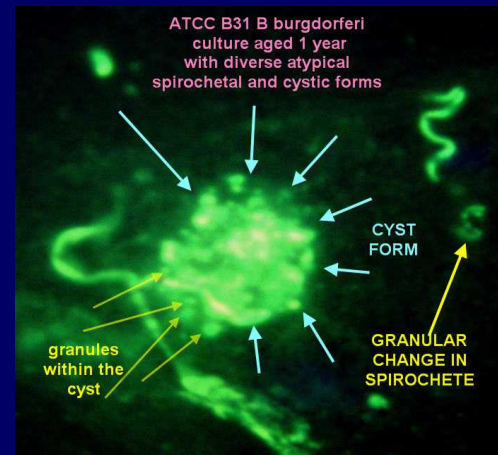
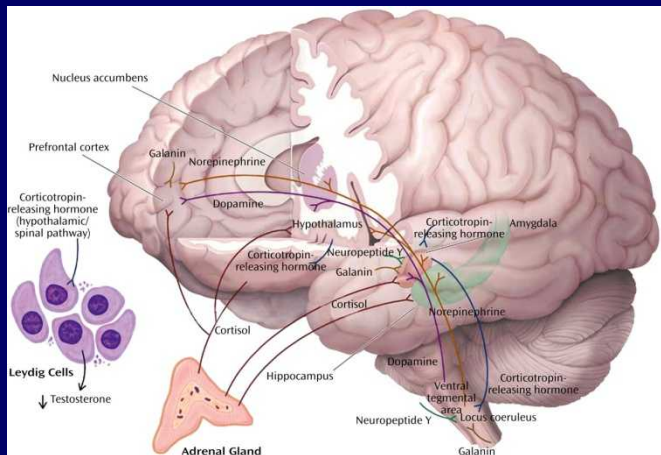


# An Overview of Neuropsychiatric Lyme Disease



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

# Outline

- Background
- Theory
- Pathophysiological models
  - Lyme/tick-borne disease
- Assessment
- Treatment strategies

# Can Microbes & Immune Reactions Contribute to...

- Mental illness?
- Personality change?
- Violent & criminal behavior?
- Cognitive decline?
- Degenerative neurological disease?
- Changes in sexual functioning?
- Obesity?
- Developmental disabilities?
- Improved human functioning?

# Basic Hypothesis

- Infectious diseases and the immune reactions to them contribute to causing psychiatric symptoms and illness.
- Acute stress & inflammatory reactions are adaptive to short term environmental stress, but chronic stress & inflammatory reactions are pathogenic.
- Hepatitis C treatment is a model for immune mediated psychiatric symptoms & illness and Lyme/Tick-Borne diseases are a model for a chronic relapsing infection causing mental illness.
- Identifying & treating infections and other causes of immune dysfunction improve the treatment effectiveness of mental illness.

# Personal Experience

- Primarily clinical practice
- Interest in infectious causes of mental illness for 30+ years.
- About 2000+ patients in with infections and other causes of inflammation, especially Lyme/tick-borne disease. 1000 data points kept on each patient. Many have progressive systemic illnesses with encephalopathy.
- Moderator of Microbes and Mental Illness Internet discussion group (9 years).
- President Elect ILADS (International Lyme and Associated Disease Society)

Theory

# Physics, Math & Astrophysics: Newton to Einstein

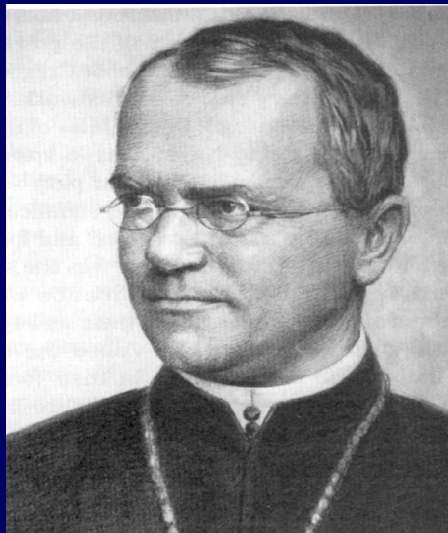


- Newton-Universal gravitation and the three laws of motion



- Einstein-Theory of relativity, mass-energy equivalence, ( $E=mc^2$ ), nonuniform motion & a new theory of gravitation

# Complex Human Diseases Beyond Koch and Mendel



Mendel-Human traits are determined by **individual** genes which function **independently** of other genes and of environmental influences



Koch-Many human diseases are caused by microbes which exert their effect **independently** of other microbes, environmental factors and genes



# Gene-Environmental Interactions

## *Beyond Koch's Postulates*

- ❑ **Most common human diseases are caused by the interaction of environmental insults and susceptibility genes.**
- ❑ **Many of the susceptibility genes are diverse determinants of human response to environmental factors to infection.**
- ❑ **Informative laboratory methods for complex disorders have to address both genetic and environmental factors.**
- ❑ **Prevention or treatment of the infections may result in the effective treatment of complex disorders:**
  - ❑ **Helicobacter-Peptic Ulcer**
  - ❑ **HPV-Genital Cancer**
  - ❑ **Chlamydia-Cardiac Disease?**



# Emerging Infectious Determinants of Chronic Diseases

- Evidence now confirms that non-communicable chronic diseases can stem from infectious agents.
- Identifying the relationships can affect health across populations, creating opportunities to reduce the impact of chronic disease by preventing or treating infection.
- Infectious agents likely determine more cancers, immune-mediated syndromes, neurodevelopmental disorders, and other chronic conditions than currently appreciated.
- To capitalize on these opportunities, clinicians, public health practitioners, and policymakers must recognize that many chronic diseases may indeed have infectious origins.

# The Human Microbiome Project

- A study researching all of the various microbes that live in people. The project has already established that the bacteria in the human microbiome collectively possess at least 100 times as many genes as the 20,000 or so in the human genome.
- Bacterial cells outnumber human cells by 10 to 1.
- Humans depend on their microbiome for essential functions, including digestion, leading microbiologists to conclude that a person should really be considered a superorganism.

# Mental Illness and Parasites

- Mental patients have much higher rates of parasitic infection than the general population. Between 1995 and 1996 researchers at the University of Ancona did stool tests on 238 residents of four Italian psychiatric institutions and found parasites in 53.8 percent of the residents including all of those residents with behavioral aberrations.

# Psychiatric Syndromes & Infections

- The same syndrome may be caused by different infections in different individuals
- The same infection can cause different syndromes in different individuals
- Lyme/tick-borne disease can cause any psychiatric syndrome in the DSM-IV

# Microbes that Can Cause Mental Symptoms

- Syphilis
- Malaria
- Toxoplasmosis
- Candidiasis
- Other spirochetes
- 1. *Borrelia burgdorferi sensu stricto* (USA, UK, Europe)
- 2. *Borrelia garinii* (UK, Europe)
- 3. *Borrelia afzelii* (UK, Europe)
- "CHRONIC LYME DISEASE" or "NEW LYME DISEASE" is a combination of LYME DISEASE and one or more of the following Co-infections:
  - Relapsing Fever caused by the spirochetes:
    - *Borrelia hermsii*
    - *Borrelia turicatae*
  - Mycoplasmas:
    - *Mycoplasma fermentans*
    - *Mycoplasma pneumoniae*
  - Babesiosis:
    - *Babesia microti*
    - *Babesia WA* and other *Babesia* species
  - *Chlamydia pneumoniae*
- Rickettsial Diseases:
  - Rocky Mountain Spotted Fever
  - *Coxiella burnetii* (Q-Fever and "Post-Q Fever Fatigue Syndrome")
  - Colorado Tick Fever
  - Eastern tick-borne Rickettsiosis
  - Rickettsialpox
  - Tularemia (rabbit fever)
  - Ehrlichiosis (caused by Ehrlichia, and rickettsia-like bacteria)
- Anaplasmas (related to the genera *Rickettsia* and *Ehrlichia*)
- - Hepatitis-C
- Bartonellosis:
  - *Bartonella henselae* (cat scratch fever), *Bartonella rochalimae*
  - *Bartonella quintana* (trench fever)
  - Viral Meningitis
- *Candida dubliniensis*
- Asfarviridae, Reoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Flaviviridae & Arenaviridae family viruses (38+ species)
- Streptococcus
- Japanese B encephalitis
- HHV-1
- Borna virus
- Epstein-Barr virus
- Pandemic Influenza of 1918
- Hong Kong flu
- Coxsackie virus
- Pneumococcus
- Haemophilus
- Meningococcus
- Leptospira
- *Mycobacterium tuberculosis*
- Cytomegalovirus
- Enterovirus
- HIV
- Pandemic Influenza of 1918
- Influenza virus
- Measles
- Papovirus
- Poliovirus
- Rabies
- Toga virus
- Toxoplasmosis
- Cryptococcus
- Coccidiomycosis
- Histoplasmosis
- Cysticercosis
- Rubella,
- Herpes simplex
- *Mycoplasma pneumoniae*
- Shigella
- Neurocysticercosis
- Unknown
- Various viral infection
- Borna
- Herpes virus family
- Malaria
- Blastocystis
- Cytomegalovirus
- Syphilis
- Varicella
- Toxoplasmosis
- Yet unrecognized infectious

# Associations between *Chlamydomphila* infections, schizophrenia and risk of HLA-A10

- Several microbes have been suspected as pathogenetic factors in schizophrenia. We have previously observed increased frequencies of chlamydial infections and of human lymphocyte antigen (HLA)-A10 in independent studies of schizophrenia.
- We found chlamydial infection in 40.3% of the schizophrenic patients compared to 6.7% in the controls. The association of schizophrenia with *Chlamydiaceae* infections was highly significant ( $P=1.39 \times 10^{-10}$ , odds ratio (OR)=9.43), especially with *Chlamydomphila psittaci* ( $P=2.81 \times 10^{-7}$ , OR=24.39).
- Schizophrenic carriers of the HLA-A10 genotype were clearly most often infected with *Chlamydomphila*, especially *C. psittaci* ( $P=8.03 \times 10^{-5}$ , OR=50.00). *Chlamydomphila* infections represent the highest risk factor yet found to be associated with schizophrenia. This risk is even further enhanced in carriers of the HLA-A10 genotype.

# Selected Infectious Agents and Risk of Schizophrenia Among U.S. Military Personnel

- The authors found significant associations between increased levels of scaled *T. gondii* IgG antibodies and schizophrenia for antibodies measured both prior to and after diagnosis.



# Maternal Exposure to Herpes Simplex Virus and Risk of Psychosis Among Adult Offspring

- Background: Viral exposure during gestation is thought to be a risk factor for schizophrenia. Previous studies have indicated that prenatal exposure to herpes simplex virus type 2 (HSV-2) may be a risk for the subsequent development of schizophrenia in some populations. In this investigation, we tested a large and diverse population to assess the risk of psychoses among offspring of mothers with serological evidence of HSV-2 infection.
- Results: Offspring of mothers with serologic evidence of HSV-2 infection were at significantly increased risk for the development of psychoses (odds ratio [OR] = 1.6; 95% confidence interval [CI] = 1.1–2.3). This risk was particularly elevated among women with high rates of sexual activity during pregnancy (OR = 2.6; 95% CI = 1.4–4.6).
- Conclusions: Maternal exposure to herpes simplex virus type 2 is associated with an increased risk for psychoses among adult offspring. These results are consistent with a general model of risk resulting from enhanced maternal immune activation during pregnancy.

# Obsessive Compulsive Disorder & Infectious Disease

- Strep
- Lyme/tick-borne disease
- Hong Kong flu
- Coxackie
- Mycoplasma
- Flu
- Toxoplasmosis
- Morgellons (C Pneumonia & B Burgdorferi)
- Pandemic of 1918 (historical references)

# Pathophysiology

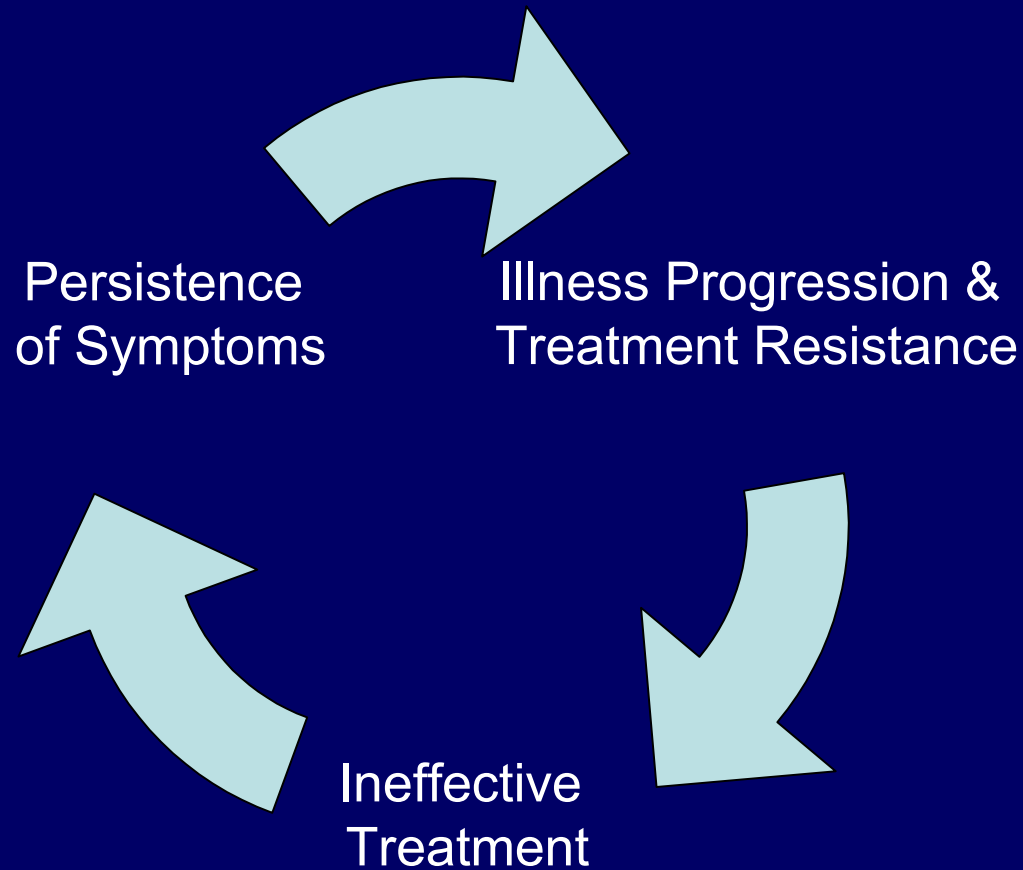
# Pathological Cascade

Causes of Disease

Genetic, Developmental, Proximate



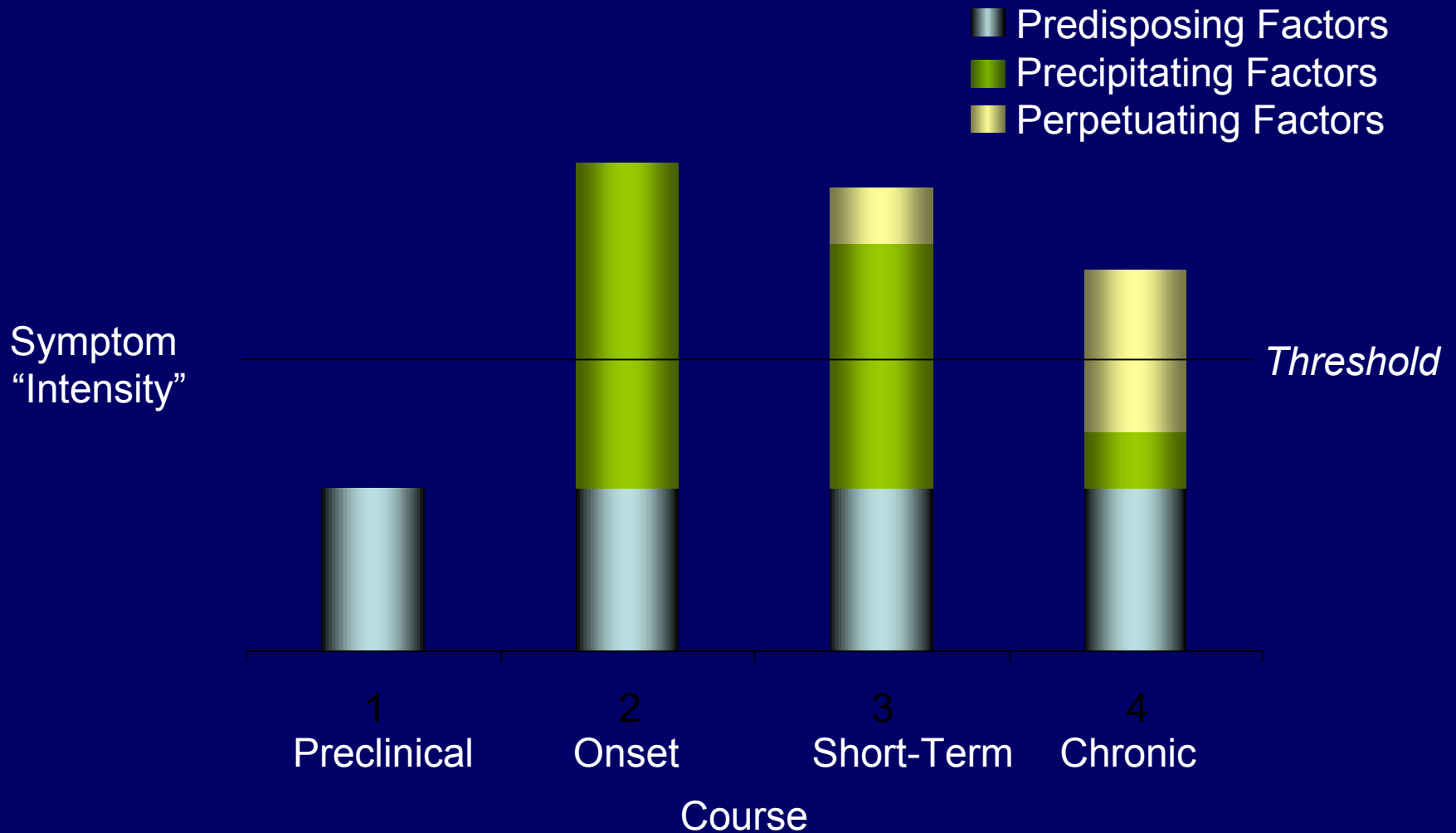
# Disease Progression



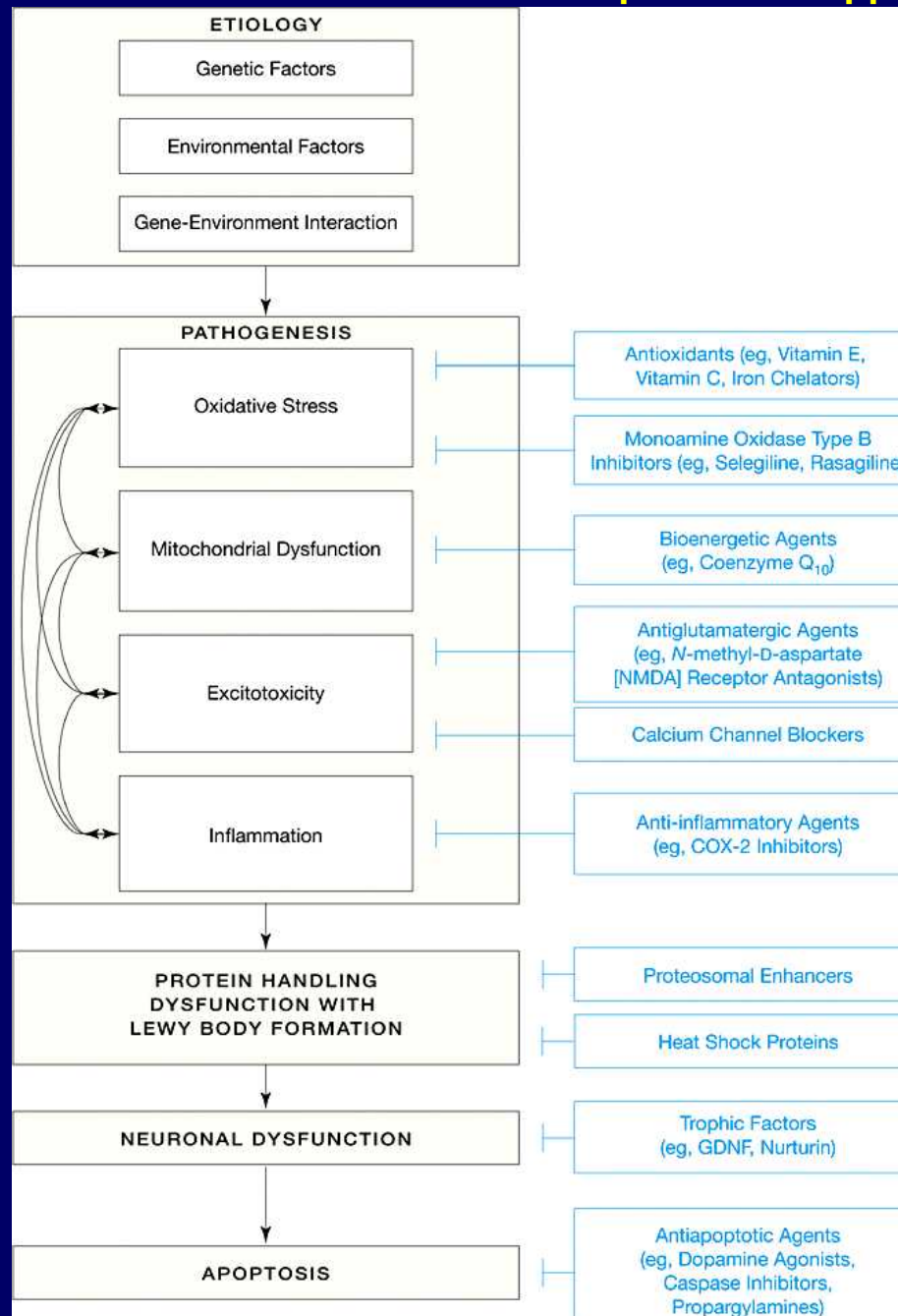
# Understanding the Cause Over Time

- Predisposing factors
- Precipitating factors
- Perpetuating & disease progression factors
- Pathophysiology
- The next step is disease modifying treatments

# Disease Contributors Change with Time



# Schema of Etiologic and Pathogenetic Factors That Have Been Implicated in Cell Death in Parkinson Disease and Possible Neuroprotective Approaches



Schapira, A. H. V. et al.  
JAMA 2004;291:358-364.



# Is Trauma from Infection from Infection or from the Host's Immune Reaction?

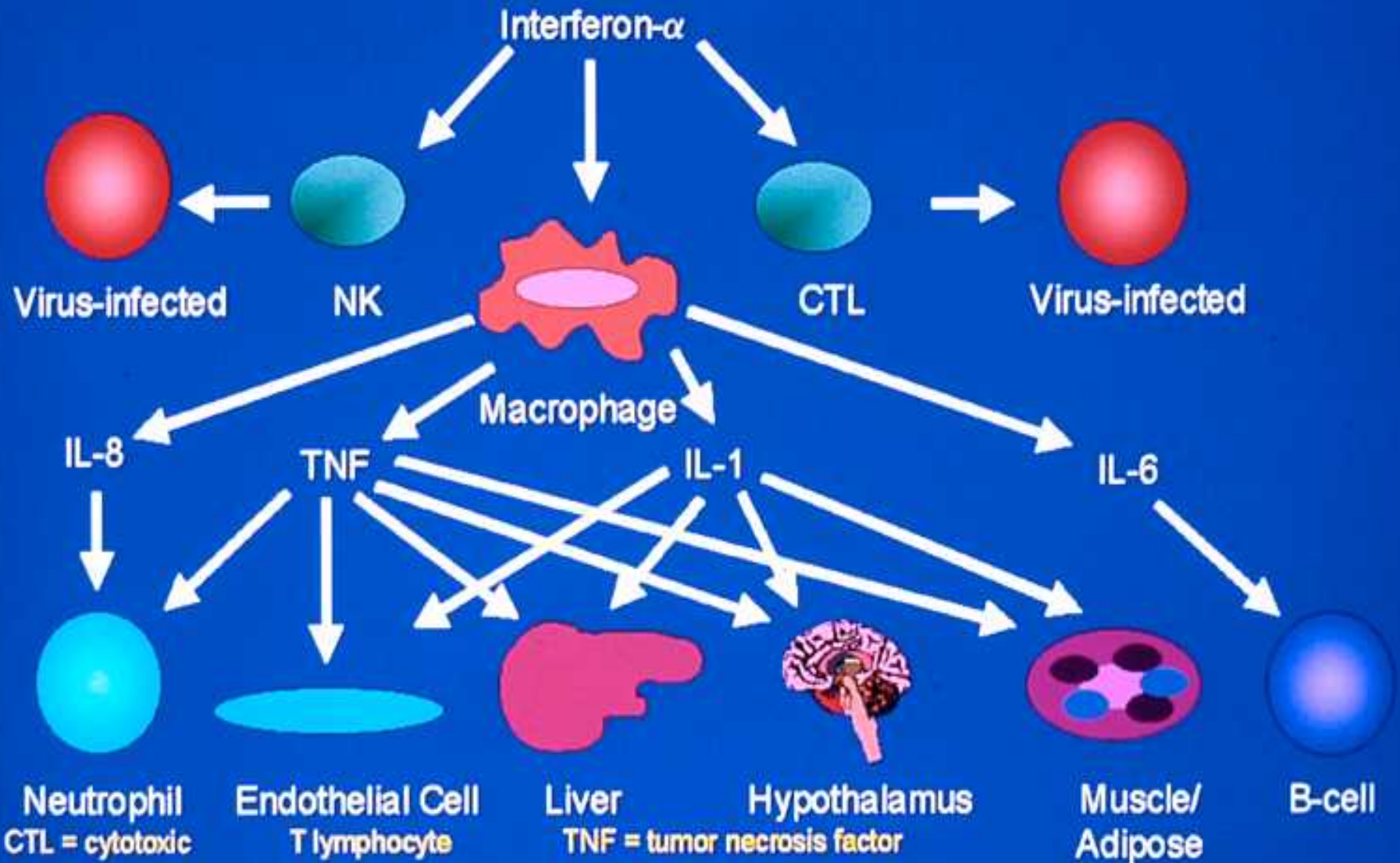
## Parasite

- Cell penetration
- Toxin release
- Incorporation of parasite genes into host genome

## Host

- Cytokine release
- Antibodies
- Inflammation
- Other cellular response

# IFN Cascade



Adapted courtesy of Sidney Grossberg, MD, Medical College of Wisconsin

# Hepatitis C & Interferon Treatment

- A good model for inflammation mediated mental symptoms
- Symptoms include depression, anxiety, mania, irritability, impulsiveness, hostility, relapse of substance abuse & lassitude.[1]
- Many patients with mild symptoms of depression and fatigue respond to a combination of modafinil and sertraline
- Pre-treat before starting interferon

# Hepatitis C & Interferon: Watch for Hostility, Impulsivity

- “Most studies describe depressive states, although manic states—irritability, aggression, anger, emotional lability, anxiety attacks, panic attacks, and insomnia—also have been reported.”

# Treatment of Interferon-Induced Psychosis in Patients with Comorbid Hepatitis C and HIV

- “Four out of six patients with comorbid hepatitis C and HIV developed psychosis during interferon alpha therapy...none had a previous history of psychosis.”

# Tryptophan, Serotonin & Inflammation

- Kynurenine pathway a major route of L-tryptophan catabolism with a number of metabolites that include:
  - Serotonin
  - Kynurenic acid NMDA antagonist (neuroprotective)
  - Quinolinic acid NMDA agonist (neurotoxic)
- In an inflammatory state there is decreased serotonin & a shift to quinolinic acid rather than kynurenic acid.

# Proinflammatory Cytokines Increase Indoleamine 2,3-dioxygenase (IDO)

- The IDO enzyme converts tryptophan into kynurenine, because IDO activation leads to reduced levels of tryptophan, the precursor of serotonin (5-HT), and thus to reduced central 5-HT synthesis.
- Kynurenine metabolites such as 3-hydroxy-kynurenine (3-OH-KYN) and quinolinic acid (QUIN) have toxic effects on brain function. 3-OH-KYN is able to produce oxidative stress by increasing the production of reactive oxygen species (ROS), and QUIN may produce overstimulation of hippocampal N-methyl-D-aspartate (NMDA) receptors, which leads to apoptosis and hippocampal atrophy. Both ROS overproduction and hippocampal atrophy caused by NMDA overstimulation have been associated with depression.

# Tryptophan metabolites and brain disorders

- Tryptophan is metabolised primarily along the kynurenine pathway, of which two components are now known to have marked effects on neurons in the central nervous system. **Quinolinic acid is an agonist at the population of glutamate receptors** which are sensitive to N-methyl-D-aspartate (NMDA), and kynurenic acid is an antagonist at several glutamate receptors. Consequently quinolinic acid can act as a **neurotoxin** while kynurenic acid is neuroprotectant. A third kynurenine, 3-hydroxykynurenine, can **generate free radicals** and contribute to, or exacerbate, neuronal damage. Changes in the absolute or relative concentrations of these kynurenines have been implicated in a variety of central nervous system disorders such as the AIDS-dementia complex and Huntington's disease



# Quinolinic Acid

- Quinolinic acid (QUIN) is a product of tryptophan metabolism that can act as an endogenous brain excitotoxin when released by activated macrophages.
- Previous studies have shown correlations between **increased CSF QUIN levels and the presence of the AIDS dementia complex (ADC)**, a neurodegenerative condition complicating late-stage human immunodeficiency virus type 1 (HIV) infection in some patients.
- CSF **QUIN** is putatively one of the important molecular mediators of the brain injury in this clinical setting and, more generally, serves as a **marker of local macrophage activation**.

# **Role of indoleamine 2,3-dioxygenase in antimicrobial defence and immuno-regulation: tryptophan depletion versus production of toxic kynurenines**

Tryptophan metabolism occurs via the protohemoprotein enzymes tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO), the latter action of which has a number of effects in the body including both antimicrobial defense and immune regulation. Whilst the antimicrobial action of IDO is largely due to depletion of the essential amino acid tryptophan, the immune regulatory function of IDO is still unclear and controversial. The list of pathogens that are "sensitive" to IDO-mediated tryptophan degradation covers intra-cellular parasites such as toxoplasma and possibly plasmodia, viruses (herpes viruses) to intra-cellular bacteria (chlamydia and rickettsia) and extra-cellular bacteria such as streptococci, enterococci and staphylococci. Immune regulation may be a consequence of tryptophan depletion, the accumulation of immune-active or toxic metabolites or due to other signaling events. This review covers the latest data and controversy pertaining to the antimicrobial and immune regulatory effects of tryptophan metabolism.

# Neuroactive Kynurenines in Lyme Borreliosis

- We conclude that CSF QUIN is significantly elevated in *B burgdorferi* infection--dramatically in patients with CNS inflammation, less in encephalopathy.
- The presence of this known agonist of NMDA synaptic function--a receptor involved in learning, memory, and synaptic plasticity--may contribute to the neurologic and cognitive deficits seen in many Lyme disease patients.

# Neopterin production and tryptophan degradation in acute Lyme neuroborreliosis versus late Lyme encephalopathy

- Fourteen patients with *Borrelia burgdorferi* infection were investigated for possible abnormalities of tryptophan and neopterin metabolism. Four patients (2 were investigated before therapy, 2 when therapy had been already started) had acute Lyme neuroborreliosis, and 10 patients were investigated months to years after an acute infection. Increased concentrations of neopterin and of the tryptophan-degradation product, L-kynurenine, were detected in the cerebrospinal fluid of patients with acute Lyme neuroborreliosis; one patient presented with subnormal tryptophan. Similar but less marked changes were seen in the treated patients and in some of the patients with Lyme encephalopathy. No such abnormalities were seen in the serum of the patients. The data indicate a role of the immune system and particularly of endogenously formed cytokines, like interferon-gamma and tumour necrosis factor-alpha, effecting tryptophan and neopterin metabolism in patients with acute Lyme neuroborreliosis.

# The “Blood Brain Barrier”

- Partial barrier
- Penetration early in infection
- Penetration through cranial nerves
- Infected immune cells penetrate CNS
- Neurotoxins and cytokines
- Partial barrier to treatment
- No barrier to HERV or other parasite sequences incorporated in DNA
- Infections in the body can cause immune effects in the brain

# Lyme/Tick-Borne Disease

# Factors associated with risk for Lyme disease and its associated manifestations

- Predisposing factors
  - HLA DR2, HLA DR4 genotype
  - Compromised immune system
  - Coinfections that cause immunosuppression
  - Ecosystem that fosters tick-borne disease (infection)
  - Outdoor activities (infection)
- Precipitating factors
  - Tick bite (initial infection)
  - Episode of acute stress (relapse)
  - Immunosuppression (relapse)
  - Vaccination (relapse)
  - Childbirth (relapse)
  - Auto accident (relapse)
  - Coinfection (relapse)
- Perpetuating factors
  - High bacterial load
  - Virulent strain of Bb.
  - Reinfections
  - Coinfections
  - Chronic unremitting stress
  - Sleep deprivation
  - Steroid exposure
  - Misdiagnosis
  - Under-treatment

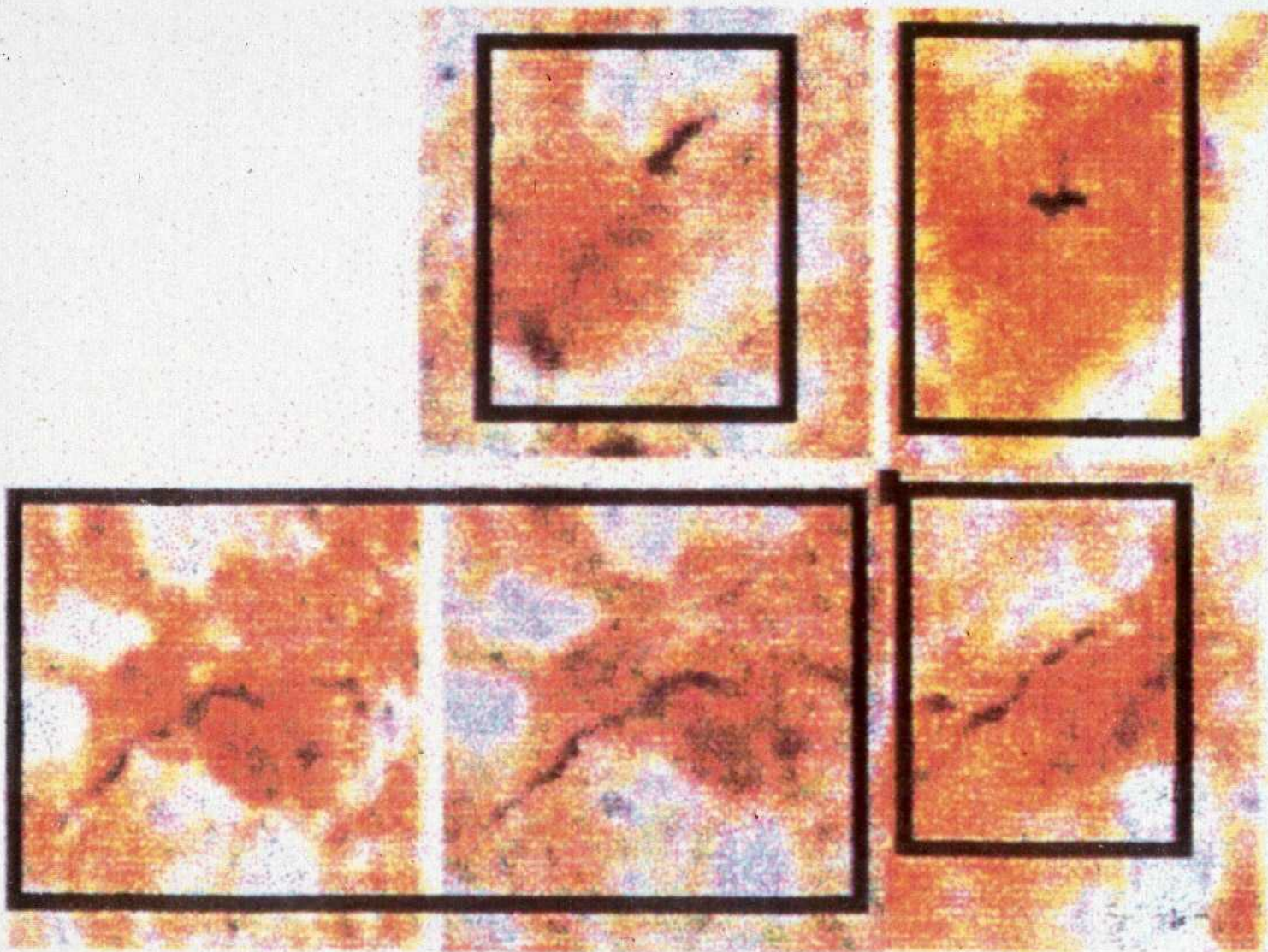
# Higher prevalence of antibodies to *Borrelia burgdorferi* in psychiatric patients than in healthy subjects.

Hajek T, Paskova B, Janovska D, Bahbouh R, Hajek P, Libiger J, Hoschl C.

*Am J Psychiatry* 2002 Feb;159(2):297-301

- **CONCLUSIONS:** These findings support the hypothesis that there is an association between *Borrelia burgdorferi* infection and psychiatric morbidity. In countries where this infection is endemic, a proportion of psychiatric inpatients may be suffering from neuropathogenic effects of *Borrelia burgdorferi*.





**Figure 3: INTRACELLULAR  
SPIROCHETES IN NEURONS OF GRAY  
MATTER**

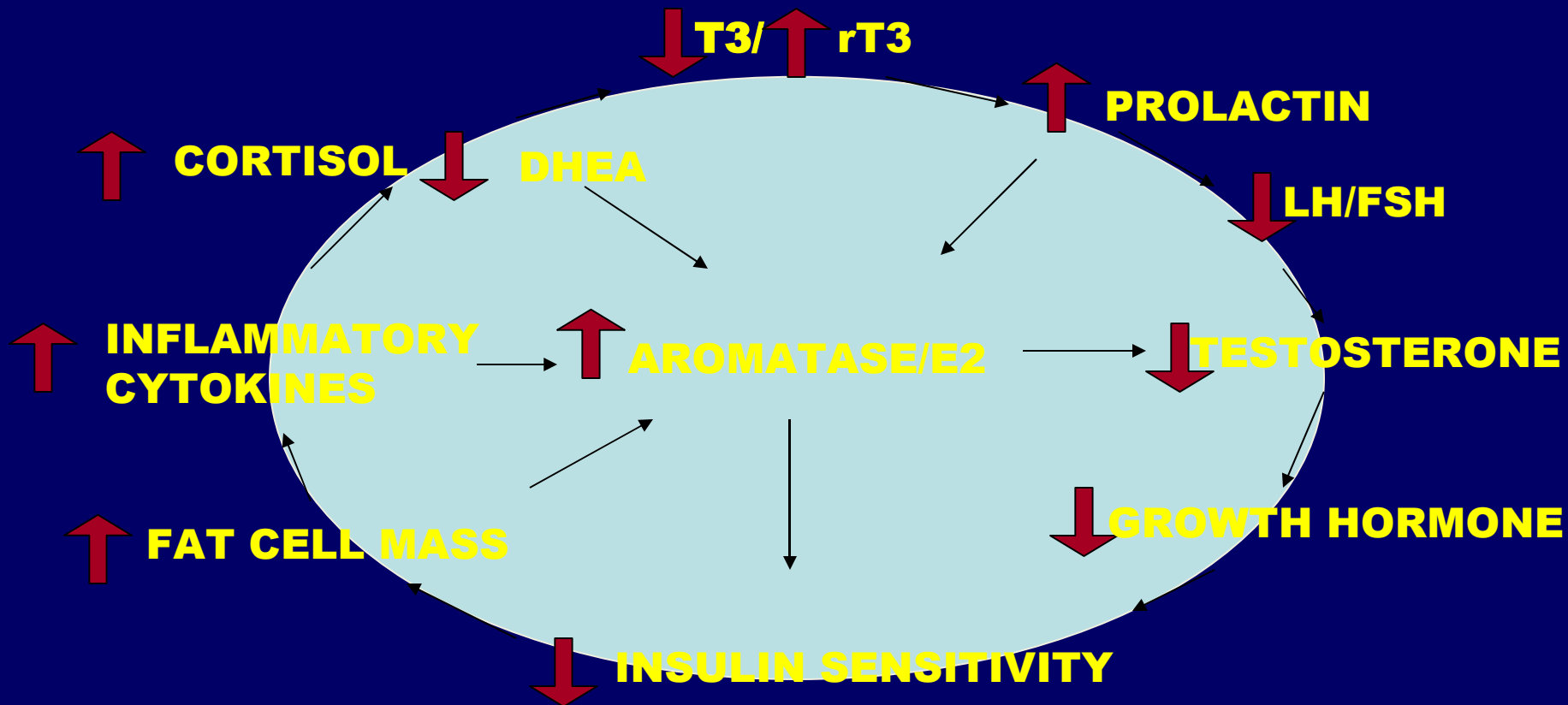
# Invasion of human neuronal and glial cells by an infectious strain of *Borrelia burgdorferi*

- Human infection by *Borrelia burgdorferi*, the etiological agent for Lyme disease, can result in serious acute and late-term disorders including neuroborreliosis, a degenerative condition of the peripheral and central nervous systems. To examine the mechanisms involved in the cellular pathogenesis of neuroborreliosis, we investigated the ability of *B. burgdorferi* to attach to and/or invade a panel of human neuroglial and cortical neuronal cells. In all neural cells tested, we observed *B. burgdorferi* in association with the cell by confocal microscopy. Further analysis by differential immunofluorescent staining of external and internal organisms, and a gentamicin protection assay demonstrated an **intracellular localization of *B. burgdorferi***. A non-infectious strain of *B. burgdorferi* was attenuated in its ability to associate with these neural cells, suggesting that a specific borrelial factor related to cellular infectivity was responsible for the association. Cytopathic effects were not observed following infection of these cell lines with *B. burgdorferi*, and internalized spirochetes were found to be viable. **Invasion of neural cells by *B. burgdorferi* provides a putative mechanism for the organism to avoid the host's immune response while potentially causing functional damage to neural cells during infection of the CNS.**

# Is CNS infection always present?

- Lyme/tick-borne disease in the body can have immune effects that impair cognitive, psychiatric and neurological functioning.

# ENDOCRINE DYSREGULATION



# The association between tick-borne infections, Lyme borreliosis and autism spectrum disorders

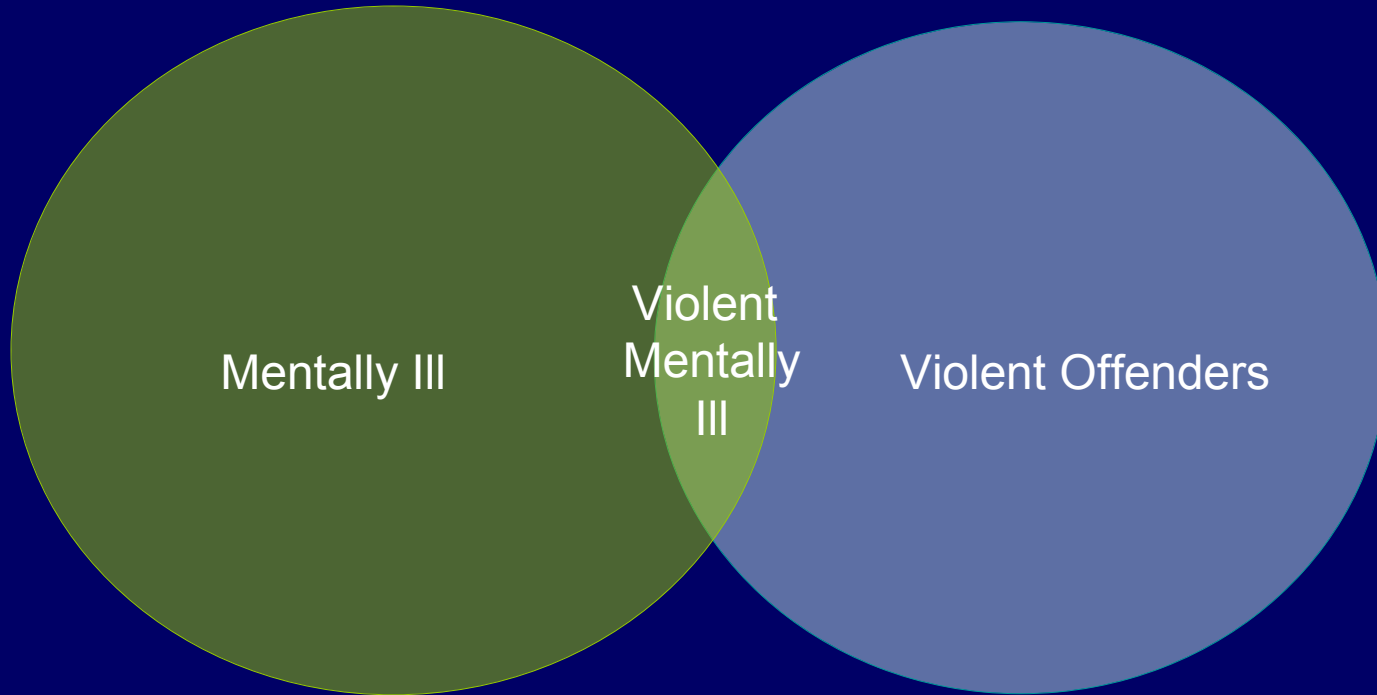
- Tick-borne infections, including Lyme disease contribute to developing autism spectrum disorders (ASD) by direct effects, promoting other infections and immune effects during fetal development and infancy. Combined with other predisposing and contributory factors these infections may provoke immune reactions in susceptible individuals that result in inflammation, molecular mimicry, kynurenine pathway changes, increased quinolinic acid and decreased serotonin, oxidative stress, mitochondrial dysfunction and excitotoxicity that impair the development of the amygdala and other neural structures and neural networks resulting in a partial Klüver–Bucy Syndrome and other deficits resulting in autism spectrum disorders and/or exacerbating ASD from other causes.
- Supporting data includes multiple cases of mothers with Lyme disease and children with ASD; fetal neurological abnormalities associated with tick-borne diseases; similarities between tick-borne diseases and ASD regarding symptoms, pathophysiology, immune reactivity, temporal lobe pathology, and brain imaging data; positive reactivity in several studies with ASD patients for Lyme disease (22%, 26% and 20–30%) and 58% for mycoplasma; similar geographic distribution and improvement in autistic symptoms from antibiotic treatment.

# LYME NEUROBORRELIOSIS & AGGRESSION

- The link between Lyme neuroborreliosis (LN) and aggression is reviewed from multiple perspectives. Cases are presented and discussed. It appears Lyme disease (LD) and other related tick-borne diseases contribute towards causing human aggression and violence. Greater attention to this area has the potential of reducing crime and saving lives. Narrow and restrictive opinions on the diagnosis and treatment of Lyme disease can contribute to the increased consequences of late stage disease, which includes aggression and violence associated with Lyme disease and other related tick-borne diseases.

# Mental Illness & Violence

10% of Murders are from Mental Illness



# Assessment



# The Voices of Lyme Disease- Breaking the Silence

by Victoria Wilcox & Sara Lynch

- The following short video was created by Victoria Wilcox, a 16 year old girl and her friend, Sara Lynch:
- <http://www.youtube.com/watch?v=mpB287Yx9iQ>

# Screening for suspected late or complicated Lyme disease

- 1. Do you live or have you vacationed in areas that may expose you to ticks?
- 2. Have you engaged in activities that may have exposed you to ticks?
- 3. Have family members, neighbors, or the family dog been infected?
- 4. Is there a history of a tick bite, possibly with a flu-like illness and/or a bull's eye or other rash?
- 5. Is there a point at which the patient's health declined, followed by a relapsing progression and development of multi-systemic symptoms, including cognitive, psychiatric, neurological, and physical symptoms?
- 6. Have antibiotics ever caused a sudden worsening followed by an improvement of symptoms?

# Assessment

- In depth history, review of systems
- Thorough exam relevant to patient's complaints and findings from history
- “If you listen long enough, the patient will give you the diagnosis.” *Wm Osler*
- Laboratory testing as indicated (**no test can rule out the possibility of TBD infection**)
- Medical judgment

# Common Differential Diagnosis for LYD/TBD

- Chronic fatigue
- Fibromyalgia
- Epstein-Barr
- Multiple Sclerosis
- Lupus
- Posttraumatic stress disorder
- Hypochondriasis

# Psychiatric Assessment

- Cognitive
- Emotional
- Vegetative
- Behavioral
- Psychiatric syndromes
- Neurological
- Somatic



“Don’t mess with  
my brain. It’s my  
second favorite  
organ.”

from *Sleeper*

# Cognitive Symptoms

- Attention
- Memory
- Processing
- Imagery
- Executive functioning

# Attention Span

- Sustained attention
- Allocation of attention
- Distracted by frustration
- Distracted by hyperacuity to:
  - Sound
  - Light
  - Touch
  - Smell



# Memory

- Working memory
- Working spatial memory
- Recent memory
- Remote memory
- Encoding errors
- Retrieval difficulties: words, numbers, names, faces, geographical, motor sequences
- Sequential memory: letter reversals, spelling errors, word reversals, number reversals

# Processing

- Reading comprehension
- Auditory comprehension
- Sound localization
- Spatial processing
- Left-right confusion
- Transposition of laterality
- Calculation
- Optic ataxia
- Fluency of speech
- Stuttering
- Slurred speech
- Fluency of written language
- Handwriting
- Depersonalization
- Derealization
- Imagery
  - Intrusive images
  - Hypnagogic hallucinations
  - Vivid nightmares
  - Illusions
  - Hallucinations

# Executive Functioning

- Unfocused concentration
- Brain fog
- Organizing, prioritizing, planning
- Multitasking
- Racing thoughts
- Obsessive thoughts
- Mental apathy

# Emotional

- Decreased frustration tolerance
- Irritability
- Sudden abrupt mood swings
- Hypervigilance
- Paranoia
- Dysphoria
- Anxiety
- Apathy

# Behavioral

- Disinhibition
- Exaggerated startle
- Explosive anger
- Suicidal
- Homicidal
- Accident prone
- Decreased social functioning
- Decreased school/job performance
- Marital/family problems
- Substance abuse
- Compensatory compulsions
- Dropping objects
- Crying spells

# Psychiatric Syndromes

- Depression
- Rapid cycling bipolar
- Panic disorder
- Obsessive compulsive disorder
- Social anxiety disorder
- Generalized anxiety disorder
- Posttraumatic stress disorder
- Mostly any psychiatric syndrome

# Vegetative Functioning

- Sleep
- Eating
- Sexual
- Temperature control

# Sleep

- Not well rested in morning
- Insomnia
  - Initial
  - Mid
  - Late
- Hypersomnia
- Loss of normal circadian rhythm



# Eating

- Anorexia
- Weight loss
- Non-appetite motivated over-eat
- Weight gain w/o increased food intake
- Weight gain with increased food intake

# Sexual

- Decreased libido
- Decreased capacity for arousal
- Decreased capacity for orgasm
- Menstrual irregularity
- Decreased capacity for pleasure

# Temperature Control

- Body temperature fluctuations
- Flushing
- Intolerance to heat
- Intolerance to cold
- Decreased body temperature
- Low grade fevers
- Night sweats
- Chills

# Neurological

- Headaches
- Cranial nerves
- Seizures
- Sensory
- Motor
- Reflexes

L'imagination.



Le mal de tête.

*Hola! hola!... pan! pan!... dindrelindin— dindrelindin hola! hola! hola!!*

# Headaches

- Cervical radiculopathy
- Migraines
- Temporal mandibular joint
- Tension
- Cluster
- Sinus
- Thunderclap



# Cranial Nerves II

- Blurred vision
- Photophobia
  - Bright lights
  - Florescent & flicker
- Floaters
- Flashes
- Conjunctivitis
- Eye pain
- Dry eyes
- Papilledema
- Blind spots
- Night blindness
- Peripheral shadows
- Iritis
- Uveitis
- Optic neuritis
- Panopsia
- Other



# Cranial Nerves: I-XII

- I: Loss of smell, altered taste
- III, IV, VI: Double vision, eyes drift when tired
- V: Sensory loss on face
- VII: Bell's palsy
- VIII: Tinnitus, hearing loss, dizziness, vertigo, motion sickness, Tullio's
- IX, X: Episodic loss of speech, choking on food, difficulty swallowing
- XI: SCM & Trapezius pain and paresis
- XII: Tongue deviates to side

# Seizures

- Grand Mal
- Complex partial

# Somatic

- Musculoskeletal
- Cardiac
- Pulmonary, upper respiratory
- Gastrointestinal
- Genitourinary
- Other

# Musculoskeletal

- Joint: Pain, swelling, tightness, crepitations
- Bone thinning fractures
- Periostitis: Tibia, ribs, iliac crest, sternum, clavicle, etc.
- Epicondilitis
- Plantar fasciitis
- Fatigue, chronic fatigue
- Fibromyalgia
- Myalgia
- Chondritis: ear, nose, chostochondral, xyphoid
- Tendonitis
- Carpal tunnel syndrome

# Cardiac

- Chest pain
- Heart block
- Mitral valve prolapse
- Racing pulse
- Episodes of rapid & slow heart rate
- Murmur
- Other

# Pulmonary, Upper Respiratory

- Shortness of Breath
- Cough
- Sore throats
- Swollen glands
- Asthma
- Other

# Gastrointestinal

- Upper GI
- Irritable bowel
- Abdominal bloating
- Other

# Genitourinary

- Genital pain
- Breast tenderness
- Lactation
- Irritable bladder
- Urinary incontinence
- Recurrent urinary infections
- Other



# Other

- Alcohol intolerance
- Hair loss
- Thyroid dysfunction
- Vasculitis
- Ankle edema
- Allergies
- Multiple chemical sensitivity
- Tooth pain
- Peridontal disease
- Nose bleeds
- Ecchymosis
- Chronic pain
- ACA
- Lymphocytoma
- Other

# Pattern of Symptoms

- Herxheimer reaction
- Multi-systemic progression of symptoms
- Symptoms fluctuate throughout the day
- Stress increases symptoms
- Concomitant infection increases infection
- 28 day cycle or longer
- Perimenstrual relapse
- Episodic relapses
- Antibiotics reduce symptoms

# McHUMOR

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**“I’d say you’re suffering from an arrow through your head, but if you want, I’ll order a bunch of tests.”**

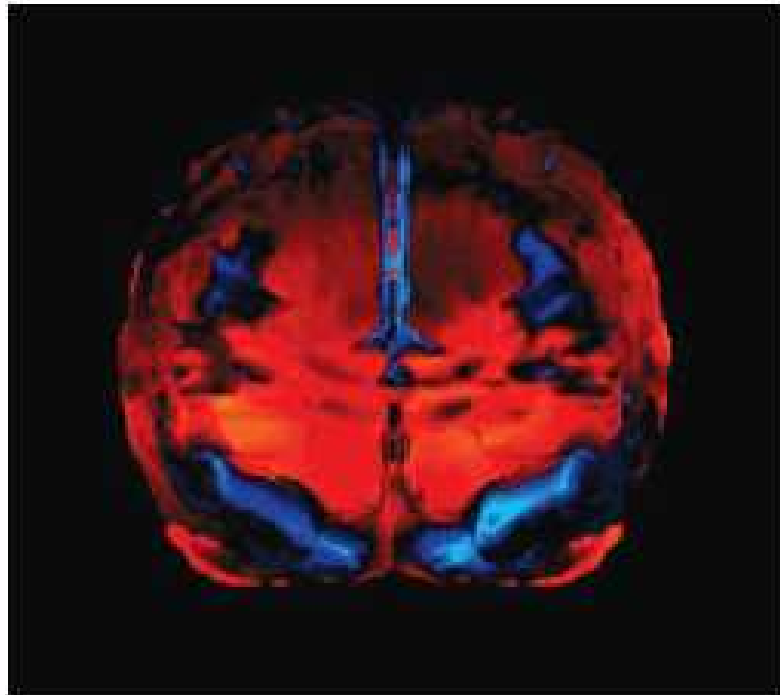
# Laboratory Testing

- Lyme Western Blot from a reliable lab
- CD-57 NKC Panel (Stricker Panel)
- Flow Cytometry (Central Florida Research Lab)
- PCR
- C4a complement levels
- Testing for co-infections
- C-6 ELISA in spinal fluid
- Microarray
- SPECT & PET
- Cognitive testing

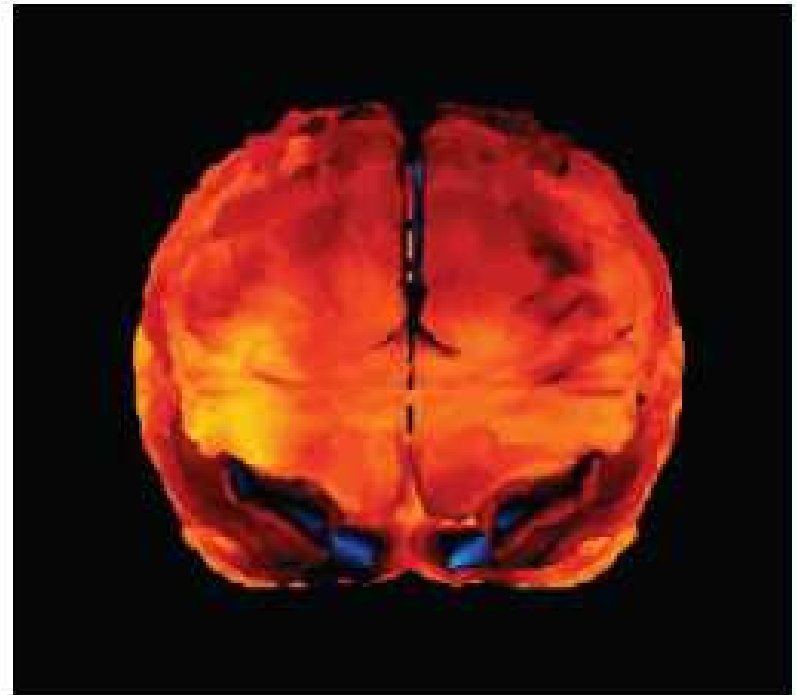
## Figure

# SPECT images of the brain before and after treatment with ceftriaxone

**Before**



**After**



Initial SPECT scan shows extensive hypoperfusion, predominantly in the frontal and temporal lobes and to a lesser degree in the parietal and occipital lobes. After treatment, there is marked improvement of the hypoperfusion pattern in the temporal, frontal, and parietal lobes; only small areas of the hypoperfusion pattern remain.

---

SPECT, single photon emission CT.

Treatment

# IDSA Guidelines

- The IDSA guidelines totally ignored psychiatric symptoms associated with Lyme disease and tick-borne diseases.
- There were over 160 citations for prior works of the authors & contributors.
- Although there was minimal attention to cognitive functioning, there was not a single citation addressing psychiatric symptoms.

Do Psychotropics Have  
Antimicrobial Effects or Immune  
Effects?



# Antibiotics: The First Antidepressants

- In 1952, Zeller and associates found that “MAO was inhibited by the hydrazine MAOI, iproniazid,” and Selikoff and co-workers and Bloch and colleagues fortuitously noticed mood elevation in tuberculosis patients treated with iproniazid. Crane and Kline independently studied iproniazid in depressed patients and reported favorable results. The use of iproniazid was associated with hepatic toxicity, however, and as a result, other drugs that differed in a variety of properties and structures but shared the same common property of MAO inhibition were studied.
- The other hydrazines--isocarboxazid, nialamide and phenelzine in this regard and also notes that as far back as 1948

Klein DF, Gittelman R, Quikin F, Rifkin A. Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children. Second Edition. Williams & Wilkins, Baltimore. 1980 [a] pp 303-306; [b] p 464; [c] p 269

# **Antimicrobial activity of psychotropic drugs: selective serotonin reuptake inhibitors**

Psychotropic drugs have been shown to have antimicrobial activity against several groups of microorganisms. Some of these drugs, such as the new antidepressant agents sertraline, fluoxetine and paroxetine are known to act as efflux pump inhibitors in human cells. Their activity has been studied, alone and combined with antibiotics, against bacterial species, mainly in multiply resistant strains. These agents have surprising activity, mainly against Gram positive microorganisms. They also show synergistic activity when combined with some antibiotics against several bacteria, shown by a decrease in MICs, that converts strains previously resistant to the category of sensitive, and modify physiological aspects related with pathogenicity.

# Immunomodulatory effect of SSRIs on human T lymphocyte function and gene expression

- Antidepressants have an antiproliferative effect in some cell lines. Depression may be associated with activation of some pro-inflammatory cytokines.
- We found that the SSRIs, paroxetine and sertraline decreased T-cell viability with IC50 around 10  $\mu$ M.
- These SSRIs inhibit the secretion of the TH1 factor-tumor necrosis factor(TNF) $\alpha$  from the cells. On the molecular level, the SSRIs suppressed signal transducer and activator of transcription 3 (Stat3) and cyclooxygenase(Cox)2 protein expression.
- The inhibitory effects were accompanied by alterations in gene expression as assessed in the gene array. These findings reveal an immunomodulatory effect of the SSRIs paroxetine and sertraline in human T cells.

# The immunostimulating and antimicrobial properties of lithium and antidepressants

Eicosanoids are products of arachidonic acid (AA), an essential fatty acid. They include prostaglandins (PGs), prostacyclin (PGI<sub>2</sub>), thromboxanes (TXs), leukotrienes (LTs) and hydroxy fatty acids. AA is derived enzymatically from membrane phospholipids and to a lesser extent the diet. Eicosanoids self-regulate every cell, including those synthesizing serotonin, norepinephrine and dopamine and those subserving immune function, such as T-cells, B-cells, natural killer cells, macrophages, monocytes and dendritic cells. There is objective evidence that prostaglandins regulate the physiology of the hypothalamic-pituitary-adrenal axis (HPA). Elucidation of the structure and metabolic pathways of eicosanoids galvanized researchers into illuminating their role in physiology, pathology and pharmacology. Striking contradictions arose: eicosanoids were shown to activate and suppress microorganisms, potentiate and suppress immunity and possess pro- and anticancer properties. As prostaglandins are the most heavily studied eicosanoids in the context of mood and immunity I will focus on them in this article. I will present evidence of the immunostimulating and antimicrobial properties of lithium and antidepressants and propose that these properties are linked to the antiprostaglandin actions of these compounds.

# Antiviral and immunomodulatory effect of lithium

Experimental and clinical data pointing to antiviral and immunomodulatory effects of lithium have been reviewed in the context of new information accumulated in the last recent two decades, indicating a possible pathogenic role of viral infection and/or immune dysfunction in affective illness. Antiviral effects of lithium, particularly against herpes viruses, was demonstrated in both experimental and clinical conditions. Patients with affective illness taking lithium for prophylactic purposes have a greatly reduced frequency of labial herpes recurrences. The therapeutic action of oral and topical lithium administration on labial and genital herpes was also demonstrated in non-affective subjects. In both experimental conditions and in clinical studies with affective patients, lithium was shown to exert favorable effects on many parameters of cellular and humoral immunity. The evidence was also presented that lithium may alleviate the immune-endocrine component concomitant to an acute affective episode, such as acute phase reaction, cytokine secretion and hyperactivation of hypothalamic-pituitary-adrenal axis. It is speculated that the antiviral and immunomodulatory properties of lithium may contribute to psychotropic actions of this ionic drug, especially prevention of recurrences in affective illness.

# Autophagy and Amyotrophic Lateral Sclerosis: the Multiple Roles of Lithium

The effects induced by lithium can be summarized as follows:

- (ii) The removal of altered mitochondria and protein aggregates;
- (iii) The biogenesis of well-structured mitochondria;
- (iv) The suppression of glial proliferation;
- (v) The differentiation of newly formed neurons in the spinal cord towards a specific phenotype.
- (vi) The biogenesis of mitochondria and the increase of calbindin D 28K-positive neurons, which are likely to support powerful neuroprotection towards autophagy failure, mitochondriopathy, and neuronal loss in the spinal cord.

# Antipsychotics are anti-retroviral

- antipsychotic drugs like Thorazine, Haldol and Clozapine inhibit viral replication and that the cerebrospinal fluid of patients with recent-onset schizophrenia shows a significant increase in reverse transcriptase (an enzyme) activity - which is an important component of infectious retroviruses (a type of virus). Furthermore, when the CSF (cerebral spinal fluid) from these patients was used to inoculate a New World monkey cell line there was a tenfold increase in reverse transcriptase activity which suggests the presence of a replicating virus. Malhotra has demonstrated the *absence of CCR5-32 homozygotes (specific matching genetic codes) in over 200 schizophrenic patients - which dramatically increases susceptibility to retroviral infection.*

# Neuroprotective activities of sodium valproate in a murine model of human immunodeficiency virus-1 encephalitis

- Human immunodeficiency virus-1 (HIV-1) infection of the nervous system can result in neuroinflammatory events leading first to neuronal dysfunction then to cognitive and behavioral impairments in infected people. The multifaceted nature of the disease process, commonly called HIV-1-associated dementia (HAD), provides a number of adjunctive therapeutic opportunities. One proposed adjunctive therapy is sodium valproate (VPA), an anticonvulsant known to promote neurite outgrowth and increase beta-catenin through inhibiting glycogen synthase kinase 3beta activity and tau phosphorylation. We now show that VPA treatment of rat cortical neurons exposed to HIV-1 gp120 prevents resultant neurotoxic activities. This includes the induction of significant neurite outgrowth and microtubule-associated protein 2 (MAP-2) and neuron-specific nuclear protein (NeuN) antigens in affected neuronal cell bodies and processes. Similarly, VPA protects severe combined immunodeficient (SCID) mice against the neurodegeneration of HIV-1ADA infected monocyte-derived macrophages (MDMs). In SCID mice with HIV-1 MDM-induced encephalitis, VPA treatment significantly reduced neuronal phosphorylated beta-catenin and tau without affecting HIV-1 replication or glial activation. We conclude that VPA protects neurons against HIV-1 infected MDM neurotoxicity, possibly through its effects on the phosphorylation of tau and beta-catenin. The use of VPA as an adjuvant in treatment of human HAD is being pursued.



# Metabolites of the antipsychotic agent clozapine inhibit the replication of human immunodeficiency virus type 1

- Clozapine, an atypical antipsychotic, and nine of its metabolites were studied in vitro for possible antiviral activity against a model of a human neurotropic virus, HIV-1.
- In an assay for inhibition of virus-induced cytopathic effect two metabolites demonstrated antiviral activity.
- These data suggest that the therapeutic efficacy of some antipsychotics may be due in part to an ability to inhibit viral replication. Antiviral agents may prove to be effective adjuncts in the treatment of schizophrenia.

# Antipsychotics are anti-parasitic

- certain antipsychotic and mood-stabilizer drugs such as halperidol and valproic acid inhibited this parasite in vitro at a concentration below that found in the cerebrospinal fluid and blood of individuals being treated with this medication, suggesting that some medications used to treat schizophrenia and bipolar disorder may actually work by inhibiting the replication of **toxoplasmosis gondii**.

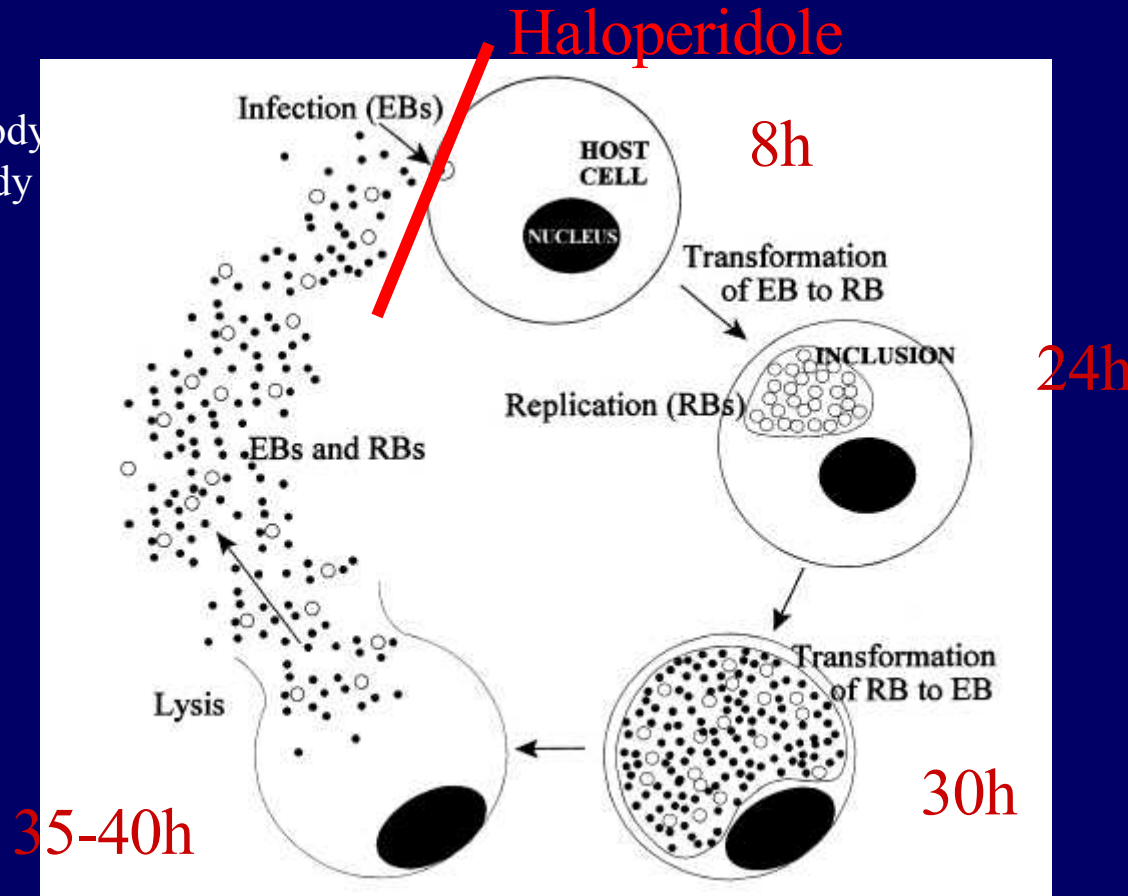
# Associations between *Chlamydophila* infections, HLA- A10 and risk of schizophrenia

The neurotropic pathogens *C. psittaci* and *C. pneumoniae*, might be involved in the pathogeneses of schizophrenia.

Eventually, there is a genetic predisposition for *Chlamydophila spec.* infections (HLA-A10).

# Chlamydiaceae and Haloperidole

EB= elementary body  
RB = reticulate body



Karin D.E. Everett (2000) *Vet. Microbiol.* **75**: 109-126  
Murray & Ward (1984) *J. Gen. Microbiol.* **130**:193-201

Barbara Fellerhoff  
Institute for Immunology | LMU Munich

# Antidepressants inhibit interferon-gamma-induced microglial production of IL-6 and nitric oxide

Circumstantial evidence has suggested that activated microglia may be associated with the pathogenesis of depression. Pro-inflammatory cytokines may also be involved. Therefore, we examined the effects of various types of antidepressants, as well as the mood-stabilizer lithium chloride, on interferon-gamma (IFN-gamma)-induced microglial production of the pro-inflammatory mediators interleukin-6 (IL-6) and nitric oxide (NO). Treatment of the murine microglial 6-3 cells with 100 U/ml of IFN-gamma resulted in an eightfold increase in IL-6 and a tenfold increase in NO into the culture medium. Pretreatment with the selective serotonin reuptake inhibitor fluvoxamine, the relatively selective noradrenaline reuptake inhibitor reboxetine, or the non-selective monoaminergic reuptake inhibitor imipramine, significantly inhibited IL-6 and NO production in a dose-dependent manner. These inhibitions were reversed significantly by SQ 22536, a cyclic adenosine monophosphate (cAMP) inhibitor, and, except for reboxetine, by the protein kinase A (PKA) inhibitor Rp-adenosine3',5'-cyclic monophosphorothioate triethylammonium salt (Rp-3',5'-cAMPS). Lithium chloride, which is believed to act by inhibiting the calcium-dependent release of noradrenaline, had a different spectrum of action on microglial 6-3 cells. It enhanced IFN-gamma-stimulated IL-6 production and inhibited NO production. The inhibitory effect of lithium chloride was not reversed by either SQ 22536 or Rp-3',5'-cAMPS. These results suggest that antidepressants have inhibitory effects on IFN-gamma-activated microglia and these effects are, at least partially, mediated by the cAMP-dependent PKA pathway. On the other hand, the mood stabilizer and anti-manic agent lithium chloride has mixed effects on IFN-gamma-induced microglial activation.

# Lithium delays progression of amyotrophic lateral sclerosis

- Daily doses of lithium delay disease progression in human patients affected by ALS. None of the patients treated with lithium died during the 15 months of the follow-up, and disease progression was markedly attenuated
- In a parallel study on a genetic ALS animal model, the G93A mouse, we found a marked neuroprotection by lithium, which delayed disease onset and duration and augmented the life span. These effects were concomitant with activation of autophagy and an increase in the number of the mitochondria in motor neurons and suppressed reactive astrogliosis. Again, lithium reduced the slow necrosis characterized by mitochondrial vacuolization and increased the number of neurons counted in lamina VII that were severely affected in saline-treated G93A mice. After lithium administration in G93A mice, the number of these neurons was higher even when compared with saline-treated WT. All these mechanisms may contribute to the effects of lithium, and these results offer a promising perspective for the treatment of human patients affected by ALS.

# Beta-lactam antibiotics are multipotent agents to combat neurological diseases

- Recently, Rothstein et al. reported that beta-lactam antibiotics, including penicillin and ceftriaxone, are potential therapeutic drugs to treat some neurological disorders, e.g., amyotrophic lateral sclerosis (ALS), by modulating the expression of glutamate transporter GLT1 via gene activation. However, considering the facts that: (i) many neurological diseases (including ALS) are associated with transition metal ions and redox stress, and ALS can be efficiently prevented by metal chelators, e.g., diethyl-dithiocarbamate (DDC); (ii) **beta-lactam antibiotics have long been known as metal chelators**, we argue that the beneficial effect of beta-lactam antibiotics on ALS likely involves Cu(II)-attenuating ability. This is partially supported by our theoretical calculations.

# Psychotropics

- Antidepressants were developed from TB drugs that had mood lifting side effects
- Psychotropics effect neurotransmitters &:
  - Are sometimes antimicrobial
  - Can be immune modulators
  - May alter CNS gene expression
  - Can be neuroprotective
  - Can increase neurogenesis and BDNF



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# General Considerations

# Adjusting to Lyme Disease

- Individuals who acquire Lyme disease are often more active than the average and invariably have great difficulty adapting to the impairments and limitations caused by this disease.
- Due to the multi-systemic nature of the disease, it is difficult to do anything that isn't adversely affected by this disease.

# Family Dynamics

- Patients also have difficulty because Lyme disease, like any other *invisible disability*, is difficult for family, employers and others to understand and acknowledge.
- Often multiple family members have Lyme disease which can result in a further decline in family stability and increased conflicts.

# Neuropsychiatric Herxheimer Reaction

- Treating Lyme/tick-borne disease patients with antibiotics may cause a Jarisch-Herxheimer reaction
- This reaction may exacerbate any symptom caused by the infection
- A sudden appearance of depression, suicide attempts, agitation & violence may be a part of this reaction. “You can’t bear to live. It is beyond the imagination.”
- Slowly starting the antibiotic, close observation & psychotropics are helpful

# Substance Abuse and LB/TBI

- Although most LB/TBI patients realize they have a reduced tolerance to alcohol, a few abuse alcohol which exacerbates their symptoms.
- Drug abuse is more common, most notably pain meds and tranquilizers.
- Well planned treatments minimize these risks.

# Antibiotics or Psychotropics?

- When a patient has been treated with just antibiotics, consider psychotropics.
- When a patient has been treated with just psychotropics, consider antibiotics.
- When a patient is treatment resistant consider both.

# Dosing Strategies

- Change one treatment at a time
- If something works, continue it
- Some patients are drug sensitive and low doses are needed



# Anticipate the Unexpected Adverse Drug Reaction

- Due to the complexity of the human brain and individual differences, **there will always be someone with an opposite response** or unusual reaction to any psychotropic.
- An apparent adverse drug reaction may instead be a symptom flare or Herxheimer reaction
- Be prepared to respond to the unexpected.

# Symptomatic Treatment

- Regardless of whether Lyme disease is active infection or something else, symptomatic treatment is beneficial.
- Symptomatic treatment improves:
  - Functioning
  - Immune functioning
  - Resistance to infection

# Minimize Life Stress

- Chronic illness decreases functioning which increases stress and contributes to perpetuating illness.
- Strategies to reduce chronic stress improve recovery.

# Symptomatic Treatment Reduces Disease Progression with:

- Insomnia
- Attention deficit hyperactivity disorder
- Anxiety disorders
- Posttraumatic stress disorder
- Depression
- Bipolar disorder
- Schizophrenia
- Alzheimer's
- Other general medical conditions

# Benefit of Symptomatic Treatment

- Chronic stress, dysregulated hyper/hypo-arousal & impaired sleep cause compromised immune functioning (increased inflammation, decreased cellular immune response) & increased oxidative stress resulting in decreased neuroprotection and increased neurodegeneration
- Symptomatic treatments can prevent and sometimes reverse progression of illness

# Symptom Priority

- A TBD patent may have over 100 different symptoms.
- After completing an assessment, prioritize which symptoms are most severe and contribute the most towards perpetuating chronic illness.
- Treat the high priority symptoms first and work your way down the list.

# What Symptoms Perpetuate TBD Disease?

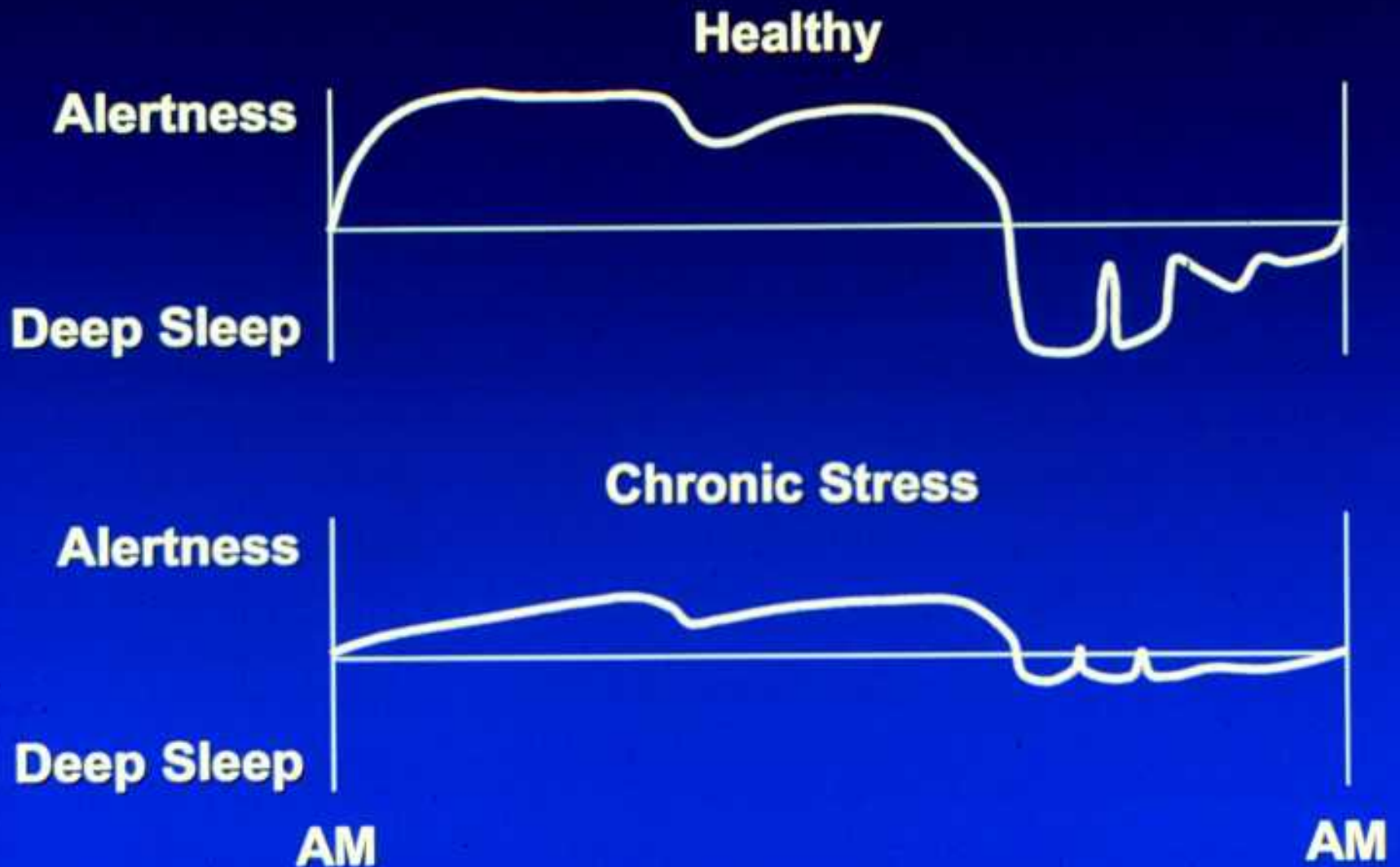
- Sleep disorders
- Fatigue
- Cognitive impairments
- Depression
- Anxiety
- Pain
- Headaches
- Others

# Sleep quality in Lyme disease

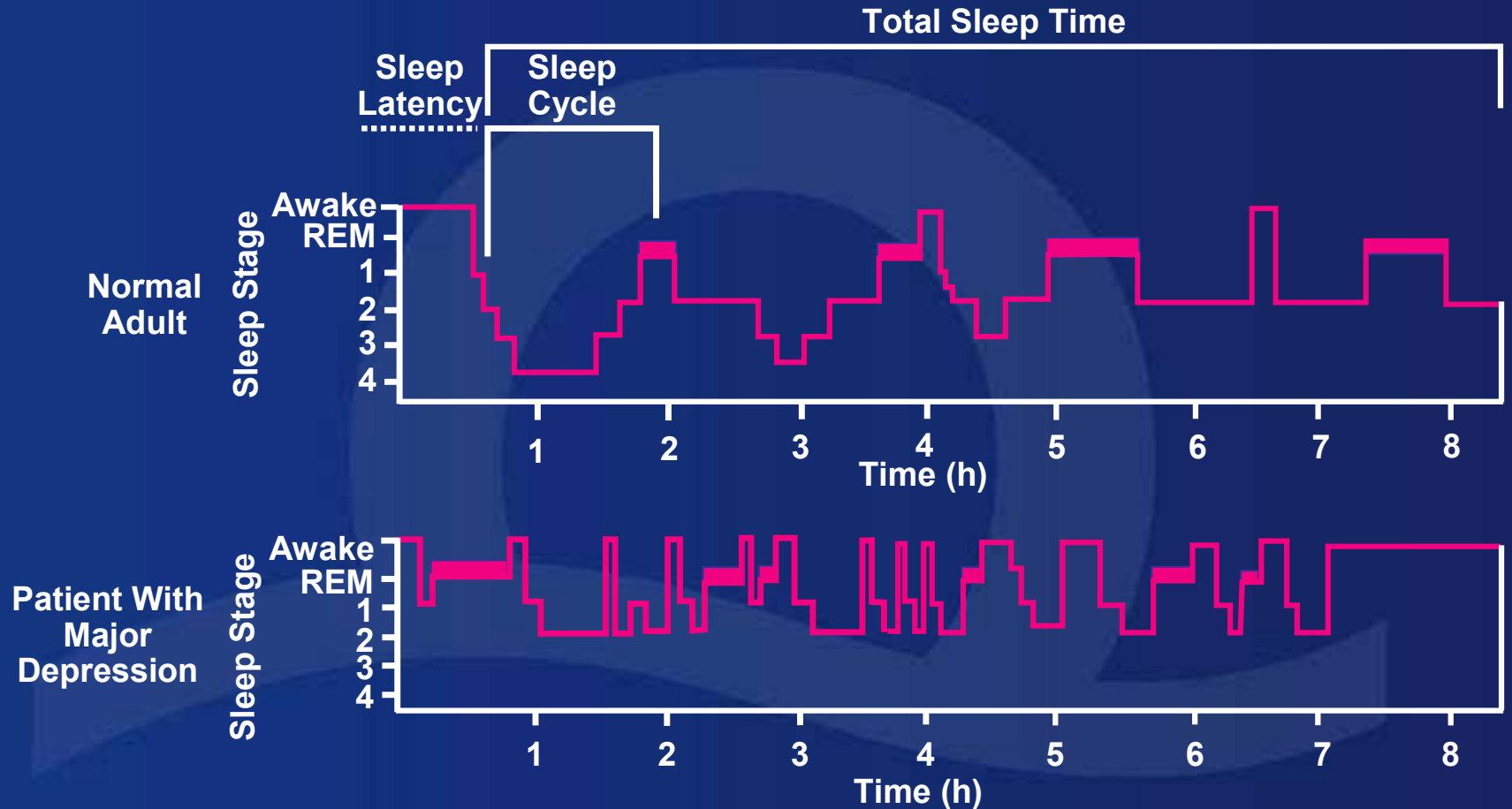
- Complaints of chronic fatigue as well as sleep disturbances are prevalent in Lyme disease. We compared polysomnographic measures of sleep in patients with documented Lyme disease with those of a group of age-matched normal control subjects.
- All patients studied reported sleep-related complaints, including difficulty initiating sleep (27%), frequent nocturnal awakenings (27%), excessive daytime somnolence (73%) and restless legs/nocturnal leg jerking (9%) Greater sleep latency, decreased sleep efficiency and a greater arousal index were noted in Lyme patients. The median length of uninterrupted occurrences of stage 2 and stage 4 non-rapid eye movement (NREM) sleep was less in Lyme patients (6.3 +/- 3.0 epochs in patients vs. 11.4 +/- 4.4 epochs in controls for stage 2,  $p < 0.01$ , and 4.3 +/- 4.4 epochs in patients vs. 11.2 +/- 6.3 epochs in controls for stage 4,  $p < 0.01$ ), indicating greater sleep fragmentation. Mean sleep onset latency during the MSLT was normal (12.7 +/- 5.6 minutes). Three patients demonstrated alpha-wave intrusion into NREM sleep. These sleep abnormalities may contribute to the fatigue and sleep complaints common in this disease.



# Circadian Rhythms



# Variability in Sleep Patterns in a Normal Adult vs a Patient With Major Depression



Adapted with permission from Winokur A, Reynolds CF III. *Primary Psychiatry*. Nov/Dec 1994:22-27.

Please see important safety information on accompanying slides and full prescribing information.

# Bidirectional Communication between the Brain and the Immune System: Implications for Physiological Sleep and Disorders with Disrupted Sleep

- **Cytokines produced by cells of the immune and nervous systems regulate sleep.**
- particularly **interleukin-1beta and tumor necrosis factor-alpha**, signal neuroendocrine, autonomic, limbic and cortical areas of the CNS to affect neural activity and modify behaviors (including sleep), hormone release and autonomic function.
- Sleep disorders are commonly associated with chronic inflammatory diseases and chronic age- or stress-related disorders. The best studied are rheumatoid arthritis, fibromyalgia and chronic fatigue syndromes.

# Sleep restriction increases IL-6 and pain-related symptoms in healthy volunteers

- Chronic under-sleeping may contribute to the high prevalence of pain experiences observed in the general population
- Chronic sleep restriction leads to mild elevations in IL-6, an important inflammatory modulator, and may contribute to the sleep loss-pain relationship we observed in the present study

# Possible Functions of Slow Wave Sleep

- Restoration and recovery<sup>1</sup>
  - SWS rebound following sleep deprivation
  - Growth hormone secretion during SWS
  - Selective SWS deprivation in animals □ physical injury and death
  - Relationship between □ SWS, aging, and sleep/wake complaints
- Energy conservation<sup>2</sup>
  - □ SWS during hibernation
  - □ Core body temperature and metabolic rate during SWS
- Predator avoidance<sup>2</sup>

1. Kryger MH et al. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 2<sup>nd</sup> ed. Philadelphia, PA: W.B. Saunders 1994: 301-308.

2. Zepelin H. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 2<sup>nd</sup> ed. Philadelphia, PA: W.B. Saunders 1994: 69-80.

# The role of growth hormone in modulation of the immune response

Growth hormone was originally discovered because of its ability to promote linear growth in rodents and humans. It is now known that this molecule also augments a number of activities of leukocytes, such as antibody synthesis, cytolytic activity of T lymphocytes, natural killer cell activity, differentiation of neutrophils, production of tumor necrosis factor-alpha (TNF-alpha), and the synthesis of a thymic hormone known as thymulin. We have shown that growth hormone mimics one action of interferon-gamma (IFN-gamma) by augmenting the production of superoxide anion by macrophages and neutrophils. Growth hormone also is synthesized by leukocytes, which creates the possibility that it may act locally as a cytokine in lymphoid tissue. These findings show that a hormone that was originally isolated from the pituitary gland is involved in regulating host defense responses of leukocytes.

# Impaired Sleep Correlates with Impaired Immune Functioning

- Sleep and the immune system. *Int J Immunopharmacol* 1995;17:649-54.
- Disordered sleep in fibromyalgia and related myofascial facial pain conditions. *Dent Clin North Am* 2001;45:701-13.
- Management of sleep disorders in fibromyalgia. *Rheum Dis Clin North Am.* 2002;28:353-65.
- Sleep, neuroimmune and neuroendocrine functions in fibromyalgia and chronic fatigue syndrome. *Adv Neuroimmunol* 1995;5:39-56.
- Fibromyalgia, sleep disorder and chronic fatigue syndrome. *Ciba Found Symp* 1993;173:262-79.

# Normalizing the Amplitude of the Circadian Rhythm

- Activating agent in the morning
- Sleep promoting agent at night
- Combination of both



# Normalizing the Amplitude of Circadian Rhythm

## Activating Agents (AM)

- Modafinil
- Stimulants
- Bupropion
- Noradrenergic agents
- SSRIs
- Activating atypicals
- Thyroid

## Sleep Promoting (PM)

- Pregabalin, Tigabine
- Trazodone, Quetiapine
- Sodium Oxybate
- Gabapentin
- Non-Benzos: Zolpidem, Zaleplon, Zopiclone
- Benzodiazepines
- Doxepin, Amitriptyline, etc.
- Mirtazapine
- Antihistamines
- Sedating atypicals
- Melatonin, Ramelteon

# Potential Uses of Modafinil in Psychiatric Disorders\*

- Modafinil was administered as part of a treatment regimen in patients (N=237) with a broad spectrum of treatment-resistant psychiatric, neurological and general medical disorders accompanied by some combination of **excessive sleepiness, fatigue, executive dysfunction and apathy**.
- In a retrospective chart review with CGI-S, 84.4% improved and most tolerated the agent well
- Modafinil may offer clinical benefit for treatment-resistant hypoarousal symptoms in a number of psychiatric, neurological and general medical conditions.

\*Bransfield RC. *The Journal of Applied Research*. Vol.4, No. 2, 2004

# Pregabalin (Lyrica)

- Initially approved for the treatment of central nervous system disorders, including epilepsy, diabetic neuropathy and post herpetic neuralgia.
- Recently FDA approved for fibromyalgia.
- Studies demonstrate efficacy for generalized anxiety and sleep disorders.
- Not a mood stabilizer.

# Memantine (Namenda)

- Memantine is FDA approved for moderate to severe Alzheimer's disease.
- It is similar to the antiviral, amantadine, and was used to treat AIDS. Although ineffective for AIDS, it was effective for AIDS dementia.
- Memantine is considered to be neuroprotective as a NMDA partial antagonist by selectively block the excitotoxic effects associated with abnormal transmission of glutamate, while allowing for the physiological transmission associated with normal cell functioning.
- Quinolinic acid is increased in infectious and other neurodegenerative encephalopathies.
- Quinolinic acid is neurotoxic as an NMDA agonist.

# Memantine Mechanism of Action

- Low to moderate affinity, uncompetitive NMDA-receptor antagonist, voltage-dependent, fast blocking/unblocking kinetics
  - Blocks the effects of abnormal glutamate activity that may lead to neuronal cell damage/loss and cognitive dysfunction
  - Preserves physiological activation of NMDA receptor required for learning and memory

# Feedback from Lyme Patients: Memantine (Namenda)

- “Without it I do less word inventions”
- “Better word retrieval when I speak”
- “Helps word finding problem”
- “It reduces the static, crackle in the head”
- “better verbal comprehension”
- “More focused”

# Recovery is a marathon with many twists and turns



# Conclusion

- Chronic infections and immune reactions contribute to causing mental illness.
- Diagnosing and treating Lyme/tick-borne diseases and other infections and immune reactions from them are new treatment opportunities for mental illness.
- Since interaction between infections, the immune and nervous systems can cause mental illness, greater interaction is needed between infectious disease physicians, immunologists and practicing psychiatrists to more effectively treat mental illness.



# Website

Mental Health and Illness .com

[www.mentalhealthandillness.com](http://www.mentalhealthandillness.com)