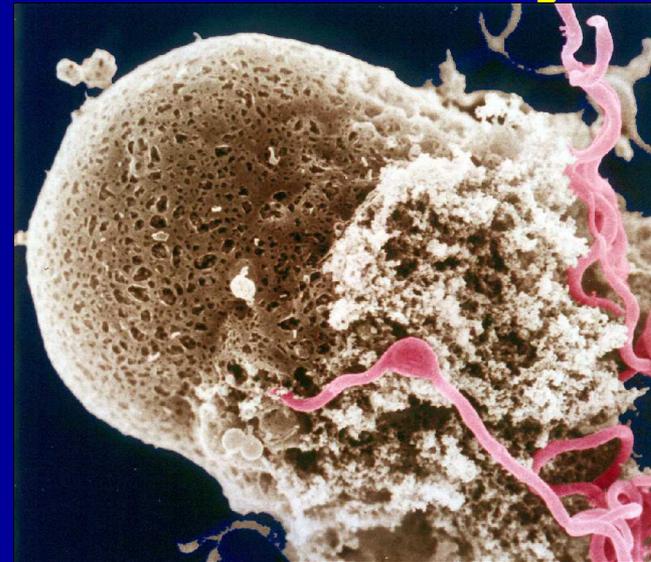
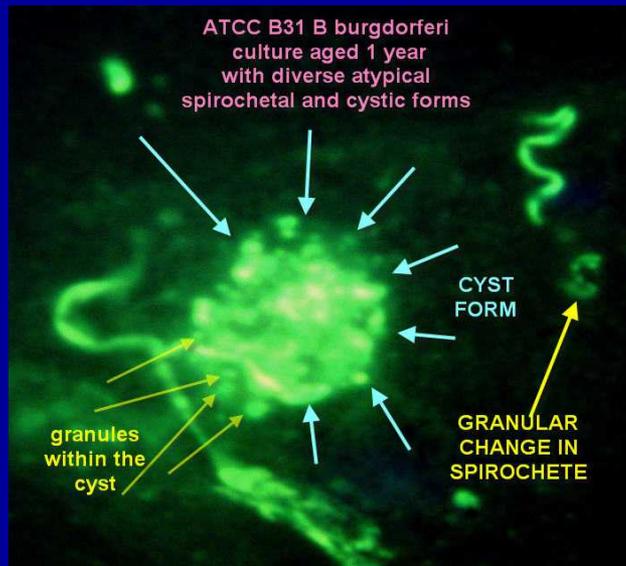


Chronic Lyme Disease/Tick-Borne Disease: the Controversy



Robert C Bransfield, MD, DFAPA
LDA 7th Tick Borne Diseases Conference
Leicester University: Leicester England
July 18, 2008

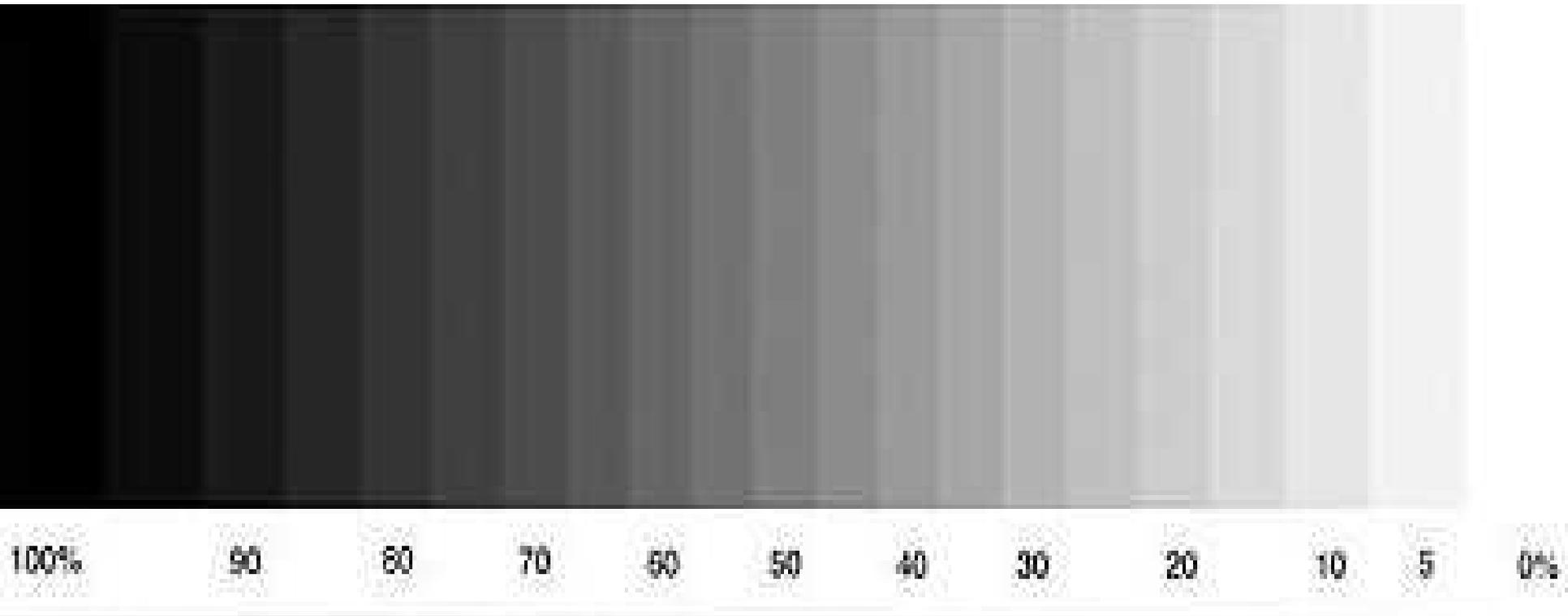
Disclaimer

- Patients pay me money in return for trying to help them.
- I have no contract with any insurance company or other payer that might restrict or alter patient care in return for referring patients or providing other benefits.
- I have been an expert witness in cases involving Lyme disease.
- Speaker for various pharmaceutical companies.

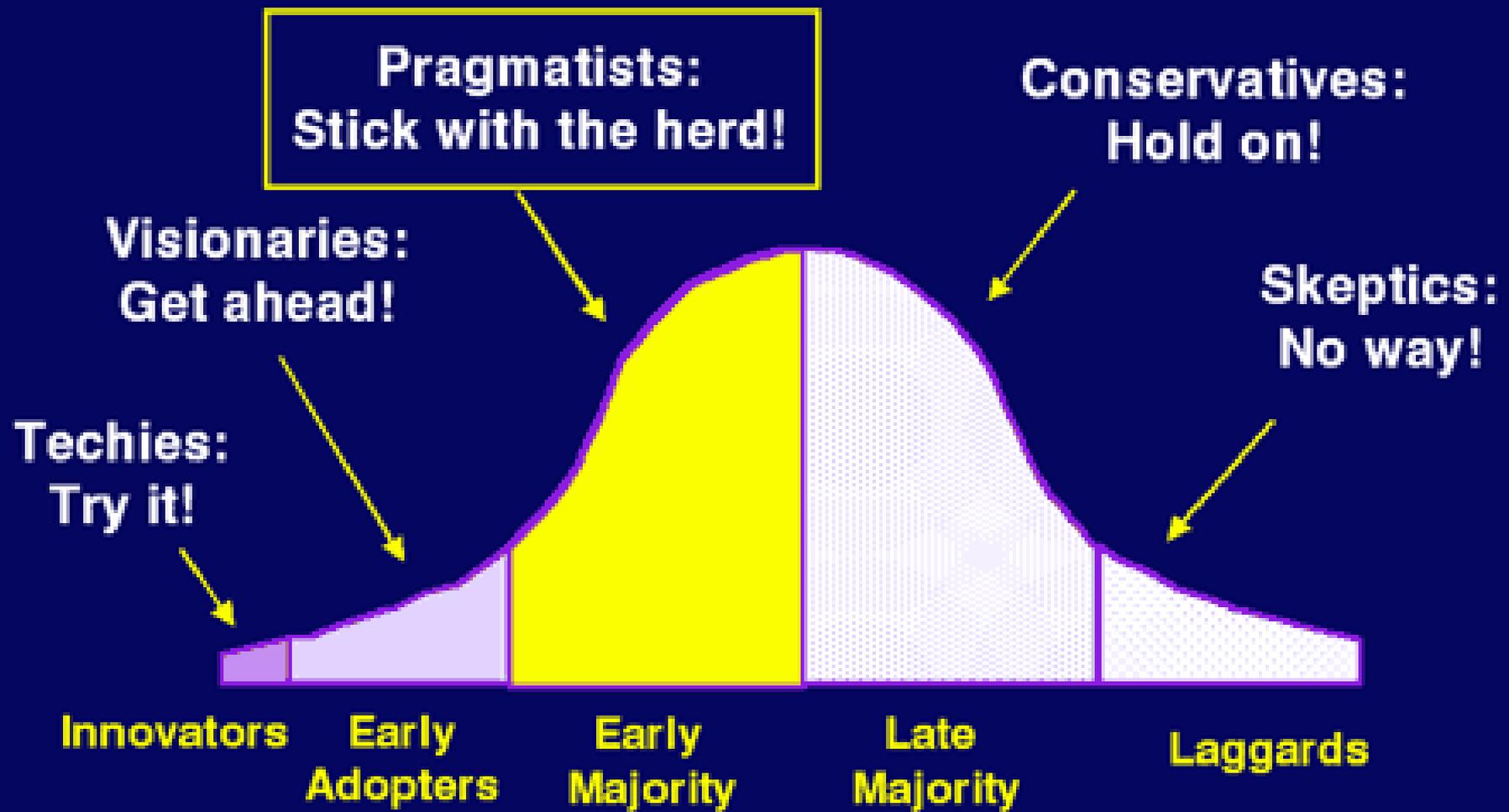
Lyme Controversy: Key Issues

- How do you define Lyme disease?
- Is there long term persistent infection?
- What Bb. strain(s) or other microbe(s)?
- How restricted or broad are the symptoms of these chronic tick-borne diseases?
- How reliable is the testing?
- What is the best treatment?
- Risk of disease vs. risk of treatment?
- Are IDSA or ILADS guidelines more valid?
- Do self interests impair objectivity & ethics?

Are the answers black & white or shades of gray?



Technology Adoption Life Cycle



Pragmatists cast the deciding vote

PubMed Citations

- Tick borne diseases: 20,000
- Lyme disease: 8,200
- *Borrelia burgdorferi*: 6,250
- Mycoplasma: 18,000
- Babesia: 2,900
- Bartonella: 1,900
- Ehrlichia: 1,900
- Anaplasma: 1,500
- Masters Disease or Stari: 700

Acute vs. Chronic Infections

- Most physicians are oriented towards an acute infectious disease model.
- Chronic persistent infections are different from acute infections and require a different approach.

How much is still unknown?

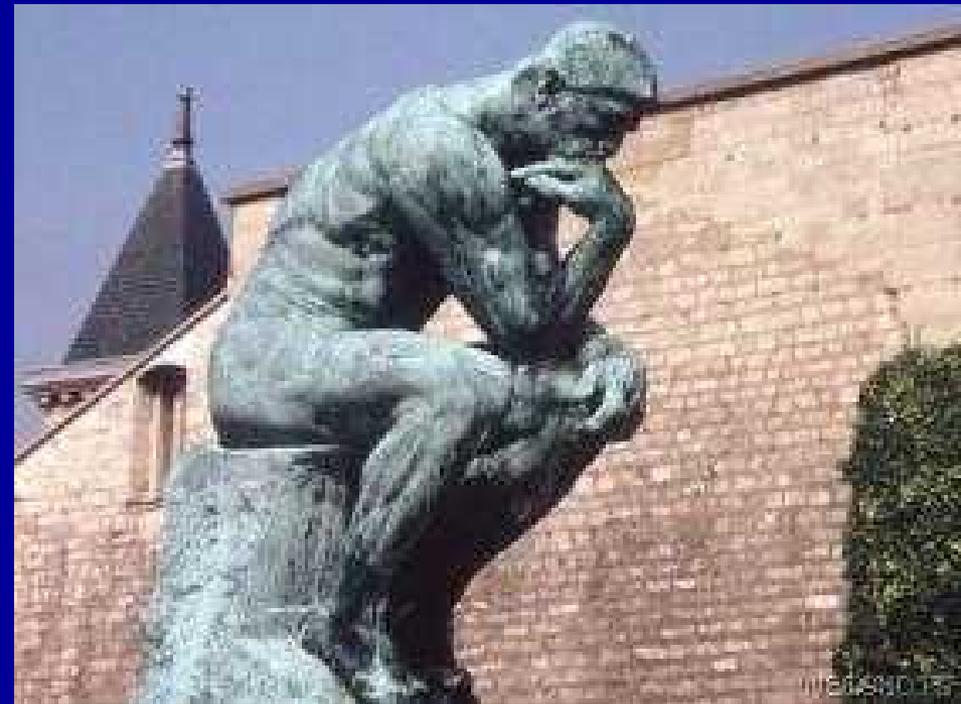
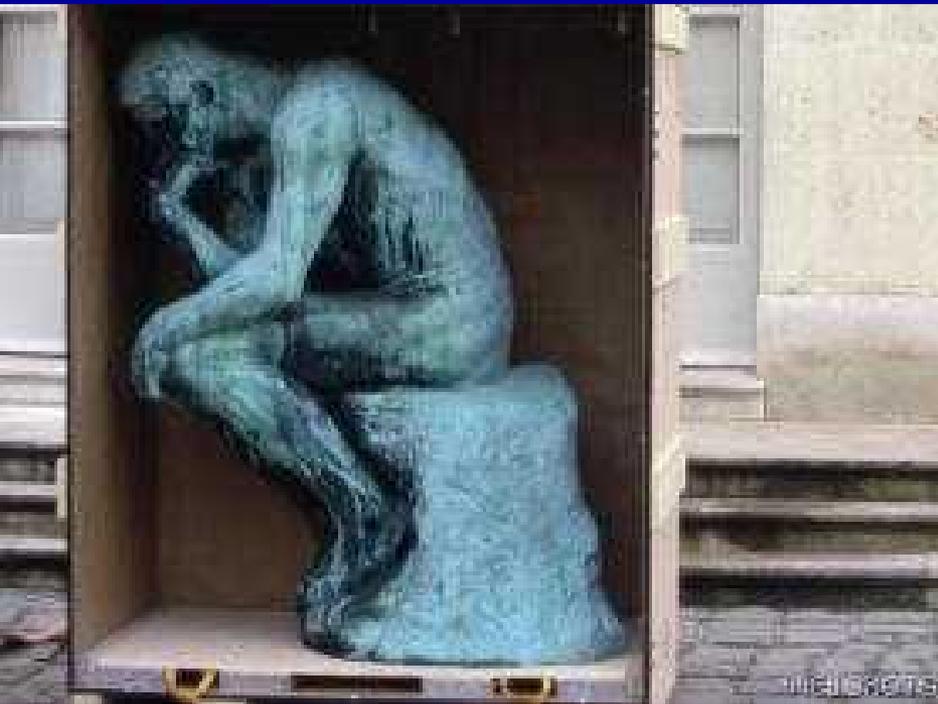
"Half of what doctors know is wrong." This quote is from the article by Lisa Sanders, which also includes the quote "the history of medicine is a long, serpentine narrative of the death of old ideas giving way to the birth of new ones."

Unknown or Unknowns

- "As we know there are **known knowns**. There are things we know we know.
- We also know there are **known unknowns**. That is to say we know there are some things we do not know.
- But there are also **unknown unknowns**, the ones we don't know we don't know."

Donald Rumsfeld

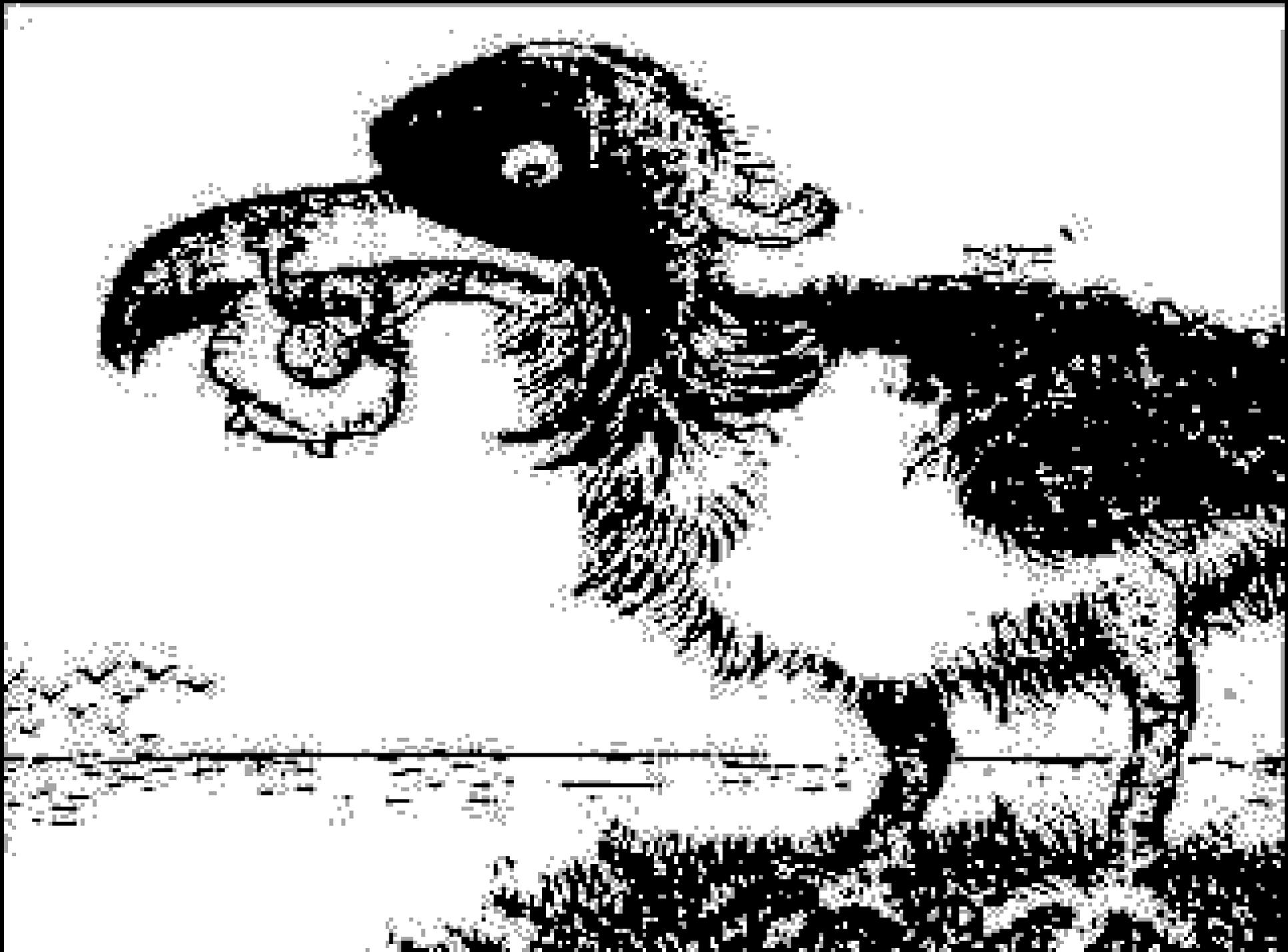
Confront Dogma Think Outside the Box



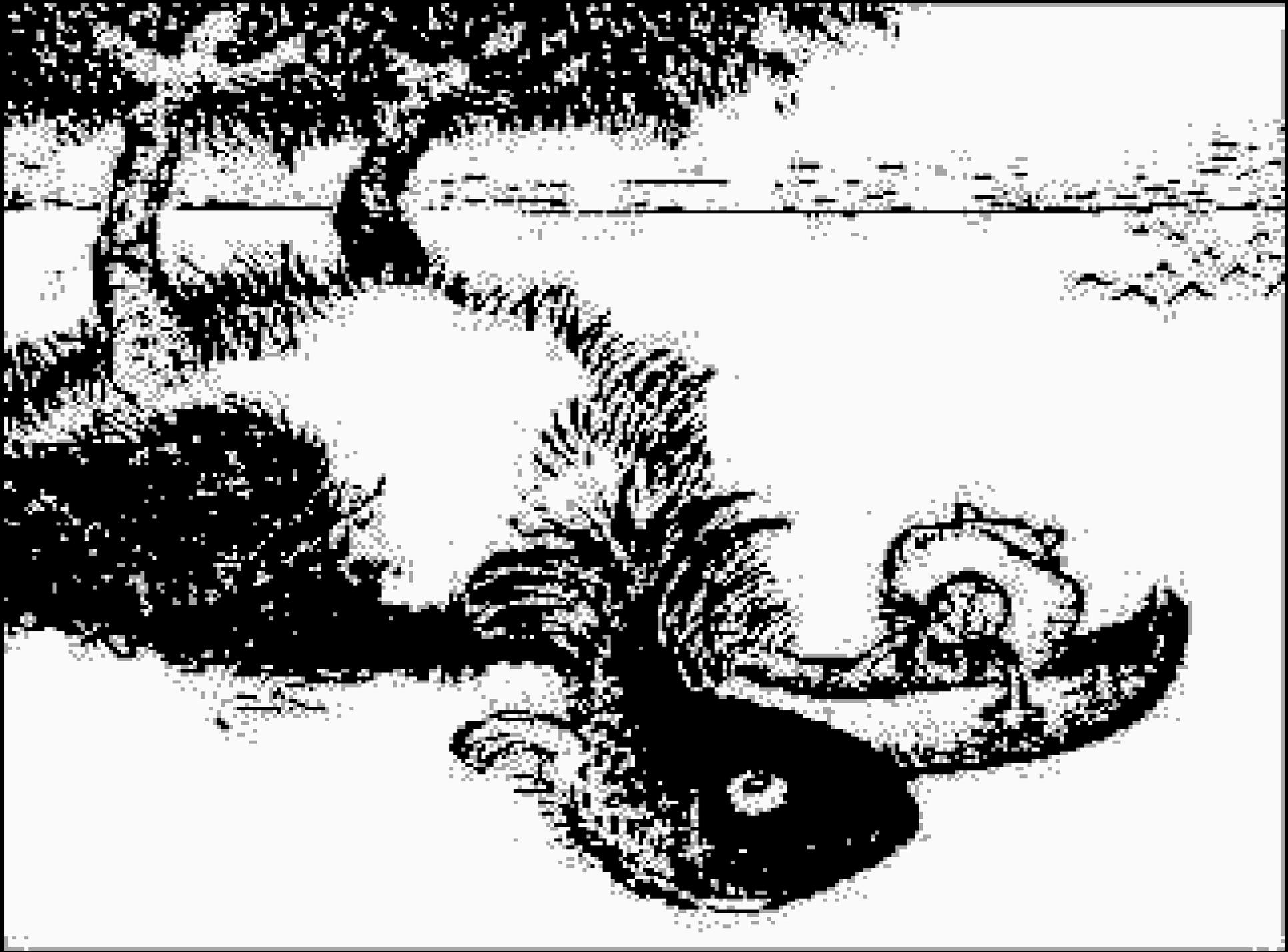
Scientific Illusions

What do you see?





Now, what do you see?



Can you look at other things
differently?



Some of the evidence for chronic infections

- Clinical observation of persistent symptoms
- Animal studies
- Autopsies and pathological specimens
- Case reports and laboratory data
- Theoretical biology
- Multiple studies
- Complexity of *Borrelia* and coinfections
- Therapeutic response to antimicrobial treatments
- Other explanations are non-viable

Lyme Disease: The Quest for Magic Bullets

- *Borrelia burgdorferi* is one of the most complex bacteria known to man.
- Two major clinical hurdles are the absence of a therapeutic endpoint in treating Lyme disease and the presence of tick-borne coinfections that may complicate the course of the illness.

Can Infectious diseases be Chronic?

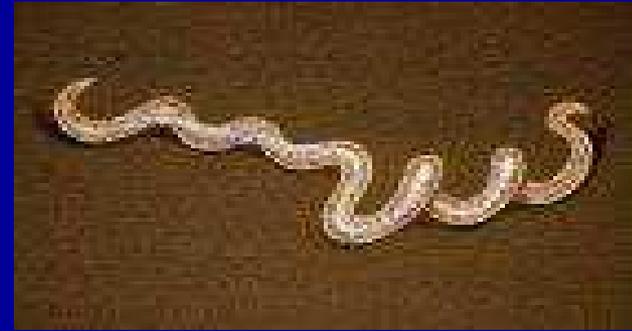
- Syphilis
- Leprosy
- Tuberculosis
- AIDS
- Hepatitis B & C
- Malaria
- Etc, etc.

Cousins: Lyme Disease & Syphilis



Lyme disease

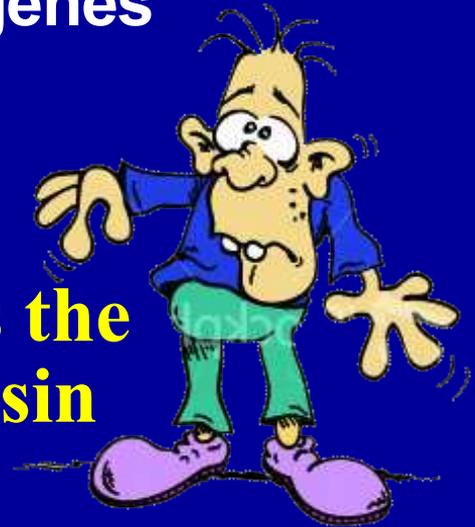
- Chromosome + 21 plasmids
- 132 genes
- More genetic material
- 90% genes unrelated to any other known bacteria
- Perhaps the most complex bacteria known



Syphilis

- Only 22 genes

Syphilis is the dumb cousin



Wide Distribution of a High-Virulence *Borrelia burgdorferi* Clone in Europe and North America

- The *ospC*-A clone appeared to be highly prevalent on both continents, and isolates of this clone were uniform in DNA sequences, which suggests a recent trans-oceanic migration.
- We conclude that the *ospC*-A clone has dispersed rapidly and widely in the recent past. The spread of the *ospC*-A clone may have contributed, and likely continues to contribute, to the rise of Lyme disease incidence.

Virulent strain of Lyme disease spreading in the U.S. & Europe

- Wei-Gang Qiu, PhD, Benjamin Luft, MD, and colleagues find that the particularly nasty ospC type A strain appears to be the most common of the 20 or so *B. burgdorferi* strains found in the U.S. The spread of this virulent strain, they suggest, could be part of the reason for the increase in Lyme disease cases seen over the past two decades.
- Luft says the spread of the ospC type A strain may explain part of the U.S. Lyme disease epidemic.

B31 Strain

- The common B31, first collected by Benach, isolated by Burgdorfer and cultured by Barbour from the ticks on Shelter Island. Luft estimates it has exploded since about the 1970s.
- Of 14 found to cause erythema migrans, only 4 (including B31) disseminate to cause late stage Lyme.
- This means that the rash studies of early Lyme disease (which assume that ALL of the 14 strains disseminate) are highly skewed, the data needs to be tossed, reevaluated or reinterpreted --early Lyme disease may not be as curable as we thought -- if it is of the disseminating variety. This is just one more leg of the stool that is the IDSA paradigm that is turning out to be completely wrong

Tick-borne Pathogens

- Humans have 400 different species of bacteria in their mouth.
- Ticks live in filth and suck on the blood of rodents.
- What pathogens known and unknown can be transmitted in a tick bite?

Tick Saliva Causes Immunospression

- Kyckova & Kopecky. Effect of tick saliva on mechanisms of innate immune response against *Borrelia afzelii*. *J Med Entomol*. 2006 Nov;43(6):1208-14.
- Holden K, Hodzic E, Feng S, Freet KJ, Lefebvre RB, Barthold SW. Coinfection with *Anaplasma phagocytophilum* alters *Borrelia burgdorferi* population distribution in C3H/HeN mice. *Infect Immun*. 2005 Jun;73(6):3440-4.
- Hannier S, Liversidge J, Sternberg JM, Bowman AS. Characterization of the B-cell inhibitory protein factor in *Ixodes ricinus* tick saliva: a potential role in enhanced *Borrelia burgdorferi* transmission. *Immunology*. 2004 Nov;113(3):401-8.
- Wikel SK. Tick modulation of host immunity: an important factor in pathogen transmission. *Int J Parasitol*. 1999 Jun;29(6):851-9.

Complex Interacitive Infections

- Biofilms
- Parasites within parasites
- Some microbes cause immunosuppression and promote their survival and the survival and growth of other parasites

Coinfections

- **Lyme-** spirochete *Borrelia burgdorferi*
– very complex bacterium
- **Bartonella-** newly discovered bacterium,
and very common
- **Babesiosis-** blood parasite distantly
related to Malaria
- **Ehrlichiosis (*Anaplasma*)-** blood
bacterium
- **Mycoplasma**
- **Probably many unknown coinfections**

TBD: *Borrelia burgdorferi*, *Babesia* Cause Immunosuppression

- ***Borrelia burgdorferi*-induced tolerance as a model of persistence via immunosuppression.** (Diterich et. al. Infect Immun. 2003 Jul;71(7):3979-87)
- **Immunodepression in *Babesia microti* infections.** (Purvis AC. Parasitology. 1977 Oct;75(2):197-205)
- Other tick-borne pathogens may also be immunosuppressant

Proposed Mechanisms of *Borrelia burgdorferi* Persistence

Active Immune Suppression

Immune Evasion

Innate:

- Complement inhibition
- Induction of anti-inflammatory cytokines
- Tolerization of monocytes

Adaptive:

- Induction of anti-inflammatory cytokines
- Tolerization of lymphocytes
- Complement inhibition
- Immune complex sequestration

Phase and antigenic variation:

- Gene conversion
- Variable expression of antigens

Physical seclusions:

- Intracellular
- Extracellular
- Cysts
- Immunologically privileged sites

Fighting Back: How *B burgdorferi* Persists I

- Spirochetes persistence in the human body has been demonstrated in both syphilis and Lyme disease. According to Charles Pavia, PhD, there are at least 6 potential explanations:
- antigenic variation (this is seen with the *Borrelia* species that cause tick-borne relapsing fever) or differential expression of antigens (especially the outer surface proteins; with *B burgdorferi*, only OspC is expressed during mammalian infection)
- production of an outer protective coat (eg, capsule, as seen with *T pallidum*)
- atypical forms (eg, cyst-like variants)
- incomplete immune response (eg, insufficient antibody, T-cell, or phagocytic response)
- deranged host immune response (eg, host-, tick-, or spirochete-derived immunosuppressive factors)
- other evasive factors (eg, motility)

Fighting Back: How *B burgdorferi* Persists II

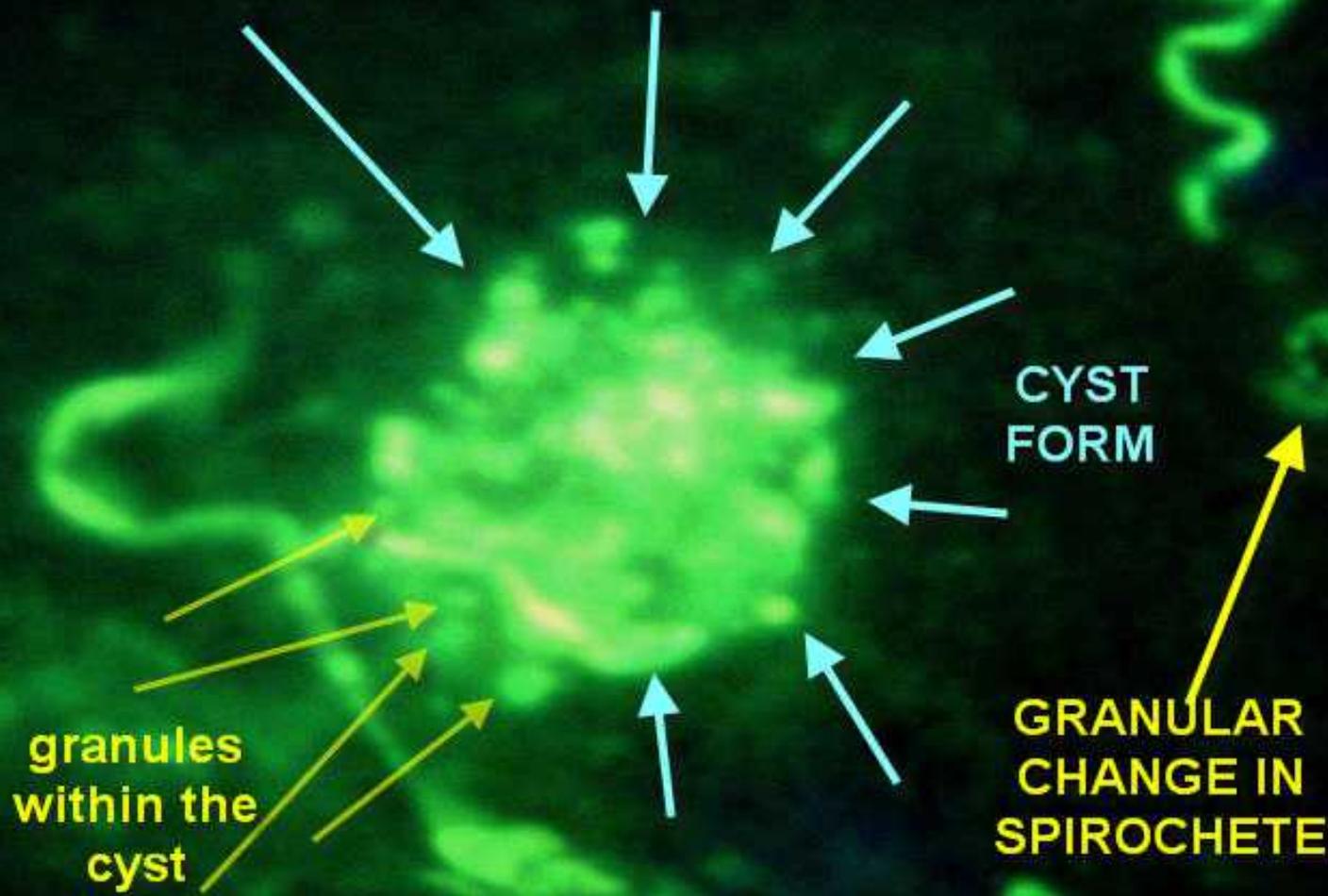
• Immune Suppression

- Is there evidence that any of these mechanisms allow *B burgdorferi* to persist in the human body? As of now, not much. However, there have been a few suggestive studies in animals that support immune suppression as a possible explanation. For instance, a study by Chiao and colleagues[2] showed that *B burgdorferi* is capable of suppressing the immune response. When sonicated *Borrelia* were added to lymphocytes, the ability of the lymphocytes to proliferate -- a measure of the immune system's ability to respond to an infectious challenge -- was inhibited. A similar study by Giambartolomei and coworkers[3] showed that *Borrelia* can stimulate interleukin-10 (IL-10) production, a downregulator of the immune system. In this series of experiments, heat-killed *B burgdorferi* caused peripheral blood mononuclear cells of humans and rhesus monkeys to produce this cytokine. Another study, by Keane-Myers and Nickell,[4] found that *B burgdorferi* could suppress T-cell responses in mice, specifically T-helper cells.
- Looking at the issue of immune suppression from the other side -- that is, by boosting the immune response with the use of cytokines -- Zeidner and colleagues[6] showed that tumor necrosis factor alpha (TNF-alpha), IL-2, and interferon-gamma could suppress *B burgdorferi* infection in mice.
- By contrast, it appears that infection with *B burgdorferi* can also overstimulate the immune system, and this may explain many of the symptoms of both acute and chronic Lyme disease. For instance, Lim and colleagues[7] showed that CD4+ T cells play a role in the arthritis seen in the hamster model of Lyme disease.

Why CNS Lyme Disease is Poorly Understood

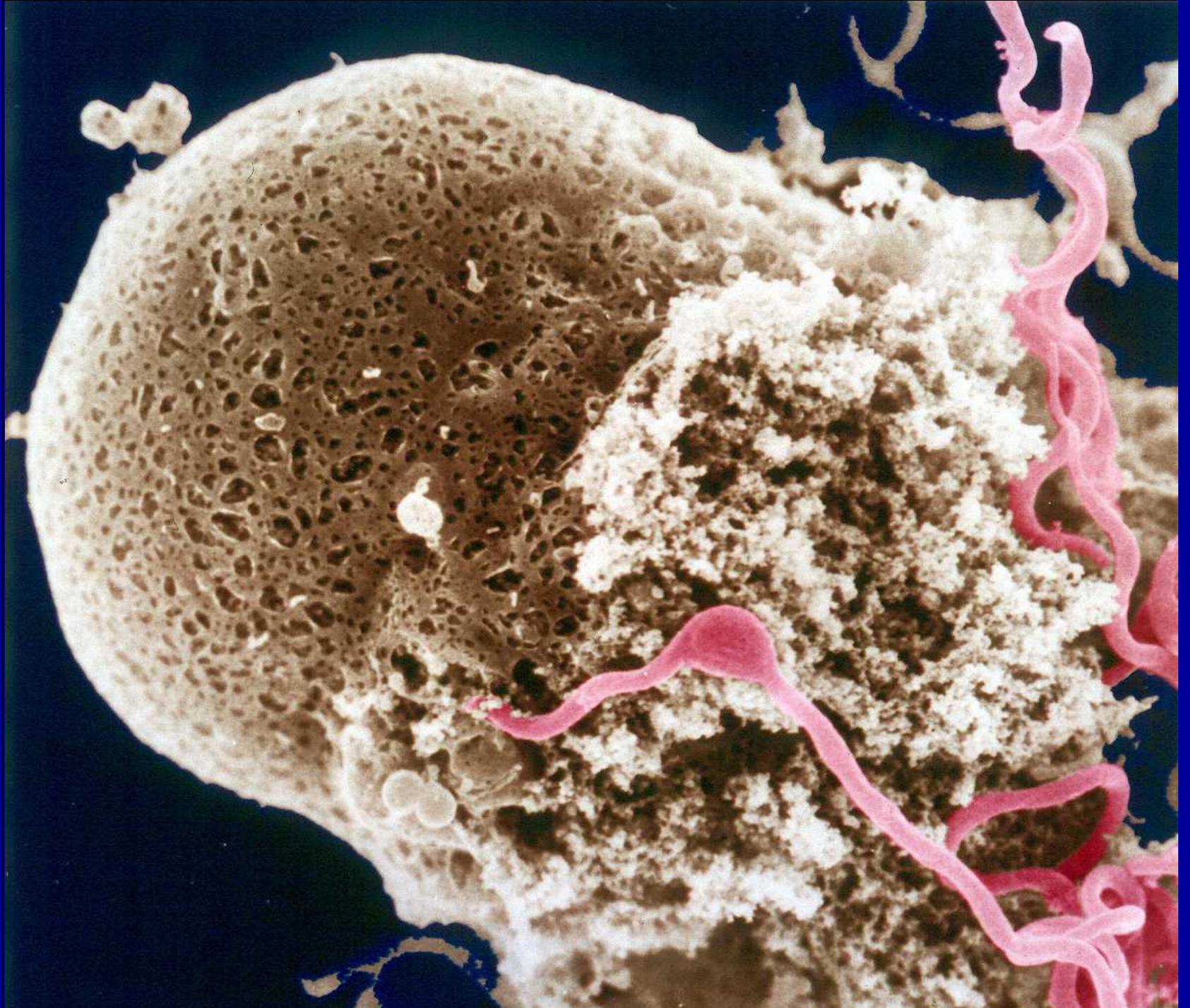
- First, we lack a definitive assay to demonstrate active infection.
- Second, Bb infection can be occult, resulting in long periods of latency before symptoms are manifest.
- Third, Bb can disseminate to sequestered compartments where antibiotic penetration is difficult and immune surveillance is lacking.
- Fourth, Bb is known to have considerable strain heterogeneity. This strain heterogeneity may result in different levels of virulence and different organotropism. For example, some strains may be more likely to result in arthritic or skin disease whereas others may target the nervous system.
- Fifth, the antigenic variability of Bb is known to result in different antigen expression in different locales. In the tick, outer surface protein (Osp) A is expressed, whereas in the human it is upregulated to Osp C (prior to transfer to the host by the tick). However, Osp A may be preferentially expressed in the CSF compartment, as the studies at Stony Brook have demonstrated. CSF studies at Stony Brook also have demonstrated a strong immunoglobulin M response, the presence of immune complexes, and a prominent TH1 proinflammatory cytokine response.
- Sixth, the significance of coinfection with other tick-borne organisms such as Babesia is not fully understood. Such co-infection may be misdiagnosed as being only Lyme disease and result in more severe and refractory cases of Lyme disease.

ATCC B31 *Burgdorferi*
culture aged 1 year
with diverse atypical
spirochetal and cystic forms



Bb and Latency

“It is clear to us that a significant proportion of our LBC cases occur as a result of a activation phenomenon, which in turn implies that Bb is a dormant or latent infection in these patients. It is probable that Bb infections, both recognized and unapparent, can result in a latent infected state with the potential for reactivation whenever immune activation occurs per “trigger phenomena. In our experience, this ‘trigger’ could be physical or emotional trauma, or cumulative effects of major stress.”



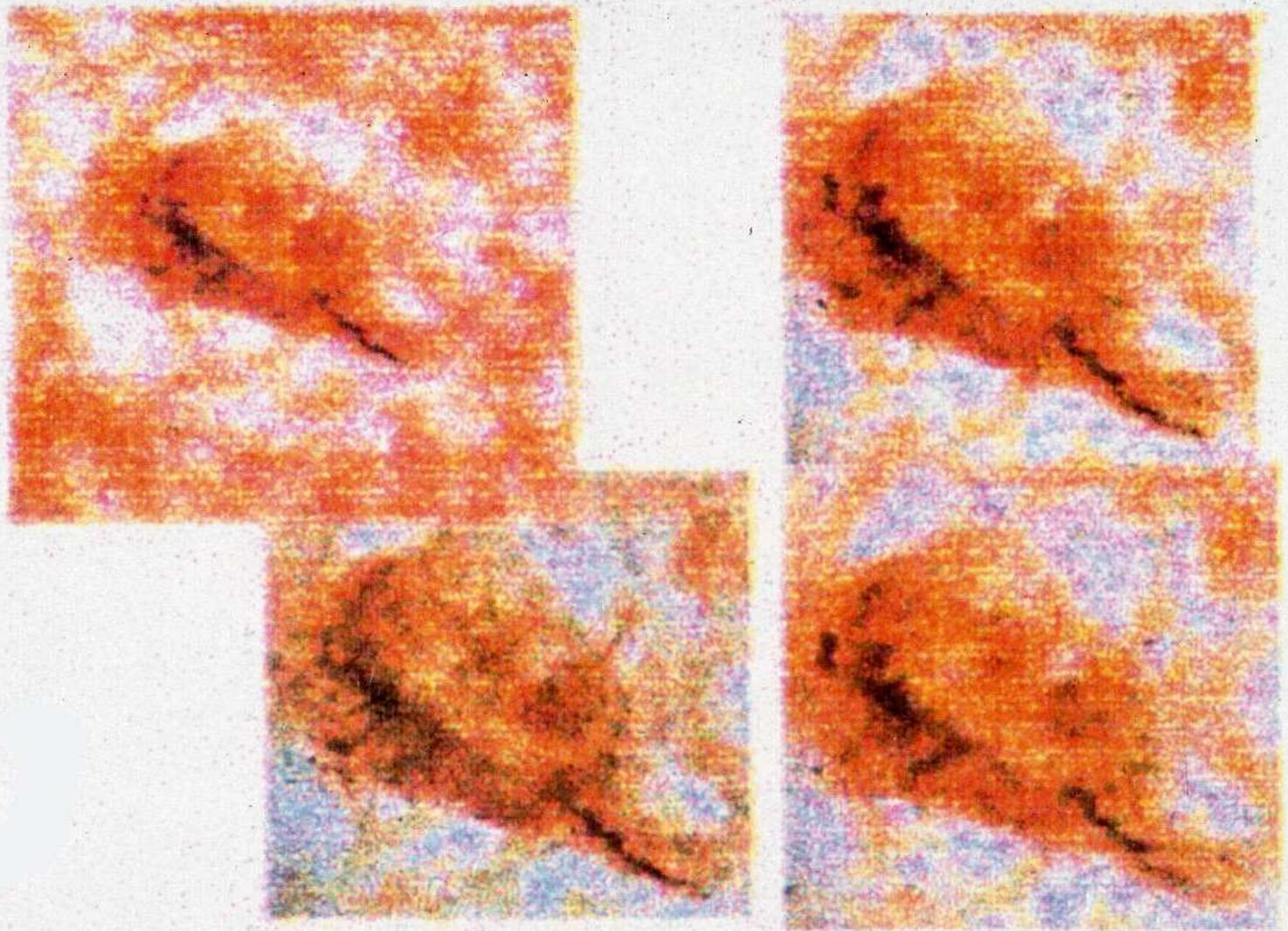
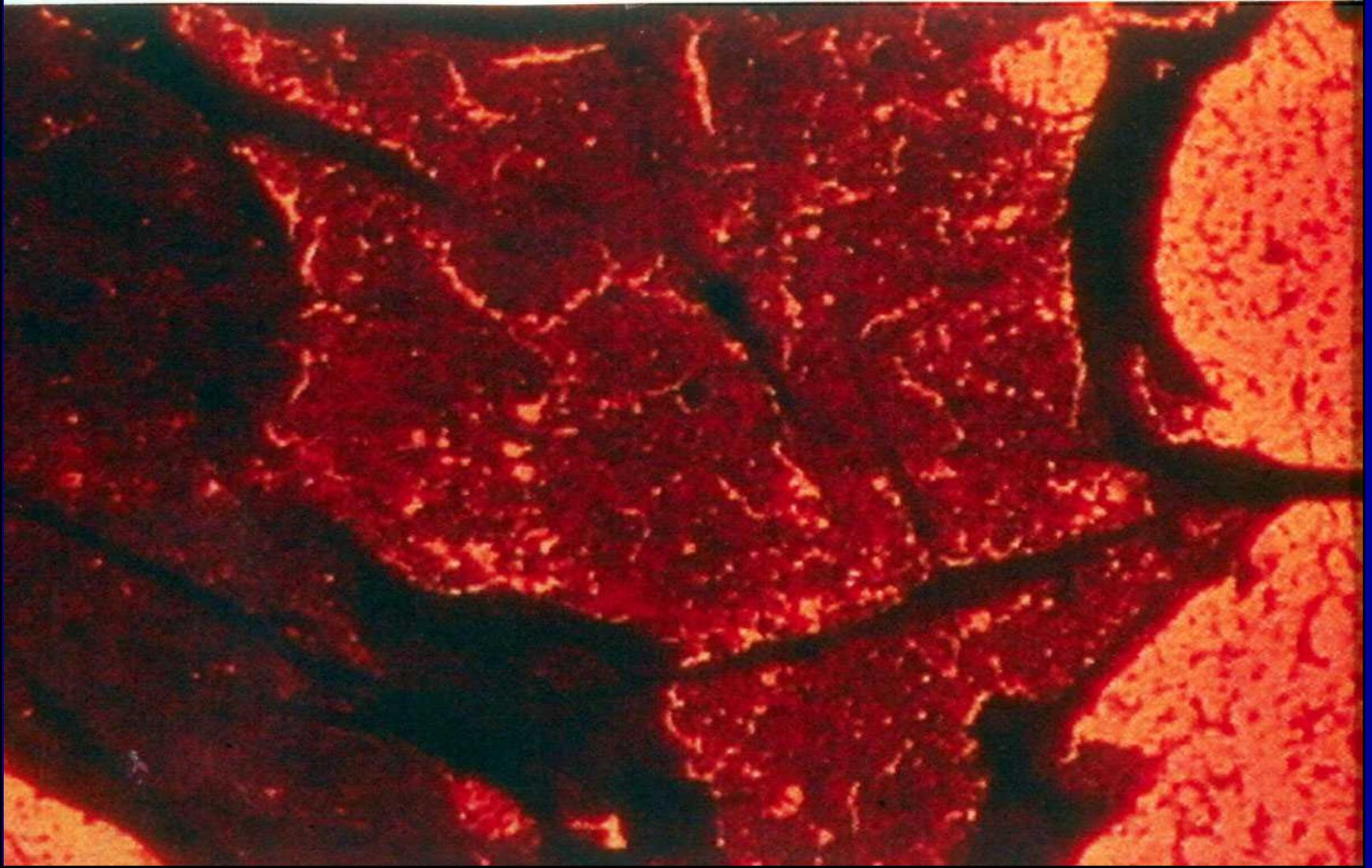


Figure 2: SERIAL IMAGES OF ONE NEURON WITH INTRACELLULAR SPIROCHETE

CO-EXISTENT FUNGAL INFECTION OFTEN MASKS THE SPIROCHETE. PHOTO SHOWS MANY SPIROCHETES EMBEDDED IN FUNGAL GROWTH. BLOOD CULTURE OF LYME PAT.



Propensity to excessive proinflammatory response in chronic Lyme borreliosis

- All the clinical manifestations, acute or chronic, are characterized by strong inflammation. *Borrelia burgdorferi* can induce the production of several proinflammatory and anti-inflammatory cytokines
- We conclude that chronic forms of Lyme borreliosis can evolve due to an aberrant innate proinflammatory response.

Harvey, WT; Salvato, P: 'Lyme Disease': Ancient Engine of an Unrecognized Borreliosis Pandemic?

Medical Hypotheses (2003) 60(5), 742-759; Elsevier Science Ltd.

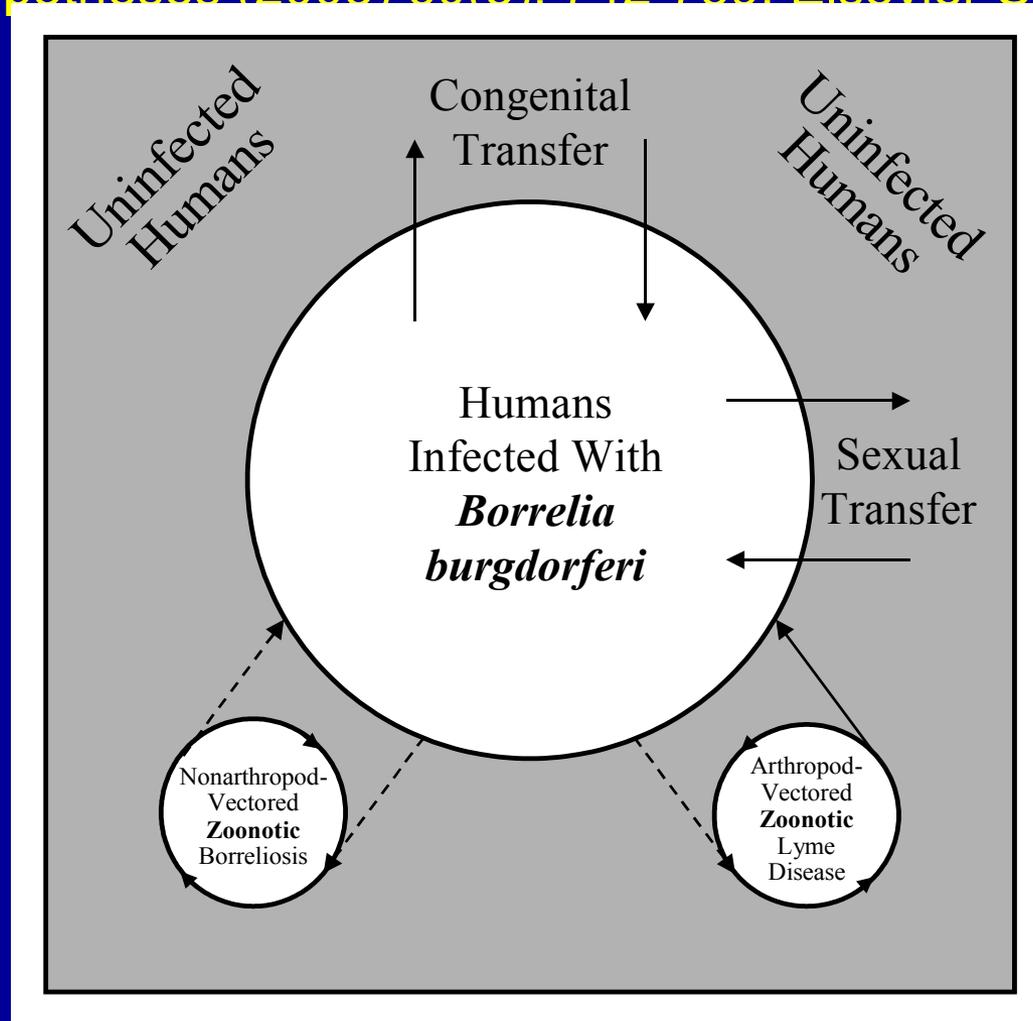


Figure 1. Revised model of human *Borrelia burgdorferi* infection

How can you prove *Borrelia burgdorferi*
has been totally eradicated?

Lyme Testing Not Reliable

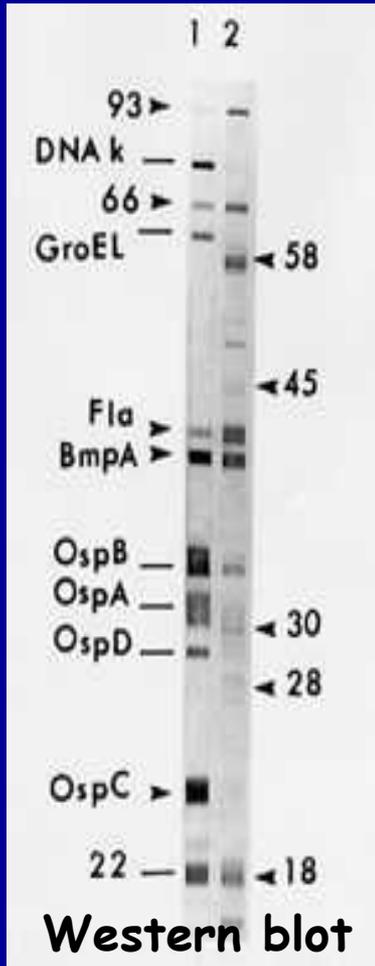
There are **12** known genospecies and one of those genospecies has over **100** strains in the United States.

BUT, current testing measures human antibodies to only a **single strain** of the bacteria.

Hence, testing is grossly unreliable.



CDC 2-tier test procedure controversy:



- CDC 2-tier test procedure controversy:
 - ✓ **ELISA**: Screening, only 30-60% accurate
 - ✓ **Western blot**: Qualitative assay, bands, 85% accurate
- **NO test** can reliably diagnose Lyme disease
- **Clinical diagnosis!** Tests supportive
- Many physicians and insurance companies using CDC surveillance criteria INCORECTLY for diagnosis and payment!

Lyme Wars: Let's tackle the testing

- The two tier testing system endorsed by the Centers for Disease Control and Prevention (CDC) has a high **specificity (99%)** and yields few false positives. But **the tests have a uniformly miserable sensitivity (56%)**—they miss 88 of every 200 patients with Lyme disease (table). By comparison, AIDS tests have a sensitivity of 99.5%—they miss only one of every 200 AIDS cases. In simple terms, the chance of a patient with Lyme disease being diagnosed using the commercial tests approved by the Food and Drug Administration and sanctioned by the CDC is about getting heads or tails when tossing a coin, and the poor test performance assures that many patients with Lyme disease will go undiagnosed.
- Until we scrap the worthless commercial tests for Lyme disease and find a better way to make the diagnosis of this protean illness, the “Lyme wars” will continue unabated.
- **Sensitivity** and **specificity** of commercial two tier testing for Lyme disease
- Schmitz et al. Eur J Clin Microbiol Infect Dis 1993;12:419-24 **66%** **100%**
- Engstrom et al. J Clin Microbiol 1995;33:419-27 **55%** **96%**
- Ledue et al. J Clin Microbiol 1996;34:2343-50 **50%** **100%**
- Trevejo et al. J Infect Dis 1999;179:931-8 **29%** **100%**
- Nowakowski et al. Clin Infect Dis 2001;33:2023-7 **66%** **99%**
- Bacon et al. J Infect Dis 2003;187:1187-99 **68%** **99%**
- **Mean of all studies** **56%** **99%**

Risk of Disease vs. Treatment

- If Lyme disease is benign, the risk of the disease may not outweigh the risk of treatment.
- If Lyme disease is serious, the risk of the disease may outweigh the risk of treatment.



Length of antibiotic therapy controversy

- Length of antibiotic therapy controversy
 - ✓ Spirochetal generation time, e.g. *Treponema pallidum*
(~33h), *Borrelia burgdorferi* (12 to 24h)
 - ✓ *E. coli* or *Salmonella* cycles are <15 minutes
 - ✓ Antibiotics kill during cell division
 - inhibiting cell wall formation, e.g., penicillins & cephalosporins
 - inhibiting protein synthesis, e.g., doxycycline & azithromycin
 - ✓ 15 min cycle = 1000 kill chances in ~10 days
 - ✓ 12 hour cycle = 1000 kill chances in ~500 days (~17m)
- **A “cure” with 14 or 30 days ATBX treatment?**

Tetracycline therapy for chronic Lyme disease

- Two hundred seventy-seven patients with chronic Lyme disease were treated with tetracycline for 1 to 11 months (mean, 4 months); the outcomes for these patients were generally good. Overall, 20% of the patients were cured; 70% of the patients' conditions improved, and treatment failed for 10% of the patients.
- These results support the use of longer courses of treatment in the management of patients with chronic Lyme disease.

Counterpoint: long-term antibiotic therapy improves persistent symptoms associated with lyme disease

- The complex "stealth" pathology of *B. burgdorferi* allows the spirochete to invade diverse tissues, elude the immune response, and establish long-term infection. Commercial testing for Lyme disease is highly specific but relatively insensitive, especially during the later stages of disease. Numerous studies have documented the failure of standard antibiotic therapy in patients with Lyme disease. Previous uncontrolled trials and recent placebo-controlled trials suggest that prolonged antibiotic therapy (duration, >4 weeks) may be beneficial for patients with persistent Lyme disease symptoms. Tick-borne coinfections may increase the severity and duration of infection with *B. burgdorferi*.
- **CONCLUSIONS: Prolonged antibiotic therapy may be useful and justifiable in patients with persistent symptoms of Lyme disease and coinfection with tick-borne agents.**

Access to Care

Recent Developments

- Attorney General report
- Under Our Skin
- Cure Unknown and other recent books
- TV reports on ABC & CNN
- Favorable New York Times article
- National Foundation for Women
Legislators recommending the creation of independent and public Medical Board Oversight Committees in each state

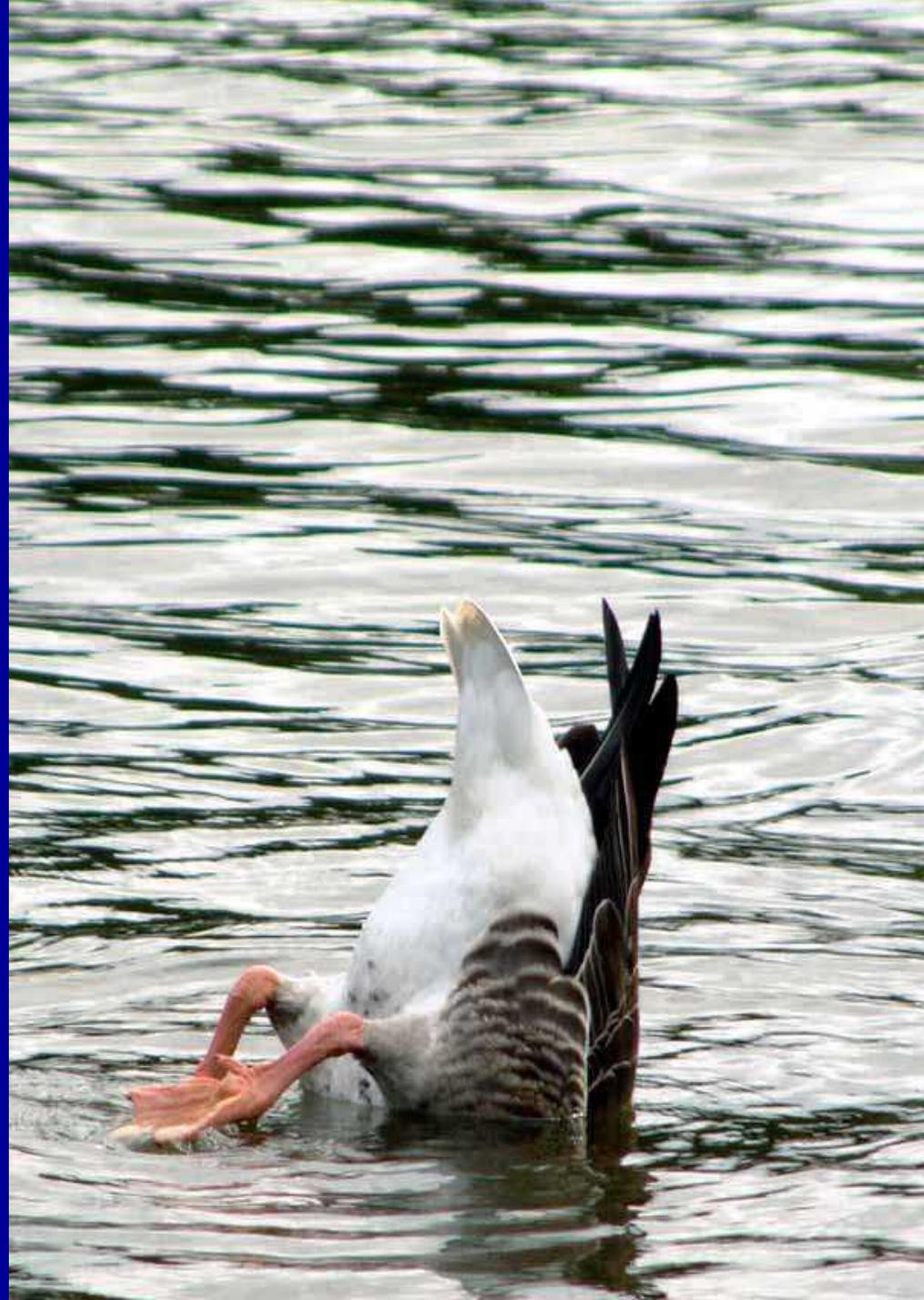
Antitrust Investigation Shows Guidelines Flawed

- Connecticut Attorney General Richard Blumenthal announced that his antitrust investigation has uncovered serious flaws in the Infectious Diseases Society of America's (IDSA) process for writing Lyme disease guidelines.
- Blumenthal found that IDSA failed to conduct a conflicts-of-interest review and that influential panelists had a conflict. Failure to follow its own procedures enabled the chairman to appoint a hand-picked panel, without scrutiny. The Lyme panel refused to consider dissenting opinions, and once even removed a member in order to achieve "consensus." IDSA tried to portray the guidelines promulgated by the American Academy of Neurology (AAN) as independent corroboration, when in fact the panels shared key members, came to the same conclusions, and used the same wording. IDSA then used the AAN's supposedly independent findings in attempt to defeat federal legislation to establish a Lyme disease advisory panel and state legislation to support antibiotic therapy for chronic Lyme disease.
- "When a positive result is found, they discredit the study," notes neurologist Lawrence R. Huntoon, M.D., Ph.D.

The AAN Lyme Guidelines: Through the Looking Glass

- AAN panel members cite what they consider the “highest level of evidence” in characterizing chronic Lyme disease as a “post-infectious” syndrome.
- These statements are put forth despite numerous animal and human studies gleaned from more than 19,000 peer-reviewed publications showing persistent infection with the invasive and elusive Lyme spirochete, *Borrelia burgdorferi*, following standard short-course antibiotic therapy. The guidelines ignore high-level evidence that neurologic Lyme disease is often not eradicated by such therapy, and they dismiss more recent high-level evidence that prolonged antibiotic treatment is effective in patients with chronic Lyme disease. Furthermore, the “highest level of evidence” challenging long-term antibiotic therapy has itself been challenged recently due to the limited patient population that was examined and the poor generalizability of the studies that provided the evidence. The application of internally valid high-quality trial results to inappropriate patient populations has recently been recognized as a major problem in guideline development.

We often form
impressions
with limited
information



Doctors should treat patients, not diseases

- Physicians need to rely less on clinical guidelines for managing single diseases and more on their own clinical judgment to create treatment plans that are tailored to meet the needs of individual patients.
- Current clinical practice guidelines followed by doctors are aimed primarily at managing single diseases. These guidelines, therefore, are of little help in aiding physicians when it comes to treating patients who have multiple conditions.
- A lot of the clinical guidelines are written by disease-specific specialists who may not take into account the whole clinical picture.

From Controversy to Collaboration

- Psychoimmunologists don't have to be convinced that infections cause immune dysfunction that in turn causes mental disorders. Some don't understand brain physiology and need to listen more attentively to psychoimmunologists.
- Since interaction between the immune and nervous systems can cause mental illness, greater interaction is needed between immunologists and practicing psychiatrists.
- It is time to stop fighting each other and direct all our efforts towards fighting these diseases instead.