

Oct 30, 2005
ILADS National Meeting
Philadelphia, Pennsylvania
Borrelia and Alzheimer's Disease

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Smithtown, New York

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Plaques



GVB

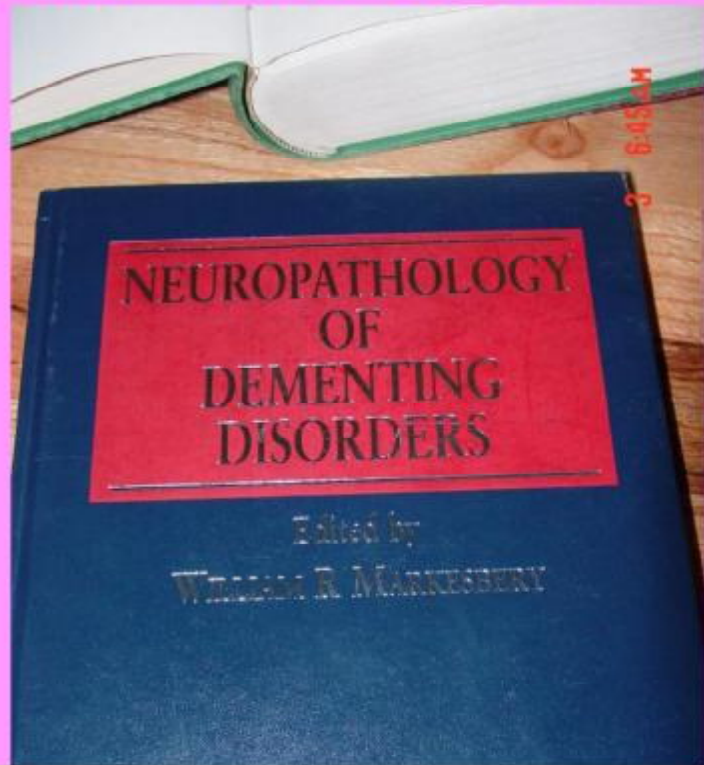
Tangles



Alzheimer's
patterns of
injury
Nerve cell
loss

How do we know?

Is the Textbook version correct?



Should We Kill the Messenger?

- “Lyme Borreliosis”
- Vs
- “Lyme Disease”
- Allowed Manifestations
- Arthritis, Carditis, Skin- “it is”, Meningitis

Can You Identify the duck if you only see
A Keyhole view ...
Can you “Connect the Dots???”



Connecting.....
The Dots
Figurative
and
Literal

In Dementia
You
lose the
Ability to

Connect the dots

Dementia in Syphilis

- Noguchi
- Nonne
- A Morality Play
- Science versus Dogma
- 500 years of Medical “Intelligence” vs
- A Contrary View from the Loyal
Opposition

Mise en Scene

- Central Islip, Long Island, New York
- Mentally Ill persons in a Warehouse
- Locked Up
- Left to Die
- Forgotten
- Ignored

A National Hero from Japan

- Enter Stage Left
- Hideyo Noguchi, MD



Act One

- Syphilis 30 years ago
- Dementia, develops slowly
- Personality changes
- Lost to Society

Skip to ...Act Three

- Autopsy study of the Brain
- 70 cases
- 58 negative for *Treponema Pallidum*
- 12 Positive for the Spiral Bacterium
- A New paradigm proposed
- Old paradigm Overturned



Act Two



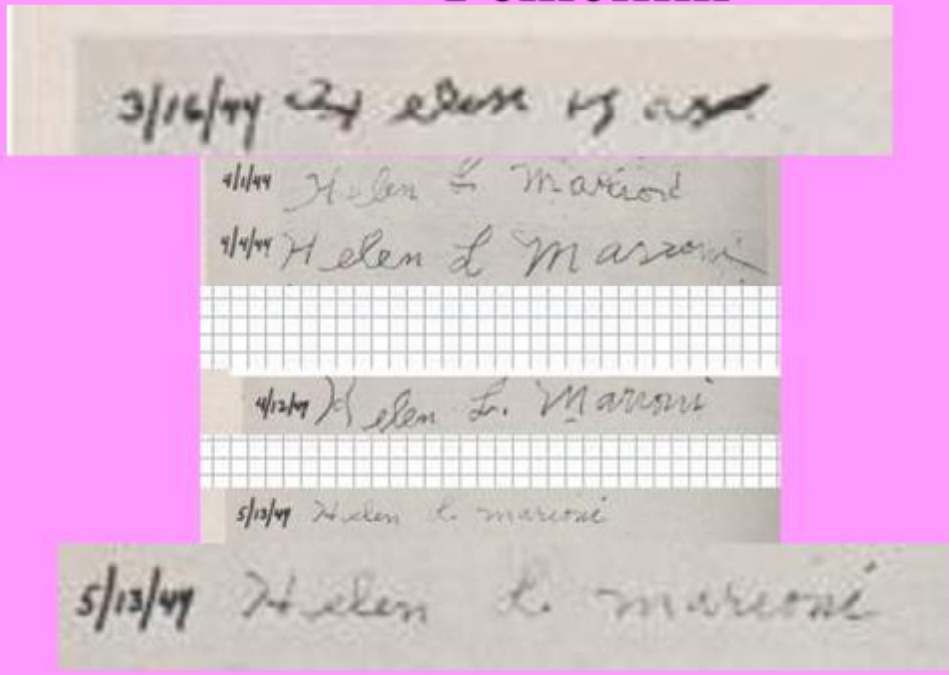
- Clinical thinking about Syphilitic Dementia
- “Coincidence” versus “Causation”
- Persistence of an infection for 30 years
- Clinical thinking
- Pathology based thinking
- A Grrreat Experiment will offer answers



Helen Marioni

- Syphilis in her past
- Dementia
- Hospitalization – “Long Term Parking”
- Antibiotic treatment
- Clinical Improvement
- Dementia is REVERSED

Helen's handwriting after Penicillin



TEXTBOOK MEDICINE

“TEXTBOOK EXAMPLES”

THE “Central Dogma” –

..... And

Dogma “Rewritten and Corrected Version”

?Should I Apologize for

Treating Dementia with Antibiotics?

Look it up!!!

Images of Truth Rewritten

- Thank you
- Dr Barry Marshall and Dr. Robin Warren



Nice Wallpaper

Barry and Robin

What's the Pattern?????



The Medical – Industrial Complex Apologies

- “Dr. Marshall and Dr. Warren, please
accept our apologies
for unkind words
and for uncollegial thoughts

You were Right 20 years ago

.... The textbooks Got it wrong>>>>>

Take HOME MESSAGE

- A microbe
- Recovered
- From a diseased
- Tissue
- May be the **CAUSE**
- *OF THE DISEASE*

“NORMAL FLORA”

- Is there
- A
- “normal” flora
- In the
- CENTRAL NERVOUS SYSTEM???
-please vote on this question

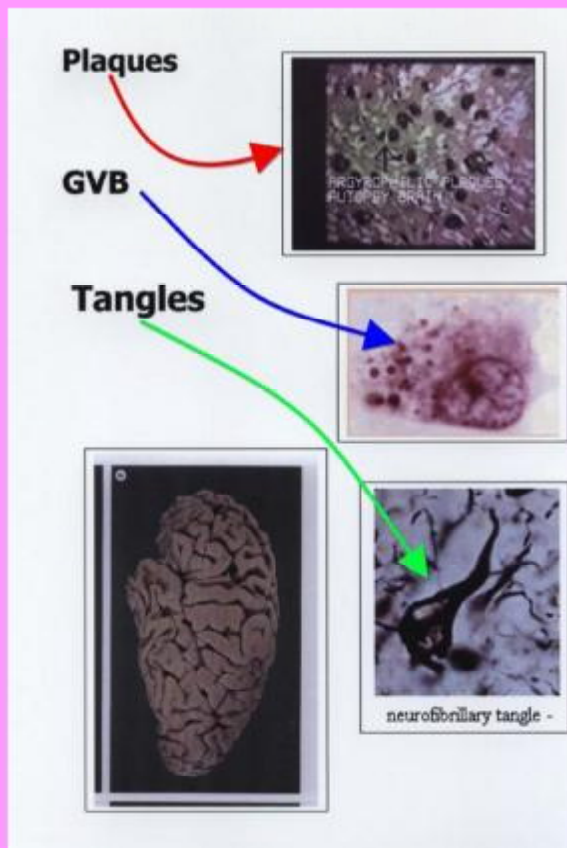
Borrelia burgdorferi
is not normal flora

Philosophical Issues on
Microbiology
Idiopathic Diseases.

Are Fair Game

For microbiologists
and Molecular Pathologists

Let us go Hunting



Alzheimer's Disease –
Microscopic paradigms

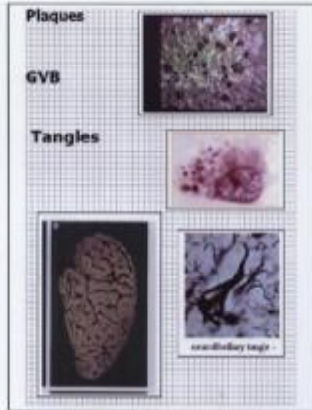
Plaques

GVB

Tangles

MacDonald 1986, 1987, 1988
Borrelia and Alzheimer's

Fluorescent Antibodies



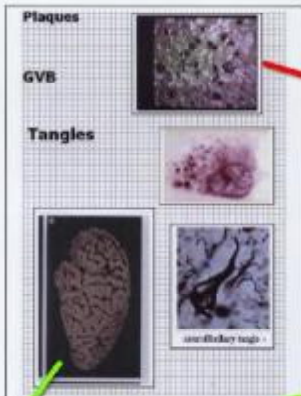
Cultures

?

Treponema
pallidum
model
for
dementia

MacDonald 1986, 1987, 1988
Borrelia and Alzheimer's

Fluorescent Antibodies



Cultures

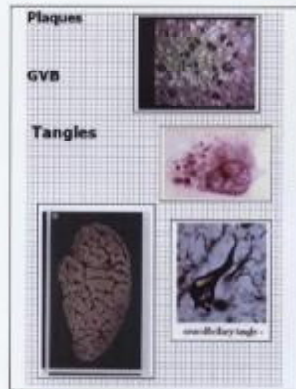
positive
in
plaque

positive for
spirochetes

Positive
results
+ in plaque
+ in culture
+ spirochetes
in brain

Miklossy 1993,1994
Borrelia and Alzheimer's

Fluorescent Antibodies



DNA study

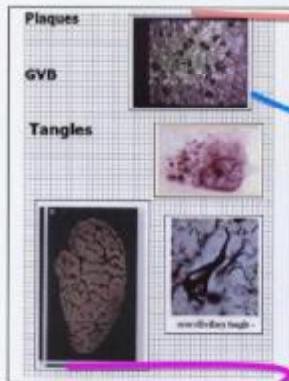
Cultures

?
Treponema
pallidum
model
for
dementia

Miklossy 1993,1994
Borrelia and Alzheimer's

plaques
positive for
borrelia
proteins

Fluorescent Antibodies



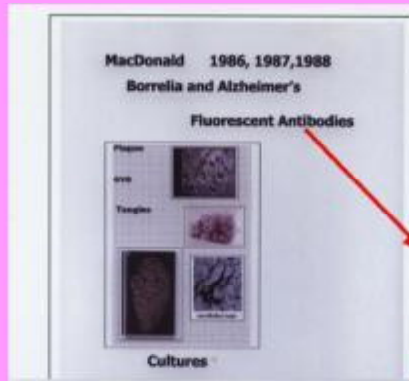
DNA study

plaques
positive
for DNA

Cultures

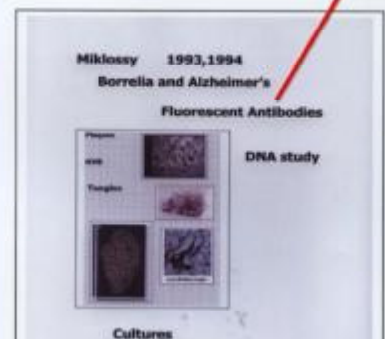
positive for
spirochetes

Positive results
+ in plaque
+ in culture
+ spirochetes
+ DNA in
Plaque



ANTIBODY
POSITIVE
MONOCLONAL
SPECIFIC FOR
BORRELIA

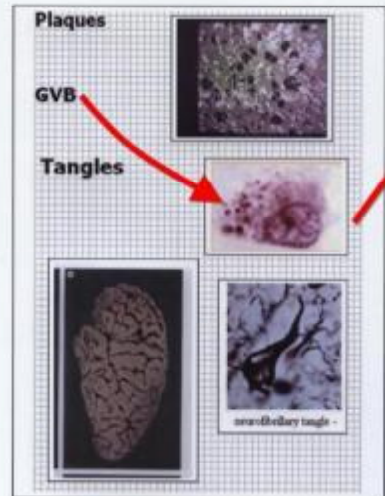
CULTURE POSITIVE



CULTURE POSITIVE

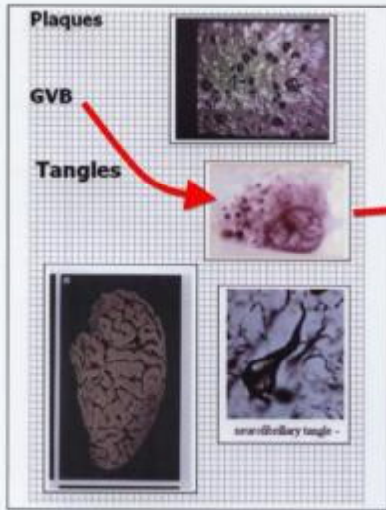
Positive
results
independent
replicated
... and
?? So what

**MIKLOSSY 2005
TISSUE CULTURE
RAT NERVE CELLS
COINCUBATED WITH
*Borrelia burgdorferi***



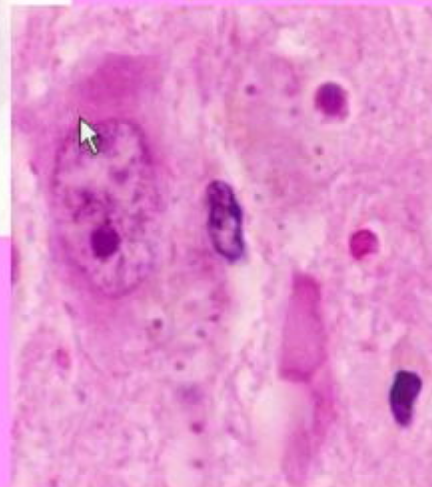
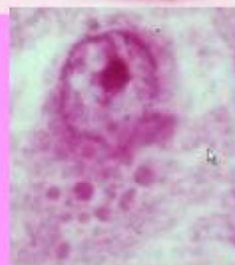
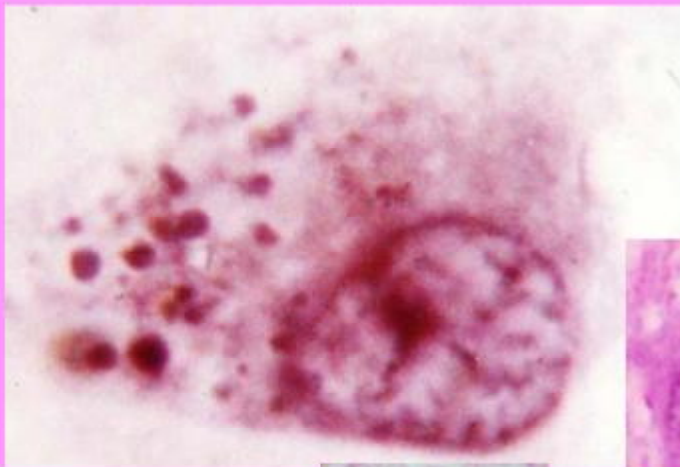
2005
Miklossy
beta
Amyloid
changes
by *Borrelia
burgdorferi*

MACDONALD 2005
IN SITU
DNA
HYBRIDIZATION
OF ALZHEIMER DISEASE NERVE CELLS
WITH *Borrelia burgdorferi* DNA
PROBES



2005
MacDonald
GVB
are positive
for
Borrelia
burgdorferi
DNA

Take this GVB,... Please



GVB deciphered

- Cytoplasm, ... Not in the Nucleus
- Rounded “granules”
- Vacuole “surround”
- Size differences in granules
- Variable number of granules

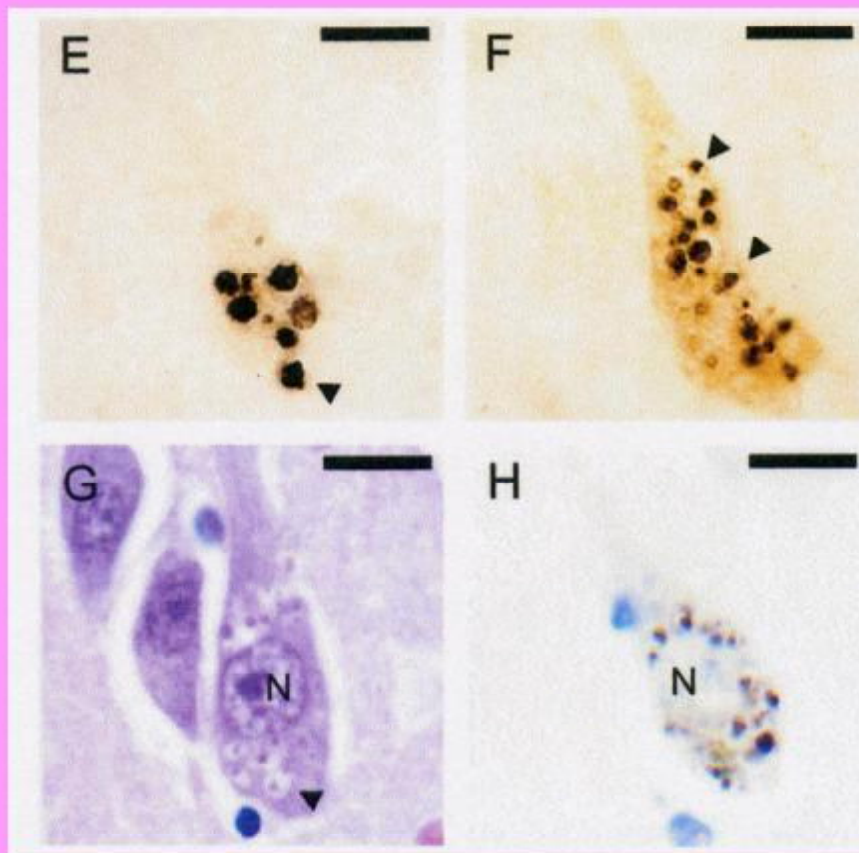
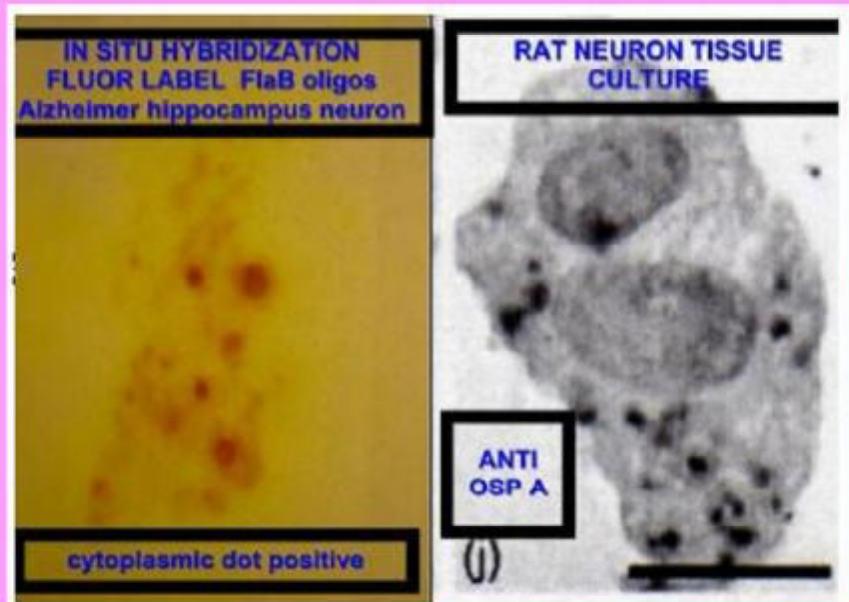
GVB “Checklist”

Alzheimer’s disease
Hippocampus
Variable in Number



Granules vary in size ---little to big

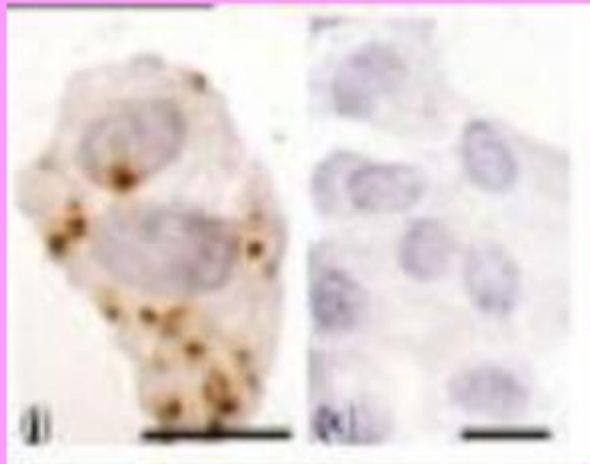
In Situ Dna and Rat Tissue culture



GVB PROFILES

Binder Lab
Northwestern
Univ. School
of Medicine

MIKLOSSY RAT TISSUE CULTURE

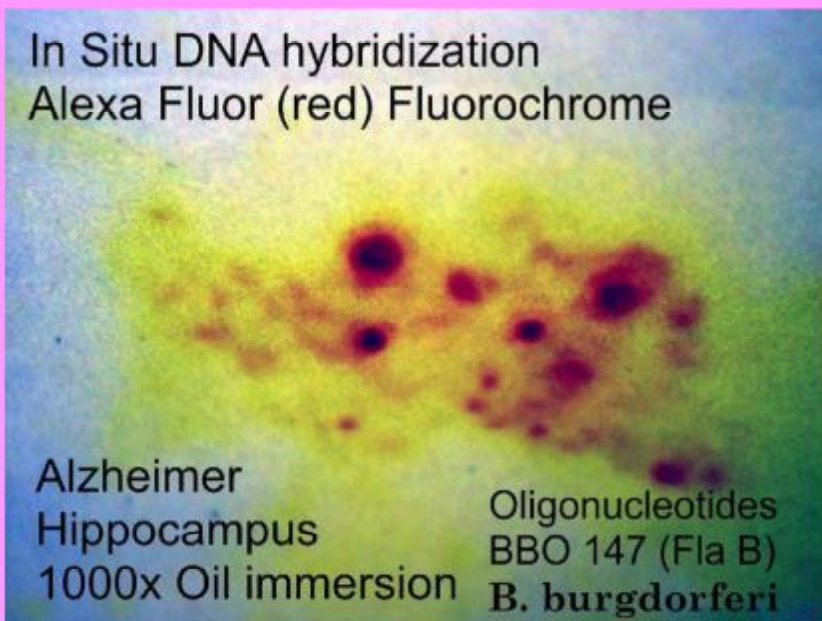


MacDonald human Alzheimer In situ DNA

In Situ DNA hybridization
Alexa Fluor (red) Fluorochrome

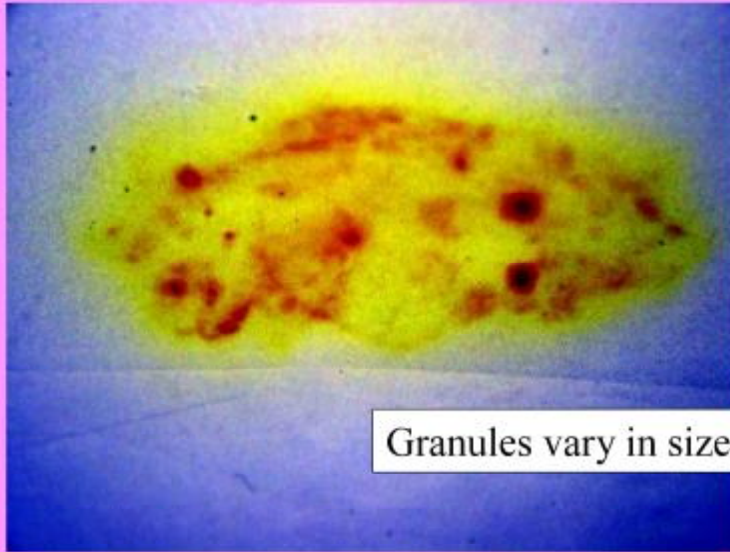
Alzheimer
Hippocampus
1000x Oil immersion

Oligonucleotides
BBO 147 (Fla B)
B. burgdorferi



Human Alzheimer

In situ DNA hybridization for *Borrelia burgdorferi* DNA



Granules vary in size – from little to big

Miklossy

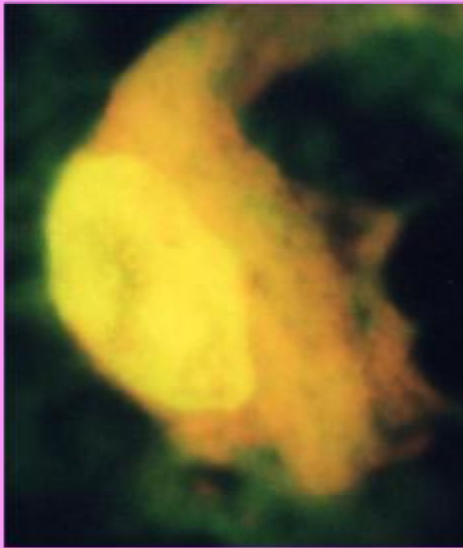
Rat nerve cell

H5332 monoclonal +



Granules vary in size – from little to big

Human nerve cell
not diseased
from Alzheimer Brain



AO stain Acridine Orange

DNA = Yellow to green

RNA = red to orange



Miklossy

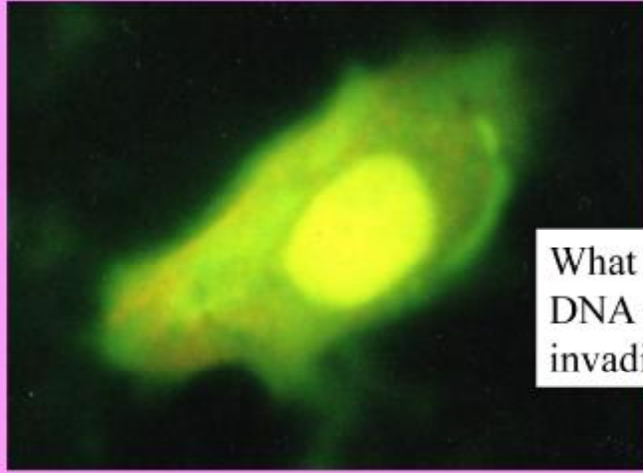
2004

Rat Neuron

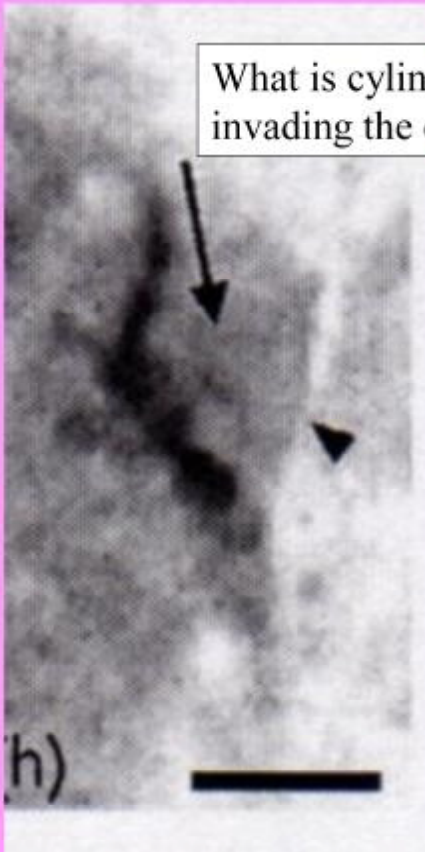
Tissue Culture with

B. burgdorferi

Human Nerve cell
from Alzheimer Brain
with + cytoplasmic DNA



What is Cylindrical, contains DNA and is capable of invading the Cytoplasm??



What is cylindrical, contains DNA and is capable of invading the cytoplasm??

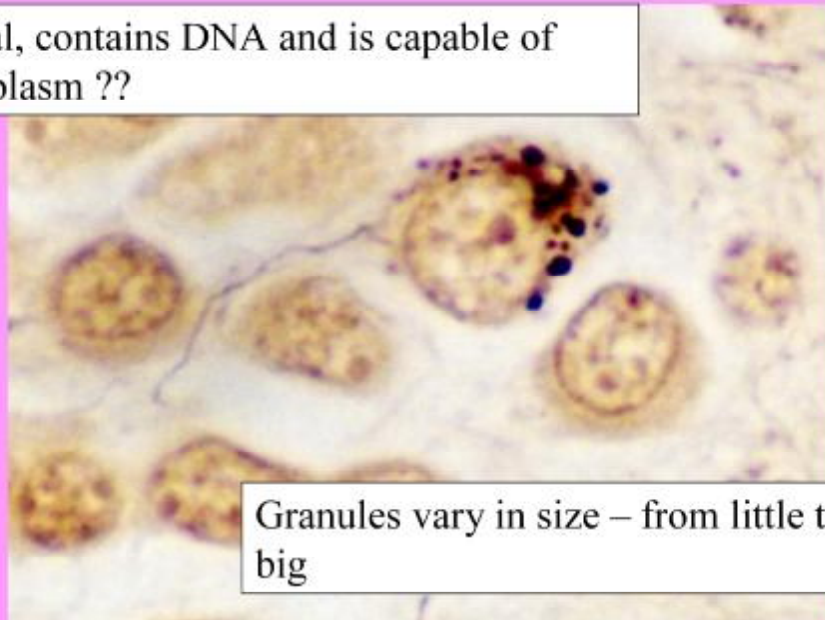
Miklossy rat
nerve cell
in tissue culture
with *B. burgdorferi*.
Spirochete
inside the cell



Miklossy rat
nerve cell
tissue culture
with B.burgdorferi
spirochete
inside the cell

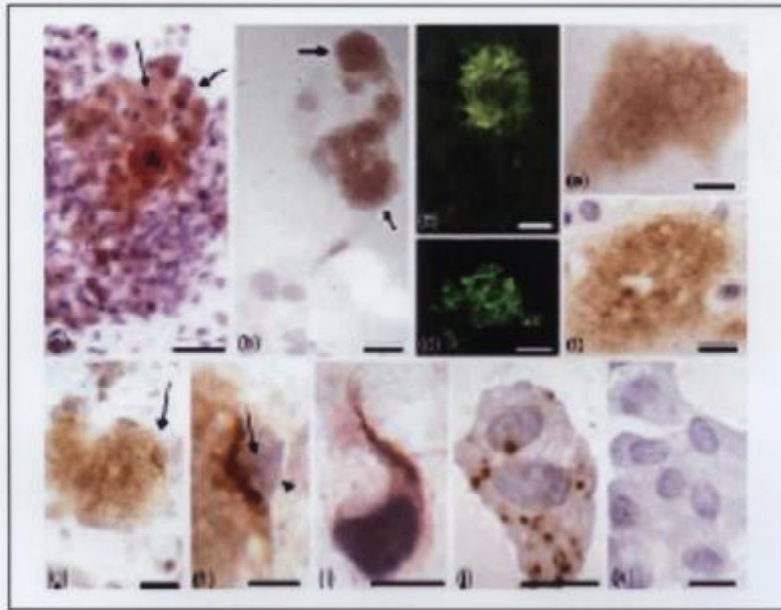
Human Nerve cell from
Alzheimer's with GVB
and ? Spirochetal form at 9 o'clock

What is cylindrical, contains DNA and is capable of
invading the cytoplasm ??



Granules vary in size – from little to
big

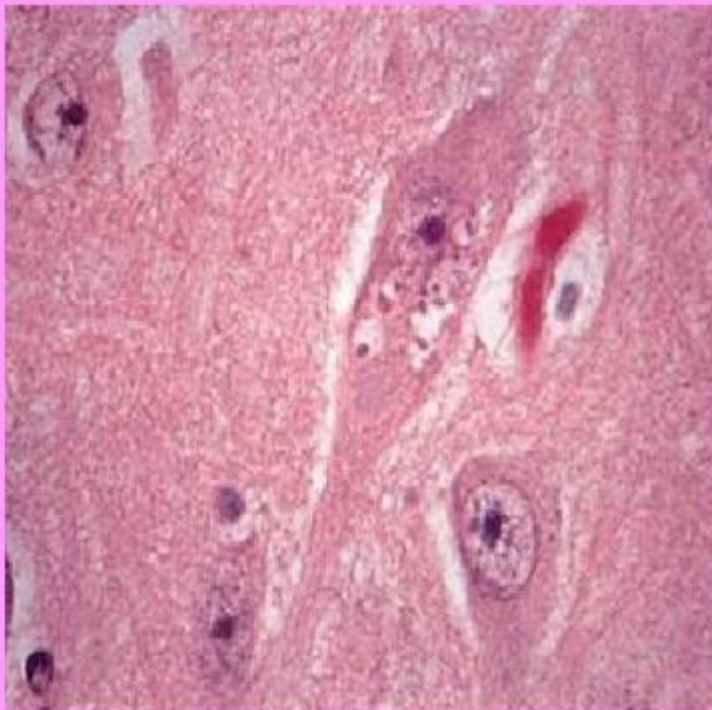
Miklossy 2005 Rat nerve cells



Granules vary in size from little to big

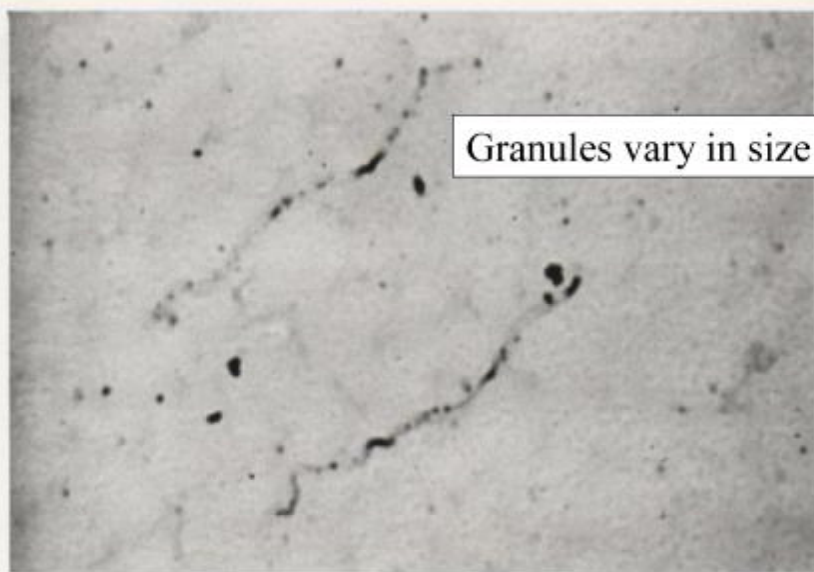


Miklossy
2004
Rat Neuron
Tissue
Culture with
B. burgdorferi
OSP A +
“dots”



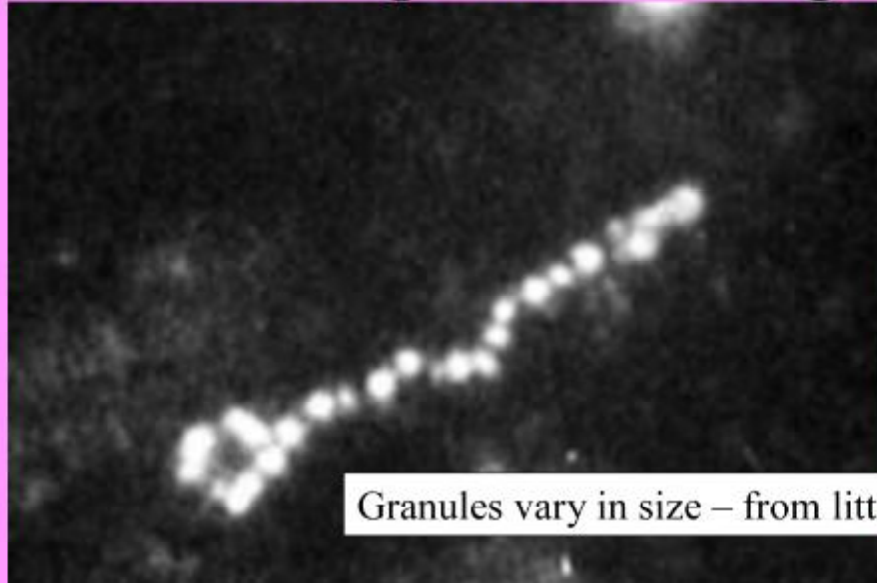
GVB
Alzheimer
hippocampus

Borrelia burgd. In transformation
to granular forms



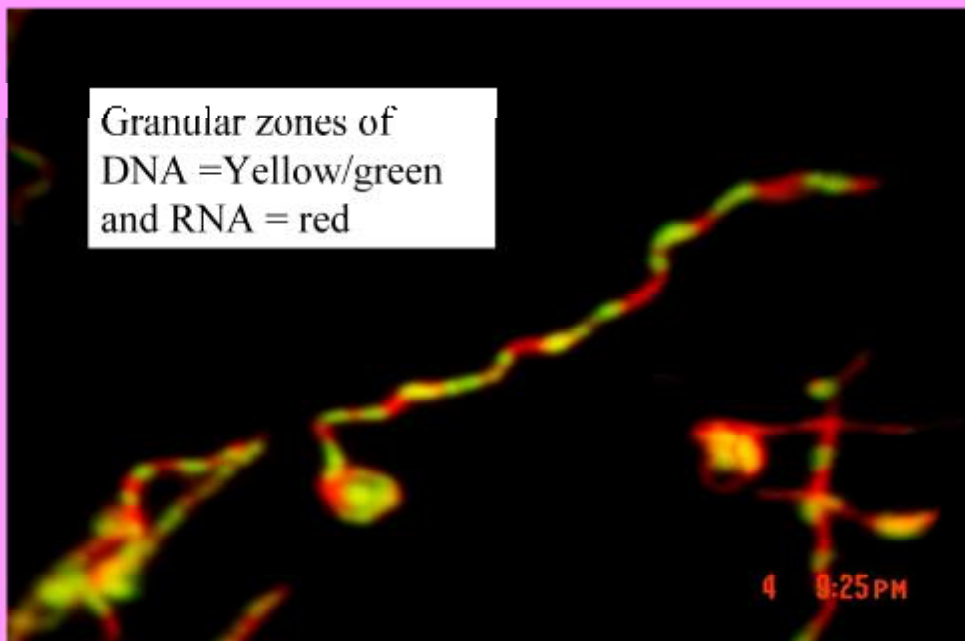
Granules vary in size – from little to big

Alzheimer brain
H5332 – OSP A-
outer surface protein B.Burgdorf

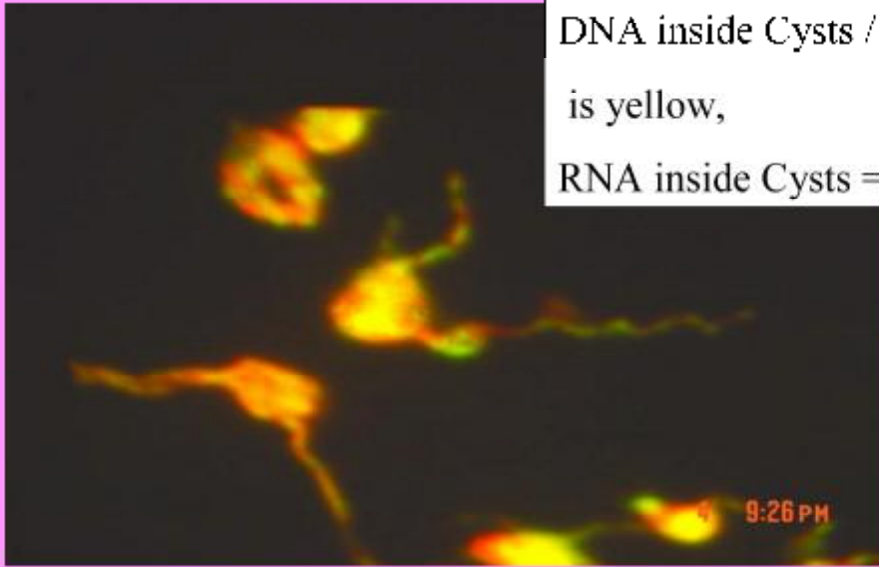


Granules vary in size – from little to big

DNA= yellow/green
RNA= red

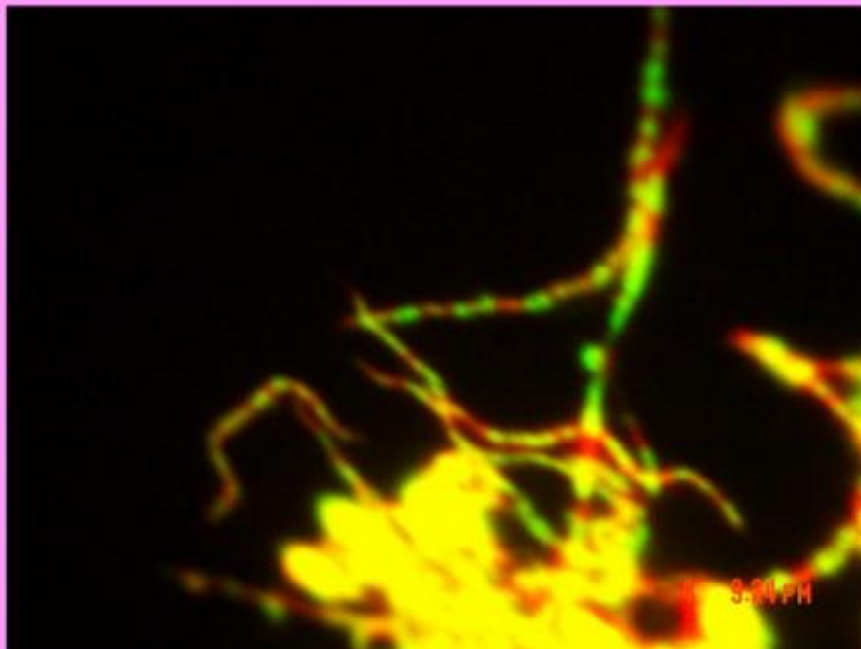


Cyst forms emerging from *Borrelia burgdorferi*

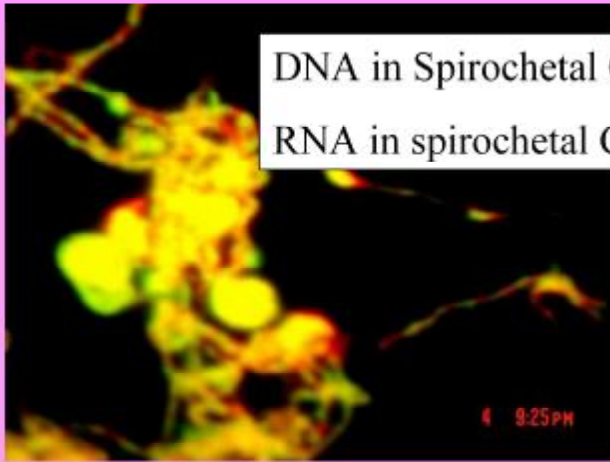


DNA inside Cysts / Rounded forms
is yellow,
RNA inside Cysts = Red

Striated (striped) DNA/Rna patterns in *Borrelia burgdorferi*

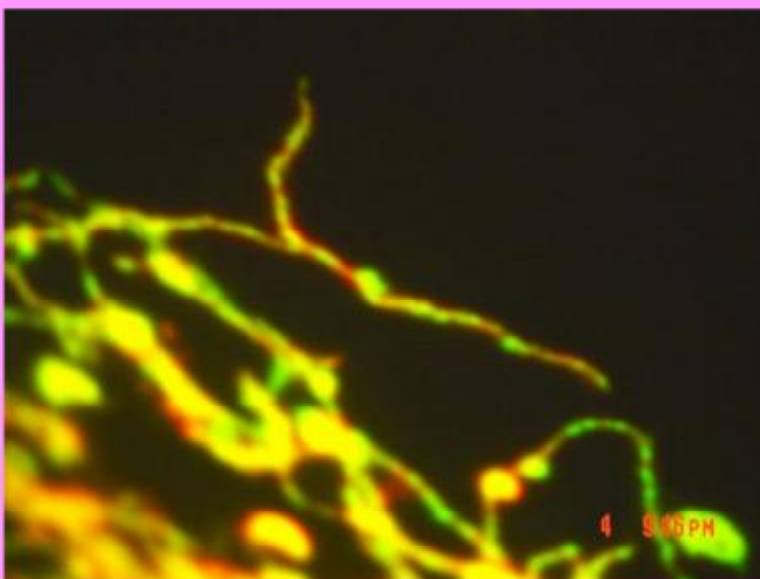


Cystic forms outnumber
all others
acridine orange stain for
DNA / Rna

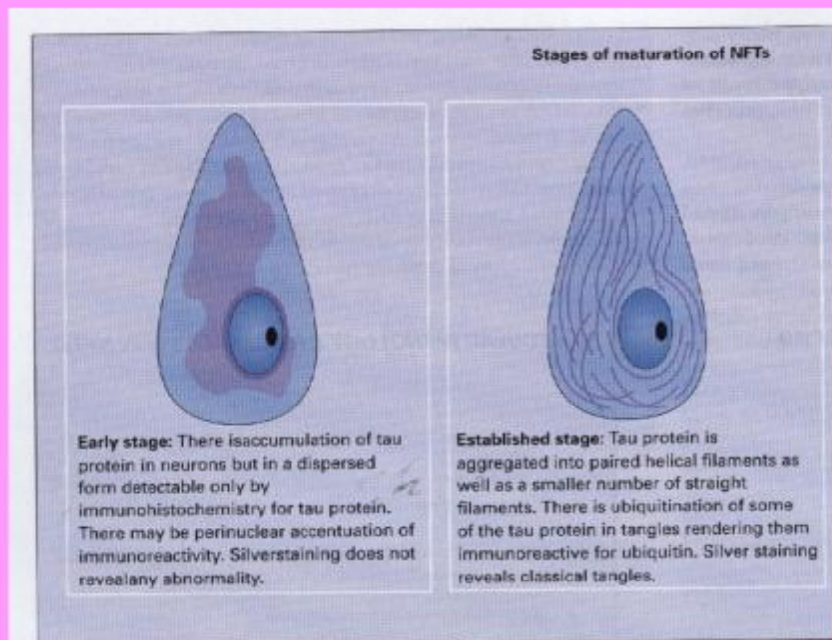


DNA in Spirochetal Cysts = Yellow/green
RNA in spirochetal Cysts = Red

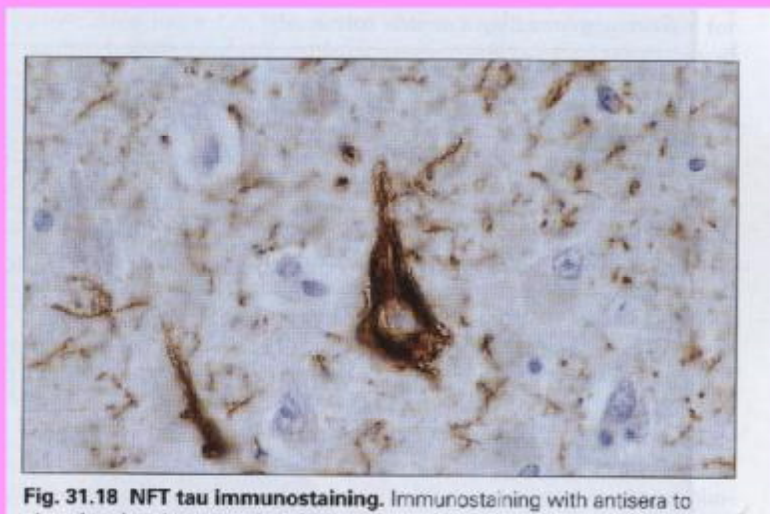
Segments- some with DNA
some with Rna



Tangles – the loose ends



Tangles + Tau staining

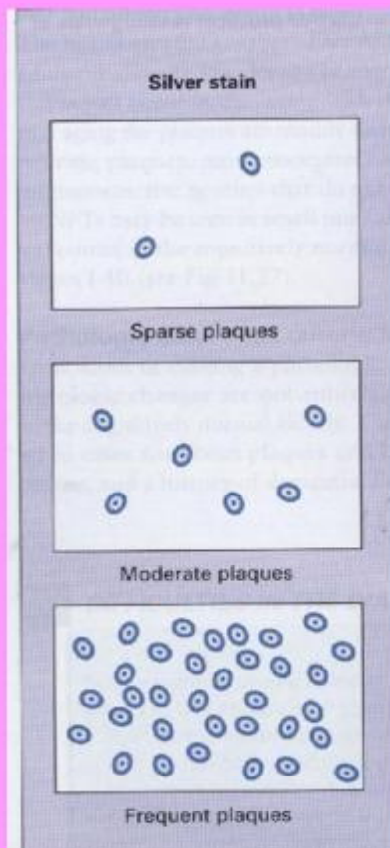
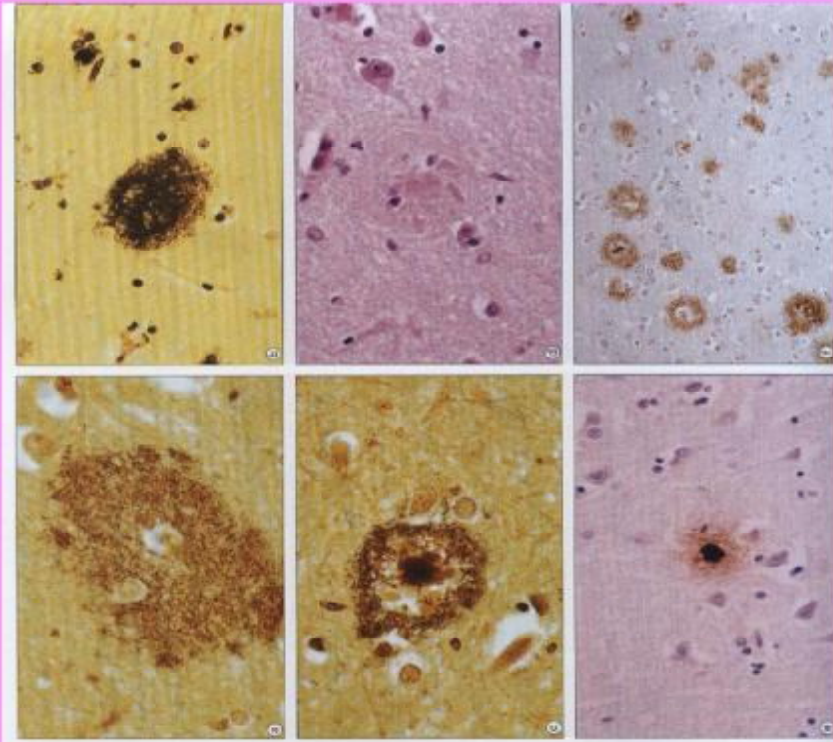


Tangles – diseased microtubules?



Broken or Ruptured
Spirochetal Cyst forms
and
Plaques of Alzheimer's
A Structural link

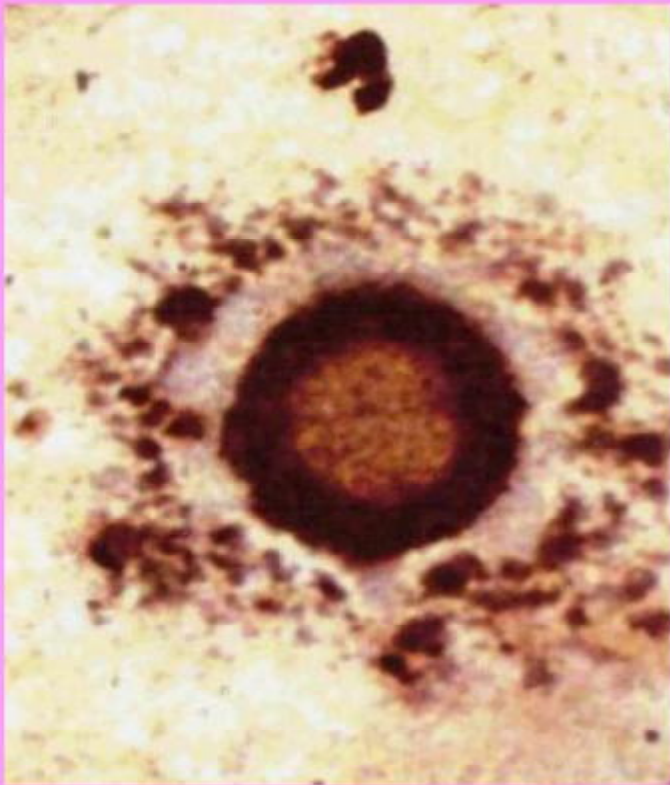
Plaques in Alzheimer's



Plaque
Density
a
measure of
Alzheimer
severity

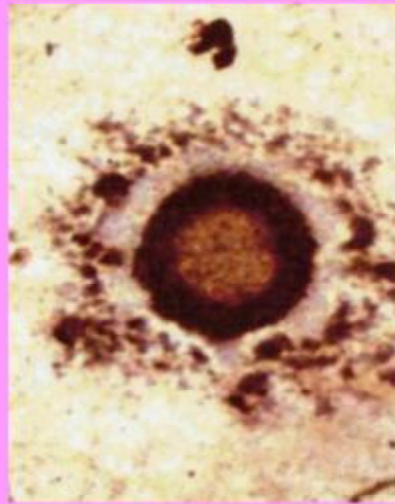


One
Alzheimer
Plaque
with Amyloid
center

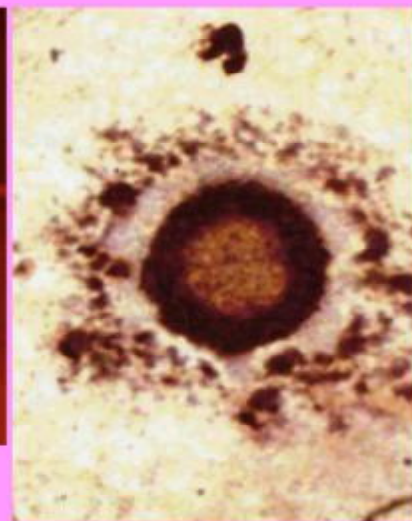


?Plaque
?central
core
?circular
ring zone

Comparison of Plaques



Comparisons with Edgerton



Edgerton's "splash" is a "Broken" Drop

Nelson – Dynamic equilibrium of *Borrelia burgdorferi* cysts to vegetative forms



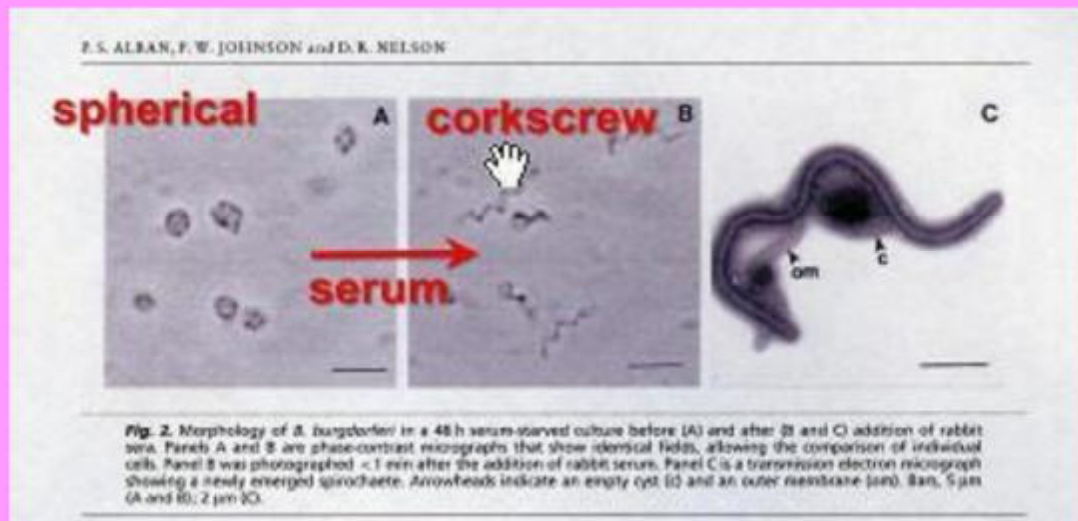
Cysts as “droplets” - eligible to participate in a “splash”

Nelson Cysts Alone

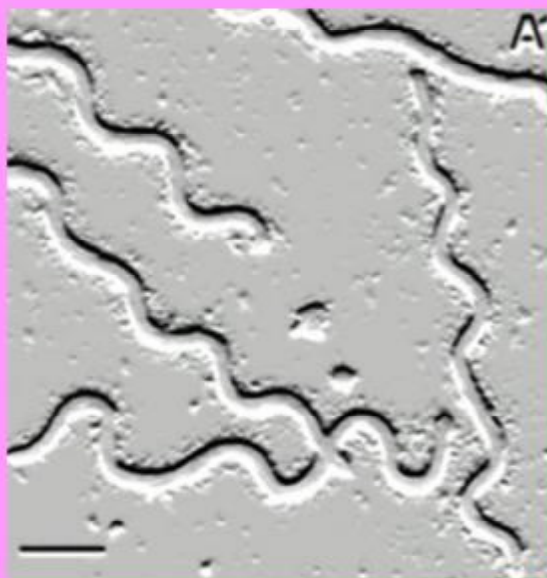


A cyst is a “Water Balloon – like
structure”

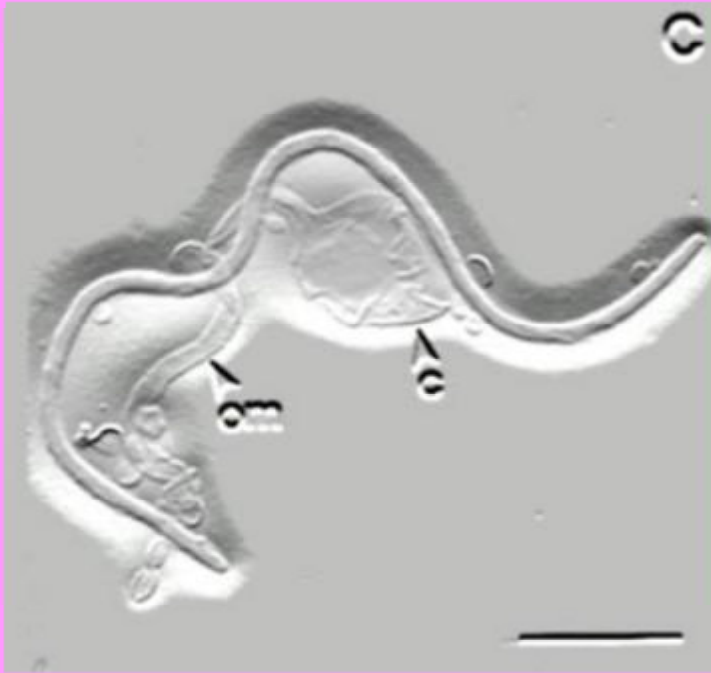
Nelson – “Stress Altered” euphemism for Cyst form



Nelson – vegetative forms of *B. Burgdorferi*

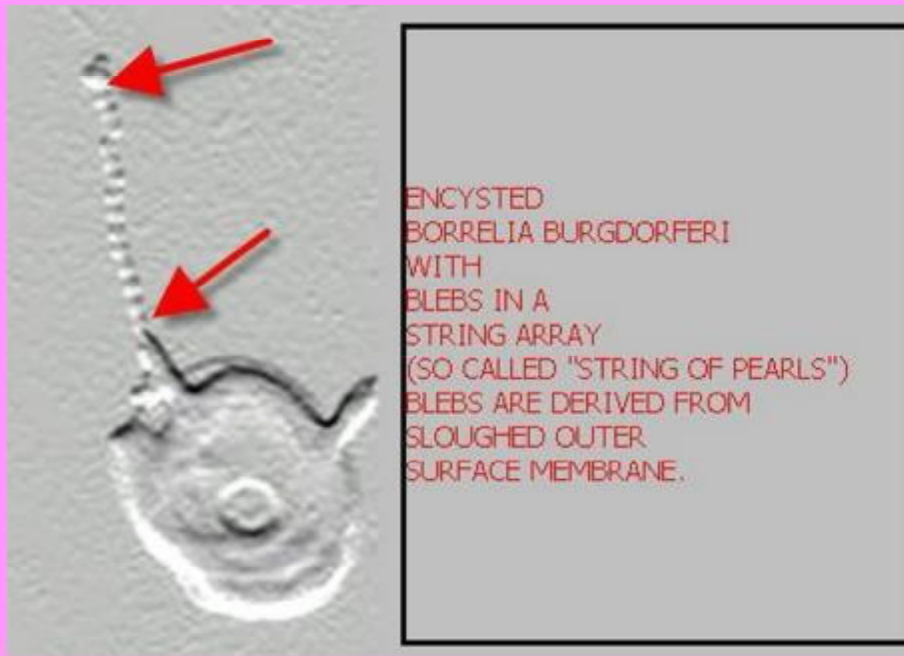


Nelson – Conversion to Cystic



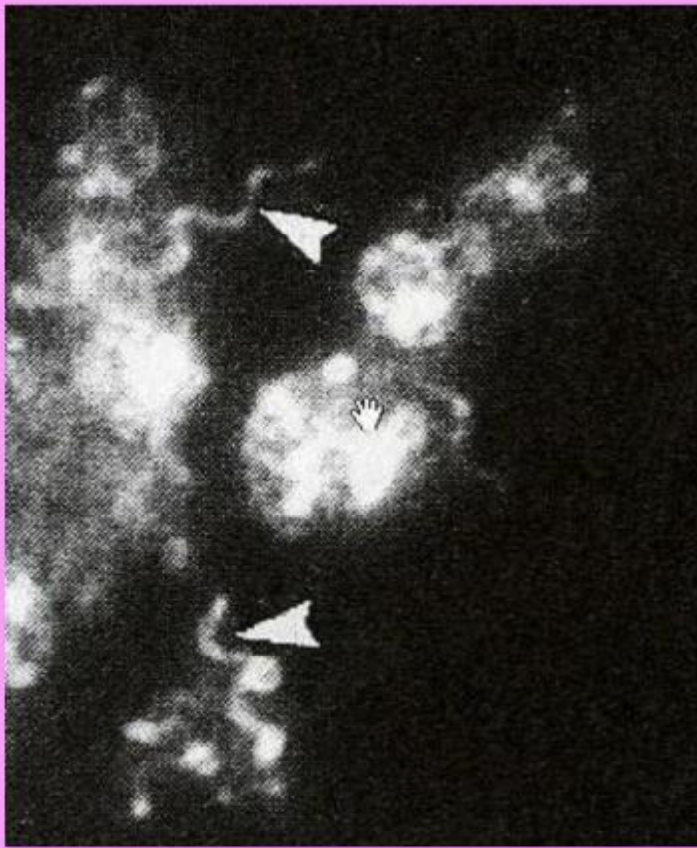
Nelson Cystic
“stress
altered” form

Nelson Cyst form with Blebs



Brorson and Brorson Cyst forms of *B. burgdorferi*





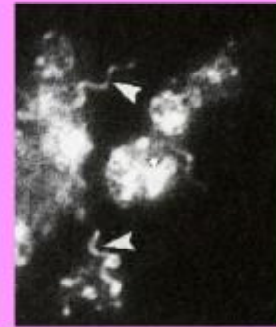
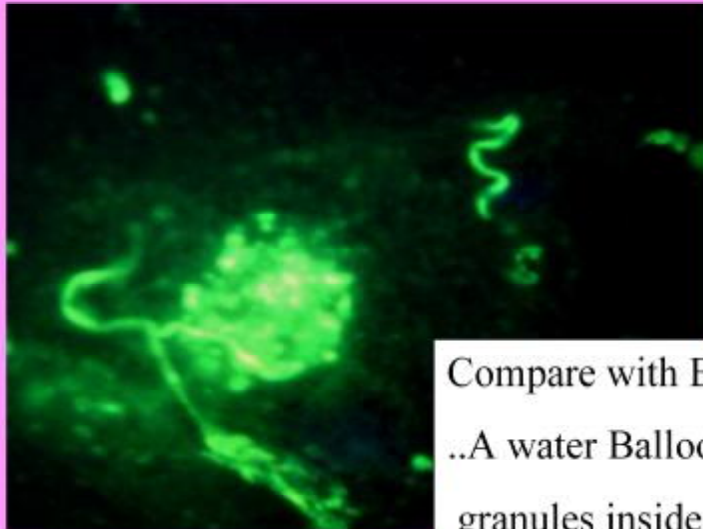
Brorson
evolving
Cyst forms
of Bb

MacDonald 1987
Cyst form H9724 +
Alzheimer Brain



A "water balloon" containing Granules

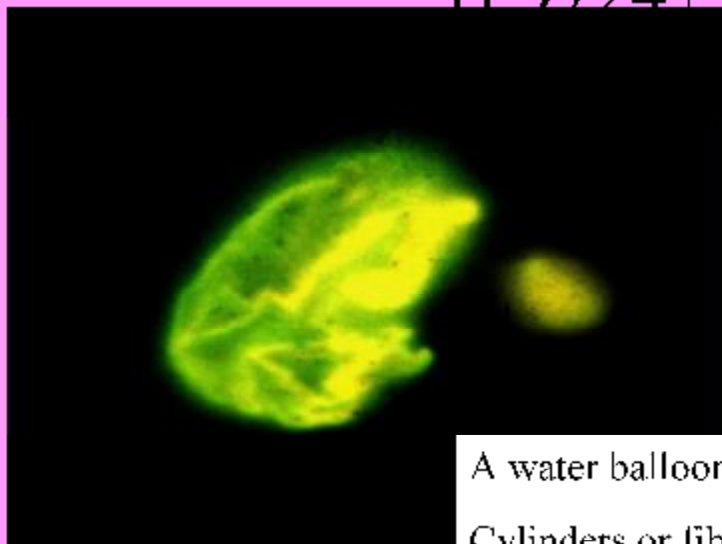
MacDonald – Aged B31 Bb
H9724 +
Cyst form attached to Vegetative



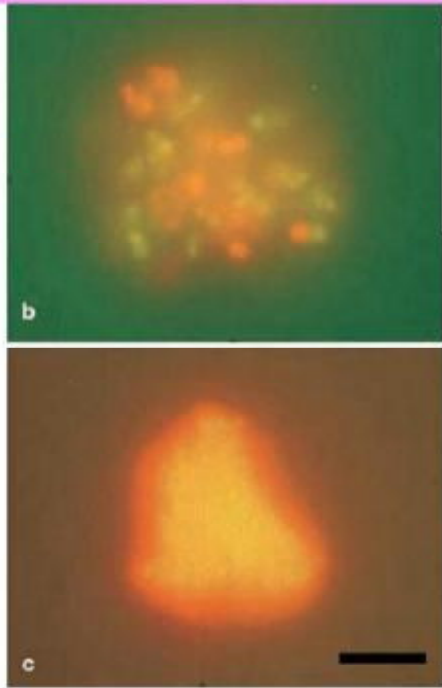
Compare with Brorson Cysts

..A water Balloon –like structure with
granules inside it

MacDonald – 1987
Cyst form Alzheimer Brain
H 9724+



A water balloon like structure with
Cylinders or fibers inside it



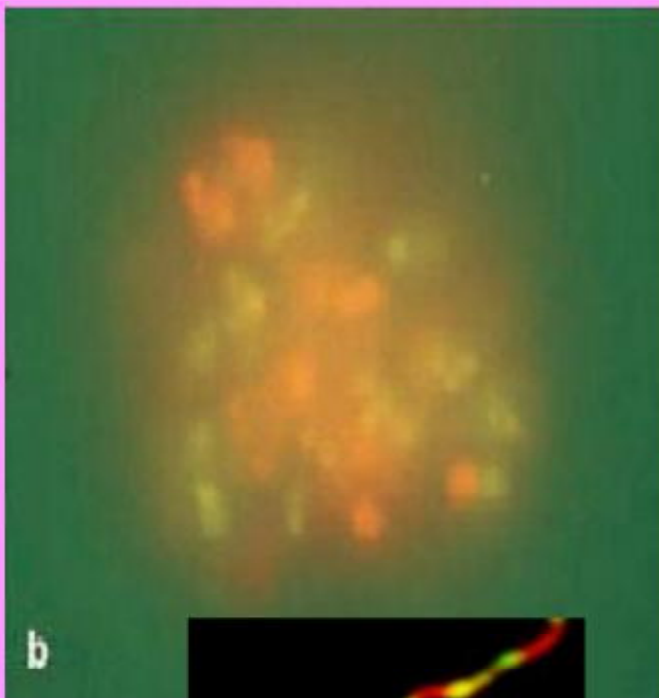
Acridine Orange stain

DNA = Yellow /green

RNA = Red

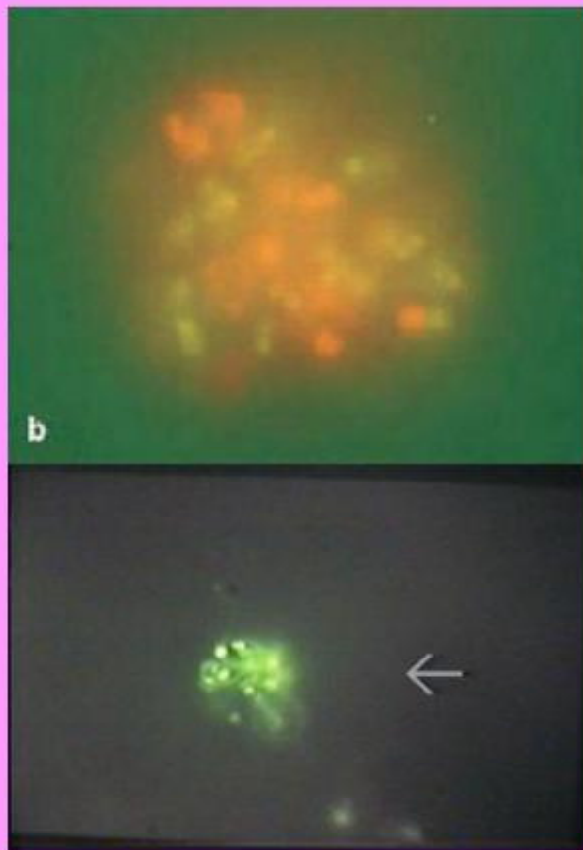
Brorson cyst forms of *Borrelia burgdorferi*

Fig. 3a-c Susceptibility testing of old cystic forms of *B. burgdorferi*, using RBC in distilled water at 37 °C for 14 days. **a** RBC=1 µg/ml: the cyst contains green cores (living organisms). **b** RBC=2 µg/ml: the cyst contains both green and orange cores. **c** RBC=256 µg/ml: The cyst contains only red core/granules (biologically inactive organisms) and no distinct cyst/core can be seen. Vital AO-staining, pH 7.4. Bar 5 µm

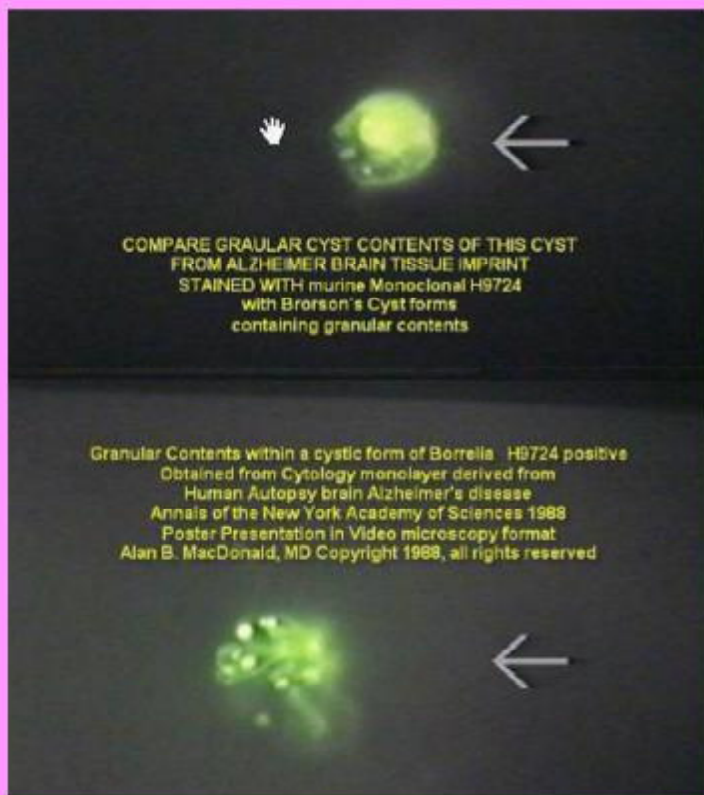


Brorson Cyst of *Borrelia burgdorferi* with Granules

Borrelia burgdorferi B31 -Comparison

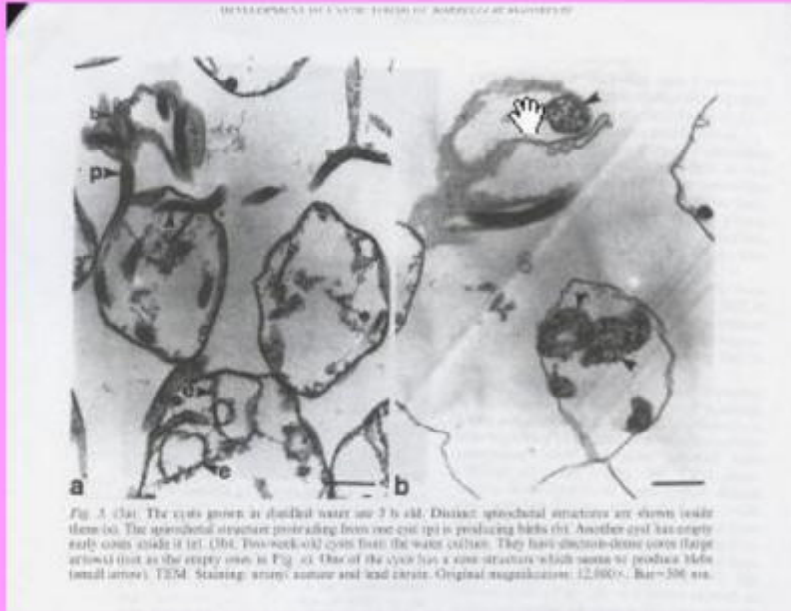


Brorson Cyst of
 B. Burgdorferi
 compared
 with
 MacDonald
 Cyst
 from
 Alzheimer brain



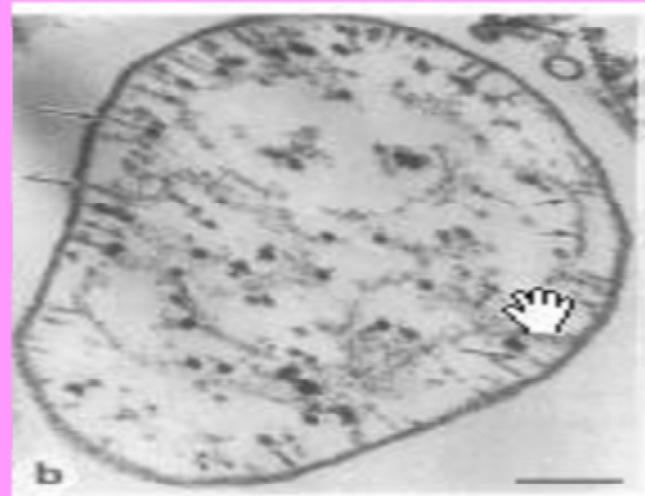
Alzheimer
 brain
 Cysts
 H9724
 positive
 with inner
 granular
 elements

Brorson Cystic Bb by Electron microscopy



“Tail” of the Phage is the Hypodermic needle

Hayes 1983 Bacteriophage of Bl



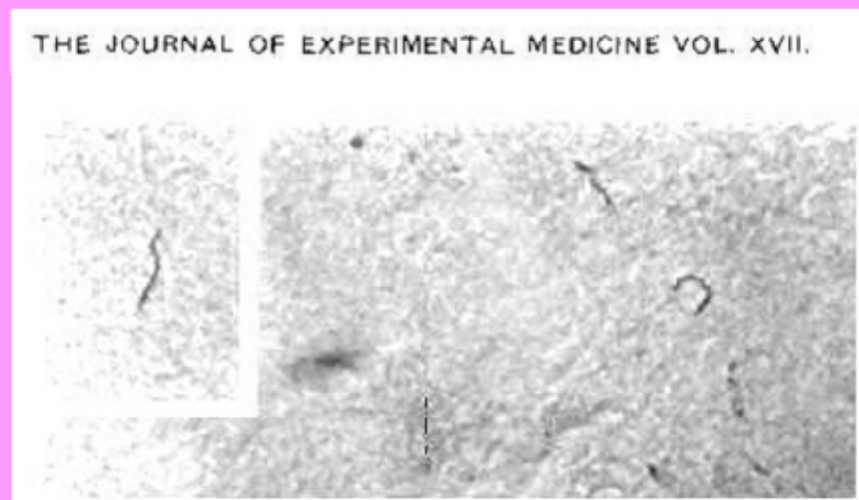
Inside / Outside of the membrane labeled by attached Bacteriophage

TEM. Staining: uranyl acetate and lead citrate. Original magnification: 12,000x. Bar=500 nm.

Noguchi's legacy

This author, however, in commenting on the hitherto vain attempts to find *Treponema pallidum* in the tissues and body fluids of paresis, remarks, "This does not mean that the spirochæta is never present in the body of the parietic. It may have assumed forms so far unknown to us or have located in places where it has not yet been sought or where it is hard to find."

Noguchi's spirochetes



Fikrig's primate model

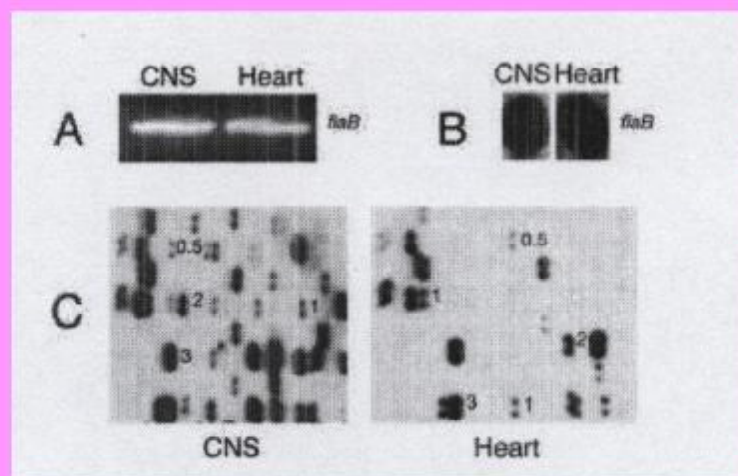
***Borrelia burgdorferi* transcriptome in the central nervous system of non-human primates**

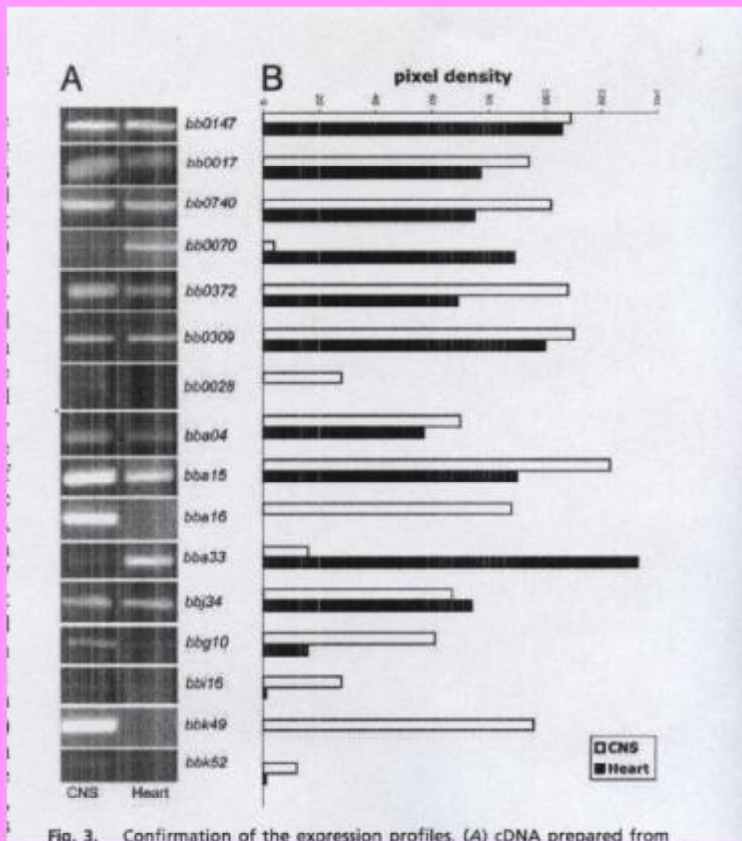
Sukanya Narasimhan*, Melissa J. Calmano**, Fang Ting Liang*, Felix Santiago*, Michelle Laskowski*, Mario T. Philipp[§], Andrew R. Pachner[§], Justin D. Radolf[§], and Erol Fikrig^{*,**}

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Edited by Richard A. Flavell, Yale University School of Medicine, New Haven, CT, and approved September 9, 2003 (received for review April 23, 2003)

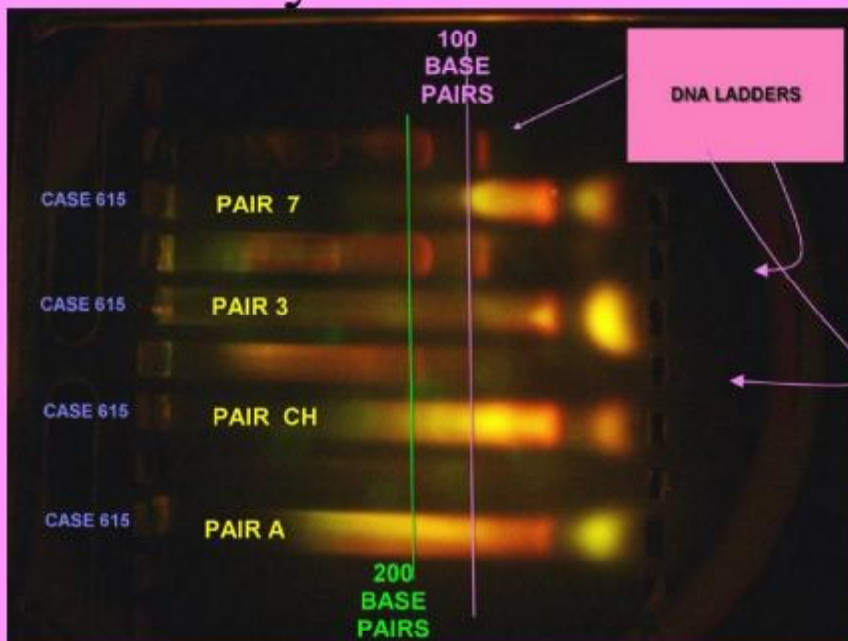
Fikrig's Fla B “Ruler” Primate Brain DNA Probes





Fikrig's
Gene
probes
for
DNA
of Bb

Molecular Interrogation Early studies of Alzheimer's



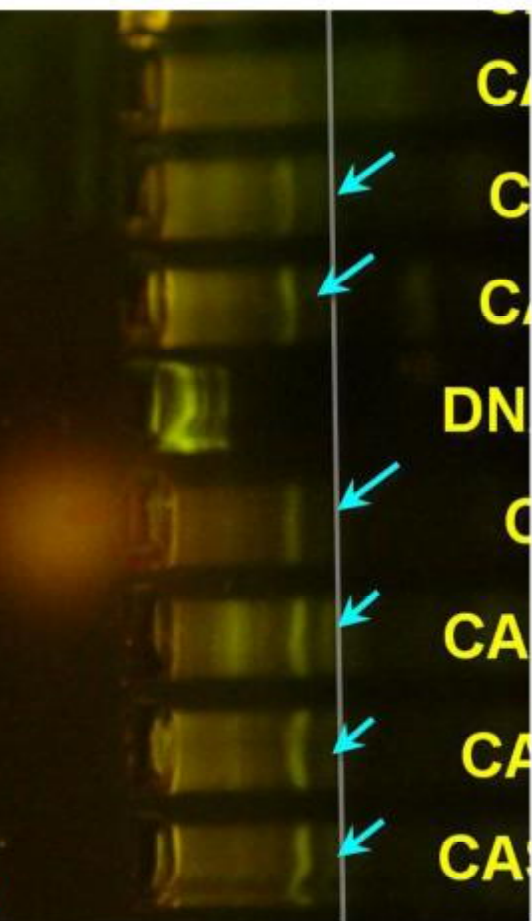
Molecular Interrogation

8 cases positive for Fla B Probe

PCR



SH AUTOPSY
POCAMPUS
A EXTRACTS
WITH pcr
SING Primers
Open Reading
me BBO 0147
Fla B gene)
ed for 500 BP DNA



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2 Transfection "Junk" DNA – A link to the 3 pathogenesis of Alzheimer's disease?

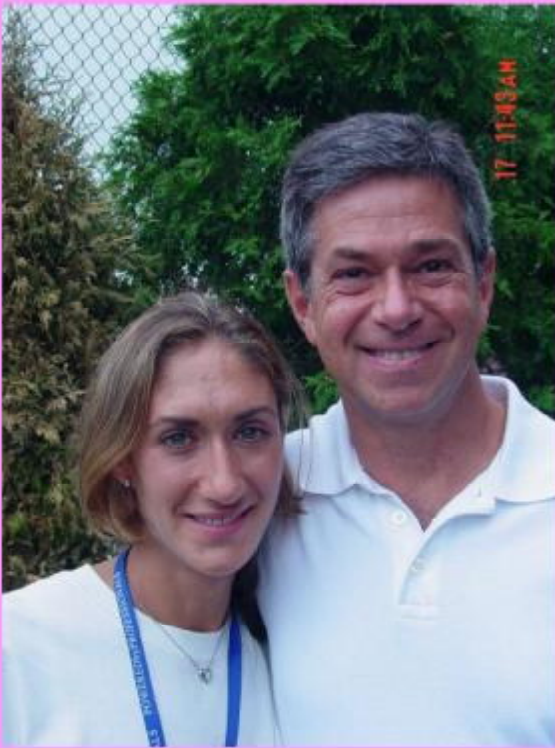
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6 Received 27 November 2005; accepted 1 December 2005

7

8 **Summary** A transfection product incorporates in one molecule of human DNA, an inserted segment of DNA from
9 another species. This communication addresses the hypothesis that a novel variation of the theme of transfection,
10 namely "junk transfection" for which no protein product and no RNA is transcribed, might offer insights into the
11 pathogenesis of Alzheimer's disease. It is hypothesized that spirochetal DNA gains access to the intracellular
12 compartment of nerve cells during the subclinical latency phase of neuroborreliosis and chemically combines with
13 human DNA. A previously reported Molecular interrogation of Alzheimer's disease autopsy tissues has yielded novel
14 DNA sequences containing the 11. a human chromosome and a short piece of the *Borrelia burgdorferi* Flaellin B DNA.



Thanks
to
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Support
for this
scientific investigation
from
Turn the Corner Foundation
New York, New York
and ILADS
is gratefully
acknowledged