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

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Field Code Changed

20 ABSTRACT

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

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

41

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

57

58 PREVALENCE OF AD

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

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

70

71 NEUROPATHOLOGICAL CHARACTERISTICS OF THE AD BRAIN

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

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

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

96
97 Furthermore, the senile plaques (A β ₄₂) are recognized as triggers that stimulate activation of
98 microglial cells and initiate local immune responses (24). Activated microglia are the most
99 important contributors of inflammation in the central nervous system (CNS) (25). They
100 secrete a number of proinflammatory cytokines (24-26) and recognize pattern associated
101 molecular patterns (PAMPs) on bacteria and their cellular debris (27-30) ~~to deal with~~ in
102 response to CNS infection.

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

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

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

119

120 THE AMYLOID CASCADE HYPOTHESIS

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

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

142

143 THE INFLAMMATORY HYPOTHESIS

144 **The intrinsic model**

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

157

158 **The extrinsic model**

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

164 originating from Gram-negative, highly virulent oral pathogens, bronchopneumonia and
165 urinary tract infections (3, 4, 7, 57, 58) reach all organs including the CNS. ~~The consequences~~
166 ~~products entering the bloodstream trigger the~~ ~~are that the~~ innate immune responses of ~~hosts~~
167 ~~pattern recognition receptors (PPR) and TLRs via pattern recognition receptors (PPR) and~~
168 ~~infectious threat by secreting~~ ~~to the threat of infection by secreting~~ immune mediators
169 agents. Increased risk of dementia in the elderly following multiple infectious episodes has
170 been reported ~~It is reported that multiple episodes of infections in the elderly likely end up~~
171 ~~being diagnosed with dementia~~ (4). In addition, systemic infections appear to contribute
172 towards delirium in some clinically diagnosed AD patients and such episodes can exacerbate
173 a premorbid cognitive status (3). Holmes et al. proposed that since cytokines are primary
174 mediators released by the host to defend against infection, such secondary stimuli (IL-1 β and
175 TNF- α) may mediate their effect on the brain and indirectly contribute to cognitive decline (3,
176 57).

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177

178 NON-ORAL BACTERIA RELATED TO AD

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

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

190 Using various techniques Balin et al. (9) found *C. pneumoniae* in 80-90% of LOAD brain
191 tissue specimens. *C. pneumoniae* infection was correlated with the *APOEε4* allele expression.

192 The same researchers subsequently demonstrated that astroglia, microglia, neurons,
193 endothelial cells and monocytes in the LOAD brain are permissive to this bacterium. The
194 mechanisms of pathogenesis differ between actively- and persistently-infecting chlamydiae
195 and it is in the persistent state that these organisms cause chronic disease (64, 65). *C.*
196 *pneumoniae* was cultured from two AD brain samples after one or two passages in HEp-2
197 cells (66). Interestingly, the study indicated that brain isolates were more related to respiratory
198 than to vascular/atheroma strains of *C. pneumoniae*. This suggested that *C. pneumoniae*
199 infection of the brain was secondary to bronchopneumonia and at the end stages of LOAD.

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

205 In a meta-analysis based on 25 relevant, primarily case-control studies Maheshwari and Eslick
206 (60) found a statistically significant association between AD and detectable evidence of
207 infection caused by *C. pneumoniae* or spirochetes. They reported over a ten-fold increased
208 occurrence of AD when there was evidence of spirochetal infection (OR: 10.61; 95% CI:
209 3.38-33.29) and over a four-fold increased occurrence of AD with a conservative risk estimate
210 (OR: 4.45; 95% CI: 2.33-8.52). There was a five-fold increase in occurrence of AD with *C.*
211 *pneumoniae* infection (OR: 5.66; 95% CI: 1.83-17.51). Accordingly, a strongly positive

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

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

223 Miklossy (68, 69) analyzed data on the ability of spirochetes to induce pathological and
224 biological hallmarks of AD *in vitro* following Koch's and Hill's postulates and demonstrated
225 a plausible causal relationship between neurospirochetosis and AD. The data revealed a
226 statistically significant association between spirochetes and AD (P = 1.5 x 10⁻¹⁷, OR = 20,
227 95% CI = 8-60, N = 247). When mammalian cells were exposed to spirochetes, the
228 pathological and biological hallmarks of AD were reproduced *in vitro* (68, 69). ~~Miklossy (72)~~
229 ~~also found that historical~~ Historical observations supported the conclusion that that
230 ~~observations paved the way for drawing conclusions such as~~ chronic spirochetal infections
231 can cause dementia and reproduce the neuropathological hallmarks of AD (72). According to
232 Miklossy (72), these observations represent further evidence in support of a causal
233 relationship between various spirochetal infections and AD.

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

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

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

252

253 ORAL BACTERIA RELATED TO AD

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

Commented [PB2]: Unclear. Do you mean as a monoinfection?

Commented [PB3]: Should be harbors if American English is used. Be consistent throughout MS

Commented [PB4]: There are differences however there is also significant overlap.

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

270 Periodontal bacterial pathogens are related to AD

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

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

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

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

308

309 **Possible consequences to the brain-~~of~~ carrying oral bacterial pathogens**

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

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

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

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

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

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

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

359

360 ORAL VIRUS RELATED TO AD

361 Herpes simplex virus (HSV) is present in more than 70% of the population after 50 years age
362 (114-116). It persists latently in the peripheral nervous system and is periodically reactivated.
363 Characteristically, HSV-1 has been designated as the enemy within (10). Herpes viruses,
364 including Epstein-Barr virus and cytomegalo-virus, are found in high copy counts in
365 aggressive periodontitis, and may interact synergistically with periodontopathic bacteria in the
366 pathogenesis of this disease (117). Periodontal infections activated by Herpes virus ~~Herpes~~
367 ~~virus active periodontal infections~~ may impair local host defenses and thus increase the
368 aggressiveness of resident periodontopathic bacteria. The bacteria, in turn, may augment the
369 virulence of the herpes viruses.

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

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

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381 on the discovery of soluble species of this protein and later confirmed by Zlokovic et al. (123)
382 (123) ~~to be the case. Thus it~~ It is now widely accepted that defective clearance of this protein
383 brains ~~that leads~~ leading to its accumulation in the form of insoluble A β _{40/42} plaques.
384 and cytomegalovirus have been detected in the brains of older adults with and without AD
385 (124-126), HSV-1 viral DNA is present in a higher proportion of AD patients (127). It is
386 particularly seen in the temporal and frontal cortices which are the brain regions that are most
387 damaged in AD (128, 129). The relevance of this association is still under investigation;
388 however a plausible role for the HSV-1 viral DNA could be ~~in-associated with~~ the plaque
389 maturation process. Jamieson et al. (127) found that the virus was absent from the brains of
390 most young people, probably because it enters the brain during old age either ~~when the~~
391 senescence (130) or the virus itself is initially responsible for weakening the host's immune
392 defenses ~~first~~. This latter explanation is likely and is supported by us and others (131).
393 HSV-1 is a strong risk factor for AD in the brains of those with the *APOE ϵ 4* allele (125, 132).
394 This virus is not only a dormant passenger but can persist in the latent form in neurons or
395 replicate at a very low level in neuroglia (133). During persistence it may release toxic
396 products continuously and induce pro-inflammatory cytokines at low levels which become an
397 additional burden to ~~the a~~ host ~~who is~~ already challenged by age, poor diet, ~~failing-restricted~~
398 exercise as well as any genetic susceptibilities. Itzaki and Wozniak (10) suggested that stress
399 or peripheral infection can reactivate the virus periodically from latency in the brain. This
400 may cause an acute but presumably localized infection, and subsequent damage modulated by
401 the *APOE* gene can lead to formation of A β plaques and NFTs.

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

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

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

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

418

419 ORAL YEASTS RELATED TO AD

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

428 144). Fungal molecules including proteins and polysaccharides [(1,3)- β -glucan] were detected
 429 in peripheral blood serum, and fungal proteins and DNA were demonstrated by PCR in brain
 430 tissue of AD patients. ~~Also chitin~~Chitin-like fungal structures have also been found in the AD
 431 brain (145) and chitinase activity has been proposed as a powerful biomarker of AD (146).

432 ~~Immunohistochemical analyses revealed, albeit in a few cells, in~~ In AD brains, ~~containing~~
 433 cytoplasmic material in a small number of cell cells were was targeted by antibodies with
 434 immunoreactivity to that immunoreacted with antibodies raised against some yeast cells
 435 (147). These findings were consistent with the idea that neurons can be infected by fungi.

436 Interestingly, antifungal treatment reversed the clinical symptoms of some AD patients (148,
 437 149).

438

439 HOW DO ORAL MICROORGANISMS REACH THE BRAIN?

440 **Blood stream dissemination**

441 The most likely pathway of for dissemination for of oral microorganisms to the brain is
 442 through the blood stream (150). Dental treatment procedures as well as brushing, flossing,
 443 chewing and use of tooth picks in a patient with periodontitis will release a bacteraemia (151).

444 This can occur several times during the day and has been estimated to last for up to 3 hours
 445 for oral bacteria (152). The bacteraemia is usually ~~taken care of~~ contained by immune cells of
 446 the body. However, in people with reduced immune defense, e.g. older individuals, bacteria
 447 may ~~settle down within~~ localize to crevices of the oral cavity and vascular channels (150).

448 **The blood- brain barrier**

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

Commented [PB9]: chewing while eating?

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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.

452 responses that weakened the BBB (16). ~~Actually~~ Notably, magnetic resonance imaging (MRI)
 453 confirmed loss of BBB integrity in a mouse model of disseminated candidosis (153). Loss of
 454 integrity allows microorganisms to spread through the blood stream and quietly contribute in
 455 the pathogenesis of AD. During **immunosenescence**, the innate immune system gradually
 456 takes over for the acquired immune system. This contributes to a rise in circulating
 457 proinflammatory cytokines such as TNF- α (16). Indeed, proinflammatory mediators can
 458 cross the BBB (3, 7, 154). *APOE ϵ 4*, TNF- α and perhaps Ephrin Type-A Receptor 1 (EphA1)
 459 may influence BBB integrity and thus be important for penetration of bacteria, LPS and other
 460 toxic bacterial products as well as yeasts into the brains of AD patients (16). *APOE ϵ 4* affects
 461 the integrity of the BBB by activating the cyclophilin A matrix metalloproteinase MM-9
 462 pathway (155).

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

468

469 **Circumventricular organs and perivascular spaces**

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

475

Commented [PB11]: May want to briefly define. I had to look it up. Eg. Small organs in the brain that allow peptide hypothalamic hormones to leave the brain without disrupting the BBB

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476 **The olfactory hypothesis**

477 The “olfactory hypothesis” suggests the olfactory tract as a potential route for pathogenic
478 bacteria to enter the brain and thereby trigger the production of A β and NFTs (158). The
479 olfactory and trigeminal nerves are known to be used by periodontal pathogens to bypass the
480 BBB for direct passage to the CNS (5, 150, 159, 160). Identification of oral treponemes in the
481 trigeminal ganglia supports such a route of dissemination (5). Further, sSpirochetes may also
482 spread along the fila olfactoria and tractus olfactorius (68, 69).

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

488

489 GENETIC, NUTRITIONAL AND ENVIRONMENTAL FACTORS PROMOTING AD

490 While early-onset AD is genetically determined, LOAD is thought to result from interaction
491 between genetic and environmental factors (12). Several mutated genes are associated with
492 the familial **AD**, such as the amyloid beta (A β) precursor protein (*A β PP*) gene and the
493 presenelin-1 (*PSEN-1*) and *PSEN-2* gene (164-166). A major risk factor for LOAD is
494 polymorphism in the *APO ϵ 4* allele (2). Also cytokine-related genes seem to be involved in the
495 susceptibility to inflammation in both LOAD (167, 168) and periodontitis (169-171). Thus,
496 polymorphisms that increase TNF- α also increase the risk of both AD and periodontitis (172,
497 173). Lambert et al. (174) found that 20 different loci can increase host susceptibility to AD
498 including polymorphisms in genes associated with interleukin-1 (IL-1) (71, 175-178) and
499 TNF α (71, 172, 179-181). The *APO ϵ 4* gene which is one of these 20 loci is highly correlated

500 with AD (182) but it is also a risk factor for infection and increases the expression of
501 inflammatory mediators (11). Recently, genetic overlap between AD, C-reactive protein
502 (CRP) and plasma lipids was demonstrated by using summary statistics from GWAS of over
503 200,000 individuals (183). There may also be interplay between genetic risk and
504 environmental risk factors such as toxins and or bacterial, viral and fungal pathogens in
505 LOAD reflecting its complex and multifactorial etiology (1).

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

509

510 ASSOCIATION BETWEEN CHRONIC PERIODONTAL DISEASE AND AD

511 There is increasing evidence for an association between chronic periodontitis and LOAD
512 (185). Cross-sectional and longitudinal studies have demonstrated that gingival bleeding, loss
513 of periodontal attachment, periodontal probing depth, alveolar bone loss and antibodies to
514 periodontal pathogens are significantly associated with lower cognitive function and decline
515 after adjustment for co-variables (for a review see (12)). Acute phase proteins, including
516 cytokines are possible indirect links between periodontal pathogens and/or their virulence
517 factors (12, 13). Elderly often show neglect of oral hygiene (~~Figs. 3-5~~) which can stimulate
518 recurrent chronic oral infection (150). This again promotes inflammation which can lead to
519 confusion and dementia (3, 4, 154). In 152 subjects 50-70 years of age who were followed for
520 20 years, greater levels of periodontal inflammation correlated with lower cognitive levels
521 (186). **Furthermore**, gingival bleeding and loss of periodontal attachment ~~apparatus~~ were
522 associated with cognitive impairment in a cohort of 5,138 people aged 20-59 years (187). In
523 144 nuns, those ~~with encoding APOEε4~~ and ~~who had~~ fewer teeth ~~had experienced~~ more rapid

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

535

536 PUTATIVE TREATMENT AND PROPHYLAXIS OF AD

537 There is no effective treatment or prophylaxis yet for AD, but several approaches have been
 538 proposed. Efforts in this respect are important. If we could delay onset of dementia by only 2
 539 years we might lower the prevalence of AD by more than 22 million cases over the next 40
 540 years (14). ~~Indeed, delaying the disease process is a better option as the~~ Notably ~~Notably, the~~
 541 of the APOE ϵ 4 allele in the very old (90+) age group, appears to confer protection (192),
 542 having bypassed a period of being at risk around 85+ years of age.

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

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

Commented [PB12]: This is a bit confusing. Please clarify

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Commented [PB13]: Are there other antibiotic studies. It would make sense that other individuals who had long term antibiotic use (for other reasons) would perhaps be at lower risk for AD.

548 ~~study in subjects with mild to moderate AD~~ (193). It was concluded that use of antibacterial
549 the treatment of *C. pneumoniae* but had a beneficial effect on cognitive decline in AD (193).

550 This might be related to prevention or attenuation of a number of peripheral infections or
551 dampening down the proinflammatory cytokine response. ~~Minicycline~~ Minocycline was found
552 early, pre-plaque neuroinflammation and inhibit the APP cleaving enzyme 1 (BACE-1) in a
553 transgenic model of Alzheimer's disease-like amyloid pathology (194). It was suggested that
554 interfering with inflammation could be a useful therapeutic approach in early, pre-plaque
555 stages of AD-like amyloid pathology.

556 Anti-inflammatory drugs given for at least 2 years before the onset of dementia delayed the
557 disease process (~~194195-196197~~). It may also be beneficial to combine anti-inflammatory
558 antibacterials (193). Examination of several available Non-steroidal Anti-Inflammatory Drugs
559 (NSAIDs) showed that only a few of them had any useful A β -modifying or other activity of
560 therapeutic use in LOAD (for a review see (1)).

561 Itzhaki and Wozniak (10, ~~197198~~) suggested that antiviral therapy and perhaps vaccination
562 against HSV-1 in early life could be useful. If HSV-1 is implicated in AD, vaccination could
563 prevent the excessive accumulation of A β in the brain. **Vaccination** with mixed HSV
564 glycoproteins prior to HSV infection protected against viral latency in mouse brains (~~198199~~).

565 Also Mori (~~199200~~) maintained that antiviral approaches including chemotherapy and
566 vaccination are promising for prevention and treatment of AD and remain to be validated.

567 Furthermore, Carter (118) suggested that vaccination or antiviral agents and immune
568 suppressants may be considered as therapeutic options before or ~~in~~ during the early stages of
569 AD. Interestingly, exposure of HSV-1-infected cell cultures to intravenous immunoglobulin
570 acting via anti- β -amyloid ~~antibodies~~ antibodies reduced the accumulation of A β and
571 phosphorylated tau (~~200201~~).

572 Angiotensin-converting enzyme (ACE) from *Stigmatella aurantiaca* may cleave the A β
573 peptide similar to human ACE and may be used as a novel form of treatment against AD
574 ([201202](#)). Furthermore, Chiarini et al. ([202203](#)) maintained that calcilytics could halt AD
575 progression and preserve the patients' cortical neurons, cognitive abilities, and eventually life
576 if given at minimal cognitive impairment or at earlier stages. Studies ~~from~~ using mice
577 suggested the use of tau aggregation inhibitors as potential drugs for the treatment of AD and
578 other tauopathies ([203204](#)).

579 Resveratrol is a polyphenol present in red wine. Its capability of directly interfering with the
580 toxic β -amyloid protein aggregation in AD has recently been shown ([204205](#)). Resveratrol
581 was found to reduce A β -induced toxicity in a *Caenorhabditis elegans* model of AD by
582 targeting specific proteins involved in proteostasis and thereby reducing the amount of
583 aggregated A β ([205206](#)). This is in concert with our previous finding that the effect of a
584 drinking pattern of 2-7 times per week reduced the risk of myocardial infarction among men
585 who had a history of tooth extractions due to periodontal/dental infection ([206207](#)).

586 Potent inhibitors of A β oligomer formation or A β -induced cell toxicity have proven to be
587 attractive means for therapeutic intervention of AD. Song et al. ([207208](#)) found that the anti-
588 Alzheimer effects of centipede grass, which contains several C-glycosyl flavone constituents,
589 occurred through inhibition of neuronal cell death by intervening with oligomeric A β
590 formation and reducing beta-site amyloid precursor protein cleaving enzyme 1 (~~BACE1~~)
591 activity. The authors suggested that Maysin, a major flavonoid of corn silk, in centipede grass
592 could be an excellent therapeutic candidate for the prevention of AD.

593 Active immunization against important domains of Alzheimer tau eliminated tau aggregation
594 and neurofibrillary pathology ([208209](#)). The AD type of tau hyperphosphorylation was
595 abolished in transgenic mice by vaccination across a wide range of AD phospho-epitopes.

596 Kontsekova et al. (2008,2009) demonstrated that active immunization of rats with a tau peptide
 597 encompassing the epitope revealed by monoclonal antibody DC8E8 led to elimination of all
 598 major hallmarks of neurofibrillary pathology involving a 95% reduction in the AD-type
 599 hyperphosphorylation of tau.

600

601 CONCLUSIONS

602 LOAD which is the predominant form of AD, does not seem to have a single cause. On the
 603 contrary, a multitude of factors may be involved and they may act in concert. ~~Of these~~ Among
 604 ~~others,~~ both genetic and environmental factors may be involved. Even among
 605 ~~cooperation,~~ ~~action~~ may occur since the brain can hardly differentiate between different

606 microbial insults which ~~collectively contribute capacity for enhancing all end up in~~

607 Irrespective of the cause, systemic inflammation may predict the onset of dementia.

608 Organisms such as spirochetes, *P. gingivalis*, *C. pneumoniae*, *H. pylori*, ~~H~~erpes simplex type
 609 virus and *Candida* are ~~among the prime candidate pathogens~~ ~~the most suspected pathogens~~ in
 610 events ~~causing AD, oral microorganisms may~~ play a role, particularly anaerobic bacteria such
 611 as treponemes, *P. gingivalis*, *Prevotella* spp., *Fusobacterium* and *Actinomyces*, but also

612 facultative anaerobic *Candida* species. It is important to recognize that infection can occur

613 decades before the manifestation of dementia. The most convincing evidence for a causal

614 relationship between oral bacteria and AD is ~~that noted~~ for spirochetes which are both

615 neurotropic and motile. ~~They also fulfill Koch's and Hill's postulates for a causal relationship.~~

616 It is likely that oral infection can be a risk factor for Alzheimer's disease but it is not the only

617 one. Experiments ~~in humans~~ ~~in vivo~~ may require long exposure times to disclose key events

618 and mechanisms of AD. There is, as yet, no cure for AD ~~despite concerted efforts and~~

619 ~~investment by industry~~ ~~and this is not without concerted efforts from investment by industry~~

620 ~~but because drug discovery in dementia is hugely challenging.~~ ~~Prevention of AD through~~

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Commented [PB15]: Is this accurate? Certainly not in humans

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Commented [PB16]: Human?

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

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

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

636

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640

641 CONFLICT OF INTEREST AND FUNDING

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

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1244 *Fig. 1.* The pathological hallmarks of AD, numerous extracellular amyloid-A β plaques

1245 and intra-neuronal neurofibrillary tangles (NFTs). Although there are several NFTs,

1246 only one is picked out in boxes at x 10 and x 40 objective lens magnification.

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1248 *Fig. 2.* Immunofluorescence labelling (green dots) of hippocampal CA neurons

1249 opsonised by iC3b following mono-infection with *P. gingivalis* at 24 weeks of *APOE*

1250 gene knockout (*ApoE*^{-/-}) mice. This is indirect evidence of an oral infection having

1251 affected the host's brain.

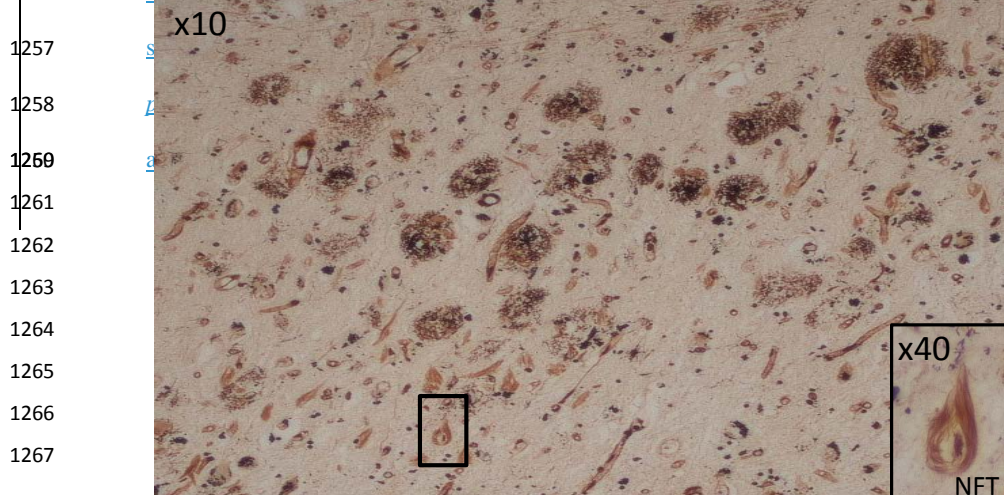
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1253 *Fig. 3.* Photo of a Sabouraud agar model made from the upper denture of an old patient

1254 with denture stomatitis and heavy accumulations of denture plaque on the fitting

1255 surface. *Candida* species are growing profusely.

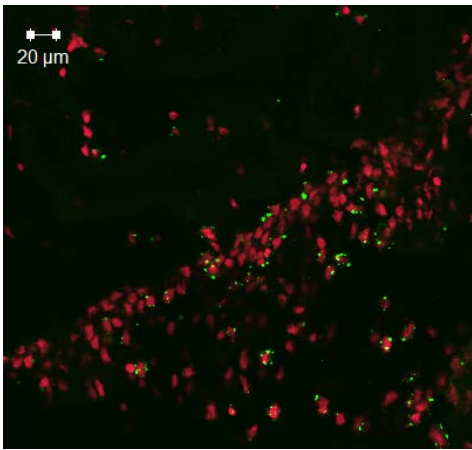
1256 *Fig. 3* Section of non-amyloid area of Alzheimer's disease brain from an 84-year-old female



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1275 *Fig. 1.*

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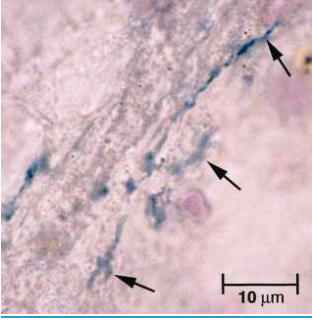


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Fig. 2.

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Fig. 3.