

# Alzheimer's Disease: Future Efforts to Thwart Memory Loss

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**Abbreviations:** AD: Alzheimer's Disease; PCR: Polymerase Chain Reaction; GP: General Paresis; ABPP: Abeta Precursor Protein

## ABSTRACT

During the past few years, Alzheimer's disease (AD) has been shown to be a chronic infection. Spirochetes, Lyme Borrelia and dental treponemes, are the etiologic agents; these spirochetes make biofilms, and, in so doing, are responsible for the formation of beta amyloid and hyperphosphorylated tau protein. The pathways for all these components of AD has been outlined. The following are possible future efforts based on the above information. These include attempting to culture the dental spirochetes as well as attempting to develop a serologic test for pre-AD. A trial for early AD is proposed, as is a possible way of preventing AD with periodic courses of effective antibiotics.

## Commentary

It has been shown recently that Alzheimer's disease (AD) is a chronic infectious disease with the causative microbe being a spirochete. Lyme (Borrelial) spirochetes have been cultured from affected brains, and, they and dental spirochetes (various treponemata) have been found by polymerase chain reaction (PCR) [1-3]. Further, the infection has been shown to satisfy Koch-Hill postulates relating to, and firmly establishing, its infectious nature [2]. The spirochetes have been visualized pathologically and have been shown to create pathological changes similar, in every way, to those seen in another spirochetal disease, syphilitic dementia, which is termed general paresis (GP) [4]. Further, no coccobacillary forms and no viral changes have been noted in the pathology specimens examined. The pathology of AD is strictly "helical".

The spirochetes form biofilms like most other microbes; and, in large measure, the biofilms contribute to the chronicity of the disease [5]. Once in a biofilm, the microbes become resistant to antibiotics and to both arms of the immune system, innate and adaptive. In the extracellular space, the biofilms attract Toll-like receptor 2 (they have receptor sites for this molecule), and, by known pathways (MyD88 and NFkB), this interaction leads to the production of beta amyloid (Abeta) [6,7]. The Abeta, which is also anti-microbial,

cannot penetrate the biofilm, just like antibiotics, and it has been shown that it encases the biofilm without engaging the spirochetes within [7]. The spirochetes also make biofilms intracellularly, and somewhat surprisingly, make Abeta precursor protein (ABPP) and Abeta simultaneously [8,9]. This process has been demonstrated both *in vitro* and *in vivo*. It has also been discovered recently that Abeta in contact with tau protein causes the tau protein to become phosphorylated, and it no longer functions as a dendrite stabilizer leading to dendrite and cell collapse [10,11]. With that, the neuron is no longer functional. With this as background, the contemplated future actions related to this hypothesis, are at least five in number:

- a. Popularize the concept of a bacterial origin for AD.
- b. Culture the dental spirochetes.
- c. Develop a serologic test that would identify AD before it is clinically apparent similar to the RPR in GP (tertiary syphilis).
- d. Treat with penicillin or another bactericidal antibiotic for three weeks once yearly.
- e. Initiate a clinical trial in mild cognitive impairment (MCI) to discern whether the disease progression can be stopped or slowed. Each of these 5 will be discussed further in the following.

For the past twenty-five years, the beta amyloid causation of AD has been predominant. This is understandable because this molecule is abundant in affected brains. However, as it has been shown, the microbes make Abeta while they are in the process of making biofilms [9]; further, the response of the innate immune system to the biofilms also creates Abeta. Thus, its creation is largely dependent on the microbes making biofilms. P-tau has recently been implicated in causing AD. As has been previously outlined, this is also directly related to the microbes making biofilms. The Abeta, which is produced at the same time as the biofilms, interacts with tau protein and converts it to p-tau [10,11]. Thus, p-tau is also largely dependent on the microbes making biofilms. When Lister made his monumental discovery about microbes causing the incredible suppuration rates after surgery and a way to prevent it, it took 20 years before the concept became widely known and practiced. His method for disseminating the information was by teaching students (he taught hundreds) and by writing about it. Fortunately, the British Medical Journal was receptive to his findings and became the beacon for the discovery [12]. Once the current concept gains traction, there are many more ways of disseminating information than were available to Lister. AD is such a catastrophe in human and financial terms that all the modalities for transmission of microbial nature of this dreaded disease should be employed. Culturing the oral spirochetes would be a useful undertaking. Treponema, in general and *T. pallidum* (syphilis) in particular, have evaded being cultivated. However, very recently, *T. pallidum* has apparently been cultured [13].

With similar techniques, it may be possible to culture the many dental spirochetes. *T. pallidum* takes considerable time to divide (as much as 3 months) and this may be one of the difficulties in getting it into culture. The serologic test for syphilis, together with penicillin treatment for positive tests, has relegated tertiary syphilis, including GP, to history. That disease has been eradicated. Currently, there is a microarray test for MCI, or early AD [14]. Perhaps this test can be modified to include pre-AD; such an alteration would lead to treatment before the disease begins, which is crucial. Treatment after the disease begins is fraught with difficulty, as is documented by 200 failed clinical trials in disease that has already begun. This fits with the pathology showing nearly all the neurons in the AD patients filled with biofilms. Until a serologic test is available, it is reasonable to consider treating with yearly penicillin (ex. Amoxicillin 500mg tid x 3 weeks) which would very likely prevent the disease. Penicillin crosses the blood brain barrier and the neuronal cell membrane and is bactericidal to sensitive microbes. All spirochetes are sensitive to penicillin. Consequently, a yearly course of penicillin would most likely kill the spirochetes prior to their making biofilms. This correlates with its treatment in GP; if penicillin is given anytime prior to the onset of dementia, this disease would be prevented, just as GP has been prevented. Again, where GP and AD have the same pathology, one would expect these results with similar treatment.

The reason for yearly treatment is the constant seeding of dental microbes, as opposed to one time exposure to *T. pallidum* in syphilis. As to resistance, it is likely that less resistance would be forthcoming with this regimen because microbes inside biofilms trade resistance genes horizontally which increases resistance. It is apparent that spirochetes by themselves (planktonic) do not cause the disease; it is when they form communities that they assume pathogenicity. Alternative therapies include Penicillin VK 500mg qid, or for penicillin allergic, Azithromycin 500mg bid x 1 week then 500mg per day x 2 weeks. For penicillin regimens, adding probenecid 500mg tid doubles the serum concentration because it decreases renal excretion. When, and if, benzathine penicillin becomes more available, it is a better option because it, plus or minus probenecid, does not require patient compliance with the treatment regimen. It is unclear whether any treatment will stall or prevent progression of the disease. This is a place where a clinical trial would potentially be helpful. The arms of the trial would be any current regimen, such as memantine vs amoxicillin/azithromycin plus rifampin 300mg daily. The active arm of the trial includes both the antibiotic and a known biofilm disperser (rifampin) [15]. This regimen would likely need to be continued for many months. A trial prior to the onset of the disease, would hardly be ethical, because the control arm would get AD if the microbes were unopposed.

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