Our first results were published in 1993 in NeuroReport

Miklossy J. Alzheimer's disease--a spirochetosis? Neuroreport. 1993 Jul;4(7):841-8.

Abstract

The aetiology of Alzheimer's disease (AD), which affects a large proportion of the aged population, is unknown and the treatment unresolved. The role of beta amyloid protein (beta A4), derived from a larger amyloid precursor protein (APP) in AD is the subject of intense research. Here I report observations that in 14 autopsy cases with histopathologically confirmed AD, spirochetes were found in blood and cerebrospinal fluid and, moreover, could be isolated from brain tissue. Thirteen age-matched control cases were without spirochetes. Reference strains of spirochetes and those isolated from brains of AD patients, showed positive immunoreaction with monoclonal antibody against the beta amyloid precursor protein. These observations suggest that spirochetes may be one of the causes of AD and that they may be the source of the beta amyloid deposited in the AD brain.
A press release and an editorial comment accompanied this initial article

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Press release of Rapid Communications of Oxford Ltd accompanying the manuscript ALZHEIMER'S DISEASE LINKED TO BACTERIAL INFECTION, CLAIMS REPORT

"A new scientific report claims that Alzheimer's Disease may be caused by spirochaetal bacteria.
The findings – reported in the July edition of the specialized scientific journal NeuroReport – presents novel data which could redirect current research into the causes of Alzheimer's Disease.
Alzheimer's Disease is characterized by a slow, progressive decline of cortical functions particularly cognition and memory. The disease is associated with the formation of plaques in the brain, the main component of which is a peptide called beta-amyloid.
Molecular and biochemical studies have shown that an excess of beta-amyloid is the primary event in Alzheimer's Disease - but to date its source has not been established.
This report by Judith Miklossy, from the University Institute of Pathology, Switzerland suggests that spirochaetal bacteria may be the source of this peptide.
Perhaps the most important implication of a spirochaetal cause of Alzheimer's Disease is that, because of the long latent stage of the spirochaetal diseases (the time between the primary infection and the development of dementia, which may be as long as 43 years), the screening by diagnostic tests and the treatment of the younger population may prevent Alzheimer's Disease.
The research has been fully per-reviewed prior to acceptance for publication in this journal.
In an accompanying editorial the significance of the article is discussed. The authors comment that "If the current findings are confirmed in other laboratories, this would certainly rank among the most significant contributions in the history of medicine…"

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An editorial comment accompanied the article

Hammond RR, Gage FH, Terry RD. Alzheimer's disease and spirochetes; a questionable relationship. Neuroreport. 1993 Jul;4(7):840.
At that time, my answer to the editorial comment was mostly the expression of my gratitude for the acceptation of the manuscript "so far removed from the current thrust of investigations into the pathogenesis of AD".

Despite the respectful skepticism they generously stated: " If the current findings are confirmed in other laboratories, this would certainly rank among the most significant contributions in the history of medicine"

Letter to the editor, by Judith Miklossy, 1993: Jul;4 (7)

"Dear Sir,
I would like to express my sincere thanks for the editorial comment which accompanied my article entitled: Alzheimer's disease – A spirochetosis?" published in July's issue of NeuroReport. I thank the authors of the editorial comment, not only for their generous remarks on the importance of the data (if it can be confirmed in other laboratories), but also because they express my own skepticism and criticism that I experienced while working on this matter. I am the first to hope that my hypothesis will soon be either confirmed or rejected by other laboratories, because of the hopes that may be raised from antibiotic treatment, which may prevent or arrest Alzheimer's dementia.
The only comment I would like to make, which is I think a misunderstanding on the part of the authors of the commentary, when they wrote "…It is surprising that with the quoted yield of spirochetes from the identified cases, no images are available of the organisms in the brain of the 14 specimens…" and they continue, "…We do not find the photomicrographs and electronmicrographs of the putative spirochetes from the AD cases…" In the article there are photomicrographs of spirochetes isolated from the cortex of two Alzheimer disease (AD) cases (Fig1D and E) and a photomicrograph of a histological section from the cortex of one of the 14 AD cases showing spirochetes in the brain visualized by a silver stain /Warthin and Starry technique; Fig. 3B), designed to demonstrate spirochetes; the second part of the sentence seems to be a contradiction of the previous statement.
Finally, I would like to thank the Editors of NeuroReport and the referees of the article who made it possible for such a finding " so far removed from the current thrust of investigations into the pathogenesis of AD…" to appear in this scientific journal. Indeed, publication of these findings offers the possibility for other laboratories to reject or to confirm such a hypothesis. In view of the current concepts regarding Alzheimer's disease, the decision of the referees and of the Editor-in-Chief could not have been an easy one.

Judith Miklossy

University of Pathology, Division of Neuropathology, University of Lausanne, Rue du Bugnon 27, 1005 Lausanne, Switzerland"

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Now, 20 years later, accumulating evidences from historical data and increasing number of recent observations from our and other laboratories answer the main concerns raised by the editorial comment (*comments in italic*):

"Alzheimer's disease continues to grow in prevalence, in its cost to society and in its share of research expenditure. Few diseases have received so much attention from both the scientific community and the public, and fewer still will continue to be as extensively investigated in this decade of the brain. Until the present the puzzle has been assembled a piece at a time, with small advances gradually adding to the overall picture. There has been extensive peer review with confirmation and rejection of hypotheses. As a result the collective experience in this field is both formidable and highly critical, and also all parties hope for a significant breakthrough, the findings in the article by Judith Miklossy in this issue (1), are so far removed from the current thrust of investigations into the pathogenesis of AD that we are certainly interested but respectfully skeptical.
Interestingly, it is not the first time and possibly not the last) that spirochetes have been blamed for an idiopathic neurological disease. (2,3) In the previous two notable examples, the spirochetes were found to be artifact and contaminant, respectively, and the etiology of multiple sclerosis remained enigmatic. If the current findings are confirmed in other laboratories, this would certainly rank among the most significant contributions in the history of medicine, but there remain several concerns regarding the present findings and

several AD phenomena that are difficult to explain in light of an infectious cause."

Growing number of epidemiological studies in the U.S. and Europe indeed show that dementia will be the most intractable health problem to confront in the next decades. Alzheimer's disease is the sixth leading cause of all deaths in the United State, and the fifth leading cause of death in Americans aged 65 and older. Whereas other major causes of death are decreasing, deaths due to Alzheimer's disease are dramatically increasing. Between 2000 and 2006, heart-disease deaths decreased nearly 12%, stroke deaths decreased 18%, and prostate cancer-related deaths decreased 14%, whereas deaths attributable to Alzheimer's disease increased 47%. An estimated 5.3 million Americans have Alzheimer's disease. It is expected that the incidence of the disease may double or triple by 2050 (Alzheimer's Association, 2009; Kulasingam, 2004; Bloom et al., 2003).

It is certainly not the first and not the last time that spirochetes will be blamed for idiopathic neurological, neuropsychiatric and systemic diseases. Recently, several of the "so called" commensal spirochetes revealed to be invasive. More than 60 different Treponema species harbor the oral cavity and several of them revealed to be invasive and predominant periodontal pathogens. As spirochetes are able to invade almost all mammalian cells and tissues and are strongly neurotropic, we can expect that similarly to *Treponema pallidum* and *Borrelia burgdorferi* they may be implicated in the pathogenesis of various disorders. Increasing amount of observations from various laboratories from around the world indeed show that they can play an important role in various chronic inflammatory disorders, including Alzheimer's disease (e.g. MacDonald and MIranda 1987; Foschi et al., 2006; Cavrini et al., 2005; Riviere et al., 2002; Zaremba et al., 2007; Miklossy 2011a,b; Shoemark and Shelley, 2015; Maheswari and Eslick, 2015).
Other spirochetes inhabit the human intestinal and the urogenital tracts and other not yet known spirochetes may be candidates as well.

My initial paper of 1993 was the first of a series of investigations, which analyzed the involvement of various spirochetes in Alzheimer's disease. Substantial amount of historic and recent observations accumulated from 1993, which enable us to understand and answer the questions raised by the editorial comment. Our results were reinforced and confirmed by other authors from various laboratories and in various countries. A recent review based on all data available in the literature shows a significant association between Alzheimer's disease and various spirochetes with a high risk factor (Miklossy, 2011a,b.) and a recent review reported historic evidence to support a causal relationship between spirochetes and Alzheimer's disease (Miklossy, 2015)

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"It is surprising that with the quoted yield of spirochetes from the identified cases, no images are available on the organisms in the brains of the 14 specimens and although we do not claim to be expert in the identification of spirochetes, we do not find the photomicrographs and electron micrographs of the putative spirochetes from the AD cases to be unquestionably compelling."

This question has been already answered in my reply in 1993, which referred to the photomicrographs illustrating spirochetes isolated from the cortex of Alzheimer cases (Fig1D and E) and those taken form histological sections, where spirochetes were visualized by the Warthin and Starry technique (Fig. 3B), Miklossy J. Alzheimer's disease--a spirochetosis? Neuroreport. 1993 Jul;4(7):841-8. ,which was developed to detect spirochetes. In addition to the elelctron microscopy images, we have also shown species-specific immunostaining of Borrelia spirochetes in an additional Alzheimer patient with Alzheimer's disease and concurrent Lyme neuroborreliosis.

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"The immunohistochemical positivity of spirochetes for amyloid precursor protein (APP) is intriguing but APP is a ubiquitous and highly conserved protein at least in mammals. It may not be surprising that it is present in

bacteria as well. Alternatively, the positive reaction may have been the result of binding to an unrelated but cross-reaction bacterial protein epitope. Ultimately, the reported immunohistochemical association would at some point have to be supported by Western blot analysis and/or protein sequencing; this is not within the scope of the current paper."

Based on the observations made in this initial report of 1993, we indeed suggested that amyloidogenic proteins might be an integral part of spirochetes and can contribute to Aβ deposition in Alzheimer's disease (Miklossy, 1993). These observations were reinforced by others, who showed that the BH(9–10) peptide on a β-hairpin segment of the outer surface protein A (OspA) of *Borrelia burgdorferi* forms amyloid fibrils *in vitro* similar to those observed in human amyloidosis (Ohnishi et al., 2000, 2001, Otzen and Nielsen 2008). Recent observations established that amyloid proteins constitute a previously overlooked integral part of the cellular envelope of many bacteria (Kim and Hecht, 2005; Otzen and Nielsen 2008; Chapman et al., 2002; Larsen et al., 2007; Jordal et al., 2009). Amyloid fibril formation not only results in toxic aggregates, but provides biologically functional molécules as well (Otzen and Nielsen, 2008; Chapman et al., 2002; Wang et al., 2008). Bacterial amyloids are involved in bacterial cell–cell interactions, in their attachment to inert solid surfaces, and in spore and biofilm formation (Wang et al., 2008). Microbial amyloids, through interaction with host proteases, also contribute to bacterial virulence, to colonization of the host and to the invasion of host cells. This would indeed be in harmony, as we have suggested in 1993, that bacterial amyloids may participate in human amyloidoses. This is in agreement with the established knowledge that chronic bacterial infections are frequently associated with amyloidosis and with the fact that inflammation and amyloidosis can be induced in vitro or in vivo by bacteria or their toxic products.

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"It is difficult to understand the absence of round cell inflammation within the parenchyma and in the CSF at all stages of the presumed infection. It is also surprising that none of the control cases had any Alzheimer' type changes, since these are very common in the elderly and which the author's proposal are indicative of an early stage of infection. This is unlike the pattern observed in other spirochetal and bacterial infections of the CNS. Furthermore, we know that AD patients show no signs or symptoms specific to a chronic ongoing infection, nor do their tissues or body fluids display round cell inflammatory changes."

That pathogens may suppress, subvert or evade host defenses and establish chronic or latent infection has received little attention in the past.

The critical role of chronic inflammation in Alzheimer's disease is now widely recognized. The role of neuroinflammation and the importance of interleukin (IL)-1 signalling were first documented by McGeer (1987), Rogers (1987) and Griffin (1989). Cellular and molecular components of the immune system reactions are associated with cortical lesions in AD. Immunohistochemical markers detected both T- helper or inducer and T-cytotoxic or suppressor lymphocytes. Activated microglia surround senile plaques. They may be proinflammatory, releasing inflammatory cytokines and other inflammatory mediators, or anti-inflammatory, promoting the healing process. In AD, they are in a proinflammatory state (Ref. 100). A series of inflammatory mediators, including cytokines, chemokines, proteases, adhesion molecules, free radicals, pentraxins, prostaglandins, anaphylatoxins and activated complement proteins, is present at the site of cortical lesions in AD (Refs 101, 102, 103). The membrane attack complex (MAC, C5b-9), which is known to play an important role in host defenses against microorganisms is also associated with plaques, tangles and neuropil threads (Refs 100, 104).

The recognition that pathogens can produce slowly progressive chronic diseases has resulted in a new concept of infectious diseases. Increasing number of recent observations show the involvement of pathogens in various chronic inflammatory disorders, *e.g.* in stomach ulcer, atherosclerosis, cardio- and cerebrovascular disorders,

diabetes and various other neurodegenerative disorders, including Alzheimer's disease. Activated macrophages and microglial cells are the principal players in pathogen-host interactions. Chronic infection leads to slowly progressive parenchymal damage, tissue atrophy and amyloid deposition (for a review based a high number of references see Miklossy, 2011a,b).

Polymorphisms in the gene encoding TNF-α might determine a strong cell-mediated immune response or a weak or absent cellular response, reflecting the genetic variability in cytokine production (Knight and Kwiatkowski, 1999, Shaw et al. 2001). In the absence of cell-mediated immune responses, the microorganism can spread freely and accumulate in infected host tissues (Roy et al. 1997). Accordingly, in Mycobacterium leprae infection, these distinct phenotypes are the tuberculoid and the lepromatous leprosy. In the tuberculoid or paucibacillary form, there is a strong inflammatory infiltration and the number of microorganisms is very low. Conversely, in the lepromatous or bacillary form, the inflammatory infiltrates are poor or absent and the number of Mycobacterium leprae is high.

A similar polarity in host reactions – the infiltrative form with strong cell- mediated immune responses and few spirochetes versus the atrophic form, lacking lymphoplasmocytic infiltrates but with numerous spirochetes – also occurs in response to *Treponema pallidum*and *Borrelia burgdorferi* infection (Pacheco e Silva, 1926, 1926-27; Rizzo, 1931; Miklossy, 2008; Miklossy, 2004). The influence of TNF-α polymorphism on spirochetal infections has also been demonstrated (Marangoni et al. 2004).

General paresis of the insane, paretic dementia or dementia paralytica is a chronic meningoencephalitis caused by the direct invasion of brain parenchyma by *Treponema pallidum*. In the infiltrative form, mood disorders and psychosis predominate, and lymphoplasmocytic meningoencephalitis is the characteristic pathology (Rizzo, 1931, Miklossy, 2008). The atrophic form is characterized by slowly progressive dementia and cortical atrophy, more accentuated in the frontotemporal regions (Pacheco e Silva 1926, 1926-27). Spirochetes form masses, plaques or colonies and disseminate as individual filaments restricted to the cerebral cortex (Pacheco e Silva 1926, 1926-27). These spirochetal masses and individual spirochetes are morphologically undistinguishable from senile plaques and neuropil threads. Pacheco e Silva (Pacheco e Silva 1926, 1926-27) analyzing the brains of more than 60 patients with the atrophic form of general paresis, reported that the number of spirochetes and spirochetal 'plaques', particularly numerous in the hippocampus and the frontal cortex, increases in parallel with the severity of cortical atrophy (Pacheco e Silva 1926, 1926-27). In this form, lymphoplasmocytic infiltrates are rare or absent. Severe neuron loss, reactive microgliosis and astrocytosis together with accumulation of 'paralytic iron' are the additional pathological characteristics of this form (Merritt, 1946). The occurrence of neurofibrillary tangles is also documented (Perusini 1987; Miklossy 2008 Handbook; Bonfiglio 1908; Vinken and Bruyn, 1978) such as the presence of local amyloid deposition (Volland, 1938), which, as in Alzheimer's disease, revealed to be beta-amyloid (Miklossy et al., 2005).

It is also noticeable that in one of the four famous cases of Aloïs Alzheimer there is a 30 years history of syphilis. I cite here Bonfiglio: "I must mention that I had found these same foci ("senile plaques") even in other cases given to me by Alzheimer, cases which, as far as I know, have only one common feature, that is a "history of syphilis" (p. 29); he added "I think the coincidence of this foci with the neurofibrillary alterations described above cannot be disregarded". (F. Bonfiglio). "Indeed, many of the alterations observed in my own cases are similar to those found in certain forms of neurosyphilis" 19.

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Other aspects of the demographics of AD would remain puzzling should it be recognized as an infectious disease. For instance, it is difficult to explain how persons in close contact with AD patients do not exhibit a greater risk for developing the disease that the population at large. It is equally difficult to account for the clear pattern of inheritance of AD in the significant number of cases that are familial. The frequent dementia

and Alzheimer-like pathology of trisomy 21 is also not easily explained on the basis of an infectious agent unless it is proposed that Down's syndrome and familial AD impart some universal susceptibility to this organism, a phenomenon for which there is poor precedent.

Only around 0.1% of Alzheimer's cases are familial forms of autosomal dominant inheritance (Blennow et al., 2006). Ttoday we know that APP is an inflammatory molecule and plays an important role in the regulation of immune system reactions and in T-cell differentiation (Allen et al. 1991; Mönning U et al. 1990; Ledoux et al. 1993). Genetic mutations occurring in the APP, PS1 and PS2 genes are all related to the processing of APP (Hardy, 1997). Therefore, defects in these genes may result, as we suggested in 1993, in an increased susceptibility to infection. APOE ε4 enhances the expression of inflammatory mediators (Urosevic and Martins, 2008, Licastro et al. 2007) and has a modulatory function in susceptibility to infection as well, as shown for various bacteria, viruses and protozoa (Urosevic and Martins, 2008; Licastro et al. 2007; Corder et al. 1998; Itzhaki, R.F. et al. 2004; Bhattacharjee et al. 2008).

Because of the role of various types of spirochetes, but particularly because of the high incidence of periodontal pathogen spirochetes one may expect the possibility of a familial aggregation. The long latent stage, sometimes several decades, between primary infection and the manifestation of dementia should be considered in future studies. The increasing number of cases with age might be in harmony with such slowly progressive infection. That a slow-acting unconventional infectious agent, acquired at an early age and requiring decades to become active, might be involved in Alzheimer's disease was considered by several authors (Wisniewsky, 1978; Khachaturian, 1985). A growing number of recent observations indicate that infectious agents are indeed involved in the pathogenesis of Alzheimer's disease.

Analyzing a substantial number of Alzheimer's cases spirochetes detected by anti-bacterial peptidoglycan antibodies were present not only in definite Alzheimer's cases but in 10 cases with mild or moderate Alzheimer-type changes as well. This indicates that controls used in Alzheimer research should be without any AD-type changes.

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Finally we look to Koch's postulates for the common basis and minimal criteria for the classification of a disease as infectious. Indeed, the putative organisms is claimed to be present in all of the index cases and in none of the control cases. The authors also report that they have been able to culture the organism. However, it has yet to be transmitted to another animal, identified therein and recovered from the recipient animal. This missing evidence will like wise leave doubts about the reported findings and conclusions until successfully performed. Its lack of transmissibility is instead confirmed in the world's experience of the demographic patterns of this disease in man. It should be noted that the reported transmission of AD to primates has since been retracted (4) (see also authors' reference 16).

In a recent review (Miklossy, 2011) a statistical analysis showed a strongly significant association between spirochetes and AD when considering all positive and negative data available in the literature A critical analysis of the substantial amount of data following established criteria of Koch and Hill was in favor of a causal relationship. Persisting inflammation and amyloid deposition initiated and sustained by chronic spirochetal infection form together with the various hypotheses suggested to play a role in the pathogenesis of AD a comprehensive entity.

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The paper remains an infringing report that will raise the interest, if not voices and blood pressure, of many in the neuroscience community. We remain skeptical and even incredulous at the thought that such an etiology

for such an important and exhaustively studied disease could have been overlooked by so many including ourselves. This is not a condemnation but it should be emphasized that such remarkable results would have to be consistently replicated, and expanded upon by other investigators before the conclusions of this report will undoubtedly receive the judgments that will follow

It has been known from a century that chronic spirochetal infection can cause slowly progressive dementia and amyloid deposition, which, in addition, revealed to be beta-amyloid. As it is known and it is established that chronic bacterial infection can cause dementia, it is our obligation to follow this line of research. That microorganisms may play a role in senile plaque formation has been suggested by Oskar Fischer in 1907 a century ago and was cited and discussed by Aloïs Alzheimer and his colleagues. It is noticeable that one of the four first famous cases of Alzheimer had 30 years history of syphilis. As mentioned by Perusini (1922) the pathological findings in the brain were identical to those of the three other cases given to him by Aloïs Alzheimer. As expressed by Katherine Bick and Luigi Amaducci (1987) in their introduction to the book entitled Early Story of Alzheimer's disease: "For the time, the relatively recent demonstration that such disorders could be the result of a bacterial infection colored the thinking of many of the neurologists and neuropsychiatrists of the day. Thus, one finds many efforts in the papers attempting to find other infectious agents, which could be considered as the primary cause of the dementias seen in the institutions for the deranged……With the promise of the tools of modern scientific neurology and serendipity, it may be our generation's good fortune to reach the high ground and see answers plainly. " This is indeed the goal of all of us.

Following our initial manuscript on the role of various spirochetes in Alzheimer's disease (Miklossy, 1993), we presented further evidences that the helically shaped filaments compatible with spirochetes observed in the brain, CSF and blood taxonomically belong to the order Spirochaetales (Miklossy, 1994a) as they possess endoflagellae. Atypical, filamentous L forms of spirochetes were also observed in the blood of living patients and were absent in controls (1994b). They were positive for DAPI indicating that they contain DNA and were immuno-reactive to bacterial peptidoglycan (Miklossy, 1995). In three of the 14 initial AD cases we cultivated in BSK II medium (Miklossy, 1993). A molecular analysis definitely identified the spirochetes cultivated from the brains of these 3 AD cases as *Borrelia burgdorferi sensu stricto* (Miklossy, 2004). Species-specific antigens and DNA were detected in the brains of these same patients and serological analysis of the blood and CSF was positive for *Borrelia burgdoferi* (Miklossy et al., 2004). Furthermore, lesions similar to senile plaques, neurofibrillary tangles, neuropil threads, and granulovacuolar degeneration, accumulation of Aβ, increased APP levels and phosphorylated tau were induced by exposure of mammalian neuronal and glial cells and CNS organotypic cultures to spirochetes (Miklossy et al., 2006).

We have also shown that neuropil threads and neurofibrillary tangles accumulate very early in the olfactory bulb and tract in Alzheimer's disease (Christen-Zaech et al., 2003) and that the local amyloid deposits in general paresis, as in AD, is beta amyloid (Miklossy et al., 2006). We have shown that similarly to general paresis the capillary network is severely damaged in Alzheimer's disease and causes watershed cortical microinfarcts (Suter et al., 2002). As in neurosyphilis, concurrent cerebral infarcts and cortical atrophy frequently occur in AD. Finally a strongly significant association with high risk factor was found between spirochetes and Alzheimer's disease and an analysis following objective criteria of Koch and Hill showed that he association is in favor of causal relationship (Miklossy, 2011a).

In conclusion, evasion of pathogens from host defense reactions results in sustained infection and inflammation. Pathogens, and their poorly degradable debris are powerful inflammatory cytokine inducers and activators of complement. They affect vascular permeability, generate nitric oxide and free radicals, and induce apoptosis and amyloidosis. The microorganisms and their toxic components can be observed in the affected brains, along with host immunological responses.

Several types of spirochetes can co-infect together (Blatz et al., 2005) and coinfection by various types of spirochetes occurs in Alzheimer's disease (Riviere et al., 2002). Coinfection of spirochetes with other bacteria

and viruses can accelerate the degenerative process, exacerbate brain damage and worsen dementia.

Infectious agents can initiate the degenerative process in Alzheimer's disease, sustain chronic inflammation, and lead to progressive neuronal damage and amyloid deposition. The accumulated knowledge, views and hypotheses proposed to explain the pathogenesis of Alzheimer's disease fit well with a spirochetal origin of the disease. The outcome of infection is determined by the genetic predisposition, by the virulence of the infecting agent, and by various environmental factors, such as exercise, stress and nutrition.
As suggested by Hill, once the probability of a causal relationship is established prompt action is needed. More attention and support is needed for this emerging field of research. Infection starts long before the manifestation of dementia; therefore, an adequate treatment should start early. As antibacterial therapy is available, as in syphilis, one could prevent and eradicate dementia. We should not wait another century, as the effect on the suffering of patients and on the reduction of healthcare costs would be considerable.

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FURTHER RESEARCH

ROLE OF INFECTION IN STROKE AND ALZHEIMER?S DISEASE

Treponema pallidum and *Borrelia burgdorferi* spirochetes, in late syphilis and late Lyme disease can cause cerebral infarct and cognitive decline (dementia) in parenchymatous neurosyphilis and Lyme neuroborreliosis. The cognitive decline (dementia) is caused by the direct invasion of brain parenchyma by spirochetes (direct parenchymal involvement) years or decades follwoing the primary infection.

Cerebral infarcts in the meningovascular form of neurospirochetoses (Meningovascular form of neurosyphilis and Lyme neuroborreliosis) is not caused by spirochetal invasion of brain tissue. The parenchymal involvement is secondary to the occlusion of affected meningeal arteries. It may lead to"vascular" dementia.

Consequently, to exclude infection by *Borrelia burgdorferi*, in patients with stroke, particularly in endemic areas of Lyme disease is primordial. As T. pallidum also caused cerebral infarcts, the possibility that various other spirochetes can also cause stroke and cerebral infarcts should be also considered.

Here we describe the line of research we have followed during the last 15 years with respect to the involvement of spirochetes in Alzheimer's disease and in cerebral infarcts. This line of research represents a panel of experiments, listed below, which are linked to each other. The goal is to answer the question, whether several types of spirochetes, including *Borrelia burgdorferi,* various periodontal pathogen spirochetes, intestinal spirochetes etc., may be involved in Alzheimer disease and stroke.