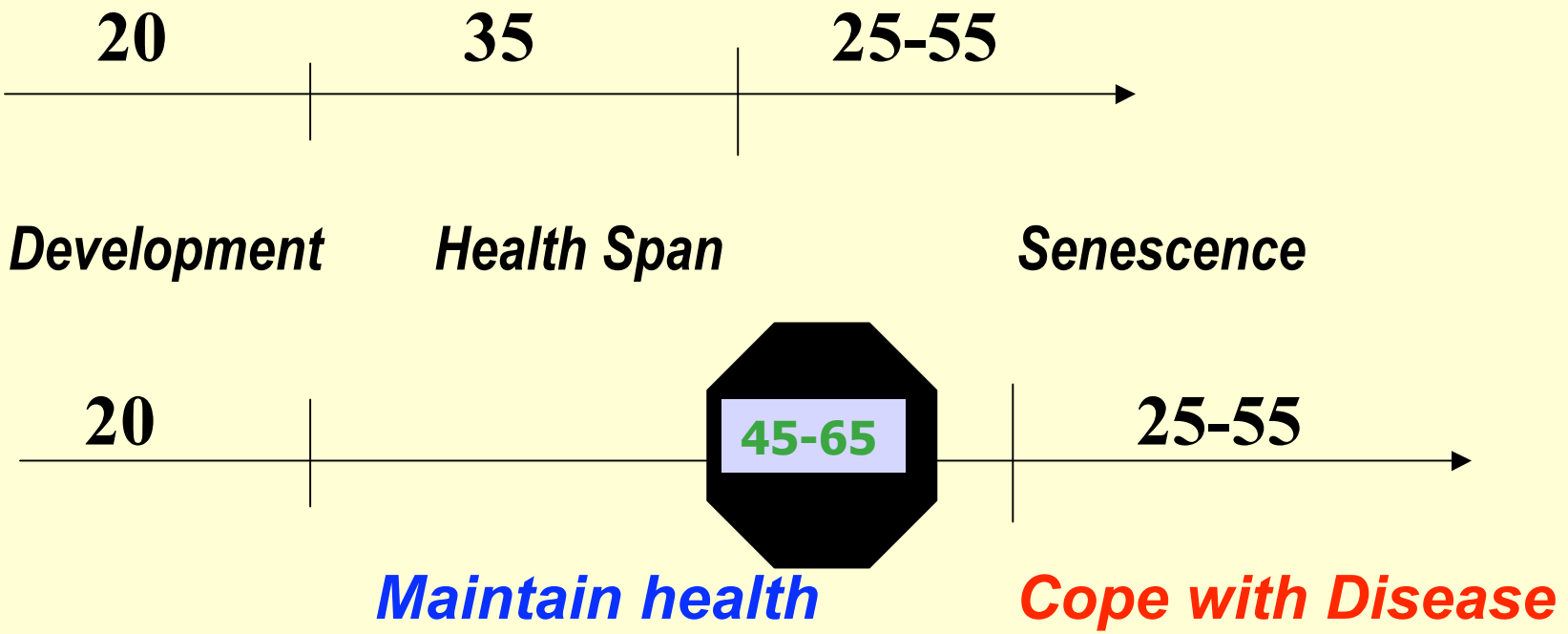
after Finkel et al, Nature 448:767, 2007

Life Span =

Health Span +	Transition +	Senescent Span
gene-dependent	*event-dependent*	*stochastic*
Longevity Determinant Mechanisms Operative	Altered Balance of Cell's Defenses due to Accumulated Damage&/or Loss of Signal	Degradation of Gene/Protein Interaction Networks
Homeostatic Ability Sensitive & Reliable	Abnormal Proteins Aggregate, Exceed Chaperone Capacity; Positive Feedback =>Lowered Cell Function	Cell's Regulatory Ability Decreases, Tissue/Systemic Functions Deteriorate
Low ISP Levels High Stress Resistance High Repair Levels	Damaged Cells Survive, Apoptosis decreases, Tumors increase	Feedback Cascades Ruin Homeostatic Ability, Critical Thresholds Passed

from Arking 2006

Potential Effects on Human Lifespan



The "Problems" of Increasing the Health Span are Preferred Compared to those of Increasing the Senescent Span

"An aging society constitutes a serious problem"

- *Economic shortfall*
- *Social unrest & labor shortages*
- *Health problems, chronic ills & quality of life*
- *Generational equity issues*

These critics labor under the false assumption that 'extra years' can only be added to the senescent span.

Opponents of Delayed Onset of Senescence:

Leon Kass **"…the finitude of human life is a blessing for every human individual, whether he knows it or not"**

L'Chaim and its limits: Why not immortality? First Things, No. 113 (2001), 17-24).

Proponents of Delayed Onset of Senescence:

Christine Overall **"Other things being equal, a long life is a better life, and a social policy that promotes the extension of human life is amply justified."**

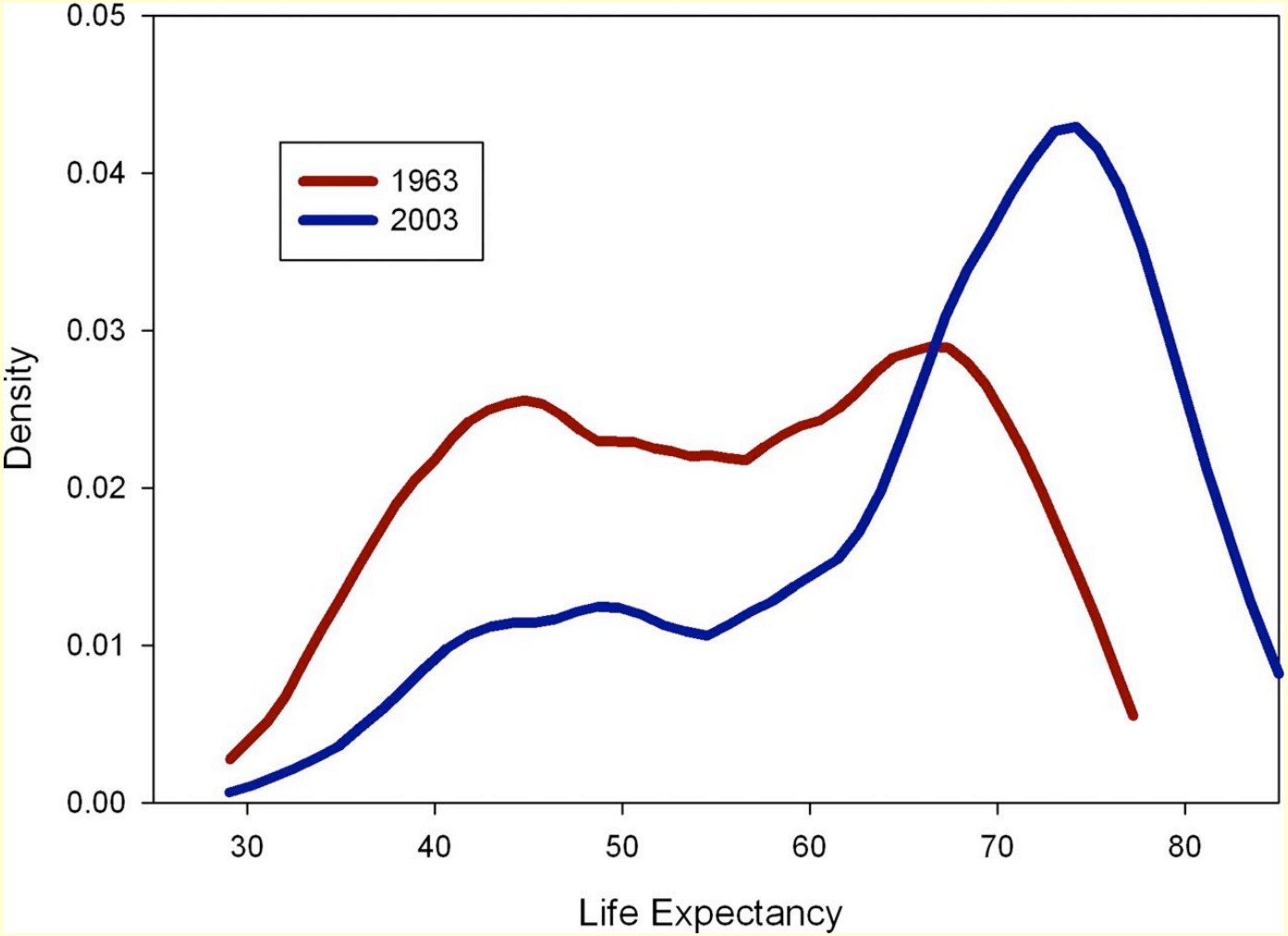
Aging, Death, and Human Longevity: A Philosophical Inquiry. Univ Calif Press, 2003

WHAT ABOUT OVERPOPULATION?

Less Developed Countries		AGE GROUP		Developed Countries
42.7%		0-14		25.2%
52.2%		15-64		60.5%
4.9%	*250 million*	65-84	*168 million*	12.8%
0.2%		85-100+		1.2%
4.9 billion		**TOTAL POPULATION**		**1.2 billion**

from UN Population Division, 2002 data

What about justice?



Bloom and Canning (2007) Proc. Natl. Acad. Sci. USA 104, 16044-16049

Possible Effects of a Longer Health Span

1900 =/= 2007 =/= 2100

There is no Utopia

Increasing the Health Span is like pouring sand into the top of the hourglass.

The mechanisms are well known & susceptible to pharmecutical intervention.

It may be difficult but it is not likely to be impossible

It will be controversial, for it lies on the intersection of biology with public policy

It will change society

Schrodinger asked, "What is Life?"

My answer:"Life is to be lived, both long & well."

Thank You