Evolution of the human life span: the nexus of inflammation, diet, and aging

Caleb Finch
Arterial lesions progress across the life span
Oil-red positive areas postmortem (D’Armiento et al Stroke 2001)
myocardial infarction despite normative cholesterol: 26-year follow-up of the Framingham study
Cytokines and Danish Centenarians

H. Bruunsgaard et al., J Gerontol 1999

IL-6  TNFα  sTNFR-II

18-30y  55-65y  80y  100y
Risk of MI: the additivity of IL-6 & LDL cholesterol.

IL-6 also correlated with CRP and fibrinogen

PRIME study: G. Luc et al., *Arterioscler Thromb Vasc Biol.* 2003
C-reactive protein (CRP) marker for vascular disease & dementia
very bioactive

* Chronic CRP elevations predict heart attacks
* CRP is a rapid acute inflammatory response
* CRP binds bacteria for phagocytosis
* CRP increases uptake of LDL by macrophages
* CRP activates complement and is neurotoxic

**********
ancient pentraxin (Limulus)
Physicians' Health Study P.M. Ridker et al. *Circulation*, 1998

CRP and risk of first MI in healthy men
Aging and inflammation
KS Krabbe et al. Exp Gero 2004

- strong age-related trend for 2-4-fold increase of CRP, IL-6, TNFa (inflammatory acute phase proteins)
- much smaller increase than in acute infection or major trauma
- associated with chronic vascular disease, obesity, and diabetes
  - IL-6, TNFa procoagulant; dyslipidemias
  - TNFa increases insulin resistance
  - CRP stimulates LDL uptake by macrophages, activates complement
- IL-6 and TNFa may be independent risk factors for mortality
- polymorphisms in IL-6 and IL-10 promoters may influence blood levels and disease risk (controversial).
Mammalian Longevity

% vs. YEARS

mouse rat  dog  cat  horse  cow  human

0 5 20 40 60 80 100 120

Caleb Finch
Historical phases of life expectancy

Phase 1
early urban

Phase 2
sanitation-nutrition

Phase 3?
regeneration

modern medicine

Caleb Finch
Jean Calment 122 year life span without dementia
Caloric restriction increases rodent lifespan & delays tumors and other diseases

![Graph showing survival curves and age-specific tumor incidence of control mice (slightly restricted, *) and test mice (severely restricted, o) with restriction initiated at time of weaning. Symbols show age of death for tumor-bearing mice. Adapted from Weindruch et al. (1986).](graph.png)
Caloric restriction (CR) attenuates brain amyloid (Aβ) in two transgenic mouse models
Patel, Morgan, Finch; 2004
Diet and Alzheimer

diets high in fat/cholesterol increase risk of Alzheimer in humans &
promote Alzheimer-like changes in AD-mice

would reducing food intake slow Alzheimer changes?
Ancient history of amyloid $\beta$

**A peptide & APP strongly conserved**
- Zebra fish (Musa et al Genes Devel 2001)
- most mammals
- Lab rodent A exceptions:
  - 3 substitutions reduce A aggregation
    (Johnstone et al, Mol Br Res 1991)

**Alzheimer-like amyloid A accumulations**
- in most mammals
- non-mammalian vertebrates
  - birds
  - fish
60 gm
60 d gestation
2-3 offspring
puberty 1 y
females reproduce up to oldest ages of 12-14 yr

early AD-like brain aging

Mouse lemur

neuropathology of aging

abnormalities in neurocytoskeleton
2-3 yr, progressive phospho-tau-IR

Aβ-deposits
8-13 y, progressive cerebral vessels senile plaques

motor dysfunctions
primates evolved longevity & delayed brain aging

Finch & Sapolsky, Neurobiol Aging 1999
hominid life spans

- vegan
- Chimpanzee... 60 yr
- Gorilla.........60
- Orangutan.......60
- omnivore
- Human..........>100
How did humans evolve longer life spans despite major increases in meat eating?
Evolution of the human life span:
humans are the longest-lived primate

chimpanzees
* 30 year shorter life spans than humans
<60 years in zoos and in the wild
* higher mortality at all ages
* earlier acceleration of mortality
Chimpanzees age faster than humans
Wild chimps vs Hunter-gatherers
Kaplan et al Evolutionary Anthropol 9 (2000)

Survival

Mortality rates
humans evolved longer life spans with slower maturation (and aging?)

mx (puberty), 0.04/y

chimpanzee 14 y

1st child

human 18 y

mx, 0.015/y

prostate enlargement (PSA)

lifespan 50-60 y

menopause

multigenerational care & training
Vascular disease in chimps

More spontaneous aortic and cerebral atherosclerosis in chimps [in captivity] than any other nonhuman primate”  (Blanton et al 1972)
laboratory chimpanzees highly susceptible to hypercholesterolemia, obesity, and vascular disease on diets with animal tissues

<table>
<thead>
<tr>
<th>blood cholesterol</th>
<th>(15 reports/19 groups; 239 chimps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>high ( \geq 240 \text{ mg/dl} )</td>
<td>5/19 groups ( = 26% )</td>
</tr>
<tr>
<td>borderline 200-239</td>
<td>8/19 ( = 42% )</td>
</tr>
<tr>
<td>normal (&lt; 200)</td>
<td>4/19 ( = 21% )</td>
</tr>
</tbody>
</table>

Finch CE & Stanford C (Q Rev Bio, 2004)
Evolution of the human life span: humans are the longest-lived primate

chimpanzees vs humans
*30 year shorter life spans than humans
*how did human ancestors evolve the diet shift from vegetarian to meat and increase longevity

*this is a puzzle: meat-rich diets leading to elevated blood cholesterol can accelerate Alzheimer, vascular, cancer

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

* cholesterol elevations:
  pro- cardiovascular & Alzheimer
* infectious agents (raw meat):
  parasites
  viruses & prions

*Hypothesis of evolved meat-adaptive genes
hypothesis: **meat-adaptive genes** evolved to allow greater consumption of animal tissues
ApoE4 “bad apoE”, the ancestral gene elevated LDL and cholesterol

increased heart attacks, strokes, & Alzheimer disease;
brain deficits in middle-age (frontal cortex glucose metabolism)
Evolution of ApoE alleles
Hu-ApoE3 spread 225,000 years ago
(176,000-579,000) (Fullerton et al 2000)
Evolution of ApoE Gene

chimp apoE may be functionally more like E3 than E4

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

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

Ancestral origin of human ApoE4 (T61R) not dated but clearly in genus Homo

Hu-ApoE3 spread 225,000 years ago (176,00-579,000) (Fullerton et al 2000)
further implications of E3

*E3 smaller inflammatory responses
*E3 less damage after head trauma,
*E3 more neurite sprouting
*E3 higher forebrain glucose utilization

*E3 higher threshold for hyperlipidemia
*lower cholesterol promotes
β-secretase APP processing & less Aβ
*But, E3 have more liver damage in hep-C implies trade-off of apoE4 and apoE3
ApoE4 alleles shorten dendritic spine length in AD and normal aging
apoE transgenic targeted replacement APOE3 < apoE4 IL-6 & TNF inflammatory responses to LPS in serum and brain
Lynch et al. JBC 2003
Venus of Willendorf

23,000 yr BCE
Naturhistorisches Museum, Vienna
Anti-inflammatory drugs & statins
unexpectedly general protection
against chronic diseases of aging

1. Cardiovascular (aspirin, statins) 30-50%
2. Cancer 30-50%
   colo-rectal (NSAIDs)
   esophageal (NSAIDs)
   breast (aspirin, statins)?
3. Alzheimer disease
   (NSAIDs, aspirin, statins)?
# Shared inflammatory subsets: atheroma & senile plaque

<table>
<thead>
<tr>
<th>Cells</th>
<th>Atheroma</th>
<th>Senile Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocyte activation</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Macrophages (CD68)</td>
<td>+++ (foam cells)</td>
<td>++ (microglia)</td>
</tr>
<tr>
<td>T helper (Th1)-cells</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Mast cells, platelets</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Neovascularization</td>
<td>++</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proteins</th>
<th>Atheroma</th>
<th>Senile Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloids</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>( \beta )</td>
<td>? (platelet APP)</td>
<td>+++</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Serum amyloid P (SAP)</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Clotting factors</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Complement: C3, C5b-9</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cytokines: IL-1, IL-6</td>
<td>++</td>
<td>++</td>
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Caleb Flinch
atheromas and inflammation
temperature of the endoaortic surface

A, control, no plaque

B, 6 mo high cholesterol
‘hot plaque’

C, +3 mo low cholesterol
plaque regressed
macrophage density determines plaque temperature, not plaque thickness
Early elevations of CRP and later dementia

25-year follow-up of Honolulu-Asia Aging Study

Serum CRP taken in In 1975
Upper 3/4-tiles of serum CRP linked to 3-fold higher risk for all dementias

Caleb Finch
Alzheimer prevalence increases exponentially with aging

% with AD doubles each 5 years

relationship to inflammatory changes of aging??
Senile plaque with abnormal neurites & glia
### Inflammatory markers in Alzheimer & brain aging

<table>
<thead>
<tr>
<th></th>
<th>Senile plaque</th>
<th>Normal human</th>
<th>Normal rodent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glial activation:</strong></td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GFAP (astro), MhcII (µglia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>α1-ACT</strong></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>α2-macroglobulin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>apoE, apoJ, CRP, HOX-1, RAGE</strong></td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Complement</strong></td>
<td>++</td>
<td>corpora amylacea</td>
<td>+ C1q mRNA</td>
</tr>
<tr>
<td>C1q, C3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IL-1, IL-6, TNF-α</td>
<td></td>
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</table>
Complement pathways: activated during aging?

Classical Activation Pathway

- Ag
- Ab
- C1
- C2
- C3
- C4
- C5
- DAF
- C1q

Alternate Activation Pathway

- C3
- C3b
- C4b
- C5
- C5a
- C5b
- DAF

Activated:
- C1q
- C2a
- C3b
- C5a
- C5b

Chemotactant:
- C1q
- C2a
- C3b
- C5a
- C5b

Inhibitor:
- DAF
- C1q

Adapted and modified from images and text provided.
Complement deposits in very early AD (CDR 0.5)

H Zanjani, C Finch
J Morris, J Price
in prep.
C3, C4 deposits in normal aging diffuse plaques (CDR 0)

H Zanjani, C Finch
J Morris, J Price,
in prep.
Age increase of IL-6 in brain glia

Xie et al
Exp Neurol
2003

Ratio of Old/Young

<table>
<thead>
<tr>
<th></th>
<th>Cx</th>
<th>Hc</th>
<th>St</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 mRNA</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 Protein</td>
<td></td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>
Microglia/monocytes in white matter are activated during aging
Morgan et al Neuroscience 1999

Hypothesis: glial activation impairs myelinated pathways that mediate high speed integrative functions
Alzheimer prevalence increases exponentially with aging

% with AD doubles each 5 years

?relationship to inflammatory changes of aging?
Historical phases of life expectancy

**Phase 1**
early urban

**Phase 2**
sanitation-nutrition
regeneration

**Phase 3?**
modern medicine
Inflammatory hypothesis of the historical increase of human life spans

C Finch & E Crimmins (USC)
Cohort mortality in Sweden 1751-1940

“cohort morbidity phenotype”

same slope but different intercepts

Mortality for Swedish Birth Cohorts 1751-1940
Infant mortality is the strongest predictor of later life span in a cohort. $r^2$ for cohort $40\% > r^2$ for period.

Decrease in Mortality at age 70-74 with a .1 decrease in Annual Probability of Dying During Infancy, Young Childhood, and Older Childhood. Sweden (1751-1899).
Causes of infant-child mortality in the 19th-early 20th Centuries that are now rarer in the fortunate

diarrhea (bacteria, worms)
measles
respiratory infections
rheumatic fever
scarlet fever
typhus
chronic physical trauma
Chronic inflammatory conditions in the 19th-early 20th Centuries that are now much rarer

- aerosols (dust, fecal endotoxins, smoke)
- contaminated food
- diarrhea (bacteria, worms)
- ectoparasites (fleas, ringworm, scabbies)
- Helicobacter pylori
- periodontal disease
- TB and viral respiratory infections
Flies carry germs
0.5-1 M bacteria/fly
cholera
hepatitis
pinworm
salmonellosis
shigellosis
typhoid fever
trachoma

Herm’s Medical Entomology,
p 260-2; 1960, 6th ed,
MT James, RF Harwood, Macmillan
Hypothesis:

survivors of infections carry inflammatory loads even if infections are latent or cured

Infections chronically elevate CRP & IL-6
  diarrhea
  Helicobacter pylori
tuberculosis
IL-6 induces CRP

chronic inflammation is a risk factor in vascular disease and earlier mortality
resource allocation
during infections
?impaired growth, shorter life span?

reprod-growth

voluntary behavior
host defense
acute phase
(infection/inflamm)

basal metabolism

Caleb Finch