Borrelia Attack Models

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Some Parasitic Diseases

Actually

Require Long Term

Antiparasitic Therapy
Spirochetes are Parasites

*Therapy for Spirochetal parasites should be*

*Customized by the Physician to*

*Eliminate*

*The Parasitic Spirochetal Infestation*
Module #1
Examples of Spirochetes *INSIDE*
of Living cells
Preface

“Members of the Genus Borrelia display one of the most unusual genome structures in the bacterial world, if not in creation”

Dr George Chaconas
Professor and Canadian Research Chair in the Molecular Biology of Lyme Disease
University of Calgary, Canada
Miklossy Rat Neuron
Miklossy Rat Neuron
Livengood and Gilmore
Human Nerve cells
Livengood and Gilmore
Human Nerve cells
Livengood and Gilmore
Human Nerve cells
Thomas and Comstock
Human Endothelial cells
Invaded by Borrelia
Montgomery – Macrophages Invaded by Borrelia
Syphilis Spirochete and Sperm
Spirochetes Invade Cells Because Spirochetes are Parasites
Syphilis Spirochetes Invade Cells

*T. pallidum (T) inside plasma cell.*
Ovcinnikov NM; Delektorskij VV. 1971.
Syphilis Spirochetes Block Nerves- Painless Chancre

*Intact T. pallidum (T) inside a cell, in ultrathin section of material from the site of a chancre.*

Ovcinnikov NM; Delektorskij VV. 1971.
Module #2
Examples of Spirochetal Life Cycles
Borrelia Life Cycle Concepts

A Life Cycle – Typical of Parasites

Multiple Forms of the Parasite

Blood Phase Forms

Tissue Phase Forms

Insect Vector Forms

A circular Loop or Loops of Interconnections between the Various Forms
After swimming about for some time in this form, the spirochaete appears to rupture at one end and the coccoïd bodies escape into the surrounding medium, leaving an empty sheath behind them. In some cases the whole cell-wall seems to disintegrate before the coccoïd bodies escape, but the final result is the same, viz. the liberation of a varying number of minute round or oval bodies. Although in some respects they resemble the spores of bacteria—especially the Diaporthe—in their formation, yet the fact that they stain deeply and also multiply at once differentiates them from true spores.

In order to develop into spirochaetes it is necessary for them to escape from the cell into a fluid medium....

—Hindle, 1912.
Spirochete Life Cycle
McDonough
Year
1913
Spirochete Life Cycle

The Reiter treponeme: a proposed life cycle.
Al-Qudah AA; Mostratos A; Quesnel LB. 1983.
Life Cycle for Treponemes
Dr Delamater – Year 1950
A life cycle for *Borrelia* spirochetes?

Alan B. MacDonald

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MacDonald – Borrelia Life Cycle

Figure 1 Cystic Forms of *Borrelia burgdorferi* (American Type Culture Collection 35210), darkfield image 1000x, original, Alan MacDonald, MD unpublished, Photograph date 1988
MacDonald – Borrelia Life Cycle
MacDonald – Borrelia Life Cycle
Module #3
Examples of Borrelia as Weapons
Borrelia Cysts as Weapons
Borrelia Cysts as Weapons
Borrelia Cysts as Weapons
Borrelia Granules as Weapons

FORMATION OF COCCOID BODIES IN BLOOD

Hindle, 1912, emergence of granular "coccoid" forms from spirochetes
Borrelia Granules as Weapons
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.
Borrelia Granules as Weapons

Hindle E. 1912.
Borrelia Granules as Weapons

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. (Miklossy 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.)
Module #4
Skin
as Target Site
for
Virulent
Borrelia
Erythema Migrans

FIGURE 1: A tiny tick, *Ixodes dammini*, atop an early papule of erythema chronicum migrans.

FIGURE 4: Two somewhat oval plaques of erythema chronicum migrans.
Borrelia in Erythema migrans
Borrelia in Erythema migrans
Is this a Borrelia spirochete?
Is this a *Borrelia* spirochete?
Module #5
Brain and Spinal Cord as Targets of Virulent Borrelia
Borrelia in the Brain

Borrelia in the Brain
Borrelia in the Brain
Brain Monkey Model of Dr Fikrig

Skin – Hypodermic Needle Injection mimics Bite site

Autopsy Study of Monkey months later

BRAIN and Heart sites

Site Specific Molecular “signatures” of the Spirochetes

Brain signature differs from Cardiac signature
Brain Monkey Model of Dr Fikrig

Fikrig’s Gene probes for DNA of Bb
Brain Alzheimer Model of Dr MacDonald

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

Nelson Cystic “stress altered” form

“c plethora” - eligible to participate in a “splash”
Brain Alzheimer Model of Dr MacDonald

Invade, Penetrate, Injure or Kill

Nelson – Dynamic equilibrium of Borrelia burgdorferi
cysts to vegetative forms

Cysts as “droplets” - eligible to participate in a “splash”
Brain Alzheimer Model of Dr MacDonald
Invade, Penetrate, Injure or Kill

In Situ DNA and Rat Tissue culture
Module #6
Immunologic Diversity of Borrelia and its Genetic Basis
Antigenic Variation in Borrelia

“In Lyme disease Borrelia, antigenic variation involves segmental gene conversion.....Gene Conversion events involve replacement of random, variable length segments...As a result, mammals could harbour Thousands of different variants at any one time... confounding efforts by the immune system to keep up with the sequence variation.”

Dr Steven Norris
Professor, University of Texas Medical School at Houston
Molecular Microbiology, 2006
Antigenic Variation in Borrelia

Pattern in relapsing fever

- Core Temperature °C
  - First antigenic challenge
  - First antibody response
  - Second antigenic challenge
  - Second antibody response
  - Third antigenic challenge
  - Third antibody response

Days

1 2 4 6 8 10 12 14 16 18 20 22 24

Normal temperature
Antigenic Variation in Trypanosome

SEQUENCE OF EVENTS

Skin Bite by Arthropod Vector

Chancre

Blood Forms of Trypanosome

Relapses of Trypanosomes in Blood with Fever Spikes

Invisible Trypanosomes in Brain after Death from Sleeping Sickness
Antigenic Variation in Trypanosome
Module #7
Borrelia
in the
Pregnant patient
Pregnancy Borrelia

Skin bite Site – (no Chancre) - Erythema Migrans Absent

Blood Phase – Spirochetes travel through Umbilical Cord to Reach the Placenta (No Barrier in Placenta)

Placental Villi – Oxygen, Carbon Dioxide, Spirochetes

Infection Sequelae in the Developing Fetus

Miscarriage, Malformation, Stillbirth, Sudden Death of Infant in 1st year,

Tertiary Lyme Borreliosis in Youth or Adolescence
Pregnancy Borrelia

Antibodies

From Mother

From Fetal Immune Response to intrauterine infection

Pregnancy and the Maternal Immune System - Down Regulated

Teratogen Issues in the Developing Fetus –

Rubella infection model for Intrauterine Infections
Pregnancy Borrelia
Module #8
Multiple Infections in the Borrelia Attack Model
Multiple Infections Borrelia

Co-Infections

Babesia

Ehrlichia

Bartonella

Anaplasma

Theileria

Mycoplasma
Multiple Infections Borrelia

Repeat ARTHROPOD ASSAULT

Mosquito
Biting Flies
Ticks
Blood Transfusion
Organ Transplantation
??Gastrointestinal Routes
Venereal routes
Module #9
Latency in Borrelia Infections
Latency Model for Borrelia

Spirochete – (Borrelia burgdorferi) – Resting State

Months

Years

Decades

“Bad Blood” -- No Blood Donation??????

??Issue of the eligibility for blood
donation in Borreliosis patients??
Latency Model for Syphilis

Spirochete – (Treponema Pallidum) – Resting State

Months

Years

Decades

“Bad Blood” -- No Blood Donation ever if you have

had syphilis
Latency – Other Microbes

Bugs in your body which lie in a dormant “Resting” state and which are capable of

“Reactivation”

Whipple’s Disease
Tuberculosis
Chicken Pox – Varicella Zoster
Herpes Simplex (Cold Sore)
Borrelia Burgdorferi
Module #10
Borrelia Genomes in Flux
Borrelia Genomes in Flux

by a bacterial cell, through a horizontal gene transfer (HGT), uptake (1), recombination which is mediated...
Genome in Flux

Bacteriophages are Parasites of Spirochetal Parasites
Genome in Flux

DNA in Blebs of Borrelia burgdorferi
Genome in Flux

Chromosome and Plasmids

Fig. 1. The segmented and antigentic genome of S. burgdorferi. Sizes are not drawn to scale. This figure is adapted from the study by Stewart et al. (2006) with permission from Elsevier.
Genome in Flux

DNA “Inside” the Cell Wall Region
  Chromosome (S)
  Plasmids (S)
  Copy Number Issues

**Chromosome to Plasmid** “Shuffle” Like a Deck of cards

*Plasmids as “Mini- Chromosomes”*

DNA “Outside” of the Cell wall region (“Blebs with DNA”)

Genome in Flux

**Fig. 5.** Telomere exchange by RestT-mediated telomere fusion. Fusion 1 links an unknown linear plasmid (IpX) to the right end of the E. burgdorferi R-IP3 chromosome to generate the structure of the right-end telomere found in the B31 chromosome. The identity of IpX is not clearly discernible and the right end of the B31 chromosome shares homology with several linear plasmids (Casjens et al., 1997; 2000). Fusion 2 shows a telomere exchange that converts the right end of B31 to the right and observed for the Sh-2-82 chromosome through fusion with Ip21 (see Casjens et al., 1997; Huang et al., 2004b). Successive rounds of telomere fusion with deletion formation can also explain the many examples of telomere exchange observed in the E. burgdorferi linear plasmids (Casjens et al., 2000). This figure has been adapted from the study by Kobryn and Chaconis (2005).
Genome in Flux

DNA and RNA In Borrelia B 31
DNA in Flux model
Module #11
Blebs of Borrelia as Weapons
Blebs as Weapons

Blebs
Are
Released
From Borrelia
Blebs as Weapons

“Shedding” of “Blebs” from Outer Membrane

DNA in Blebs – Origins?? Participation in “fluxes”

“Blebbing” as a Verb and as an Adjective

“Blebs as Projectiles”

Big Cysts from Little Blebs – Electron Microscopy
Blebs as Weapons
Blebs as Weapons
Module #12
Flagellae of Borrelia
as
Hypodermic Needles
Flagellae Hypodermic Needle

Flagellin Structure
Hollow Core
“Cap”
Rotor Base
Inner Fla B
Type III Secretion
Type IV Secretion
Flagellae Hypodermic Needle
Module #13
Borrelia infections
Inside of Neurons
Which
Transit Across
Synapses
### Infections Inside of Neurons, Schwann cells or Glia

(* * * documents Transsynaptic transmission of Infection)

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<tr>
<th>Virus/Agent</th>
<th>Reference(s)</th>
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<td>Rabies Virus</td>
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<td>Pseudorabies Virus</td>
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<td>Herpes Zoster (Varicella Zoster) Virus</td>
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<td>Herpes Simplex Virus</td>
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<td>Tick Borne Encephalitis virus</td>
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<td>Prion Agent of Creutzfeldt Jacob</td>
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<td>Prion Agent of Transmissible Mink Encephalopathy</td>
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<td>Kuru Agent</td>
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<td>Scrapie Agent</td>
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<td>Leprosy (Mycobacterium Leprae)</td>
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<td>Listeria infection of Trigeminal Nerve in Mouse</td>
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<td>Treponemal Spirochetes (Oral) via Trigeminal Nerve to Brain</td>
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<td>Various Mosquito borne encephalitis viruses</td>
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Trans-Synaptic Borreliosis
Module #14
Neural Network
Borrelia Infection
Borrelia Infection Neural Networks
Borrelia Image Review
Borrelia Image Review
Blebs and L forms
L Forms of Borrelia
L forms of Borrelia
L form
Borrelia
Borrelia L Form UltraStructure
Borrelia Bleb Model
Ring Form of Borrelia
Aberer and Duray Borrelia form
Cystic Borrelia with Granules
Cystic Borrelia with Granules
Experimental Borrelia Infection

- Borrelia burgdorferi
- in Hamster kidney
- Experimental infection
- Uncoiled spirochete
- Monoclonal Antibody H5332 (OspA)
Cystic Form of Borrelia

Cystic Borrelia burgdorferi cultured from Spinal fluid
Alan B. MacDonal d MD
2006
Cystic Form of Borrelia
Cystic Form of B31 Borrelia
Perfect Spirochetes –
All of These
The Research Support of the Turn the Corner Foundation
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