



# Plaques of Alzheimer's disease originate from cysts of *Borrelia burgdorferi*, the Lyme disease spirochete

Alan B. MacDonald \*

St. Catherine of Siena Medical Center, Department of Pathology, 50 Rte 25 A, Smithtown, NY 11787, USA

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**Summary** Here is hypothesized a truly revolutionary notion that rounded cystic forms of *Borrelia burgdorferi* are the root cause of the rounded structures called plaques in the Alzheimer brain. Rounded 'plaques' in high density in brain tissue are emblematic of Alzheimer's disease (AD). Plaques may be conceptualized as rounded 'pock mark-like' areas of brain tissue injury. In this century, in brain tissue of AD, plaques are Amyloid Plaques according to the most up to date textbooks. In the last century, however, Dr. Alois Alzheimer did not require amyloid as the pathogenesis for either the disease or for the origin of its plaques. Surely, amyloid is an event in AD, but it may not be the primal cause of AD. Indeed in plaques, amyloid is regularly represented by the 'conophilic core' structure which is so named because the waxy amyloid material binds the congo red stain and is conophilic. However an accepted subset of plaques in AD is devoid of a conophilic amyloid core region (these plaques 'cotton wool' type plaques, lack a central conophilic core structure). Furthermore, there is 'plaque diversity' in Alzheimer's; small, medium and large plaques parallel variable cystic diameters for *Borrelia burgdorferi*. Perturbations of AD plaque structure (i.e. young plaques devoid of a central core and older plaques with or without a central core structure) offer room for an alternate pathway for explanation of ontogeny of the plaque structures. If amyloid is not required to initiate all of the possible plaques in Alzheimer's, is it possible that amyloid just a by product of a more fundamental primal path to dementia? If a byproduct status is assigned to amyloid in the realm of plaque formation, then is amyloid also an epiphenomenon rather than a primary pathogenesis for Alzheimer's disease. In the 'anatomy is destiny' model, cysts of borrelia are always round. Why then not accept roundness as a fundamental 'structure determines function' argument for the answer to the mystery of why Alzheimer plaques are always round? Parataxis causality, a concept borrowed from philosophy, is the error that comes from linking two events, which occur contemporaneously or in close proximity to one another with a cause and effect relationship. Parataxis tells us that what appears to be cause and effect in the couplet 'amyloid plaque' merely by a proximity relationship may be 'spurious causality' which is a cognitive dead end.

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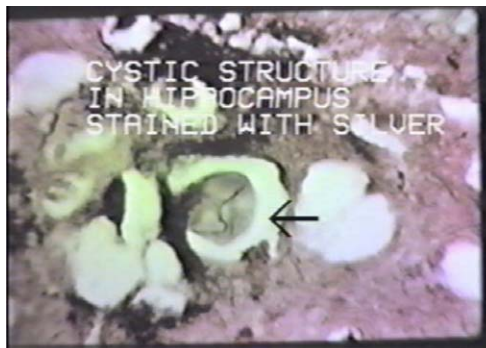
## Introduction

The first published report of a cystic form for *Borrelia burgdorferi*, the etiologic agent of Lyme

Borreliosis, was offered as a video poster presentation 'Concurrent Neocortical Borreliosis and Alzheimer's Disease — Demonstration of a Spirochetal Cyst Form', at the International Conference on Lyme Disease and Related Disorders which was sponsored by the New York Academy of Sciences and the New York

\* Tel.: +631 862 3764; fax: +631 862 3863.  
E-mail address: [inmacdonald@yahoo.com](mailto:inmacdonald@yahoo.com).

Department of Health on September 14–16, 1987 [1].



Cyst of *Borrelia* in Alzheimer brain tissue section stained with Krajian silver impregnation, 400x original magnification, this image from the Original video poster presented at the New York Academy of Sciences, 1987.



Cystic *Borrelia burgdorferi* from Alzheimer brain fingerprint with H9724 monoclonal Antibody 400x magnification. Note the internal structures within the cyst, some granular and others filamentous in profile.

Photograph date 1987



Cystic *Borrelia burgdorferi* in fingerprint monolayers from fresh Alzheimer autopsy brain tissue. (400x original magnification) Fluorescence shows reactivity with protein epitopes specific for *Borrelia burgdorferi* and *B. hermsii*, murine monoclonal Antibody H9724, a gift from Alan G Barbour, MD.

Photograph date 1987

Subsequently, beginning in 1994, published reports of cysts of *Borrelia burgdorferi* began to appear in the peer reviewed literature, and to date more than 40 articles from workers in Europe and the United States have ratified the scientific validity of rounded cystic forms of the spirochete

emerging from the corkscrew forms under conditions of adversity (starvation, osmolar shock, acid pH, and antibiotic effects) [2].

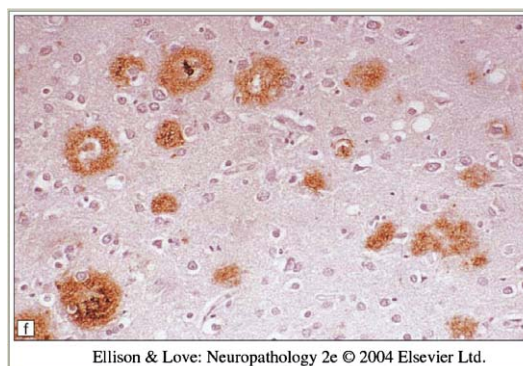
Alzheimer's disease associated with corkscrew shaped *Borrelia* spirochetes in autopsy brain tissue has been reported by two pathologists [3–6], but cystic forms of *Borrelia burgdorferi* in Alzheimer brain tissues have only been the focus of research for one pathologist in the world [7].

Cystic profiles of borrelia closely correspond to the diverse profiles of plaques, namely they are always round, and are capable of increase in size from little to big as cystic spirochetal growth progresses. Maturation of cysts parallels "maturation" of plaques of increasing age, based on observations of spirochetal cysts in a tissue culture model. Cystic spirochetes in tissue culture incorporate injured cells into their interior regions. Amyloid fibrils within blood vessels of the brain may wind up within the plaque region, now redefined as spirochetal cyst "territory", merely because the rounded cyst "landed on a blood vessel" which contained amyloid in its wall. DNA hybridization methods demonstrate the areas where *Borrelia* DNA is deposited in the Alzheimer brain. Hybridizations using DNA from the spirochete develop a "map" of the terrain of the brain where, like little rounded villages and cities, rounded "map sites" of spirochetal DNA appear. Spirochetal sites on these "DNA maps" match the sites of the plaques in the Alzheimer brain. Now is the time for a new opportunity to re-evaluate Alzheimer's disease with DNA mapping methods.

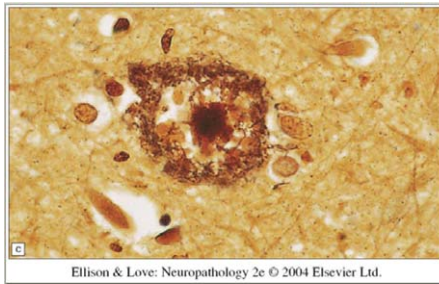
## The hypothesis

Cystic spirochetes show close structural similarities to the profiles of AD plaques. First, will be images of the plaques, second will be spirochetal cysts.

Therefore, the hypothesis was formulated that the cysts of the spirochete are the actual cause of the plaques.

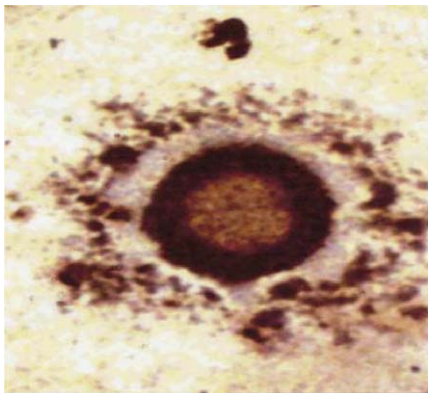


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#### Mature plaque in Alzheimer's disease

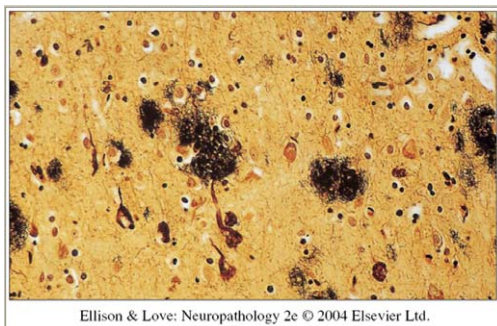
Maturity is typified by the well developed central amyloid core region, and by zonation within the plaque structure, including a Coronal zone of increased silver staining at the outer edges of the plaque and clearing of the region flanking the central amyloid core



Cystic form of *Borrelia burgdorferi* stained with silver showing rounded contour and zonation within the center of the cyst. Pure culture of *Borrelia burgdorferi* from the American Type Culture collection, allowed to age for one year Magnification 1000x.

Year 1996

Currently, there is no iterated model to explain, in the absence of the cystic pathway to plaque formation in AD, a mechanism to define the facts that plaques in AD are virtually always round in contour, variable in diameter and separated by neural tissue that is "plaque free", in the planes of histological section.

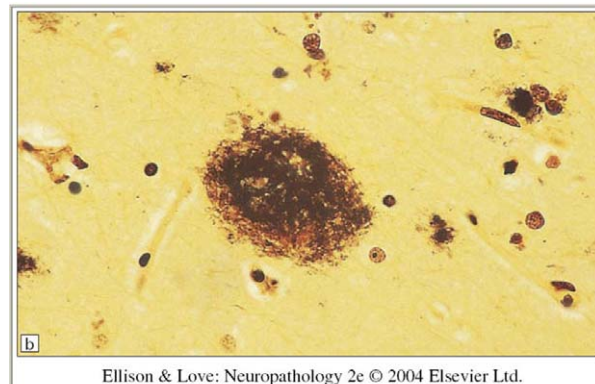


Diverse plaque sizes in Alzheimer's disease

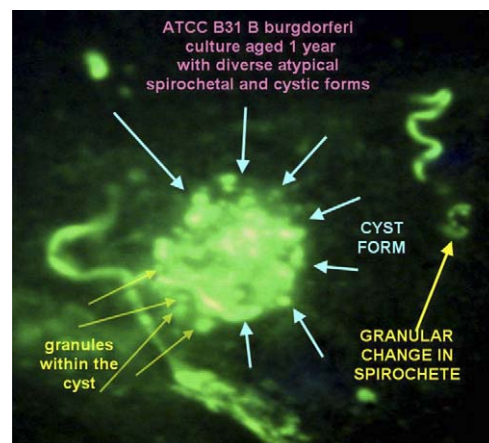
If "bad human DNA" is responsible for the origin of Plaques in AD, the chronology, topography, and ontogeny of plaques should be monotonous in image profiles, with all plaques emerging from a common morphology, and all plaques showing the same maturation sequence. In practice, plaques in AD are diverse in morphology and heterogeneous in maturation (as would be expected in maturation of spirochetal cysts). Diversity and heterogeneity are the "stuff" of cystic spirochetes.

Cyst forms, intruded into brain tissue, as a consequence of chronic infection, would solve the puzzle of the origins of the plaques. Morphologic issues in plaque ontogeny, heterogeneity, and maturity are surveyed in Illustrations in captions I through VII:

[I] Plaque roundness, corresponds to spirochetal cyst form roundness:

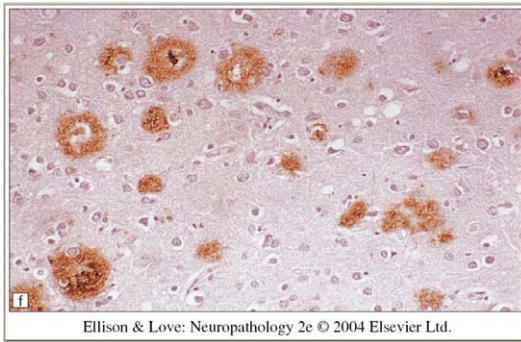


One plaque stained with silver – Alzheimer's disease – Note the round contour- and diminutive emerging plaque-like structures at 2:30 o'clock and 4 o'clock positions

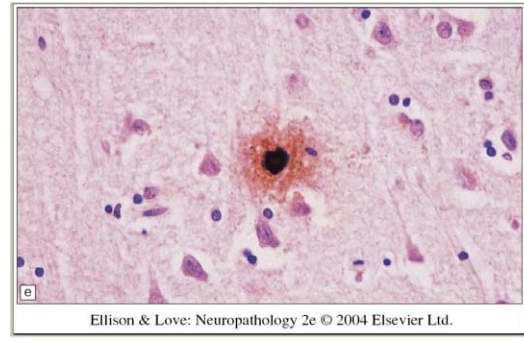


[II] Plaque diversity in diameter (small, medium, large), corresponds to variable spirochetal cyst diameters. Small plaques lack a waxy amyloid core region.



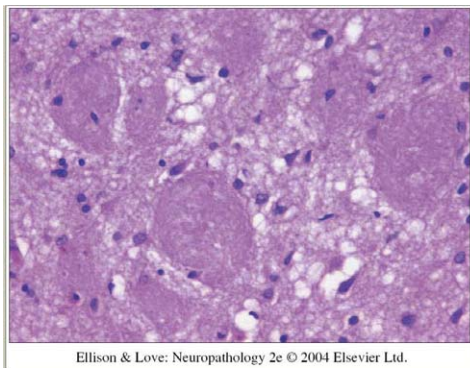


Plaques of varying size in Alzheimer's disease

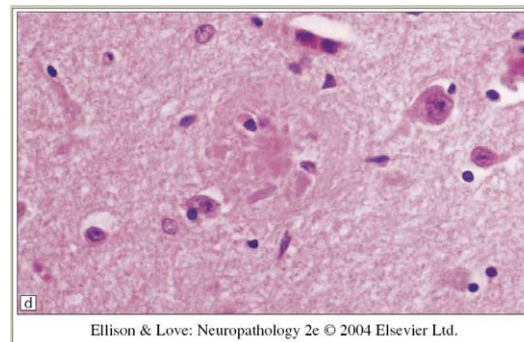


An Old plaque in Alzheimer's disease showing involutinal changes in the amyloid core "Burnt-out"(end stage) plaques. From figure 31-8 e, Ellison and Love (above)

- [III] Some "cotton wool" plaques defy the congophilic amyloid core dogma for amyloid plaques. Note that all spirochetal cysts in culture conditions, are independent of a congophilic amyloid core structure.

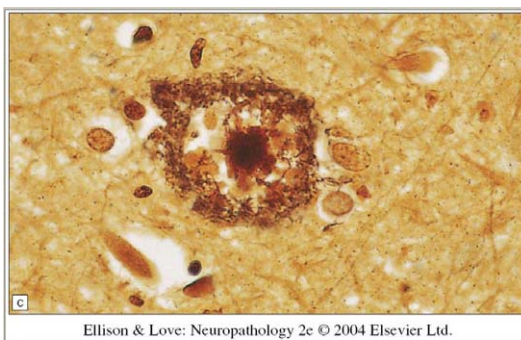


Cotton wool type plaque in Alzheimer's – note the lack of a central amyloid core structure



Plaque in Alzheimer brain without special silver staining or Tau immunostaining

- [IV] The phenomenon of evolution towards "histologic maturity" in plaques in AD is reminiscent of centrifugal enlargement of cystic spirochetal profiles.



A Mature plaque in Alzheimer's disease with a well-defined central amyloid core

- [V] Low plaque density in brains of persons without dementia may be a manifestation of subclinical spirochetal infection which has not progressed as far as the cases of Alzheimer's.

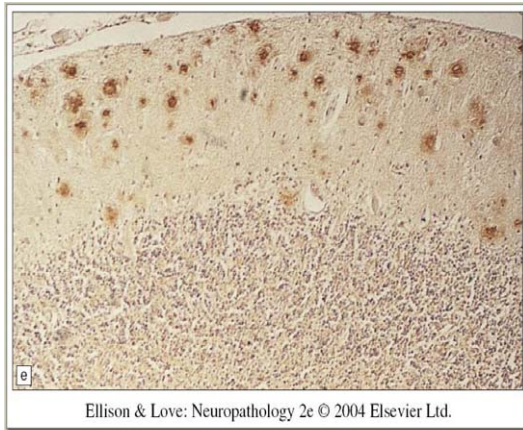
[No Image shown for incidental Plaques in autopsy brain from patients without dementia.]

Plaque densities in the CERAD system for Alzheimer grading or the Braak and Braak system for Alzheimer grading, correlate the number of plaques per unit area in the brain with degrees of dementia and stages of Alzheimer's disease.

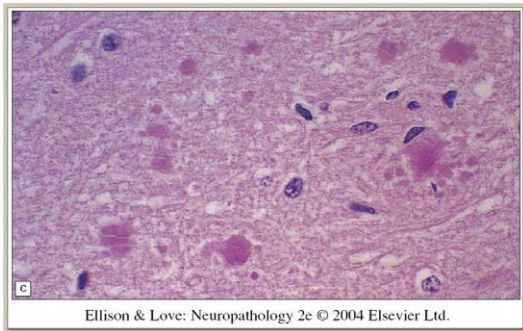
- [VI] Plaques in the brains of Down's syndrome (a manifestation of spirochetal infection acquired in utero).

[No image shown for Down's syndrome Plaques].

- [VII] Plaques in the brains of patients with other neurodegenerative disorders of the Non-Alzheimer type (Creutzfeldt Jacob Disease). Morphologic similarity between plaques in various Non Alzheimer's type neurodegenerative disorders, is striking.



PLAQUES, in Creutzfeldt Jacob disease of the usual type



Plaques, in Variant form of Creutzfeldt Jacob disease

Origin of plaques in diseases other than Alzheimer's, such as Creutzfeldt Jacob disease in which prions rather than amyloid proteins are the root cause, creates further problems for the amyloid plaque dogma. If amyloid is indeed the root cause of plaques in Alzheimer's, and prions are the root cause of Creutzfeldt Jacob disease, then what is left over to explain Creutzfeldt Jacob plaques? The common thread linking all plaques in all categories of diseased neural tissues could be the spirochete model. Diversity of clinical expressions of neuroborreliosis parallels the protean clinical expressions of *Treponema pallidum* infection in the nervous system. Tabes dorsalis and General paresis are two radically different clinical presentations of the same spirochete.

Differences of the "Neurodegenerative Phenotypes" as is shown in the Tabes to Paresis dichotomies, might be traced to differences in spirochetal neurotropisms, based on genomic strain differences in the same spirochetal family of organisms. Variant pathogenicity in the *Borrelia* spirochetes, genetically determined, might result in diverse

patterns of clinical diseases, just like the Tabes to Paresis dichotomy for *Treponema pallidum*. One spirochete produces two totally different diseases.

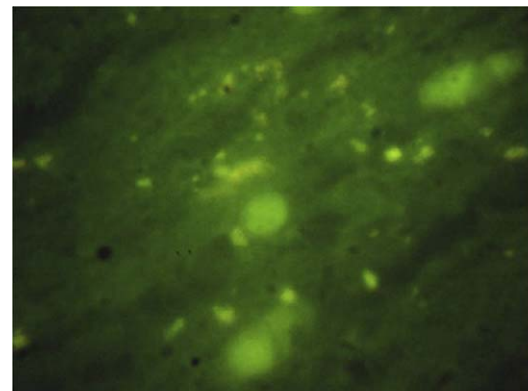
## Evaluation of the hypothesis

Molecular interrogation of Alzheimer brain tissues has yielded evidence of specific flagellin B sequences which are recoverable from DNA digests of autopsy frozen brain tissues provided by the Harvard University McLean Hospital Brain Bank, with seven cases yielding essentially identical and heretofore unique PCR products which have been reported previously [8].

The specific DNA of *Borrelia burgdorferi* which was recovered from the Harvard Alzheimer brains was used to design DNA probes (molecular beacons). These beacons were used to interrogate the autopsy brain tissue from a single case of Alzheimer's disease, which developed 8 years after the detection of *Borrelia burgdorferi* specific antibodies in the patient's spinal fluid.

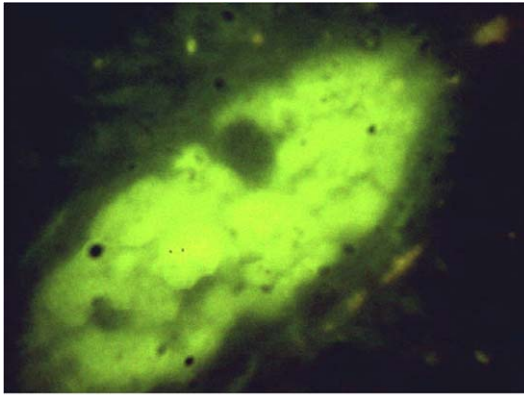
Solid phase in situ DNA hybridization was accomplished using the deparaffinized autopsy hippocampus slides with the molecular beacon for a flagellin B DNA sequence which was found in seven Harvard McLean Hospital Alzheimer Brain Bank cases [8].

The positive domains of in situ DNA hybridization recapitulated the topographic distribution, and size, and shape of Alzheimer plaques in the hippocampus, using conventional staining methods to define plaque topography.

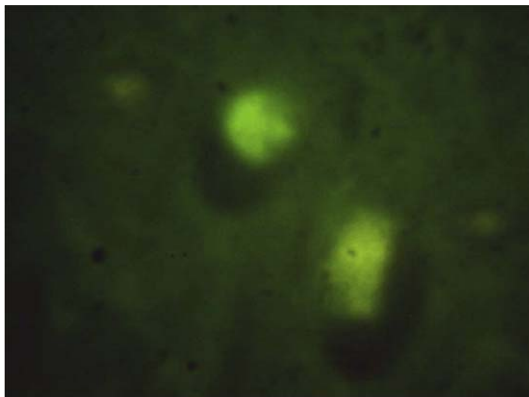


*Borrelia burgdorferi* flagellin DNA in situ DNA hybridization, Alzheimer hippocampus 1000x magnification.

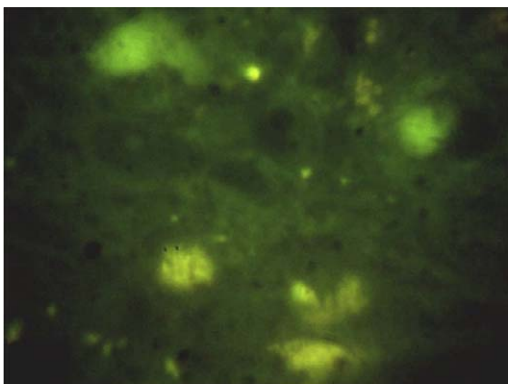




*Borrelia burgdorferi* Flagellin DNA , In situ hybridization, Large Plaque  
1000x original magnification

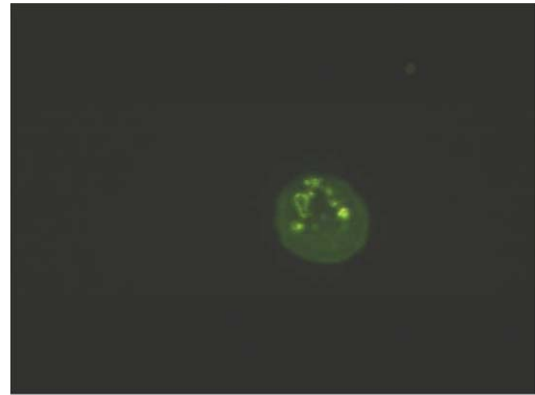


*Borrelia burgdorferi* Flagellin DNA , hippocampus Alzheimer's disease  
1000x magnification



*Borrelia burgdorferi* flagellin DNA hybridizes to autopsy Alzheimer hippocampus,  
1000x magnification

field at commencement of culture, with cysts detected at 16 months later. Spinal fluid antibodies positive in ImmunoBlot at a regional reference laboratory.

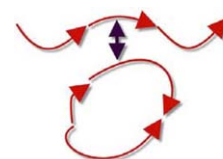


Cystic *Borrelia burgdorferi* from spinal fluid culture  
Magnification 1000x



Cystic *Borrelia burgdorferi* from spinal fluid culture,  
Magnification 1000x.

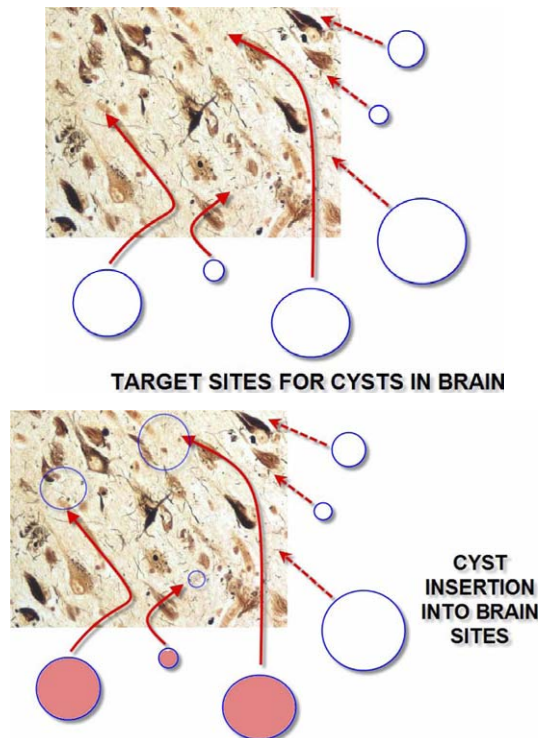
Line drawings of the interconversions of corkscrew shaped *Borrelia burgdorferi* into Cystic spirochetes.



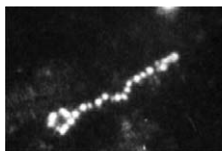
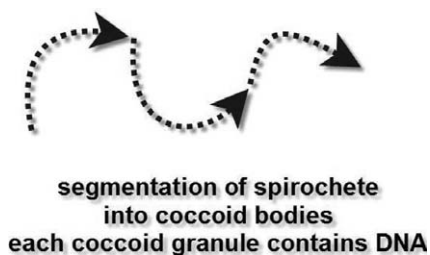
SCHEMATIC CORKSCREW  
TO  
CYST CONVERSION  
INSERTION of Cysts Cartoon

## Empiric data

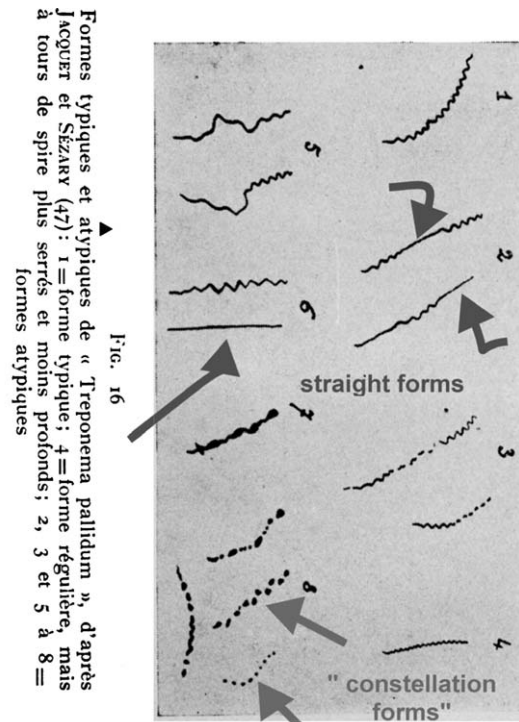
In vitro Culture of Cysts of *Borrelia burgdorferi* from the spinal fluid of another patient (no dementia). Spinal fluid negative for spirochetes by dark-



Line drawings of the interconversion of corkscrew shaped *Borrelia burgdorferi* into coccoid "dot-like" spirochetal "packets" of DNA, (also called granular spirochetes, which might explain all cases of granulovacuolar degeneration of hippocampal neurons in Alzheimer's disease [9].



*Borrelia burgdorferi* with murine monoclonal antibody H5332 fingerprint from fresh brain Alzheimer's disease year 1987



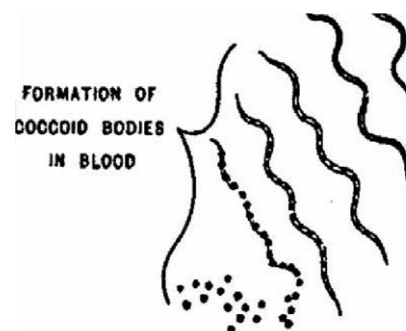
BULL SOC. MED. HSP. PARIS VOL 24: 114-116, 1907

Montage of variant spirochetal profiles from syphilis

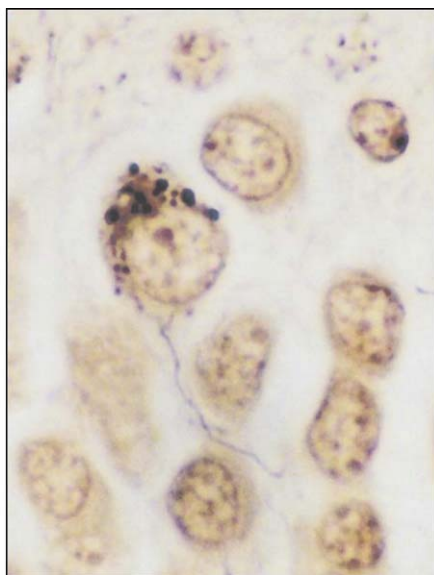
Year 1907



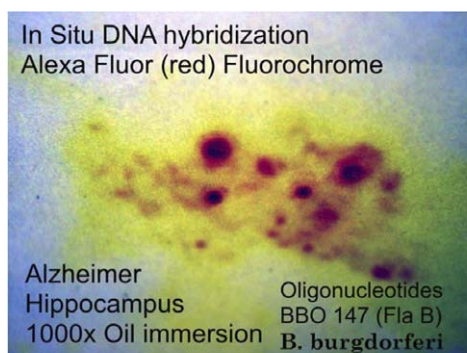
Year 1907, Paris France  
Jacquet and Sezary  
line drawings of syphilis granular "constellation" forms of *Treponema pallidum*



Hindle, 1912, emergence of granular "coccoid" forms from spirochetes



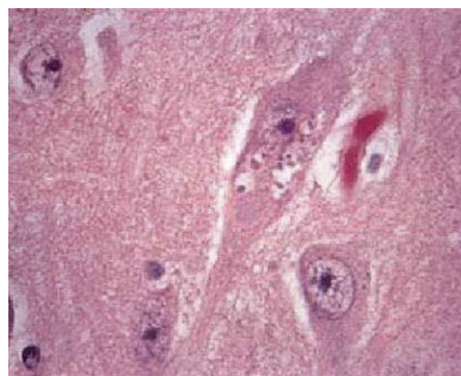
Granular bodies within hippocampal nerve Alzheimer's disease at 9 o'clock to 2 o'clock positions with spirochete – like profile at 6 o'clock, Bielschowsky stain, original slide borrowed from the Harvard McLean Brain Bank. This case was used in Reference 8 (Polymerase Chain Reaction – Molecular Interrogation for Flagellin B DNA study), Magnification 1000x,



In situ DNA hybridization with flagellin DNA probes from *Borrelia burgdorferi*. Alzheimer hippocampus. Red signals within the cytoplasm of a nerve cell recapitulate the cytoplasmic profiles of granulovacuolar degeneration in Alzheimer's disease.

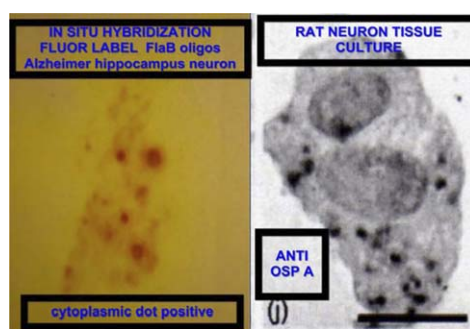


In situ DNA hybridization hippocampus tissue section from Alzheimer's disease showing dot like positive signals within the cytoplasm of nerve cells using flagellin DNA probe for open reading frame BBO 0147 of *Borrelia burgdorferi*, 1000x magnification



Granulovacuolar degeneration in neuron Alzheimer's disease

From Ellison and Love, Neuropathology, Copyright Elsevier pub. all rights reserved.



Reference 9.

#### Comparison of intracellular *Borrelia* spirochetal profiles

Right panel shows rounded coccoid bodies within the cytoplasm of a rat nerve cell incubated in tissue culture with virulent *Borrelia burgdorferi* for several weeks to yield evidence of intracellular penetration of spirochete fragments (reactive with monoclonal antibody H5332, which uniquely recognizes an epitope of outer surface protein A (OspA) which defines *Borrelia burgdorferi* at the proteomic level. (Miklosy et al) Left panel is a human Alzheimer nerve cell which shows positive signals in the cytoplasm in a granulovacuolar degeneration profile. (In situ DNA hybridization with flagellin B DNA of *Borrelia burgdorferi*.)

## Consequences of the hypothesis

The hypothetical proof that *ALL* of the plaques in the brains of patients with Alzheimer's disease are positive for the DNA of *Borrelia burgdorferi* would silence the argument, now currently discussed by some neuropathologists which is as follows: "...coincidence links those cases of Alzheimer's disease showing detection of antibodies in blood testing against *Borrelia burgdorferi*..." This argument is wrapped in the caveats that Alzheimer's is a relatively common disease. Lyme borreliosis is a common disease. Overlap of the two conditions is expected by chance alone.

Refutation of the "pure coincidence" gambit is found in the localization of the DNA of the alleged pathogen to the sites of tissue injury which are definitional for Alzheimer's. DNA of the alleged perpetrator at the scene of the crime constitutes "molecular proof" of a spirochetal (*Borrelia burg-*



*dorferi*) pathogenesis. I offer these ideas as a gift to anyone who might find some logic in them; the fruit of 20 years of labor by one man working to find the cause of the disease which took the life of his grandfather, with the hope that Alzheimer's disease might follow the eventual pathway to antispirechetral therapy, which was blazed by a hero, Dr. Hideyo Noguchi, in the year 1913, when he proved the spirochetral pathogenesis of General Paresis of the Insane.

## Acknowledgements

This work was supported by a research grant from the Turn the Corner Foundation, New York and ILADS (International Lyme Disease and Related Disorders Society), and generous institutional support from the St. Catherine of Siena Medical Center, Smithtown, New York.

The Harvard University McLean Hospital Brain Bank provided frozen Alzheimer's disease brain tissues for the molecular interrogation studies by polymerase chain reaction with flagellin B primer oligonucleotides.

Sequencing of PCR products was completed at Lark Technologies, a division of Genaissance Inc. Molecular beacons were designed by Alan B. MacDonald, MD, and synthesized by Gene Link Inc, Hawthorne, New York.

Judith Miklossy MD offered expert critiques for improving the experimental designs for the granulovacuolar degeneration module in this work. Dr. Miklossy's work in *Borreliosis* and Alzheimer's disease has been a source of inspiration and a model of academic excellence.

## References

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- [7] MacDonald AB. Cystic *borrelia* in Alzheimer's disease and in non-dementia neuroborreliosis. In: Proceedings of the 10th international conference on Alzheimer's disease and related disorders [ICAD]. Abstract 06-A-2798-Alz; 2006.
- [8] MacDonald AB. Transfection "Junk" DNA — A link to the pathogenesis of Alzheimer's disease? *Med Hypotheses* 2006; 66:1140–1.
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