~~July 13, 2015~~August 20, 2015. Revised version

Journal of

Oral

Microbiology

Can oral infection be a risk factor for Alzheimer's disease?

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ABSTRACT

Alzheimer's disease (AD) is a scourge of longevity that will drain enormous resources from public health budgets in the future. Currently, there is no diagnostic biomarker and/or treatment for this most common form of dementia in humans. AD can be of early familial-onset or sporadic with a late-onset. Apart from the two main hallmarks, amyloid-beta and ~~the~~ neurofibrillary tangles, inflammation is a characteristic feature of AD neuropathology. Inflammation may be caused by a local central nervous system insult and/or by peripheral infections. Numerous microorganisms are suspected in AD brains ranging from bacteria (mainly oral and non-oral *Treponema* species), viruses (Herpes simplex type I) and yeasts (*Candida* species). A causal relationship between periodontal pathogens/non-oral *Treponema* species of bacteria has been proposed via the amyloid-beta and inflammatory links. Periodontitis constitutes a peripheral oral infection that can provide the brain with intact bacteria and virulence factors and inflammatory mediators due to daily, transient bacteraemias. If and when genetic risk factors meet environmental risk factors in the brain, disease is expressed, in which neurocognition may be ~~exacerbated~~ impacted, leading to the of dementia. To achieve the goal of finding a diagnostic biomarker and possible prophylactic treatment for AD, there is an initial need to solve the etiological puzzle contributing to its pathogenesis. This review therefore addresses oral infection as the plausible aetiology of late onset AD (LOAD). ~~the plausible aetiology of the late-onset AD being an oral infection.~~

Keywords: *Alzheimer's disease*; *pathogenesis*; *microorganisms*; *oral bacteria*; *direct cause*

Alzheimer's disease (AD) is a neurodegenerative disease and the most common example of a group of diseases that manifest as dementia. It is associated with atrophy and specific neuronal death particularly in the hippocampal region of the brain (1). Research into AD pathogenesis~~,~~ has flagged two main categories of the disease~~. A~~: the familial ~~onset~~ onset ~~that~~ accounts for around 2% of all AD cases and the sporadic form of late-onset AD also to as LOAD ~~that~~ constitutes approximately 98% of the cases. LOAD displays genetic susceptibility traits of which the well-known risk factor is inheritance of the apolipoprotein (*APOEε4*) gene allele (2) and, appears to require an environmental factor for disease expression. For example a pathogen-host interaction~~,~~ can exacerbate neurocognition in some elderly individuals who if in their 80+ years likely become diagnosed with LOAD (3, 4). The rationale for this review therefore is to try to explain the aetiology in the vast proportion of LOAD cases that relies upon common risk factors~~, and to date, .several.~~ Several scientists these to be peripheral infections (5-11)~~,~~ and the accompanying systemic and local inflammatory mediators (11-13). Of these, the plausible risk from oral infection is the main focus of this review.

PREVALENCE OF AD

AD is a ~~scourge~~ burden of longevity resulting from the superior quality of health care This factor is likely to contribute to quadrupling of AD subjects living in our society during the next 40 years (14). It is estimated that by 2050 about 13-14 million people are likely to suffer from AD in the USA with a rise in the total costs estimated to be more than $1 trillion. The odds of having a diagnosis of AD when over 85 years of age exceed 1:3 (15). One in six people over 80 years in the UK ~~have~~ has dementia (16). Estimates for the prevalence of AD in USA indicate that more than 5 million individuals who are 65 years or older currently suffer from AD (1, 15). About 200,000 subjects have been diagnosed with the early-onset familial

AD form and health care costs for this disease are about $200 billion per year (1). It is clear that AD is fast becoming a major health challenge in the USA and around the globe that will financially drain public health budgets and care giver services.

NEUROPATHOLOGICAL CHARACTERISTICS OF THE AD BRAIN

The AD brain is characterized by several neuropathological features of which two seminal hallmarks (Fig. 1) arise from proteostasis of the ongoing neurodegenerative processes and are essential for a definitive diagnosis of the disease ~~at~~ post mortem (17). One of the hallmark proteins is made up of fibrils in the form of extracellular, insoluble plaques and consists primarily of amyloid-beta (Aβ) (18). These peptide deposits in variable sizes depend upon the secretase enzymes (α-, β-- and ϒ-secretases) that cleave it from the longer amyloid precursor protein (APP). Initial reports suggested fibrillar Aβ to be neurotoxic (19) as it has been shown to kill all types of cells by apoptosis induction (20). However, there are two known insoluble fibrillar Aβ amyloid peptides comprised of $A\beta_{40}$ and $A\beta_{42}$ amino-acid residues ~~as well as their different~~ which exhibit distinct physiological states within the human brain. There is a general consensus among scientists that the larger ($A\beta_{42}$) peptide is the neurotoxic form as the ageing brain of cognitive intact individuals also displays Aβ plaques. However, in the cognitively intact brain they are fewer in number and usually of the diffuse $A\beta_{40}$ type that appears not to bear any, as yet known, pathological significance ~~in the elderly who age successfully.~~. In monomeric, dimeric and the multimeric forms of Aβ (21). The relative neurotoxicity of these isoforms remains unclear ~~It is not clear as to which one of these is more neurotoxic~~ (22).

More recently, the fibrillary forms of the $A\beta_{(40/42)}$ peptides released in the AD brain ~~are~~ were also recognized as “defensin” or innate immune defense molecules that act to protect the host against infection (23). For example, both of the aforementioned amyloidogenic peptides can

bind to bacterial membranes and in that way lyse bacterial cells. Although Aβ is acting as an antimicrobial peptide (AMP), it may be a part of the brain's ancient/modern innate immune defense mechanism. AMPs are potent, broad-spectrum, pore-forming agents ~~against~~ targeting Gram-negative and Gram-positive bacteria, enveloped viruses and protozoans (23), thereby supporting the hypothesis that AD has an infectious origin.

Furthermore, the senile plaques ($A\beta_{42}$) are recognized as triggers that stimulate activation of microglial cells and initiate local immune responses (24). Activated microglia are the most important contributors of inflammation in the central nervous system (CNS) (25). They secrete a number of proinflammatory cytokines (24-26) and recognize pattern associated molecular patterns (PAMPs) on bacteria and their cellular debris (27-30) ~~to deal with~~ in response to CNS infection.

The other pathological characteristic of AD is an accumulation of intracellular hyperphosphorylated tau and heat shock proteins constituting the neurofibrillary tangles (NFTs). Hyperphosphorylated tau protein alters the polymerization and stability of microtubules compromising their function (31). NFTs in AD reflect the severity of disease; however, the significance of pathogen-host interaction to the occurrence of NFTs in the AD brain is poorly understood. Current genetic evidence is pointing to aberrant innate immune responses (32, 33) and cholesterol lipid genes (~~see~~ 34) having greater significance in AD pathogenesis. A dysfunctional immune system and predisposition to hyperlipidaemia also support the role of reduced blood flow due to the vascular lesions and inflammation, Aβ deposition and microorganisms in AD.

In advanced AD pathology, synaptic dysfunction is another structural defect associated with a decline in memory (35-37). Although a circular argument, malnutrition plays a role in the gradual loss of synapses and fewer teeth during life is a known risk factor for AD (38).

Neurons are capable of responding to injury by expressing multiple neurotransmitters. In AD, selective loss of cholinergic neurons in the basal forebrain (39) also correlates with the loss of cognitive function (18, 35).

THE AMYLOID CASCADE HYPOTHESIS

Several hypotheses have been ~~launched for~~ advanced regarding the development of AD. The amyloid cascade hypothesis serves as a model particularly for the familial form of AD (40) which is a disease caused by mutations involving the amyloid-β protein precursor, located on chromosome 21 and presenilin 1 and 2 on chromosomes 14 and 1 respectively that enhance the APP gene processing towards Aβ deposition (41, 42). The model, which was first proposed by Glenner and Wong (43), maintains that the neurodegenerative disease is due to an imbalance between the generation and clearance of Aβ. Genome wide association studies (GWAS) highlighted the complement receptor 1 (*CR1*) gene playing a role in AD pathogenesis (44). One recognized role of CR1, a membrane bound regulatory protein, is its ability to bind C3b opsonins (Fig. 2). It is abundantly expressed especially on erythrocyte membranes and as such participates in immune complex clearance by transporting waste to the liver and the spleen. As the *CR1* gene is a risk factor for LOAD, this suggests loss of function as a possibility for the defective clearance of Aβ in the brain. Other tentative explanations suggest variation in CR1 protein isoforms (longer and shorter forms) (45), whereby the longer form is ~~somehow negatively~~ less involved in the disease process via its ability to bind more C3b and facilitate more effective clearance of Aβ in the brain (46). This is a process that inevitably fails favo~~u~~ring disease expression with more Aβ proteostasis buildup and complement pathway activation. The amyloid hypothesis has been modified several times, particularly due to the finding that soluble oligomers of Aβ may contribute to

early preclinical stages of the disease that initiate the cascade leading to synaptic dysfunction, atrophy and neuronal loss (47).

THE INFLAMMATORY HYPOTHESIS

The intrinsic model

Currently there are two models of the inflammatory hypothesis of AD, an intrinsic and an extrinsic. The intrinsic inflammation model accounts for the intact "blood-brain barrier" (BBB) restricting entry of neurotoxic immune molecules and systemic lymphocytes to the brain. As a consequence, the brain glial cells are able to generate a local and complete innate immune system when challenged by foreign agents (26, 48-50). Historically, neuroinflammation has largely been viewed as being a downstream consequence of the amyloid hypothesis, whereby the presence of amyloidogenic peptides result in the activation of microglia initiating pro-inflammatory cascades and the release of potentially neurotoxic substances resulting in degenerative changes in neurons. GWAS now implicates innate immune genes (44, 51) as being a risk factor and supports a primary role for the inflammatory elements of AD pathology via inappropriate activation of the complement system (52-54) in association with Aβ plaques and NFTs (55).

The extrinsic model

The extrinsic model accounts for communication of the glial cells with the immune challenges presented via the blood vascular system using the circumventricular organs and the choroid plexus that are devoid of the BBB (56). The cells from this region of the brain are fully equipped with the CD14 receptor and the toll-like receptor 4 (TLR 4) to ~~recognise~~ recognize the peripheral blood circulation (27, 28). Hence, elements of systemic infections such as those

originating from Gram-negative, highly virulent oral pathogens, bronchopneumonia and urinary tract infections (3, 4, 7, 57, 58) reach all organs including the CNS. ~~The consequences~~ products entering the bloodstream trigger the ~~are that the~~ innate immune responses of ~~hosts'~~ pattern recognition receptors (PPR) and TLRs ~~via pattern recognition receptors (PRR) and~~ infectious threat by secreting ~~to the threat of infection by secreting~~ immune mediators agents. Increased risk of dementia in the elderly following multiple infectious episodes has been reported ~~It is reported that multiple episodes of infections in the elderly likely end up being diagnosed with dementia~~ (4). In addition, systemic infections appear to contribute towards delirium in some clinically diagnosed AD patients and such episodes can exacerbate a premorbid cognitive status (3). Holmes et al. proposed that since cytokines are primary mediators released by the host to defend against infection, such secondary stimuli (IL-1β and TNF-α) may mediate their effect on the brain and indirectly contribute to cognitive decline (3, 57).

NON-ORAL BACTERIA RELATED TO AD

Honjo et al. (59) using Bradford Hill's criteria for assessing the relationship between bacteria and disease found *Chlamydophila pneumoniae* to be a likely infectious agent related to the pathogenesis of AD. Maheshwari and Eslick (60) reported a strong correlation between *C. pneumoniae* and AD, and according to Shima et al. (61) *C. pneumoniae* is currently the most plausible of all infectious agents proposed to be involved in AD. Lim et al. (62) suggested that the pro- and chronic inflammatory states in AD pathogenesis may in part be due to *C. pneumoniae* infection of monocytes. *C. pneumoniae* antibodies from typical intracellular and atypical *C. pneumoniae* antigens have been identified both ~~from typical intracellular and~~ of ~~the~~ brains from AD patients (63). Amyloid deposit and NFTs were detected in the same

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regions in apposition to one another suggesting that *C. pneumoniae* infection is involved in the development of AD pathology.

Using various techniques Balin et al. (9) found *C. pneumoniae* in 80-90% of LOAD brain tissue specimens. *C. pneumoniae* infection was correlated with the *APOEε4* allele expression. The same researchers subsequently demonstrated that astroglia, microglia, neurons, endothelial cells and monocytes in the LOAD brain are permissive to this bacterium. The mechanisms of pathogenesis differ between actively- and persistently-infecting chlamydiae and it is in the persistent state that these organisms cause chronic disease (64, 65). *C. pneumoniae* was cultured from two AD brain samples after one or two passages in HEp-2 cells (66). Interestingly, the study indicated that brain isolates were more related to respiratory than to vascular/atheroma strains of *C. pneumoniae*. This suggested that *C. pneumoniae* infection of the brain was secondary to bronchopneumonia and at the end stages of LOAD.

It has been suggested that the phages phiCPAR39 and phiCPG1, associated with *C. pneumoniae*, may enter mitochondria of the bacterial host and work as slow viruses initiating AD (67). These authors hypothesized that mitochondrial recruitment by *C. pneumoniae* phages may be the primary initiating event in the pathogenesis of neurodegenerative disorders.

In a meta-analysis based on 25 relevant, primarily case-control studies Maheshwari and Eslick (60) found a statistically significant association between AD and detectable evidence of infection caused by *C. pneumoniae* or spirochetes. They reported over a ten-fold increased occurrence of AD when there was evidence of spirochetal infection (OR: 10.61; 95% CI: 3.38-33.29) and over a four-fold increased occurrence of AD with a conservative risk estimate (OR: 4.45; 95% CI: 2.33-8.52). There was a five-fold increase in occurrence of AD with *C. pneumoniae* infection (OR: 5.66; 95% CI: 1.83-17.51). Accordingly, a strongly positive

association between bacterial infection and AD was shown for both types of bacteria, but it was strongest for spirochetes.

It is generally accepted that the syphilis spirochete *Treponema pallidum* can cause chronic neuropsychiatric disorders including dementia as well as other neurodegenerative disorders (11). *T. pallidum* causes brain atrophy and Aβ deposition in the atrophic form of general paresis (68, 69) and is a strong indication for involvement of spirochetes in AD pathogenesis. Chronic diseases such as syphilis are frequently associated with deposition of amyloid (68, 69). ~~Actually, amyloid is considered as~~ Amyloid is an integral ~~part~~ component of spirochetes which may contribute to amyloid deposition in AD (70). ~~Syphilis accumulation of spirochetes~~ Spirochete accumulation in the cerebral cortex in the context of syphilis will also lead to formation of senile plaques, NFTs and granulovacuolar degeneration (71).

Miklossy (68, 69) analyzed data on the ability of spirochetes to induce pathological and biological hallmarks of AD *in vitro* following Koch's and Hill's postulates and demonstrated a plausible causal relationship between neurospirochetosis and AD. The data revealed a statistically significant association between spirochetes and AD (P = 1.5 x 1017, OR = 20, 95% CI = 8-60, N = 247). When mammalian cells were exposed to spirochetes, the pathological and biological hallmarks of AD were reproduced *in vitro* (68, 69). ~~Miklossy (72) also found that historical~~ Historical observations supported the conclusion ~~that~~ that ~~observations paved the way for drawing conclusions such as~~ chronic spirochetal infections can cause dementia and reproduce the neuropathological hallmarks of AD (72). According to Miklossy (72), these observations represent further evidence in support of a causal relationship between various spirochetal infections and AD.

Another spirochete also implicated in AD is~~,~~ *Borrelia burgdorferi*, ~~has also been implicated in AD. This is~~ the causative agent of Lyme disease ~~which is~~ which is transfected to humans via

tick vectors ~~through infected tick bites~~. There are great similarities in the clinical and syphilis and Lyme disease (72, 73). The occurrence of *B. burgdorferi* in the brains of AD patients was first reported by MacDonald and Miranda (74) and was confirmed later by MacDonald (75, 76), Riviere et al. (5) and Miklossy et al. (77). Interestingly, Bu et al. (78) found that the infectious burden consisting of *B. burgdorferi*, *C. pneumoniae*, *Helicobacter pylori*, cytomegalovirus ~~cytomegalo virus~~ and Herpes simplex-1 (HSV-1) is associated with Gutacker et al. (79) and Pappolla et al. (80) found no evidence for an association between *B. burgdorferi* and AD.

Among other bacterial species, *H. pylori* ~~alone~~ (monoinfection) has been found to be related to AD (59). These authors suggested that AD pathology can be initiated and exacerbated by some microorganisms with inflammatory and oxidative responses which may affect the brain continuously and gradually over time. However, the *H. pylori* status ~~did not depend on~~ was not associated with AD in a study from Japan, probably due to the high prevalence of the organism in controls (81). This was refuted by Kountouras et al. (82) who had previously found that successful eradication of *H. pylori* infection was associated with significantly lower mortality risk in AD patients [HR (95% Cl)=0.287 (0.114-0.725), p=0.008] (83).

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ORAL BACTERIA RELATED TO AD

The oral cavity harbo~~u~~rs an impressive range of bacterial phylotypes (84). Molecular identification methods have detected close to 900 different predominant bacterial species of which 35% cannot yet be cultured (85). The oral microbiome profiles appear to be individualized (86), meaning that bacterial microbiomes can vary both qualitatively and quantitatively between individuals, although there are also significant overlaps. Each individual can ~~harbour~~ harbor up to 200 different bacterial taxa in their mouth and there is a

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variation in the microbiota in different oral sites (84, 87). Furthermore, the composition of the oral microbiota irrespective of being indigenous or pathogenic in the oral cavity keeps changing in view of major oral diseases (caries, gingivitis, aggressive and chronic periodontitis, periodontal-endodontic lesions, peri-implantitis and mucositis) (88-94). Particularly plaque-induced oral diseases such as periodontitis are associated with a change in the oral microbiota. There is a predominance of anaerobic bacteria in the oral cavity. Many of the major periodontal microorganisms are anaerobic, e.g., *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*. The abundance of anaerobes tend to increase with the development of plaque-induced oral diseases.

Periodontal bacterial pathogens are related to AD

Major pathogens of chronic periodontitis such as *P. gingivalis*, *T. forsythia*~~,~~ and *T. denticola* are implicated in the development of several inflammatory diseases at remote organ sites. Except for *T. forsythia*, all ~~the above~~ three of the above-named organisms of which *T. denticola* represents a spirochete~~s~~, have been found in the AD brain (5, 8). Spirochetes are strongly neurotropic. They can spread along nerve fibers and via lymphatics (67, 68) and have been detected in the trigeminal nerve and trigeminal ganglia (95). Spirochetes and their antigens as well as DNA have been found associated with AD and are strongly implicated as the causative agents leading to dementia (68, 69). In 14 studies spirochetes were detected in AD by different authors in different laboratories and countries by means of different techniques (for ~~a~~ reviews see Miklossy (68, 69). Riviere et al. (5) demonstrated the presence of seven different oral *Treponema* species in 14 out of 16 AD brain specimens (Fig. 3). Spirochetes were even cultivated from the brains of AD patients indicating that they were viable in the brain (67, 68, 77). Miklossy suggested a co-infection by several spirochetes in

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AD including the oral varieties (*T. socranskii*, *T. pectinovorum, T. denticola, T. medium, T. amylovorum* and *T. maltophilum*) as demonstrated by Riviere et al. (5). Spirochetes reproduced the biological and pathological hallmarks of AD after exposure of mammalian neuronal and glial cells in organotypic cultures (68, 69).

It ~~has been~~ was demonstrated that LPS from periodontal bacteria can access the AD brain during life ~~as~~ while detection in corresponding controls, with equivalent or longer postmortem interval was absent (8). This study supports the literature on elevated antibodies to periodontal disease-associated bacteria such as *P. gingivalis*, being found in AD patients (7). Furthermore, in 2,355 people 60 years and over, the third NHANES study found associations between periodontitis and cognitive impairment and between measures of immunoglobulin to *P. gingivalis* and cognitive test performance (96, 97) ~~used cohort methodology analyzing serum levels of antibodies to periodontal disease~~. ~~All~~ In this study all participants were cognitively intact at baseline. Those who went on to develop AD had higher levels of serum antibodies to periodontal pathogens at baseline. ~~This~~ The study ~~sugggested~~ suggested a temporal periodontal disease came before AD.

Other important periodontal pathogens related to AD are *Fusobacterium nucleatum* and *Prevotella intermedia*. In the NHANES study antibody ~~Antibody~~ levels to these organisms were significantly increased ($\alpha = 0.05$) at baseline serum in patients with AD compared to controls (97). The results were significant after controlling for baseline age, Mini-Mental State Examination score, and allele *APOEε4* status. Noble et al. (98) found that a high anti-*Actinomyces naeslundii* titer (> 640 ng/ml, present in 10% of the subjects) was associated with increased risk of AD (HR=2.0, 95% CI: 1.1-3.8). This association was stronger after adjusting for other significant titers (HR=3.1, 95%CI: 1.5-6.4) and confirmed that periodontal pathogens ~~can~~ may be associated with AD.

Possible consequences to the brain ~~of~~ carrying oral bacterial pathogens

The fact that inflammation is sustained in the AD brain suggests that local immunogenic hallmark proteins and/or peripheral infections are key perpetrators. This is supported by reports highlighting microorganisms and their toxic products as well as DNA in brain tissue of AD patients and experimental animals (see ~~later~~ below). Bacteria activate pathways that include the integrin receptor CR3 (CD11b/CD18) and TLR signalling (99) and the complement cascade (100). The NF-κB signalling pathway for cyto/chemokine release (TNF-α, IL-8) (101) produces free radicals, nitric oxide triggers and apoptosis (102). The oral cavity, lungs and gastrointestinal and urinary tracts are plausible sources of brain microorganisms. The likely passage of the microorganisms of interest from their original sites to the brain is described below.

Infections with spirochetes can cause cerebral hypoperfusion (103), cerebrovascular lesions and a severely disturbed capillary network (68, 69). Chronic spirochetal infections can also induce slowly progressive dementia, cortical atrophy, chronic inflammation and Aβ deposition, ~~which cannot be distinguished~~ indistinguishable from that occurring in AD brains (for reviews see 68, 69, 72). Furthermore, cultured neuronal cells exposed to spirochetes produce Aβ (104). Spirochetes are also able to form plaque-, tangle- and curly fiber-like lesions (72, 105). They induce a latent and slowly progressive infection by evading host defenses. This promotes their survivial and proliferation in the brain by blocking the complement cascade. Spirochetes may even survive and proliferate in hosts that are immune-competent. ~~By evading host's defenses, spirochetes induce a latent and slowly progressive infection to promote their survival and proliferation in the brain and by blocking the complement cascade spirochetes may survive and proliferate even in hosts that are immuno-competent.~~ Interestingly, the remarkable ability of *T. pallidum* to evade clearance from the

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immune system has earned it the designation “stealth pathogen” (106). ~~Also an~~The activated complement cascade ~~can be seen~~ following spirochete infections (11) ~~which~~ may be used as a non-specific marker of CNS inflammation. Spirochete-host interactions initiate and sustain chronic inflammation triggering various immune responses that activate ~~and end up with various immune responses activating~~ the innate and adaptive immune system, free radical~~s~~ production, apoptosis and amyloid deposition typically seen in AD brains (107).

P. gingivalis has been designated as one of the “keystone” periodontal pathogens because it is able to establish and maintain the periodontal disease-associated “inflammophillic” microbiota (108). It is able to perform this task as it possesses an awesome variety of virulence factors, recently reviewed by Singhrao et al. (109), to evade the host immune defenses, thus serving two major functions: initial~~ly for~~ survival of *P. gingivalis* itself via a sustainable inflammatory milieu and ~~then to satisfy its~~ sustainment of nutritional sources by eliminating microbial competitors ~~needs and to stamp out competition~~ (108).

The *P. gingivalis* endotoxin LPS demonstrates differences in the number of phosphate groups together with both the amount of lipid A fatty acids and their specific position. The presence of multiple lipid A structures makes it more difficult for the innate host responses to ~~recognise~~ recognize the molecule thereby aiding the virulence of *P. gingivalis* (110). The consequences of finding *P. gingivalis* LPS in the host’s body, e.g. the brain (8), ~~are~~ include priming of cells for differential activation of the TLR-mediated NF-κB signalling pathway (111) leading to cytokine liberation, complement activation and maintenance of intracerebral inflammation.

P. gingivalis evades circulating phagocytes by adhering to erythrocytes (112). An active invasion of *P. gingivalis* and infection-induced complement activation with bystander neural injury was detected in the brains of $ApoE^{-/-}$ mice (113). This supported previous notions that bacterial infections can contribute to the development of AD pathology via mechanisms

involving acute phase proteins such as cytokines and the complement cascade where neurons would be attacked.

ORAL VIRUS RELATED TO AD

Herpes simplex virus (HSV) is present in more than 70% of the population after 50 years age (114-116). It persists latently in the peripheral nervous system and is periodically reactivated. Characteristically, HSV-1 has been designated as the enemy within (10). Herpes viruses, including Epstein-Barr virus and cytomegalo-virus, are found in high copy counts in aggressive periodontitis, and may interact synergistically with periodontopathic bacteria in the pathogenesis of this disease (117). Periodontal infections activated by Herpes virus ~~Herpes virus active periodontal infections~~ may impair local host defenses and thus increase the aggressiveness of resident periodontopathic bacteria. The bacteria, in turn, may augment the virulence of the herpes viruses.

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High proportions of viral-associated proteins in amyloid-containing plaques and/or NFTs corroborate with the involvement of HSV-1 in AD pathology (118). ~~This supports a study by~~ Notably, De Chiara et al. (119) ~~who found~~ reported an association between Aβ accumulation in the brain and HSV infection. Itzhaki et al. (120) suggested that not only does HSV-1 produce the main components of amyloid plaques and NFTs (i.e. Aβ and hyperphosphorylated tau), but it also interferes with the autophagic events that prevent degradation of these proteins and eventually leading to their accumulation in the AD brain. Further, *in vitro* and *in vivo* investigations ~~using mouse~~ in murine models following HSV-1 demonstrated Aβ accumulation (121).

A number of scientists have suggested that there is imbalance between production and clearance of β-amyloid in the brain, a ~~thought~~ premise first proposed by Wisniewski et al.

on the discovery of soluble species of this protein and later confirmed by Zlokovic et al. (123) (123) ~~to be the case~~. ~~Thus it~~ It is now widely accepted that defective clearance of this protein brains ~~that leads~~ leading to its accumulation in the form of insoluble $A\beta_{40/42}$ plaques. and cytomegalovirus have been detected in the brains of older adults with and without AD (124-126), HSV-1 viral DNA is present in a higher proportion of AD patients (127). It is particularly seen in the temporal and frontal cortices which are the brain regions that are most damaged in AD (128, 129). The relevance of this association is still under investigation; however a plausible role for the HSV-1 viral DNA could be ~~in~~ associated with the plaque maturation process. Jamieson et al. (127) found that the virus was absent from the brains of most young people, probably because it enters the brain during old age either ~~when the~~ senescence (130) or the virus itself is initially responsible for weakening the host's immune defenses ~~first~~. This latter explanation is likely and is supported by us and others (131).

HSV-1 is a strong risk factor for AD in the brains of those with the *APOEε4* allele (125, 132). This virus is not only a dormant passenger but can persist in the latent form in neurons or replicate at a very low level in neuroglia (133). During persistence it may release toxic products continuously and induce pro-inflammatory cytokines at low levels which become an additional burden to ~~the~~ a host ~~who is~~ already challenged by age, poor diet, ~~failing~~ restricted exercise as well as any genetic susceptibilities. Itzaki and Wozniak (10) suggested that stress or peripheral infection can reactivate the virus periodically from latency in the brain. This may cause an acute but presumably localized infection, and subsequent damage modulated by the *APOε* gene can lead to formation of Aβ plaques and NFTs.

The presence of anti-HSV IgM, a sign of reactivated infection, almost doubled the risk for AD while anti-HSV IgG did not influence the risk (134). Kobayashi et al. (135) suggested that the anti-HSV-1 Ig antibody avidity index could be a useful biomarker for early diagnosis of

anamnestic mild cognitive impairment, which is prodromal to AD, as well as for AD sufferers.

Reactivation of HSV seropositivity is highly correlated with incident-AD (136). Letenneur et al. (136) speculated that AD pathology starts many years before frank dementia and recurrent reactivation of HSV can act as a potent stimulus to brain microglia, increasing cytokine levels, and triggering a positive feedback cycle leading to increasing accumulation of neurohistopathological changes. In other words, infection, followed by local CNS inflammatory reaction is the likely primary ~~occurrence~~ stimulus wheras proteostasis is a consequence of the primary event leading to the development of AD.

Hill et al. (137) suggested a role for HSV-1-induced miRNA-146a in the evasion of HSV-1 from the complement system~~. which This~~ which is a major first-line host defense mechanism, and the activation of key elements in the arachidonic acid cascade known to contribute to AD-type neuropathological changes.

ORAL YEASTS RELATED TO AD

Oral yeast infection ~~is~~ represents a secondary opportunistic infection ~~disease of the diseased where~~ particularly involving *Candida albicans*, but increasingly ~~also~~ non-*albicans* species, e.g. *Candida glabrata* ~~are involved~~. With a growing population of elderly, severe systemic fungal infections have increased dramatically in this age group during the last 30 years (138, 139). Oral yeasts can be found in periodontal pockets, in root canals, on the mucosae and underneath dentures (denture stomatitis) (140-142). Denture stomatitis is prevalent in elderly wearing dentures that are heavily contaminated with yeasts which can be a source of systemic mycosis ~~(Fig. 3)~~. Disseminated mycoses have recently been reported in AD patients (143,

144). Fungal molecules including proteins and polysaccharides [(1,3)-β-glucan] were detected in peripheral blood serum, and fungal proteins and DNA were demonstrated by PCR in brain tissue of AD patients. ~~Also chitin~~Chitin-like fungal structures have also been found in the AD brain (145) and chitinase activity has been proposed as a powerful biomarker of AD (146). ~~Immunohistochemical analyses revealed, albeit in a few cells, in~~ In AD brains~~,~~, ~~containing~~ cytoplasmic material in a small number of ~~cell~~ cells ~~were~~ was targeted by antibodies with immunoreactivity to ~~that immunoreacted with antibodies raised against some~~ yeast cells (147). These findings were consistent with the idea that neurons can be infected by fungi. Interestingly, antifungal treatment reversed the clinical symptoms of some AD patients (148, 149).

HOW DO ORAL MICROORGANISMS REACH THE BRAIN?

Blood stream dissemination

The most likely pathway ~~of~~ for dissemination ~~for~~ of oral microorganisms to the brain is through the blood stream (150). Dental treatment ~~procedures~~ as well as brushing, flossing, chewing and use of tooth picks in a patient with periodontitis will release a bacteraemia (151). This can occur several times during the day and has been estimated to last for up to 3 hours for oral bacteria (152). The bacteraemia is usually ~~taken care of~~ contained by immune cells of the body. However, in people with reduced immune defense, e.g. older individuals, bacteria may ~~settle down within~~ localize to crevices of the oral cavity and vascular channels (150).

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Commented [PB10]: also in the general population. Although not on a regular basis, tooth extraction provides a huge bolus of bacteria.

The blood- brain barrier

An intact blood-brain barrier (BBB) prevents microorganisms in the blood from accessing the brain. However, aging favors overgrowth of oral microorganisms, particularly anaerobic bacteria and facultative yeasts that established earlier in life and provoked pro-inflammatory

responses that weakened the BBB (16). ~~Actually~~Notably, magnetic resonance imaging (MRI) confirmed loss of BBB integrity in a mouse model of disseminated candidosis (153). Loss of integrity allows microorganisms to spread through the blood stream and quietly contribute in the pathogenesis of AD. During immunosenescence, the innate immune system gradually takes over for the acquired immune system. This contributes to a rise in circulating proinflammatory cytokines such as TNF-α (16). Indeed, proinflammatory mediators can cross the BBB (3, 7, 154). *APOEε4*, TNF-α and perhaps Ephrin Type-A Receptor 1 (EphA1) may influence BBB integrity and thus be important for penetration of bacteria, LPS and other toxic bacterial products as well as yeasts into the brains of AD patients (16). *APOEε4* affects the integrity of the BBB by activating the cyclophilin A matrix metalloproteinase MM-9 pathway (155).

It is also plausible to suggest that the permeability of the BBB increases with age and thus promotes AD pathogenesis making the brain accessible to microorganisms. Mice with a mutation in the amyloid precursor protein gene which is related to early-onset AD in man, showed increased permeability of the BBB and increased formation of senile plaque as compared to control mice (156). The changes increased with age.

Circumventricular organs and perivascular spaces

Circumventricular organs (permit polypeptide hypothalamic hormones to leave the brain without disrupting the BBB) are not dependent on the BBB (56) and may act as another entry portal to the brain for bacteria (157). Poole et al. (8) postulated that bacteria and their products may also directly access the brain via the systemic circulation through the perivascular spaces.

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The olfactory hypothesis

The "olfactory hypothesis" suggests the olfactory tract as a potential route for pathogenic bacteria to enter the brain and thereby trigger the production of Aβ and NFTs (158). The olfactory and trigeminal nerves are known to be used by periodontal pathogens to bypass the BBB for direct passage to the CNS (5, 150, 159, 160). Identification of oral treponemes in the trigeminal ganglia supports such a route of dissemination (5). Further, s~~S~~pirochetes may ~~also~~ spread along the fila olfactoria and tractus olfactorius (68, 69).

Olfactory unsheathing cells (OECs) engulf bacteria and migrate towards TNF-α released by activated astrocytes (161). Therefore, OECs could be a vehicle for transporting live bacteria to the brain (i.e., Trojan horse). The olfactory bulb was the first area where NFTs and Aβ deposition were detected in the neuropathological trajectory of AD in humans (162) and in mouse models of AD (163).

GENETIC, NUTRITIONAL AND ENVIRONMENTAL FACTORS PROMOTING AD

While early-onset AD is genetically determined, LOAD is thought to result from interaction between genetic and environmental factors (12). Several mutated genes are associated with the familial AD, such as the amyloid beta (Aβ) precursor protein (*AβPP*) gene and the presenelin-1 (*PSEN-1*) and *PSEN-2* gene (164-166). A major risk factor for LOAD is polymorphism in the *APOε4* allele (2). Also cytokine-related genes seem to be involved in the susceptibility to inflammation in both LOAD (167, 168) and periodontitis (169-171). Thus, polymorphisms that increase TNF-α also increase the risk of both AD and periodontitis (172, 173). Lambert et al. (174) found that 20 different loci can increase host susceptibility to AD including polymorphisms in genes associated with interleukin-1 (IL-1) (71, 175-178) and TNFα (71, 172, 179-181). The *APOε4* gene which is one of these 20 loci is highly correlated

with AD (182) but it is also a risk factor for infection and increases the expression of inflammatory mediators (11). Recently, genetic overlap between AD, C-reactive protein (CRP) and plasma lipids was demonstrated by using summary statistics from GWAS of over 200,000 individuals (183). There may also be interplay between genetic risk and environmental risk factors such as toxins and or bacterial, viral and fungal pathogens in LOAD reflecting its complex and multifactorial etiology (1).

Diet with its content of essential B-vitamins, phospholipids and other micronutrients are important for forming new nerve synapses (184). Nutritional deficiencies are common both in elderly and in dementia subjects as briefly discussed by Singhrao et al. (150).

ASSOCIATION BETWEEN CHRONIC PERIODONTAL DISEASE AND AD

There is increasing evidence for an association between chronic periodontitis and LOAD (185). Cross-sectional and longitudinal studies have demonstrated that gingival bleeding, loss of periodontal attachment, periodontal probing depth, alveolar bone loss and antibodies to periodontal pathogens are significantly associated with lower cognitive function and decline after adjustment for co-variates (for a review see (12)). Acute phase proteins, including cytokines are possible indirect links between periodontal pathogens and/or their virulence factors (12, 13). Elderly often show neglect of oral hygiene ~~(Figs. 3-5)~~ which can stimulate recurrent chronic oral infection (150). This again promotes inflammation which can lead to confusion and dementia (3, 4, 154). In 152 subjects 50-70 years of age who were followed for 20 years, greater levels of periodontal inflammation correlated with lower cognitive levels (186). Furthermore, gingival bleeding and loss of periodontal attachment ~~apparatus~~ were associated with cognitive impairment in a cohort of 5,138 people aged 20-59 years (187). In 144 nuns, those ~~with~~ encoding *APOEε4* and who had fewer teeth ~~had~~ experienced more rapid

decline than those with neither or either of these risk factors (188). Clinical and epidemiological studies showed that loss of teeth is associated with poor memory (6, 96, 187, 189). In another study ~~with~~ of 597 community dwelling men followed for 32 years, tooth loss, increasing periodontal pocket~~s~~ depths and progression of alveolar bone loss were associated with impaired cognition particularly in those over 45 years of age (190). Recently, de Souza Rolim et al. (191) found that periodontal infections were more frequent in patients with mild AD than in healthy subjects. Another interesting feature related to the pathogenesis of AD is the low level of infection by "commensals on the loose" (16). These "immuno-tolerated" bacteria may silently multiply in sites outside of their primary niche and an ongoing ~~illness~~ at their secondary location may have significant deleterious effects upon the health of the elderly or demented host with an existing immunocompromised status.

PUTATIVE TREATMENT AND PROPHYLAXIS OF AD

There is no effective treatment or prophylaxis yet for AD, but several approaches have been proposed. Efforts in this respect are important. If we could delay onset of dementia by only 2 years we might lower the prevalence of AD by more than 22 million cases over the next 40 years (14). ~~Indeed, delaying the disease process is a better option as the~~ ~~Notably~~Notably, the of the *APOEε4* allele in the very old (90+) age group, appears to confer protection (192), having bypassed a period of being at risk around 85+ years of age.

If periodontal disease is implicated in AD, periodontitis prophylaxis ~~should be feasible~~ could be of help. It would be interesting to see if this has any effect on the initiation and aggravation of AD but an observation period of decennia is probably needed.

In a study of subjects with mild to moderate AD, a ~~A~~ 3-month course of doxycycline and rifampicin reduced cognitive deterioration ~~in~~ during a 6 months' ~~follow up~~follow-up interval

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~~study in~~ ~~subjects with mild to moderate AD~~ (193). It was concluded that use of antibacterial the treatment of *C. pneumoniae* but had a beneficial effect on cognitive decline in AD (193). This might be related to prevention or attenuation of a number of peripheral infections or dampening down the proinflammatory cytokine response. ~~Minicycline~~Minocycline was found early, pre-plaque neuroinflammation and inhibit the APP cleaving enzyme 1 (BACE-1) in a transgenic model of Alzheimer's disease-like amyloid pathology (194). It was suggested that interfering with inflammation could be a useful therapeutic approach in early, pre-plaque stages of AD-like amyloid pathology.

Anti-inflammatory drugs given for at least 2 years before the onset of dementia delayed the disease process (~~194~~195-~~196~~197). It may also be beneficial to combine anti-inflammatory antibacterials (193). Examination of several available Non-steroidal Anti-Inflammatory Drugs (NSAIDs) showed that only a few of them had any useful Aβ-modifying or other activity of therapeutic use in LOAD (for a review see (1)).

Itzhaki and Wozniak (10, ~~197~~198) suggested that antiviral therapy and perhaps vaccination against HSV-1 in early life could be useful. If HSV-1 is implicated in AD, vaccination could prevent the excessive accumulation of Aβ in the brain. Vaccination with mixed HSV glycoproteins prior to HSV infection protected against viral latency in mouse brains (~~198~~199). Also Mori (~~199~~200) maintained that antiviral approaches including chemotherapy and vaccination are promising for prevention and treatment of AD and remain to be validated. Furthermore, Carter (118) suggested that vaccination or antiviral agents and immune suppressants may be considered as therapeutic options before or ~~in~~ during the early stages of AD. Interestingly, exposure of HSV-1-infected cell cultures to intravenous immunoglobulin acting via anti-β-amyloid ~~antibodies,~~antibodies reduced the accumulation of Aβ and phosphorylated tau (~~200~~201).

Angiotensin-converting enzyme (ACE) from *Stigmatella aurantiaca* may cleave the Aβ peptide similar to human ACE and may be used as a novel form of treatment against AD (~~201~~202). Furthermore, Chiarini et al. (~~202~~203) maintained that calcilytics could halt AD progression and preserve the patients' cortical neurons, cognitive abilities, and eventually life if given at minimal cognitive impairment or at earlier stages. Studies ~~from~~ using mice suggested the use of tau aggregation inhibitors as potential drugs for the treatment of AD and other tauopathies (~~203~~204).

Resveratrol is a polyphenol present in red wine. Its capability of directly interfering with the toxic β-amyloid protein aggregation in AD has recently been shown (~~204~~205). Resveratrol was found to reduce Aβ-induced toxicity in a *Caenorhabditis elegans* model of AD by targeting specific proteins involved in proteostasis and thereby reducing the amount of aggregated Aβ (~~205~~206). This is in concert with our previous finding that the effect of a drinking pattern of 2-7 times per week reduced the risk of myocardial infarction among men who had a history of tooth extractions due to periodontal/dental infection (~~206~~207).

Potent inhibitors of Aβ oligomer formation or Aβ-induced cell toxicity have proven to be attractive means for therapeutic intervention of AD. Song et al. (~~207~~208) found that the anti-Alzheimer effects of centipedegrass, which contains several C-glycosyl flavone constituents, occurred through inhibition of neuronal cell death by intervening with oligomeric Aβ formation and reducing beta-site amyloid precursor protein cleaving enzyme 1 ~~(BACE1)~~ activity. The authors suggested that Maysin, a major flavonoid of corn silk, in centipedegrass could be an excellent therapeutic candidate for the prevention of AD.

Active immunization against important domains of Alzheimer tau eliminated tau aggregation and neurofibrillary pathology (~~208~~209). The AD type of tau hyperphosphorylation was abolished in transgenic mice by vaccination across a wide range of AD phospho-epitopes.

Kontsekova et al. (~~208~~209) demonstrated that active immunization of rats with a tau peptide encompassing the epitope revealed by monoclonal antibody DC8E8 led to elimination of all major hallmarks of neurofibrillary pathology involving a 95% reduction in the AD-type hyperphosphorylation of tau.

CONCLUSIONS

LOAD which is the predominant form of AD, does not seem to have a single cause. On the contrary, a multitude of factors may be involved and they may act in concert. ~~Of these~~Among others ~~,~~ both genetic and environmental factors may be involved. Even among co~~operation ,action~~ may occur since the brain can hardly differentiate between different microbial insults which collectively contribute capacity for enhancing ~~all end up in~~ Irrespective of the cause, systemic inflammation may predict the onset of dementia. Organisms such as spirochetes, *P. gingivalis*, *C. pneumoniae*, *H. pylori*, H~~h~~erpes simplex type virus and *Candida* are among the prime candidate pathogens ~~the most suspected pathogens~~ in events causing AD, oral microorganisms may play a role, particularly anaerobic bacteria such as treponemes, *P. gingivalis*, *Prevotella* spp., *Fusobacterium* and *Actinomyces*, but also facultative anaerobic *Candida* species. It is important to recognize that infection can occur decades before the manifestation of dementia. The most convincing evidence for a causal relationship between oral bacteria and AD is ~~that~~ noted for spirochetes which are both neurotropic and motile. ~~They also fulfill Koch's and Hill's postulates for a causal relationship.~~ It is likely that oral infection can be a risk factor for Alzheimer's disease but it is not the only one. Experiments in humans ~~*in vivo*~~ may require long exposure time~~s~~ to disclose key events and mechanisms of AD. There is, as yet, no cure for AD despite concerted efforts and investment by industry.~~and this is not without concerted efforts from investment by industry but because drug discovery in dementia is hugely challenging.~~ Prevention of AD through

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long-term use of antibiotics may be impractical and could select for resistant bacteria. This is worrisome as the prevalence of AD and the public expenses related to its management are expected to increase greatly in the next decade.

in AD, ~~then~~ dental hygiene and treatment will provide the AD prophylaxis from an early age ~~this oral disease~~ periodontitis is modifiable. However, improving oral hygiene and treating in the AD patient can be challenging since patients are often uncooperative.~~-~~ There is also for training care-givers to assist with oral care in such patients.

Vaccination against key organisms and important domains of AD has had some beneficial effect. Also several agents interfering directly with the pathogenesis of AD have been tested. In order to find a cure, there is a need for clinical diagnostic information and knowledge of the causal agents for AD ~~AD causative agents~~ so that specific treatment options targeting these organisms~~, against these organisms,~~ can be developed. As for diagnostic biomarkers, increased antibody levels to specific oral pathogens in particular to *P. gingivalis* may be used as a ~~preventive~~ monitoring tool years before clinical manifestation of AD. This is important because treatment will probably have to start early.

ACKNOWLEDGEMENT~~S~~

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I.O. wants to acknowledge funding through the European Commission (FP7-HEALTH-306029 'TRIGGER'). ~~and Steinar Stølen for help with scanning electron microscopy.~~

CONFLICT OF INTEREST AND FUNDING

There is no conflict of interest in the present study for any of the authors. Funding was as given under Acknowledgement.

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REFERENCES

1. Balin BJ, Hudson AP. Etiology and pathogenesis of late-onset Alzheimer's disease. Curr Allergy Asthma Rep 2014; 14: 417. doi 10.1007/s11882-013-0417-1.
2. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993; 261: 921-3.
3. Holmes C, El-Okl M, Williams AL, Cunningham C, Wilcockson D, Perry VH. Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2003; 74: 788-9.
4. Dunn N, Mullee M, Perry VH, Holmes C. Association between dementia and infectious disease: evidence from a case-control study. Alzheimer Dis Assoc Discord 2005; 19: 91-4.
5. Riviere GR, Riviere KH, Smith KS. Molecular and immunological evidence of oral *Treponema* in the human brain and their association with Alzheimer's disease. Oral Microbiol Immunol 2002; 17: 113-8.
6. Stein PS, Desrosiers M, Donegan SJ, Yepes JF, Kryscio RJ. Tooth loss, dementia and neuropathy in the NUN study. J Am Dent Assoc 2007; 138: 1314-22; quiz 1381-2.
7. Kamer AR, Craig RG, Pirraglia E, Dasanayake AP, Norman RG, Boylan RJ, et al. TNF-α and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. J Neuroimmunol 2009; 216: 92-7.
8. Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. J Alzheimers Dis 2013; 36: 665-77. doi: 10.3233/JAD-121918.

669 9. Balin BJ, Little CS, Hammond CJ, Appelt DM, Whittum-Hudson JA, Gérard HC, et al.
670 *Chlamydophila penumoniae* and the etiology of late-onset Alzheimer's disease. J
671 Alzheimer's Dis 2008; 371-80.
672 10. Itzhaki RF, Wozniak MA. Herpes simplex virus type 1 in Alzheimer's disease: the
673 enemy within. J Alzheimer's Dis 2008; 13: 393-405.
674 11. Miklossy J. Chronic inflammation and amyloidogenesis in Alzheimer's disease – role of
675 spirochetes. J Alzheimer's Dis 2008; 13: 381-91.
676 12. Kamer AR, Dasanayake AP, Craig RG, Glodzik-Sobanska L, Bry M, de Leon MJ.
677 Alzheimer's disease and peripheral infections: the possible contribution from
678 periodontal infections, model and hypothesis. J Alzheimer's Dis 2008; 13: 437-49.
679 13. Watts A, Crimmins EM, Gatz M. Inflammation as a potential mediator for the
680 association between periodontal disease and Alzheimer's disease. Neuropsychiatr Dis
681 Treat 2008; 4: 865-76.
682 14. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global
683 burden of Alzheimer's disease. Alzheimers Dement 2007; 3: 186-91.
684 15. Ouerfurth HW, LaFerla FM. Alzheimer's disease. New Engl J Med 2010; 362: 329-44.
685 16. Shoemark DK, Allen SJ. The microbiome and disease: reviewing the links between the
686 oral microbiome, aging and Alzheimer's disease. J Alzheimer's Disease 2015; 43: 725-
687 38.
688 17. Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. All Z Psychiat 1907; 64:
689 146-8.
690 18. Selkoe DJ. Alzheimer's disease. Cold Spring Harb Perspect Biol 2011; 2011; 3. pii:
691 a004457. doi: 10.1101/cshperspect.a004457.

19. Yankner BA, Dawes LR, Fisher S, Villa-Komaroff L, Oster-Granite ML, Neve RL. Neurotoxicity of a fragment of the amyloid precursor associated with Alzheimer's disease. Science 1989; 245: 417-20.
20. Deshpande A, Mina E, Glabe C, Busciglio J. Different conformations of amyloid beta induce neurotoxicity by distinct mechanisms in human cortical neurons. J Neurosci 2006; 26: 6011-8.
21. Glabe CC. Amyloid accumulation and pathogenesis of Alzheimer's disease: significance of monomeric, oligomeric and fibrillar Abeta. Subcell Biochem 2005; 38: 167-77.
22. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, et al. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med 2008; 14: 837-42. doi: 10.1038/nm1782.
23. Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, et al. The Alzheimer’s disease-associated amyloid beta-protein is an antimicrobial peptide. PloS One 2010; 5, e9505. doi: 10.1371/journal.pone.0009505.
24. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. Neurobiol Aging 2000; 21: 383-421.
25. Perry VH, Nicoll JA, Holmes C. Microglia in neurodegenerative disease. Nat Rev Neurol 2010; 6: 193-201. doi: 10.1038/nrneurol.2010.17.
26. Hanisch UK. Microglia as a source and target of cytokines. Glia 2002; 40: 140-55.
27. Lacroix S, Feinstein D, Rivest S. The bacterial endotoxin lipopolysaccharide has the ability to target the brain in upregulating its membrane CD14 receptor within specific cellular populations. Brain Pathol 1998; 8: 625-40.
28. Laflamme N, Rivest S. Toll-like receptor 4: the missing link of the cerebral innate immune response triggered by circulating gram-negative bacterial cell wall components. FASEB J 2001; 15: 155-63.

717 29. Beutler B, Hoebe K, Du X, Ulevitch RJ. How we detect microbes and respond to them:
718 the Toll-like receptors and their transducers. J Leukoc Biol 2003; 74: 479-85.
719 30. Rivest S. Regulation of innate immune responses in the brain. Nat Rev Immunol 2009;
720 9: 429-39. doi: 10.1038/nri2565.
721 31. Iqbal K, Grue-Iqbal I. Ubiquitination and abnormal phosphorylation of paired helical
722 filaments in Alzheimer's disease. Mol Neurobiol 1991; 5: 399-410.
723 32. Malpass K. Alzheimer disease: functional dissection of CD33 locus implicates innate
724 immune response in Alzheimer disease pathology. Nat Rev Neurol 2013; 9: 360. doi:
725 10.1038/nrneurol.2013.119.
726 33. Shulman JM, Chen K, Keenan BT, Chibnik LB, Fleisher A, Thiyyagura P, et al. Genetic
727 susceptibility for Alzheimer disease neuritic plaque pathology. JAMA Neurol
728 2013 1;70: 1150-7. doi: 10.1001/jamaneurol.2013.2815.
729 34. Guerreiro RJ, Hardy J. Alzheimer's disease genetics: lessons to improve disease
730 modelling. Biochem Soc Trans 2011; 39:910-6. doi: 10.1042/BST0390910.
731 35. Terry RD. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is
732 the major correlate of cognitive impairment. Ann Neurol 1991; 30: 572-80.
733 36. Masliah E, Mallory M, Hansen L, Alford M, Albright T, DeTeresa R, et al. Patterns of
734 aberrant sprouting in Alzheimer's disease. Neuron 1991; 6: 729-39.
735 37. Masliah E, Mallory M, Hansen L, DeTeresa R, Terry RD. Quantitative synaptic
736 alterations in the human neocortex during normal aging. Neurology 1993; 43: 192-7.
737 38. Kondo K, Niino M, Shido K. A case-control study of Alzheimer's disease in Japan--
738 significance of life-styles. Dementia 1994; 5: 314-26.
739 39. Bartus RT, Dean RL 3rd, Beer B, Lippa AS. The cholinergic hypothesis of geriatric
740 memory dysfunction. Science 1982; 217: 408-14.

741 40. Demetrius LA, Magistretti PJ, Pellerin L. Alzheimer's disease: the amyloid hypothesis
742 and the Inverse Warburg effect. Front Physiol 2015; 5:522. doi:
743 10.3389/fphys.2014.00522.
744 41. Tanzi RE, Watkins PC, Stewart GD, Wexler NS, Gusella JF, Haines JL. A genetic
745 linkage map of human chromosome 21: analysis of recombination as a function of sex
746 and age. Am J Hum Genet 1992; 50: 551-8.
747 42. Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, et al. Secreted amyloid
748 beta-protein similar to that in the senile plaques of Alzheimer's disease is increased *in*
749 *vivo* by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease.
750 Nat Med 1996; 2:864-70.
751 43. Glenner GG, Wong CW. Alzheimer's disease and Down's syndrome: sharing of a unique
752 cerebrovascular amyloid fibril protein. Biochem Biophys Res Commun 1984; 122:
753 1131–5.
754 44. Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, et al. Genome-wide
755 association study identifies variants at CLU and CR1 associated with Alzheimer's
756 disease. Nat Genet 2009; 41: 1094-9. doi: 10.1038/ng.439.
757 45. Thambisetty M, An Y, Nalls M, Sojkova J, Swaminathan S, Zhou Y, et al. Effect of
758 complement CR1 on brain amyloid burden during aging and its modification by APOE
759 genotype. Biol Psychiatry 2013; 73: 422-8. doi: 10.1016/j.biopsych.2012.08.015.
760 46. Killick R, Hughes TR, Morgan BP, Lovestone S. Deletion of Crry, the murine ortholog
761 of the sporadic Alzheimer's disease risk gene CR1, impacts tau phosphorylation and
762 brain CFH. Neurosci Lett 2013; 533: 96-9. doi: 10.1016/j.neulet.2012.11.008.
763 47. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al.
764 Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade.
765 Lancet Neurol 2010; 9: 119-28. doi: 10.1016/S1474-4422(09)70299-6.

766 48. Morgan BP, Gasque P. Expression of complement in the brain: role in health and
767 disease. Immunol Today 1996; 17: 461-6.
768 49. Benveniste EN. Cytokine actions in the central nervous system. Cytokine Growth Factor
769 Rev 1998; 9: 259-75.
770 50. Gasque P. Complement: a unique innate immune sensor for danger signals. Mol
771 Immunol 2004; 41: 1089-98.
772 51. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, et al.
773 Genome-wide association study identifies variants at CLU and PICALM associated with
774 Alzheimer's disease. Nat Genet 2009; 41: 1088-93. doi: 10.1038/ng.440. Erratum in: Nat
775 Genet 2009; 41: 1156. Nat Genet 2013; 45: 712. Haun, Reinhard [added].
776 52. Eikelenboom P, Stam FC. Immunoglobulins and complement factors in senile plaques.
777 An immunoperoxidase study. Acta Neuropathol 1982; 57: 239-42.
778 53. McGeer PL, Akiyama H, Itagaki S, McGeer EG. Activation of the classical complement
779 pathway in brain tissue of Alzheimer patients. Neurosci Lett 1989; 107: 341-6.
780 54. Rogers J, Cooper NR, Webster S, Schultz J, McGeer PL, Styren SD, et al. Complement
781 activation by beta-amyloid in Alzheimer disease. Proc Natl Acad Sci U S A 1992; 89:
782 10016-20.
783 55. Shen Y, Lue L, Yang L, Roher A, Kuo Y, Strohmeyer R, et al. Complement activation
784 by neurofibrillary tangles in Alzheimer's disease. Neurosci Lett 2001; 305: 165-8.
785 56. Oldfield BJ, Mckinley MJ. Circumventricular organs. In The Rat Nervous System.
786 Paxinos G, ed. Academic Press, San Diego 1995, pp 391-403.
787 57. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, et al. Systemic
788 inflammation and disease progression in Alzheimer disease. Neurology 2009; 73: 768-
789 74. doi: 10.1212/WNL.0b013e3181b6bb95.

790 58. de Oliveira JM, Lisboa Lde B. Hospital-acquired infections due to gram-negative
791 bacteria. N Engl J Med 2010; 363: 1482-3; author reply 1483-4.
792 59. Honjo K, van Reekum R, Verhoeff NPLG. Alzheimer's disease and infection: Do
793 infectious agents contribute to progression of Alzheimer's disease? Alzheimers Dement
794 2009; 5: 348-60. doi: 10.1016/j.jalz.2008.12.001.
795 60. Maheshwari P, Eslick GD. Bacterial infection and Alzheimer's disease: a meta-analysis.
796 J Alzheimer's Dis 2015; 43: 957-66.
797 61. Shima K, Kuhlenbäumer G, Rupp J. *Chlamydia pneumoniae*-infection and Alzheimer's
798 disease: a connection to remember? Med Microbiol Immunol 2010; 199: 283-9. doi:
799 10.1007/s00430-010-0162-1.
800 62. Lim C, Hammond CJ, Hingley ST, Balin BJ. *Chalmydia pneumoniae* infection of
801 monocytes *in vitro* stimulates innate and adaptive immune responses relevant to those in
802 Alzheimer's disease. J Neuroinflammation 2014; 11: 217. doi: 10.1186/s12974-014-
803 0217-0.
804 63. Hammond CJ, Hallock LR, Howanski RJ, Appelt DM, Little CS. Immunohistological
805 detection of *Chlamydia pneumoniae* in the Alzheimer's disease brain. Neuroscience
806 2010; 11: 121.
807 64. Hogan RJ, Mathews SA, Mukhopadhyay S, Summersgill JT, Timms P. Chlamydial
808 persistence: beyond the biphasic paradigm. Infect Immun 2004; 72: 1843-55.
809 65. Whittum-Hudson JA, Schumacher HR, Hudson AP. *Chlamydia pneumoniae* and
810 inflammatory arthritis. In: Yamamoto Y, Friedman H, Bendinelli M, editors. *Chlamydia*
811 *pneumonia* infection and diseases. New York: Kluwer/Academic Press; 2004. p. 227-38.
812 66. Dreses-Werringloer U, Bhuiyan M, Zhao Y, Gérard HC, Whittum-Hudson JA, Hudson
813 AP. Initial characterization of *Chlamydophila* (*Chlamydia*) *pneumoniae* cultured from
814 the late-onset Alzheimer brain. Int J Med Microbiol 2009; 299: 187-201.

815 67. Dezfulian M, Shokrgozar MA, Sardari S, Parivar K, Javadi G. Can phages cause
816 Alzheimer's disease? Med Hypotheses 2008; 71: 651-6. doi:
817 10.1016/j.mehy.2008.07.005.
818 68. Miklossy J. Alzheimer's disease - a neurospirochetosis. Analysis of the evidence
819 following Koch's and Hill's criteria. J Neuroinflammation 2011; 8: 90. doi:
820 10.1186/1742-2094-8-90.
821 69. Miklossy J. Emerging roles of pathogens in Alzheimer disease. Expert Rev Mol Med
822 2011; 13:e30. doi: 10.1017/S1462399411002006.
823 70. Ohnishi S, Koide A, Koide S. Solution conformation and amyloid-like fibril formation
824 of a polar peptide derived from a beta-hairpin in the OspA single-layer beta-sheet. J Mol
825 Biol 2000; 301: 477-89.
826 71. McGeer PL, McGeer EG. Polymorphisms in inflammatory genes and the risk of
827 Alzheimer disease. Arch Neurol 2001; 58: 1790-2.
828 72. Miklossy J. Historic evidence to support a causal relationship between spirochetal
829 infections and Alzheimer's disease. Front Aging Neurosci 2015; 7:46. doi:
830 10.3389/fnagi.2015.00046.
831 73. Fallon BA, Nields JA. Lyme disease: a neuropsychiatric illness. Am J Psychiatry 1994 ;
832 151: 1571-83.
833 74. MacDonald AB, Miranda JM. Concurrent neocortical borreliosis and Alzheimer's
834 disease. Hum Pathol 1987; 18: 759-61.
835 75. MacDonald AB. Concurrent neocortical borreliosis and Alzheimer's Disease.
836 Demonstration of a spirochetal cyst form. Ann N Y Acad Sci 1988; 539, 468–70. doi:
837 10.1111/j.1749-6632.1988.tb31909.x
838 76. MacDonald AB. Transfection "Junk" DNA - a link to the pathogenesis of Alzheimer's
839 disease? Med Hypotheses 2006; 66:1140-1.

840 77. Miklossy J, Khalili K, Gern L, Ericson RL, Darekar P, Bolle L, et al. *Borrelia*
841 *burgdorferi* persists in the brain in chronic lyme neuroborreliosis and may be associated
842 with Alzheimer disease. J Alzheimers Dis 2004; 6: 639-49; discussion 673-81.
843 78. Bu XL, Yao XQ, Jiao SS, Zeng F, Liu YH, Xiang Y, et al. A study on the association
844 between infectious burden and Alzheimer's disease. Eur J Neurol 2014. doi:
845 10.1111/ene.12477.
846 79. Gutacker M, Valsangiacomo C, Balmelli T, Bernasconi MV, Bouras C, Piffaretti JC.
847 Arguments against the involvement of *Borrelia burgdorferi* sensu lato in Alzheimer's
848 disease. Res Microbiol 1998; 149: 31-7.
849 80. Pappolla MA, Omar R, Saran B, Andorn A, Suarez M, Pavia C, et al. Concurrent
850 neuroborreliosis and Alzheimer's disease: analysis of the evidence. Hum Pathol 1989;
851 20: 753-7.
852 81. Shiota S, Murakami K, Yoshiiwa A, Yamamoto K, Ohno S, Kuroda A, et al. The
853 relationship between *Helicobacter pylori* infection and Alzheimer's disease in Japan. J
854 Neurol 2011; 258: 1460-3. doi: 10.1007/s00415-011-5957-5.
855 82. Kountouras J, Zavos C, Boziki M, Gavalas E, Kyriakou P, Deretzi G, et al. Association
856 between *Helicobacter pylori* infection and Alzheimer's disease in Japan. J Neurol 2011;
857 258: 2086. doi: 10.1007/s00415-011-6054-5.
858 83. Kountouras J, Boziki M, Gavalas E, Zavos C, Deretzi G, Chatzigeorgiou S, et al. Five-
859 year survival after *Helicobacter pylori* eradication in Alzheimer disease patients. Cogn
860 Behav Neurol 2010; 23: 199-204. doi. 10.1097/WNN.0b013e3181df3034.
861 84. Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora
862 of the oral cavity. J Clin Microbiol 2005; 43: 5721-32.
863 85. Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, et al. The human
864 microbiome. J Bacteriol 2010; 192: 5002-17. doi: 10.1128/JB.00542-10.

865 86. Imangaliyev S, Keijser B, Crielaard W, Tsivtsivadze E. Personalized microbial network
866 inference via co-regularized spectral clustering. Methods 2015. pii: S1046-
867 2023(15)00123-1. doi: 10.1016/j.ymeth.2015.03.017.
868 87. Segata N, Haake SK, Mannon P, Lemon KP, Waldron L, Gevers D, et al. Composition
869 of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils,
870 throat and stool samples. Genome Biol 2012; 13: R42. doi: 10.1186/gb-2012-13-6-r42.
871 88. Axelsson P, Lindhe J, Nyström B. On the prevention of caries and periodontal disease.
872 Results of a 15-year longitudinal study in adults. J Clin Periodontol 1991; 18: 182-9.
873 89. Flemmig TF. Periodontitis. Ann Periodontol 1999; 4: 32-8.
874 90. Armitage GC. Development of a classification system for periodontal diseases and
875 conditions. Ann Periodontol 1999; 4: 1-6.
876 91. Holt SC, Ebersole JL. *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella*
877 *forsythia*: the "red complex", a prototype polybacterial pathogenic consortium in
878 periodontitis. Periodontol 2000 2005; 38: 72-122.
879 92. Colombo AP, Boches SK, Cotton SL, Goodson JM, Kent R, Haffajee AD, et al.
880 Comparisons of subgingival microbial profiles of refractory periodontitis, severe
881 periodontitis, and periodontal health using the human oral microbe identification
882 microarray. J Periodontol 2009; 80: 1421-32. doi: 10.1902/jop.2009.090185.
883 93. Preza D, Olsen I, Willumsen T, Boches SK, Cotton SL, Grinde B, et al. Microarray
884 analysis of the microflora of root caries in elderly. Eur J Clin Microbiol Infect Dis 2009;
885 28: 509-17. doi: 10.1007/s10096-008-0662-8.
886 94. Torlakovic L, Klepac-Ceraj V, Ogaard B, Cotton SL, Paster BJ, Olsen I. Microbial
887 community succession on developing lesions on human enamel. J Oral Microbiol 2012;
888 4. doi: 10.3402/jom.v4i0.16125.
889 95. Hardy JA, Mann DM, Wester P, Winblad B. An integrative hypothesis concerning the

pathogenesis and progression of Alzheimer's disease. Neurobiol Aging 1986; 7: 489-502.

96. Noble JM, Borrell LN, Papapanou PN, Elkind MSV, Scarmeas N, Wright CB. Periodontitis is associated with cognitive impairment among older adults: Analysis of NHANES-III. J Neurol Neurosurg Psychiatry 2009; 80: 1206-11. doi:10.1136/jnp.2009.174029.

97. Sparks Stein P, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E, et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. Alzheimers Dement 2012; 8: 196-203. doi: 10.1016/j.jalz.2011.04.006.

98. Noble JM, Scarmeas N, Celenti RS, Elkind MSV, Wright CB, Schupf N, et al. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. PLoS One 2014; 9: e114959. doi: 10.1371/journal.pone.0114959.

99. Hajishengallis G. Too old to fight? Aging and its toll on innate immunity. Mol Oral Microbiol 2010; 25: 25-37. doi: 10.1111/j.2041-1014.2009.00562.x.

100. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. Nat Immunol 2010; 11: 785-97. doi: 10.1038/ni.1923.

101. Fong ON, Chan KY, Leung KT, Lam HS, Cheung HM, Leung TY, et al. Expression profile of cord blood neutrophils and dysregulation of HSPA1A and OLR1 upon challenge by bacterial peptidoglycan. J Leukoc Biol 2014; 95: 169-78. doi: 10.1189/jlb.0413219.

102. Bibi F, Yasir M, Sohrab SS, Azhar EI, Al-Qahtani MH, Abuzenadah AM, et al. Link between chronic bacterial inflammation and Alzheimer disease. CNS Neurol Disord Drug Targets 2014; 13: 1140-7.

103. Miklossy J, Kraftsik R, Pillevuit O, Lepori D, Genton C, Bosman FT. Curly fiber and

915 tangle-like inclusions in the ependyma and choroid plexus--a pathogenetic relationship
916 with the cortical Alzheimer-type changes? J Neuropathol Exp Neurol 1998; 7: 1202-
917 12.
918 104. Miklossy J, Kis A, Radenovic A, Miller L, Forro L, Martins R, et al. Beta-amyloid
919 deposition and Alzheimer's type changes induced by *Borrelia* spirochetes. Neurobiol
920 Aging 2006; 27: 228-36.
921 105. Hachinsky V, Munoz DG. Cerebrovascular pathology in Alzheimer's disease: cause,
922 effect or epiphenomenon? Ann N Y Acad Sci 1997; 826:1-6.
923 106. Radolf JD, Desroisers DC. *Treponema pallidum*, the stealth pathogen, doth change,
924 but how? Mol Microbiol 2009; 72: 1081-6. doi: 10.1111/j.1365-2958.2009.06711.x.
925 107. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR.
926 Brain infarction and the clinical expression of Alzheimer disease. The Nun Study.
927 JAMA 1997; 277: 813-7.
928 108. Hajishengallis G. The inflammophilic character of the periodontitis-associated
929 microbiota. Mol Oral Microbiol 2014; 29: 248-57. doi: 10.1111/omi.12065.
930 109. Singhrao SK, Harding A, Poole S, Kesavalu L, Crean S. *Porphyromonas gingivalis*
931 periodontal infection and its putative links with Alzheimer's disease. Mediators
932 Inflamm 2015; 2015:137357.
933 110. Reife RA, Coats SR, Al-Qutub M, Dixon DM, Braham PA, Billharz RJ, et al.
934 *Porphyromonas gingivalis* lipopolysaccharide lipid A heterogeneity: differential
935 activities of tetra- and penta-acylated lipid A structures on E-selectin expression and
936 TLR4 recognition. Cell Microbiol 2006; 8: 857-68.
937 111. Kocgozlu L, Elkaim R, Tenenbaum H, Werner S. Variable cell responses to *P.*
938 *gingivalis* lipopolysaccharide. J Dent Res 2009; 88: 741-5. doi:
939 10.1177/0022034509341166.

940 112. Belstrøm D, Holmstrup P, Damgaard C, Borch TS, Skjødt MO, Bendtzen K, et al. The
941 atherogenic bacterium *Porphyromonas gingivalis* evades circulating phagocytes by
942 adhering to erythrocytes. Infect Immun 2011; 79: 1559-65. doi: 10.1128/IAI.01036-
943 10.
944 113. Poole S, Singhrao SK, Chukkapalli S, Rivera M, Velsko I, Kesavalu L, et al. Active
945 invasion of *Porphyromonas gingivalis* and infection-induced complement activation in
946 ApoE-/- mice brains. J Alzheimer's Dis 2015; 43: 67-80.
947 114. Xu F, Sternberg MR, Kottiri BJ, McQuillan GM, Lee FK, Nahmias AJ, et al. Trends
948 in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA
949 2006; 296: 964-73.
950 115. Bünzli D, Wietlisbach V, Barazzoni F, Sahli R, Meylan PR. Seroepidemiology of
951 Herpes simplex virus type 1 and 2 in Western and Southern Switzerland in adults aged
952 25-74 in 1992-93: a population-based study. BMC Infect Dis 2004; 17: 10.
953 116. Malkin JE, Morand P, Malvy D, Ly TD, Chanzy B, de Labareyre C, et al.
954 Seroprevalence of HSV-1 and HSV-2 infection in the general French population. Sex
955 Transm Infect 2002; 78:201-3.
956 117. Slots J. Herpesvirus periodontitis: infection beyond biofilm. J Calif Dent Assoc 2011;
957 39: 393-9.
958 118. Carter CJ. Alzheimer's disease plaques and tangles: Cemeteries of a Pyrrhic victory of
959 the immune defense network against herpes simplex infection at the expense of
960 complement and inflammation-mediated neuronal destruction. Neurochem Int 2011;
961 58: 301-20. doi: 10.1016/j.neuint.2010.12.003.
962 119. De Chiara G, Marcocci ME, Civitelli L, Argnani R, Piacentini R, Ripoli C, et al. APP
963 processing induced by herpes simplex virus type 1 (HSV-1) yields several APP
964 fragments in human and rat neuronal cells. PLoS One 2010; 5: e13989. doi:

965 10.1371/journal.pone.0013989.
966 120. Itzhaki RF, Cosby SL, Wozniak MA. Herpes simplex virus type 1 and Alzheimer's
967 disease: the autophagy connection. J Neurovirol 2008; 14: 1-4. doi:
968 10.1080/13550280701802543.
969 121. Wozniak MA, Mee AP, Itzaki RF. Herpes simplex virus type I DNA is located within
970 Alzheimer's disease amyloid plaques. J Pathol 2009; 217: 131-8.
971 122. Wisniewski T, Ghiso J, Frangione B. Alzheimer's disease and soluble A beta.
972 Neurobiol Aging 1994; 15:143-52.
973 123. Zlokovic BV, Yamada S, Holtzman D, Ghiso J, Frangione B. Clearance of amyloid
974 beta-peptide from brain: transport or metabolism? Nat Med 2000; 6:718-9.
975 124. Aiello AE, Haan M, Blythe L, Moore K, Gonzalez JM, Jagust W. The influence of
976 latent viral infection on rate of cognitive decline over 4 years. J Am Geriatr Soc 2006;
977 54: 1046-54.
978 125. Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA. Herpes
979 simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet 1997; 349: 241-
980 4.
981 126. Lurain NS, Hanson BA, Martinson J, Leurgans SE, Landay AL, Bennett DA,
982 Schneider JA. Virological and immunological characteristics of human
983 cytomegalovirus infection associated with Alzheimer disease. J Infect Dis 2013; 208:
984 564-72. doi: 10.1093/infdis/jit210.
985 127. Jamieson GA, Maitland NJ, Wilcock GK, Yates CM, Itzhaki RF. Herpes simplex virus
986 type 1 DNA is present in specific regions of brain from aged people with and without
987 senile dementia of the Alzheimer type. J Pathol 1992; 167: 365-8.
988 128. Ball MJ. "Limbic" predilection in Alzheimer dementia: is reactivated herpesvirus
989 involved? Can J Neurol 1982; 9: 303-6.

129. Ball MJ, Lukiw WJ, Kammermann EM, Hill JM. Intracerebral propagation of Alzheimer's disease: strengthening evidence of a herpes virus etiology. Alzheimers Dement 2013; 9:169-75. doi: 10.1016/j.jalz.2012.07.005.

130. Gibson KL, Wu YC, Barnett Y, Duggan O, Vaughan R, Kondeatis E, et al. B-cell diversity decreases in old age and is correlated with poor health status. Aging Cell 2009; 8:18-25.

131. Wozniak MA, Shipley SJ, Combrinck M, Wilcock GK, Itzhaki RF. Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. J Med Virol 2005; 75: 300-6.

132. Lin WR, Graham J, MacGowan SM, Wilcock GK, Itzhaki RF. Alzheimer's disease, herpes virus in brain, apolipoprotein E4 and herpes labialis. Alzheimer's Rep 1998; 1: 173-8.

133. Urovesic N, Martins RN. Infection and Alzheimer's disease: the APOE epsilon4 connection and lipid metabolism. J Alzheimer's Dis 2008; 13: 421-35.

134. Lövheim H, Gilthorpe J, Adolfsson R, Nilsson LG, Elgh F. Reactivated herpes simplex infection increases the risk of Alzheimer's disease. Alzheimers Dement 2014 pii: S1552-5260(14)02421-2. doi: 10.1016/j.jalz.2014.04.522.

135. Kobayashi N, Nagata T, Shinagawa S, Oka N, Shimada K, Shimizu S, et al. Increase in the IgG activity index due to herpes simplex virus type 1 reactivation and its relationship with cognitive function in amnestic mild cognitive impairment and Alzheimer's disease. Biochem Biophys Res Commun 2013; 430: 907-11.doi: 10.1016/j.bbrc.2012.12.054.

136. Letenneur L, Pérès K, Fleury H, Garrigue I, Barberger-Gateau P, Helmer C, et al. Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. PLoS One 2008; 3: e3637.

137. Hill MJ, Zhao Y, Clement C, Neumann DM, Lukiw WJ. HSV-1 infection of human brain cells induces miRNA-146a and Alzheimer-type inflammatory signaling. Neuroreport 2009; 20: 1500-5. doi: 10.1097/WNR.0b013e3283329c05.

138. Lewis RE. Overview of the changing epidemiology of candidemia. Curr Med Res Opin 2009; 25:1732-40. doi: 10.1185/03007990902990817.

139. Miceli MH, Diaz JA, Lee SA. Emerging opportunistic yeast infections. Lancet Infect Dis 2011; 11:142-51. doi: 10.1016/S1473-3099(10)70218-8.

140. Song X, Eribe ER, Sun J, Hansen BF, Olsen I. Genetic relatedness of oral yeasts within and between patients with marginal periodontitis and subjects with oral health. J Periodontal Res 2005; 40: 446-52.

141. Kumar J, Sharma R, Sharma M, Prabhavathi V, Paul J, Chowdary CD. Presence of *Candida albicans* in root canals of teeth with apical periodontitis and evaluation of their possible role in failure of endodontic treatment. J Int Oral Health 2015; 7: 42-5.

142. Olsen I. Denture stomatitis. Occurrence and distribution of fungi. Acta Odontol Scand 1974; 32: 329-33.

143. Alonso R, Pisa D, Marina AI, Morato E, Rábano A, Carrasco L. Fungal infections in patients with Alzheimer's disease. J Alzheimer's Dis 2014; 41: 301-11. doi: 10.3233/JAD-132681.

144. Alonso R, Pisa D, Rábano A, Carrasco L. Alzheimer's disease and disseminated mycoses. Eur J Clin Microbiol Infect Dis 2014; 33: 1125-32. doi: 10.1007/s10096-013-2045-z.

145. Castellani RJ, Perry G, Smith MA. The role of novel chitin-like polysaccharides in Alzheimer disease. Neurotox Res 2007; 12: 269-74.

146. Watabe-Rudolph M, Song Z, Lausser L, Schnack C, Begus-Nahrmann Y, Scheithauer MO, et al. Chitinase enzyme activity in CSF is a powerful biomarker of Alzheimer

disease. Neurology 2012; 78: 569-77. doi: 10.1212/WNL.0b013e318247caa1.

147. Pisa D, Alonso R, Juarranz A, Rábano A, Carrasco L. Direct visualization of fungal infection in brains from patients with Alzheimer's disease. J Alzheimer's Dis 2015; 43: 613-24. doi: 10.3233/JAD-141386.

148. Ala TA, Doss RC, Sullivan CJ. Reversible dementia: a case of cryptococcal meningitis masquerading as Alzheimer's disease. J Alzheimer's Dis 2004; 6: 503-8.

149. Hoffmann M, Muniz J, Carroll E, De Villasante J. Cryptococcal meningitis misdiagnosed as Alzheimer's disease: complete neurological and cognitive recovery with treatment. J Alzheimer's Dis 2009; 16: 517-20. doi: 10.3233/JAD-2009-0985.

150. Singhrao SK, Harding A, Simmons T, Robinson S, Kesavalu L. Crean StJ. Oral inflammation, tooth loss, risk factors, and association with progression of Alzheimer's disease. J Alzheimer's Disease 2014; 42: 723-37.

151. Olsen I. Update on bacteraemia related to dental procedures. Transfus Apher Sci 2008; 39: 173-8. doi: 10.1016/j.transci.2008.06.008.

152. Tomas I, Diz P, Tobias A, Scully C, Donos N. Periodontal health status and bacteraemia from daily oral activities: systematic review/meta-analysis. J Clin Periodontol 2012; 39: 213-28.

153. Navarathna DH, Munasinghe J, Lizak MJ, Nayak D, McGavern DB, Roberts DD. MRI confirms loss of blood-brain barrier integrity in a mouse model of disseminated candidiasis. NMR Biomed 2013; 26: 1125-34. doi: 10.1002/nbm.2926.

154. Holmes C, Cotterell D. Role of infection in the pathogenesis of Alzheimer's disease. CNS Drugs 2009; 23: 993-1002. doi: 10.2165/11310910-000000000-00000.

155. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. Nature 2012; 485: 512-6. doi:

10.1038/nature11087.

156. Ujiie M, Dickstein DL, Carlow DA, Jefferies WA. Blood-brain barrier permeability precedes senile plaque formation in an Alzheimer disease model. Microcirculation 2003; 10: 463-70.

157. Fry M, Ferguson AV. The sensory circumventricular organs: brain targets for circulating signals controlling ingestive behavior. Physiol Behav 2007; 91: 413-23.

158. Mann DM, Tucker CM, Yates PO. Alzheimer's disease: an olfactory connection? Mech Ageing Dev 1988; 42: 1-15.

159. Danielyan L, Schäfer R, von Ameln-Mayerhofer A, Buadze M, Geisler J, Klopfer T, al. Intranasal delivery of cells to the brain. Eur J Cell Biol 2009; 88: 315-24. doi: 10.1016/j.ejcb.2009.02.001.

160. Johnson NJ, Hanson LR, Frey WH. Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and orofacial structures. Mol Pharm 2010; 7: 884-93. doi: 10.1021/mp100029t.

161. Leung JY, Chapman JA, Harris JA, Hale D, Chung RS, West AK, et al. Olfactory ensheathing cells are attracted to, and can endocytose, bacteria. Cell Moll Life Sci 2008; 65: 2732-9. doi: 10.1007/s00018-008-8184-1.

162. Kovács T, Cairns NJ, Lantos PL. beta-amyloid deposition and neurofibrillary tangle formation in the olfactory bulb in ageing and Alzheimer's disease. Neuropathol Appl Neurobiol 1999; 25: 481-91.

163. Wesson DW, Levy E, Nixon RA, Wilson DA. Olfactory dysfunction correlates with amyloid-beta burden in an Alzheimer's disease mouse model. J Neurosci 2010; 30: 505-14. doi: 10.1523/JNEUROSCI.4622-09.2010.

164. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with

familial Alzheimer's disease. Nature 1991; 349: 704-6.

165. Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Jondro PD, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 1995; 269: 973-7.

166. Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature 1995; 376: 775-8.

167. Nicoll JA, Mrak RE, Graham DI, Stewart J, Wilcock G, MacGowan S, et al. Association of interleukin-1 gene polymorphisms with Alzheimer's disease. Ann Neurol 2000; 47: 365-8.

168. McGeer PL, McGeer EG. History of innate immunity in neurodegenerative disorders. Front Pharmacol 2011; 2:77. doi: 10.3389/fphar.2011.00077.

169. Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW, et al. The interleukin-1 genotype as a severity factor in adult periodontal disease. J Clin Periodontol 1997; 24: 72-7.

170. Galbraith GM, Hendley TM, Sanders JJ, Palesch Y, Pandey JP. Polymorphic cytokine genotypes as markers of disease severity in adult periodontitis. J Clin Periodontol 1999; 26: 705-9.

171. Shao MY, Huang P, Cheng R, Hu T. Interleukin-6 polymorphisms modify the risk of periodontitis: a systematic review and meta-analysis. J Zhejiang Univ Sci B 2009; 10: 920-7. doi: 10.1631/jzus.B0920279.

172. Di Bona D, Candore G, Franceschi C, Licastro F, Colonna-Romano G, Cammà C, et al. Systematic review by meta-analyses on the possible role of TNF-alpha polymorphisms

in association with Alzheimer's disease. Brain Res Rev 2009; 61: 60-8. doi: 10.1016/j.brainresrev.2009.05.001.

173. Yang W, Jia Y, Wu H. Four tumor necrosis factor alpha genes polymorphisms and periodontitis risk in a Chinese population. Hum Immunol 2013; 74: 1684-7. doi: 10.1016/j.humimm.2013.08.009.

174. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 2013; 45: 1452-8. doi: 10.1038/ng.2802.

175. Yuan H, Xia Q, Ge P, Wu S. Genetic polymorphism of interleukin 1β-511C/T and susceptibility to sporadic Alzheimer's disease: a meta-analysis. Mol Biol Rep 2013; 40: 1827-34. doi: 10.1007/s11033-012-2237-0.

176. Di Bona D, Plaia A, Vasto S, Cavallone L, Lescai F, Franceschi C, et al. Association between the interleukin-1beta polymorphisms and Alzheimer's disease: a systematic review and meta-analysis. Brain Res Rev 2008; 59: 155-63. doi: 10.1016/j.brainresrev.2008.07.003

177. Zhu XC, Tan L, Jiang T, Tan MS, Zhang W, Yu JT. Association of IL-12A and IL-12B polymorphisms with Alzheimer's disease susceptibility in a Han Chinese population. J Neuroimmunol 2014; 274: 180-4. doi: 10.1016/j.jneuroim.2014.06.026.

178. Payão SL, Gonçalves GM, de Labio RW, Horiguchi L, Mizumoto I, Rasmussen LT, et al. Association of interleukin 1β polymorphisms and halotypes with Alzheimer's disease. J Neuroimmnol 2012; 247: 59-62. doi: 10.1016/j.jneuroim.2012.03.012.

179. Wang B, Zhou S, Yang Z, Xie YC, Wang J, Zhang P, et al. Genetic analysis of tumor necrosis factor-alpha (TNF-alpha) G-308A and Saitohin Q7R polymorphisms with Alzheimer's disease. J Neurol Sci 2008; 270: 148-51. doi: 10.1016/j.jns.2008.02.021.

180. Lio D, Annoni G, Licastro F, Crivello A, Forte GI, Scola L, et al. Tumor necrosis

factor-alpha -308A/G polymorphism is associated with age at onset of Alzheimer's disease. Mech Ageing Dev 2006; 127: 567-71.

181. Kornman KS. Interleukin 1 genetics, inflammatory mechanisms, and nutrigenetic opportunities to modulate diseases of aging. Am J Clin Nutrit 2006; 83: 475S-83S.

182. Sando SB, Melquist S, Cannon A, Hutton ML, Sletvold O, Saltvedt I, et al. APOE epsilon 4 lowers age onset and is a high risk factor for Alzheimer's disease: a case control study from central Norway. BMC Neurol 2008; 8, 9. doi: 10.1186/1471-2377-8-9.

183. Desikan RS, Schork AJ, Wang Y, Thompson WK, Dehghan A, Ridker PM, et al. Polygenic overlap between C-Reactive Protein, plasma lipids and Alzheimer's Disease.
Circulation 2015 pii: doi: 10.1161/CIRCULATIONAHA.115.015489.

184. Engelborghs S, Gilles C, Ivanoiu A, Vandewoude M. Rationale and clinical data supporting nutritional intervention in Alzheimer's disease. Acta Clin Belg 2014; 69: 17-24. doi: 10.1179/0001551213Z.0000000006.

185. Cerajewska TL, Davies M, West NX. Periodontitis: a potential risk factor for Alzheimer's disease. Brit Dent J 2015; 218: 29-34.

186. Cicciù M, Matacena G, Signorino F, Brugaletta A, Cicciù A, Bramanti E. Relationship between oral health and its impact on the quality life of Alzheimer's disease patients: a supportive care trial. Int J Clin Exp Med 2013; 6: 766-72.

187. Stewart R, Sabbah W, Tsakos G, D'Aiuto F, Watt RG. Oral health and cognitive function in the Third National Health and Nutrition Examination Survey (NHANES III). Psychosom Med 2008; 70: 936-41. doi: 10.1097/PSY.0b013e3181870aec.

188. Stein PS, Kryscio RJ, Desrosiers M, Donegan SJ, Gibbs MB. Tooth loss, apolipoprotein E, and decline in delayed word recall. J Dent Res 2010; 89: 473-7. doi:

10.1177/0022034509357881.

189. Gatz M, Mortimer JA, Fratiglioni L, Johansson B, Berg S, Reynolds CA, et al. Potentially modifiable risk factors for dementia in identical twins. Alzheimers Dement 2006; 2: 110-7. doi: 10.1016/j.jalz.2006.01.002.

190. Kaye EK, Valencia A, Baba N, Spiro A 3rd, Dietrich T, Garcia RI. Tooth loss and periodontal disease predict poor cognitive function in older men. J Am Geriatr Soc 2010; 58: 713-8. doi: 10.1111/j.1532-5415.2010.02788.x.

191. de Souza Rolim T, Fabri GM, Nitrini R, Anghinah R, Teixeira MJ, de Siqueira JT, Cestari JA, de Siqueira SR. Oral infections and orofacial pain in Alzheimer's disease: a case-control study. J Alzheimers Dis 2014; 38: 823-9. doi: 10.3233/JAD-131283.

192. Corrada MM, Paganini-Hill A, Berlau DJ, Kawas CH. Apolipoprotein E genotype, dementia, and mortality in the oldest old: the 90+ Study. Alzheimers Dement 2013; 9:12-8.

193. Loeb MB, Molloy DW, Smieja M, Standish T, Goldsmith CH, Mahony J, et al. A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. J Am Geriatr Soc 2004; 52: 381-7.

194. Ferretti MT, Allard S, Partridge V, Ducatenzeiler A, Cuello AC. Minocycline corrects early, pre-plaque neuroinflammation and inhibits BACE-1 in a transgenic model of Alzheimer's disease-like amyloid pathology. J Neuroinflammation 2012; 9: 62. doi: 10.1186/1742-2094-9-62.

~~194.~~195. in't Veld BA, Ruitenberg A, Hofman A, Stricker BH, Breteler MM. drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 2001; 22: 407-12.

~~195.~~196. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997; 48: 626-32.

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~~196.~~197. McGeer PL, McGeer EG. Anti-inflammatory drugs in the fight against disease. Ann N Y Acad Sci 1996; 777: 213-20.

~~197.~~198. Itzhaki R, Wozniak MA. Could antivirals be used to treat Alzheimer's disease. Future Microbiol 2012; 7: 307-9.

~~198.~~199. Lin WR, Jennings R, Smith TL, Wozniak MA, Itzhaki RF. Vaccination prevents latent HSV1 infection of mouse brain. Neurobiol Aging 2001; 22: 699-703.

~~199.~~200. Mori I. "Spontaneous molecular reactivation" of herpes simplex virus type 1 in the brain as a pathogenic mechanism of Alzheimer's disease. Correspondence/Med Hypotheses 2011; 77: 462.

~~200.~~201. Wozniak MA, Itzhaki RF. Intravenous immunoglobulin reduces β amyloid and abnormal tau formation caused by herpes simplex virus type 1. J Neuroimmunol 2013; 257: 7-12. doi: 10.1016/j.jneuroim.2013.01.005.

~~201.~~202. Jalkute CB, Sonawane KD. Evaluation of a possible role of *Stigmatella aurantiaca* ACE in Aβ peptide degradation: a molecular modeling approach. J Mol Microbiol Biotechnol 2015; 25: 26-36. doi: 10.1159/000370114.

~~202.~~203. Chiarini A, Gardenal E, Whitfield JF, Chakravarthy B, Armato U, DaI Pra I. Preventing the spread of Alzheimer's disease neuropathology: a role for calcilytics? Curr Pharm Biotechnol 2015 May 5. [Epub ahead of print].

~~203.~~204. Hochgräfe K, Sydow A, Matenia D, Cadinu D, Könen S, Petrova O, et al. methylene blue treatment preserves cognition in mice expressing full-length pro-aggregant human Tau. Acta Neuropathol Commun 2015; 3: 25. doi: 10.1186/s40478-

015-0204-4.

~~204.~~205. Richard T, Pawlus AD, Iglésias ML, Pedrot E, Waffo-Teguo P, Mérillon JM, et al.
Neuroprotective properties of resveratrol and derivatives. Ann NY Acad Sci 2011; 1215: 103-8. doi: 10.1111/j.1749-6632.2010.05865.x.

~~205.~~206. Regitz C, Fitzenberger E, Mahn FL, Dußling LM, Wenzel U. Resveratrol amyloid-beta (Aβ1-42)-induced paralysis through targeting proteostasis in an Alzheimer model of *Caenorhabditis elegans*. Eur J Nutr 2015 Apr 8. [Epub ahead of print].

~~206.~~207. Håheim LL, Olsen I, Rønningen KS. Oral infection, regular alcohol drinking pattern, and myocardial infarction. Med Hypotheses 2012; 79: 725-30. doi: 10.1016/j.mehy.2012.08.010.

~~207.~~208. Song Y, Kim HD, Lee MK, Kim MK, Kang SN, Ko YG, et al. Protective effect of centipedegrass against Aβ oligomerization and Aβ-mediated cell death in PC12 cells. Pharm Biol 2015; 8: 1-7.

~~208.~~209. Kontsekova E, Zilka N, Kovacech B, Novak P, Novak M. First-in-man tau vaccine targeting structural determinants essential for pathological tau-tau interaction reduces tau oligomerisation and neurofibrillary degeneration in an Alzheimer's disease model. Alzheimers Res Ther 2014; 1; 6:44. doi: 10.1186/alzrt278.HillH pylori.

Fig. 1. The pathological hallmarks of AD, numerous extracellular amyloid-Aβ plaques and intra-neuronal neurofibrillary tangles (NFTs). Although there are several NFTs, only one is picked out in boxes at x 10 and x 40 objective lens magnification.

Fig. 2. Immunofluorescence labelling (green dots) of hippocampal CA neurons opsonised by iC3b following monoinfection with *P. gingivalis* at 24 weeks of *APOε* gene knockout (ApoE−/−) mice. This is indirect evidence of an oral infection having affected the host's brain.

~~*Fig. 3.* Photo of a Sabouraud agar model made from the upper denture of an old patient with denture stomatitis and heavy accumulations of denture plaque on the fitting surface. *Candida* species are growing profusely.~~

Fig. 3 Section of pons area of Alzheimer's disease brain from an 84 year old female

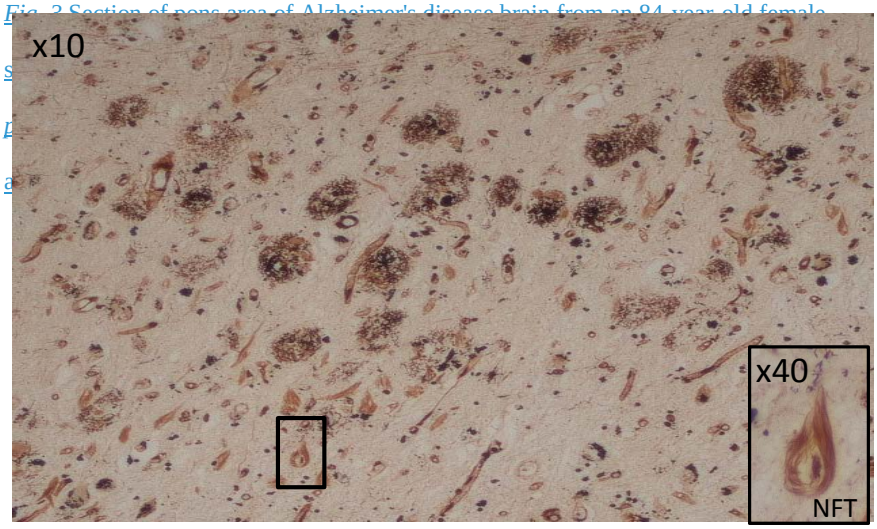

Fig. 1.

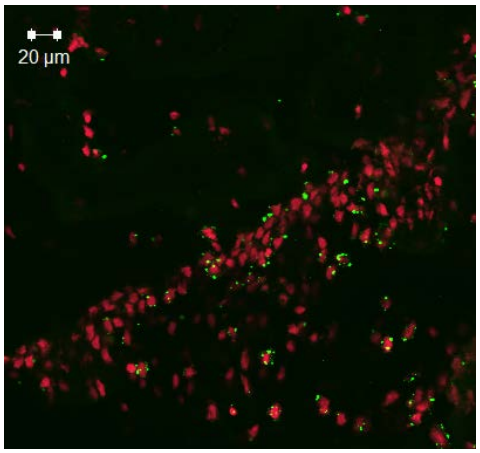

Fig. 2.

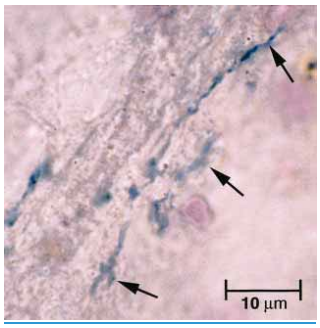

Fig. 3.