

# Chronic Infections

Dietrich Klinghardt MD, PhD

# Brain and Borrelia

## ***Borrelia burgdorferi* infection of the brain**

Characterization of the organism and response to antibiotics and immune sera in the mouse model

**NEUROLOGY 1990;40:1535**

Andrew R. Pachner, MD and Andrea Itano, BS

From the Department of Neurology, Georgetown University Hospital, Washington, DC.

- To learn more about the neurologic involvement in Lyme disease, we inoculated inbred mice with the causative agent of Lyme disease, *Borrelia burgdorferi*. We cultured brains and other organs, and measured anti-*B burgdorferi* antibody titers. We further studied a brain isolate for its plasmid DNA content and its response in vitro to immune sera and antibiotics. One strain of *B burgdorferi*, N40, was consistently infective for mice, and resulted in chronic infection of the bladder and spleen. SJL mice developed fewer culture-positive organs and had lower antibody titers than Balb/c and C57B1/6 mice. Organism was cultured from the brain early in the course of infection, and this isolate, named N40Br, was further studied in vitro. The plasmid content of N40Br was different from that of the infecting strain, implying either a highly selective process during infection or DNA rearrangement in the organism in vivo. N40Br was very sensitive to antibiotics, but only after prolonged incubation. Immune sera from both mice and humans infected with *B burgdorferi* were unable to completely kill the organism by complement-mediated cytotoxicity. These data demonstrate that *B burgdorferi* infects the brain of experimental animals, and is resistant to immune sera in vitro but sensitive to prolonged treatment with antibiotics.

# Brain and Borrelia

**Infect Immun. 2005 February; 73(2): 1014–1022**

## ***Borrelia burgdorferi*, Host-Derived Proteases, and the Blood-Brain Barrier**

Dennis J. Grab,<sup>1\*</sup> George Perides,<sup>2</sup> J. Stephen Dumler,<sup>3</sup> Kee Jun Kim,<sup>1</sup> Jinho Park,<sup>3</sup> Yuri V. Kim,<sup>1</sup> Olga Nikolskaia,<sup>1</sup> Kyoung Seong Choi,<sup>3</sup> Monique F. Stins,<sup>1</sup> and Kwang Sik Kim<sup>1</sup> Department of Pediatrics,<sup>1</sup> Department of Pathology, The Johns Hopkins University School of Medicine

### ABSTRACT

Neurological manifestations of Lyme disease in humans are attributed in part to penetration of the blood-brain barrier (BBB) and invasion of the central nervous system (CNS) by *Borrelia burgdorferi*. However, how the spirochetes cross the BBB remains an unresolved issue. We examined the traversal of *B. burgdorferi* across the human BBB and systemic endothelial cell barriers using in vitro model systems constructed of human brain microvascular endothelial cells (BMEC) and EA.hy 926, a human umbilical vein endothelial cell (HUVEC) line grown on Costar Transwell inserts. These studies showed that *B. burgdorferi* differentially crosses human BMEC and HUVEC and that the human BMEC form a barrier to traversal. During the transmigration by the spirochetes, it was found that the integrity of the endothelial cell monolayers was maintained, as assessed by transendothelial electrical resistance measurements at the end of the experimental period, and that *B. burgdorferi* appeared to bind human BMEC by their tips near or at cell borders, suggesting a paracellular route of transmigration. Importantly, traversal of *B. burgdorferi* across human BMEC induces the expression of plasminogen activators, plasminogen activator receptors, and matrix metalloproteinases.

Thus, the fibrinolytic system linked by an activation cascade may lead to focal and transient degradation of tight junction proteins that allows *B. burgdorferi* to invade the CNS.

# Bartonella

Infect Dis Clin North Am. 1998 Mar;12(1):137-55. Links

## **Bartonella-associated infections.**

[Spach DH](#), [Koehler JE](#).

Division of Infectious Diseases, University of Washington, Seattle, USA.

*Bartonella-associated infections occur in immunocompetent and immunocompromised patients.*

The spectrum of diseases caused by Bartonella species has expanded and now includes cat-scratch disease, bacillary angiomatosis, bacillary peliosis, bacteremia, **endocarditis**, and trench fever. Most Bartonella-associated infections that occur in North America and Europe are caused by *B. henselae* or *B. quintana*. The domestic cat serves as the major reservoir for *B. henselae*; the reservoir for the modern day *B. quintana* infection remains unknown. Methods used to diagnose Bartonella-associated infections include histopathologic analysis of biopsy specimens, culture of tissue samples, blood culture, and serology. Available data on treatment of Bartonella-associated infections remain relatively sparse but would suggest that erythromycin or doxycycline provide the best responses.

# Bartonella

## **Bartonella hensalae encephalopathy**

Presse Med. 2005 Feb 26;34(4):297-8 [Article in French]

[Angibaud G](#), [Balagué JP](#), [Lafontan JF](#).

Service de neurologie, Clinique du Pont de Chaume, 82 017 Montauban, France.

Abstract:

### **Bartonella henselae is a poorly known cause of encephalopathy in young subjects.**

A 17 year-old adolescent was admitted in a state of emergency because of frequent convulsive seizures and inter-critical drowsiness. The diagnosis of encephalopathy was made on the association of these clinical signs and electro-encephalographic abnormalities. The presence of a cat in his home, a right axillary lymph node that had appeared in a context of fever, and positive serological kinetics related this encephalopathy to a bartonellosis. The course was good. DISCUSSION: Diagnosis of a Bartonella hensalae encephalopathy is based on a range of anamnestic, clinical and microbiological arguments. The potential interest of antibiotic therapy and its modalities remains to be established.

# Bartonella

Journal of Neuroimaging

Volume 13 Issue 1 Page 79-82, January 2003

## Diffusion-Weighted Magnetic Resonance Imaging Abnormalities in Bartonella Encephalopathy

Aneesh B. Singhal MD, Michael C. Newstein MD, Ronald Budzik MD, Jang-Ho Cha MD, PhD, Guy Rordorf MD, Ferdinando S. Buonanno MD, Michael A. Panzara MD  
Department of Neurology, Massachusetts General Hospital, Boston. Department of Infectious Diseases, Massachusetts General Hospital, Boston. Department of Biogen, Inc. (MAP), Boston.

### ABSTRACT

- The authors describe 2 patients with new-onset, refractory status epilepticus and serological evidence for Bartonella infection. Brain magnetic resonance imaging (MRI) in patient 1 showed transient diffusion abnormalities in the posterior (pulvinar) thalami. In patient 2, brain MRI showed several enhancing cortical lesions, of which one lesion was bright on diffusion-weighted imaging (DWI).
- In patients with *unexplained, refractory seizures*, the presence of DWI abnormalities warrants a search for unusual infectious or inflammatory disorders, like *Bartonella encephalitis*.

## Bartonella

Multifocal osteomyelitis due to *Bartonella henselae* in a child without focal pain

[Journal of Infection and Chemotherapy](#)

[Volume 13, Number 5 / October, 2007](#)

Yuichi Kodama<sup>1</sup>, Nobuaki Maeno<sup>2</sup>, Junichiro Nishi<sup>1</sup>, Naoko Imuta<sup>1</sup>, Hiroshi Oda<sup>2</sup>, Satoru Tanaka<sup>1</sup>, Yukiharu Kono<sup>1</sup> and Yoshifumi Kawano Department of Infection and Immunity, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

### **Abstract**

We describe a case of an 11-year-old girl who presented with osteomyelitis of the vertebrae and right femur due to *Bartonella henselae*. Her only symptom was prolonged fever without focal pain. Magnetic resonance imaging (MRI) and nested polymerase chain reaction (PCR) were useful for the diagnosis. Osteomyelitis due to *B. henselae* should be considered in cases of prolonged fever of unknown origin.

# Bartonella

**J Am Dent Assoc, Vol 132, No 7, 911-914.**

© 2001 LOUIS MANDEL, D.D.S., FARISA SURATTANONT, B.S., M.S. and REZA MIREMADI, M.D., D.D.S.

**Background.** Cat-scratch disease, or CSD, results from inoculation of the gram-negative bacillus *Bartonella henselae* via a cat's scratch. A regional lymphadenitis, which usually is cervical, develops and may progress to suppuration. It is necessary to differentiate CSD from other lymphadenopathies.

**Case Description.** A patient who had close contact with a cat subsequently developed a localized, suppurative cervical lymphadenitis. As *B. henselae* was identified in 1992, the authors were able to confirm the existence of CSD serologically. Surgical drainage resulted in a successful resolution of the disease process.

**Clinical Implications.** As patients with CSD may be seen in the dental office, an awareness of its symptomatology can prevent unnecessary dental intervention and facilitate early treatment.

Patients with submandibular swellings often are examined in dental offices because a dental etiology is suspected. Many of these submandibular swellings represent lymphadenopathies. Proper diagnosis requires an ability to differentiate the many causes, which include oral sepsis, skin infections, tuberculosis, leukemia, neoplasms and cat-scratch disease, or CSD. Familiarity with these diverse processes is incumbent on the dentist. Thorough examinations and laboratory investigations usually lead to a diagnosis.

Diagnosing cat-scratch disease is problematic because it masquerades as other causes of cervical lymphadenopathy.

It is estimated that 70,000 new cases of CSD occur each year.<sup>1</sup> Although systemic manifestations have been reported, Cats are a natural reservoir for the causative microorganism. Because infected cats rapidly develop antibodies, they appear healthy despite a bacteremia that can be present for at least 12 months. A positive serology has been reported in up to 56 percent of North American cats.<sup>3</sup> The etiologic organism, transmitted to humans by a cat's scratch, lick or bite, was identified in 1992 by Regnery and colleagues<sup>5</sup> as the gram-negative bacillus *Bartonella henselae*.

Because some patients who have CSD will be examined in the dental office, we present a case report and review of CSD to heighten dentists' awareness of signs, symptoms and methods of diagnosis.



## Bartonella

### **Bartonella quintana in a 4000-year-old human tooth**

- The Journal of infectious diseases (J. Infect. Dis.)  
2005, vol. 191, no4, pp. 607-611

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Méditerranée, Marseille, FRANCE

### Abstract

- Bacteria of the genus *Bartonella* are transmitted by ectoparasites (lice, fleas, ticks) and have mammalian reservoirs in which they cause chronic, asymptomatic bacteremia. Humans are the reservoir of *B. quintana*, the louse-borne agent of trench fever.
- We detected DNA of *B. quintana* in the dental pulp of a person who died 4000 years ago.

# Babesia

## ***Concurrent Lyme disease and Babesiosis.***

JAMA 1996. 275 (21):1657 Krause, PJ, Telford, SR, Spielman, A, et.al.

Piroplasms are not bacteria, they are protozoans. Therefore, they will not be eradicated by any of the currently used Lyme treatment regimens. Therein lies the significance of co-infections — if a Lyme patient has been extensively treated yet is still ill, suspect a co-infection.

Babesia infection is becoming more commonly recognized, especially in patients who already have Lyme Disease. It has been published that as many as **66% of Lyme patients show evidence of co-infection with Babesia.** It has also been reported that Babesial infections can range in severity from mild, subclinical infection, to fulminant, potentially life-threatening illness. The more severe presentations are more likely to be seen in immunocompromised and elderly patients. Milder infections are often missed because the symptoms are incorrectly ascribed to Lyme. Babesial infections, even mild ones, may recrudesce and cause severe illness. This phenomenon has been reported to occur at any time, even up to several years after the initial infection. Furthermore, asymptomatic carriers pose risks: to the blood supply as this infection has been reported to be passed on by blood transfusion, and to the unborn child from an infected mother as it can be transmitted ***in utero.***

Some quotes from the literature: Krause, PJ, Spielman, A, Telford, SR et.al. *Persistent parasitemia after acute Babesiosis* N Engl J Med 1998. 339:160

# Babesia

- **Human babesiosis – an unrecorded reality: Absence of formal registry undermines its detection, diagnosis and treatment, suggesting need for immediate mandatory reporting**

*Medical Hypotheses, Volume 63, Issue 4, 2004, Pages 609-615*

Virginia T. Sherr

## **Abstract**

- Human babesiosis, caused by parasitic protozoa of erythrocytes, has escaped usual associates – lower mammals. Thriving in tick guts, it has spread inland from the coasts of America, adopting mankind as a host. Babesia spp. threaten life quality of unsuspecting humans in quickly expanding territories worldwide, including the state of Pennsylvania, USA. The causative spirochetes of Lyme disease often similarly co-exist in ticks. Singly or together they may, by causing persistent and chronic infections, duplicate any symptom in the medical literature – including **depression and hypochondriasis**. Physicians practicing throughout Pennsylvania have identified patients with symptomatic babesiosis, but without governmental surveillance or health registries that require doctors to consider and report babesiosis, these cases have not prompted epidemiological concern. Misunderstandings such as, “Isn't that an obscure tropical disease?” are usual responses when doctors are asked about babesiosis, inadvertently trivializing patients and disease. Mandatory reporting of babesiosis should now be considered a medical necessity.

# Brain and Herpes

- **Herpes Virus May Play Role In Central Nervous System Diseases**
- American Society for Microbiology (2007, December 25). Herpes Virus May Play Role In Central Nervous System Diseases. *ScienceDaily*. Retrieved December 26, 2007, from [http://www.sciencedaily.com- /releases/2007/12/071221094901.htm](http://www.sciencedaily.com/releases/2007/12/071221094901.htm)
- *ScienceDaily (Dec. 25, 2007)* — Scientists have discovered evidence suggesting a herpesvirus may be responsible for some cases of **meningitis and encephalitis**.
- Human herpesvirus 6 (HHV-6) is one of the most prevalent in humans. There are two variants of HHV-6, HHV-6A and HHV-6B which is attributed to a common childhood disease characterized by a high fever and rash. Studies indicate that by age 3 the majority of children have been infected by HHV-6, after which the virus persists in the salivary glands into adulthood. The virus may remain dormant or reactivate in immunocompetent or immunocompromised individuals.
- Over a span of four years, researchers from the New York State Department of Public Health, Albany and SUNY, Albany collected specimens from patients hospitalized with symptoms of encephalitis and meningitis, and tested them for the presence of HHV-6. The majority of the specimens were taken from cerebrospinal fluid and some of the symptoms exhibited by the patients include fever, **altered mental status**, and abnormal CSF profile, as well as **seizures in those ages 3 and under**.

# Herpes and Alzheimer

- [^](#) Middleton PJ, Petric M, Kozak M, Rewcastle NB, McLachlan DR (May 1980). "Herpes-simplex viral genome and senile and presenile dementias of Alzheimer and Pick". *Lancet* **315** (8176): 1038. [doi:10.1016/S0140-6736\(80\)91490-7](https://doi.org/10.1016/S0140-6736(80)91490-7). [PMID 6103379](https://pubmed.ncbi.nlm.nih.gov/6103379/).
- [^](#) Dobson CB, Itzhaki RF (1999). "Herpes simplex virus type 1 and Alzheimer's disease". *Neurobiol. Aging* **20** (4): 457–65. [doi:10.1016/S0197-4580\(99\)00055-X](https://doi.org/10.1016/S0197-4580(99)00055-X). [PMID 10604441](https://pubmed.ncbi.nlm.nih.gov/10604441/).
- [^](#) Pyles RB (November 2001). "[The association of herpes simplex virus and Alzheimer's disease: a potential synthesis of genetic and environmental factors](#)" (PDF). *Herpes* **8** (3): 64–8. [PMID 11867022](https://pubmed.ncbi.nlm.nih.gov/11867022/). [http://www.ihmf.com/journal/download/83pyles\(64\)vol864.pdf](http://www.ihmf.com/journal/download/83pyles(64)vol864.pdf).
- [^](#) Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA (January 1997). "Herpes simplex virus type 1 in brain and risk of Alzheimer's disease". *Lancet* **349** (9047): 241–4. [doi:10.1016/S0140-6736\(96\)10149-5](https://doi.org/10.1016/S0140-6736(96)10149-5). [PMID 9014911](https://pubmed.ncbi.nlm.nih.gov/9014911/).
- [^](#) Wozniak MA, Mee AP, Itzhaki RF (January 2009). "Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques". *J. Pathol.* **217** (1): 131–8. [doi:10.1002/path.2449](https://doi.org/10.1002/path.2449). [PMID 18973185](https://pubmed.ncbi.nlm.nih.gov/18973185/).

## Herpes in the brain

- **Human Herpes Virus 6B Is Associated With Mesial Temporal Lobe Epilepsy**
- *ScienceDaily (May 30, 2007)* — There is strong evidence that one particular type of epilepsy is associated with a viral infection, according to new research. The international group of researchers, led by Steve Jacobson from National Institute of Neurological Disorders and Stroke, USA, found DNA from the virus, Human Herpes Virus 6B (HHV-6B) in specific regions of the brains in 11 of 16 patients with mesial temporal lobe epilepsy (MTLE) referred for investigation compared with zero of seven (0%) patients without MTLE.
- Citation: Fotheringham J, Donati D, Akhyani N, Fogdell-Hahn A, Vortmeyer A, et al. (2007) Association of human herpesvirus- 6B with mesial temporal lobe epilepsy. PLoS Med 4(5): e180.(<http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0040180>)

# HHV-6, EBV and CFIDS

- Gow JW and Behan PO. Viruses and chronic fatigue syndrome. *J CFS*. 1996; 2: 67-83.
- Komaroff AL. The biology of chronic fatigue syndrome. *Am J Med*. 2000; 108: 169-71.
- Straus SE et al. Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection. *Ann Intern Med*. 1985; 102: 7-16.
- Hotchin NA et al. Active Epstein-Barr virus infection in postviral fatigue syndrome. *J Infect*. 1989; 18: 143-50.
- Bell DS. Chronic fatigue syndrome update: findings now point to CNS involvement. *Postgrad Med*. 1994; 96: 73-81.
- Levine PH and Komaroff AL. Human herpesvirus type 6 and chronic fatigue syndrome. *Arch Intern Med*. 1993; 153: 661.
- Deluca J et al. HHV-6 and HHV-7 in CFS. *J Clin Microbiol*. 1995; 33: 1660-61.
- Ablashi DV et al. Frequent HHV-6 reactivation in multiple sclerosis and chronic fatigue syndrome patients. *J Clin Virol*. 2000; 16: 179-91.
- Reeves et al. Human herpesviruses 6 and 7 in chronic fatigue syndrome: a case-control study. *Clin Infect Dis*. 2000; 31: 48-52.
- De Freitas E et al. Retroviral sequences related to human T-lymphotropic virus type II in patients with chronic fatigue immune dysfunction syndrome. *Proc Natl Acad Sci USA*. 1991; 88: 2922-26.

# Chronisches Muedigkeitssyndrom und

- **Das XMRV Retrovirus**

In weißen Blutkörperchen von 101 untersuchten CFS-Patienten fanden US-amerikanische Wissenschaftler um Vincent Lombardi vom [Wittemore Patterson Institute](#) in Reno in 68 Fällen das "**X**enotrope **M**äuse-Leukämievirus-**v**erwandte **V**irus" (XMRV). Es handelt sich um ein Retrovirus (wie HIV). Die US Originalarbeit finden Sie auch weiter unten. Nur acht von 218 gesunden Kontrollpersonen trugen das Virus in sich. Vergleichbare Ergebnisse lieferten zwei voneinander unabhängige Untersuchungen zu Prostatatumoren. Die Forscher fanden im Krebsgewebe von Prostatapatienten auffallend häufig XMRV. XMRV könnte in den Zellen möglicherweise ein unkoordiniertes Wachstum und damit auch Prostata-Krebs auslösen, vermuten Singh und ihre Kollegen - eine Vermutung, für die sie derzeit im Labor die Bestätigung suchen. Diese Seite beschäftigt sich aber schwerpunktmäßig mehr mit dem Thema CFS und XMRV.



# Lyme and Mycoplasma

- **What If It's Not Lyme Disease? - Groundbreaking Research May Provide Answers To Why Many Chronic Sufferers Don't Respond To Treatment**

- Main Category: University of New Haven  
Article Date: 13 Jun 2007 - 1:00 PDT

Sapi, an assistant professor of biology and environmental science at the University of New Haven, and several graduate students recently presented research demonstrating that **over 84 percent of the ticks they tested were infected by Mycoplasma** pathogens, bacteria which can wreak havoc reminiscent of the *Borrelia* bacterium responsible for Lyme disease. "Doctors are starting to realize that some of the patients who exhibit symptoms of Lyme disease but don't respond to treatment may be infected with a *Mycoplasma* pathogen," Sapi says. "We now have evidence of the presence of human pathogenic *Mycoplasma* species in deer ticks."

Sapi presented the research, "Recent Discoveries of Novel Pathogens in Ixodes Ticks in Southern Connecticut," during the national Lyme disease conference at UNH in May, and will submit it for publishing later this month. She notes that other studies have shown that some patients not responding to treatment for Lyme disease have responded to treatment for *Mycoplasma*. Determined to find the "missing link," Sapi and her cohorts tested 150 deer ticks for *Mycoplasma* bacteria, with over 84 percent of the ticks exhibiting infection with a single *Mycoplasma* pathogen. Co-infection rates were also very significant, at 27 percent, and three percent of the ticks were infected with all three *Mycoplasma* pathogens.

# Mold

- **Action of tremorgenic mycotoxins on GABA sub(A) receptor.**  
Gant, DB; Cole, RJ; Valdes, JJ; Eldefrawi, ME; Eldefrawi, AT  
**Life Sciences [LIFE SCI.]. Vol. 41, no. 19, pp. 2207-2214. 1987.**

The effects of four tremorgenic and one nontremorgenic mycotoxins were studied on gamma -aminobutyric acid (GANA sub(A)) receptor binding and function in rat brain and on binding of a voltage-operated Cl super(-) channel in Torpedo) electric organ.

- The data suggest that the tremorgenic action of these mycotoxins may be due in part to their inhibition of GABA sub(A) receptor function.

# Mold

- **Fumonisin B1 in developing rats alters brain sphinganine levels and myelination.**

Neurotoxicology. 1997;18(2):571-79

[Kwon OS](#), [Schmued LC](#), [Slikker W Jr.](#)

Objectives of this study were to test the hypothesis that fumonisin B1 (FB1) alters sphinganine (Sa) levels and myelin synthesis in the central nervous system of developing rats. FB1 (subcutaneous, 0.4 or 0.8 mg/kg/day) from postnatal days (PND) 3 to PND 12 resulted in a significant reduction of body weight gain and decreased survival rates. Both Sa levels and Sa/sphingosine (So) ratios were significantly increased in the brain of rats given 0.8 mg FB1/kg/day. To confirm the effect of limited nutrition on changes in the Sa levels and myelinogenesis, rats given 0.8 mg FB1/kg/day or treated by limited nutrition (temporary removal from dam during postnatal period) were compared to those in saline controls. Sa levels and Sa/So ratios were increased significantly in the 0.8 FB1-treated, but were not altered in the limited nutrition group. Myelin deposition in the corpus callosum and 2',3'-cyclic nucleotide 3'-phosphohydrolase (CNP) activities were decreased significantly in both nutritionally limited and FB1-exposed rats.

- **These data indicate that sphingolipid metabolism in the central nervous system of developing rats is vulnerable to FB1 exposure. The hypomyelination associated with FB1-treatment may be mediated by limited nutrition.**

# Mold and the Brain

Arch Environ Health. 2003 Jul;58(7):406-9

**Use of functional brain imaging in the evaluation of exposure to mycotoxins and toxins encountered in Desert Storm/Desert Shield.**

[Simon TR](#), [Rea WJ](#).

In this retrospective analysis the authors compared brain scintigrams, performed using triple-head single-photon emission computed tomography (tripleSPECT), of subjects who were judged clinically impaired from exposure to toxins during the Desert Storm/Desert Shield military action, and of subjects exposed to mycotoxins, with those of normal controls. The scintigrams for both exposed groups exhibited similar patterns of abnormalities, which were consistent with neurotoxic impairment. The authors conclude that further study is needed to determine whether mycotoxin exposure may be a cause of abnormalities seen in tripleSPECT images.

- **Endotoxin exposure alters brain and liver effects of fumonisin B1 in BALB/c mice: Implication of blood brain barrier**

Marcin F. Osuchowski, Quanren He and Raghubir P. Sharma,

- **Abstract**

Fumonisin B1 (FB1), a mycotoxin produced by *Fusarium verticillioides*, causes equine leukoencephalomalacia and hepatotoxicity. We studied the modulation of FB1 toxicity in brain and liver of female BALB/c mice after endotoxin administration to compromise the blood–brain barrier (BBB) integrity. Mice were injected intraperitoneally with saline or 3 mg/kg of lipopolysaccharide (LPS) followed 2 h later by either a single or three daily subcutaneous doses of 2.25 mg/kg of FB1. After 4 h of a single FB1 injection the inhibition of sphingolipid biosynthesis occurred in liver. Circulating alanine aminotransferase increased by LPS alone at this time. In brain LPS triggered inflammation increasing the expression of tumor necrosis factor (TNF)  $\alpha$ , interferon (IFN)  $\gamma$ , interleukin (IL)-1 $\beta$ , IL-6, and IL-12; no effect of FB1 was observed. In liver LPS + FB1 attenuated the expression TNF $\alpha$  and IFN $\gamma$  compared to LPS alone. One day after the 3-day FB1 treatment the biosynthesis of sphingolipids was markedly reduced in brain and liver and it was further inhibited when LPS was given before FB1. FB1 induced hepatotoxicity, as measured by circulating liver enzymes, was reduced after the combined treatment with LPS + FB1 compared to FB1 alone. FB1 decreased the LPS-induced brain expression of IFN $\gamma$  and IL-1 $\beta$ , whereas the expression of IL-6 and IL-12 was augmented. In liver FB1 also reduced the expression of IL-1 $\beta$  and IFN $\gamma$  compared to LPS alone.

**Results indicated that endotoxemia concurrent with FB1 intoxication facilitated the permeability of fumonisin in brain indicated by increased accumulation of sphinganine and endotoxin modified the effects of FB1 in both brain and liver.**

[Food and Chemical Toxicology](#)

[Volume 43, Issue 9](#), September 2005, Pages 1389-1397

## **Implications in the treatment of illnesses due to indoor chronic toxigenic mold exposures.**

ScientificWorldJournal. 2004 Mar 12;4:167-77.

Chronic exposure to toxigenic molds in water-damaged buildings is an indoor environmental health problem to which escalating health and property insurance costs are raising a statewide concern in recent times. This paper reviews the structural and functional properties of mycotoxins produced by toxigenic molds and their interactive health implications with antifungal drugs. Fundamental bases of pathophysiological, neurodevelopmental, and cellular mechanisms of mycotoxic effects are evaluated. It is most likely that the interactions of mycotoxins with antifungal drugs may, at least in part, contribute to the observable persistent illnesses, antifungal drug resistance, and allergic reactions in patients exposed to chronic toxigenic molds. Safe dose level of mycotoxin in humans is not clear. Hence, the safety regulations in place at the moment remain inconclusive, precautionary, and arbitrary. Since some of the antifungal drugs are derived from molds, and since they have structural and functional groups similar to those of mycotoxins, the knowledge of their interactions are important in enhancing preventive measures.

- This article links **mycotoxins and antifungal drug interactions**

# Mercury

## Increased blood mercury levels in patients with Alzheimer's disease

### Journal of Neural Transmission

1998, vol. 105, no1, pp. 59-68 (1 p.1/4)

HOCK C. (1) ; DRASCH G. (2) ; GOLOMBOWSKI S. (1) ; MÜLLER-SPAHN F. (1) ; WILLERSHAUSEN-ZÖNNCHEN B. (3) ; SCHWARZ P. (3) ; HOCK U. (1) ; GROWDON J. H. (4) ; NITSCH R. M. (5)

Alzheimer's disease (AD) is a common neurodegenerative disorder that leads to dementia and death. In addition to several genetic parameters, various environmental factors may influence the risk of getting AD. In order to test whether blood levels of the heavy metal mercury are increased in AD, we measured blood mercury concentrations in AD patients (n = 33), and compared them to age-matched control patients with major depression (MD) (n = 45), as well as to an additional control group of patients with various non-psychiatric disorders (n = 65). **Blood mercury levels were more than two-fold higher in AD patients** as compared to both control groups (p = 0.0005, and p = 0.000, respectively). In early onset AD patients (n = 13), blood mercury levels were almost three-fold higher as compared to controls (p = 0.0002, and p = 0.0000, respectively). These increases were unrelated to the patients' dental status. Linear regression analysis of blood mercury concentrations and CSF levels of amyloid  $\beta$ -peptide (A $\beta$ ) revealed a significant correlation of these measures in AD patients (n = 15, r = 0.7440, p = 0.0015, Pearson type of correlation). These results demonstrate elevated blood levels of mercury in AD, and they suggest that this increase of mercury levels is associated with high CSF levels of A $\beta$ , whereas tau levels were unrelated. Possible explanations of increased blood mercury levels in AD include yet unidentified environmental sources or release from brain tissue with the advance in neuronal death.

# Brain and Borrelia



## Brain and Borrelia

**Lyme is a spirochetal illness resembling syphilis.**

## Brain and Borrelia

**Lyme is a spirochetal illness resembling syphilis.  
Can mimic MS, myelopathy, polyneuropathy, brain**

## Brain and Borrelia

**Lyme is a spirochetal illness resembling syphilis.  
Can mimic MS, myelopathy, polyneuropathy, brain  
tumor, encephalopathy.  
(Neurosurgery.1992May;30(5):769-73)**

## Brain and Borrelia

**Lyme is a spirochetal illness resembling syphilis.  
Can mimic MS, myelopathy, polyneuropathy, brain  
tumor, encephalopathy.**

(Neurosurgery.1992May;30(5):769-73)

**Lyme can cause meningitis, encephalitis, neuritis,  
mania, depression, OCD, schizophrenia, anorexia,  
dementia.**

(Am J Psychiatry. 1994 Nov;151(11):1571-83)

## Think tank chat: Isn't it all psychological?

- A well know scientist:

I would like to disagree with your perception that the missing "lynchpin" is in the emotional and spiritual arena. While I whole-heartedly agree that suffering patients cannot help but have important and spiritual issues, as this epidemic of difficult-to-characterize illnesses has evolved, it looks more and more to me that it is abnormal biochemistry and physiology that triggers it.

When "fibrositis", now called fibromyalgia and chronic fatigue, first entered its epidemic phase in the 1980s, the medical community assumed that it was all psychogenic, and my patients received superb psychotherapy and spiritual counseling, to no avail. They didn't get better.

As we learned about adrenal, thyroid, and other hormonal imbalances, as well as heavy metal toxicity, a myriad of infective causes, methylation abnormalities, etc, with each new piece of information we gained tools that helped a large percentage of these patients to improve and even recover. I used to believe that spiritual and emotional issues were paramount, but what is evolving here has persuaded me that what I don't yet know about chemistry and physiology is what limits my ability to help these patients.

## Think tank: another scientist on CFIDS

- More importantly, I think there is the real possibility of a revolution in the dispersion of gut pathogens into naive populations due to differences in human waste disposal practices. People who use nightsoil for fertilizing food crops are now meeting people who don't. That can lead to a revolutionary change in gut biota in human populations throughout the world.
- It should be considered and studied in diseases like CFS, autism, and Lyme where there is a rising incidence of disease, dramatically so in some cases, and clear evidence of changes in gut biota.
- Globalization is not just a matter of better communications. It is also a time of unprecedented mixing of human populations and the community of organisms they carry in their guts, some of which are pathogens.

## Think tank: Pandemic of degenerative diseases

- There is a general consensus in the more progressive medical communities that unrelieved oxidative stress feeds chronic inflammation, which is at the base of our current pandemic of degenerative diseases. There is also widespread agreement that the main initiating cause of this is our toxic environment: The synthetic chemicals and heavy metals in our air, water and soil; toxins in our food; and OTC and pharmaceutical drugs. These are biochemical, or physiological stressors. Some people also include today's ubiquitous electromagnetic fields as an important bioenergetic stressor with tangible physiological consequences.

## Think tank: P.C. reflecting

- Thanks and very interesting. This reminds me of the yeast related biotoxins found highly expressed in urine chromatography of many psychiatric ward inmates admitted with various psychotic diagnoses.
- The liver/gut guards the brain from the intrinsically toxic gut microbiome and brain issues erupt, when either something is present in the gut, the liver or the gut enterocytes can't handle it or something's affecting the liver detox system - and even normal gut toxicity is enough to make you crazy or sick or both.
- Is it the bug/toxin or is it the terrain? This has been argued for 150 years. I favor the latter as I think it yields better results in chronic complex illness but the former is worrisome in some phenotypes.
- Perhaps external environmental forces are conspiring to exert a constraint on our species to move us toward some as yet unknown future and certain phenotypes are the first but perhaps not the last casualties. Attacking children would cause the greatest and quickest genetic shift of our species.



## Think tank: Stool Transplants

- I had another CFS patient seen in the same week with relapsing/remitting C. Difficile linked diarrhea followed chronically at Duke U. for years with intermittent severe cramping and diarrhea relieved promptly with antibiotics (now using Xifaxan or Rifaximin) but she typically breaks through as antibiotic resistance eventually develops.
- Duke now recommends an NG stool microbial transplant from mixed healthy donor stool available in Duluth, MN which they say works better than antibiotics over the long haul for chronic relapsing C. Difficile associated diarrhea.
- The Xifaxan currently helps her diarrhea and cramps but not her CFS.

## Think tank chat between scientists: C.difficile

- There is a physician -- Derrick F. MacFabe -- at the University of Western Ontario, specializing in autism, who has studied C difficile in regard to its production of propionic acid. MacFabe injected PPA directly into the brains of rats and produced classic and severe autistic behavior.

MacFabe notes that oral vanomycin is sometimes effective in treating C difficile. The autism community also almost automatically puts kids on the spectrum on allergy elimination diets -- gluten-free, casein-free, etc. -- and puts them on a probiotics regimen

I wonder if you might also be getting into the controversial biofilm territory with refractory GI infections, and the use of bacteriophages to break through the protective barriers and expose and make vulnerable the C difficile or whatever beasties.

Here's an excerpt from MacFabe's article on "Neurobiological effects of intraventricular propionic acid in rats"

[http://www.ihausa.org/newsletters/PDF\\_dec2005\\_July2007/2007%20June%20Newsletter-email.pdf](http://www.ihausa.org/newsletters/PDF_dec2005_July2007/2007%20June%20Newsletter-email.pdf)

- PPA and enteric bacteria

The human digestive tract is host to a wide variety of intestinal bacterial flora, both harmful and protective, that produce a number of metabolic products capable of entering the systemic circulation in both normal and pathological conditions [184]. Many of these bacteria produce a number of short chain fatty acids, such as acetate, butyrate, and PPA, via the break down of carbohydrates, and amino acids [52]. Of particular interest are the Clostridia, a family of heterogeneous anaerobic, spore forming Gram-positive rods. Clostridia are major gut colonizers in early life and many of which are producers of PPA and other short chain fatty acids [159]. Clostridium difficile is known to be a major cause of severe gastroenterological diseases such as pseudomembranous colitis, but may also be a major cause of antibiotic associated diarrhoea, both pre- and post-natally [61]. This pathogen is known to produce an enterotoxin A, primarily responsible for gastrointestinal symptoms through mucosal damage and lymphocyte infiltration, and cytotoxin B. However, the exact mechanism by which this gut pathology is produced is unknown [61]. Antibiotic resistant clostridial strains play a role in a wide variety of hospital and community acquired infections [102] in adult patients, but their role in paediatric diarrhoea related to antibiotic treatment has not been extensively studied [61]. Spore forming anaerobes and microaerophilic bacteria, particularly from **clostridial species, have been shown to be elevated in late-onset autistic children but absent in controls [64]**. As well, PCR analyses of stool samples from patients with regressive autism have revealed increases in clostridial species including C. difficile [157]. The eradication of the pathogen with oral vancomycin treatment has improved symptoms in some patients.

Although I've read worldwide reports of symptom mitigation for at least several months following fecal transplantation — it's not something that would be mandatory in my ideal medical republic! The fact, though, that Duke is recommending it is somewhat amazing and encouraging.

## C.diff

- The C. difficile patient got acutely sick in 1980, also with a mono-like illness that evolved into CFS with POTS, and C. Difficile related diarrhea began in 1983 and followed at Duke for twenty years at the "Chronic C. Difficile GI Clinic" at Duke.
- It is interesting that Duke is recommending donor stool transplants now.
- Makes you wonder about the long term reliance on antibiotics to treat what is really a terrain issue and I wonder what might be at the core of this remarkably coherent terrain problem we call CFS.
- As for the gut in CFS, I like Jeremy Nicholson's view that we are neither gut or human but a symbiote involving both. It is hard to separate the two and blame one for the ills of the other. The core problem may belong to neither sphere of influence completely but affects both as they are one.

# Lungworm

- The gut is where it all starts and ends.
- Reading about the fecal transplant work on the recent GI postings, I wonder if human to animal fecal transplants have been tried as an assay for human intestinal pathogens? I would be interested in CFS patients donors with *Vk* parasitism to rodent recipients, with running wheel activity monitoring. The *Vk* parasite is a member of a lung/intestinal worm genus, *varestrongylus*, infecting grazing caprids (goats and sheep) and cervids (deer) which has become chronic in mammals, given up its invertebrate intermediate host (snails), and crossed over to man. The ability to infect divergent mammal types seem inherent in the species. Patients often report that their pets got sick with a fatiguing illness after they did. I'd be interested in bringing together those with access to CFS patients, capable of obtaining fresh fecal material, and lab folks with animal raising capabilities and pathogen control.

# The gut

- My own view is that the gut involvement, which, as you point out, occurs in many but not all CFS patients, is itself diverse. Some suffer from leaky gut leading to the development of multiple food allergies, some suffer from irritable bowel syndrome, some suffer from other difficulties and of course some have multiple types of gut dysfunction.
- I think the reason that the gut is so often impacted is because the bacteria of the gut, like many bacteria can trigger inflammatory responses, because there are so many cells of the immune system concentrated around the gut often leading again to a major inflammatory response and also because of the role of the enteric nervous system which has receptors implicated in the NO/ONOO- cycle, notably the NMDA and TRPV1 and other TRP receptors.
- So I have no doubt that the gut has an important role in many cases, but that does not mean that is where the disease always starts.

# Most CFIDS patients are infected with lungworm (V.Klapowi)

- In a retrospective study done in England, CFS patients most often saw their doctors for respiratory symptoms in the five year period before they got typical CFS symptoms. Hamilton WT, Hall GH and Round AP; Frequency of attendance in general practice and symptoms before the development of chronic fatigue syndrome: a case control study; Br.J Gen Pract 2001, Jul:51(468):553-8.

In my own case, I traveled to France in April 1976, where I got an acute digestive problem ( pain with constipation for ~4 days) which almost took me to the hospital. By August I was having a consistent and troublesome dry cough. Then a day or so after taking the Swine Flu vaccine in October 1976 I had my first full blown episode of CFS.

An interpretation of the experience: I acquired the intestinal tissue boring larval stage of a lung parasite by eating contaminated food (salads I was served in France often had gritty dirt in them: apparently washing is considered to ruin the flavor of lettuce according to my brother). It migrated to the lungs, became chronic, and grew slowly. Finally when a vaccine stimulated a generalized up-regulation of the immune response, the parasite secreted neurotoxin and cytokine mimics to suppress the immune response, producing the symptoms of CFS. I hope to test the latter mechanism in provocation experiments. I don't think it will take thirty years.

So it starts in gut (initial infection), goes to the lungs, then circulates between the gut and lungs continuously via a chronic auto-infectious migratory life cycle. Maybe the parasite is better able to suppress the lung response (~30-40 percent CFS have lung symptoms while >80 have GI problems), while most are infected with the parasite. The initial gut symptoms associated with acquiring a parasite might not have been noticed or recorded because it is an isolated single event separated from the main body of CFS symptoms (very low parasite growth rate), and most of us get short GI episodes once in a while.

Of course a great many physiological, infectious, and physiological abnormalities would be expected to follow, producing a rich area for theory development and hopefully empirical testing

Certainly, given our level of knowledge, and the obvious complexity of the illness, there can be many complementary and competing explanations for the phenomenon that has come to be called CFS. From the onset I have maintained that the ability to understand the right direction to go requires that we get beyond the, how shall I say chauvinism, no, professional pride we naturally have for our particular scientific disciplines, and try to understand CFS as a multidimensional phenomena.

My own view is strongly influenced by what I understand as the epidemiology of the illness, and responses to treatment, additional dimensions which suggest that it could predominantly be a new parasite species spreading into previously naive populations. I've called this the "Asian" hypothesis, but really It should be called the "Nightsoil" hypothesis.

"Nightsoil" as you may know is the practice of using untreated human fecal waste to fertilize food crops. It is the dominant practice of Southeast Asian farming, where household fecal waste is collected daily and immediately spread untreated on food crops at night. The CFS of the Victorian Era, neurasthenia, corresponded to the colonization of this region by European powers, most notably France, and the beginning of transatlantic tourism by wealthy individuals made possible by the advent of the steamship.

The dispersion of several million rural Asian farmers, the "boat people" escaping the Cambodian genocide to the "Western" alliance countries in the 1979-81 period preceded the CFS outbreaks and what the CDC has called the "renewed interest" in CFS/neurasthenia. I don't think doctors woke up one day and said lets revive neurasthenia under the name of CFS. Much more likely there was a sharp increase in incidence. I've interested some folks into looking at the epidemiology, and try to keep these ideas among scientists for obvious reasons.



# Varestronglylus Klapowi and CFIDS

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- On the treatment side, all of the CFS symptoms I have are reduce by anthelminthics, for a few months. Andy Wright in England tried multiple day courses of ivermectin after we spoke and got the same result, significant symptom improvement in ~75 percent of patients, about half had virtually no symptoms. Unfortunately their experience turned out like mine, the sickness returned. The parasite was not eradicated. My life-cycle studies indicates that the Vk parasite lives and reproduces in at least the lungs and GI track and possible other reservoirs, within a circa two week lifecycle. If we had an easliy tolerated anthelminthi/immune stimulant/physiology correcting treatment regimen which could be applied continuously or at least weakly for a long period of time (Vkt appears to have a very long lived tissue phase), eradication might be possible.
- I don't know how others feel, but I would consider transfer of the infection to animals, and the subsequent development of CFS symptoms proof of causation a la Koch. That may become possible if I can get live worms from my "proof of life experiments". In the meantime I am very gratified to know that some important CFS doctors are doing experiment anthelminthic treatments, either on diagnosed Vk patients or presumed infections with the parasite.

## Amoebas Act as Trojan Horses for Salmonella

The research, done in the UK and supported by the Society for Applied Microbiology, the Department for Environment, Food and Rural Affairs (DEFRA), and the Higher Education Funding Council for England (HEFCE), is published in the journal *Applied and Environmental Microbiology*. The work was done at the University of Liverpool, in collaboration with the Institute for Animal Health. **23 March 2009**

Scientists said today they've learned that [Salmonella](#) get inside [amoebas](#) — single-celled organisms common on land and in water — and protect themselves with a secretion system.

The research suggests that amoebas may be a major source of Salmonella within the environment and could play a significant role in transmission of infection to man and animals.

Salmonella uses a system, called SP12 type III, which acts as a bacterial machine inside organisms and causes disease in humans, animals and plants. The system employs a syringe-like mechanism to inject bacteria into cells that would normally release compounds to rid the body of harmful substances. This system changes the structure of the cell and prevents these compounds from coming into contact with pathogens and destroying them.

"Salmonella has managed to survive extremely successfully in the environment, finding its way into our food and causing illness, despite the body's best efforts to fight it off," explained Paul Wigley, from the National Centre for Zoonosis Research and the University of Liverpool. "We found that it uses a system which operates in the human immune system as well as inside amoeba living in the environment."

This system essentially protects Salmonella within cellular compartments, called phagosomes, where it can survive and multiply.

"Its ability to survive in amoeba is a huge advantage to its continued development as it may be more resistant to disinfectants and water treatment," Wigley said. "This means that we need to work to understand ways of controlling amoeba in water supplied to animals and prevent it acting as a 'Trojan Horse' for Salmonella and other pathogens."