Santa Fe Institute, July 2009
the eco-physiology of human aging: a systems approach

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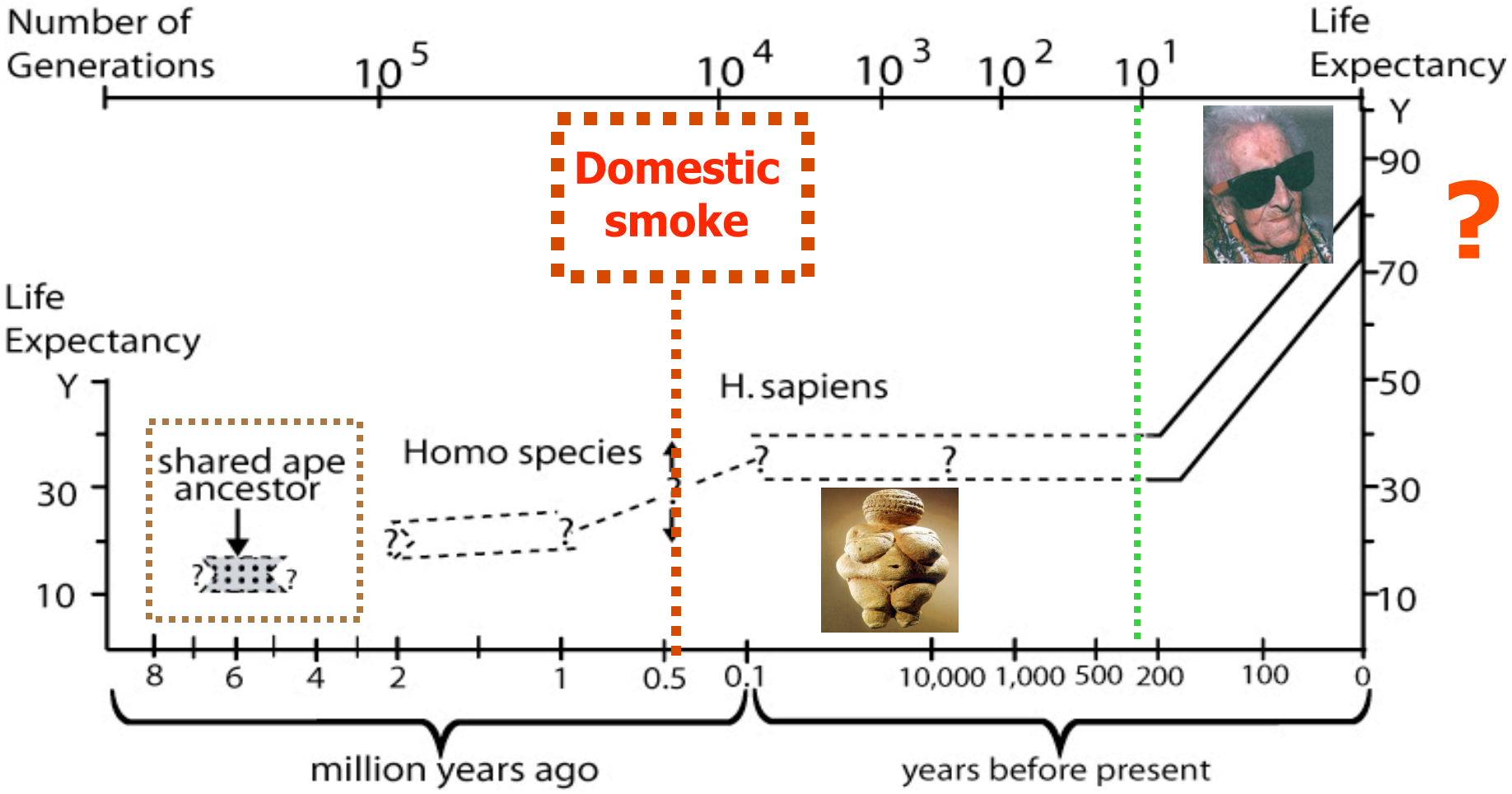
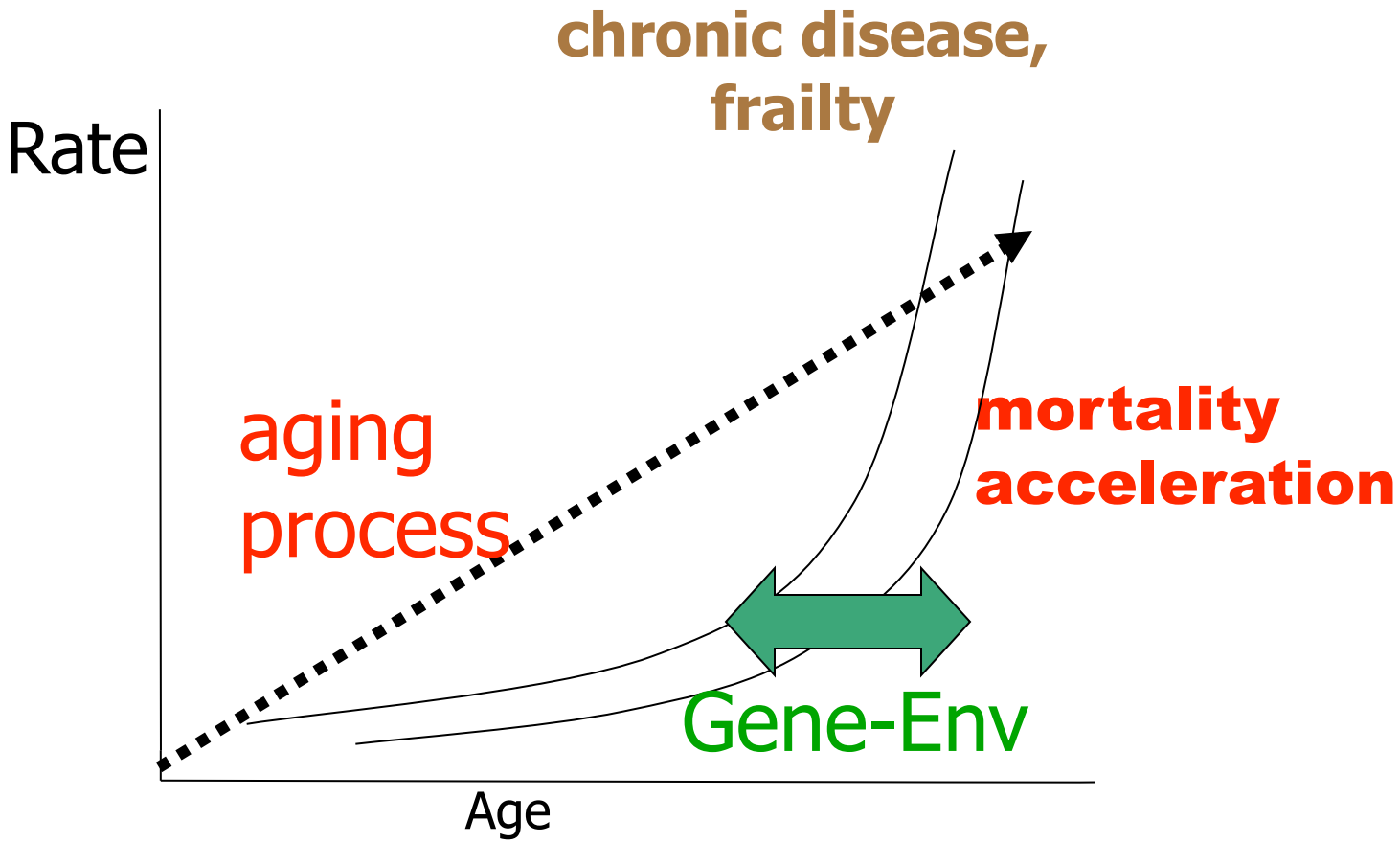
Evolution of human lifespans

genetic changes ⟺ environment
culture-technology



Aging, geriatric diseases, and mortality



Puzzles requiring new 'integrative' approaches

- Relationships of morbidity to mortality,
  e.g women have higher morbidity but lower mortality
- How does caloric restriction (CRx) delay aging,
  e.g. not only energy thru-put
- Cause of death in CRx rodents without histopathology

  e.g. transient instability in myocardial conduction (fibrillation) or glucose transients
- Small fraction of variance in aging changes explained by any factor, e.g. coronary risk factors
- Species differences in aging within groups, e.g. human vs great apes: longer lifespan, but more cancer and neurodegeneration

four determinants of individual aging

- I, inherited genetic differences
- II, random cell variations during development
- III, somatic cell DNA damage during aging
- IV, somatic cell damage from environment: infection, inflammation, nutrition, stress
- III-IV random hits during aging create *individual mosaics* of diverse tissue differences
- ?Role of environment?

Genes determine species differences in lifespan

BUT! heritability of lifespan is ≤35%

Heritable variance in lifespan	
Human twins	23-35%
Mouse	29%
Fly	9%
Worm	34%

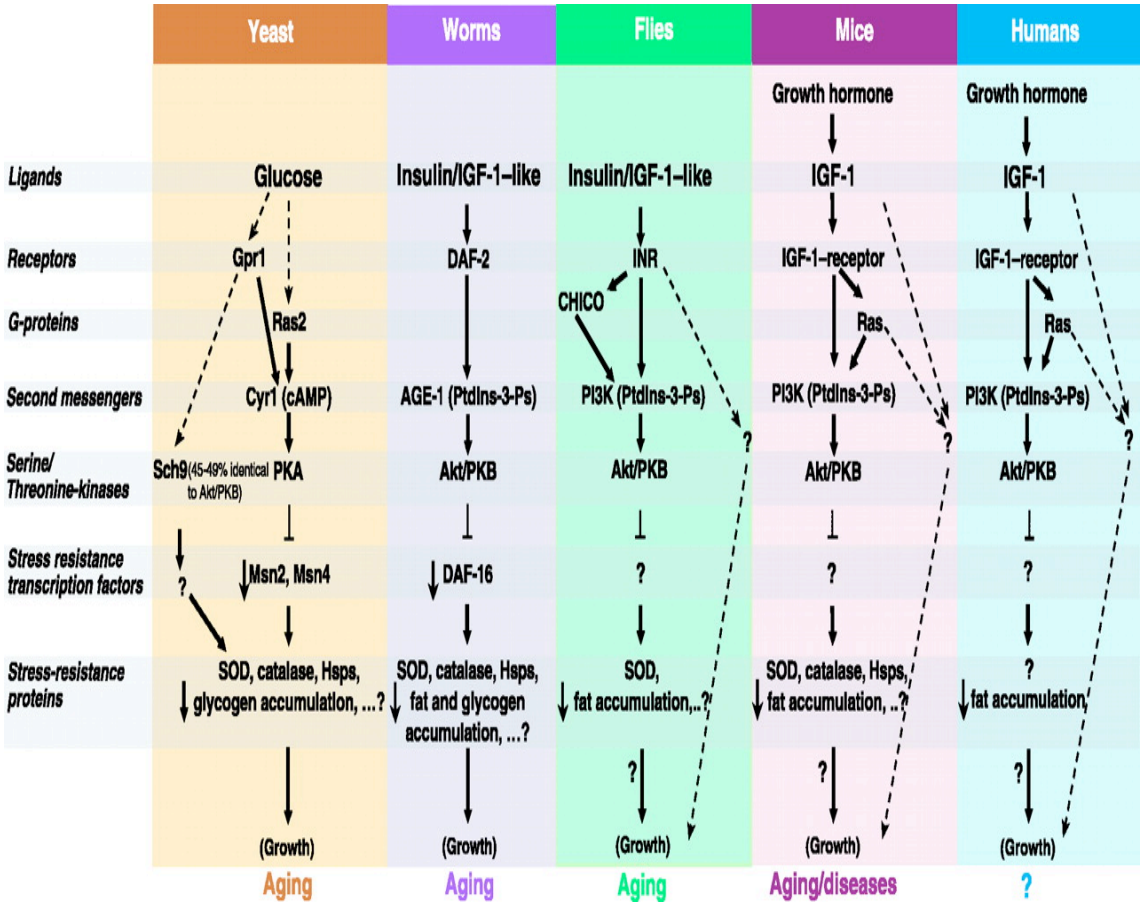
major influence of environment on aging

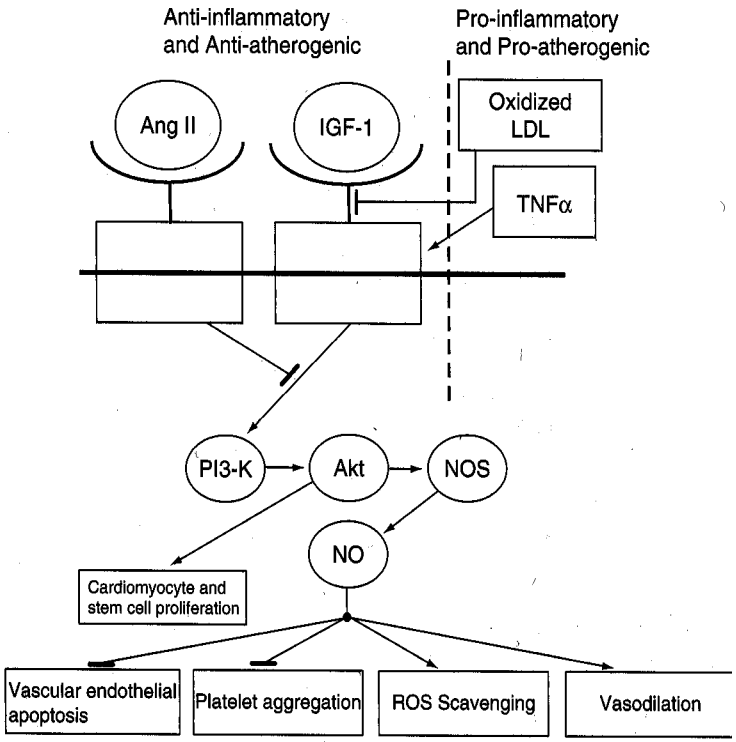
Finch CE, Tanzi R Science 1997

Finch and Kirkwood, *Chance Development and Aging*, 2000

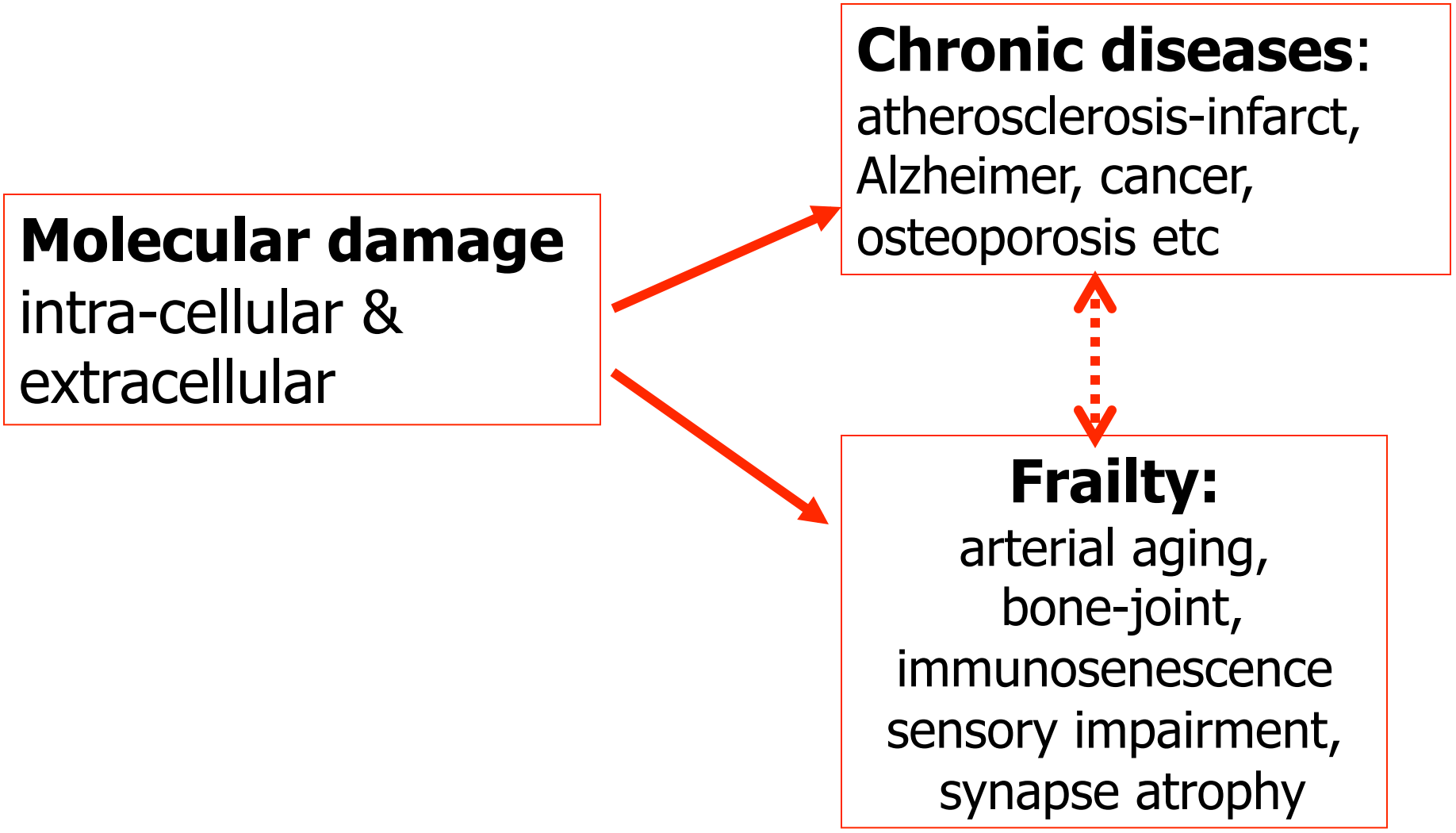
longevity mutants and atherosclerosis share insulin-like signaling pathways

Finch CE 2007: The Biology of Human Longevity, Fig. 1.3





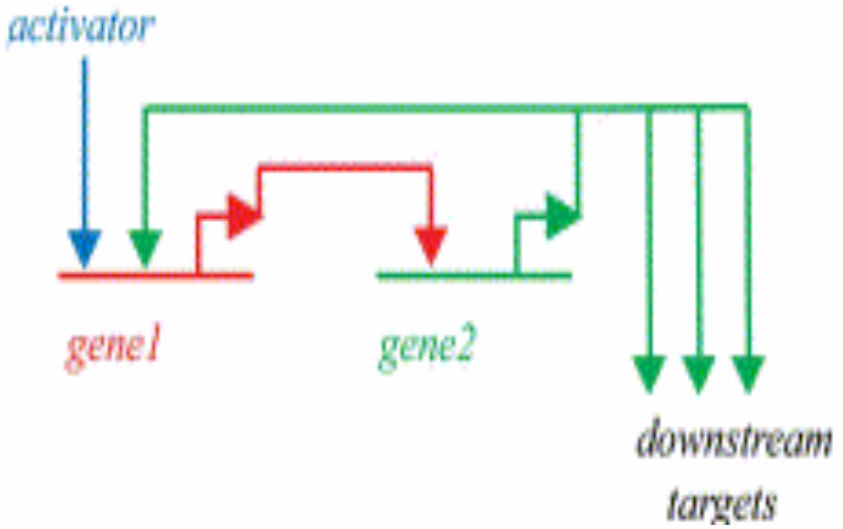
Major human aging processes



Molecular and cell aging

Lifespans of molecules and cells:
determined during development
by patterns of gene expression
for each cell type

Transcription factors
'lock-in' or 'lock-out' gene
activity for cell and
molecule and cell
regeneration,
e.g. elastin and stem cells

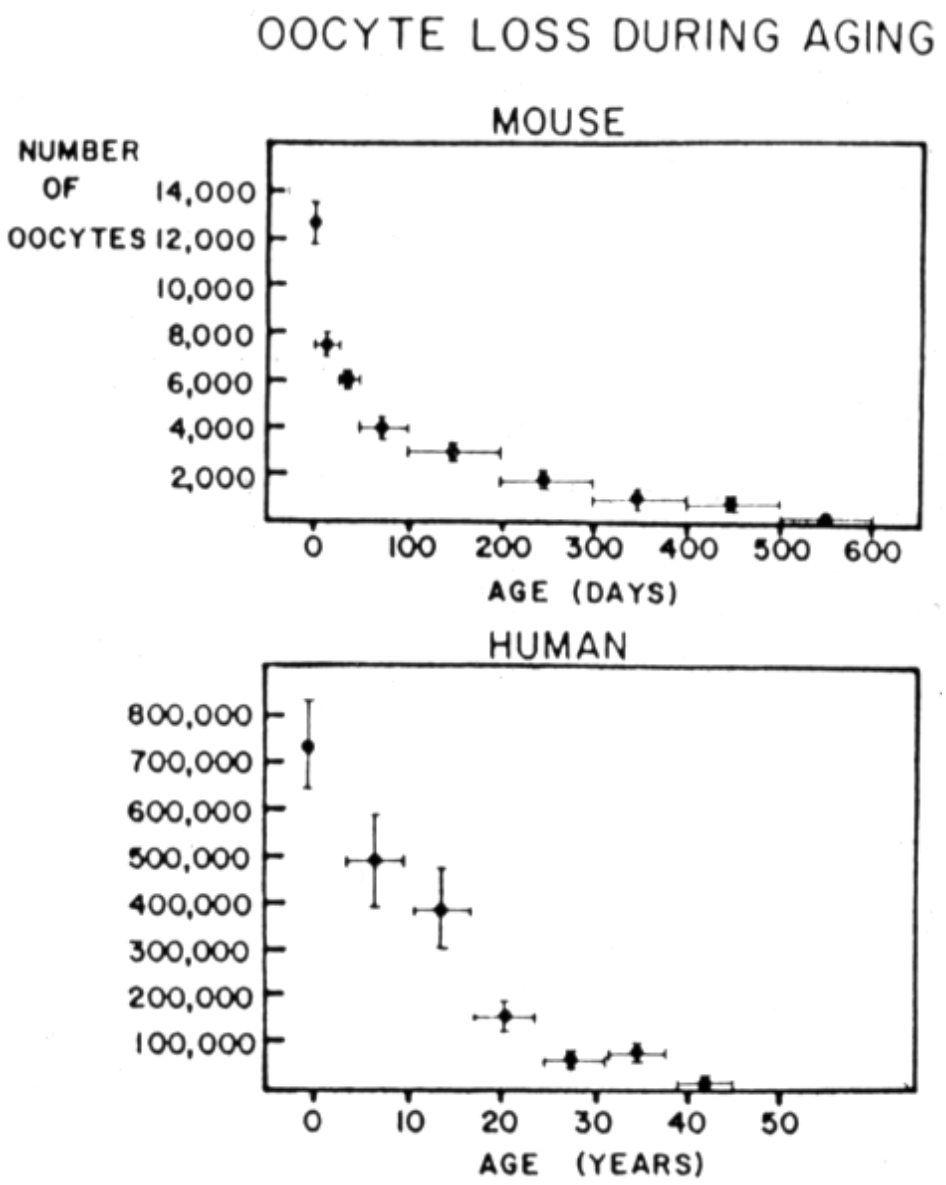


genetically programmed non-replaceable elements that age irreversibly

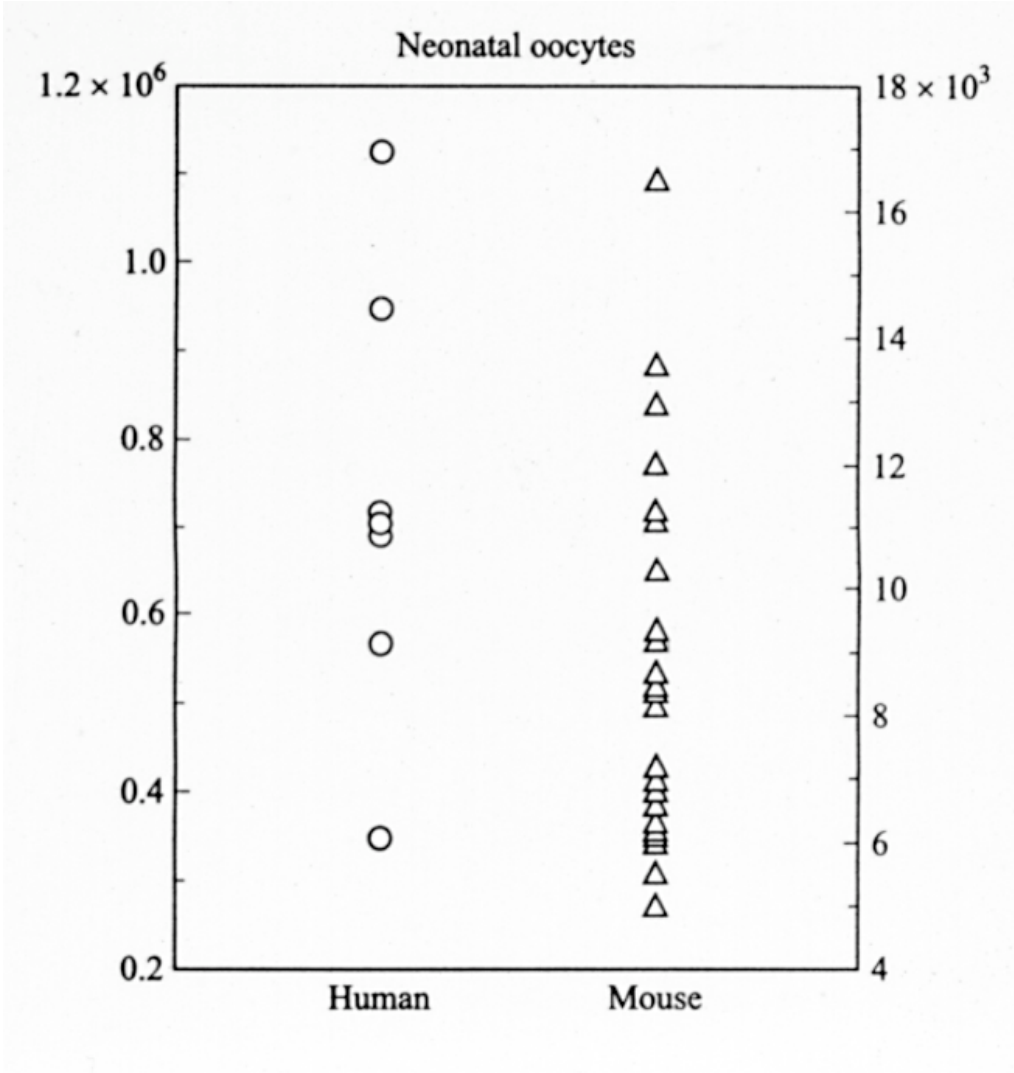
- Ovary: cell number determined prenatally and lost exponentially
- Arterial elastin: extracellular, racemization

mouse

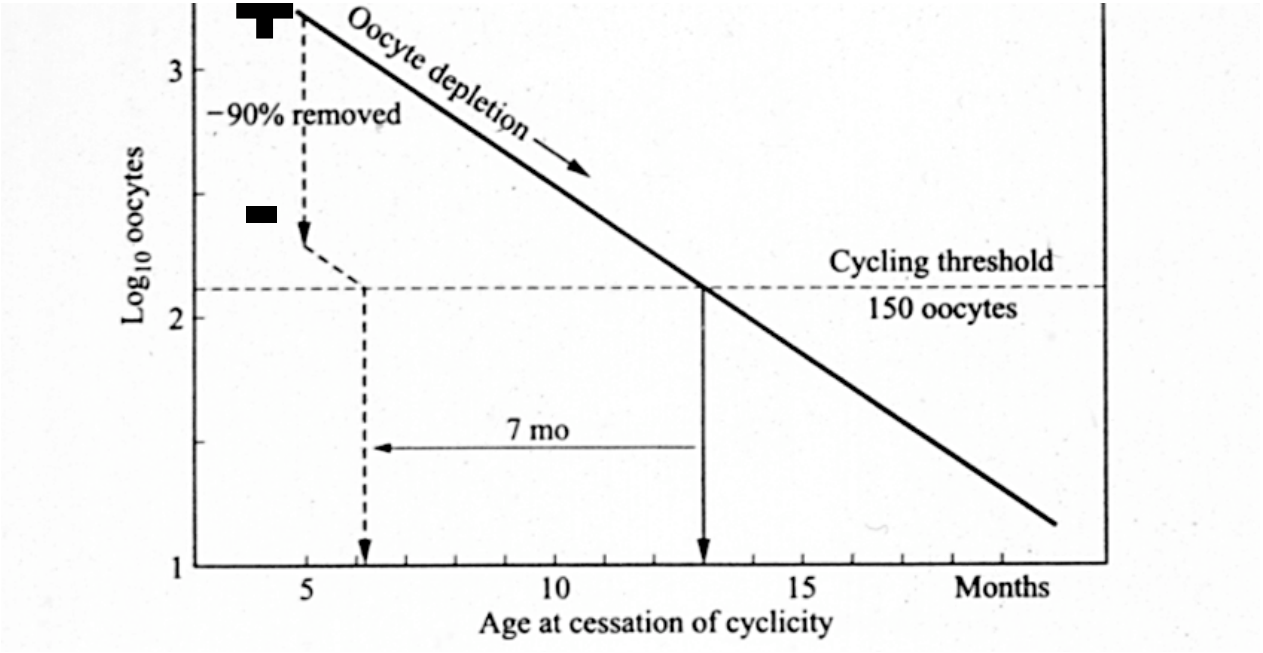
human


OOCYTE LOSS DURING AGING
MOUSE
NUMBER OF OOCYTES
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
100
200
300
400
500
600
AGE (DAYS)
HUMAN
800,000
700,000
600,000
500,000
400,000
300,000
200,000
100,000
0
10
20
30
40
50
AGE (YEARS)

Neonatal oocyte numbers of humans and inbred mice have same coefficient of variation



Partial ovariectomy proportionately accelerates reproductive senescence



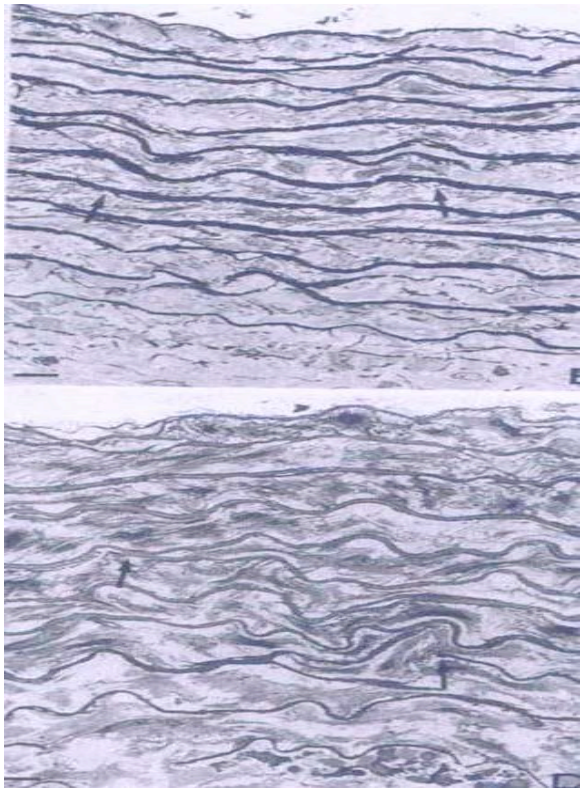
Hypothesis: more eggs at birth give later menopause

Nelson&Felicio, Biol Repro 1986

aorta - aging of irreplaceable elastin: racemization and damage from glucose and inflammation

Fornieri C, Arterioscler Thromb 1992 ; Finch CE, 2007, p.17

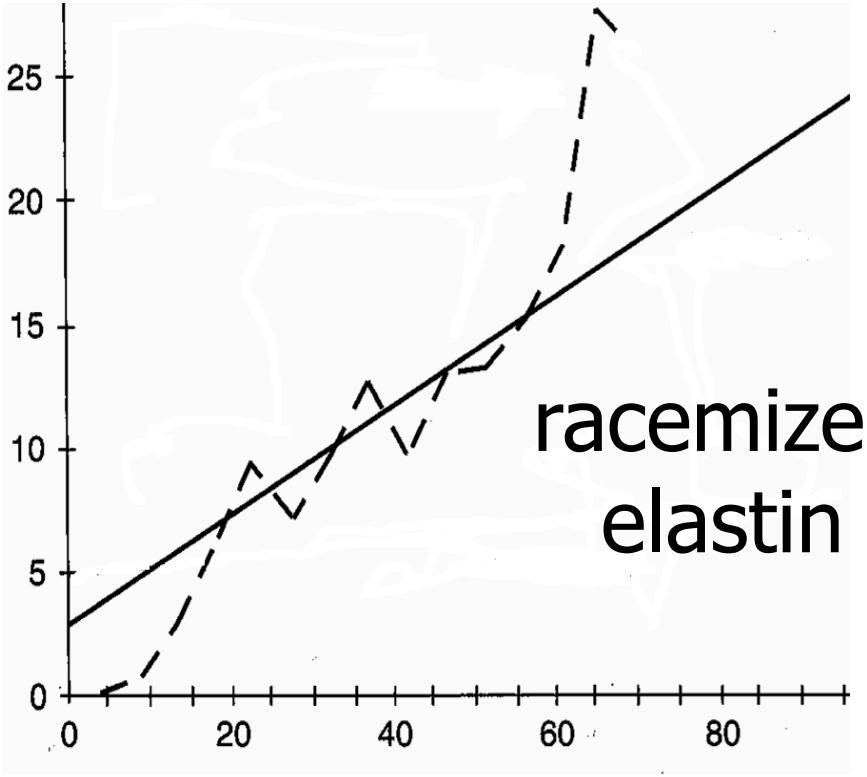
young rat



old rat

elastin fragmentation

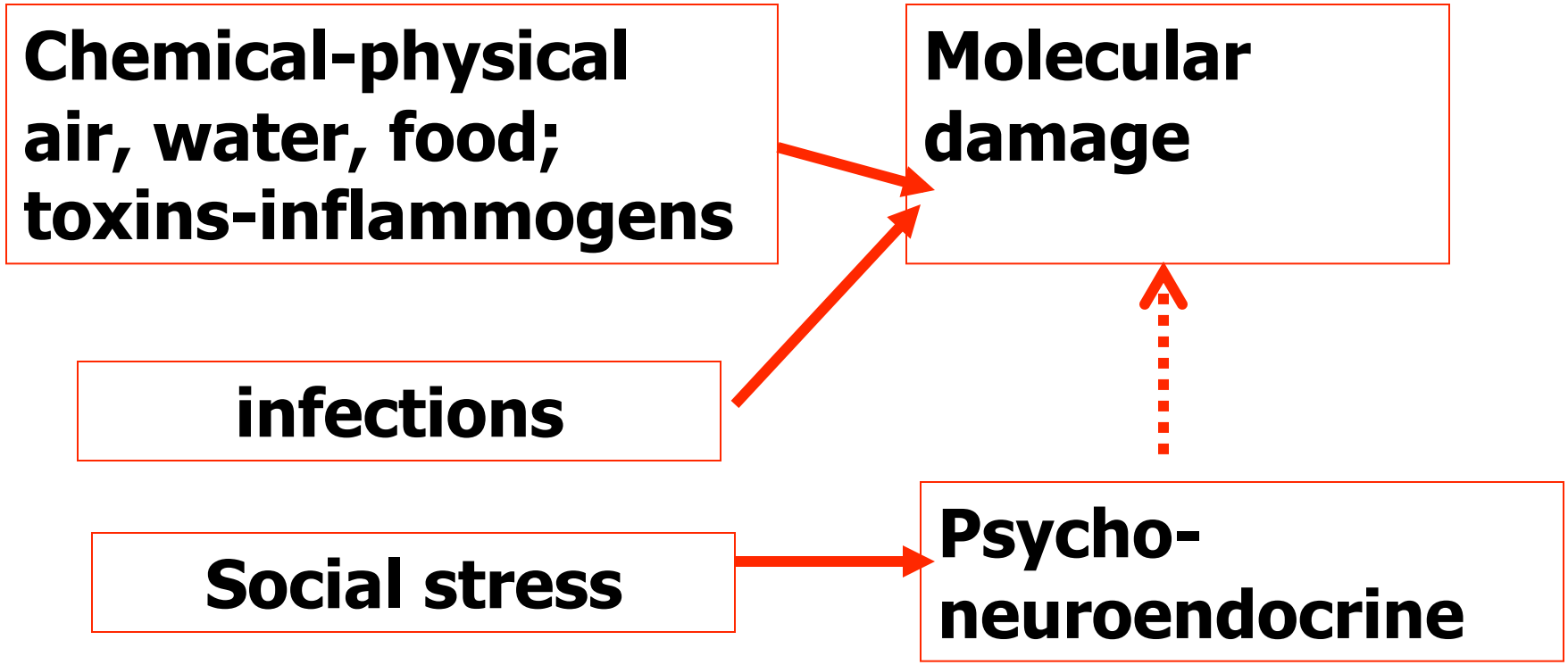
glyco-oxidized elastin



racemized elastin

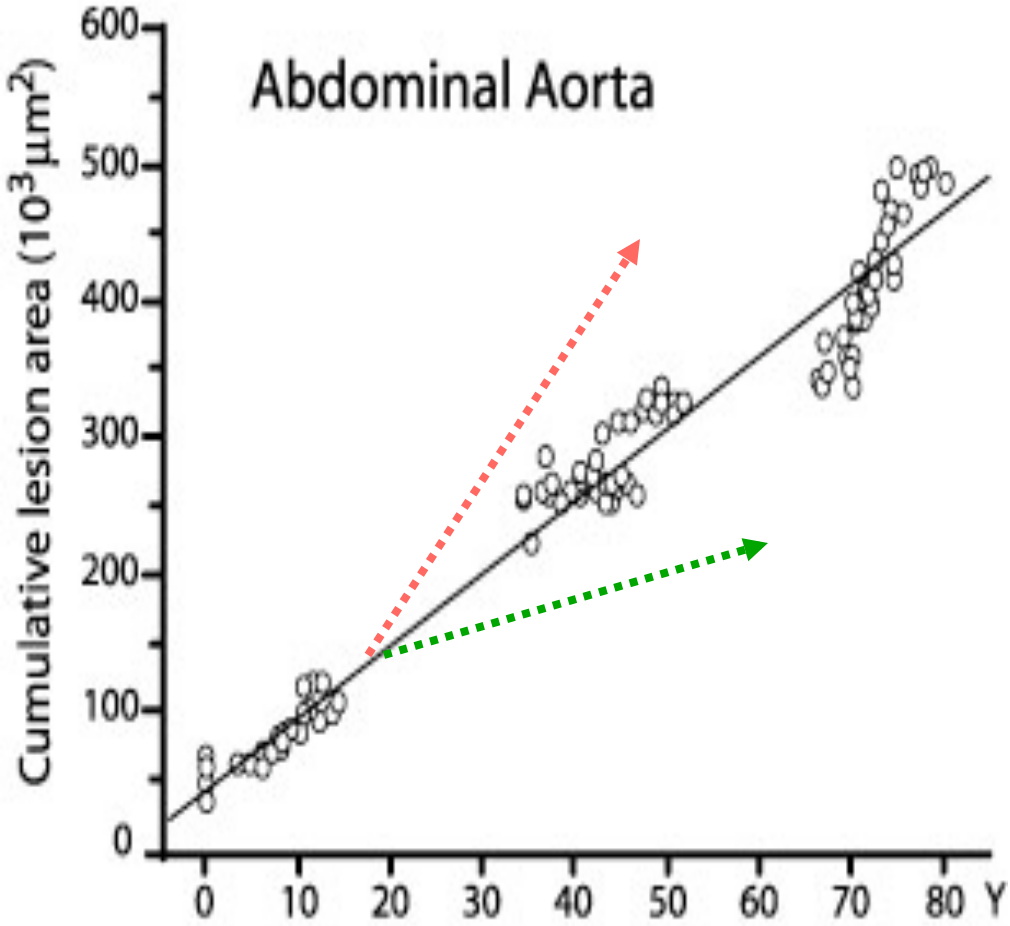
human age

The environment in human aging



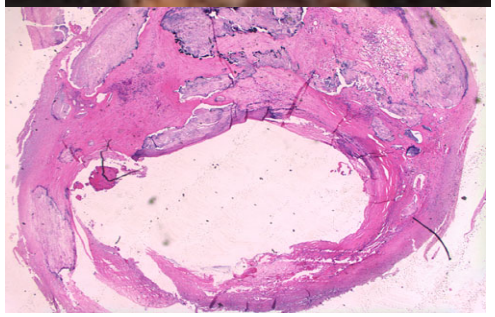
atherosclerosis begins before birth; progresses across the life span

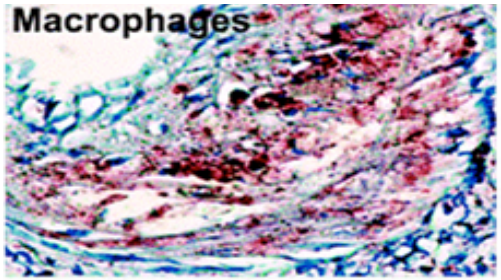
fatty streaks with macrophages



(W Palinski, Stroke 2001)

aging aorta

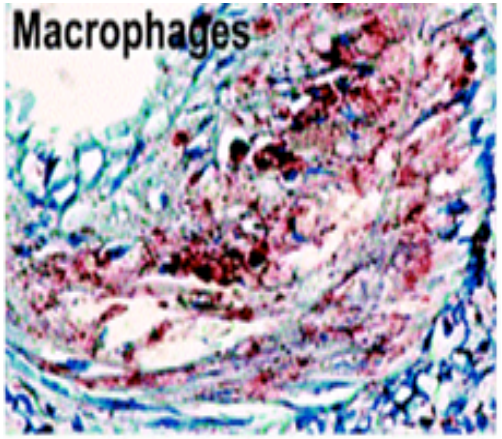




Shared inflammatory processes in normal aging and chronic diseases

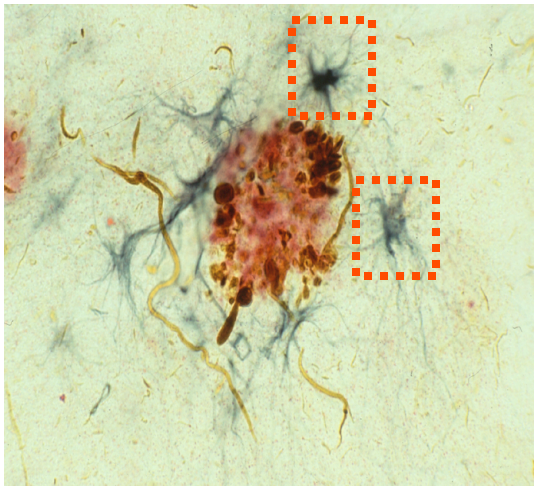
active macrophages/inflammatory cells

arterial atheroma



J-O Daguchi Circ 2006

Alzheimer senile plaque



CJ Pike, pers comm

Shared inflammatory mechanisms?

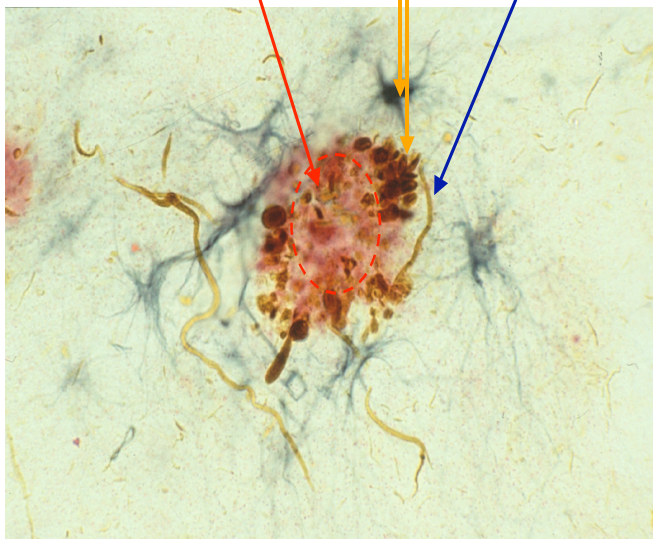
Finch CE Neurobiol Aging, 2004

	atheroma	senile plaque
cells		
macrophages (CD68)	++ (foam cells)	++ (microglia)
T helper (Th1)-cells	++	0
mast cells, platelets	++	0
Neovascularization	++ ++	+ ++
cholesterol		
proteins		
amyloids	++	++
Abeta	? (platelet APP)	+++
C-reactive protein serum amyloid P (SAP)	++	+
clotting factors	++	++
complement: C3, C5b-9	++	0
cytokines: IL-1, IL-6	++	++
	++	++

inflammatory markers in Alzheimer & brain aging

inflammatory changes	senile plaque	normal human
glial activation: GFAP (astro), MhcII (µglia)	++	+
$_1$-ACT $_2$-macroglobulin	+	+
apoE , apoJ, CRP, HOX-1, RAGE	++	+
Complement C1q, C3	++	+
Cytokines IL-1, IL-6, TNF-	++	+

Alzheimer-type changes are common in aging mammals
accumulations of amyloid ∃-peptide (A∃)
Senile plaque around A∃core with glia and abnormal neurites



Inflammatory hypothesis of the historical increase of human life spans

C Finch & E Crimmins *Science* 2004, 2005; *PNAS* 2006

***Strong correlations of early & later age mortality in cohorts, but not in periods**

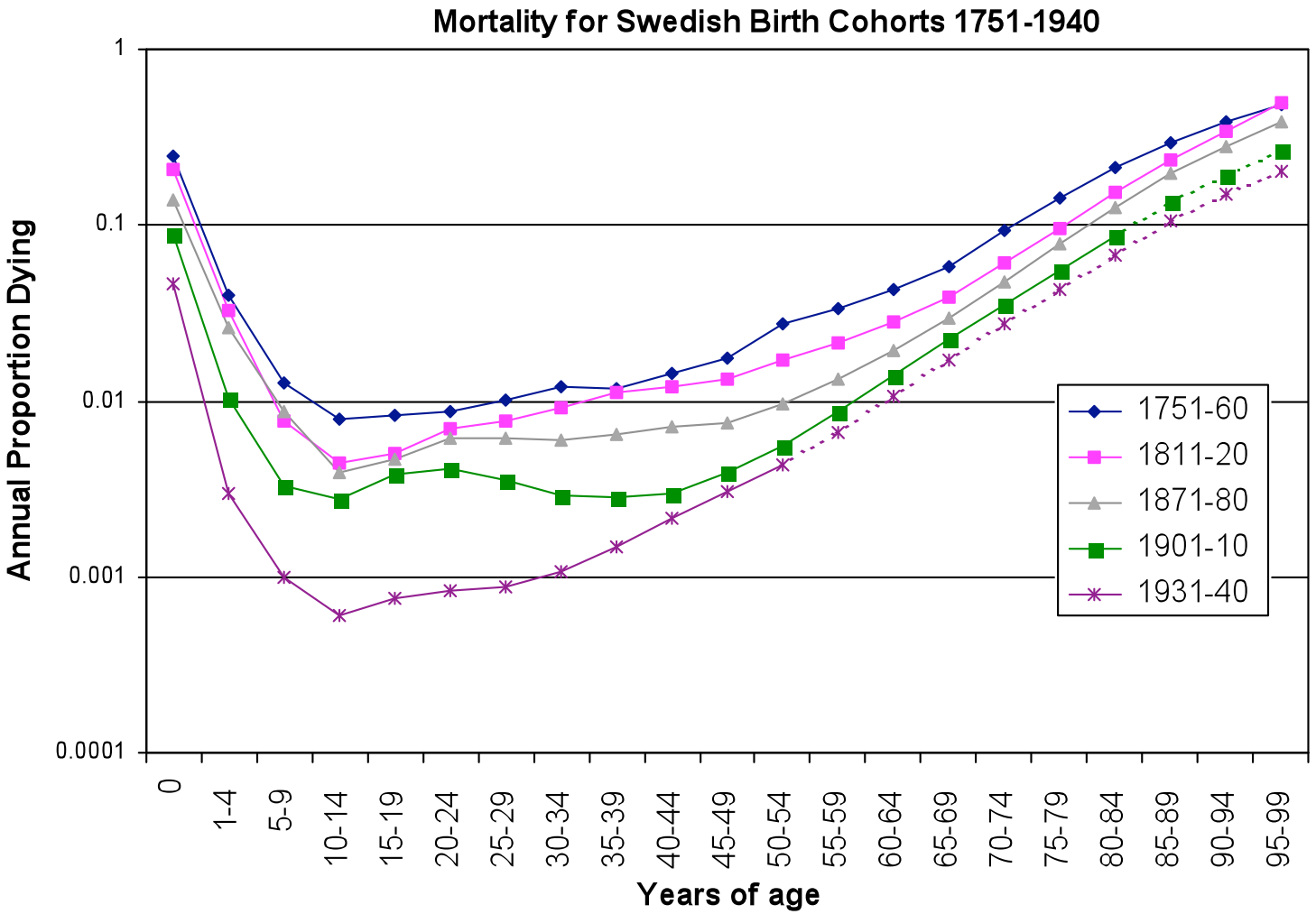
***survivors of early infections carry inflammatory loads, which promote chronic diseases : atherosclerosis, cancer, immunosenescence etc**

*** Reduced inflammatory loads in 19th and 20th C slowed aging**

Cohort mortality in Sweden 1751-1940

"cohort morbidity phenotype"

same slope but different intercepts



Infant mortality predicts heart disease by cohort 40-69 yr later

(Norway)

survivors in cohorts with high infant mortality "carry life-long vulnerability"

Forsdahl A
Brit J Prevt Social Med
31: 91-95 1977

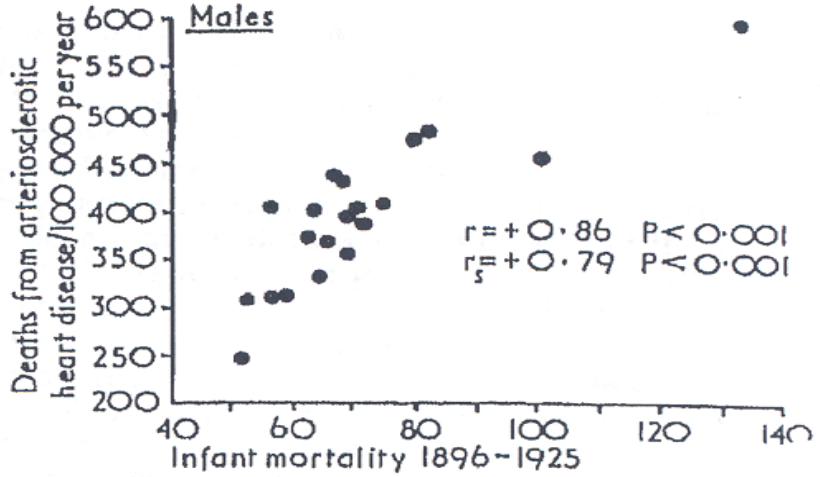
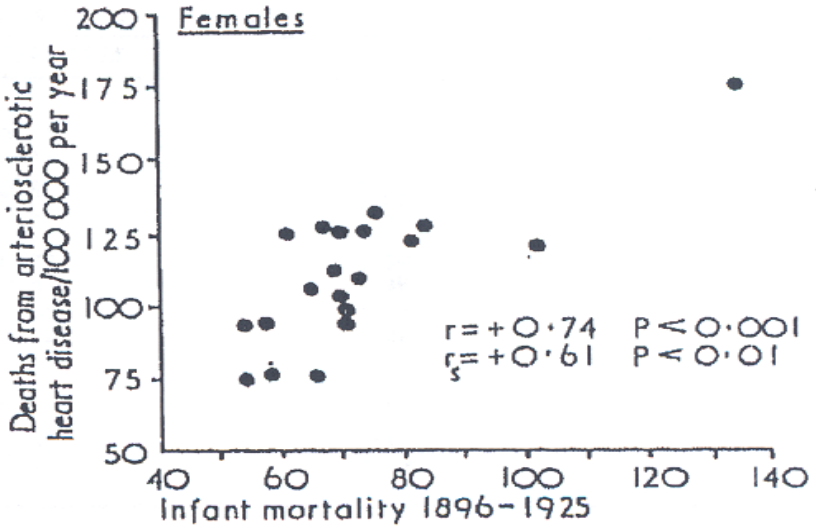


Fig. 2 *Correlation between mortality from arteriosclerotic heart disease, 1964-67, in men aged 40 to 69 years (standardised rates/100 000 population) and infant mortality rates 1896-1925.*



Lingering prenatal effects of the 1918 Influenza pandemic on cardiovascular aging

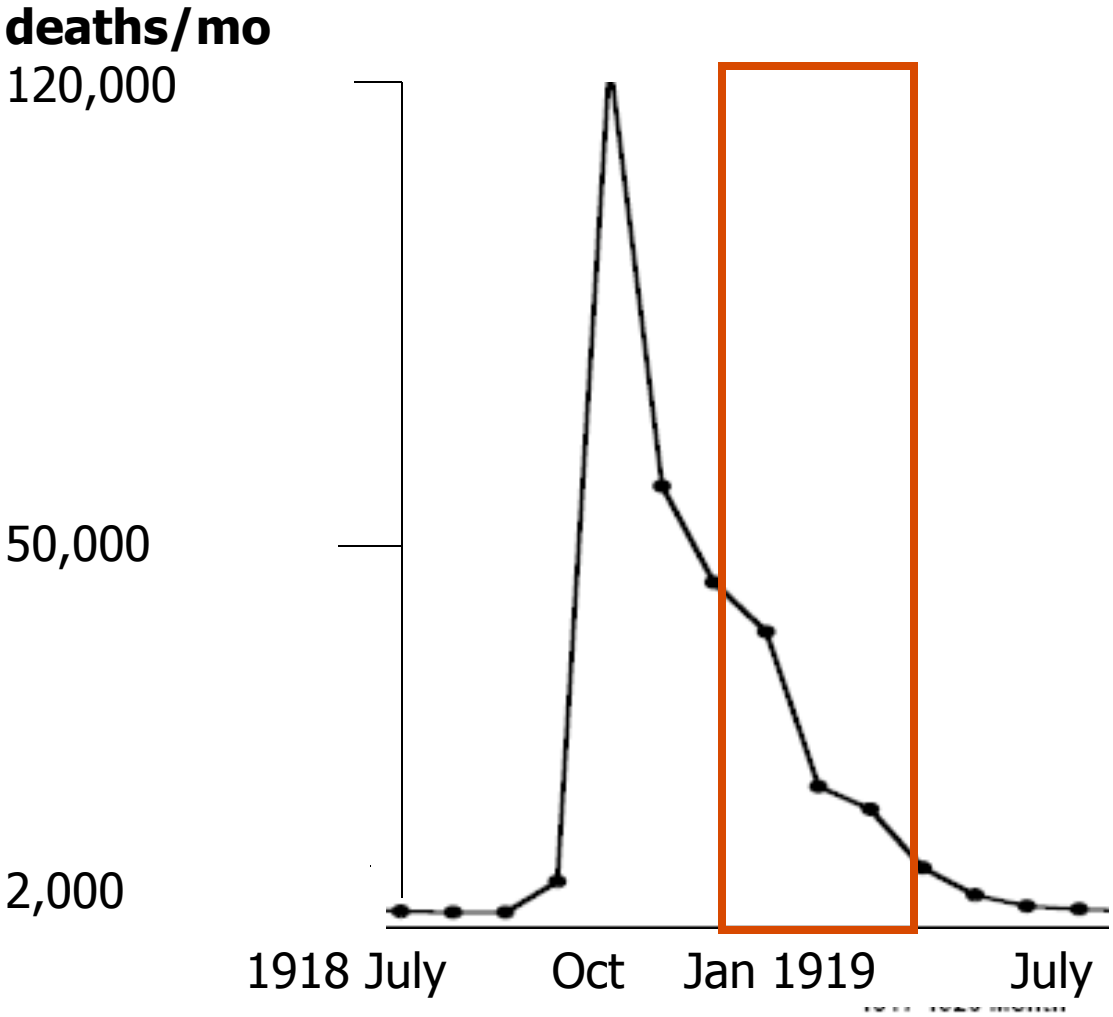
Almond D, Mazumder B, Park K, Crimmins EM, Finch CE

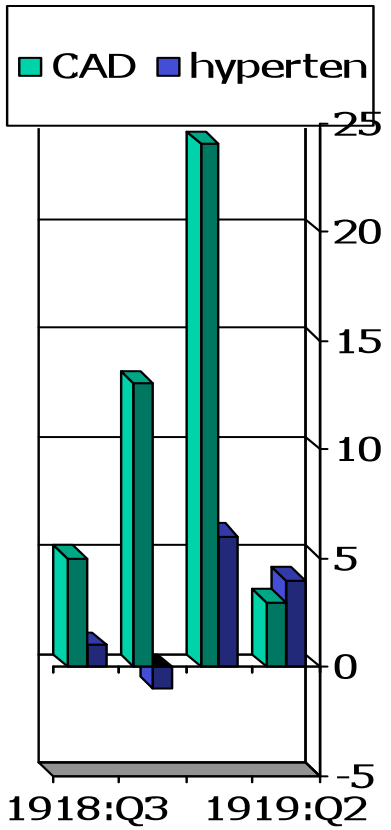
Prenatal exposure to the 1918 influenza pandemic (H1N1) was associated with ≥20% excess CAD at ages 60-82, relative to adjacent cohorts defined by quarter of birth.

- Males were differentially susceptible.
- Possible mechanisms: elevations of maternal IL-6 and cortisol, which increase the risk of adult hypertension.
- Roles for maternal infections in the fetal programming of CAD risk factors distinct from maternal malnutrition.

[National Health Interview Surveys]

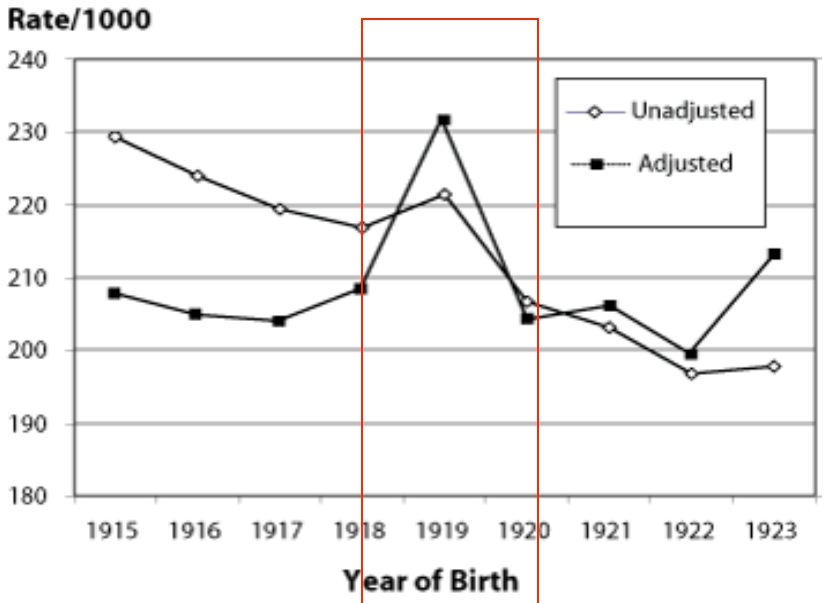
Births in 1919:Q1 >20% more CAD than flanking quarters: prenatal exposure flu peak



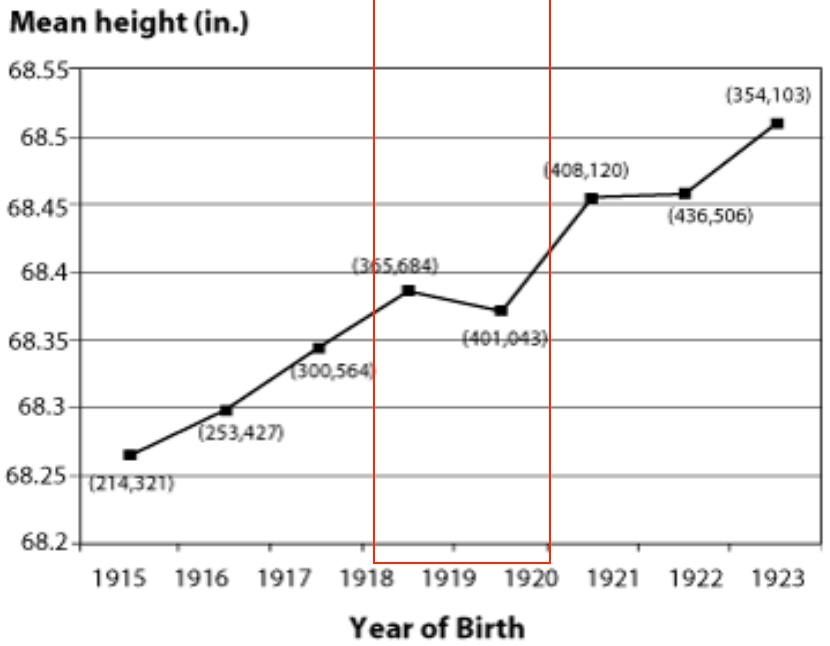


Cardiovascular disease (1982-96) and mean height (1941-42) by birth year

A.



B.



?Causes of death in early populations?
paleopathology is very obscure!

- *Infections*
- Heart disease and stroke?
- Cancer?

Paleopathology: arterial degeneration

- **Tyrolean Ice-Man (5300 years ago):**
  carotid bilateral calcification;
  distal aorta, right illiac artery
  (Murphy et al *Radiology* 2003)

- **Egyptian mummies (3500 yr ago 18th Dyn.)**
  67% large arteries atherosclerotic (16/24);
  50% of these calcified (9/16)
  (Ruffer MA, *J Path Bacteriol*, 1911)

bone tumors are well documented

- **Ancient Egypt 5.5/1000 adult skeletons**
- **Medieval Germany 5.1/1000**
- **England 1905 6.1/1000**

  (Nerlich et al *Oncol. Reports*, 2006).

- **Baboons (estimated)** **0.7/1000** (Ciancolo *J Med Primatol*, 2006)

Chimps age faster than humans

Flo at 42 yr: worn teeth, wrinkles, hair loss

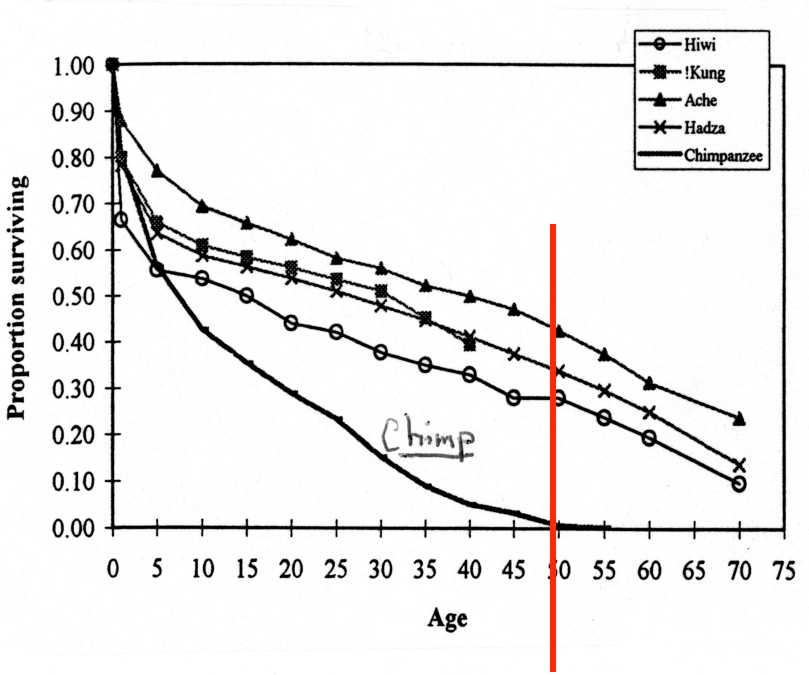
Jane Goodall, Chimpanzees of Gombe, 1986

Chimps life expectancy < humans
higher mortality rates m(x) at all ages

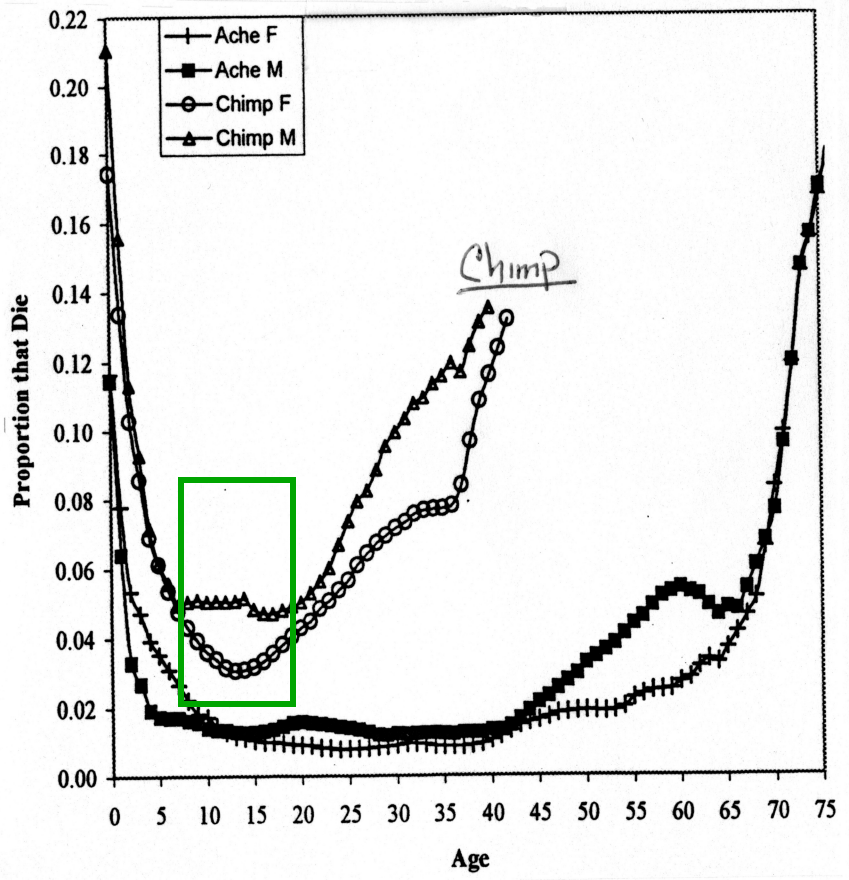
Wild chimps vs Hunter-gatherers

Kaplan et al Evolutionary Anthropol 9 (2000)

Survival



Mortality rates



MP
same age

Comparative adult morbidity

	human, pre1900	chimp
Main cause of adult mortality	**infections & septic wounds**	**similar**
erosive arthritis	**common**	**common**
cancers	**?**	**less prevalent than modern***
atherosclerosis and calcification	**present**	**less prevalent***
Alzheimer dis.	**present**	**absent***

***captive**

Tumors are much less common in aging primates than modern humans

* **USA 2006: 40% lifetime cancer incidence**

*cancer incidence for nonhuman primates **2-4% ….even lower in great apes".** Varki (2000):

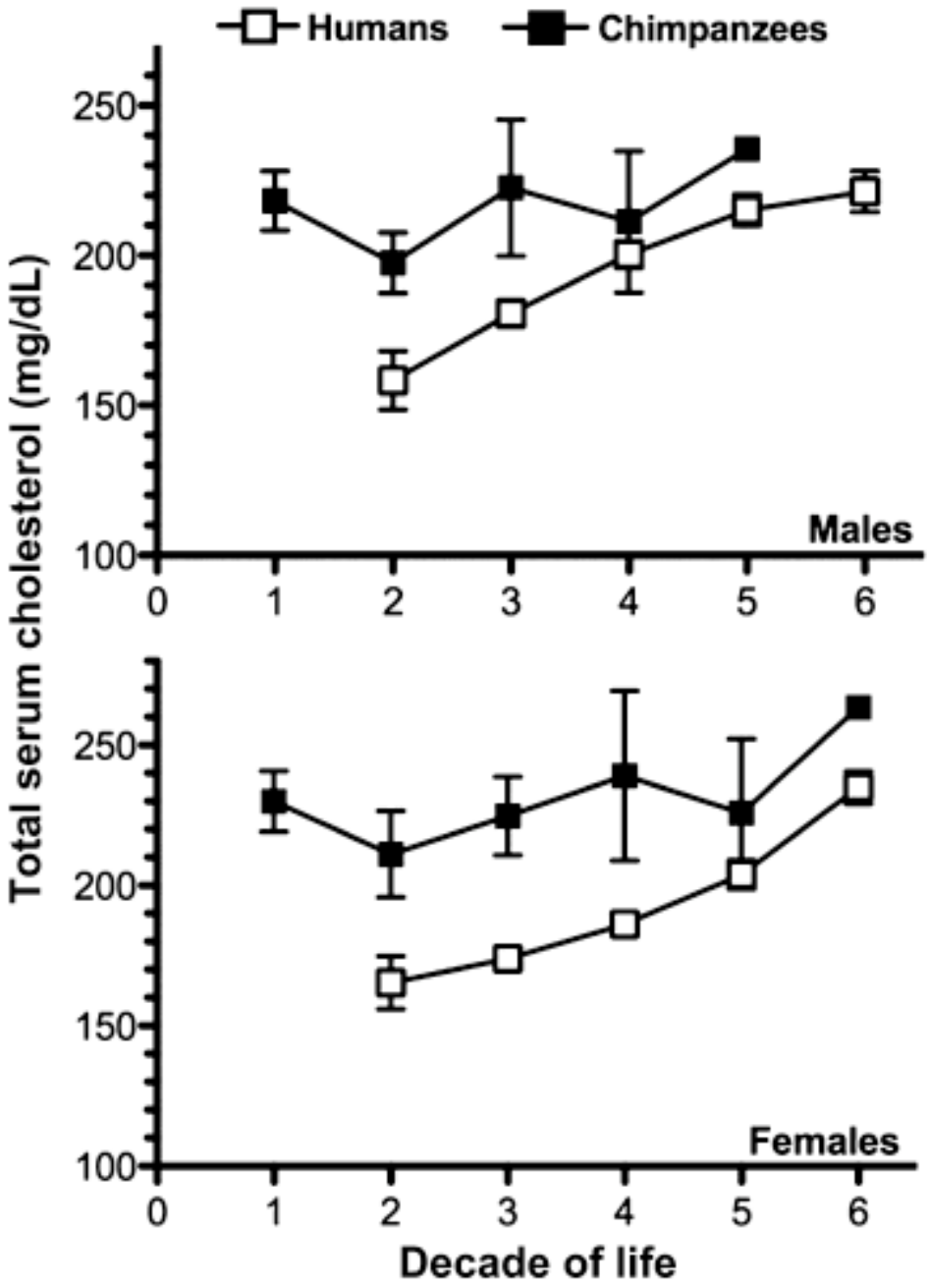
* baboon (4,000 necropsies): **0.5-1% lifetime incidence.** Cianiolo (2006)

- Baboons/monkeys **(13,700**): **2.6% lifetime incidence.** Lapin (1982) 363 neoplasms; 25 in female reprod tract

- Puente (2006): "small differences in (most) tumor suppressor genes" *e.g BRCA1* of chimp has 8 kb deletion.

Yerkes chimp serum cholesterol elevated vs human Framingham population

Varki 2009



Coronary artery disease (CAD) in captive chimpanzees

- **Pre1980: diet not standardized; few regular systematic necropsies**

  Schmidt 1978: 13.5% gross CAD lesions (20/268)

  Other case records of fatal myocardial infarcts

  (Finch & Stanford *Q Rev* Biol 2004).

- **Post 1980 Yerkes colony on low fat diet**:

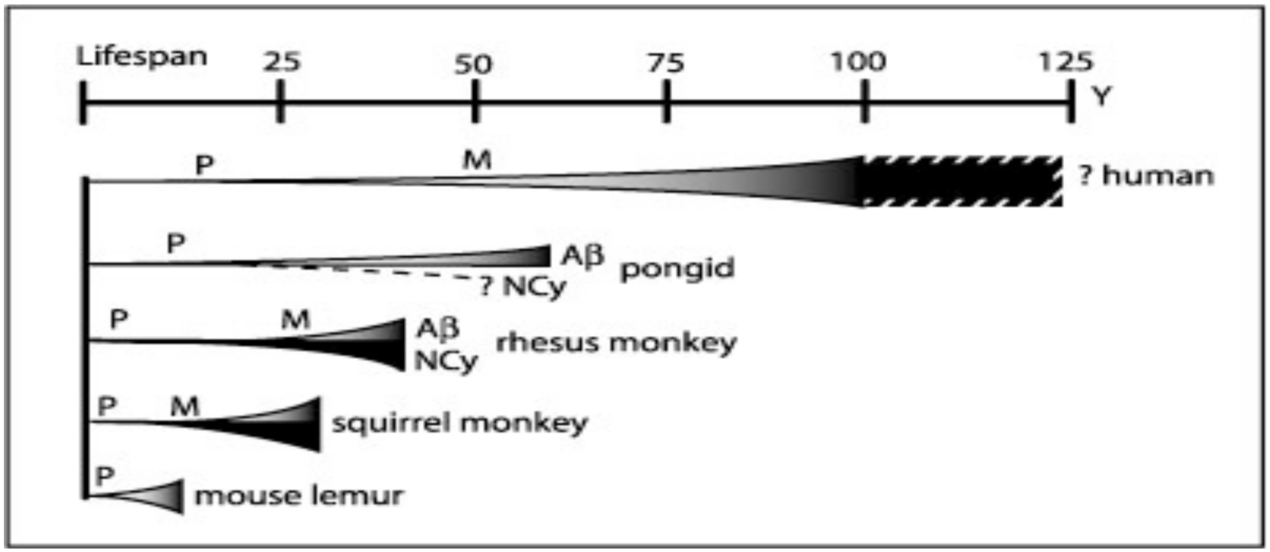
  no CAD, but moderate aortic atherosclerosis.

  diffuse myocardial fibrosis

  arrhythmias and congestive heart failure

  (Varki et al *Evol App , 2009)*

some Alzheimer-like neurodegeneration in most aging primates except great apes



oldest chimps (56 & 59 y):
diffuse amyloid (Aβ) in cortex and in arteries;
few neuritic plaques or tauopathic neurons
No obvious large neuron loss

(Gearing 1997; Erwin 2001, Finch & Stanford, 2004)

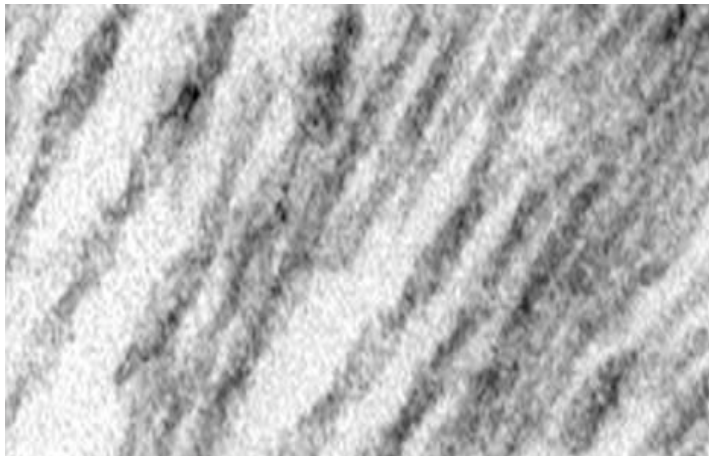
Neurodegenerative changes

- **may be milder in great apes than other primates and humans**
- **All primates have same beta-amyloid sequence, like most other vertebrates**
- **Chimpanzees and most other mammals have apoE that is predicted to function like apoE3**

New chimp case: age-stroke interactions?

Rosen *J Comp Neurol* 2008

- 41 yr chimp at Yerkes had stroke; history of obesity & hypercholesterolemia (244-359 mg/dl)
- most A-beta plaques were diffuse
- **Neuronal tauopathy & paired helical filaments in "indistinguishable from human AD"**

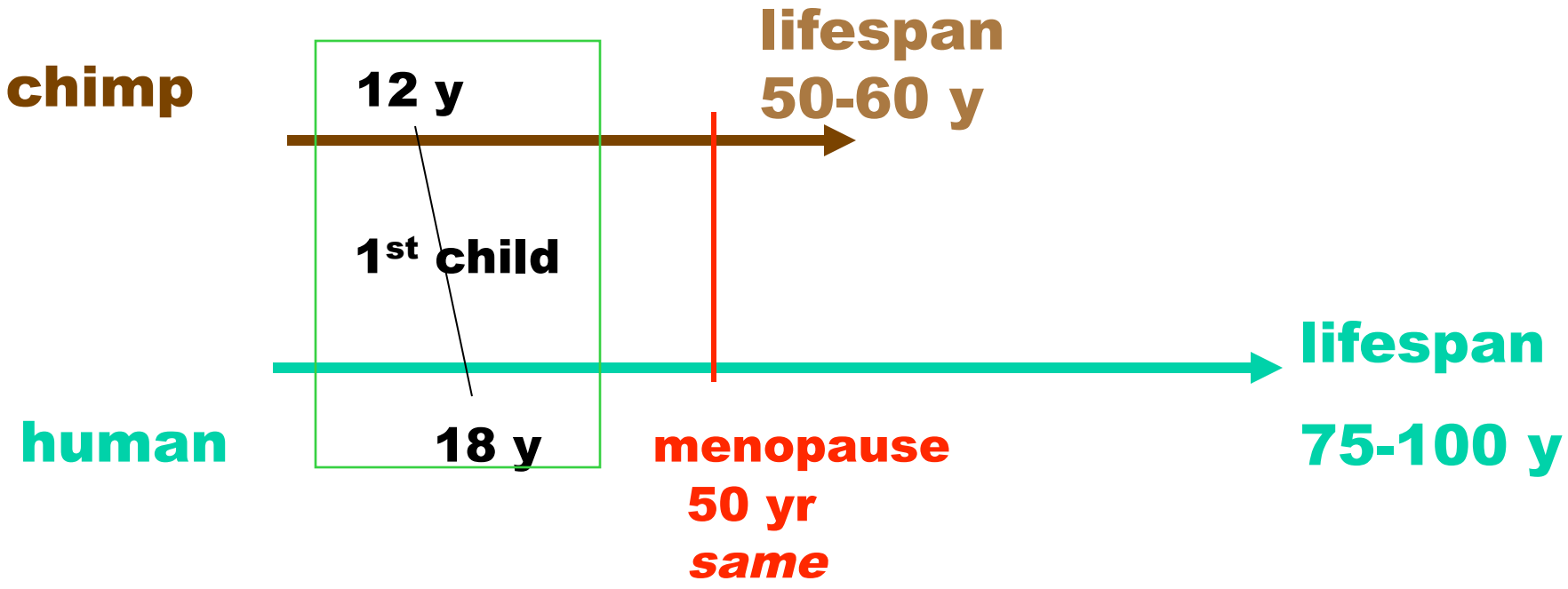


puzzles of chimp aging

- Menopause at advanced age for lifespan
- In captivity,
  - low incidence of malignancy during aging
  - Low incidence of CAD
  - Low incidence of Alzhemer changes
- What conditions cause CAD, stroke, and Alzheimer changes in the few cases?

humans evolved longer life spans with slower maturation; *menopause may be same*

Flo and her daughter had babies after 40!



chimpanzees vs humans

***how did human ancestors evolve the diet shift from vegetarian to meat and increase longevity**

***meat-rich diets and elevated blood cholesterol accelerate Alzheimer & vascular disease**

***Hypothesis of evolved meat-adaptive genes**

Finch CE & Sapolsky RM (1999)
Evolution of Alzheimer disease, the reproductive schedule, and apoE. Neurobiol Aging 20: 407-428

Finch CE & Stanford CB (2004)
Meat-adaptive genes & the evolution of slower aging in humans. Quart Rev Biol 79: 3-50

Finch CE: The Biology of Human Longevity (Elsevier, 2007)

Hypothesis:
diet and inflammation
major factors in the evolution of human lifespans

by influencing progression of

atherosclerosis
cancer
immunosenescence
metabolic dysregulation,
neurodegeneration

Benefits of meat-rich diet

- **Concentrated nutrients- need much less time to eat and digest daily food than vegan diets**
- **Micronutrients: iron, vitamins**
- **Polyunsaturated fatty acids (DHA) - neuroprotective**
  - **Children on vegan diets are at risk for retarded development from deficiencies in Vit D, B12**
  - **In Alzheimer transgenic mice, DHA supplements lowed brain amyloid accumulation.**

dangers of eating meat

* **Excess cholesterol**

pro- cardiovascular & Alzheimer in clinical and animal models;

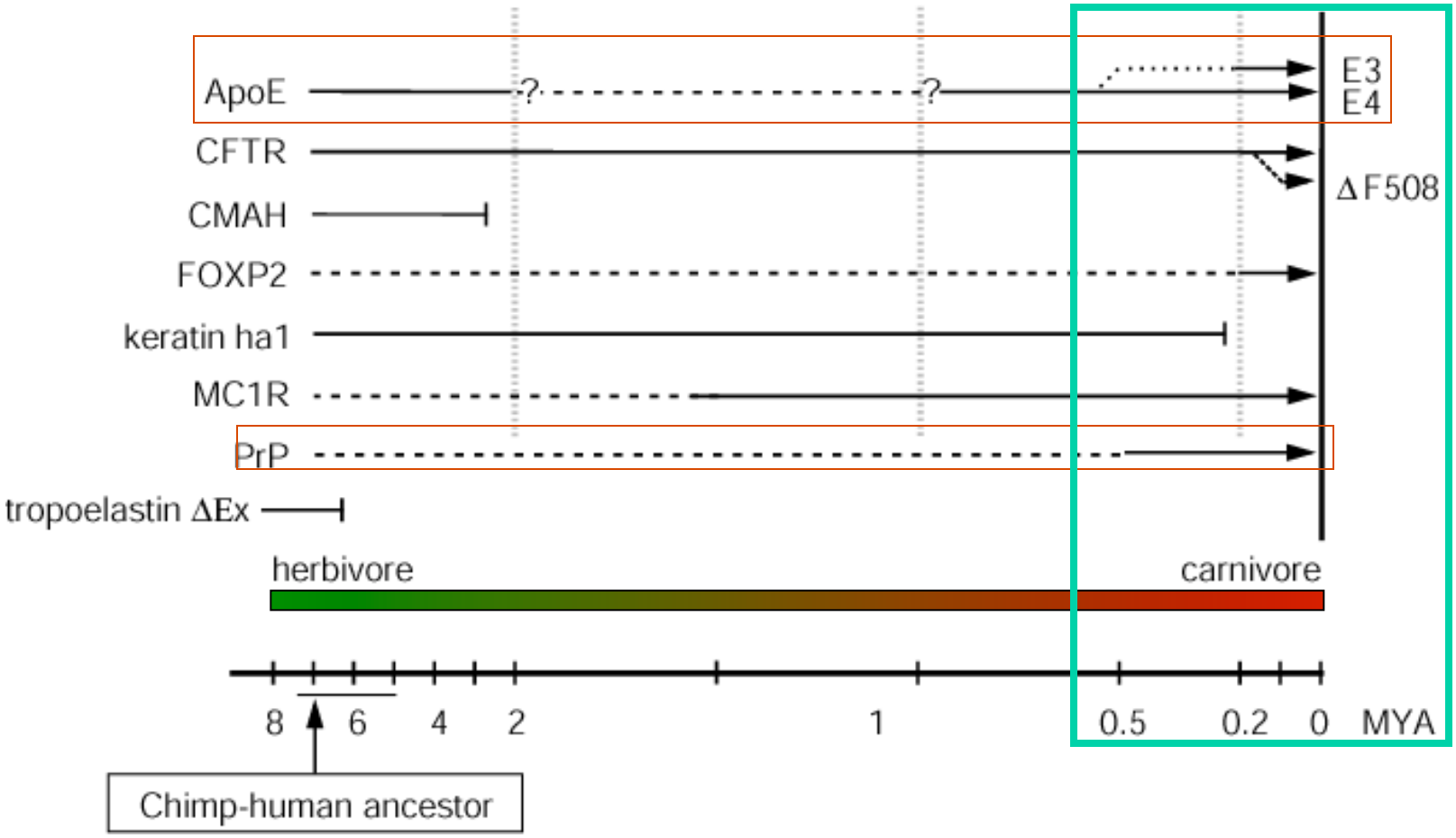
caloric restriction inhibits in animals

* **infectious agents (raw meat):**

parasites

viruses & prions

hypothesis: meat-adaptive genes evolved to allow greater consumption of raw tissues



Diet shift: vegan to omnivore during human evolution

Increased fat & cholesetrol

1.Higher risk to heart & brain vascular & Alzheimer disease

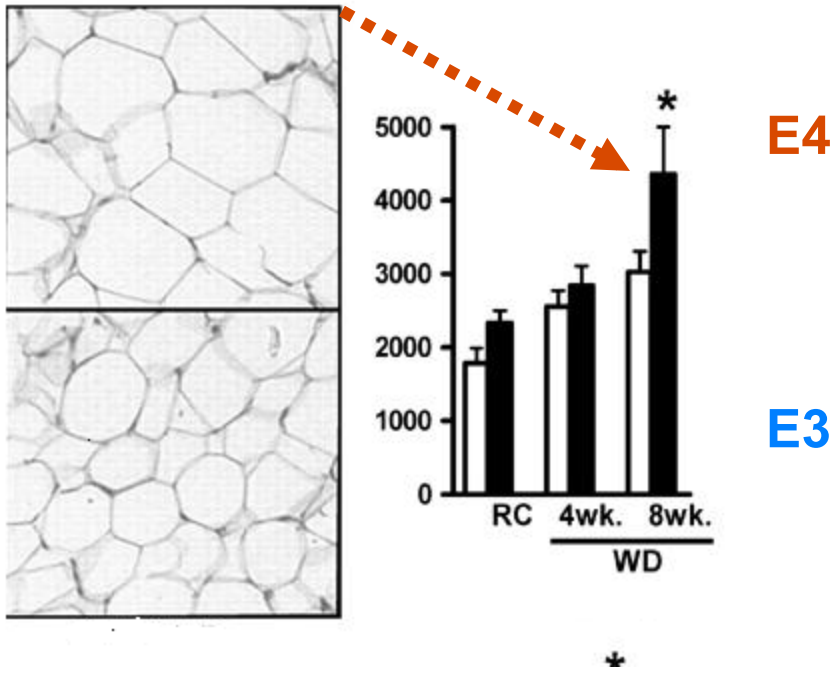
2. apoE4 carriers highest risk

3. BUT apoE4 is ancestral allele

apoE alleles (E3, E4) influence fat cell size in transgenic mice on Western diet (WD)

E4

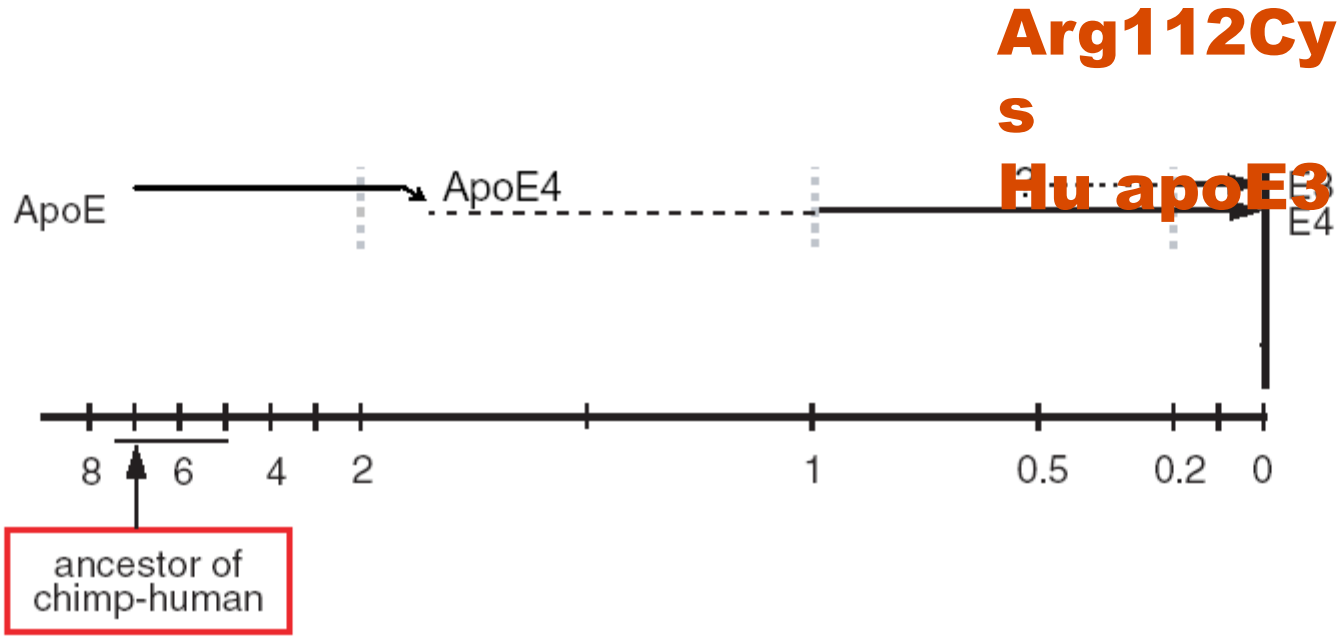
E3



Arbones-Mainar *Int J. Obesity*, 2008

Evolution of ApoE alleles

apoE4 is ancestral allele;
apoE3 present
before modern *H sapiens* and
before1st migration from Africa



Hu-ApoE3 spread 225,000 years ago (176,00-579,000)

(Fullerton et al, Am J Hum Genet, 2000)

Evolution of ApoE Gene

chimp apoE may be functionally more like E3 than E4

T61 causes domain interactions that convert apoE4 to E3-like lipid binding (Raffai et al PNAS 2001)

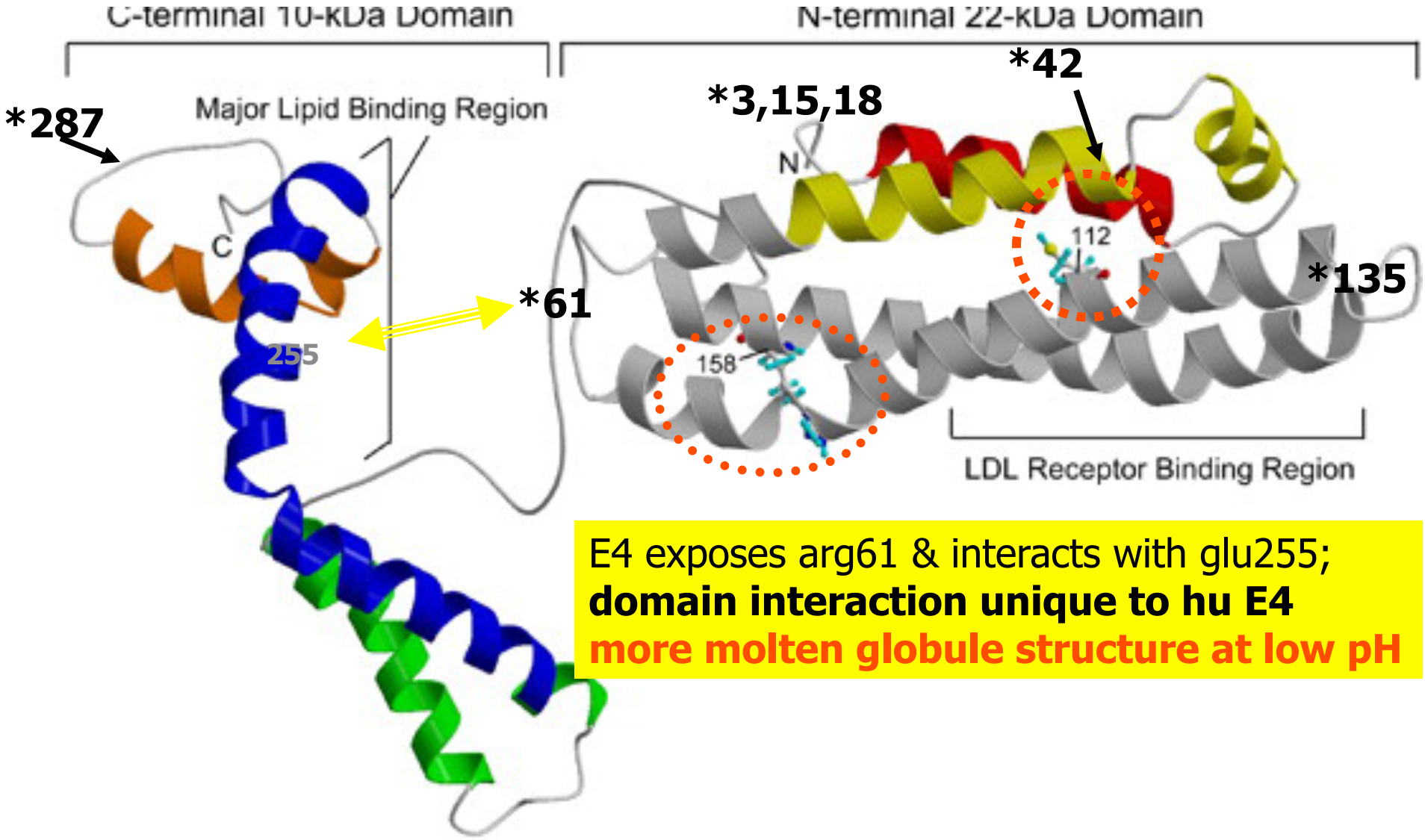
Chimp:	**T61**	**R112**	**R158**
Human E4	**R61**	**R112**	**R158**
Human E3	**R61**	**C112**	**R158**

origin of human ApoE4 (T61R) not dated
clearly present in genus *Homo*

Benefits of apoE*3 to arteries, brain, and aging*

*E3 40% lower heart disease
*E3 lower cholesterol
*E3 less damage after head trauma,
*E3 longer neurites
*E3 higher forebrain glucose utilization
**E3* higher threshold for hyperlipidemia
*E3 less atherosclerosis
*E3 slower cognitive decline
*E3 lower cholesterol promotes
beta-secretase APP processing
& less Amyloid-beta

apoE structure*, chimp-hu

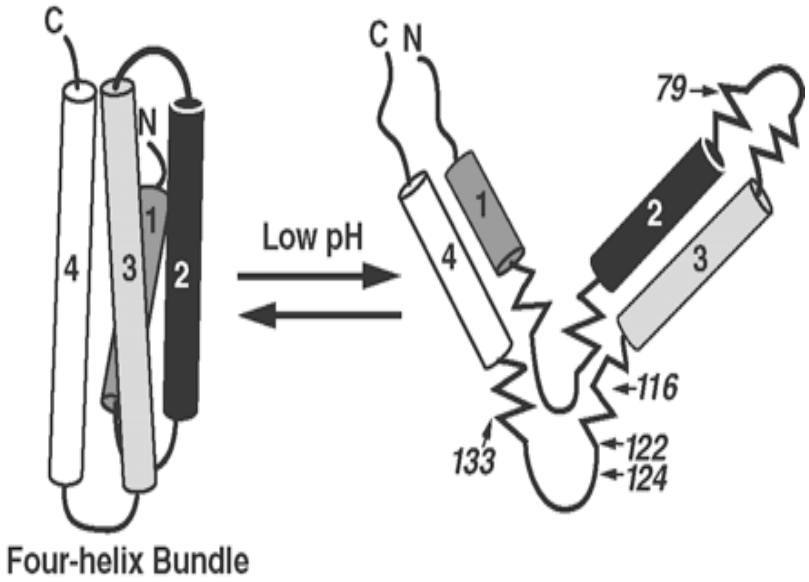


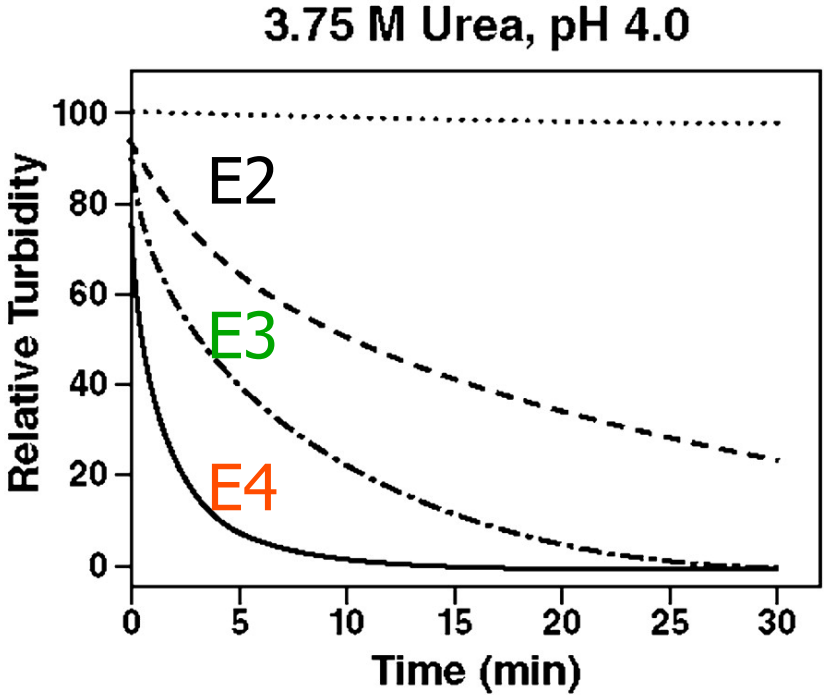
E4 exposes arg61 & interacts with glu255;
domain interaction unique to hu E4
more molten globule structure at low pH

(Chou CY JBC 2006

apoE4 forms
molten globule at low pH
unique human function

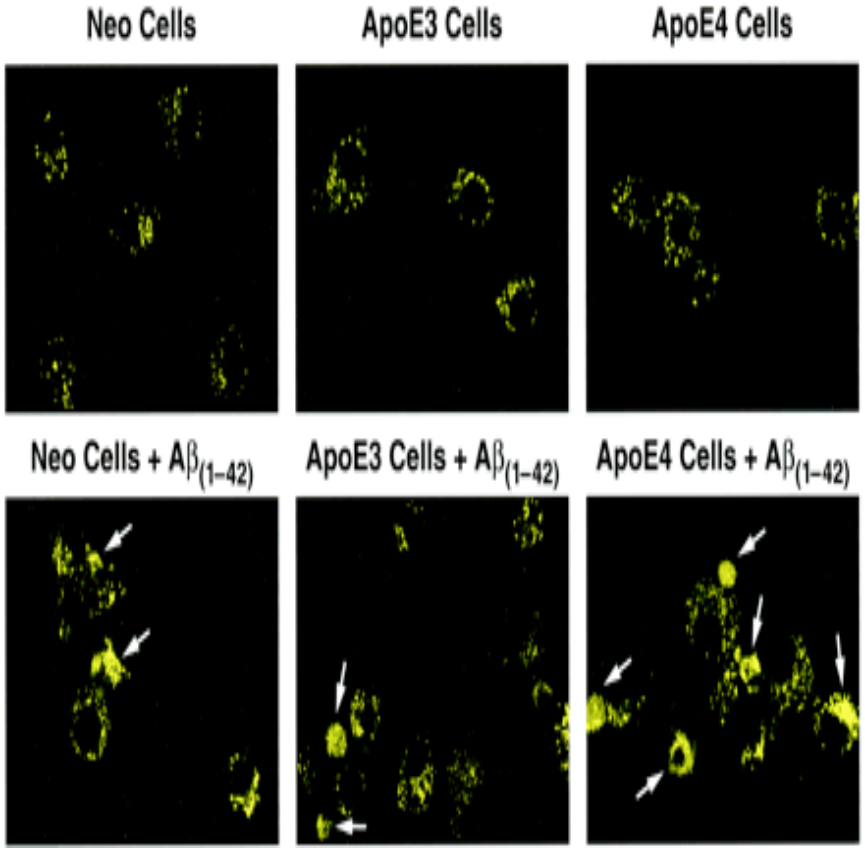
apoE4 at low pH
destabilizes lipid
vesicles

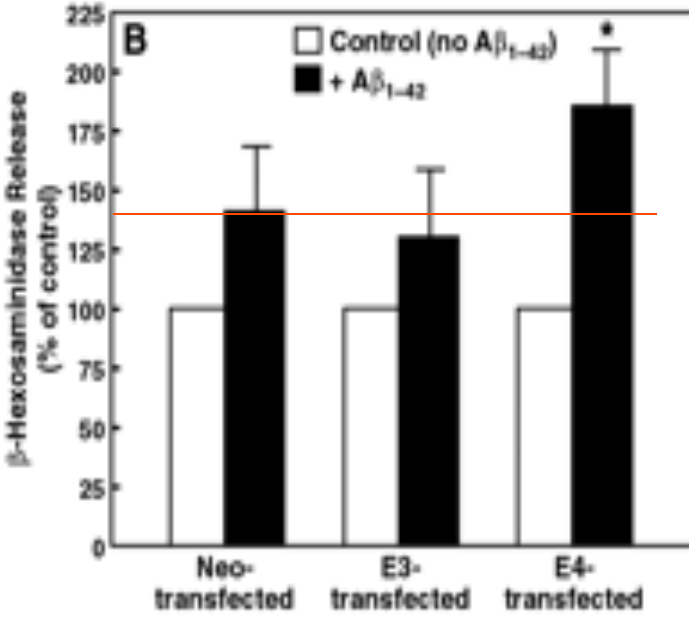




Morrow et al *JBiol Chem* 2002

apoE4 increases Aβ-induced lysosomal leakage

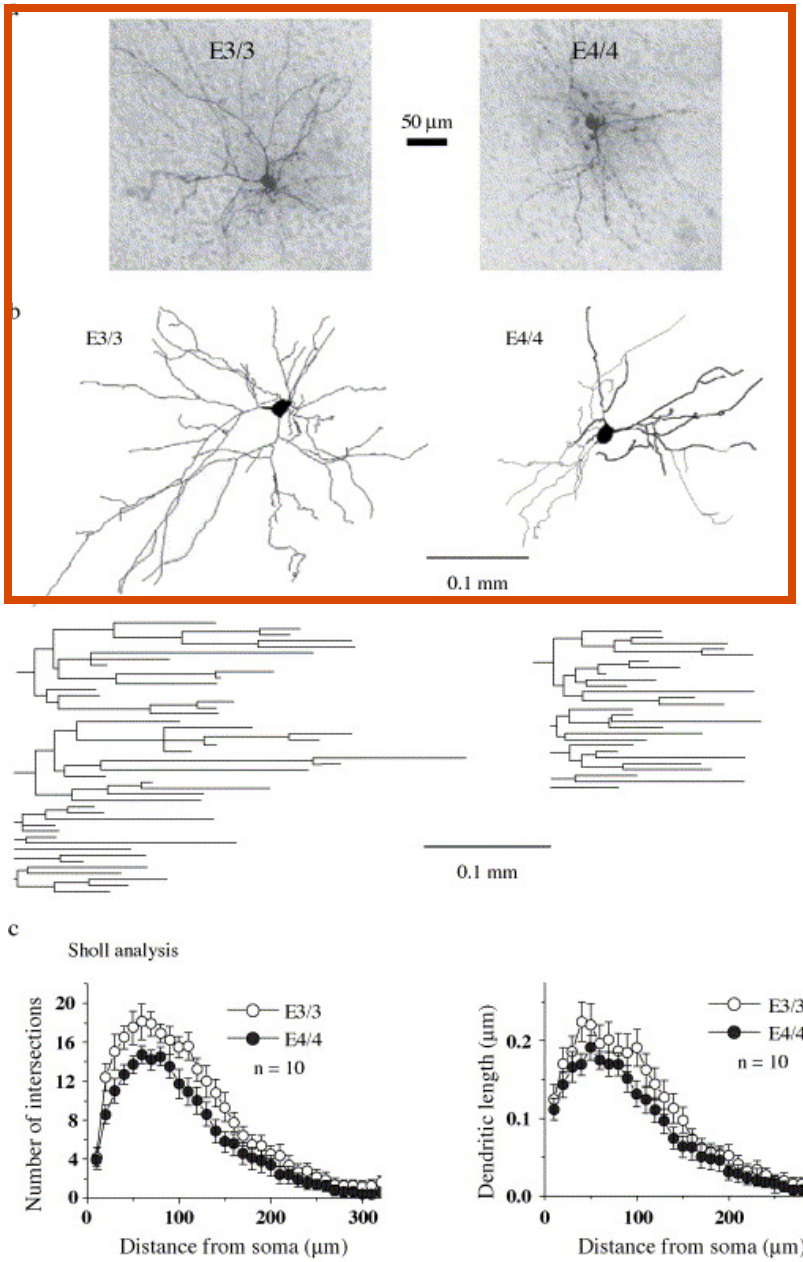




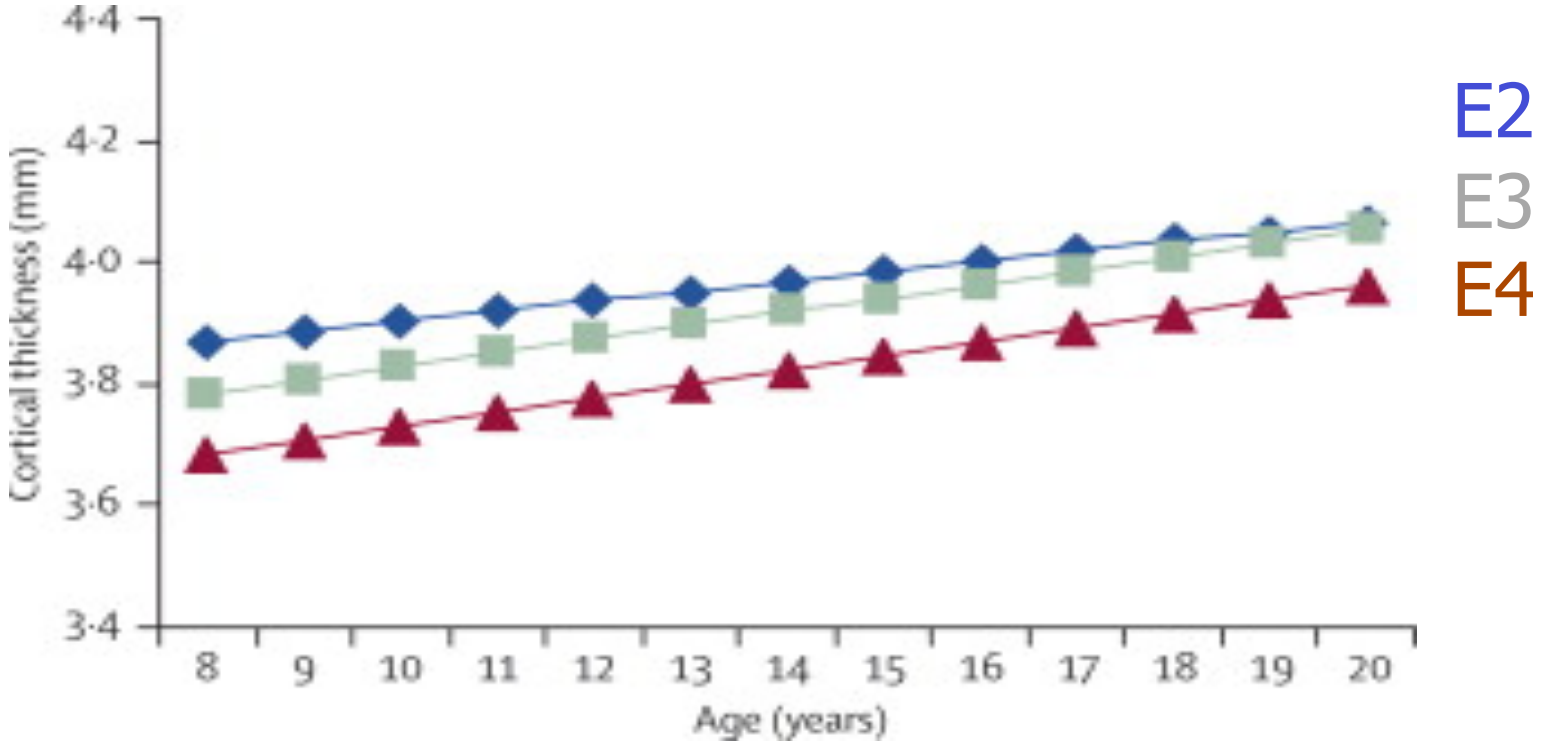
N2a cells, Ji JBC 2002

ApoE3 & brain transgenic mice with hu-apoE3 have more synapses

Wang…Sullivan
Neurobiol Disease 2005



ApoE alleles influence entorhinal cortex thickness during postnatal development in normal children



P Shaw et al *Lancet Neurology* **6**: 494-500; 2007

ApoE4 "bad apoE", ancestral gene

?balancing allelic effects?

apoE4 carriers

***hepatitis-C: less liver damage**

***greater inflammatory responses**
higher TNFa after surgery-

****? In* childhood chronic diarrhea**
better cognitive development?

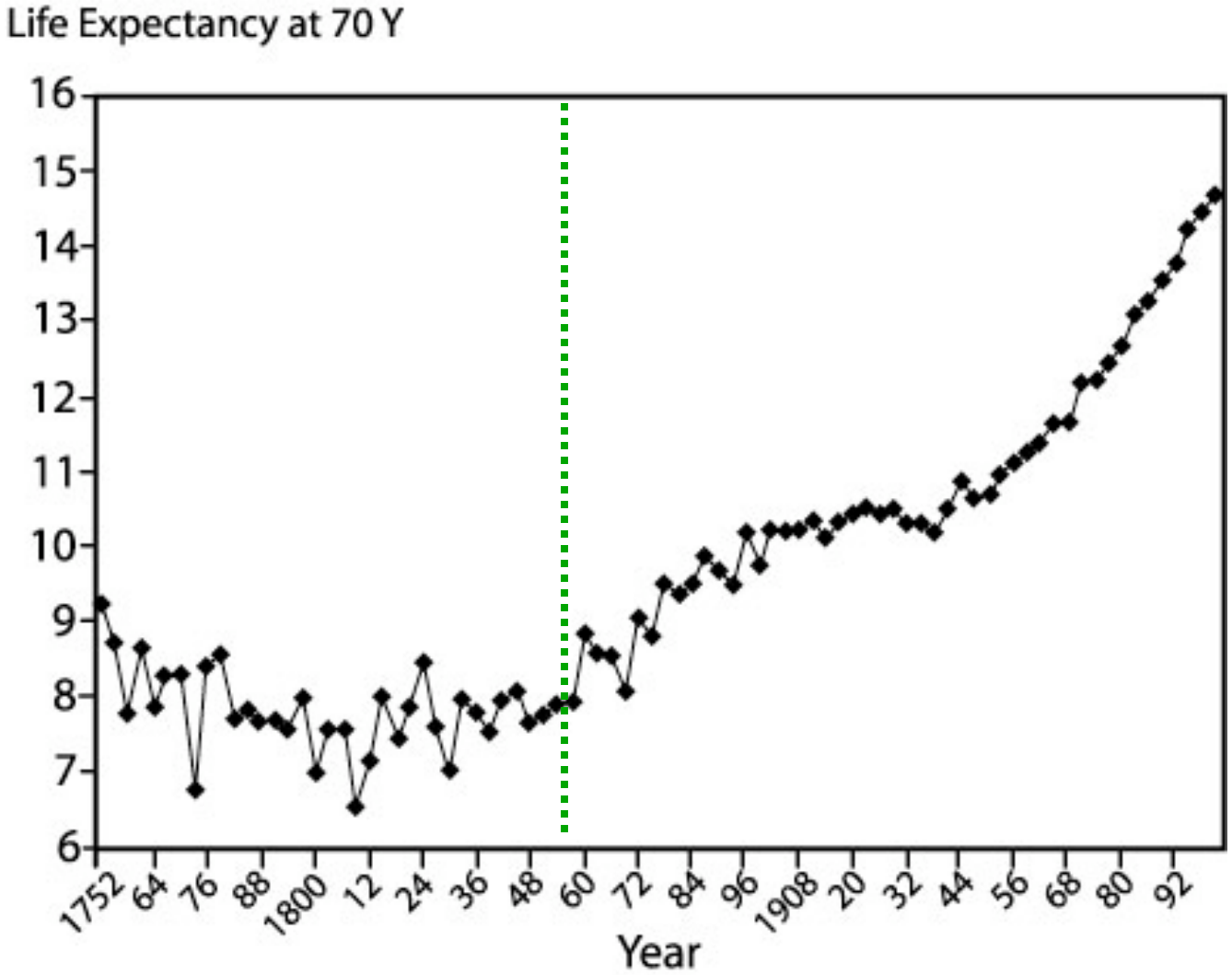
***?resistance to malaria?**

Open questions: chimp vs human

- **need detailed postmortem histopathology**
  brain, bone, vasculature, reproductive tract
- **Genomics**
  - blood lipids: apoE, L(p)a, others?
  - immunity
  Mhc (selective sweep)
  innate immunity: siglecs; cytokines??
  age changes in telomers??
- **metabolism and adipose tissue??**
- **somatic growth schedules??**
- ***Population genetics- natural populations??**

Age 70 life expectancy in Sweden began to increase in birth cohort of 1790

Finch & Crimmins, *Science* 2005



Opposing changes
in the future of longevity

Pro-longevity

1. **new drugs**
2. **pharmacogenetics**
3. **regenerative medicine: stem cells**

Anti-longevity

1. **obesity epidemic**
2. **growing air pollution and inflammogens**
3. **new infections with global crowding and decreased sanitation**
4. **rapid spread due to commerce and travel**

Russian longevity crash

example of unstable lifespan

3 y

14 y

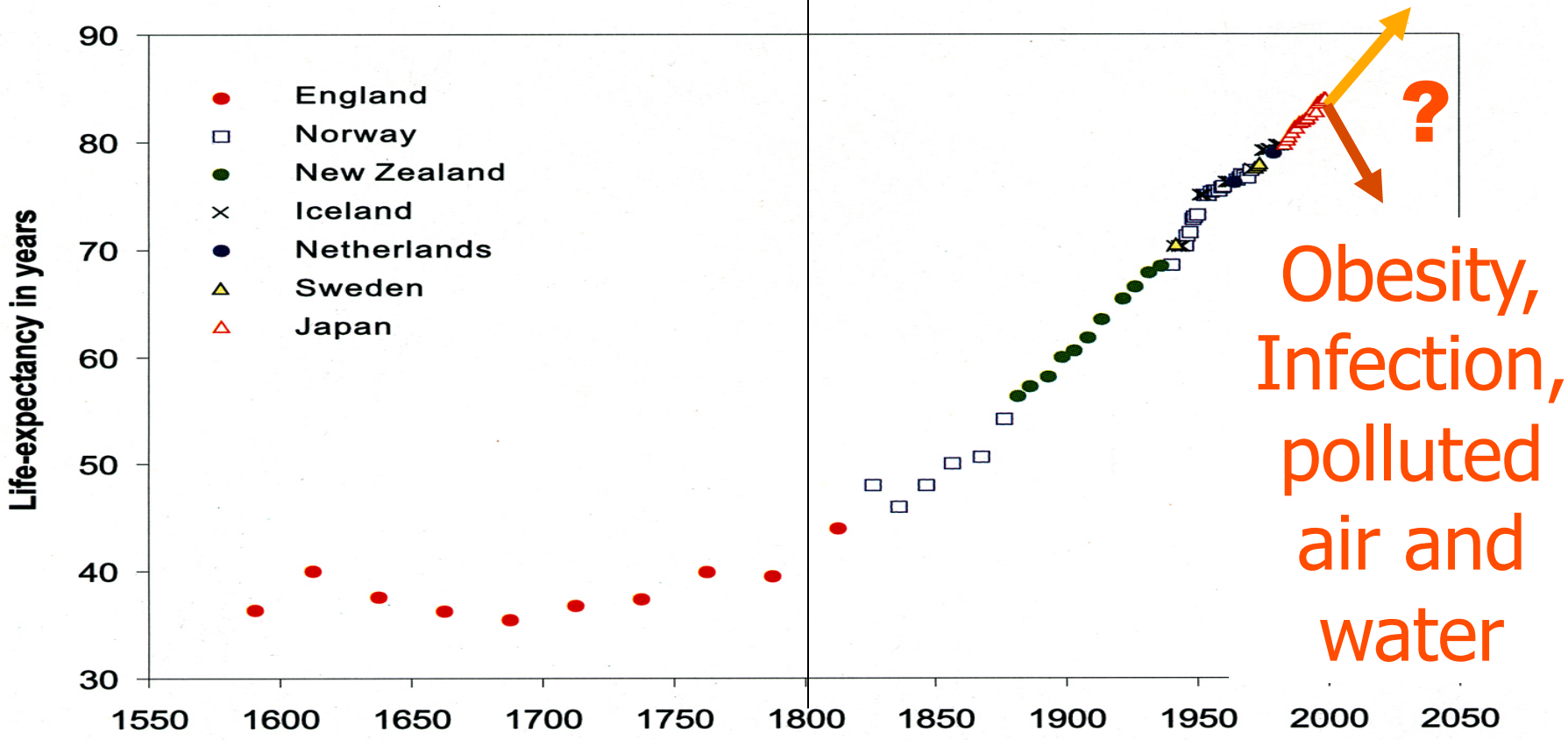
Historical phases of life expectancy

Oepen and Vaupel, Science 2002; C Finch adaptation

Phase 1
early urban

Phase 2
sanitation-nutrition

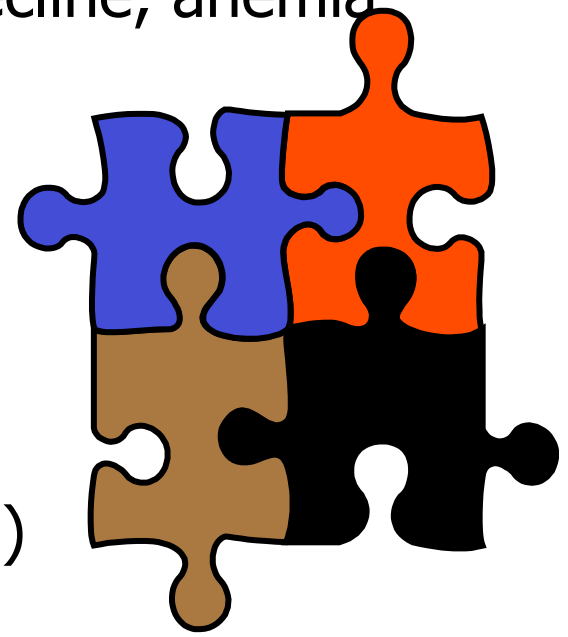
Phase 3?
regeneration
modern medicine



Obesity, Infection, polluted air and water

Targets in geriatric frailty:
interlocking domains with shared molecular processes
of inflammation and oxidative damage

1. Vulnerability to stress, infection
   loss of homeostatic reserve; immune decline, anemia
2. Diminished physical activity
   fatigue, muscle weakness, joint pain,
   vascular, heart, and lung insufficiency
   falls and osteoporotic fractures
3. Impaired nervous and sensory systems
   blindness and deafness
   cognitive impairment (not only dementia)
   peripheral neuropathy
   depression and social disengagement
4. *Aging increases co-morbidities in multiple dysfunctions*



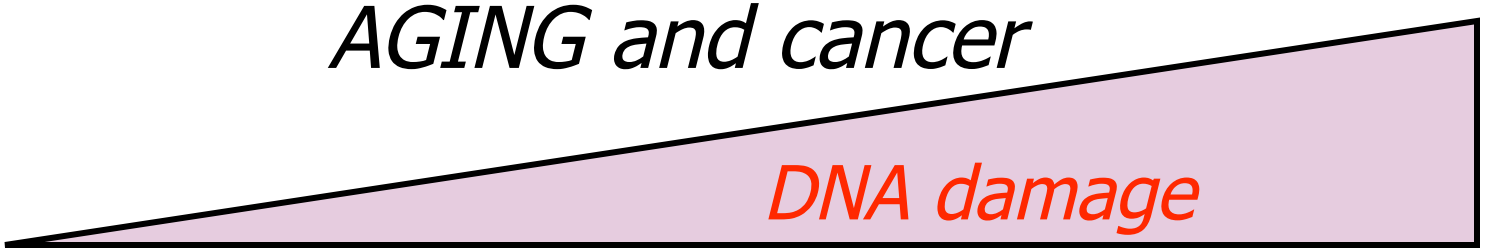
Immunosenescence:
correlates with T cell changes
and pathogen antigen stimulation

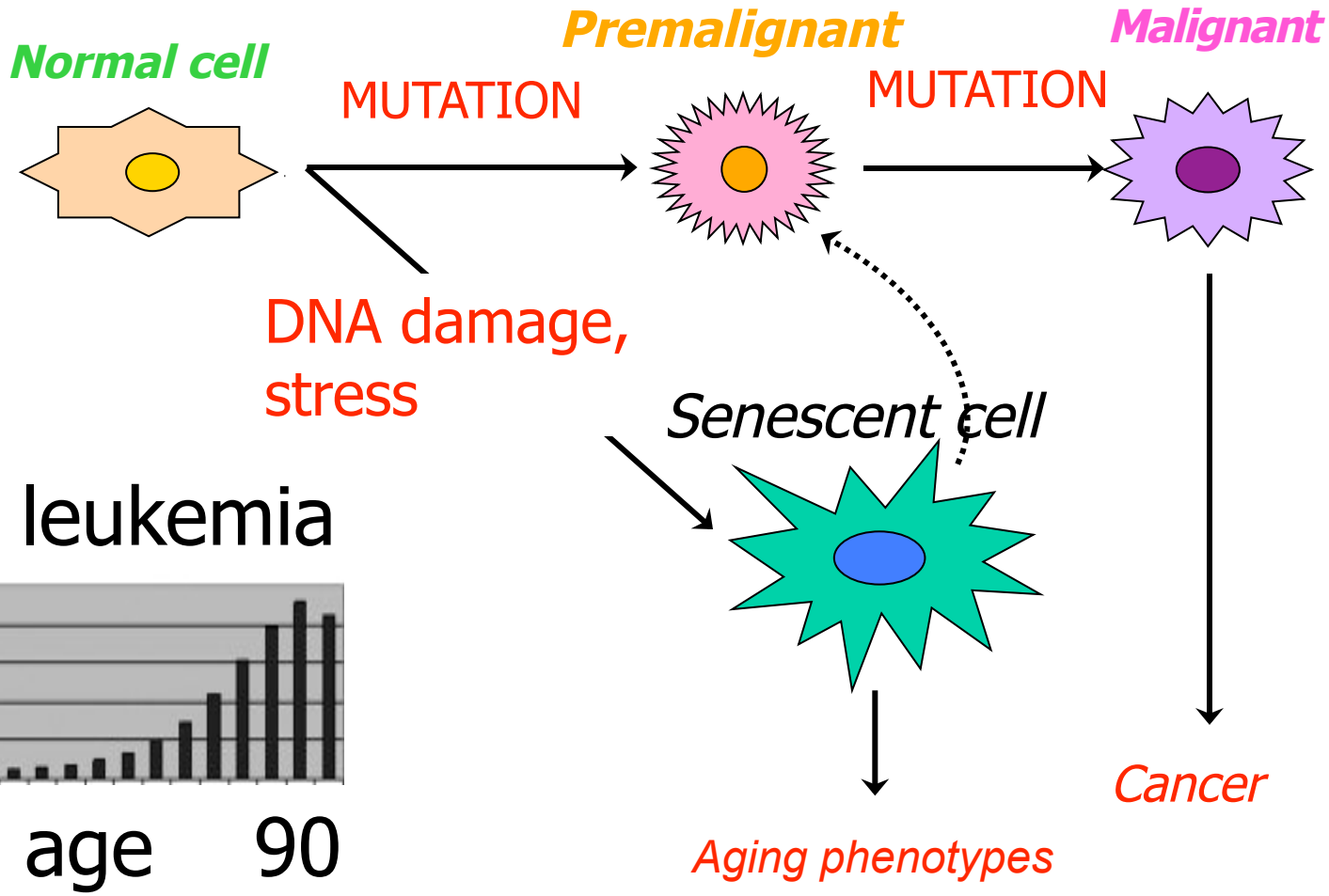
longitudinal studies define
"immune risk phenotype" for infections

*poor response to flu vaccine
*senescent T cells with narrow responses
*senescent T cells are proinflammatory
*short telomeres - 7x higher mortality

Antigen exposure (HIV, CMV) accelerates immunosenescence and telomere loss

AGING and cancer





Acute leukemia

10 age 90