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Inflammation in aging processes: an integrative and ecological perspective

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I. Introduction

This review surveys inflammation during aging and chronic disease in an integrative and ecological perspective that emphasizes generalizable changes, interactions of inflammation with oxidative damage, and environmental influences. Inflammation may be considered a core process of human aging because of its involvement in baseline aging and in the major degenerative diseases of later life, atherosclerosis, Alzheimer disease, and cancer. Blood levels of C-reactive protein (CRP), IL-6, and other proinflammatory cytokines are risk indicators of cardiovascular events and mortality. Even in the absence of specific pathological lesions, inflammatory gene expression increases during aging in humans and animal models, in mammals and in several invertebrate models. Nonetheless, inflammatory mediators are essential to normal function and health, as illustrated by the importance of IL-6 secretion to normal metabolic activities, e.g. IL-6 is released by skeletal muscle in proportion to exercise intensity, while IL-6 also regulates insulin sensitivity of adipocytes (Finch 2007, p. 58).

Many inflammatory changes are highly plastic and influenced by nutrition and physical activity. Inflammation may prove central to therapeutic interventions for specific diseases as well as to general anti-aging strategies. Moreover, the global spread of obesity and the increasing inflammatory load from polluted air and water may be a limiting factor in future increases in life expectancy. This integrative perspective on inflammation in aging considers all levels of function and causality, from the atomic to cellular to environmental. A leading question is the role of endogenous vs extrinsic factors in the perpetuation of chronic elevations of acute phase innate immune responses. Outlining these broad domains and links in a concise review necessarily precludes in depth review of most topics and neglects mention of a great amount of excellent relevant science.

II. Overview of Inflammatory Responses

Inflammatory responses are part of the host immune defenses to pathogens and tissue responses to injury. Inflammatory responses engage and operate at all levels of biological organization (Fig. 1A,B) from atomic free radicals to behavior. Inflammatory responses can be focal (a few cells) or systemic. The temporal organization of host immune responses is described in two phases: acute (<1 week) and chronic (>1 week, possibly lifelong). The acute phase of inflammation largely involves the 'innate' immune responses, whereas subsequent phases may include 'adaptive' immune responses of antigen-selected T and B cells, but with continuing mediation by various innate immune factors. These highly evolved processes remove and regenerate damaged tissues, while minimizing infection.

The 'cardinal signs' of inflammation known for millennia still give instructive descriptions of the general responses to traumatic injury: redness and swelling with heat and pain[1]. The redness represents increased local blood flow; the swelling or edema, is associated with increased tissue fluid, leukocyte infiltration, and cell proliferation; the heat is produced by local mitochondria or fever due to increased whole body metabolism. Besides local responses to focal injury, acute phase systemic inflammatory responses are governed through neuroendocrine and autonomic activation involving hypothalamic-pituitary-adrenal cortex axis (HPA) and the vagal nerve afferents to the brain stem and hypothalamus. Pain as a cardinal sign of

[1]The four cardinal signs of Celsus *rubor et tumor cum calor et dolore*; in *De Medicina,* written *circa* 50 C.E. by Cornelius Celsus, a Roman encyclopedist. A fifth sign, *functio laesa* (disturbed function), is often attributed to Galen 150 years after Celsus, but was most likely introduced in the mid-19thCentury by Rudolph Virchow (*Cellularpathologie,*1858) (Majno, 1975, pp. 412-413).

inflammation is part of a suite of changes that minimize aggravation to the injured region, along with 'sickness behaviors of lethargy and loss of appetite. Inflammation can be energetically expensive: basal metabolism increases 10% per centigrade degree of fever (Finch 2007, p 5). Inflammation thus involves an integrative system of focal and responses throughout the body.

At molecular levels (Fig. 1A), systemic infections and traumatic wounds can trigger rapid innate immune responses with hepatic secretion of IL-6 and TNFα which mediate systemic energy metabolism and adaptive immunity. The liver secretes C-reactive protein (CRP), an ancient protein of innate immunity with many activities: CRP assists in pathogen clearance by binding to bacterial endotoxins, e.g. the Gram-negative lipopolysaccharide (LPS); CRP activate the complement cascade by direct binding to C1q, to produce anaphylactic peptides (C3a, C4a, C5a) that enhance macrophage production of ROS. However, during chronic inflammation, CRP can also aggregate in tissues to form amyloids with complex fibrils that are found in many chronic inflammatory diseases (see below). Scavenger receptors on hepatocytes and other cells are activated by pathogen-associated molecular patterns (PAMPs), which are endotoxin epitopes shared by groups of pathogens (Chou et al 2008; Ranjan et al 2009; Vance et al 2009). Additionally, tissue amyloids may accumulate during chronic inflammation from the acute phase hepatic secretion of CRP, serum amyloid A (SAA), and serum amyloid P (SAP), all of which can bind microbial pathogens (Finch 2007, pp. 59-60). Notably, the amyloid β-peptide (Aβ42) of senile plaques and blood platelets also potently inhibits growth of *Staphyloccoci*, *Candida*, and other common human pathogens (Soscia et al 2010).

Macrophages, as part of the initial host defense system, rapidly respond to PAMPS by phagocytosis and killing of microorganisms via generation of reactive oxygen species (ROS). During the acute phase, adaptive immune responses may be induced with antigen-specific clonal responses of B and T cells. However, there is no real dichotomy between innate and adaptive mechanisms which synergize at many levels with multiple pleiotropies. For example, IL-6 is a mediator of fever during acute phase innate responses to LPS, while IL-6 also mediates adaptive immune response by stimulating somatic mutation of immunoglobulin genes (Wu et al 2009).

The huge complexity of immune responses is being considered in the context of 'integrative systems' approaches, which range from cellular level analysis of transcription networks during *in vitro* macrophage responses to LPS (Tegner et al., 2006) to systemic level analysis of inflammation with in silico modeling (Vodovotz et al, 2010; Daun et al 2008; Gardy et al 2009; Zak and Aderem 2009; Finch, 2007, pp 318-323). Hundreds of genes and multiple signaling pathways are involved, Energy allocation is regulated through insulin-IGF, mTOR, and other pathways which are of inflammatory cascades. The ergonomics of inflammation may explain how food restriction attenuates fever in response to LPS (Inoue et al 2008) and shortens the duration of footpad edema by 50% (Klebanov et al 1995). The sensitivity of innate immune responses to energy reserves has obvious relevance to manipulations of aging by caloric restriction and exercise (Section IX) that future studies may consider in a fully quantifiable framework.

Inflammation-associated cellular-molecular damage is recognized as a major feature in aging. By-stander damage by ROS to neighboring cells and molecules is an important source of oxidative damage during aging that interacts with the endogenous damage from free radicals proposed by Harman 50 years ago (Finch 2007, pp. 60-65).The activation of macrophages and neutrophils increases secretion of ROS, which can cause oxidative by-stander damage to DNA and proteins within a cell and to neighboring cells and extracellular proteins. Immune activation in response to specific antigens can also have by-stander effects through secretion of IFNγ and

other cytokines that influence the differentiation of neighboring T cells (Fletcher et al 2005; Finch 2007, p 63). These complex cascades are attenuated by anti-oxidant systems, such as glutathione, cytokines with anti-inflammatory activities (IL-4, IL-10, and TGF-β) and resolvins (endogenous enzymatically-derived ω-3 fatty acid products).

The oxidized molecules from by-stander damage are recognized by macrophages through RAGE receptors (receptor for advanced glycation endproducts, AGE); these transmembrane receptors can stimulate further inflammatory reactions, as discussed below. RAGE has broad ligand binding and is a mediator of systemic oxidative stress and inflammatory responses (Cai et al 2008; Lin et al 2009) through ROS production by NAD(P)H oxidases and electron transport (Gao and Mann 2009; Herold et al. 2007). Microbial pathogens also activate RAGE (Chou et al 2008).

Foci of chronic inflammation also typically stimulate local cell proliferation, which in some instances progresses to cellular (proliferative) senescence. On the other hand, inflammation inhibits stem cell proliferation in adult brain (Mattieu et al 2009) and heart (Abarbanell et al 2009; Herrmann et al 2009). Because tissue damage activates gene responses shared with the acute phase, most degenerative diseases of aging involve innate immune responses. Thus, it is very difficult to resolve cause and effect in the slow inflammatory processes that may be shared across tissues during chronic degenerative diseases of aging.

III. Systemic manifestation of inflammation and aging

Blood levels of the acute phase responses CRP, IL-6, and TNFα tend to increase during aging in humans as in the InChianti study of community dwelling elderly (Ferrucci et al 2005)(Fig. 3A). Chronically elevated acute phase proteins are risk indicators for high mortality: in the National Health and Nutrition Examination Survey (NHANES III), those over 60 with elevated CRP >0.30 mg/dl serum had 2.7 times higher mortality than those below this threshhold. Interpretation is complex, because elevated blood CRP, IL-6, and other acute phase responses are also risk indicators of cardiovascular events by themselves (e.g. Danesh et al 2008; Ridker 2009) and in conjunction with LDL and other lipid risk indicators. For example, those in the top two tertiles of IL-6 and LDL showed a 10-fold higher risk of cardiovascular events (Luc et al. 2003). IL-6 elevations are among a host of other inter-correlated risk indicators of cardiovascular events and mortality (Crimmins et al 2008; Goldman et al 2006; Sattar et al 2009). In the InChianti study (Fig. 3) elevations of CRP and IL-6 were mainly attributed to cardiovascular disease and morbidity (Ferrucci et al 2005). Blood IL-6 also tends to increase during aging in rodent models (Longo and Finch 2003; Panda et al 2009). Although cardiovascular disease is very mild or absent in lab rodents, detailed histopathology is needed to evaluate possible links of IL-6 elevations to the presence of tumors and renal degeneration of individual animals.

Many aspects of chronic elevations of acute phase resonses are unresolved. Firstly, we do not know the sources of the elevated blood inflammatory markers. In the acute phase response, most of the CRP and IL-6 are attributed to increased hepatic secretion. However, arterial cells also make and secrete various acute phase proteins: CRP by vascular smooth muscle cells (Guo et al 2009) and IL-6 by the foam cells (macrophages with lipid inclusions) of atherosclerotic plaques (Groeneweg et al 2006), as well as adipose tissues (Section IX). The progression of arterial lipid accumulation (Fig. 2A) and of advanced atherosclerosis during aging (Fig. 2B) could thus contribute directly to the blood levels of CRP and IL-6. Other longitudinal

studies of vascular disease in diverse populations will further inform about diet, alcohol, and other factors in relationships of blood inflammatory markers to age-related pathology.

Secondly, we must ask if these increases indicate increased low grade infections with aging. As well documented for influenza, the elderly have increased vulnerability to infections (Elliot and Fleming 2008). Senescence in the adaptive immune system is associated with an "immune risk phenotype" of elevated blood IL-6, and TNFα, and higher mortality during seasonal influenza (Finch, 2007, pp. 19-21; McElhaney and Effros 2009; Trzonkowski et al 2003). Life-long antigenic exposure gradually accumulates highly differentiated memory cells (CD4+ T cells) at the expense of naïve CD4+/CD28+ T cells (Gruver et al. 2007). CMV and other persistent viral infections may prove to have broad importance to outcomes of aging (Gress and Deeks, 2009; Pawelec et al 2010). Obesity and diabetes type-2 also predispose to chronic low grade infections.

Moreover, the acute phase response can induce many of lipid changes that are also associated with cardiovascular risk: modified HDL ('acute phase HDL') from dissociation of paronoxenases (PON-1-3) and transferrin that decrease anti-oxidant activity; oxidized LDL; higher triglycerides; and, inhibition of reverse cholesterol transport (Finch 2007, pp. 84-86). I suggest that elderly populations should be characterized for 'acute phase HDL in relation to endogenous blood endotoxin levels. After eating, there is a minor surge of postprandial endotoxins from gut bacteria that is mediated by chylomicrons and enhanced by fatty diets (Ghoshal et al 2009). Gut aging changes may enhance postprandial endotoxemia through increased intestinal permeability (Mullin et al 2002) and crypt cell dysplasia (Martin and Kirkwood, 1998).

IV. Tissue inflammatory changes during aging

Messenger RNA prevalence analysis by microarrays has defined a consistent profile of increased inflammatory gene activity during normal aging in most tissues in the absence of clinical grade pathology (Finch 2007, pp 107-112; Park et al 2009; Schumacher et al 2008). Brain, heart, and other organs of healthy aging rodents have 50% or more increases of mRNA for IL-6 and C1q complement and other inflammatory factors. In the human brain during normal aging in the absence of Alzheimer disease, we found activated complement proteins in the diffuse amyloid deposits (Zanjani et al 2005). A generalized change of middle-age is the increase of activated microglia, which are monocyte-macrophage-like cells derived from bone marrow: *in vivo* and *in vitro*, microglia from aging rodent brain express and secrete more IL-6 (Xie et al 2003; Sierra et al 2007; Sparkman and Johnson 2008) (Fig. 4B). IL-10, an anti-inflammatory is also increased (Sparkman and Johnson 2008). Despite greater production of IL-6, the microglia from aging rat brain produce less ROS upon stimulation by LPS (Xie et al 2003; Sparkman and Johnson 2008). Glial activation arises during middle-age in lab rodents on normal diets in the complete absence of recognizable degenerative disease (Morgan et al 1999). The lab mouse and rat are important models for non-clinical aging because the standard strains on normal diets do not develop atheromas or Alzheimer-like neurodegeneration. Many of these same markers are further increased in degenerative diseases of aging (Sections V-VII, below; Table 1). The mild inflammatory changes in many tissues may be a substrate for chronic degenerative diseases with inflammatory components.

A major challenge is to identify the signaling pathways and transcriptional-translational networks that mediate the inflammatory components of aging. The insulin-IGF and mTOR signaling of 'longevity pathways' (Longo and Finch, 2003; this handbook, Brown-Borg, Chapter

2; Kapahi and Kockel, Chapter 9) also imediate inflammation (Finch 2007, p 7; Salvioli et al 2009) as well as atherosclerosis (Finch 2007, p 7) and other chronic diseases. The AMP kinases (AMPK) and hexosamine pathway may also be involved through their roles in glucose and energy regulation (Finch, 2007, p 315-323). Transcriptional regulation by NF-kB in many inflammatory pathways suggests an important role in chronic inflammation during aging (Jung et al 2009). At the translational level, microRNAs may be important to inflammatory pathways in aging (Bhaumik et al 2009; Davidson-Moncada et al 2010; Liang et al 2009). The remarkable generality of inflammatory aging changes in humans and animal models could be the basis for a comprehensive theory of aging and age-related disease (Chung et al 2009; Finch, 2007; Franceschi et al 2007; Salvioli et al 2009).

Another source of inflammatory factors results from autogenous DNA damage during cell senescence. As described by Campisi and collaborators, replicative cell senescence (Hayflick model) causes increased secretion of of IL-6, metaloproteinases, and other inflammatory factors (senescence-associated secretory phenotype) in association with DNA damage that causes cell cycle arrest (Rodier et al 2009). The primary role of DNA damage in cell senescence was shown by blocking telomere erosion by transfection with *htert*, which delayed the inflammatory secretions and cell cycle arrest*;* reciprocal experiments increased DNA damage by low dose x-rays and accelerated these changes. Other studies from Kirkwood and von Zglinicki document the importance of mitochondria DNA damage in increased production of ROS during cell senescence via a checkpoint pathway involving the cytokine TGF-β (Passos et al 2010). I suggest these generalizable phenomena be designated as 'autogenous cytoinflammation'. These findings imply that inflammation-related DNA damage to by-stander cells can cause further local inflammatory cascades through cell senescence pathways which are already documented in atherosclerosis and cancer as discussed below. Because chronic inflammation typically stimulates cell proliferation, e.g. in gut (Abreu, 2010) and lung (Bauer et al 2010), chronic inflammatory conditions of aging will also drive cell senescence, with local tissue by-stander consequences.

Aging changes are also observed in the acute phase of inflammatory processes during aging that may be considered as part of immunosenescence. In response to endotoxin (LPS), aging rats had greater elevations of IL-6, but smaller induction of T-kininogen and other acute phase responses; the high incidence of hepatic abscesses suggest weakened host defense (Gomez et al 2008). At a cellular level, neutrophils from aging rats had decreased phagocytic activities and oxidative burst (Schroder and Rink, 2003; Panda et al 2009), as did microglia as noted above. Nonetheless, the blood levels of circulating neutrophils tends to increase, in contrast to declines of monocytes, Thus, the declining resistance of elderly to infections may be understood in terms of both innate and adaptive immunity.

V. Inflammation in Atherosclerosis and Alzheimer disease

Atherosclerosis has been long recognized as an inflammatory process (Ross 1999; Galinka and Ley, 2009). In Virchow's view (*CellularPathologie*, 1858) "...inflammation of the arterial coat was the starting point of the so-called atheromatous degeneration" (Langheinrich and Bohle 2005). It is generally agreed that arterial inflammatory changes begin before birth and progress across the human lifespan (Fig. 2A,B). Prenatal human arteries have microscopic foci of macrophages associated with oxidized lipids and proteins that may be the seeds of the low grade macroscopic atheromas that are found almost universally in young adults (D'Armiento et al 2001). The postnatal accumulation of lipids is linear with age in the aorta, but may be

exponential in cerebral arteries. Activated macrophages, accumulation of inflammatory proteins, and tissue amyloids, and oxidative damage are progressive iin atheromas from early to later ages (Table 1). The accumulation of advanced atheromas continues into later ages, as shown in a community necropsy study from Japan (Fig. 2B)(Nakashima et al 2009). Moreover, even in arterial segments lacking gross fatty infiltration or focal pathology, there are inflammatory changes (Wang et al 2007, 2009). As stressed by Lakatta et al (2009) “Arterial aging and subclinical arterial disease are fundamentally intertwined at macroscopic and molecular levels.".

Atherosclerotic plaques also accumulate ‘senescent’ cells defined by markers of replicative senescence (senescence-associated β-galactosidase) and telomere shortening (Edo and Andres 2005). As noted above, replicative senesence induces inflammatory gene expression. True to Celsus' signs, atheromas are hotter than flanking arterial segments by up to 3 ^{o}C; temperature elevations are proportionate to macrophage density, and may indicate plaque instability (Madjid et al 2002;Tan et al 2008; Toutouzas et al 2007). The heat is generated by the induction of UCP2, which uncouples mitochondrial ATP production from respiration to generate radiant energy (Van De Parre et al 2008).

Atherosclerotic lesions may harbor infectious pathogens, e.g. Cytomegalovirus (CMV) and *Chlamydia pneumoniae* (Finch 2007, pp 115-121). CMV itself directly binds to vascular endothelial cells through EGF receptors to stimulate proliferation and angiogenesis during atheroma development (Bentz and Yurochko 2008). Moreover, in CMV-seropositive coronary patients, myocardial dysfunction was associated with excessive telomere shortening in CD8+CD28(-) T cells (Spyridopolous et al 2009). However, over several decades of study, links of specific pathogens to cardiovascular diseases have been less consistent than those of *H. pylori* in gastrointestinal cancer (Section VI below), and may vary because of sporadic events or pathogen clearance.

Relationships of blood vascular risk indicators (CRP, LDL-cholesterol, oxidized lipids) to the progression of atherosclerosis remains controversial. About 35% of heart attacks in the Framingham study occurred despite initially normal blood cholesterol (Castelli, 1996). The statins, which inhibit cholesterol synthesis by blocking HMG-CoA reductase, have shown remarkable efficacy in reducing the risk of heart attack. However, lower blood LDL may not be a sufficient explanation, because even in those with low cholesterol, statins lower both blood CRP and heart attack risk (Jupiter Study, Ridker et al 2009b). The emerging broad anti-inflammatory activities of statins may involve signaling pathways sensitive to isoprenoids derived from mevalonate, a cholesterol precursor which is also lowered by statins. These complex pleiotropies beyond blood cholesterol are being addressed in the Cardiovascular Inflammation Reduction Trial (CIRT) (Ridker et al 2009a).

Alzheimer disease (AD) is widely recognized as involving inflammatory processes (Akiyama et al 2000). The senile plaque (neuritic plaque) consists of extracellular fibrillar aggregates of the amyloid β-peptide (Aβ) with microglia and local neuritic degeneration with hyperphosphorylated tau. Senile plaques contain many inflammatory factors, most of which are also found in atheromas (Table 1). While fibrillar amyloid deposits of Aβ are restricted to the brain and cerebrovasculature, serum amyloid P (SAP) (acute phase response) accumulates in amyloid deposits of both brain and heart. Iron and other redox active metals in arterial and brain plaques which promote ROS formation through Fenton chemistry are a further substrate for local oxidative stress The extensive similarity of atheromas and senile plaques with shared inflammatory proteins and activated monocytes (foam cells, atheroma; microglia, senile plaque) suggests parallel mechanisms in pathogenesis. Note the progressive exponential accumulation of

lipids in cerebral arteries (Fig. 2B) which may anticipate the accelerating incidence of cerebrovascular lesions with aging (Cole and Vassar 2009).

Cardiovascular disease and Alzheimer disease share many risk factors. Genetically, both share the *apoE4* allele, which increases cardiovascular event risk by about 2-fold and Alzheimer disease risk by more than 5-fold in *E4/E4* homozygotes (Finch 2007, pp 357-368; Mahley et al 2007; Roses et al 2007; Poirier 2008). A familial study of risk factors in middle-age showed increased white blood cell production of IL-6 and other proinflammatory cytokines in Alzheimer-prone families, independent of apoE4 alleles (van Exel et al 2009). Obesity and diabetes are also shared risk factors. In the respective rodent models, high cholesterol diets accelerate, while caloric restriction retards progression of atheromas (Guo et al 2002) or Alzheimer brain amyloid (Aβ) deposits (Patel et al 2005; Wang et al 2005), discussed further in Section IX). Despite the major benefits of statins for lowering blood cholesterol and risk of cardiovascular events, statins did not alter incidence of dementia or cognitive decline in two large randomized control trials (HPS 2002, simvastatin; PROPSER, pravastatin) (McGuiness et al 2009). Resveratrol is a new candidate drug for in atherosclerosis (Marzetti et al 2009; Wang et al 2009) and Alzheimer disease (Albani et al 2010; Karuppagounder et al 2009), which may inhibit inflammation and oxidative damage by activating SIRT1 (Sulaiman et al 2010) on a 'longevity pathway' (this handbook, Sinclair and Haigis, Chapter 11) and/or inhibiting NFkB signaling (Chen et al 2005).

VI. Cancer

Cancer is deeply connected to inflammation through two processes: local inflammation acting on initially healthy proliferating cells and local inflammatory responses to neoplasia. Both processes involve synergistic mechanisms of DNA damage, ROS production, and oxidative stress, and tissue remodeling that promote accumulation of mutations, angiogenesis, and tissue invasiveness (Coppé et al 2008; Lazennec and Richmond 2010; O'Conner et al 2010). Local inflammation, by stimulating cell proliferation and causing DNA damage from ROS, increases the chance of oncogenic mutations. A classic example is the association of *Helicobacter pylori* infections with gastrointestinal cancers, which are the second ranked cause of malignant deaths (Finch 2007, pp 154-155). *H. pylori* , a common mildly pathogenic bacterium, attaches extracellularly and causes localized mucosal cell proliferation. Infiltrating monocytes produce ROS that causes telomere shortening and DNA damage (8-OHdG) (Farinati et al 2008; Kuniyasu et al 2003; O'Conner et al 2010). Suppression of *H. pylori* by the use of NSAIDS, as well as improving public health and hygiene in the 20th Century, has reduced the prevalence of gastrointestinal cancers. As another example, mice deficient in GM-CSF and interferon-γ developed lymphomas and solid tumors concurrently with chronic inflammation and bacterial infections; a link of tumors to infection was shown by the suppression of both by the antibiotic enrofloxacin (Enzler et al 2003).

Many other occurrences of neoplasia are linked to local and systemic effects of airborn combustion products from fossil fuels, tobacco smoke, and other non-infectious inflammagens (Finch 2007, pp 156-157 and 209-211). Besides the by-stander damage from ROS produced by activated monocytes during inflammation, cell senescence also causes tissue by-stander damage from inflammatory 'secretory phenotypes' that arise during proliferative senescence independently of exogenous ROS (Section IV). Moreover, replicatively senescent cells can enhance cancer metastasis by altering the microenvironment through secretion of metalloproteinases and inflammatory cytokines (Coppé et al 2010).

VII. Bone and Joints

Osteopenia of normal aging with increased risk of fractures and clinical osteoporosis begins before 30 in both sexes and preceding major decreases in blood levels of sex steroids (Riggs et al 2009). Peak bone mass, low body weight and weight loss are risk factors for osteoporotic fractures (Papaioannou et al 2009; Winslow et al 2009), which is relevant to bone fracture risk during caloric restriction (Mardon et al 2008). After menopause, obesity may be protective for osteoporosis through endogenous estrogens derived from aromatase in adipose tissue (Ablala et al 1996; Haffner and Bauer, 1992).

Bone turnover is mediated by mechanisms shared with inflammatory processes, again with prominent roles of ROS (Banfi et al 2009), macrophages and cytokines (IL-6, IL-6, TNFα) (Mundy 2007; Axman et al 2009; McLean 2009). Elevated blood IL-6 was associated with greater osteopenia in longitudinal studies (Ding et al 2008). The balance between new bone formation and resorption involves the osteoclast, which is derived from circulating macrophage-monocytes. The cytokine RANKL (receptor activator of NFκB ligand) mediates osteoclast formation and bone matrix remodeling through ROS, mediated by the differential regulation of NADPH oxidase (Nox) isoforms (Sasaki et al 2009). In hyperlipidemic mice, oxidized lipids contributed to osteopenia by enhancing RANKL production in T cells (Graham et al 2009). The protection against bone loss and fractures by estrogens also involves RANKL and Nox (Chen et al 2008). Unexpectedly, statins also show anabolic benefits to bone (Tang et al 2008). The apparent conjunction of bone and heart health in drug responses (Anagnostis et al 2009) was also noted for the benefits of resveratrol in aging mice (Pearson et al 2008).

VIII. Blood Glucose Elevations in Inflammatory Processes of Human Aging

Blood glucose concentration is directly linked to inflammatory changes in many aspects of aging, by driving the formation of advanced glycation endproducts (AGEs), which in turn is directly linked to vascular disease. As described in the 1st edition of this handbook (Andres and Tobin, 1977), many studies have shown mild elevations of fasting blood glucose after age 40. The progressive glucosemia of normal aging is emerging as a canonical feature of aging paralleling the increase in systolic blood pressure and atherosclerosis. New links of glucosemia to mortality risk and longevity have emerged from longitudinal analysis of the Framingham Study (Yashin et al 2009a,b). The total Framingham population, diabetics included, shows the strong trend for progressive increase in fasting glucose (Fig. 4A). Non-diabetics also show strong linear increases up thru the oldest ages (Fig 4B). It seems potentially important that mortality risk at later ages becomes increasingly sensitive to blood glucose (based on a Cox hazards model) (Yashin et al 2009b). These findings suggest that cardiovascular disease risk scales with modest glucosemia below conventional thresholds of glucose intolerance (Ko et al. 1998).

Blood glucose levels are directly linked to inflammation: glucose causes spontaneous oxidative damage to proteins by non-enzymatically forming covalent bonds with free -εNH2 groups to form AGEs by complex chemistry involving Maillard and Amadori reactions (Lee and Cerami, 1990; Fino, 2005; Nursten 2005). For example, glycated hemoglobin (HbA1c) can reach 30% of total hemoglobin in uncontrolled diabetes: HbA1c is a reliable indicator of glucose levels during the prior 2-3 months because of erythrocyte turnover with a half-life of 4 months. The proportionality of blood HbA1c to blood glucose, verified in a recent multi-national study (Little and Sacks 2009), is consistent with glucose as the chemical driver of HbA1c formation with 1st

order chemical kinetics. Corresponding to the progressive increases of glucose, the levels of HbA1c increase linearly with age, e.g. in non-diabetics of the Framingham Study (Fig. 4C) and in NHANES (Pani et al 2008). However, a full accounting of HBA1c during aging requires data on erythrocyte turnover at later ages.

While increased HbA1c alone does not alter oxygen binding, other AGE adducts have direct consequences for vascular disease because erythrocytes from diabetics have greater stickiness to arterial endothelial surfaces. Erythrocyte adhesion would favor thrombosis, as well as transfer of erythrocyte cholesterol and iron into the atheroma (Kolodgie et al 2003). The erythrocyte adhesion involves endothelial RAGE activation by AGE-adducts in erythrocyte membrane proteins and lipids which induce adhesion molecules, cytokines, and ROS (Grossin et al 2009; Lai et al 2004) and alter deformability and other rheologically important characteristics (Cho et al 2008). I suggest that erythrocytes from elderly non-diabetics with elevated HbA1c (Fig 4C) will also be prothrombotic, which may explain why small additional increments in blood glucose in elderly non-diabetics cause excess mortality above younger norms. Another mechanism linking the age-creep in blood glucose to vascular events is through the activation of RAGE receptors by AGE on proteins and lipids (Section II). RAGE activation is implicated in cardiovascular disease at many levels and is intensified by chronic hyperglycemia in clinical diabetes (Yan et al 2007).

These links of AGE to inflammation and vascular disease further specify Cerami's hypothesis that AGE formation is fundamental to aging (Cerami et al 1987; Lee and Cerami, 1990). Further links of AGE to mortality acceleration at later ages may emerge through associations of type 2 diabetes and obesity with certain cancers (colonic, hepatic, and pancreatic cancer (Ogunleye et al 2009; Hevener et al 2009) and with leukocyte telomere shortening (Salpea et al 2009), an indicator of immunosenescence. The browning of food by cooking also produces AGES, which can further add to the inflammatory load, as discussed below.

IX. Diet, Metabolism, and Exercise

Diet has major systemic influences on inflammation through the levels of energy intake, energy storage in fat depots, and ingested AGEs produced during cooking. As a general principle, innate immune responses are regulated by the energy available (Finch 2007, pp. 56-58). Fasting or caloric restriction, besides limiting the febrile response, as noted in the Introduction, attenuates other acute phase responses. A systemic mechanism in caloric restriction may be elevation of corticosteroids which is a broad gluconeogenic homeostatic response to partial starvation to maintain sufficient levels of blood glucose (Patel and Finch 2002). Lowering of blood glucose by caloric restriction attenuated production of advanced glycation endproducts (AGEs), e.g. N-ε-carboxy-methyl-lysine and methyl-glyoxal derivatives (Ulrich and Cerami 2001), which are proinflammatory. The oxidative load also is diminished by caloric restriction in most tissues, e.g. 10-30% reduction of carbonyl and dityrosine content (this handbook Fontana et al, Chapter 21, and Kauschnik and Cuervo, Chapter 13; Chung et al 2009; Forster et al 2000).

Gene expression profiling studies consistently show that caloric restriction attenuates the increased expression of cytokine and complement factor genes during aging in brain, heart, and liver (Park et al 2009; Schumacher et al 2009; Swindell 2009). Caloric restriction also attenuates atherosclerosis, cancer, and Alzheimer disease in rodent models (Section V, above; Kapahi and Klockel, Chapter 9; Finch 2007, pp 210-211). In inbred mice, the genotype can influence response to caloric restriction. Among 41 recombinant inbred strains, the majority did not show increased lifespan on caloric restriction; these effects can not be attributed to early deaths of non-

adapted individuals because maximum and mean lifespans were well correlated (Liao et al 2010). Future studies may consider inflammatory gene variants, which were implicated in the lack of response of the DBA/2J inbred strain, which has an inactive complement C5 peptide (Finch 2007, p. 227).

Conversely to the low lean body mass and low inflammatory tone under caloric restriction, obesity is understood as a proinflammatory state with chronic activation of acute phase responses (Korner et al 2009; Lee et al 2009; Redinger 2009). Blood CRP and IL-6 are strongly correlated with the degree of obesity across a broad range of the body mass index (BMI) (e.g. Khaodhiar et al 2004). White adipose depots contain numerous macrophages which secrete proinflammatory cytokines (Galic et al 2009; Maury and Brichard 2010). Visceral fat in particular secretes adipokines and IL-6 (Fontana et al 2007). Adipocytes from diabetics show increased cytokine production, telomere shortening, and other markers of senescence (Minamino et al 2009). The increased blood inflammatory profile in obesity is linked to insulin resistance and diabetes; to cardiovascular disease; and to cancer (Hevener et al 2010). In moderately obese patients, diet restriction lowered blood CRP and IL-6 (Salas-Salvado et al 2006), with correspondingly lower incidence of cardiovascular events (Lee and Aronne 2007). Nonetheless, there is an "obesity paradox" in which some obese patients with cardiovascular disease have a better prognosis than the non-obese (Lavie et al 2009).

Dietary AGEs can contribute to systemic inflammation, glucose-dysregulation, and vascular disease. Cooking produces AGEs as part of the chemistry of browning (see above). Vlassara and colleagues have shown in clinical studies that increasing the dietary AGE content caused rapid impairments of glucose tolerance, with concomitant elevations of blood CRP indicative of systemic inflammation (Uribarri et al 2007). Moreover, mice on caloric restriction given food heated to increase AGE content had increased oxidative stress (blood AGE, isoprostanes, GSH:GSSH ratios), impaired glucose tolerance, and shortened lifespan in association with fibrosis of heart and kidney and elevations of myocardial RAGE and $p66^{shc}$ (Cai et al 2009). AGEs can act directly on pancreatic cells to impair insulin secretion through induction of iNOS (Zhao et al 2009).

Physical activity also influences systemic inflammation. Although exercise induces IL-6 release by skeletal muscle which might be considered pro-inflammatory, this cytokine also increases blood levels of anti-inflammatory cytokines (IL-1 receptor antagonist and IL-10) and stimulates fat oxidation (Mathur and Pedersen 2009). For example, induced treadmill exercise of old rats decreased renal lipid oxidation (MDA) and increased blood IL-10 (anti-inflammatory cytokine) (Asghar et al 2007). Exercise also inhibits the accumulation of macrophages in fat depots (Wood et al 2009). The benefits of exercise are recognized as reducing the risk of many chronic conditions of aging (Bruunsgaard, 2005; Finch 2007, pp 211-223; Mathur and Pedersen 2008), and may extend to pre-clinical Alzheimer disease (Baker et al 2010). We may anticipate many new therapeutic targets in metabolism that engage the multifarious pathways of innate immunity.

X. Genetics

Among genes that influence longevity (Sutphin and Kaeberlein, Chapter 10), some pleiotropic alleles also influence inflammatory responses. An expanding example is the apolipoprotein (apoE), a blood cholesterol carrier which mediates reverse cholesterol transport to the liver and independently mediates cholesterol transport to neurons (Mahley et al 2007). The *apoE4* allele is associated with higher risk of coronary artery disease and Alzheimer disease

than the most prevalent *apoE3* allele (Section V). *ApoE4* carriers also incur more damage from head injury and stroke, for which drugs being developed (James et al 2009; Tukhovskaya et al 2009). Not surprisingly, *apoE4* is also associated with lifespan shortening: after age 80, the prevalence of the *apoE4* allele drops sharply, due to early mortality in proportion to the allele dose of *E4* (Schachter et al. 1994; Choi, 2003; Ewbank 2004; Dato et al 2007). The *apoE* allele system is unique to humans and is hypothesized to have evolved during the shift from plant-based diets of the great apes to the meat-rich diets of humans (Finch, 2010; Finch and Stanford, 2004; Finch and Sapolsky, 1999). The apoE protein of great apes, while having the residues characteristic of apoE4 (R112, R158) is predicted to function like apoE3 (C112) (Finch and Stanford, 2004; Finch 2010), because of another difference (T61) that should render peptide folding to functionally resemble the apoE3 protein (Raffai et al. 2001). Resistance to infection may have been a factor in the origins and preservation of *ApoE4,* because *apoE4* carriers have less fibrotic liver damage from hepatitis C infections (Fabris et al 2005; Wozniak et al 2002). In other circumstances, *apoE4 carriers* have greater postsurgical elevations of TNFα in humans (Grünenfelder et al 2004; Drabe et al 2001), while transgenic mice with targeted replacement of human *apoE3* and *-E4* show similar differences in cytokine response (Vitek et al 2007, 2009). These fragments of evidence suggest complex and conditional pleiotropies of inflammatory system genetics during human evolution (Finch 2007, Chapters 1 and 6).

Other longevity gene candidates are emerging from screens for cardiovascular risk factors in general populations and for enrichment in centenarians have pleiotropies with links to inflammation and oxidative stress include: besides *apoE*, the growing list includes alleles of *APOC3* (Atzmon et al 2006), FOXO3A (Flachsbart et al 2009), *IGF-1R* (Suh et al 2008), *IL-6* (Capurso et al 2007), IL-10 (Lio et al 2002), *PARP-1* (Walston et al 2009), and *PON1* (Lescai et al 2009). So far, the common polymorphisms of inflammatory genes have not shown strong associations with mortality at advanced ages, e.g. in Danish nonagenarians (Dato et al 2010).

Invertebrate aging models also show genetic influences on lifespan (this Handbook, 6th edition: Ford and Tower 2006; Henderson et al 2006) in association with host defense changes (Finch 2007, pp 318-329). In the nematode *Caenorhabditis elegans*, the *age*-1 and *daf-2* mutants that increase lifespan also increase resistance to bacterial pathogens (Garsin et al 2003; Garigan et al 2002) and expression of antibacterial host defense genes (Kurz and Tan 2004; Troemel et al 2006). Aging flies (*Drosophila*) show increased expression of toll-receptors, antimicrobial peptides, and other host defense genes (Landis et al 2004; Pletcher et al 2002). Trade-offs between immune activation and lifespan in various *C. elegans* genotypes (Libert et al 2006) are modified by caloric restriction (Libert et al 2008).

XI. Environmental Influences: an ecological perspective

The external environment has powerful life-long influences on aging and chronic disease (Fig. 1B) that underlie the recent increases of lifespan since 1800 (Finch and Crimmins, 2004; Finch 2007, 114-117). The role of adequate nutrition in adult health and longevity was emphasized in the 'techno-physiological evolution' theory of Fogel and Costa (1997) and the Barker theory of fetal origins of adult disease (Barker 1998). Additionally, infections and inflammogens influence many aspects of aging and chronic disease during the historical increase of lifespan (Finch and Crimmins, 2004, 2005; Crimmins and Finch 2006). A cohort analysis of four European countries for which data was available in the 18th and 19th centuries showed strong statistical associations of early age mortality in birth cohorts with their later mortality at age 70 (Crimmins and Finch 2006). Because neonatal mortality is largely due to infections,

Crimmins and I hypothesize that adults who survived high mortality environments before the 20th century carried inflammatory and infectious loads throughout life which accelerated aging and shortened life expectancy at later ages. Evidence for pathogens in vascular lesions was reviewed in Section V. However, early exposure to infections need not require persistence of the pathogen. Further analysis of the 1918 Influenza epidemic has yielded a new link of coronary disease to prenatal infection that does not depend on the persistence of pathogens in the vascular system (Mazumder et al 2010). Men exposed during mid- or later gestation during peak flu mortality in the Fall of 1918 had 25% excess ischemic heart disease 60 years later, relative to men born in the 3 months just before or after. Because H1N1 does not cross the placenta in rodent models (Shi et al. 2005), these gestational effects are attributed to maternal stress, e.g. elevated corticosteroids or IL-6, which can accelerate arterial degeneration postnatally (Mazumder et al 2010). In sum, the progressive 2-fold increase of life expectancy at all ages during the last 200 years is associated with progressive reductions in the inflammatory and infectious load with improved hygiene and public health. Improving nutrition year around in the industrializing countries was also a major factor in reducing infections during the past 200 years.

Environmental effects on aging extend to laboratory mice. The lifespan of C57BL/6J mouse, inbred since 1937 at the Jackson Laboratory, began to increase in the 1950s because of improvements in animal husbandry that reduced the load of infections (Fig. 5A,B), e.g. from *Mycoplasma, Salmonella,* ectromelia (mouse pox), MHV, and Sendai virus (Finch 2007 pp. 136-142). More extreme is the case of the pituitary dwarf mice currently noted for exceptional longevity. However, just two decades ago, pituitary dwarfs were considered as models of accelerated aging because of short lifespans < 6 months and with cataracts and wasting (Finch 2007, p 340; Fabris, 1988).

Airborn inflammogens from combustion products are major causes of accelerated aging. The best documented in exposure to tobacco smoke, direct or indirect, which accelerates atherosclerosis through inflammatory mechanisms involving oxidative stress (Armani et al 2009; Stephens et al 2008). These adverse effects on arterial functions extend to passive exposure to smoke in utero observed in neonates (Gunes et al 2007) and in children exposed postnatally (Kallio et al 2009; Wigle et al 2008). Fossil fuel combustion also generates toxic particles which are associated with higher cardiovascular mortality. Epidemiological studies show intra-urban gradients of cardiovascular disease and mortality that correspond to dose-dependent exposure (Pope 2009). For example, cardiovascular mortality increased by $\geq$ 25% (RR of 1.24-1.6) for each 10 mg/m^3 increase of 2.5μ particles in Los Angeles County over a 3-fold range (Jerrett et al 2005; Künzli et al 2010). Mouse models show corresponding acceleration of atherosclerosis from 3 months of exposure to peak freeway traffic levels of ambient particles (Araujo et al 2008). The effects of air pollution include neuroinflammatory responses which overlap with some aspects of Alzheimer disease (Block and Calderón-Garcidueñas 2009). Young adults exposed to the severe pollution of Mexico City had activated microglia and diffuse amyloid deposits, with indications of greater susceptibility in apoE4 carriers (Calderón-Garcidueñas et al 2009). Lastly, airborn inflammogens are anticipated to increase in most regions of the world, particularly from four sources: vehicular hydrocarbon fuels; coal in power generation; burning of trash; and fires in grasslands and forests.

XII. Conclusions

The fundamental role of inflammation in aging processes is now widely recognized, particularly for arterial disease which begins before birth. The strong age trends for elevated blood glucose and glycated proteins during starting in midlife is hypothesized to be a fundamental driver of vascular disease and the acceleration of risk for vascular events. Pre- and postnatal environmental factors influence the progression of arterial degeneration, obesity and hyperglycemia, but also airborn inflammogens from tobacco smoke and air pollution. These myriad pre- and postnatal environmental influences on arterial disease during aging give some insight into the low heritability of lifespans, which is <35% in identical twins, as well as mice, flies, and worms maintained under highly uniform environments (Finch and Tanzi, 1997; Finch and Kirkwood, 2000; Hjelmborg et al 2008).

The major effects of statins on decreasing the rate of heart attacks may be mediated by anti-inflammatory mechanisms as well as improving cholesterol indicators. The apoE4 protective drugs being developed (Section X) might also be generally benefit health in the later years by reducing the risk of arterial disease and Alzheimer's (Mahley and Huang 2009). Drugs being developed as caloric restriction mimetics may also have anti-inflammatory activities, e.g. resveritrol (Csiszar et al 2009; Issuree et al 2009). Of importance to life in the real world, resveritrol also inhibits wound healing (Bråkenhielm et al. 2001), as does caloric restriction (Hsieh et al. 2005). Despite these bright prospects, we must be concerned with global transmission of infectious diseases which can accelerate aging processes, as observed for the 1918 influenza, and the increase of airborn inflammogens from combustion products. Thus, the future of human aging may depend as much on our global ecology as on advances in medicine

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Fig. 1 Schema of inflammatory responses

(A) Biological levels

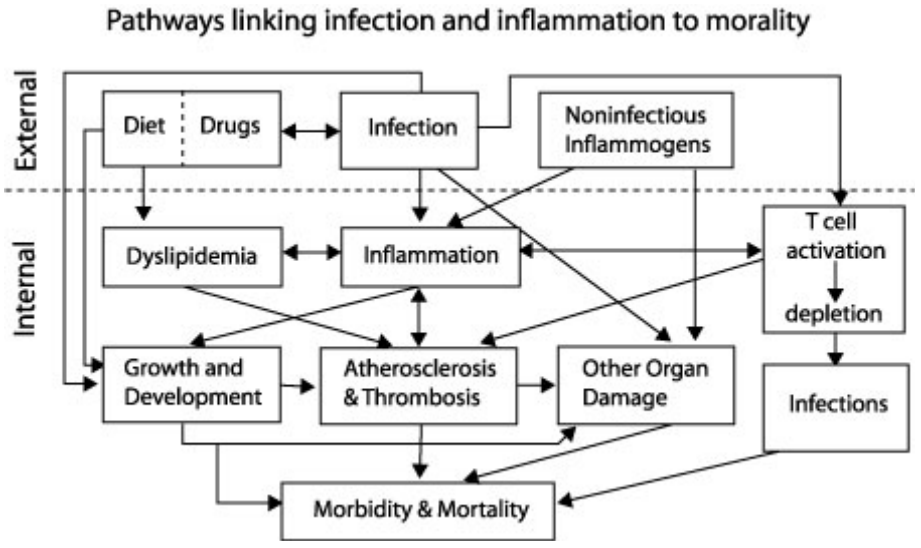
Atomic/biochemical
ROS oxidation of DNA, lipids, proteins
glycooxidation (AGE formation)

Cellular
activation of macrophages by endotoxins, oxidized proteins and lipid, and AGEs
autogenous cytoinflammation from replicative cell senescence

Systemic
humoral elevations of CRP, IL-6 and cytokines
redox shift in glutathione
induction of fever by IL-6 and TNFα; increased basal metabolic rate
sickness behaviors: lethargy and loss of apatite,

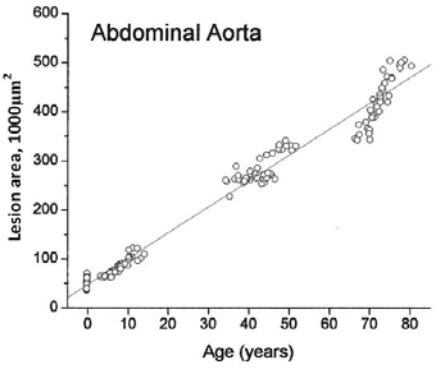
Environmental
Infectious pathogens that causes systemic inflammation and focal lesions
Ambient inflammogens from combustion of fossil fuels and tobacco

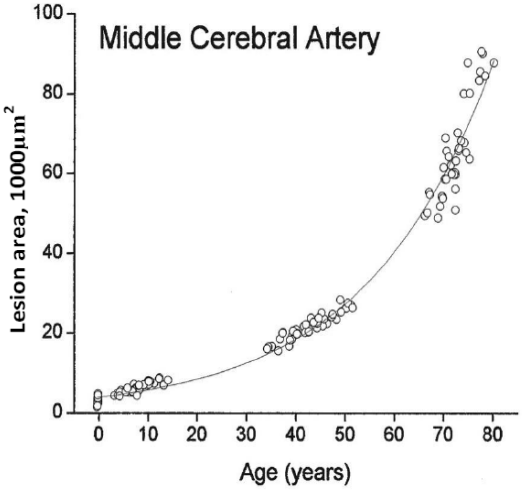
(B) Organ levels



Schema showing external influences on organ systems leading to morbidity and mortality at later ages from chronic inflammatory conditions. From Finch 2007 p5 and Crimmins and Finch 2006.

Fig. 2. Atherosclerosis progresses across the lifespan.
(A). Arterial lipid accumulations of the abdominal aorta and middle cerebral artery from birth through old age; a multi-site autopsy collection (D'Armiento et al. 2001).





(B). Cardiovascular atherosclerosis at necropsy of elderly in the Hisayama community, ages 69-90+ (80% of deaths, 1988-1996) (Nakashima et al 2009). The severity of atherosclerotic grades (scaled 0-5) increased progressively with age; by age 90, nearly all had advanced lesions. This study is among the few autopsy series of a community which included the majority of deaths at later ages.

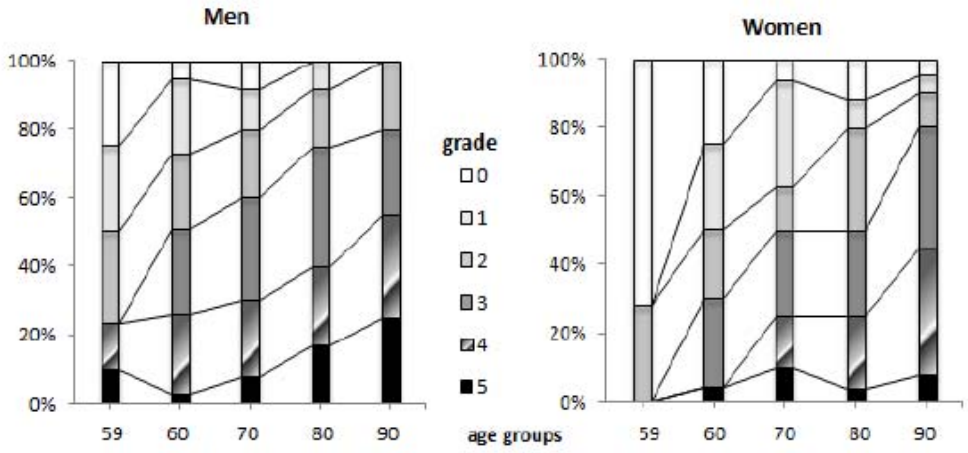
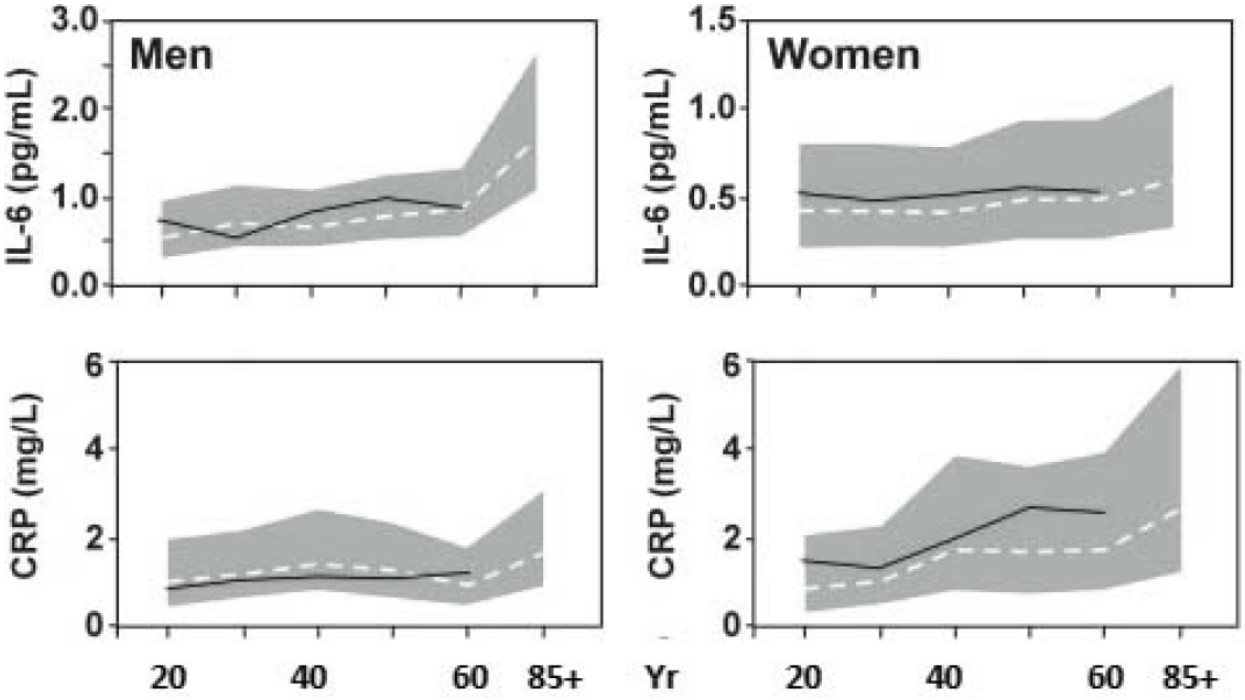


Fig. 3. Aging and IL-6
(A) Serum IL-6 and CRP in community-dwelling Italians (InCHIANTI Study) means by decade: dotted lines, total sample, shaded area 95% confidence intervals; continuous lines, means of healthy individuals <85 years, without morbidity and at low risk for cardiovascular disease (Ferrucci et al 2005). Thus, most change is attributable to cardiovascular risk factors and morbidity.



(B) Glia from aging male rats have increased levels of IL-6 mRNA and protein during primary culture mixed glia (astrocytes plus microglia). Data are shown as ratios by age (old, 24 mo: young, 3 mo) for three brain regions (Xie et al 2003).

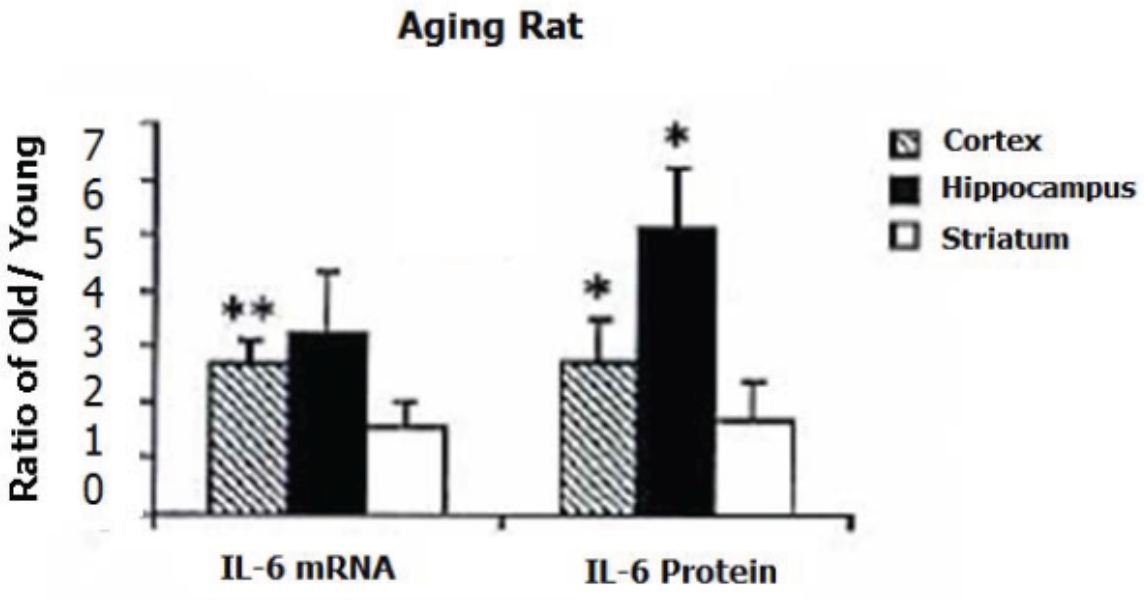
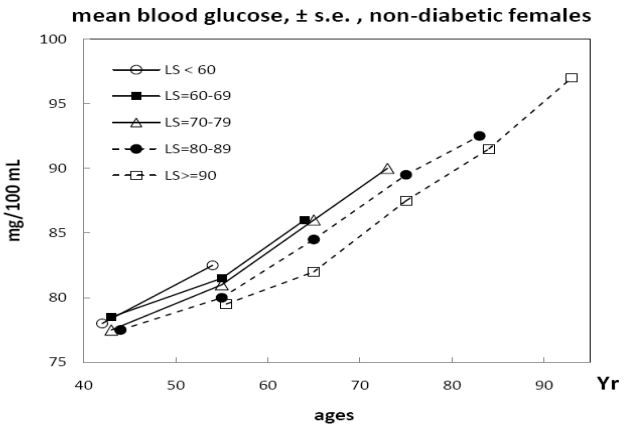


Fig. 4. Longitudinal trends of blood glucose and hemoglobinA1c from the Framingham Heart Study, approximating fasting (Yashin et al 2009).
(A) Blood glucose, total sample, shows 5% increase per decade after age 40 (calculation by CEF);
(B) Blood glucose , exclusing type-2 diabetes and stratified by lifespan (LS); the longest-lived (LS>90) show slightly delayed age-related increases in blood glucose.
(C) Hemoglobin A1c in non-diabetics (Pani et al 2008)

(A)

(B)



(c)

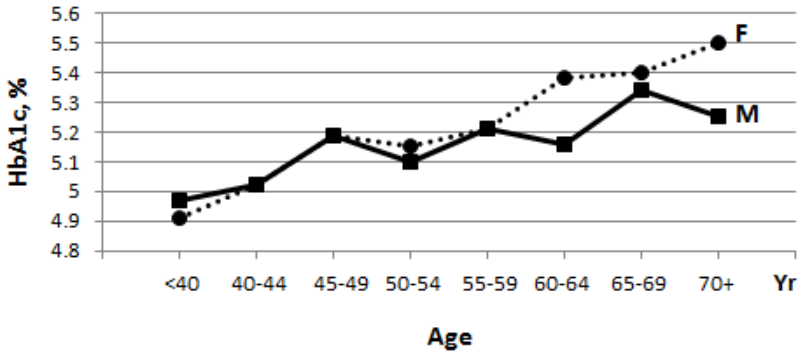
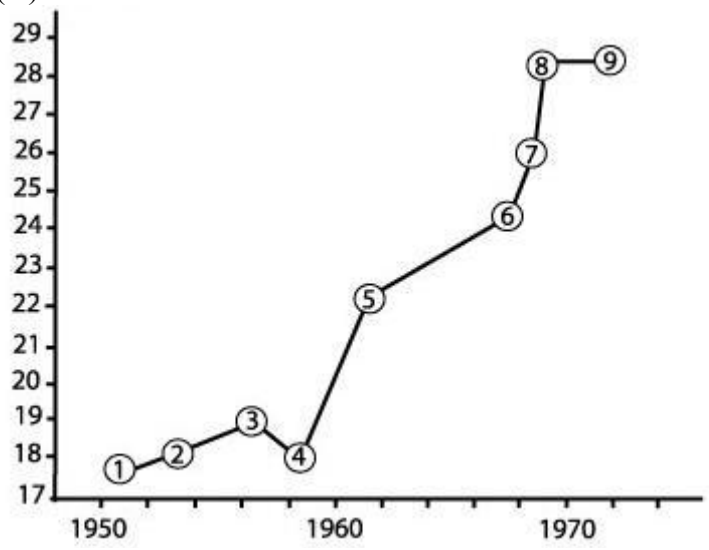


Fig. 5. The increasing lifespan of the laboratory mouse with husbandry improvements that reduced the infectious load in C57BL/6J male mice, e.g. from *Mycoplasma, Salmonella,* and ectromelia, MHV, Sendai virus.
(A) Mean lifespans from Jackson Labs, Oak Ridge National Laboratory, and other sources cited in Finch 2007, p137.
(B) Survival curves from the Jackson Lab (1948-1956) (Russell, 1966) and Rockefeller University (1966-1971) (Finch 1972).

(A)



(B)

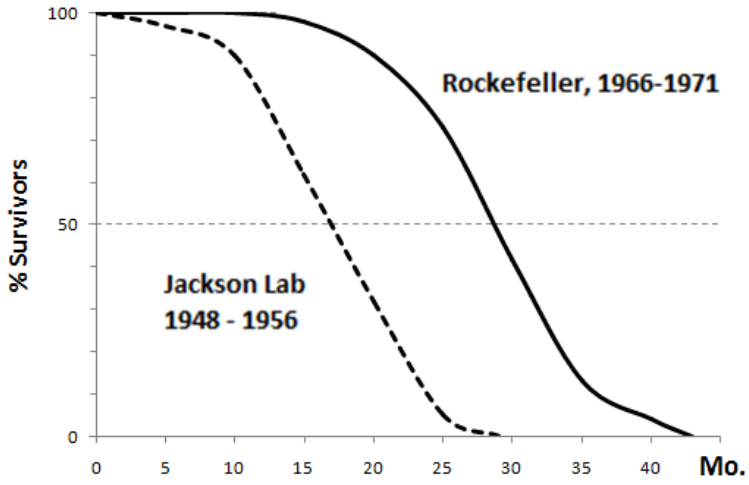


Table 1: Comparison of inflammatory factors in atherosclerosis and Alzheimer diseasea

	Atheroma	**Senile plaque**
cells		
astrocytes	0	+ +
mononuclear cells		
macrophage	+ + + (foam cell, macrophage; CD68)	+ + (microglia; CD68)
T-cell	+ + (CD3 CD4/Th1)	0
mast cells	+ +	0
platelets	+ +	0
neovascularization	+ +	+
proteins		
amyloids		
Aβ	? (macrophages with ingested platelets)	+ +
CRP	+ +	+ (neurites)
SAP	+	+
complement C5b-9	+	+
cytokines: IL-1,IL-6	+	+
metals:	Fe	Cu, Fe, Zn

For references, see Finch 2005 and Finch 2007, p.51 and 78. The sources of inflammatory proteins may be systemic or local cells, e.g. neurons express mRNA for CRP, complement C1q, and other acute phase proteins (Akiyama et al 2000; Rozovsky et al 1994; Yasojima et al 2000).