

Inflammatory Processes of Alzheimer Disease and Aging

CALEB ELLICOTT FINCH* and TODD EUGENE MORGAN

*Andrus Gerontology Center and Department of Biological Sciences,
University of Southern California, 3715 McClintock Ave, Los Angeles CA 90089-0191, USA*

(Received on 29 July 2002; Accepted after revision on 1 November 2002)

Aging is accompanied by an increased risk for developing numerous diseases, such as Alzheimers Disease (AD). However, the contribution age-related processes have in disease susceptibility and progression is largely unknown. We propose that the general inflammatory tone that develops during aging is a precondition for specific pathogenic processes. A common link between a number of disease states and normal aging is the activation of tissue macrophages. Brain macrophages (microglia) initiate a subset of specific neuroinflammatory processes that occur during both normal aging and the progression of AD. A global hypothesis of aging is emerging where chronic, initially low grade inflammatory processes progress during aging, ultimately contributing to the initiation and progression of disease.

Key Words: Microglia, Amyloid, Caloric restriction

Introduction

Aging is the major risk factor for Alzheimer disease (AD) in general populations (Katzman & Kawas 1999). However, the mechanisms behind this powerful demographic force of aging remain dimly understood and appear to represent layers of epiphenomena in which a primary cause is difficult to identify. These complex processes in AD are subject to many modulations by genetic variations at multiple loci, but also to physiological interactions through endogenous hormones and diet, as well as widely used drugs, such as the non-steroidal anti-inflammatory agents (NSAIDS). We outline a new perspective on the interactions of amyloids and AD, in which molecular and cellular changes of aging have a key role. In this view, a subset of basic mechanisms in aging has characteristics of chronic inflammatory processes, which predispose to the deposition of amyloids in the brain and other organs.

AD is diagnosed histopathologically by the presence, in sufficient numbers, of two abnormal states of proteins: intraneuronal neurofibrillary tangles (hyperphosphorylated tau) and extracellular deposits of amyloid (fibrillar amyloid

β -peptide, A β in senile plaques). There is a major debate on the relative importance of neurofibrillary tangles and amyloid to neurodegeneration in AD. We focus here on amyloids because of evidence that the amyloids of AD represent a broader phenomenon in aging throughout the body.

Rudolf Virchow introduced the term *amyloid* in the 1850's to describe 'starchy' inclusion bodies in animal tissues (Schwartz 1970, Pepys 1988, Sipe 1994). Amyloids are commonly characterized as fibrillar aggregates, which can be formed from a limited number of diverse proteins and which have extensive β -sheet interactions. Amyloids are detected histochemically by the binding of the dyes, Congo red or Thioflavin-S (Pepys 1988, Sipe 1994). Some aggregated forms of the same protein are not recognized as amyloids because of the lack of histochemical signals for bound Congo red or Thioflavin-S, e.g. the diffuse A β deposits. Yet, other aggregates are soluble oligomers as described below. Thus, the archaic term amyloid requires cautious application to molecular structure and biological activity, because it excludes many states in amyloid-forming proteins that are biologically interesting.

*Corresponding Author: Tel: (213) 740-1756; E-mail: cefinch@usc.edu

Inflammatory Processes in Alzheimer Disease

Clinical symptoms of AD are rare before the age of 60, although subclinical deterioration may exist for several decades before impairments are obvious (Katzman & Kawas 1999). After 60, the risk of AD increases exponentially and then doubles every five years. Although the incidence reaches 30-50% by the ninth decade (Meyer et al. 1998, Price et al. 1998), nonetheless some individuals reach 100 years or more, despite carrying the strong heritable risk factor of homozygotic apoE 4/4, but without clinical dementia (Meyer et al. 1998, Sobel et al. 1995). Most remarkably, the person with the greatest documented life span of 122, Mme Jeanne Calment, was tested at 118 and found in good cognitive health (Ritchie 1995, Jeune 2002). The wide individual differences in the outcomes of aging give a strong basis for ultimate optimism, as we identify segments of these complex inflammatory processes that are ongoing during life in multiple organ systems.

One of the early clues to AD as an inflammatory process was the serendipitous finding that rheumatoid arthritis patients taking high levels of anti-inflammatory drugs had a low incidence of AD (Jenkinson et al. 1989, Akiyama et al. 2000, McGeer & McGeer 2001). There is now broad and remarkably consistent evidence for about a 50% lower risk in regular users of NSAIDs and possibly aspirin (Breitner & Zandi 2001, Veld et al. 2001). Moreover, transgenic mice carrying human AD genes that were fed ibuprofen show decreased amyloid accumulation and neurodegeneration (Lim et al. 2000). Dietary anti-oxidants such as the spice curcumin are also neuroprotective in transgenic models (Lim et al. 2001).

As noted above, AD is associated with an abundance of extracellular senile plaques (SP), which contain the amyloid β -peptide ($A\beta$) in limited brain regions. The brain regions most affected in AD are the entorhinal cortex, subiculum, and hippocampus, which are the seat of declarative memory functions. The $A\beta$ peptides of up to 43 amino acid residues are endoproteolytically derived from the β -amyloid precursor protein (APP). Senile plaque amyloids consist mainly of $A\beta_{1-42}$ but with some longer and shorter peptides, whereas cerebral blood vessels accumulate amyloid

containing the slightly shorter $A\beta_{1-40}$ (Price et al. 1998). Another diagnostic of AD is the accumulation of intraneuronal hyperphosphorylated tau (neurofibrillary tangles). It is remarkable that APP, $A\beta$, and tau are widely produced by cells throughout the body: The puzzle of AD is to understand why proteins that are present throughout life in body fluids ($A\beta$) or within neurons (tau) become pathologically aggregated during aging. The accumulations of aggregated $A\beta$ and hyperphosphorylated tau are extremely common during aging of primates and most other mammals that live longer than ten years (Finch & Sapolsky 1999, Price et al. 1992). These and other species-generalized aging changes define a canonical pattern of aging in mammals (Finch 1993).

However, many other forms of aggregated $A\beta$ peptides occur during aging in the brain. These heterogeneous *extracellular* materials range widely in morphology and binding of Congo red, which is a required criterion for designation as 'amyloid'. At one extreme are oligomeric forms of $A\beta$ (ADDLs, amyloid-derived diffusible ligands, see below), which cannot be detected by the usual aqueous immunocytochemistry because of their solubility (Klein et al. 2001). A higher level of $A\beta$ aggregation is represented by the amorphous, or diffuse $A\beta$ deposits detected by immunohistochemistry to $A\beta$ -peptides, but do not distinctly bind Congo red and hence are not called amyloids (Akiyama et al. 1999, Yamaguchi et al. 1988). The highly compact, Congo red binding $A\beta$ -containing deposits of senile plaques and cerebral vessels are the classic amyloid of AD brains. Because of neurons with abnormal dystrophic neurites (swollen, twisted) that are nearby or growing through their matrix, senile plaques are also called neuritic plaques. Another type of deposit in AD brains is "fleecy amyloid" (Thal et al. 1999). Although the amorphous deposits may arise before the senile plaques, little is known about the sequence of events.

Major controversies concern the significance of the diverse $A\beta$ -containing deposits to AD pathogenesis. On one hand, some have emphasized that the amyloid load in AD cerebral cortex is only weakly correlated with the degree of clinical dementia and that the best correlation of clinical change is with synaptic loss (Terry et al. 1991).

Similarly, during clinically symptomatic AD, the total amyloid load shows little change (Hyman et al. 1993). In contrast, others find stronger correlations of cognitive functions with the total amyloid load as determined at various stages of AD (Cummings et al. 1996). Moreover, the neocortex at very early stages of AD 'minimal cognitive dysfunction' had many neuritic plaques, whereas cognitively normal individuals of the same age had a much lower density of amyloid deposits (Morris et al. 1996). Diffuse plaques are found in nearly all brains during aging and, even in early AD were 5-fold more common than neuritic plaques. Although some reports emphasize that neurons tend to have normal morphology around diffuse plaques with loss of synapses (Terry et al. 1991), others observed a smaller cholinergic neuron fiber density in nondemented elderly with diffuse A β -containing deposits consistent with early pathogenesis (Beach et al. 1992).

A huge emphasis continues to be given to the neurotoxicity of A β aggregates of various size classes. Aggregates form rapidly during incubation of various A β peptides (A β 1-40, 1-42, 25-35) at ambient temperatures. Sizes range from dimers to decamers (ADDLs range); protofibrils, 100; to higher order fibrils found in senile plaques. These high molecular weight aggregates have widely varying toxicity (Simmons et al. 1994). Work from this laboratory in collaboration with William Klein and Grant Krafft of Northwestern University has demonstrated that oligomeric (ADDLs) A β aggregates are highly toxic to neurons at submicromolar concentrations (Oda et al. 1995, Lambert et al. 1998, Klein et al. 2001). Transgenic mice that overexpress human AD mutant amyloid precursor protein (APP) genes have increased production of A β -peptides also show neuronal dysfunctions in the absence of solid A β deposits (Mucke et al. 2000, Klein et al. 2001). ADDLs have selective effects on neuronal activities, inhibiting long-term potentiation (LTP), a model for memory (Lambert et al. 2001, Wang et al. 2002). The neurotoxic pathways of ADDLs involve oxidative stress (Oda et al. 1995, Lambert et al. 1998) and involve signaling systems with Fyn and Rac1 (Lambert et al. 1998, Longo V & Finch C in prep.). Peroxynitrite and redox-active

iron are mediators of A β and ADDL neurotoxicity (Longo et al. 2000, Xie et al. 2002).

Aggregated A β peptides are potent activators of inflammatory mechanisms, which include subsets of the classical cellular and molecular changes occurring in peripheral tissues during responses to injury or in host defense. However, there are important differences to inflammatory processes in the AD brain from those of peripheral inflammation (Finch & Marchalonis 1996): First, swelling (edema) is absent. Second, there is no pain (brain parenchyma is unique in its low nociception). Third, AD brains show few, if any B- and T-cells, which sharply distinguishes AD from multiple sclerosis in which autoreactive T-cells have the major role in pathogenesis. With its peculiar 'cold' inflammation, the AD brain gives a unique opportunity to study inflammatory changes of aging independently of B- and T-cells (Akiyama et al. 2000, Finch et al. 2002). We have proposed that AD is a model for the evolutionarily early stages of inflammatory mechanisms that preceded combinatorial cellular mechanisms in immune responses (Finch & Marchalonis 1996).

Microglial activation is prominent during AD (Akiyama et al. 2000, Eikelenboom & Veerhuis 1996, Finch et al. 2002), which was originally reported by Alzheimer himself (Alzheimer 1907). Microglia are bone marrow-derived cells of the monocyte lineages that, like peripheral tissue macrophages, become phagocytic and produce reactive oxygen species. In general, fewer activated microglia are associated with diffuse A β deposits. The activation of microglia in AD may precede that of astrocytes. During AD, astrocytes also become activated, as generally evaluated by the increase of cellular extensions containing GFAP, the astrocyte intermediate filament protein. It is widely recognized that GFAP expression increases in response to local brain injury (Laping et al. 1994). Moreover, we observed that systemic pathophysiology can stimulate GFAP expression, e.g. in association with wasting diseases and pathology of nonneural organs (Goss et al. 1990).

It is now clear that ADDLs and other A β aggregates can activate microglia/monocytes (Akiyama et al. 2000, Longo et al. 2000, Xie et al. 2002), but also astrocytes (Hu et al. 1998). A β also

stimulates astrocyte production of IL-1 β (Gitter et al. 1995, Hu et al. 1998). Moreover, A β directly activates the classical complement cascade by binding to C1q, which is the initial component of the classical complement cascade (Akiyama et al. 2000). A general hypothesis being considered in AD research is that A β aggregates initiate inflammatory responses. However, it is likely that prior inflammatory processes of aging were active. Thus, we must confront the possibility of sequential epiphenomena of branching causal chains that can be influenced by many environmental factors. For example, head trauma as experienced by pugilists is a high risk for AD (e.g. Mayeux et al. 1995). Milder degrees of head injury, which may not be notable in ordinary life, could be cumulative in initiating AD processes

Many inflammatory proteins are detected in senile plaques including APP, cytokines, complement factors, and acute phase proteins

(table 1). However, these histochemical observations are semi-quantitative at best and are sensitive to fixation and to the source of the antibodies. Of great interest to inflammatory mechanisms, C1q shows strong immunostaining in senile plaques (Akiyama et al. 2000, Rozemuller et al. 1992 Yasojima et al. 1999). Activation of C1q can produce the anaphylactic peptides (C3a, C4a, C5a) that are chemoattractants and which, like C1q itself, can stimulate oxygen bursts. The complement cascade can culminate in production of the cytotoxic membrane attack complex (MAC), which contains C5b-C9. Although MAC components and MAC inhibitors are detected in AD brains (Akiyama et al. 2000, Zhan et al. 1999), there is no information on their role in neuron death during AD.

On the other hand, some inflammatory processes are neuroprotective in AD transgenic models (Wyss-Coray et al. 2002). These diverse findings are not contradictory, because

Table 1 Neuroinflammatory Changes in Alzheimer and Aging

	Alzheimer Disease senile plaques ^a	Normal aging rodent ^b	Normal aging human
astrocytes	Yes	Yes (GFAP)	Yes (GFAP) ^c
microglia	Yes	Yes (Ox-6,-42)	Yes
neurite abnormalities	Yes	Yes (no NFT)	
A β	Yes		Yes
APP	Yes		
α 1-antichymotrypsin	Yes		
α 2-macroglobulin	Yes		
apoE	Yes	Yes (mRNA)	
apoJ (clusterin)	Yes	Yes (mRNA)	
CRP	Yes		
heme oxygenase-1	Yes	Yes (ICC)	corpora amylaceae
complement factors			increase in CSF ^d
C1q	Yes		corpora amylaceae ^e
C3	Yes	Yes (mRNA)	
C9	Yes		
Cytokines			
IL-1	Yes		
IL-6	Yes		plasma
TGF β -1	Yes	Yes (mRNA)	
TNF- α	Yes		

^aAkiyama et al. 2000, Eikelenboom & Veerhuis, 1996, Yasojima et al. 1999

^bMorgan et al. 1999

^cNichols et al. 1993, Finch et al. 2002

^dLoeffler et al. 1997

^eSinghrao et al. 1995

inflammatory processes are multiphasic with local tissues responses that can appear to be opposing. Contrary to expectations from the robust inflammatory processes within the AD brain, several cytokines in the cerebrospinal fluid (IL-1 β , IL-1ra, IL-6, TNF- α) did not change. One study documented rapid brain atrophy by brain imaging during longitudinal studies, but found no changes in CSF cytokines (Lanzrein et al. 1998). These findings agree with studies of these cytokines that were based on single time CSF sampling (e.g. Marz et al. 1997). However, another study of CSF showed that C1q varied inversely with the clinical rating, consistent with C1q consumption by complement activation (Smyth et al. 1994). Moreover, we found induction of C1q in sporadic amyotrophic lateral sclerosis, a neurological disease devoid of AD-like amyloid deposits (Grewal et al. 1999). Because C1q may be activated by many components of neurodegeneration, including myelin and DNA released from dying cells, there may be multiple steps in AD that involve inflammatory mechanisms.

The sources of inflammatory proteins in AD brains are likely to be endogenous brain cells. The skeptic would simply dismiss these findings of complement in the brain as a postmortem artifact of blood-brain barrier breakdown during death. However, immunoglobulins are not found in the same senile plaques that present so many other serum proteins (Akiyama et al. 2000, Finch et al. 2002). Local brain cells are a major potential source of the inflammatory proteins associated with A β aggregates. Our laboratory was the first to show by *in situ* hybridization that C1q mRNA is relatively abundant in neurons and microglia of human and rodent brains (Lampert-Etchells et al. 1991, 1993, Pasinetti et al. 1992, Rozovsky et al. 1994). Moreover, C1q immunoreactivity is increased in surviving hippocampal CA1 pyramidal neurons after excitotoxin lesions (Rozovsky et al. 1994). We also showed that rat brain can synthesize *de novo* bioactive C1q during responses to lesions (Goldsmith et al. 1997). It is now accepted that resident brain neurons and glia express most, if not all, classical and alternate path complement components, including the C9 of the membrane attack complex (Akiyama et al. 2000). The multiple

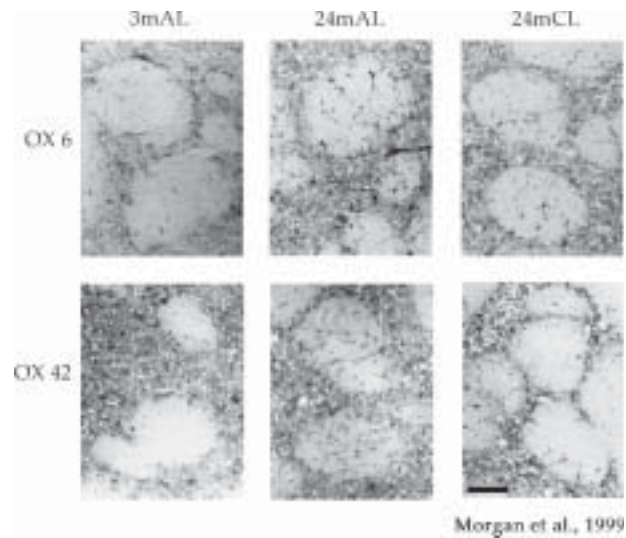


Figure 1 Cortico-striatal bundles within the caudate-putamen of 3-month *ad libitum* (3mAL), 24-month *ad libitum* (24mAL) and 24-month caloric restricted (24mCR) rat brains processed for OX6 (anti-major histocompatibility complex class II, MHCII) and OX42 (anti-complement type 3 receptor) immunoreactivity (IR). Increased OX6- and OX42-IR is evident in the 24-month *ad libitum* bundles (middle panel), an age which may be considered as middle-aged for this long-lived genotype. CR attenuates this increase (right panel). Scale bar=50 μ m.

functions of C1q include intracellular activities (binding to calreticulin) as well as interactions with a wide range of other systems that mediate normal tissue renewal.

Together, the evidence is remarkably consistent for the importance of inflammatory processes in AD. However, much remains to be discovered about the particular neuroprotective pathways that are involved. For example, NSAIDs may directly protect neurons exposed to A β aggregates, or the protection may be indirect via microglia.

Inflammatory Processes in Normal Brain Aging

Because AD shows such a strong relationship to age, it is cogent to ask what inflammatory changes occur during normal aging in the brain, in the absence of overt neurological disease. Our lab has shown in detail the activation of astrocytes and microglia in late middle-aged rodents, which at 20-24 months, were healthy and without degenerative diseases (Morgan et al. 1999, Nichols et al. 1993). For example, there is a 3-fold increase in microglial activation in cortico-striatal bundles and in corpus callosum of 24-month-old rats (Morgan et al. 1999)

(figure 1). The rats of this study were male F₁(F344 x BN) hybrids, which are in excellent health at 24 months and have mean life spans of 33 months.

Glial activation during normal aging is also documented in primates and humans (Finch et al. 2002). It can now be confidently stated that glial activation is part of normal brain aging processes. Concurrent with glial activation is a subtle regression of synaptic functions during middle age, e.g. progressive decrease of dopamine D2 receptors (Severson et al. 1982, Finch 2001). Thus, the glial activation and neuronal atrophy during AD are concurrent with milder glial and neuronal aging changes that can be traced back at least 20-40 years into middle age.

Two glial markers show robust increases in all mammals examined: GFAP in astrocytes and CR3 (complement receptor 3) in microglia: both show increases by midlife in healthy individuals (Morgan et al. 1999). We defined the regional distribution and cellular basis for increases of GFAP during aging. By *in situ* hybridization for GFAP intron RNA, as validated by nuclear run-on (Laping et al. 1994), we showed that age caused increased GFAP transcription per cell (Morgan et al. 1999). The increased expression of GFAP in rodent aging represent mainly increased activation of astrocytes, with small to negligible increases in the total numbers of astrocytes, e.g. in the hippocampus (Lindsay et al. 1979, Finch et al. 2002). We calculate that GFAP mRNA increases from puberty onwards at a rate of about 5 mRNA copies per astrocyte per month (Pasinetti et al. 1999). The increased GFAP expression was confirmed by microarray analysis (Lee et al. 2000). The increased cell expression of GFAP during aging (100-300% across the lifespan) is the first example of a gene with increased expression during normal aging in any organ of humans or short-lived rodents that is independent of pathology.

Another approach uses primary cultures of glia from adult brains (Rozovsky et al. 1998). In this paradigm, mixed glia (both astrocytes and microglia) are grown to confluence during 4-6 weeks, after which microglia can be separated by a standard shaking procedure. Many glial phenotypes of activation during aging *in vivo* persist *in vitro*, including elevated GFAP transcription. GFAP promoter elements mediating

the age increase may include overlapping NF1-NFkB elements (Krohn et al. 1999). Consistent with *in vivo* data, both astrocytes (measured by GFAP) and microglia (MHCII) retain an activated phenotype (Rozovsky et al. 1998).

IL-6 also shows increased expression during normal aging (Ye & Johnson, 1999). Both IL-6 mRNA and peptide are increased in mixed glia cultured from old brain (figure 2) (Xie et al. in press). Numerous reports indicate age-related increases in IL-6, as discussed below.

This evidence for mild but progressive inflammatory changes during normal aging is consistent with the protective effects of NSAIDs on AD. We postulate that AD represents a departure from normal brain aging only in the degree of the inflammatory process that are already underway soon after sexual maturity.

Amyloidosis and inflammation outside the brain

We now extend our discussion to tissues outside of the brain, which show many parallel changes during aging, although different amyloids are involved. Accumulations in non-neural tissues of classical extracellular amyloids during aging ("senile amyloids") are very common in human populations (table 2). About 20 different proteins form tissue amyloids (Kisilevsky & Fraser 1997, Pepys 1988, Sipe 1994). Some amyloids form aggregates with a pentameric organization (pentraxins), e.g. C-reactive protein (CRP) and serum amyloid (SAA), which are evolutionarily ancient components of host defense mechanisms with roles in antimicrobial defense and tissue repair (Finch & Marchalonis 1996). However,

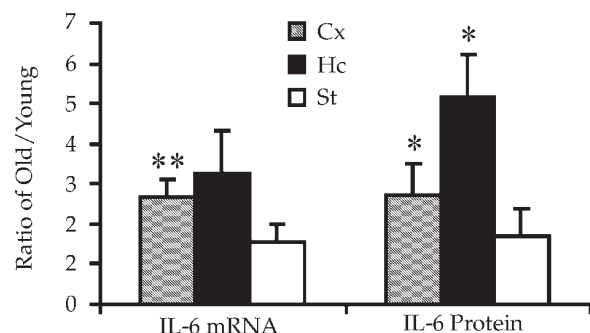


Figure 2 Basal expression of IL-6 in mixed gliacultured from three brain regions of 3 mo (Young) and 24 mo (Old) rat shown as the ratios of Old to Young. Brain regions: Cx, Cerebral cortex; Hc, hippocampus; St, striatum. * $p < 0.05$, ** $p < 0.005$, Old vs. Young (Xie et al. in press).

Table 2 *Senile Amyloids in Human Tissues*

Organ	Type of amyloid	Incidence
brain: senile plaques and cerebral vessels	A β peptide	high
heart ^a :		
aorta	apolipoprotein A1	high
atrium	α -ANF	high
myocardium	transthyretin	moderate
lumbar disks ^b	unknown	low-high
lung ^c	unknown	moderate
pituitary ^d	prolactin	unknown

^aWestermark et al. 1997^bYasuma et al. 1992^cUtz et al. 1996^dWestermark et al. 1995

other aggregated proteins do not meet the standard criteria for tissue amyloids, as noted above, which merit more consideration if we are to understand the causes of amyloid deposits in Alzheimer disease (AD) and other age-related diseases. Recall that early stages of AD have abundant non-fibrillar, diffuse deposits of A β , which do not bind Congo red or Thioflavin-S. Moreover, the skin of clinical AD patients frequently has nonfibrillar A β deposits, which are detected by immunohistochemistry at higher frequency than in age-matched controls (Joachim et al. 1989, Wen et al. 1994).

In the heart and aorta, several amyloids are increasingly found after 50 years (McCarthy & Kaspar 1998). Myocardial amyloids include atrial natriuretic peptide (ANP) (Kawamura et al. 1995) and transthyretin, particularly in African-Americans who carry the mutation (isoleu 122) (Jacobson et al. 1997). Myocardial amyloids can accumulate sufficiently to modify heart structure and function, causing arrhythmias and conduction disturbances, and may be a significant cause of heart failure in the elderly. The aorta accumulates different, and unidentified amyloids, particularly in the medial layer (Mucchiano et al. 1992). "Senile" amyloids accumulate in other vital organs to varying degrees. We note the great need for a thorough study of non-neural amyloids in individuals whose brains are characterized for the neuropathology of AD. This major project might identify a new relationship between peripheral and central inflammatory processes of aging, in which amyloid depositions could be a variable outcome.

The accumulation of brain amyloid deposits during aging does not occur in laboratory rodents

(Jucker et al. 1994), unless engineered with certain human familial Alzheimer transgenes, mainly mutant APP. However, in kidney and other non-neural tissues, senile amyloid deposits commonly increase during aging in widely used strains of mice (e.g. Higuchi et al. 1998, West & Murphy 1965). Mice that over-express TGF- β 1 showed deposits of the A β peptide in cerebral vessels, which are never seen in mice during aging (Wyss-Coray et al. 1997). This important observation indicates the importance of TGF- β 1 and other inflammatory mediators in tissue amyloid deposits during aging.

Much data indicate a progressive increase in inflammatory markers in peripheral blood during aging in the general human population, for example, elevated blood levels of IL-6 (Ershler 1993, Wilson et al. 2002). Of particular interest are the increases of IL-6 in community-dwelling elderly from the Established Populations for Epidemiological Studies of the Elderly (EPESE) (Cohen et al. 1997, Wilson et al. 2002). Plasma IL-6 showed progressive average elevations from 70-99+ years, with the strongest upward trend in white males. The subgroup of those with very high IL-6 levels (> 5pg/ml) doubled at later ages, from 10% (70-79 yr) to 20% (90-99+) (Cohen et al. 1997). Another indication is the increased frequency of apparently healthy elderly with modestly elevated plasma C-reactive protein (CRP) (Wilson et al. 2002). These and other peripheral inflammatory markers suggest that inflammatory degenerative processes may be ongoing in many organs during aging. Consistent with this possibility, the Duke EPESE sample showed a highly significant correlation between high IL-6 and poor self-rated health (Cohen et al. 1997).

At tissue levels, there are also many indications of inflammatory processes during aging, which extend the findings on brain aging. The liver, which produces CRP and other acute phase inflammatory proteins, manifests inflammatory mechanisms during aging. For example, aging mice have an increased basal level of the transcription factor, C/EBP δ , which regulates many acute phase genes and other genes that mediate responses to oxidative stress (Rabek et al. 1998). Hepatic C/EBP α mRNA increased during aging by 5-fold (mice aged 24 vs. 3 months); after injection of the inflammatory stimulus

LPS, the return to baseline was much slower. T-kininogen, another acute phase protein, shows spontaneous elevations during aging in rats that predict death within 4 months (Walter et al. 1998).

There are many links between amyloids and inflammation, because inflammation promotes amyloid formation in non-neural tissues (Kisilevsky 1994, Sipe 1994). For example, tuberculosis with major host inflammatory responses frequently leads to systemic amyloidosis. Renal dialysis, through little understood processes that lead to the accumulation of inflammatory cells, is also associated with tissue amyloids. Thus, we may consider a global hypothesis of aging, in which chronic, initially low grade inflammatory processes progress during aging to become proamyloidogenic in different tissues.

Diet and Inflammatory Processes of Aging

Individual outcomes of aging may depend on the ability of the external environment to fan smoldering inflammatory processes, according to the proclivities of the genotype. Human populations appear to show important differences in the incidence of AD, which may be major clues to environmental factors. On the basis of findings that must be considered preliminary, two populations being studied intensively in Nigeria (Hendrie et al. 2001) and India (Chandra et al. 2001) appear to have much lower AD incidence relative to US populations.

The Indo-US study of Alzheimer's disease is comparing a rural Hindi-speaking community in India (Ballabgarh, Haryana, northern India) to a well-studied reference population (Mongahela Valley, western Pennsylvania) (Chandra et al. 2001). This longitudinal study indicates one of the lowest incidences of AD in the world, possibly 80% lower than in the Mongahela Valley. While the investigators of this ongoing study urge caution, it seems likely to reveal important environmental factors in AD risk. Lacking postmortem neuropathologic data on the Ballabgarh sample, we can refer to a study of brains (N=84, 60-90 years) at the Sir J.J. Hospital in Bombay, which had a low incidence of AD characteristic changes: extensive senile plaques, neurofibrillary degeneration, and neuron loss was found in <10% overall of this

sample (calculated by the present authors for the 60 year+ group); however, cerebrovascular pathology was found in about 40% of these brains (Barodawala & Ghadi 1992). Those authors caution that the reported ages may not be reliable and that the sample is biased towards a young subset of older patients. The figure of 10% AD incidence is not remarkably different from estimates of AD in other populations of comparable ages and education levels, e.g. 3% in Shanghai (summarized in Kawas & Katzman 1999). Suffice it to say, we must await more data combining clinical and neuropathologic findings before firm conclusions can be drawn about ethnic differences in the risk of AD.

Dietary components also merit examination in these comparative studies. In India, the popular spice curcumin may have neuroprotective effect, as indicated by its decrease of oxidative damage and amyloid pathology in a transgenic mouse model (Lim et al. 2001). The Nigerian and Indian communities may share common features in the low overall calorie intake and of animal derived protein (also see comments of Barodawala & Ghadi (1992)). We may cautiously consider the pertinence of findings on caloric restriction (CR), which is the best-established physiological manipulation of aging in laboratory rodents. In the standard paradigm, postpubertal rodents are given 35% below the ad libitum food intake, which slows many aging processes, e.g. increased mean and maximum life span; reduced incidence of tumors and glomerulosclerosis, and slowed glycation-oxidation of collagen (Sohal & Weindruch 1996, Finch et al. 2002). In brain, CR attenuated the decrease of striatal dopamine D2 receptors, and related functions in aging rat (Levin et al. 1981). We added glia into this picture by showing that CR attenuated the activation of astrocytes and microglia in aging rat cerebral cortex, hippocampus, and striatum, e.g. complement receptor CR3 in microglia (figure 1) and GFAP mRNA in astrocytes (Morgan et al. 1999). Affymetrix chip analysis of neocortex and cerebellum confirmed these findings on GFAP and C-system mRNAs (Lee et al. 2000). Moreover, a prominent class of age increases in mRNAs associated with oxidative stress and inflammation is attenuated by CR (Lee et al. 2000). Conversely, age-decreases in a growth and trophic factor subset

of mRNAs are also attenuated by CR. Certain of these age- and CR- modulated mRNAs are new targets for study in AD pathogenesis. We anticipate an avalanche of further reports using microarray on different stages of AD. The difficulty in obtaining a full range of ages in normal brains makes detailed studies of aging in rodent models highly desirable.

CR has many effects on physiology and biochemistry, which appear to include anti-inflammatory actions. For example, young mice subjected to 6 weeks of CR, have attenuated peripheral inflammatory responses (footpad edema) (Klebanov et al. 1995). The slow accumulation of oxidized epitopes in long-lived proteins could be a fundamental background in these inflammatory processes. CR lowers blood glucose and the tissue levels of oxidized proteins and lipids (Sohal & Weindruch 1996, Sell et al. 1996). Among the mechanisms that cause protein oxidation is the nonenzymatic reaction of blood glucose with amino groups. In turn, glycoxidized proteins can propagate free radical reactions leading to cross-linking and the attraction of tissue macrophages. Moreover, CR attenuates cerebral injury in response to excitotoxins and ischemia (Mattson et al. 2001). This action of CR appears to

be paradoxical, because sustained elevations of glucocorticoids can potentiate neuron death from ischemia and other stressors (Patel & Finch 2002).

Conclusions

We have shown that inflammatory processes associated with Alzheimer disease, an age-related condition, also develop during “normal” aging to a lesser extent, not only in the brain but also in many other tissues. We propose that a major feature of aging is the development of a general inflammatory tone, which, in turn, is a precondition for other specific pathogenic processes. Macrophage/monocytes may be a crucial determinant of the outcomes of aging in a wide range of tissues. For example, macrophage/monocytes are prominent in brain aging (microglia), vascular aging (foam cells in the arterial wall), and in the bones (osteoclasts) and arthritic conditions of joints. Thus, we may consider a global hypothesis of aging, in which chronic, initially low grade inflammatory processes progress during aging to become proamyloidogenic in different tissues. Individual outcomes of aging may depend on the influence that the external environment has on smoldering inflammatory processes and its possible modification by diet.

References

- Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole G M, Cooper N R, Eikelenboom P, Emmerling M, Fiebich B L, Finch C E, Frautschy S, Griffin W S, Hampel H, Hull M, Landreth G, Lue L, Mark R, Mackenzie I R, McGeer P L, O'Banion M K, Pachter J, Pasinetti G, Plata-Salaman C, Rogers J, Rydel R, Shen Y, Streit W, Strommeyer R, Tooyoma I, Van Muiswinkel F L, Veerhuis R, Walker D, Webster S, Wegrzyniak B, Wenk G and Wyss-Coray T Inflammation and Alzheimer's disease 2000; *Neurobiol. Aging* **21** 383-421
- Alzheimer A 1907 Uber eine eigenartige Erkrankung der Hindrinde; in *Allgemeine Zeitschrift fuer Psychiatrie und Psychisch-Gerichtliche Medizin.* **64** pp146-148 eds E Schultze and O Snell. Translated as “A characteristic disease of the cerebral cortex:” in *The Early Story of Alzheimer's Disease.* eds K Bick, L Amaducci, G Pepeu (Livonia Press, Padova, distributed through Raven Press, New York)
- Barger S W and Harmon AD 1997 Microglial activation by Alzheimer amyloid precursor protein and modulation by apolipoprotein E; *Nature* **388** 878-881
- Barodawala S A and Ghadi P S 1992 A progress report on the prevalence of Alzheimer's lesions in a Bombay hospital population; *Current Sci.* **63** 449-455
- Beach T G and McGeer E G 1992 Senile plaques, amyloid beta-protein, and acetylcholinesterase fibres: laminar distributions in Alzheimer's disease striate cortex; *Acta Neuropathol. (Berl).* **93** 146-153
- Breitner J C and Zandi P 2001 Do nonsteroidal antiinflammatory drugs reduce the risk of Alzheimer's disease? *N. Engl. J. Med.* **345** 1567-1568
- Chandra V, Pandav R, Dodge H H, Johnston J M, Belle S H, DeKosky S T and Ganguli M 2001 Incidence of Alzheimer's disease in a rural community in India: the Indo-US study; *Neurology* **57** 985-989
- Cohen H J, Pieper C F, Harris T, Rao K M and Currie M S 1997 The association of plasma IL-6 levels with functional disability in community-dwelling elderly; *J. Gerontol. A Biol. Sci. Med. Sci.* **52** M201-M208
- Cummings B J, Pike C J, Shankle R and Cotman C W 1996 Beta-amyloid deposition and other measures of neuropathology predict cognitive status in Alzheimer's disease; *Neurobiol. Aging.* **17** 921-933

- Eikelenboom P and Veerhuis R 1996 The role of complement and activated microglia in the pathogenesis of Alzheimer's disease; *Neurobiol. Aging* **17** 673-680
- Ershler W B 1993 Interleukin-6: a cytokine for gerontologists; *J. Am. Geriatr. Soc.* **41** 176-181
- Finch C E 1993 Neuron atrophy during aging: programmed or sporadic? *Trends Neurosci.* **16** 104-110
- _____ and Marchalonis J 1996 An evolutionary perspective on amyloid and inflammatory features of Alzheimer disease; *Neurobiol. Aging.* **17** 809-815
- _____ and Sapolsky R M 1999 The evolution of Alzheimer disease, the reproductive schedule, and apoE isoforms; *Neurobiol. Aging.* **20** 407-428
- _____ 2001 Toward a biology of middle age; in *Handbook of Midlife Development* pp 77-108 (Chapt 3) ed M E Lachman (New York: John Wiley & Sons)
- _____, Morgan T E, Rozovsky I, Xie Z, Weindruch R and Prolla T 2002 Microglia and aging in the brain; in *Microglia in the Regenerating and Degenerating Central Nervous System* pp275- 305 ed W J Streit (New York: Springer-Verlag)
- Gentleman S M, Greenberg B D, Savage M J, Noori M, Newman S J, Roberts G W, Griffin W S and Graham D I 1997 Abeta 42 is the predominant form of amyloid beta-protein in the brains of short-term survivors of head injury; *Neuro. Report* **8** 1519-1522
- Gitter B D, Cox L M, Rydel R E and May P C 1995 Amyloid beta peptide potentiates cytokine secretion by interleukin-1 beta-activated human astrocytoma cells; *Proc. Natl. Acad. Sci. USA.* **92** 10738-10741
- Goldsmith S K, Wals P, Rozovsky I, Morgan T E and Finch C E 1997 Kainic acid and decorticating lesions stimulate the synthesis of C1q protein in adult rat brain; *J. Neurochem.* **68** 2046-2052
- Goss J R, Finch C E and Morgan D G 1990 GFAP RNA prevalence is increased in aging and in wasting mice; *Exp. Neurol.* **108** 266-268
- Grewal R P, Morgan T E and Finch C E 1999 C1qB and clusterin mRNA are increased in association with sporadic ALS; *Neurosci. Lett.* **271** 65-67
- Hendrie H C, Ogunniyi A, Hall K S, Baiyewu O, Unverzagt F W, Gureje O, Gao S, Evans R M, Ogunseyinde A O, Adeyinka A O, Musick B and Hui S L 2001 Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African-Americans residing in Indianapolis, Indiana; *JAMA* **285** 739-747
- Higuchi K, Kogishi K, Wang J, Chen X, Chiba T, Matsushita T, Hoshii Y, Kawano H, Ishihara T, Yokota T and Hosokawa M 1998 Fibrilization in mouse senile amyloidosis is fibril conformation-dependent; *Lab Invest.* **78** 1535-1542
- Hu J, Akama K T, Krafft G A, Chromy B A and Van Eldik L J 1998 Amyloid-beta peptide activates cultured astrocytes: morphological alterations, cytokine induction and nitric oxide release; *Brain Res.* **785** 195-206
- Hyman B T, Marzloff K and Arriagada P V 1993 The lack of accumulation of senile plaques or amyloid burden in Alzheimer's disease suggests a dynamic balance between amyloid deposition and resolution; *J. Neuropathol. Exp. Neurol.* **52** 594-600
- Jacobson D R, Pastore R D, Yaghoubian R, Kane I, Gallo G, Buck F S and Buxbaum J N 1997 Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans; *N. Engl. J. Med.* **336** 466-473
- Jenkinson M L, Bliss M R, Brain A T and Scott D L 1989 Rheumatoid arthritis and senile dementia of the Alzheimer's type; *Br. J. Rheumatol.* **28** 86-88
- Jeune B 2002 Living longer – but better? *Aging (Milano).* **14** 72-93
- Joachim C L, Mori H and Selkoe D J 1989 Amyloid beta-protein deposition in tissues other than brain in Alzheimer's disease; *Nature* **341** 226-230
- Johnson S A, Lampert-Etchells M, Rozovsky I, Pasinetti G and Finch C E 1992 Complement mRNA in the mammalian brain: responses to Alzheimer's disease and experimental lesions; *Neurobiol. Aging.* **13** 641-648
- Jucker M, Walker L C, Kuo H, Tian M and Ingram D K 1994 Age-related fibrillar deposits in brains of C57BL/6 mice. A review of localization, staining characteristics, and strain specificity; *Mol. Neurobiol.* **9** 125-133
- Katzman R and Kawas C H 1999 The epidemiology of Alzheimer disease, in *Alzheimer Disease*, second edition, pp 105-122 eds R D Terry, R Katzman and K L Bick (New York: Raven Press)
- Kawamura S, Takahashi M, Ishihara T and Uchino F 1995 Incidence and distribution of isolated atrial amyloid: histologic and immunohistochemical studies of 100 aging hearts; *Pathol. Int.* **45** 335-342
- Kisilevsky R 1994 Inflammation-associated amyloidogenesis: Lessons for Alzheimer's amyloidogenesis; *Mol. Neurobiol.* **8** 65-66
- _____ and Fraser P E 1997 A beta amyloidogenesis: unique, or variation on a systemic theme? *Crit. Rev. Biochem. Mol. Biol.* **32** 361-404
- Klebanov S, Diais S, Stavinoha W B, Suh Y, Nelson J F 1995 Hyperadrenocorticism, attenuated inflammation, and the life-prolonging action of food restriction in mice; *J. Gerontol. A Biol. Sci. Med. Sci.* **50** B79-82
- Klein W L, Krafft G A, Finch C E 2001 Targeting small A β oligomers: the solution to an Alzheimer's disease conundrum? *Trends Neurosci.* **24** 219-224
- Krohn K, Rozovsky I, Wals P, Teter B, Anderson C P and Finch C E 1999 Glial fibrillary acidic protein (GFAP) transcription responses to TGF- β 1 and IL-1 β are mediated by an NF-1 like site in the near-upstream promoter; *J. Neurochem.* **72** 1353-1361
- Lampert-Etchells M, McNeil T H, Laping N J, Zarow C, Finch C E, May P C 1991 Sulfated glycoprotein-2 is increased in rat hippocampus following entorhinal cortex lesioning; *Brain Res.* 653 101-106

- Lampert-Etchells M, Pasinetti G M, Finch C E, Johnson S A 1993 Regional localization of cells containing C1qb and C4 mRNAs in the frontal cortex during Alzheimer disease; *Neurodegeneration* **2** 111-121
- Lambert M P, Barlow A K, Chromy B, Edwards C, Freed R, Liosatos M, Morgan T E, Rozovsky I, Trommer B, Viola K L, Wals P, Zhang C, Finch C E, Krafft G A and Klein W L 1998 Diffusible, non-fibrillar ligands derived from A β_{1-42} ; *Proc. Natl. Acad. Sci. USA.* **95** 6448-6453
- _____, Viola K L, Chromy B A, Chang L, Morgan T E, Yu J, Venton D L, Krafft G A, Finch C E and Klein W L 2001 Vaccination with soluble Abeta oligomers generates toxicity-neutralizing antibodies; *J. Neurochem.* **79** 595-605
- Lanzrein A S, Johnston C M, Perry V H, Jobst K A, King E M and Smith A D 1998 Longitudinal study of inflammatory factors in serum, cerebrospinal fluid, and brain tissue in Alzheimer disease: interleukin-1beta, interleukin-6, interleukin-1 receptor antagonist, tumor necrosis factor-alpha, the soluble tumor necrosis factor receptors I and II, and alpha1-antichymotrypsin; *Alzheimer Dis. Assoc. Disord.* **12** 215-227
- Laping N J, Teter B, Nichols N R, Rozovsky I and Finch C E 1994 Glial fibrillary acidic protein: regulation by hormones, cytokines, and growth factors; *Brain Pathol.* **4** 259-274
- Lee C K, Weindruch R and Prolla T A 2000 Gene-expression profile of the ageing brain in mice; *Nat. Genet.* **25**(3) 294-297
- Levin P, Janda J K, Joseph J A, Ingram D K and Roth G S 1981 Dietary restriction retards the age-associated loss of rat striatal dopaminergic receptors; *Science* **214** 561-562
- Lim G P, Yang F, Chu T, Chen P, Beech W, Teter B, Tran T, Ubeda O, Ashe K H, Frautschy S A and Cole G M 2000 Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease; *J. Neurosci.* **20** 5709-5714
- _____, Chu T, Yang F, Beech W, Frautschy S A and Cole G M 2001 The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse; *J. Neurosci.* **21** 8370-8377
- Lindsay J D, Landfield P W and Lynch G 1979 Early onset and topographical distribution of hypertrophied astrocytes in hippocampus of aging rats: a quantitative study; *J. Gerontol.* **34** 661-671
- Loeffler D A, Brickman C M, Juneau P L, Perry M F, Pomara N and Lewitt P A 1997 Cerebrospinal fluid C3a increases with age, but does not increase further in Alzheimer's disease; *Neurobiol. Aging.* **18** 555-557
- Longo V D, Viola K L, Klein W L and Finch C E 2000 Reversible inactivation of superoxide-sensitive aconitase in Abeta1-42-treated neuronal cell lines; *J. Neurochem.* **75** 1977-1985
- Marz P, Heese K, Hock C, Golombowski S, Muller-Spahn F, Rose-John S and Otten U 1997 Interleukin-6 (IL-6) and soluble forms of IL-6 receptors are not altered in cerebrospinal fluid of Alzheimer's disease patients; *Neurosci. Lett.* **239** 29-32
- Mattson M P, Duan W, Lee J and Guo Z 2001 Suppression of brain aging and neurodegenerative disorders by dietary restriction and environmental enrichment: molecular mechanisms; *Mech. Ageing Dev.* **122** 757-778
- McCarthy R E 3rd and Kasper E K 1998 A review of the amyloidoses that infiltrate the heart; *Clinical Cardiology.* **21** 547-552
- McGeer P L and McGeer E G 2001 Polymorphisms in inflammatory genes and the risk of Alzheimer disease; *Arch. Neurol.* **58** 1790-1792
- Meyer M R, Tschanz J T, Norton M C, Welsh-Bohmer K A, Steffens D C, Wyse B W and Breitner J C 1998 APOE genotype predicts when-not whether-one is predisposed to develop Alzheimer disease; *Nat. Genet.* **19** 321-322
- Morgan T E, Xie Z, Goldsmith S, Yoshida T, Lanzrein A-S, Stone D, Rozovsky I, Perry G, Smith M A and Finch C E 1999 The mosaic of brain glial hyperactivity during normal aging and its attenuation by food restriction; *Neuroscience.* **89** 687-699
- Morris J C, Storandt M, McKeel D W Jr, Rubin E H, Price J L, Grant E A and Berg L 1996 Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and very mild Alzheimer's disease; *Neurology.* **46** 707-719
- Mucchiano G, Cornwell G G 3rd and Westermark P 1992 Senile aortic amyloid. Evidence for two distinct forms of localized deposits; *Amer. J. Path.* **140** 871-877
- Mucke L, Masliah E, Yu G Q, Mallory M, Rockenstein E M, Tatsuno G, Hu K, Kholodenko D, Johnson-Wood K and McConlogue L 2000 High-level neuronal expression of Abeta 1-42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation; *J. Neurosci.* **20** 4050-4058
- Nichols N R, Day J R, Laping N J, Johnson S A and Finch C E 1993 GFAP mRNA increases with age in rat and human brain; *Neurobiol. Aging.* **14** 421-429
- Oda T, Wals P, Osterburg H H, Johnson S A, Pasinetti G M, Morgan T E, Rozovsky I, Stine W B, Snyder S W, Holzman T F, Krafft G A and Finch C E 1995 Clusterin (apoJ) alters the aggregation of amyloid β -peptide (A β_{1-42}) and forms slowly sedimenting A β complexes that cause oxidative stress; *Exp. Neurol.* **136** 22-31
- Pasinetti G M, Osterburg H H, Kelly A B, Kohama S, Morgan D G, Rheinhard J F Jr, Stellwagen R H and Finch C E 1992 Slow changes of tyrosine hydroxylase gene expression in dopaminergic neurons after neurotoxin lesioning: a model for neuron aging; *Mol Brain Res* **13** 63-73
- _____, Hassler M, Stone D and Finch C E 1999 Glial gene expression during aging in rat striatum and in long-term responses to 6-OHDA lesions; *Synapse.* **31** 278-284

- Patel N V and Finch C E 2002 The glucocorticoid paradox of caloric restriction in slowing brain aging; *Neurobiol. Aging* (in press)
- Pepys M B 1988 Amyloidosis, in *Immunological Diseases*; (4th ed vol I) pp 631-674 ed M Samter (Boston: Little, Brown, and Co)
- Price D L, Martin L J, Sisodia S S, Walker L C and Cork L C 1992 Alzheimer's disease-type brain abnormalities in animal models; *Prog. Clin. Biol. Res.* **379** 271-287.
- _____, Tanzi R E, Borchelt D R and Sisodia S S 1998 Alzheimer's disease: genetic studies and transgenic models; *Annu. Rev. Genet.* **32** 461-93
- Rabek J P, Scott S, Hsieh C C, Reisner, P D and Papaconstantinou J 1998 Regulation of LPS-mediated induction of C/EBP delta gene expression in livers of young and aged mice; *Biochim. et Biophys. Acta.* **1398** 137-247
- Ritchie K 1995 Mental status examination of an exceptional case of longevity J. C. aged 118 years; *Br. J. Psychiatry.* **166** 229-235
- Rozemuller J M, van der Valk P and Eikelenboom P 1992 Activated microglia and cerebral amyloid deposits in Alzheimer's disease; *Res. Immunol.* **143** 646-649
- Rozovsky I, Morgan T E, Willoughby D A, Dugich-Djordjevic M N, Pasinetti G M, Johnson S A and Finch C E 1994 Selective expression of clusterin (SGP-2) and complement C1q and C4 during responses to neurotoxins *in vivo* and *in vitro*; *Neuroscience* **62** 741-758
- _____, Finch C E and Morgan T E 1998 Age-related activation of microglia and astrocytes: *in vitro* studies show persistence of phenotypes of aging, increased proliferation, and resistance to down-regulation; *Neurobiol. Aging* **19** 97-103
- Sell D R, Lane M A, Johnson W A, Masoro E J, Mock O B, Reiser K M, Fogarty J F, Cutler R G, Ingram D K, Roth G S and Monnier V M 1996 Longevity and the genetic determination of collagen glycoxidation kinetics in mammalian senescence; *Proc. Natl. Acad. Sci. USA.* **93** 485-490
- Severson J A, Marcusson J, Winbald B and Finch C E 1982 Age-correlated loss of dopaminergic binding sites in human basal ganglia; *J. Neurochem.* **39** 1623-1631
- Sierra F, Coeytaux S, Juillerat M, Ruffieux C, Gaudie J and Guigoz Y 1992 Serum T-kininogen levels increase two to four months before death; *J. Biol. Chem.* **267** 10665-10669
- Simmons L K, May P C, Tomaselli K J, Rydel R E, Fuson K S, Brigham E F, Wright S, Lieberburg I, Becker G W, Brems D N et al. 1994 Secondary structure of amyloid beta peptide correlates with neurotoxic activity *in vitro*; *Mol. Pharmacol.* **45** 373-379
- Singhrao S K, Morgan B P, Neal J W and Newman G R 1995 A functional role for corpora amylacea based on evidence from complement studies; *Neurodegeneration* **4** 335-345
- Sipe J D 1994 Amyloidosis; *Crit. Rev. Clin. Lab. Sci.* **31** 325-354
- Smyth M D, Cribbs D H, Tenner A J, Shankle W R, Dick M, Kessler J P and Cotman C W 1994 Decreased levels of C1q in cerebrospinal fluid of living Alzheimer patients correlate with disease state; *Neurobiol. Aging.* **15** 609-614
- Sobel E, Louhija J, Sulkava R, Davanipour Z, Kontula K, Miettinen H, Tikkanen M, Kainulainen K and Tilvis R 1995 Lack of association of apolipoprotein E allele epsilon 4 with late-onset Alzheimer's disease among Finnish centenarians; *Neurology* **45** 903-907
- Sohal R S, Weindruch R 1996 Oxidative stress, caloric restriction, and aging; *Science* **273** 59-63
- Terry R D, Masliah E, Salmon D P, Butters N, DeTeresa R, Hill R, Hansen L A and Katzman R 1991 Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment; *Ann. Neurol.* **30** 572-580
- Thal D R, Sassin I, Schultz C, Haass C, Braak E and Braak H 1999 Fleecy amyloid deposits in the internal layers of the human entorhinal cortex are comprised of N-terminal truncated fragments of A beta; *J. Neuropathol. Exp. Neurol.* **58** 210-216
- Utz J P, Swensen S J and Gertz M A 1996 Pulmonary amyloidosis. The Mayo Clinic experience from 1980 to 1993; *Ann. Intern. Med.* **124** 407-413
- Veld B A, Ruitenbergh A, Hofman A, Launer L J, van Duijn C M, Stijnen T, Breteler M M and Stricker B H 2001 Nonsteroidal anti inflammatory drugs and the risk of Alzheimer's disease; *N. Engl. J. Med.* **345** 1515-1521
- Walter R, Murasko D M and Sierra F 1998 T-kininogen is a biomarker of senescence in rats; *Mech. Ageing Dev.* **106** 129-144
- Wang H W, Pasternak J F, Kuo H, Ristic H, Lambert M P, Chromy B, Viola K L, Klein W L, Stine W B, Krafft G A and Trommer B L 2002 Soluble oligomers of beta amyloid (1-42) inhibit long-term potentiation but not long-term depression in rat dentate gyrus; *Brain Res.* **24** 133-140
- Wen G Y, Wisniewski H M, Blondal H, Benedikz E, Frey H, Pirttila T, Rudelli R and Kim K S 1994 Presence of non-fibrillar amyloid beta protein in skin biopsies of Alzheimer's disease (AD), Down's syndrome and non-AD normal persons; *Acta. Neuropathol. (Berl).* **88** 201-206
- West W T and Murphy E D 1965 Sequence of deposition of amyloid in strain A mice and relationship to renal disease; *J. Natl. Cancer Inst.* **35** 167-174
- Westermark P, Mucchiano G, Marthin T, Johnson K H and Sletten K 1995 Apolipoprotein A1-derived amyloid in human aortic atherosclerotic plaques; *Am. J. Pathol.* **147** 1186-1192
- _____, Eriksson L, Engstrom U, Enestrom S and Sletten K 1997 Prolactin-derived amyloid in the aging pituitary gland; *Am. J. Pathol.* **150** 67-73

- Wilson C J, Finch C E and Cohen H J 2002 Mechanisms of cognitive impairment. Cytokines and cognition – the case for a head to toe inflammatory paradigm; *J. Am. Geriatr. Soc.* (in press)
- Wyss-Coray T, Masliah E, Mallory M, McConlogue L, Johnson-Wood K, Lin C and Mucke L 1997 Amyloidogenic role of cytokine TGF-beta1 in transgenic mice and in Alzheimer's disease; *Nature* **389** 603-606
- Xie Z, Morgan T E, Rozovsky I and Finch C E 2003 Aging & glial responses to lipopolysaccharide *in vitro*: Greater induction of IL-1 and IL-6 but smaller induction of neurotoxicity; *Exp. Neurol.* (in press)
- _____, Wals P A, Walsh J P, Finch C E and Morgan T E 1998 Characterization of clusterin-induced microglial activation; *Soc. Neurosci.* **24** 1944
- _____, Wei M, Morgan T E, Fabrizio P, Han D, Finch C E, Longo V D 2002 Peroxynitrite mediates neurotoxicity of amyloid beta-peptide1-42- and lipopolysaccharide-activated microglia; *J. Neurosci.* **22** 3484-3492
- Yamaguchi H, Hirai S, Morimatsu M, Shoji M and Ihara Y 1988 A variety of cerebral amyloid deposits in the brains of the Alzheimer-type dementia demonstrated by beta protein immunostaining; *Acta. Neuropathol. (Berl).* **76** 541-549
- Yasojima K, Schwab C, McGeer E G and McGeer P L 1999 Up-regulated production and activation of the complement system in Alzheimer's disease brain; *Am. J. Pathol.* **154** 927-936
- Yasuma T, Arai K and Suzuki F 1992 Age-related phenomena in the lumbar intervertebral discs. Lipofuscin and amyloid deposition; *Spine* **17** 1194-1198
- Ye S M, Johnson R W 1999 Increased interleukin-6 expression by microglia from brain of aged mice; *J. Neuroimmunol.* **93** 139-148
- Zhan S S, Veerhuis R, Janssen I, Kamphorst W and Eikelenboom P 1994 Immunohistochemical distribution of the inhibitors of the terminal complement complex in Alzheimer's disease; *Neurodegeneration.* **3** 111-117