Evolution of Lyme Borreliosis Complex: Discoveries and Evaluation in Treatment

Revelations, Intuition and Roadblocks

ACADEMY OF NUTRITIONAL MEDICINE
NOVEMBER 18TH, 2018

Jemsek SPECIALTY CLINIC

Disclosure Statement

Dr. Joseph G. Jemsek and the Jemsek Specialty Clinic have no financial relationship or any commercial interests related to the content of this presentation.

Contents

Introduction

- Received M.D. from University of Illinois, 1974
- Novel for experience in HIV/AIDS and Lyme Borreliosis
- 23+ years background in HIV/AIDS Treatment and Research through 2006
- 17+ years in the Diagnosis and Treatment of Tick-Borne Illnesses
- Over 13,000 patients evaluated for Tick-borne illnesses

Jemsek Specialty Clinic, LLC.

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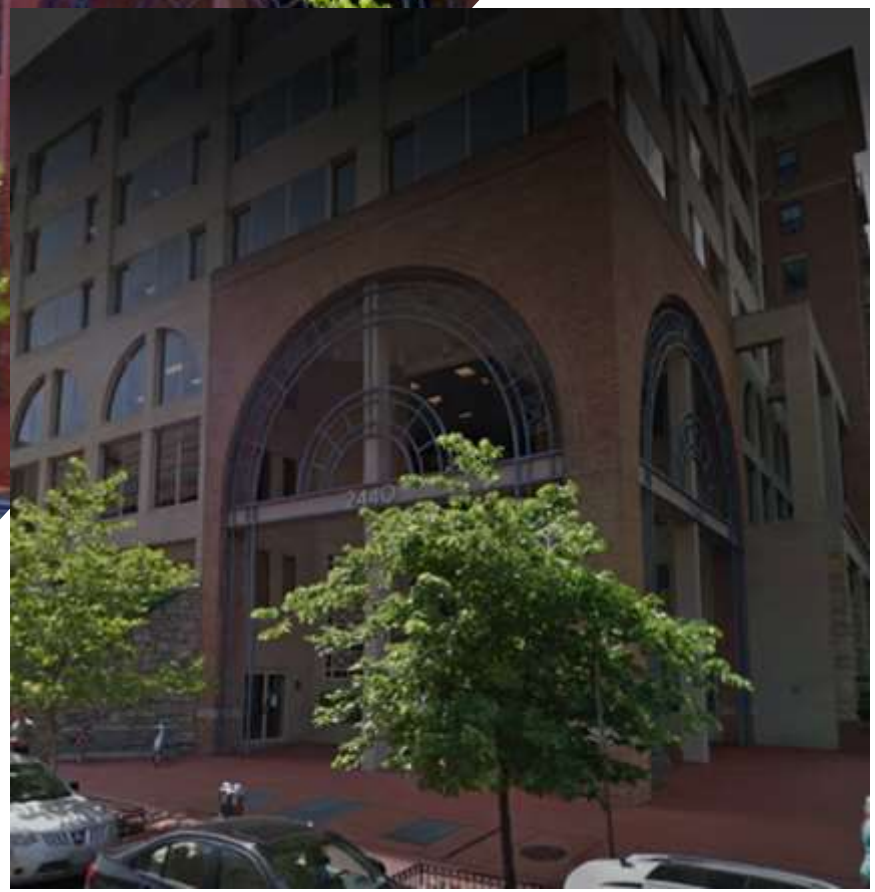
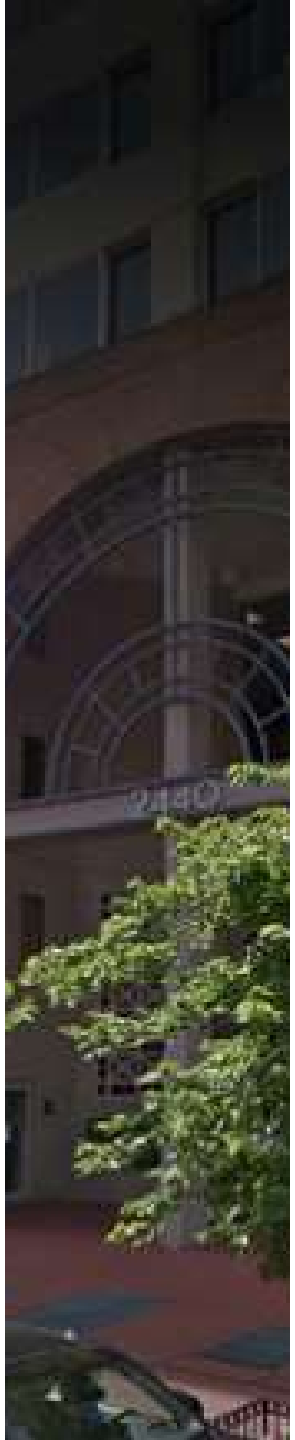


- D.C. clinic established in the year 2009
- Treated/treating patients from every state in the U.S. and over 30 countries around the world
- Assists with travel and housing services for both domestic and international patients

Lyme Borreliosis Complex
JSC Definition

"Chronic, relapsing, or otherwise 'unexplained' encephalopathy, arthritic symptoms, and neuropathy generally associated with tick-borne infections, spearheaded by *Borrelia burgdorferi* in combination with co-infecting organisms."

-Joseph G. Jemsek MD, FACP (*2004*)



Lyme Borreliosis Complex

Chronic, Relapsing, and Otherwise "Unexplained"

I. ENCEPHALOPATHY – One or more of the following Symptoms:

- Inflammatory: as in headache
- Sleep disturbances
- Mood alterations
- Cognitive changes

II. ARTHRITIC and Periarticular Symptoms

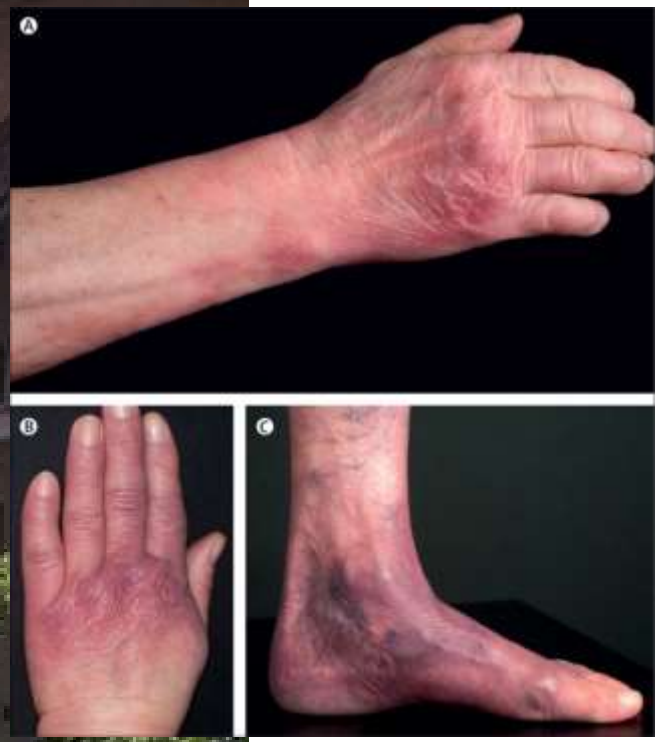
- Enthesopathy: inflammatory and non-inflammatory
- Generally migratory
- Overlap with several rheumatologic syndromes

III. POLYNEUROPATHY / MONONEURITIS MULTIPLEX

- Sensory (with fiber)
- Cord: myelitis and other syndromes
- Ganglionitis/Plexitis
- Motor neuron disease

Major Criteria

Lyme Borreliosis Complex



I. Atypical Rash or Flushing

-Erythema chronicum migrans (EM) compatible rash
-Acrodermatitis chronica atrophicans (ACA) compatible

II. Suggestive Nutrient or Cofactor Deficiencies

-Ferritin
-Vitamin D
-Hormonal Axis'

III. Supporting Serology, Tests, and/or Diagnostics

-Western Blot
-PCR Test
-ELISA – Enzyme linked immunosorbent assay
-Immunoblot

Minor Criteria and Diagnosis

Borrelia burgdorferi s.l.

Reports of *Borrelia sp*. in over

80

countries around the Globe

- The **Agent of Infection** – *Borrelia burgdorferi sensu lato (Bb)* – an extensive pathogenic subgroup of *Borrelia* species
- Transmitted through the bite of **hard-backed ticks** although research suggests there may be **other modes of transmission**
- Frequently **associated with and compounded** by one or more tick-borne pathogens (*Babesia, Bartonella,* etc.)

Global Phenomena

The United States of America	Canada	Netherlands	Spain
Austria	France	Sweden	Scotland
Belgium	Italy	Denmark	Brazil
Germany	Switzerland	Russia	Czech Republic
Ireland	Norway	Hungary	United Kingdom

Spirochetal Diderm: Gram Differentiation and Lipoprotein Dominance

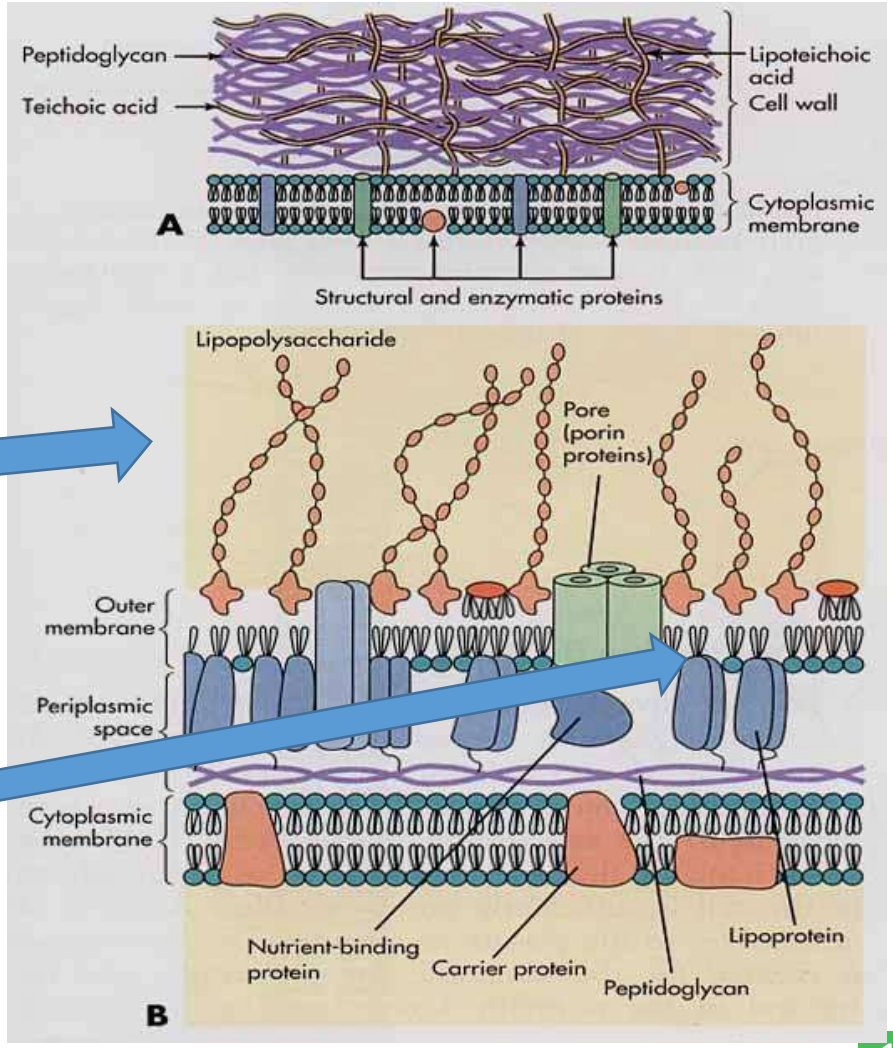
A: Gram positive cell wall with

teichoic acid (Polyribitol phosphate or glycerol phosphate) cross-linked with peptidoglycan

B: Gram negative cell wall with

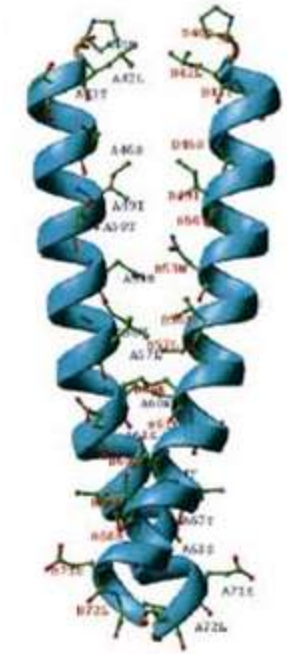
lipopolysaccharide which consists of Lipid A, core polysaccharide and antigen O. Note that Gram negative organisms have two cell membranes; cytoplasmic membrane and outer membrane.

In spirochetes lipoproteins are unique to the phyla as they make up much of the outer coat and periplasmic space



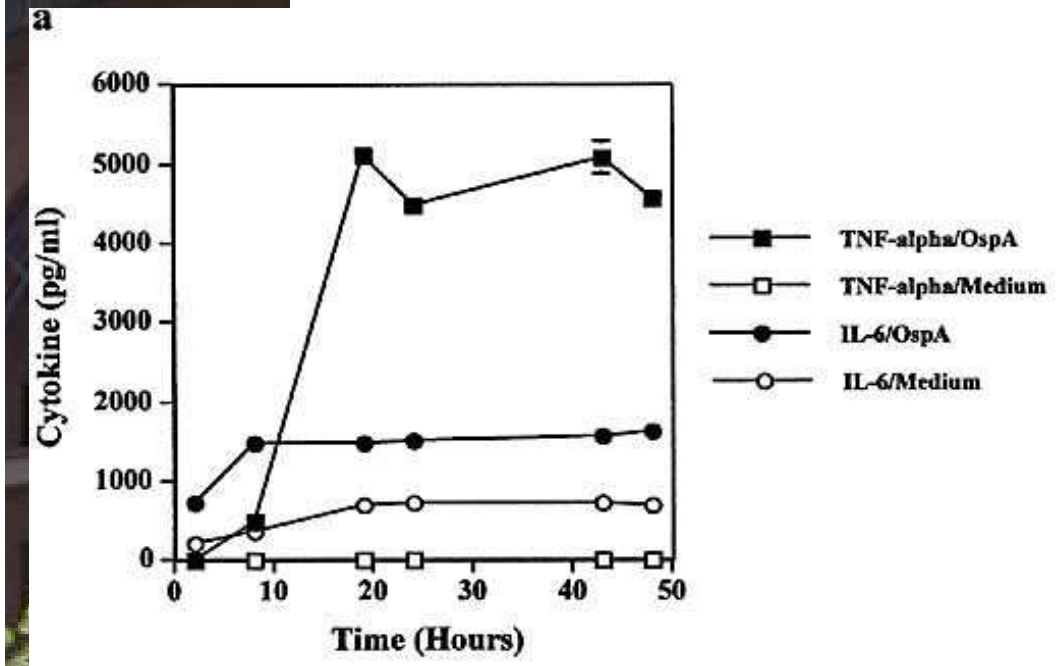
Lipoprotein Moiety

Borrelia burgdorferi lipoproteins are essential for pathogenesis.



- They are the **most abundant proteins expressed** by spirochetes
- Serve as major integral spirochetal **membrane proteins**.
- Induce **strong pro-inflammatory responses** in their hosts
- They generally **serve different functions in pathogenesis;** such as OspB and inhibition of neutrophil function and prevention of oxidative burst in tissues.
- **Bind CD14** on monocytes and macrophages (Mϕ) which **activates NF-κB pathway** which further induces pro-inflammatory responses. These activities are **mediated by TLRs**.

Lipoprotein Moiety



Borrelia burgdorferi lipoproteins are

50- to 500- fold

more active as cytokine inducers and B-cell mitogens than E. coli lipopolysaccharides (LPS)

- ↑ B-cell proliferation
- ↑ Cytokine production by MØ
- ↑ Nitric Oxide production by MØ

In astrocytes (Ramesh, 2003)

"As many as **150 open reading frames** potentially encoding lipoproteins have been identified in the genome of *B. burgdorferi*…**more than 50 times the average** of such genes in other gram-negative organisms…"

- Ramesh, 2003

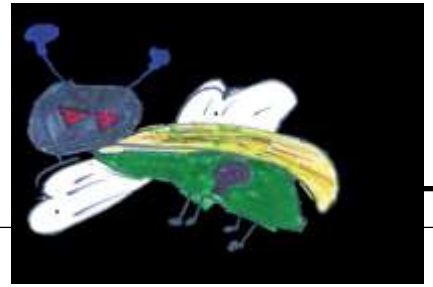
Herxheimer

Lipoprotein attaches to mammalian proteins, integrins, glycosaminoglycans, and glycoproteins to achieve tissue invasion and immune evasion.

Herxheimer reactivity

Reflects hyper-reactive immune response characteristic of lipoprotein exposure

Dr. Karl Herxheimer



Lipoprotein Reactivity

Dr. Karl Herxheimer
"The Dude"

Herxheimer reactions were first described by dermatologists **Adolf Jarisch** and **Karl Herxheimer** in the late 1800s, when they observed febrile reactions in the treatment of syphilis with mercury compounds

In the Bb infection, the **die-off** of spirochetal organisms caused by antimicrobial therapy can result in "**maniacal inflammation**" aka the '**Herxheimer' Reaction**... due to release of the lipoprotein factor and subsequent cytokine cascade

Metabolic Shift and Weight Change in Patients with Lyme Borreliosis

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A Pilot Investigation

Weight Change and Metabolic Shift

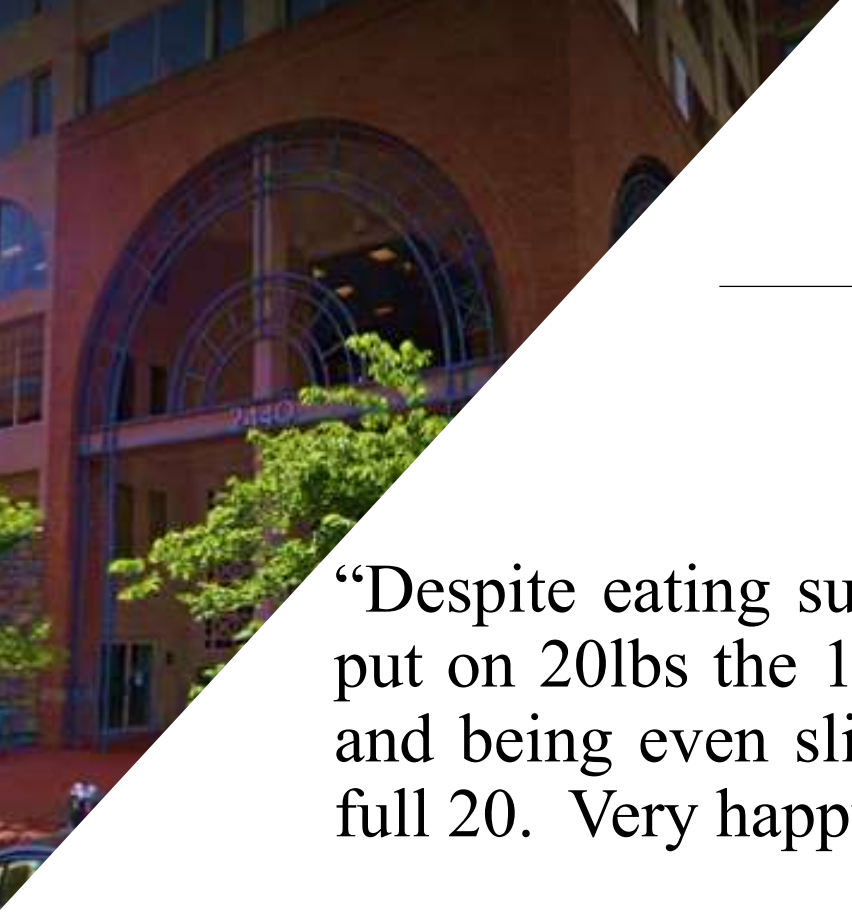
Premise

Chronic inflammation in disease contributes to uncontrolled weight change and metabolic fluctuations associated with adipocyte hypertrophy and adipogenesis.

Direct and Indirect effects on Gene Expression and Metabolic Pathways

Like obesity, Lyme Borreliosis patients exhibit variable grade inflammation with hormonal and/or nutritional fluctuations characterized by involuntary weight gain

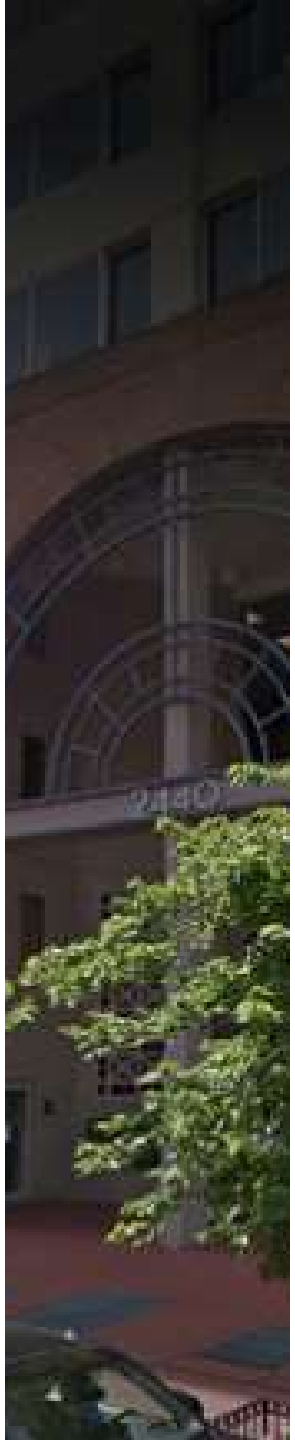
"B. burgdorferi-infected mice fed normal diet also gained weight at the same rate as uninfected mice fed high-fat diet…" (Zlotnikov et al., 2016)



A Pilot Observation

"Despite eating super clean (whole food plant based + gluten free ~1500) I put on 20lbs the 1 year prior to diagnosis and finally with start of treatment and being even slightly more diligent w/ diet, I was able to lose almost the full 20. Very happy my body seems to be finally responding."

-Patient

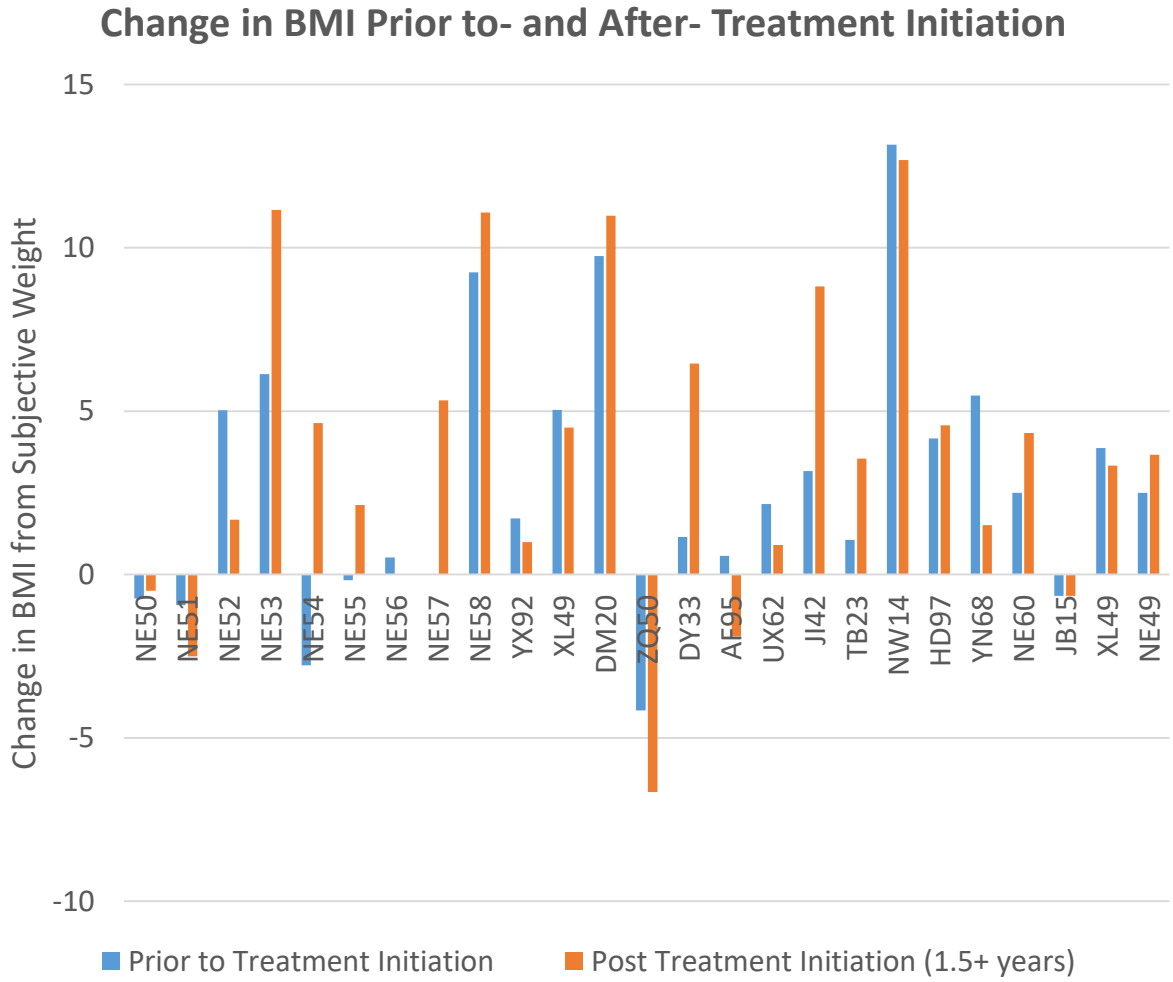


A Pilot Observation

Most **incoming patients** presenting with symptoms attributable to LBC complain of significant insidious weight gain.

Retrospective analysis on a sample of LBC patients indicate large fluctuations in weight change, typically weight gained.

Analysis focused on changes in Body Mass Index (BMI (kg/m^2)), social habits, diet, mobility, surgical intervention and weight loss programs.



Sample Size N=25

4% (1/25) used weight loss supplementation
Almost all followed “healthy” diet
79% of patients with abdominal deposition

52%

Reported a significant increase in BMI prior to treatment

28%

Of patients reported an increase in BMI >5 index points prior to treatment (Classification shift)

32%

Reported weight gain even after 1.5 years of treatment

On average, sampled patients have exhibited a

+12.7%

Increase in BMI prior to treatment

21.5 kg/m^2 → 24.2 kg/m^2

5’10 – 68.0kg → 5’10 – 76.5kg

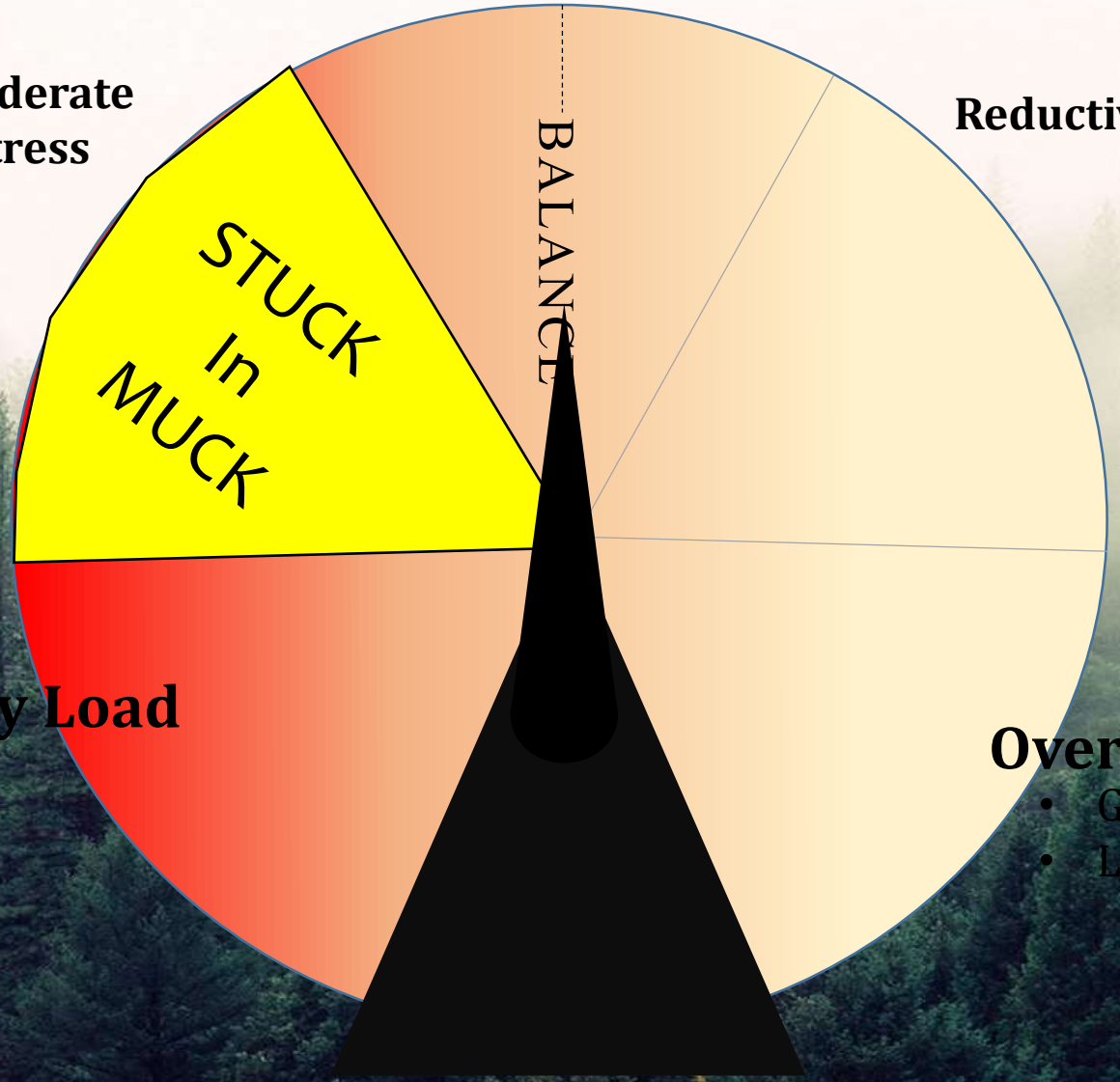
Equivalent of adding on: +8.5kg

Are Body Mass Index (bmi) Charts Effective Enough?, retrieved from https://healthy-tips-now.blogspot.com/2018/06/are-body-mass-index-bmi-charts.html

Homeostasis

Balance of Antioxidants and Oxidation

Mild to moderate oxidative stress



Reductive Stress

Severe Inflammatory Load

- Dysbiosis and leaky gut
- Nutrient Deprivation
- Inflammatory onslaught
- Catabolic State
- Weight and LBM loss

Over-methylation

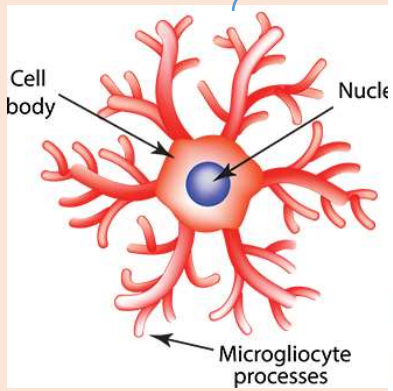
- Generally hypothetical situation
- Little-no inflammation

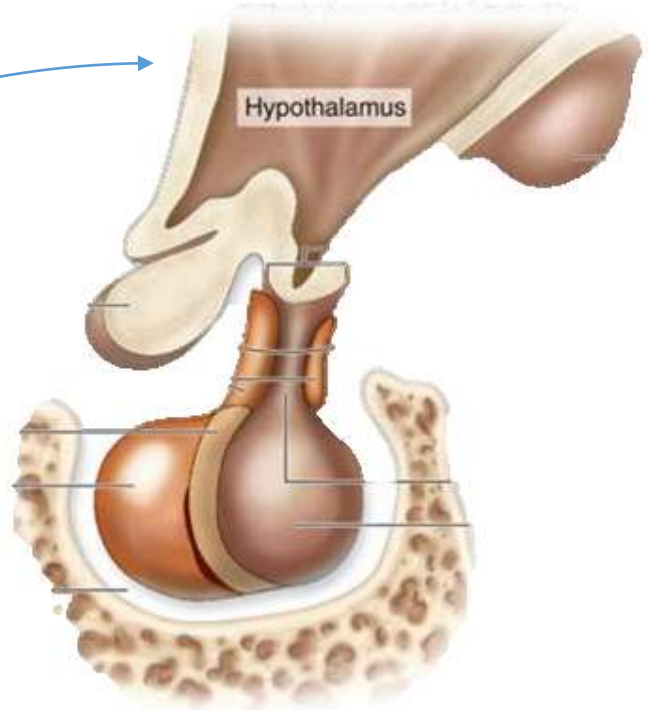
Proposed Inflammatory Mechanisms Contributing to Insidious Weight Gain

Proposed Inflammatory Mechanisms Contributing to Insidious Weight Gain

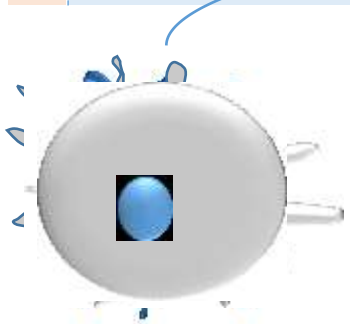
- Microgliosis in LBC – Findings in the CNS
- rophage Infiltration in Adipose Tissue
- amin D Deficiencies and Inflammation
- Leaky Gut Syndrome
- *H. Pylori* and Ghrelin

CNS and Peripheral Mechanisms in Lipogenesis





- Inflammatory cytokine release via TLR2 recognition of Bb associated lipoprotein (**50-500 fold more reactive than LPS**)
  - Modified gene expression
- **Oxidative radical** disruption of HPA-axis
- **Leptin**-potential resistance mechanisms.

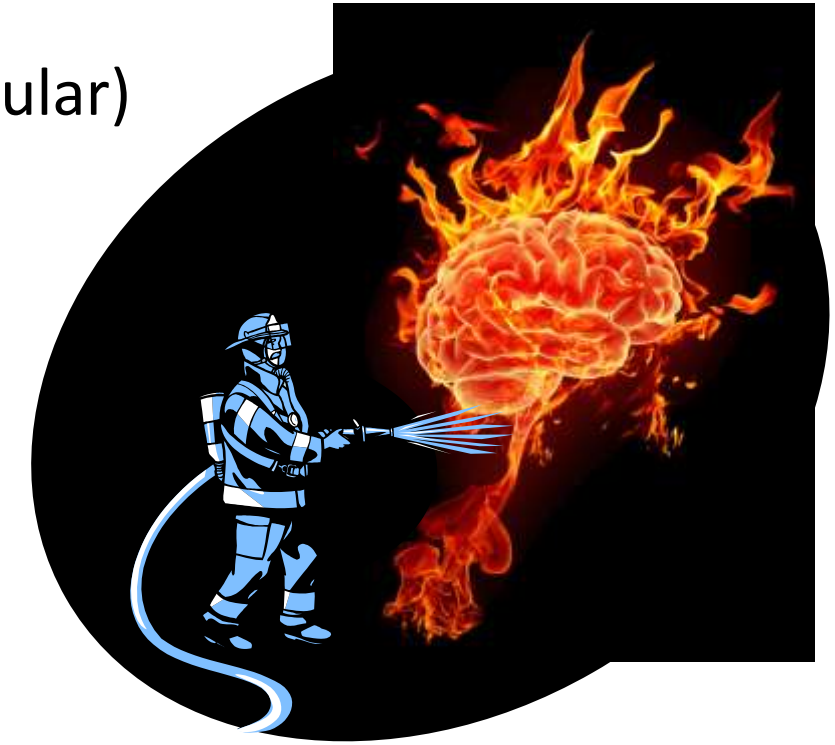


- Inflammatory cytokine release by resident macrophages leading to subsequent **inflammatory pathway activation in adipocytes**
  - Release of pro-inflammatory cytokines
  - **Adipocyte-mediated release of MCP-1** – Monocyte recruitment and differentiation – Macrophage infiltration
- Potential **insulin resistance** mechanisms

Central Nervous System:

Hypothalamus-Pituitary Axis (HPA)

- **Endocrine disorders are a common finding in LBC** patients, presumably due to high levels of infection/inflammation in HPA axis (highly vascular)

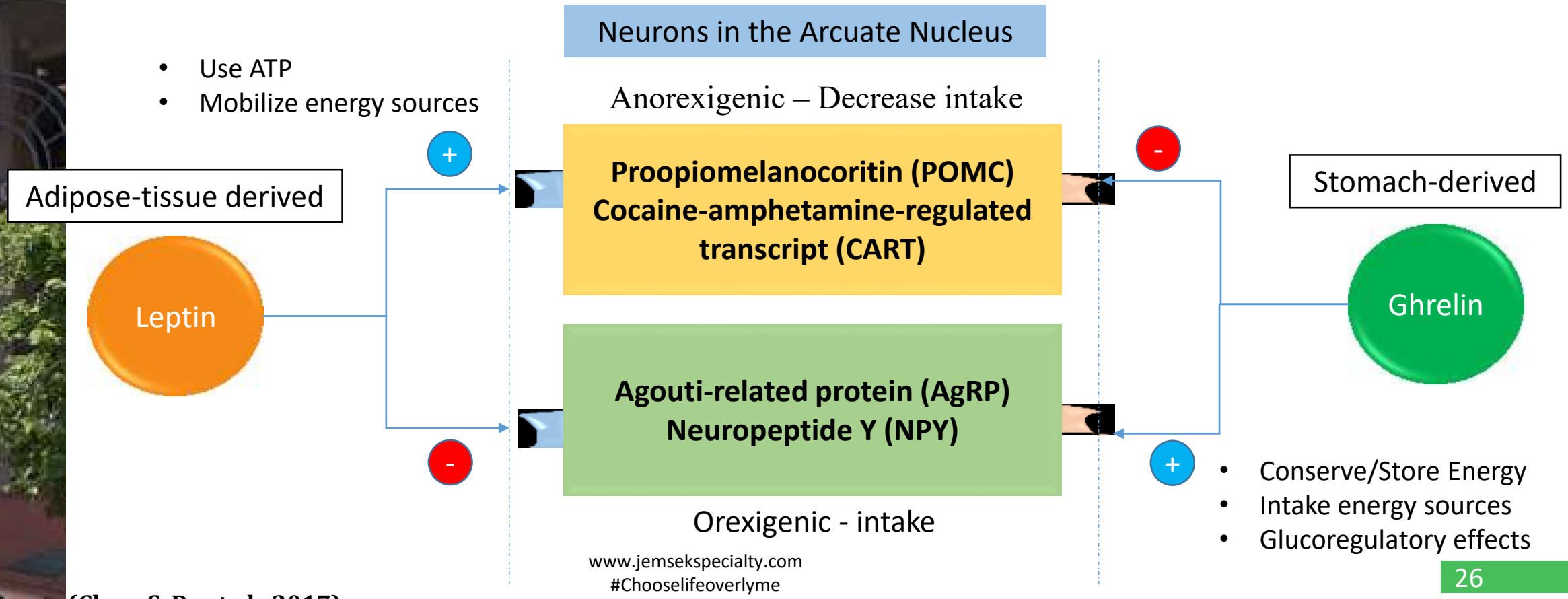


- Infection **may affect neuro-endocrine cells** by:
  - Direct lesion/inflammation
  - Oxidative stress
  - Feedback effect of chronic inflammatory state
  - Pain, Sleep disruption and psychological distress

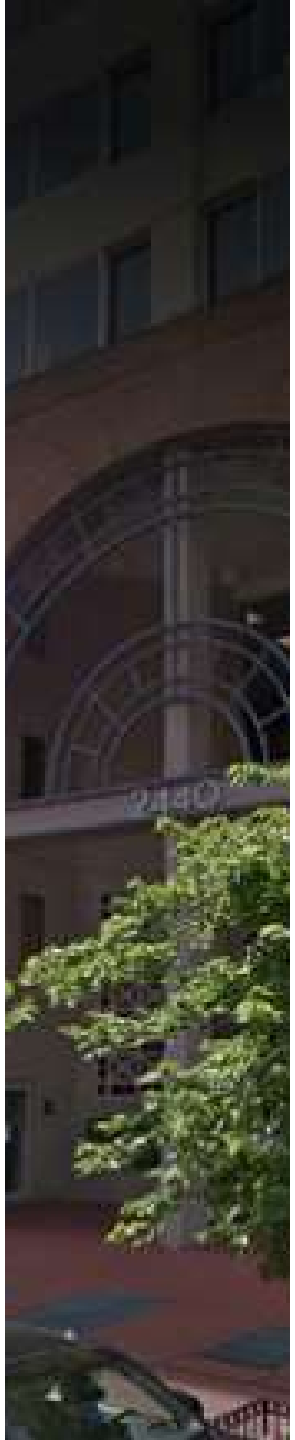
All resulting to elevation or suppression of hormonal secretion

Energy Regulation Hormones and their Receptors

There are two **major hormones responsible for energy regulation** which mainly act in the Hypothalamus: **Leptin** (the satiation hormone) and **Ghrelin** (the hunger hormone). These hormones act on neurons **in the hypothalamus** to elicit energy regulating responses.



(Chen, S. R., et al., 2017)

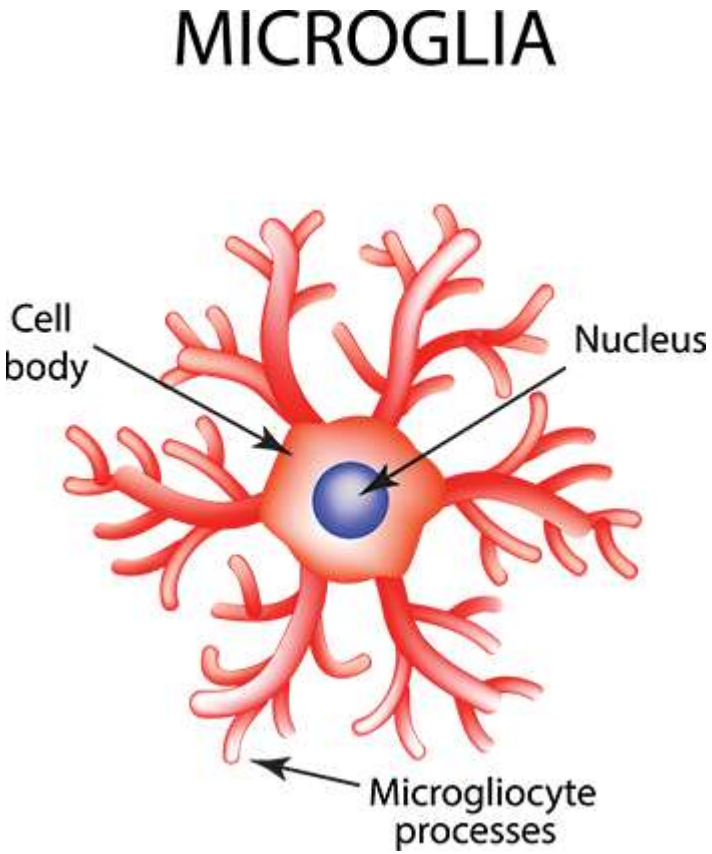


Microglia and CNS-Hypothalamus

Microglia are mononuclear phagocytes acting as macrophage of the central nervous system.

During high fat diets, the **hypothalamus recruits microglia**. It is believed that the microglia (under high fat environments) **recruits marrow-based 'backup' cells** into the brain.

Research found that inflammation of cells in the brain, as would occur in LBC, caused **weight-gain even on low-fat diets**. Removal of these microglia cells in murine hosts reduced weight gain even on high-fat diets.



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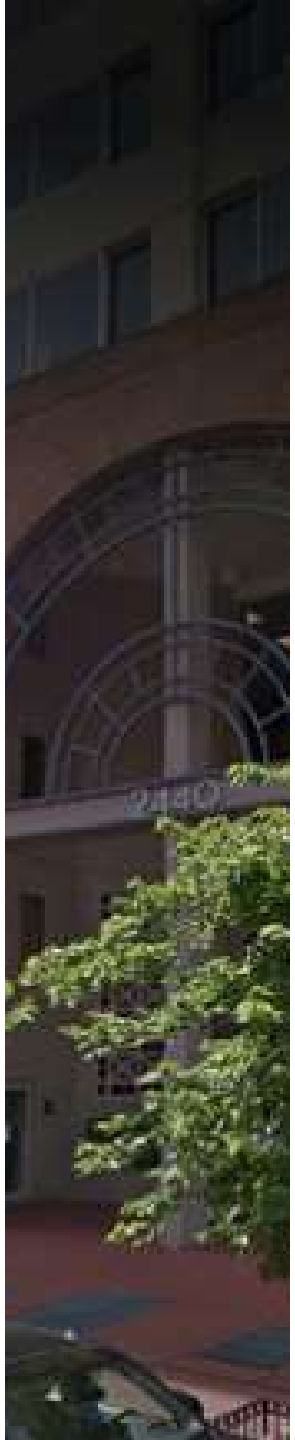


Microglia Function in the CNS

Microglia are the "brain's resident macrophages with intrinsic capability to respond to CNS damage, promoting repair and a correct brain function." (**Plaza-Zabala et al., 2017**)

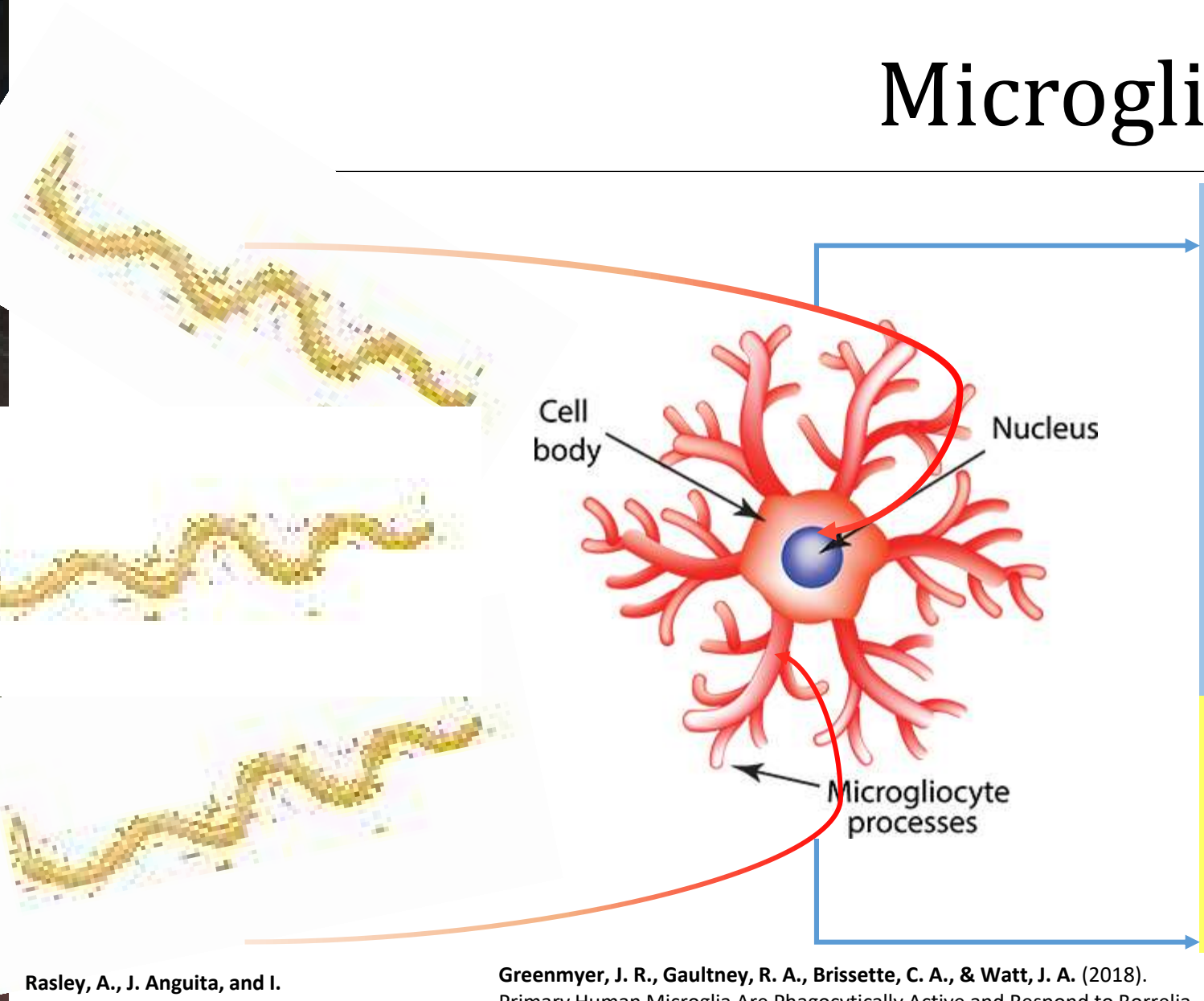
Microglia are responsible for:

- **Orchestrating the brain's inflammatory response** via the regulation of inflammatory mediators and response system to CNS damage.
- **Phagocytosing debris in the CNS** such as amyloid-β, apoptotic cells, myelin and axonal fragments, synaptic material and pathogens.

Dys(regulation) of Microglia:

- Process contributed by **inefficient or reduced autophagic capability and subsequent downregulation of phagocytic and anti-inflammatory processes.**
- **May result in build-up of toxins in the CNS** such as amyloid-β, myelin fragments (results in increased myelin breakdown), and pathogen build-up.

Microgliosis in LBC



Rasley, A., J. Anguita, and I. Marriott. 2002. *Borrelia burgdorferi* induces inflammatory mediator production by murine microglia. J. Neuroimmunol. 130:22-31.

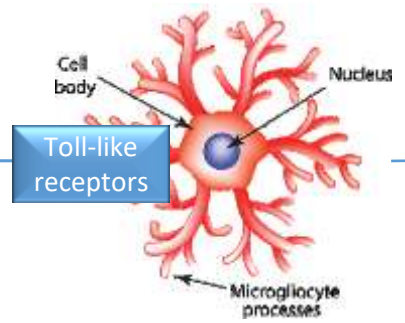
Greenmyer, J. R., Gaultney, R. A., Brissette, C. A., & Watt, J. A. (2018). Primary Human Microglia Are Phagocytically Active and Respond to Borrelia burgdorferi With Upregulation of Chemokines and Cytokines.. *Front Microbiol, 9*, 811. doi:10.3389/fmicb.2018.00811

Energy Regulating Properties:
Leptin Resistance in Obesity and LBC

Valdearcos et al., 2018

Diet [High Lipid Accumulation]

Borrelia burgdorferi



NF-κB signaling pathway activation

TNF-α

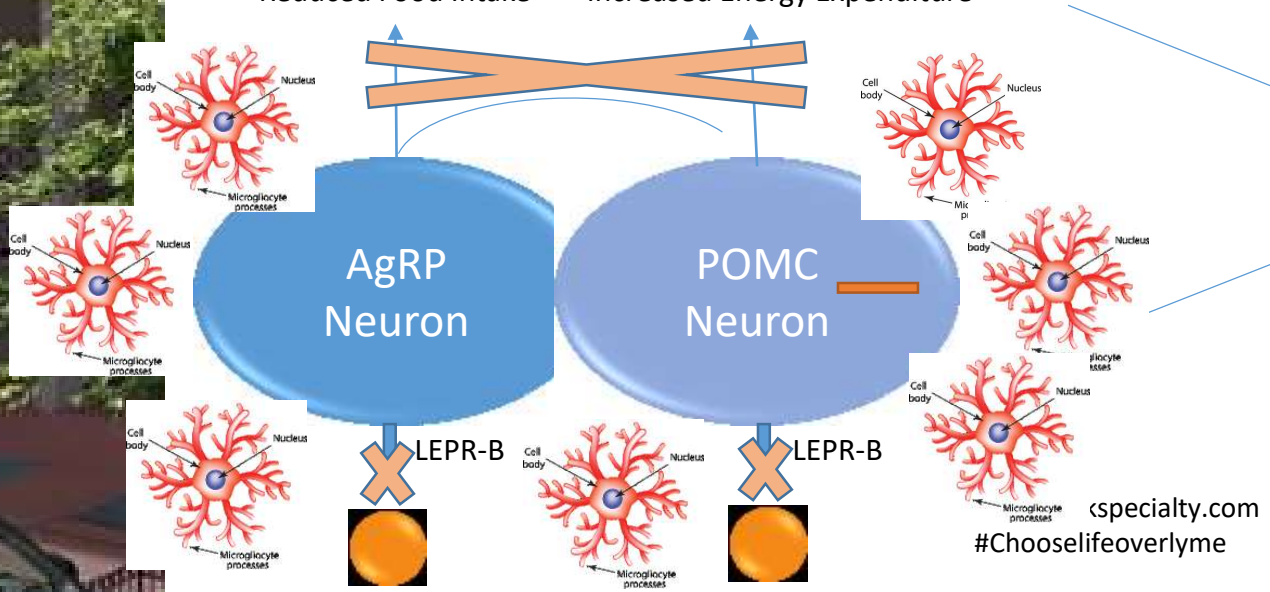
IL-6

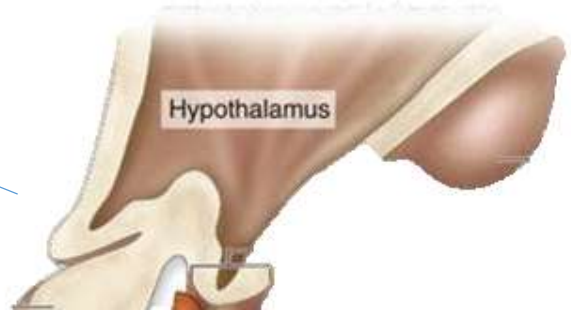
PGE_2

Chemotaxis

Rasley, Anguita & Marriott., 2002

Greenmyer, J. R., Gaultney, R. A., Brissette, C. A., & Watt, J. A. (2018).

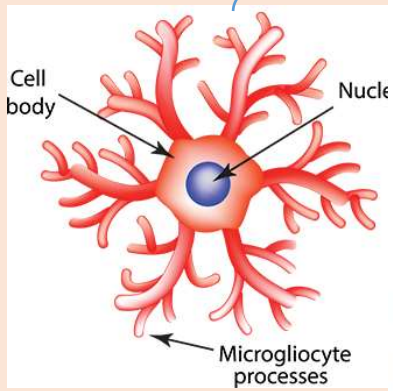


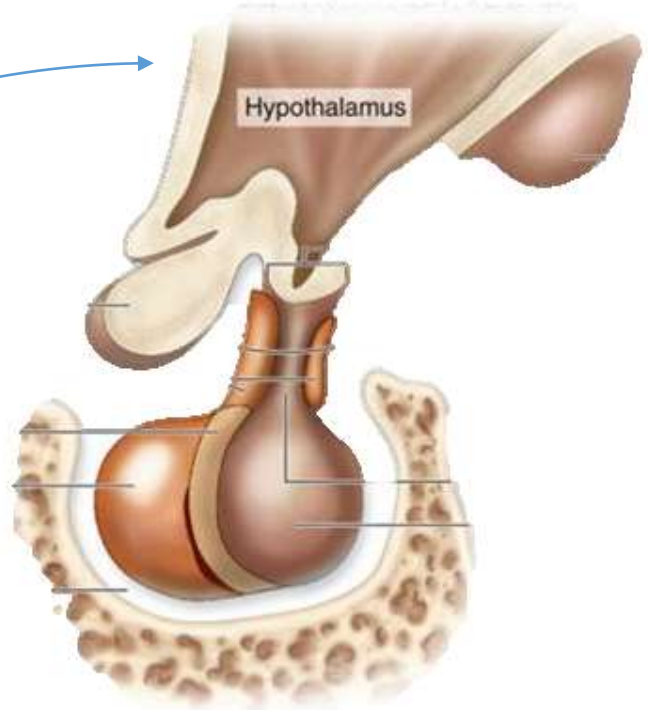


Activation of the NF-κB signaling is seen in both high fat diets and Borrelia invasion in microglia cells.

Microglia sense pro-inflammatory signals, migrate to the hypothalamus and "modulate neuronal responsiveness to leptin". (via Oxidative Stress?) In mice, this microglia influence **reduced leptin sensitivity and reduced whole body energy expenditure** associated with a reduction of proteins involved in thermogenic processes.

CNS and Peripheral Mechanisms in Lipogenesis





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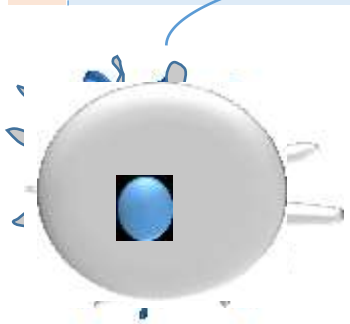

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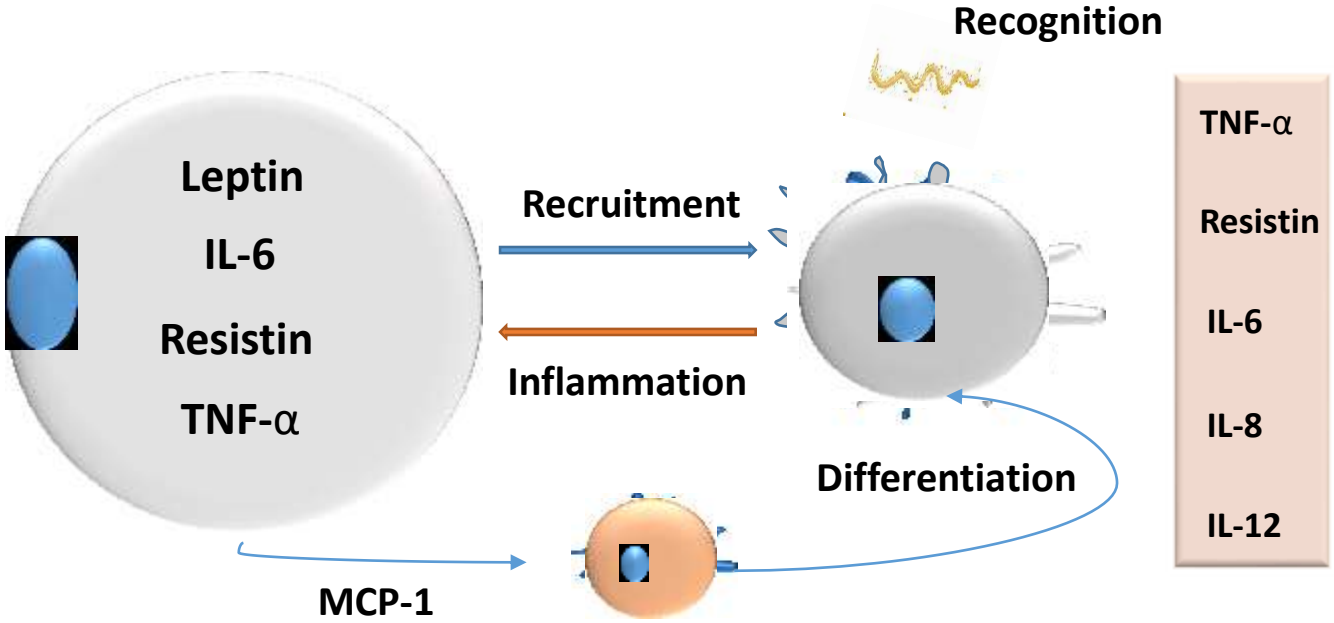
In the Periphery:

Macrophage in Periphery - Adipose Tissue

Adipose tissue is a major immunologically active organ that contributes to inflammation through the secretion of cytokines and chemokines, as well as adipokines.



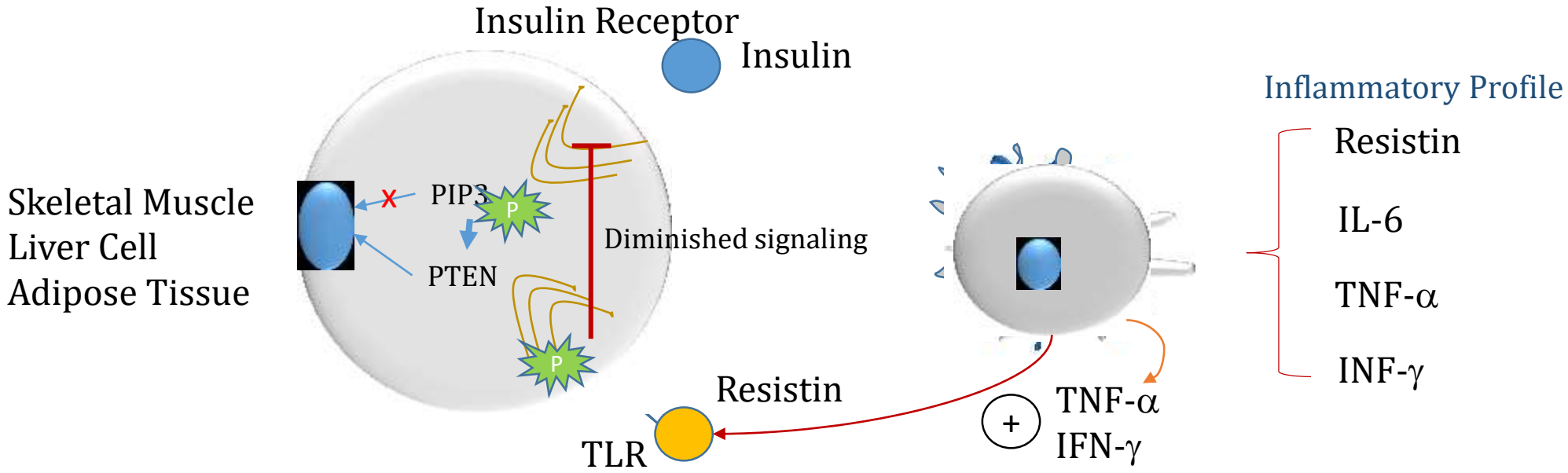
Macrophages (resident and peripheral) infiltrate adipose tissue in response to inflammatory signals sent by resident immune cells and adipocytes.

Once engaged in the adipose tissue, macrophages will **release numerous inflammatory cytokines such as TNF-α** and a chemical known as **Resistin.**

Resistin is found elevated in serum of those with type II diabetes mellitus and obesity

Peripheral Insulin Resistance in Inflammatory Processes

The molecule **Resistin** is often described as a proponent of adipocytes. But in humans, **Resistin** is mainly expressed in monocytes/macrophages (Savage *et al.*, 2001).



The potential for resistin in LBC pathogenesis models may warrant exploration as this molecule is **often described in cases of atherosclerosis** whereby macrophages engulf ox-LDL molecules to form foam cells and subsequently plaques in blood vessels.

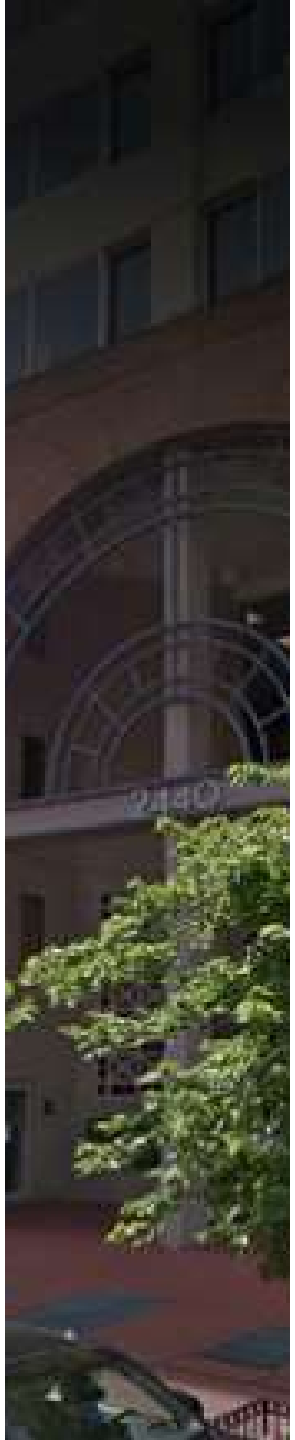
Insulin Resistance and Weight Gain

Insulin resistance is denoted by the decreased insulin signal transduction by receptors resulting in decreased sensitivity to insulin.

Decreasing insulin sensitivity in White Adipose Tissue, Liver and Skeletal Muscle:

1. Decreases glucose uptake
   - Elevated circulating glucose
2. Decreases β-oxidation processes and gene expression
3. Retains pancreatic production of insulin (build-up)
4. Decreases cellular energy expenditure

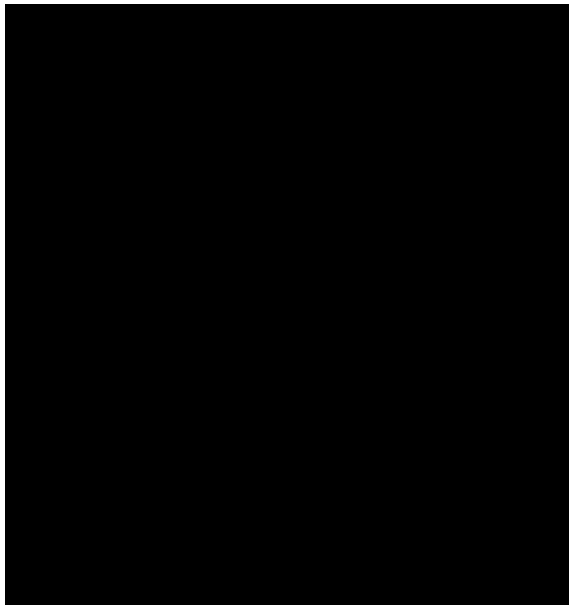
Reduction of insulin-mediated glucose uptake, and other elements such as Vitamin D availability, downregulate β-oxidation gene expression. **Thus, making it harder for individuals to lose weight.**



Vitamin D Deficiency

Vitamin D is **pro-hormone** and mediator involved in numerous processes including calcium homeostasis, immune functioning, energy metabolism and cellular proliferation. Studies suggest that **Vitamin D deficiency is linked to obesity**.

- Vitamin D and PTH interactions (*Preferential*)
  - Osteoclastogenesis
  - Calcium Homeostasis – Nerve Conduction
  - Feedback loop
- Vitamin D Receptor and Gene Expression
  - Immuno-modulatory functions
  - Essential cellular processes
  - Adipogenic gene expression
- Adrenal Dysfunction – Tyrosine Hydroxylase
  - Decreased production of energy mobilizing hormones (Norepinephrine/Epinephrine)

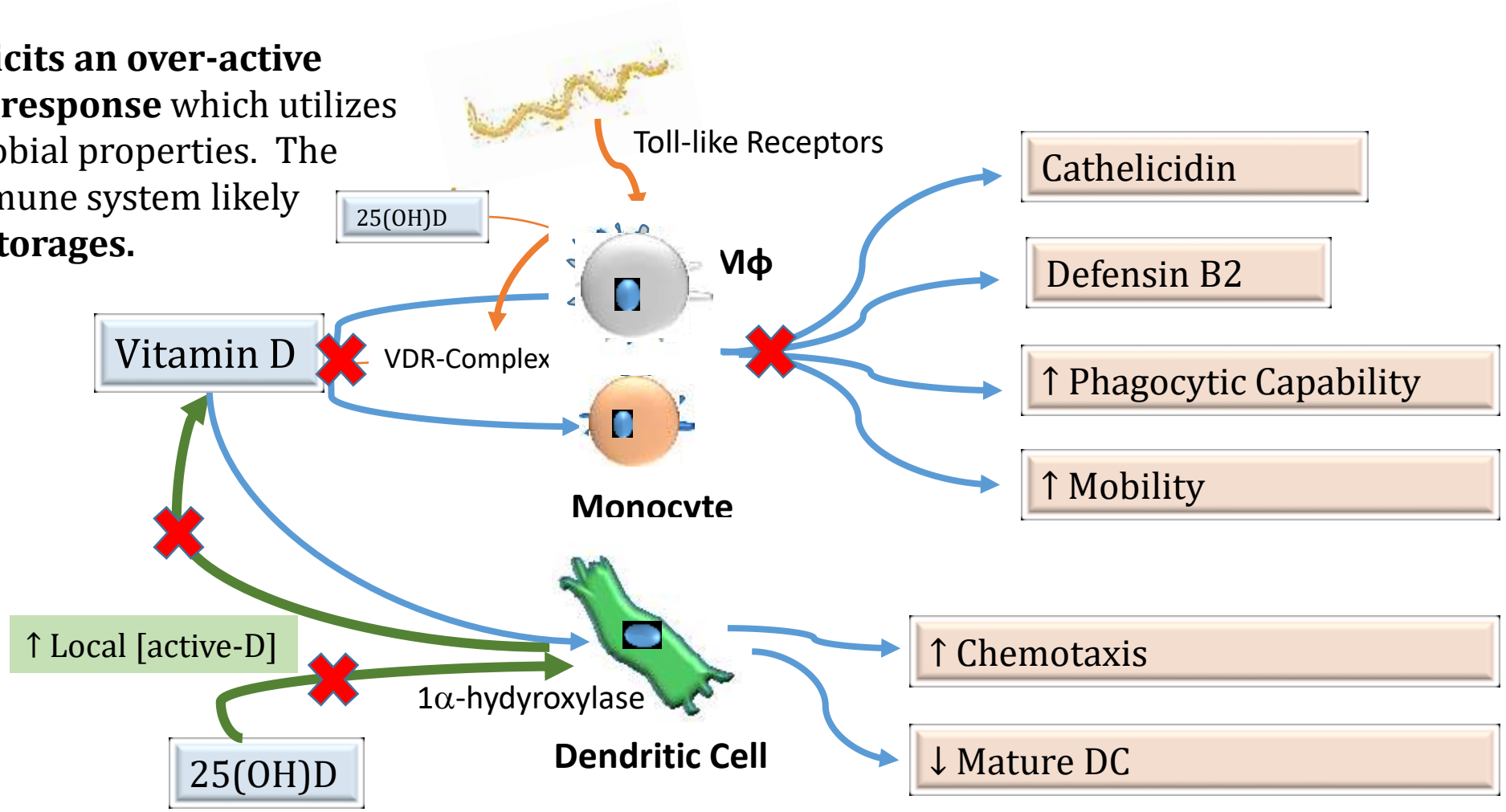


Borrelia and Vitamin D Deficiency:
Vitamin D in Innate Immune Processes

The pathogenesis of **LBC elicits an over-active 'ramping' innate immune response** which utilizes Vitamin D to elicit antimicrobial properties. The constantly active innate immune system likely **depletes local vitamin D storages.**

Local depletion is not remediated from mobilization of storages, as there are preferential uses which are more important for regulation processes.

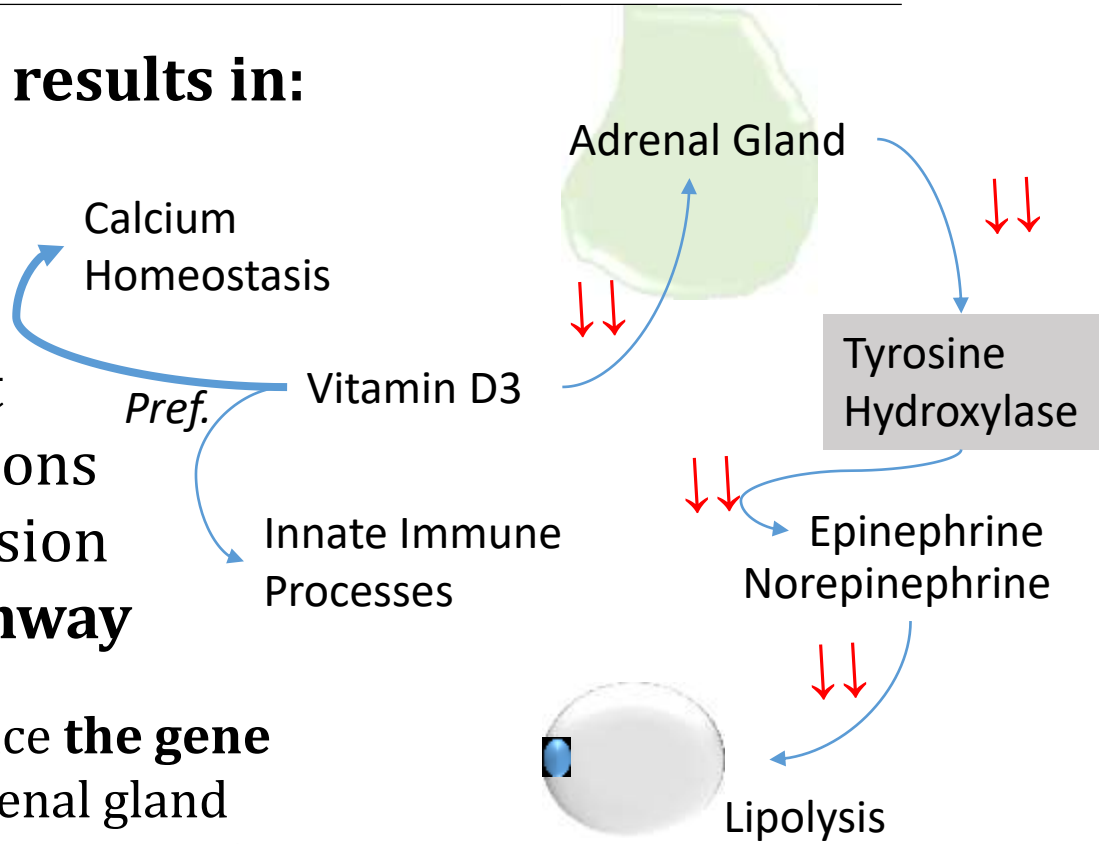
Vitamin D deficiency is linked to obesity



Vitamin D Deficiency in Adipose Tissue

Vitamin D deficiency in adipose tissue results in:

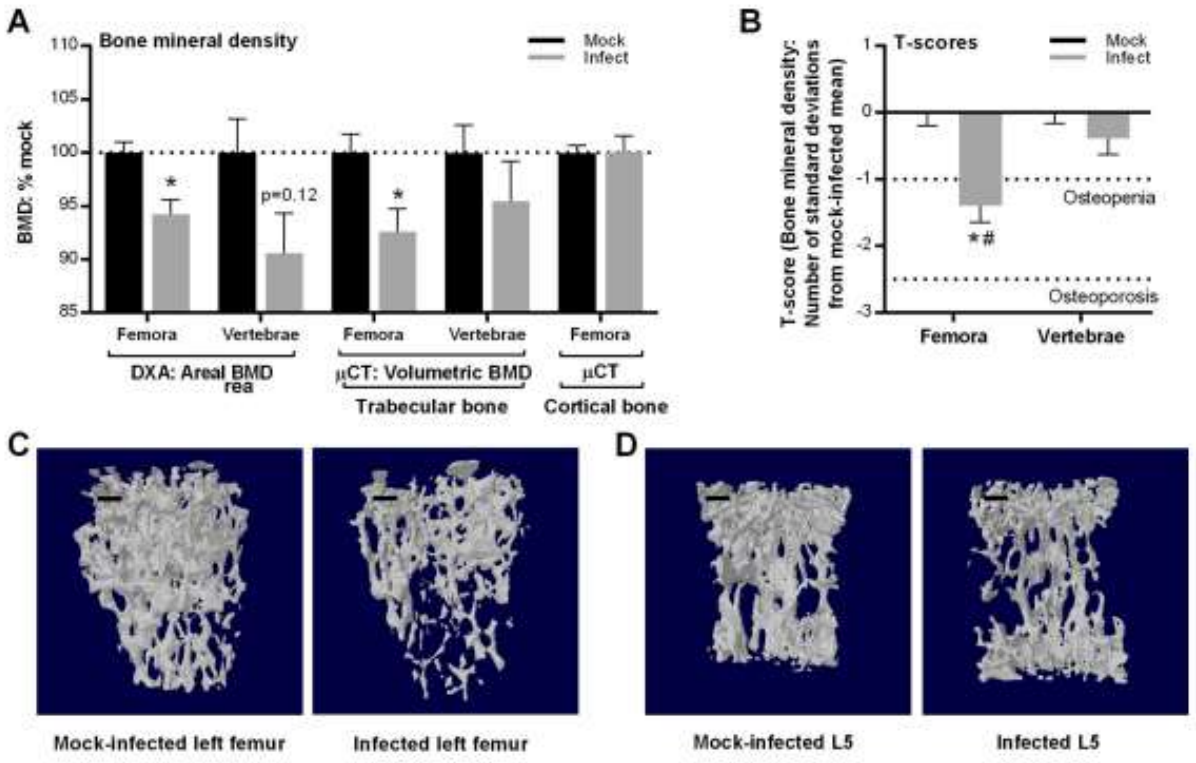
1)Inhibited lipolysis
2)Induced lipogenesis
3)Increased macrophage recruitment
4)Increased IL-6 + TNF-α concentrations
5)Decreased β-oxidation gene expression
6)Uninhibited NF-κB signaling pathway



Additionally, reduced active vitamin D may reduce **the gene expression of tyrosine hydroxylase** in the adrenal gland which is an enzyme responsible for producing L-DOPA and subsequently norepinephrine and epinephrine which mobilize glycogen in adipose tissue.

A Potential Role of Vitamin D:

Borrelia-induced Trabecular Bone Loss



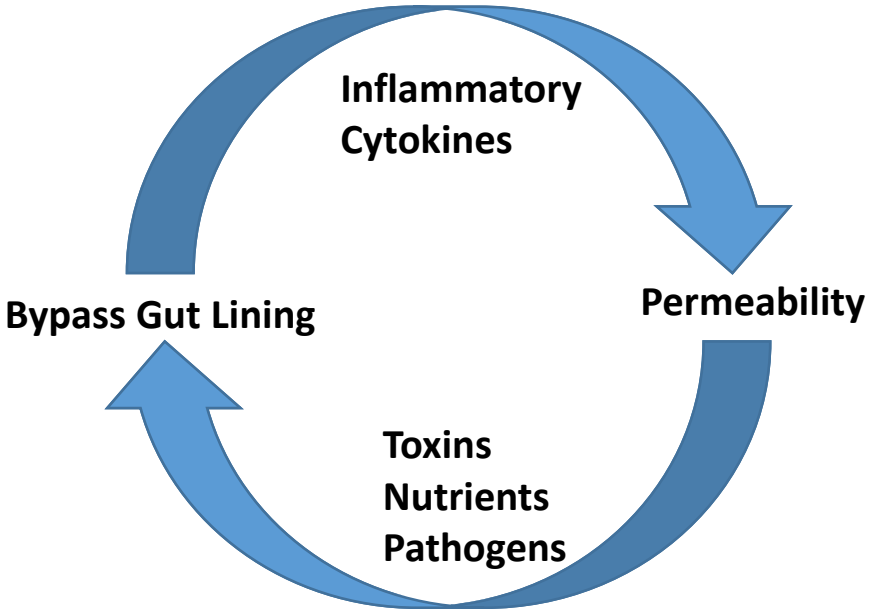
Tang, Tian Tian, et al. "The Lyme Disease Pathogen Borrelia Burgdorferi Infects Murine Bone and Induces Trabecular Bone Loss." *Infection and Immunity*, vol. 85, no. 2, 2016, doi:10.1128/iai.00781-16.

For reasons to be explained, *Borrelia burgdorferi* has been associated with significant, long-lasting contributions to trabecular bone loss **via reduction of osteoblast numbers.**

It is **unknown** if *B. burgdorferi* infection affects **mesenchymal stem cell differentiation or other growth factors or hormones**, such as parathyroid hormone, to reduce these populations.

Leaky Gut Syndrome

Leaky Gut, or increased intestinal permeability, is a Medically Unrecognized Term that often accompanies Lyme Borreliosis Complex



- Often a proponent contributing to inflammation and infiltration of inflammatory molecules such as gluten **– gluten intolerance exacerbated by histamine excess.**
- Increased inflammatory load (by nutrition or disease) contributes to **the redistribution or separation of tight junction (TJ) proteins.**
  - **Tumor Necrosis Factor – alpha (TNF-α)**
  - **Interferon – gamma (IFN-γ)**
- **Increased intestinal permeability** deprives the body of essential nutrients, normally metabolized by indigenous microflora.

Inflammatory Molecule Contributions to Intestinal Permeability

Increased exposure and elevation of inflammatory molecules in the gut are primary components which contribute to epithelial damage and tight junction permeability

- **IFN-γ increases permeability** through the **redistribution and internalization of tight junction proteins** in intestinal epithelial cells.
- **TNF-α modulates and upregulates expression of MLCK** (Myosin Light Chain Kinases) which pulls actin stress fibers attached to cadherin proteins **causing gaps in the junction**
- **NOD2 gene mutation (Crohn's)**

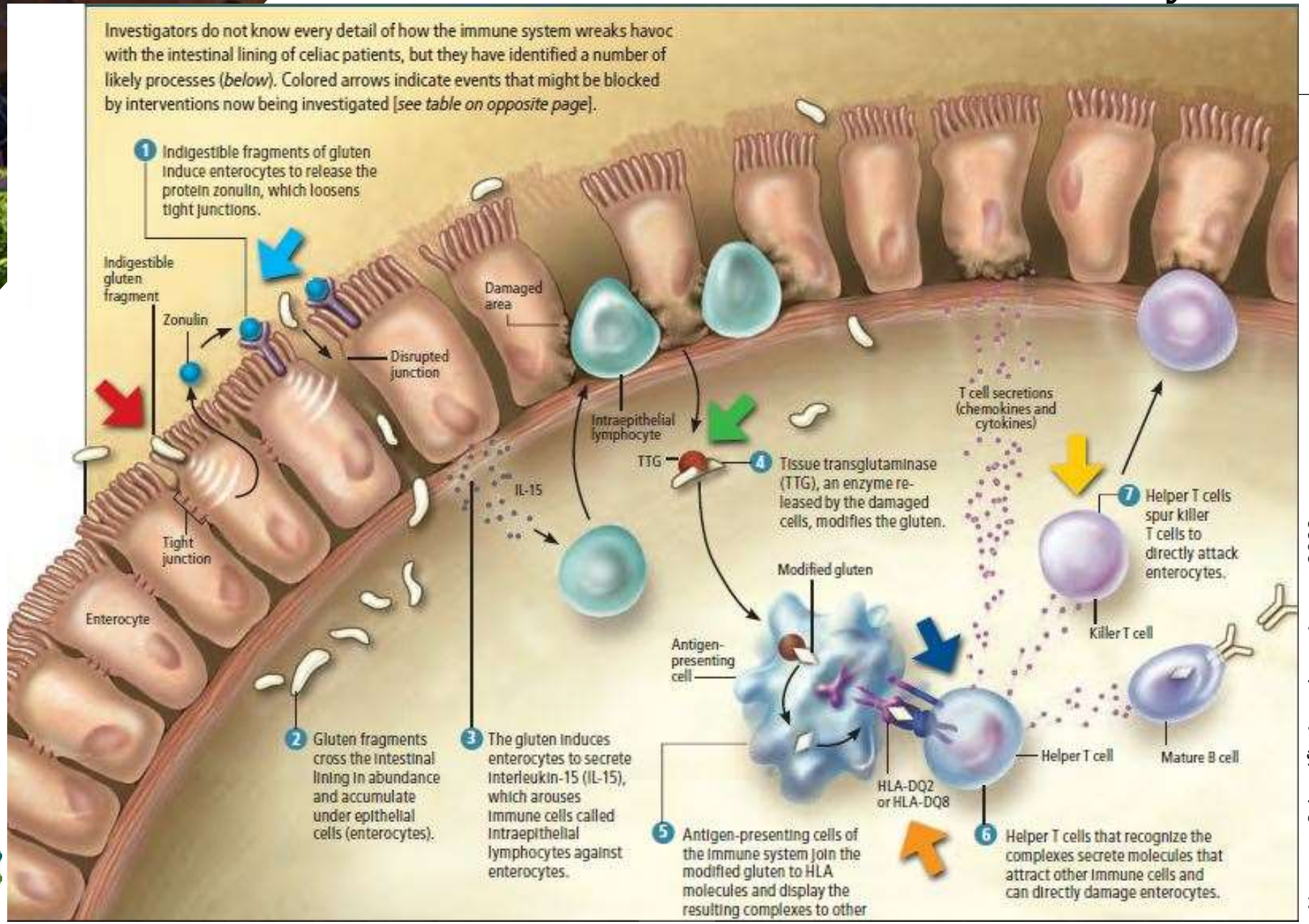
REVIEW

INTESTINAL RESEARCH

Intestinal Permeability Regulation by Tight Junction: Implication on Inflammatory Bowel Diseases

Sung Hee Lee

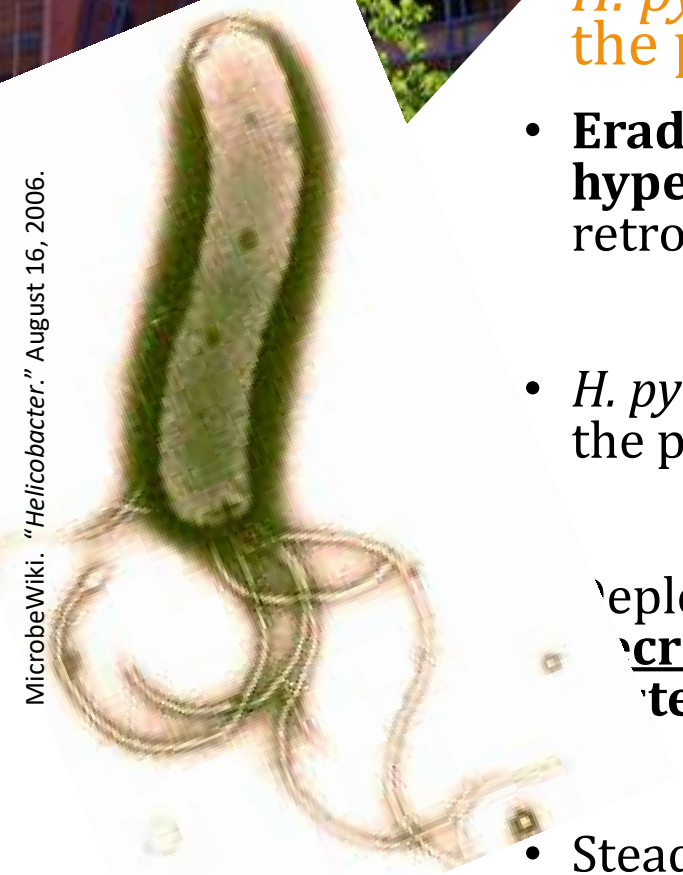
Sensitivity to Gluten and other Food Products in a Leaky Gut



Nature – Scientific American. August 2009.

Jemsek SPECIALTY CLINIC

Helicobacter and Ghrelin



MicrobeWiki. *"Helicobacter."* August 16, 2006.

H. pylori is a constituent of the indigenous microflora in around 50% of the population (Hooi, J. K. Y. et al., 2017)

- **Eradication** of *H. pylori* has been recently linked to **increases in body mass and hyperlipidemia** (Lane et al., 2011), although even more recently contested in retrospective analysis (Xu et al., 2018).

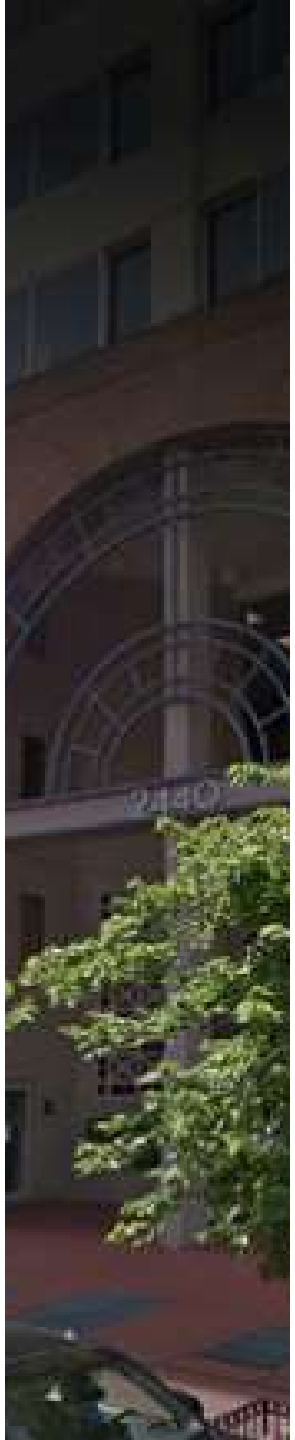
- *H. pylori* produces the enzyme urease which neutralizes the stomach's acid through the production of ammonia (potential contribution to **Hyperammonemia**)

epletion of *H. pylori* has been associated with <u>increases in gastric ghrelin and creases in plasma ghrelin concentration</u>. *H. pylori* likely **acts as buffer tem for ghrelin.** (Osawa, H., 2008)

- Falling plasma ghrelin is inversely correlated with BMI -

- Steady declines in ghrelin production are associated with **increased leptin release** and action in the HPA axis.

Innovations in Treatment and Roadblocks to Success



Requisite Skills for Managing Lyme Borreliosis Complex

Modern physicians must learn to integrate multiple skills:

- **Profound** Understanding of the role of the Physician and the Patient
- **Pain management:** Understanding and managing neurological and rheumatological symptoms
- **Pharmaceutical medicine**: kinetics, drug distribution, routes of administration, drug-drug interactions, synergism, combination therapies to limit microbial resistance, pulsing therapies, etc.
- **Nutrition**: Understanding the benefits of supplements and incorporating them in the healing process while recognizing their adverse effects
- **Barriers:** Identification of profound factors that may impact or are impacting treatment processes and disease progression and presentation

Requisite Skills for Managing Lyme Borreliosis Complex

- Neuroendocrine issues: prioritize adrenal issues, common confounding role of DI in sleep disorders
- Seizure management
- Vascular Health
- Sleep medicine
- Psychiatric management
- Gut health
- Mastering the concept of oxidative stress
- Understanding the paradigm of chronic stealth pathogen infections as relates to drug Rx bioavailability

Steps in Diagnosis and Treatment of LBC

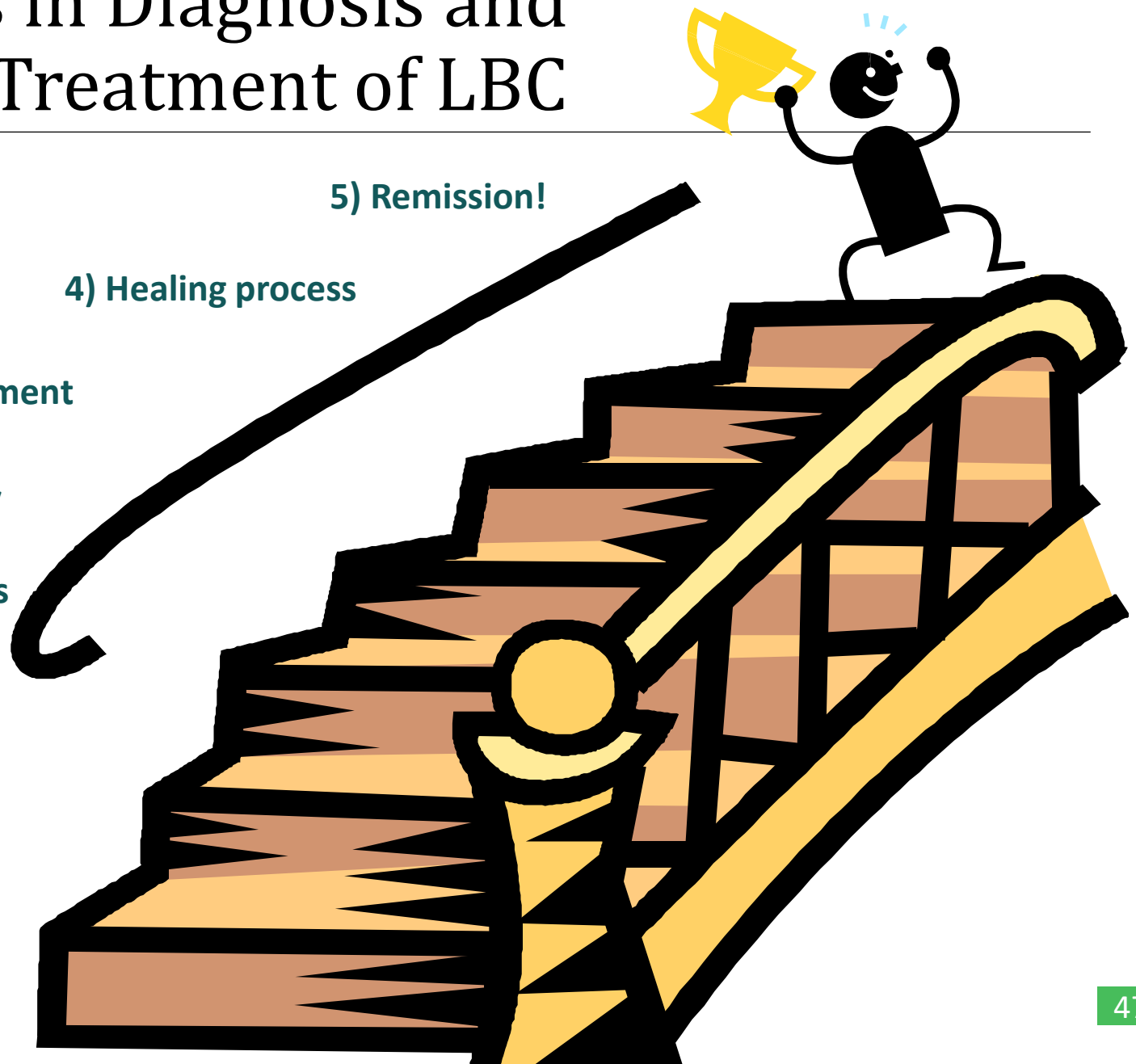
5) Remission!

4) Healing process

3) Treatment

2) Stabilization of faulty essential life functions and reversal of stressors

1) Evaluation, interpretation, and prioritization of major pathological processes based on clinical and laboratory evaluations



Jemsek SPECIALTY CLINIC

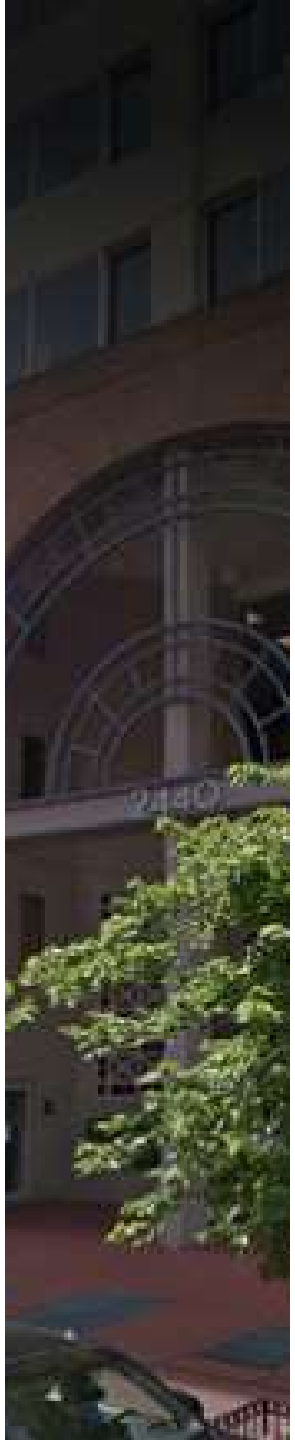
Meaningful Acronyms: ELF

ELF

Essential

Life

Functions



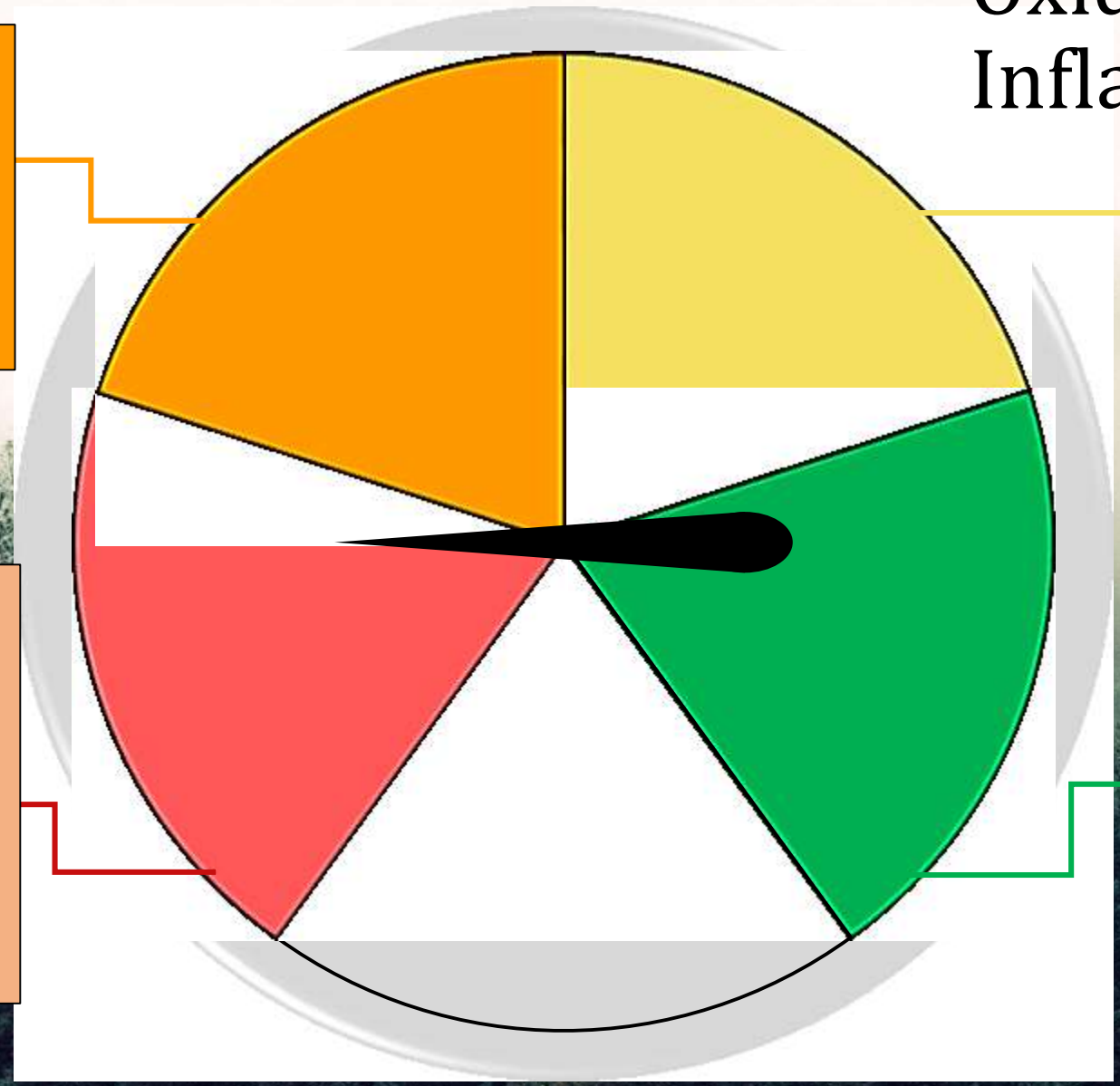
Meaningful Acronyms: POEMS

P	→	Pain
O	→	Others: Social Support
E	→	Endocrine/Metabolic
M	→	Mood/Psychiatric
S	→	Sleep

Image from wikihow.com. Accessed September 12, 2018. https://www.wikihow.com/Enjoy-Poetry

Oxidative Stress and Inflammatory Load

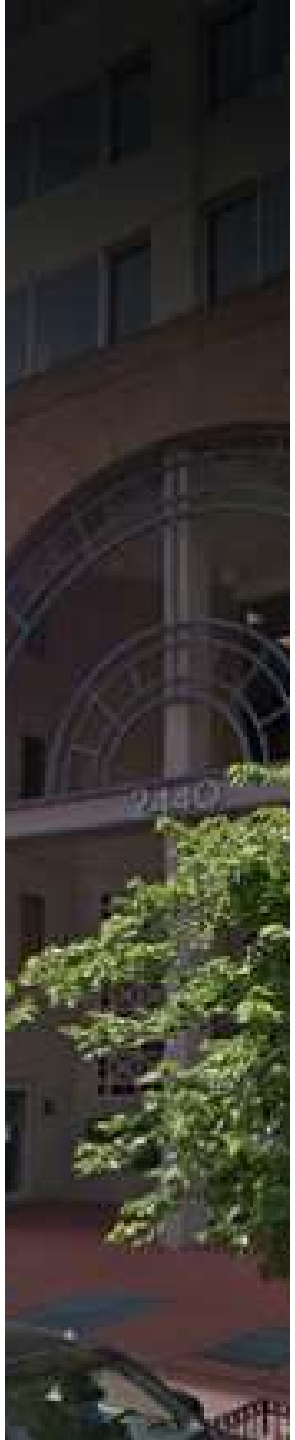
- ↑ Cellular Plasticity
- ↑↑ Cytokines
- ↑ **Reactive Species**
- Cellular **Debris**
- Reaching Energy Exhaustion
- Nutritional Usage



- Low Inflammatory Load
- Pathway **Shunts**
- **Energy Push** (Immune Cell Proliferation)
- Mitochondrial Ramping
- **Adipogenesis**

- Max Capacity – **Exhaustive** State
- **Herxheimer** Rxn
- Nutrient Deprivation
- **Energy Deficient**
- Cellular Degradation and Debris
- ROS-activated Pathways (apoptosis)

- Homeostatic
- **Negligible** Inflammatory Load
- Normal Pathways
- Normal Cell turnover



Understanding [P]OEMS

Characteristics and Supporting Therapies for Pain

Characteristics	*Support*
Neurogenic/Nociceptive/CRPS	Neurotrophic Medication Combinations & Analgesics
Musculoskeletal [N]	Nutraceuticals
Headache [N&N]	Physical Therapy
Impact of Fatigue [All]	Transcutaneous Nerve Electrical Stimulation (TCNS)
Positional, Body habitus, Occupational [All]	A Trial of Acupuncture
Often Multifactorial	Neurocognitive Feedback

Understanding P[O]EMS

POEMS: Other Considerations

- Persisting co-morbid conditions
  - Proper management of other existing medical conditions co-morbid conditions
- Encouragement and support outside of clinical setting
  - Family and social support
- Stabilizing Conditions to follow:
  - Subacute Acalculous Cholecystitis
  - Cyclical vomiting syndrome
  - *More to follow*

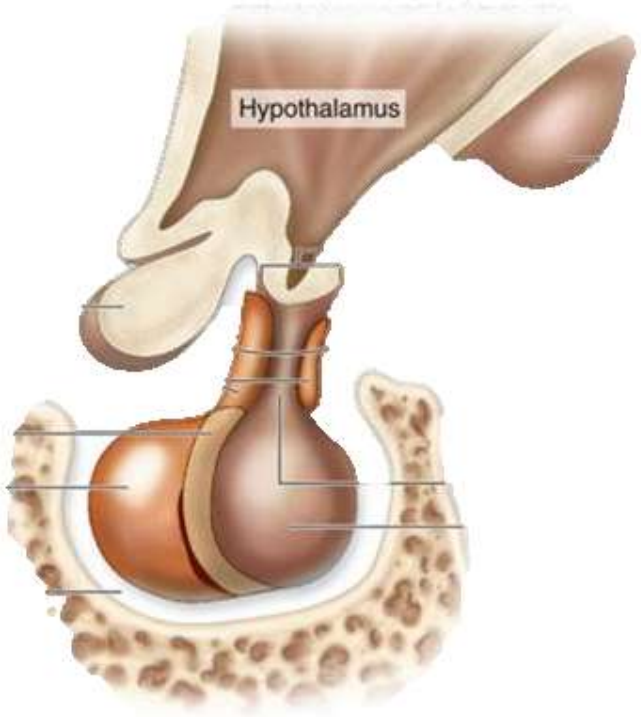
Understanding PO[E]MS

POEMS: Endocrine System

- Endocrine disorders are a common finding in LBC patients, presumably due to high levels of infection/inflammation in HPA axis (highly vascular)

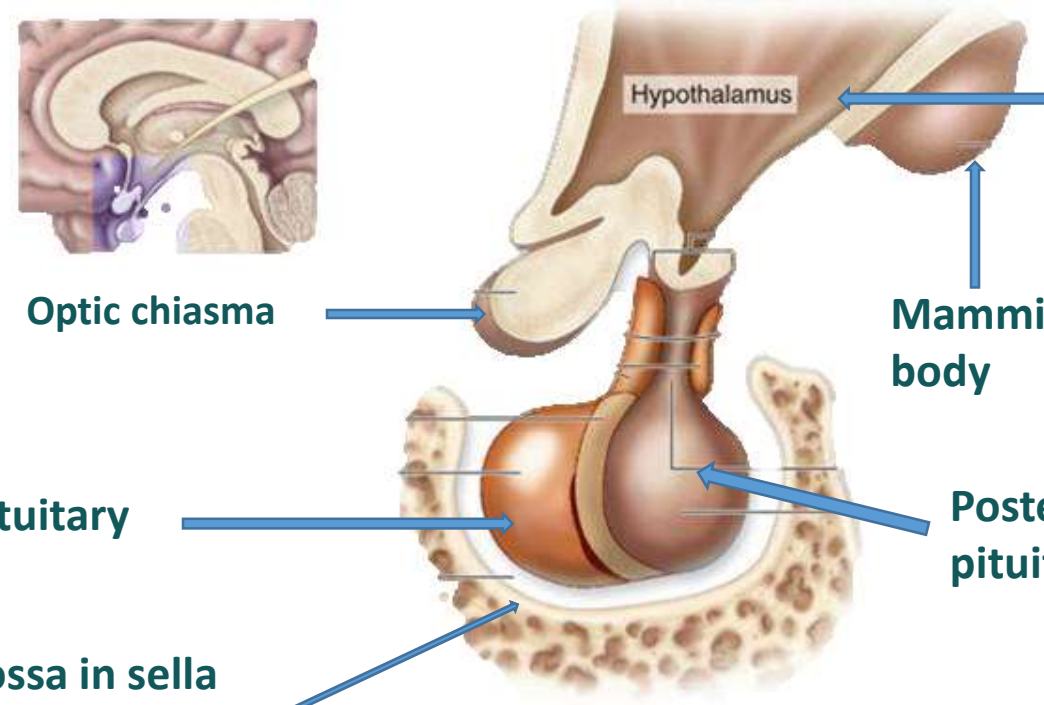
- Infection may affect neuroendocrine cells by
  - Direct lesion/inflammation
  - Oxidative stress
  - Feedback effect of chronic inflammatory state
  - Pain, Sleep disruption and psychological distress

- All resulting to elevation or suppression of hormonal secretion



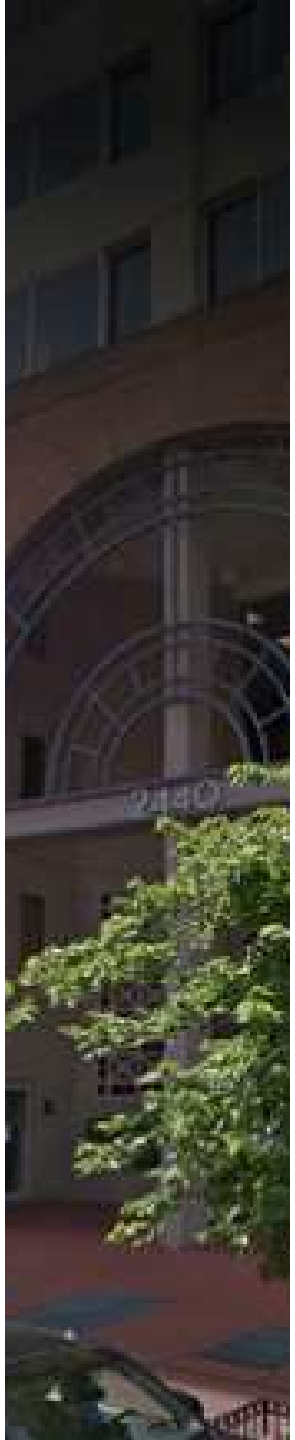
Understanding PO[E]MS

POEMS: Endocrine System



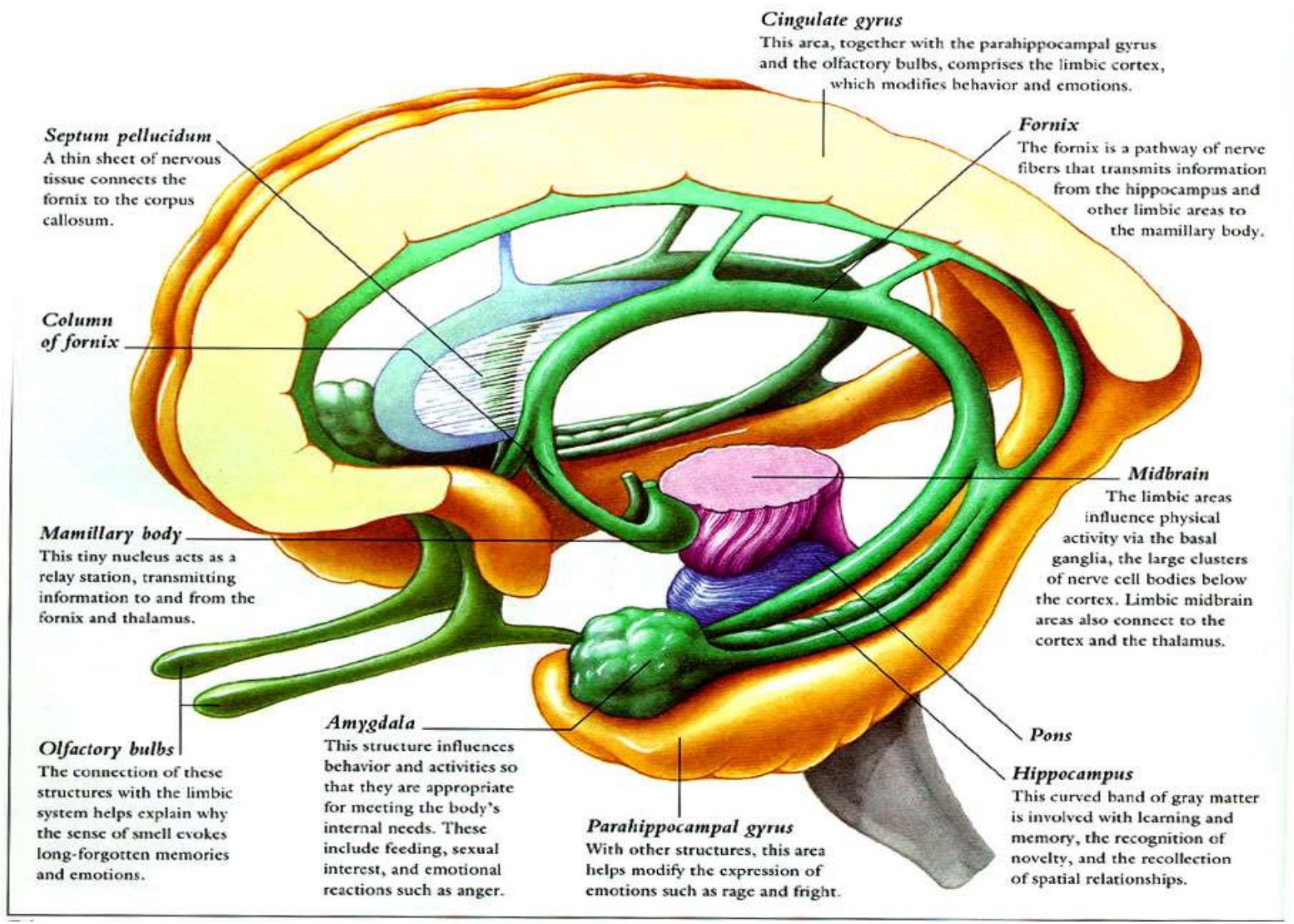
Hypothalamus-Pituitary Axis (HPA)

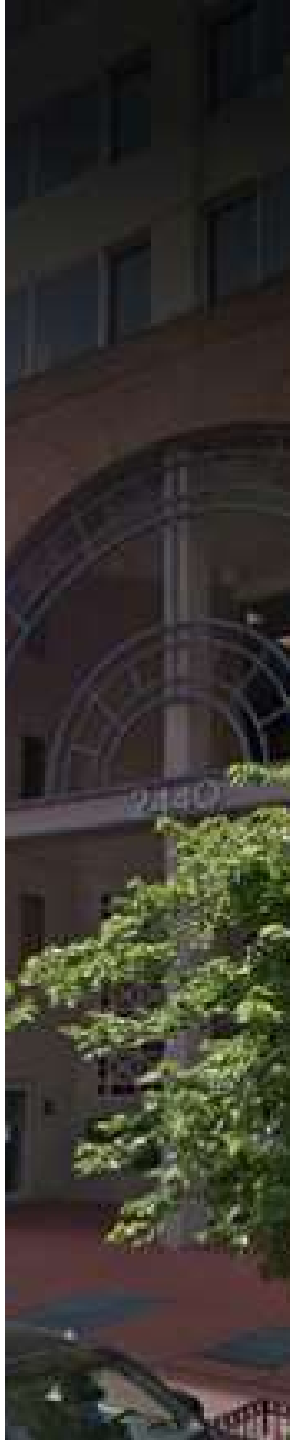
The brain, via the hypothalamus, controls endocrine functioning in the body.



POEMS: MOOD

Understanding POE[M]S

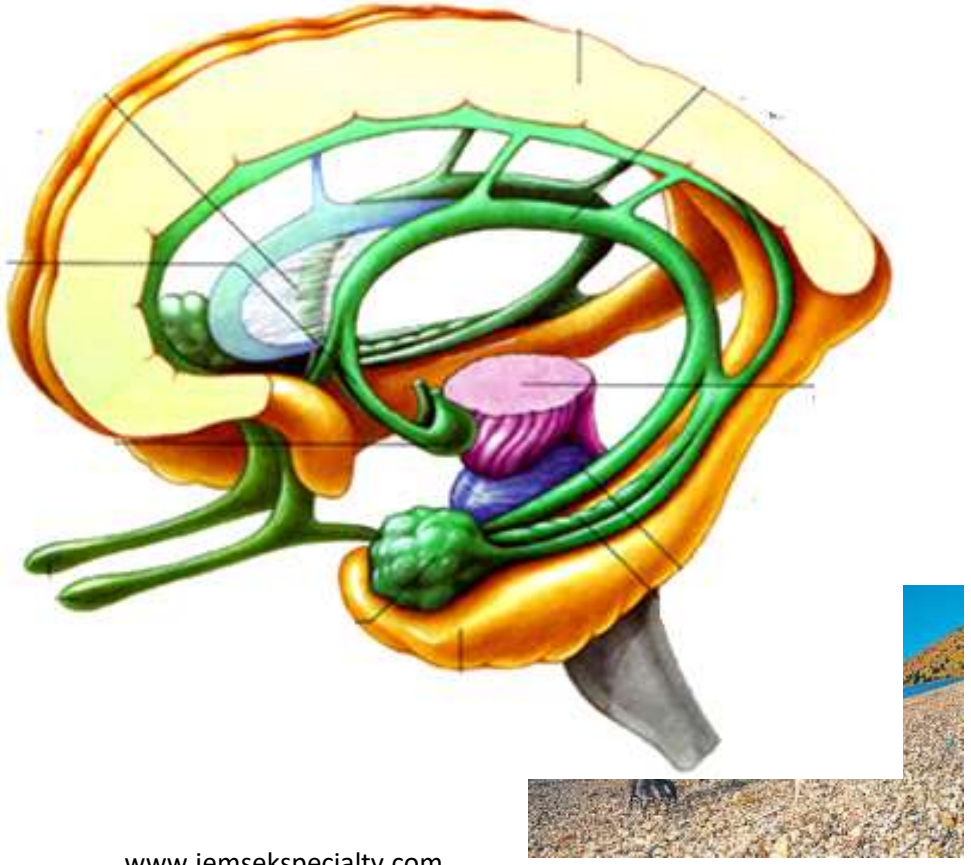




THE LIMBIC SYSTEM IS THE CENTER OF THE LBC STORM

THINK WHITE MATTER!

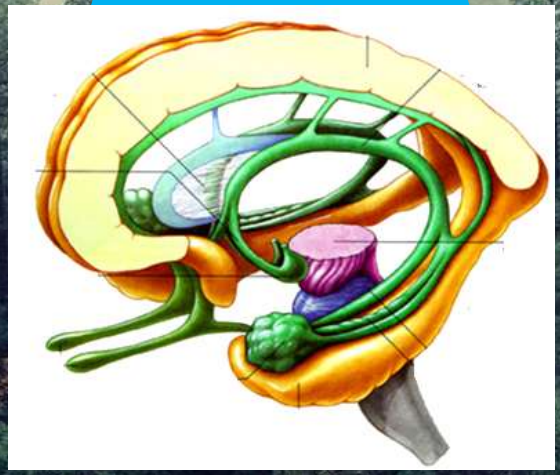
Understanding POE[M]S



- Uncharacteristic
- personality changes
- Rage, paranoia
- Hypervigilance
- Emotional lability
- Insomnia, dysomnia
- Heightened startle respor
- Unprovoked crying(dyscrastic)/gigglir gelastic seizures)

- **Pain**
- **Cravings**
- **ADD/ADHD**
- **Tremor**
- **Bruxism**
- **Photophobia, phonophobia, osmophobia**
- **Vibrations**
- **Hallucinations**

DUNCE



This brain doesn't think!

‘Komodo Syndrome’

When the limbic system is inflamed by infectious elements, the patient’s clinical picture may be characterized by marked neuropsychiatric instability, intolerance of sensory input, and inability to interact with one’s environment

Understanding POEM[S]

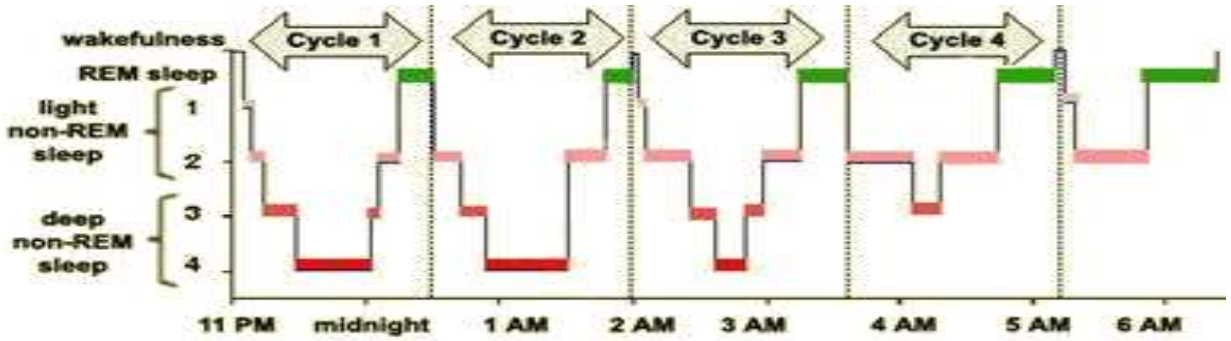
POEMS: The Sleep Cycle

The brain remains active in REM Sleep while the body muscles rest in a relaxed state of atony. The function of the REM sleep therefore is to rest the body.

In Non-REM sleep, the brain activity and metabolism significantly decreases (>50%) especially in deep sleep characterized by Delta waves, while muscles regain tone.

Lymphatic equivalent brain flushing occurring during delta sleep

Therefore the function of the Non-REM (DELTA) is to rest the brain… This is **immuno-restorative.**



LBC Roadblocks and Potholes

Focus Points

- POEMS Instability
- Babesia Recrudescence
- Subacute acalculous cholecystitis
- Peri-menstrual Volatility
- Motor Neuron Predominant Presentation (ALS Equivalence)
- Severe Dysbiosis
- Methylation Pathway Disruption

Other Major Players

- Cervical instability syndrome
- Unrecognized Stressors (including toxic relationships)
- Severe Mast Cell Disorder - Histamine
- Leaky gut
- Unresolved intestinal parasitosis
- Sphincter of Oddi
- Chronic cerebrospinal venous insufficiency (CCSVI)
- Median arcuate ligament syndrome (MALS)
- Spontaneous CSF Leaks
  - Dural Tears and CSF Venous Fistulas
- Severe Periodontal Disease
- Paradoxical reactions to neurotropics/psychotropics
- Cyclical vomiting syndrome
- Superior mesenteric artery syndrome
- Yeast Overgrowth
- Hyperammonemia
- Chronic Sinusitis

Focus Group: The Big 6

Coinfections: Babesia

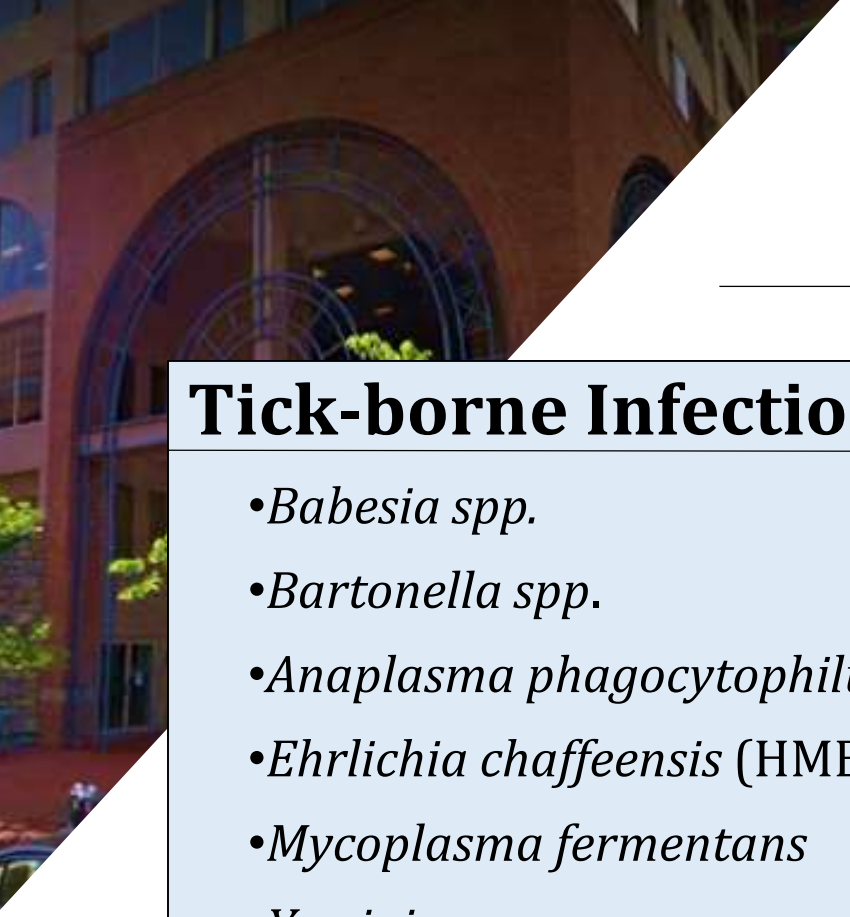
Subacute Acalculous Cholecystitis

Perimenstrual Volatility

Motor Neuron Predominant Presentation

Methylation Pathway Disruption

Severe Dysbiosis



Essential Role of Coinfections

Tick-borne Infections

- *Babesia spp.*
- *Bartonella spp*.
- *Anaplasma phagocytophilum* (HGE)
- *Ehrlichia chaffeensis* (HME)
- *Mycoplasma fermentans*
- *Yersinia*
- Powassan virus & more…

Other Infections

Fungal Overgrowth

- Candida
- Yeast

Indigenous Opportunistic Pathogens

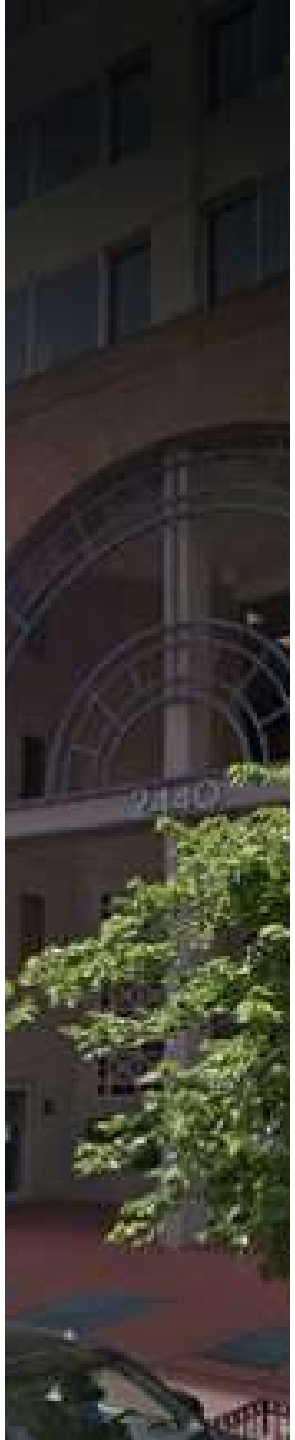
- *Chlamydia pneumonia*

Viral Resurgence

- Herpesviruses (HHV-6, A/B)
- Epstein-Barr

Am J Trop Med Hyg. 2003 Apr;68(4):431-6
Vet Immunol Immunopathol. 2001 Dec;83(3-4):125-47
Vet Immunol Immunopathol. 2003 Aug 15;94(3-4):163-75
Clin Infect Dis. 1997 Jul;25 Suppl 1:S43-7
Infect Immun 2001; 69:3359–71
JAMA 1996; 275:1657–60.

Arch Virol Suppl. 2005;(19):147-56
Parasite Immunol 2000; 22:581–8.
J Infect Dis 2002; 186:428–31.
Arch Neurol 2001; 58: 1357–63.
Transplantation. 2001 Jun 15;71(11):1678-80
Transpl Infect Dis. 2001 Mar;3(1):34-9

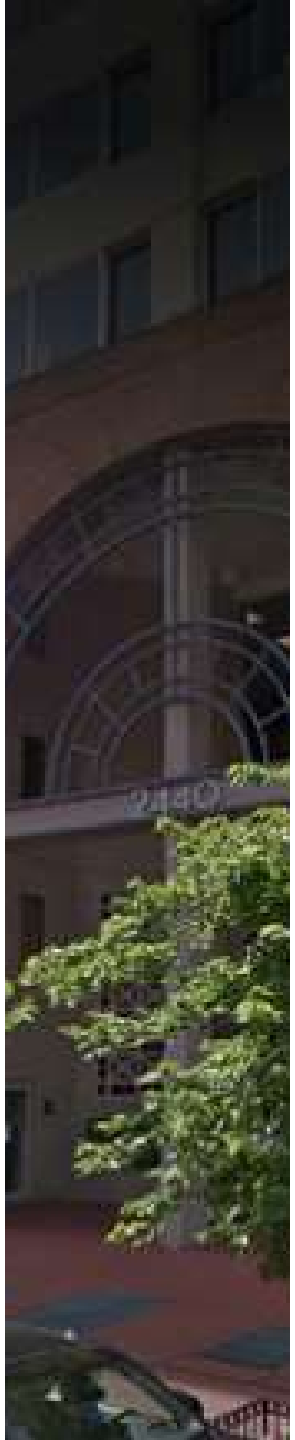


Babesia Recrudescence

Babesia is the No. 1 major player in treatment disruption or disease resurgence

Most commonly associated tick-borne coinfection in LBC patients and prime candidate as the 'engine' for LBC

- Intraerythrocytic protozoan parasite transmitted by *Ixodes* ticks
  - Less often transmitted by transfusion or through pregnancy
- Smallest genome of all Apicomplexan (*phylum*) parasites ~3600 genes
- Predominates and **contributes to disease severity and longevity** in the pathogenesis of Lyme Borreliosis
- A study done by Anderson et al. showcased that **over 50%** of sampled mice **harbored both *B.b.s.l* and *Babesia* spp.**



Disease Dynamics and Variation in Sequelae

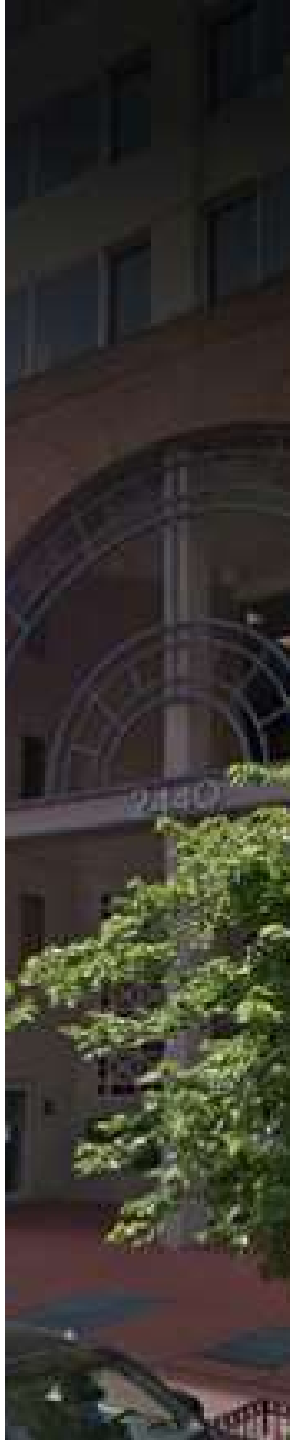
Babesia & Borrelia
Simultaneous Infection

- Symptom Severity
- Symptom Duration
- Anti-inflammatory cytokine production

- Increased arthralgia and joint swelling
- Increased presence of spirochete DNA in blood (hyper-mobilization)
- Increased duration and severity of Hepatosplenomegaly

- Experienced non-specific symptoms to a higher degree
- Reduced production of IL-10 and IL-13
- Reduced IgG response

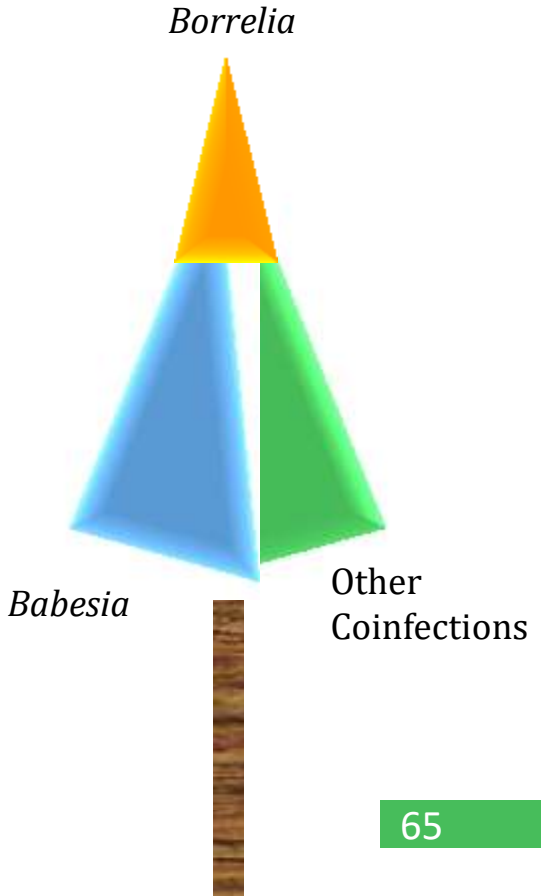
Krause et al., 1996 Moro et al. 2002 Knapp and Rice, 2015



Collective Arsenal – "*The Spear*"

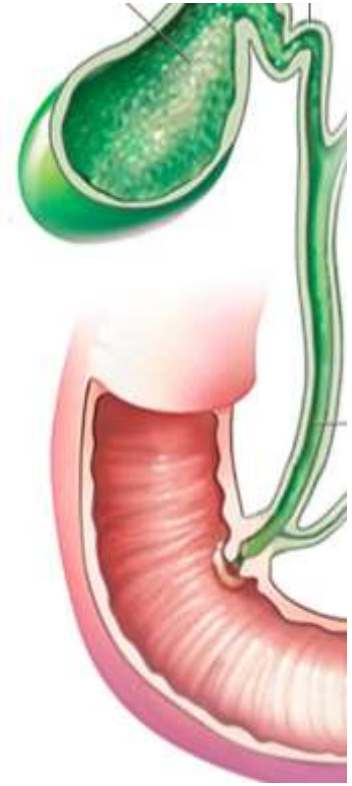
Although the **mechanisms are not well understood**, we have reasons to believe, based on both empirical and case-study support, that coinfection interactions corroborate **more intense sequelae and systemic inflammation**:

- **Immunosuppressive tactics**
  - Including tick transmission and salivary-controlled inhibition
- **Multifaceted inflammatory onslaught**
- **Multi-factorial immunomodulatory collaboration**
- **Biofilm communities**



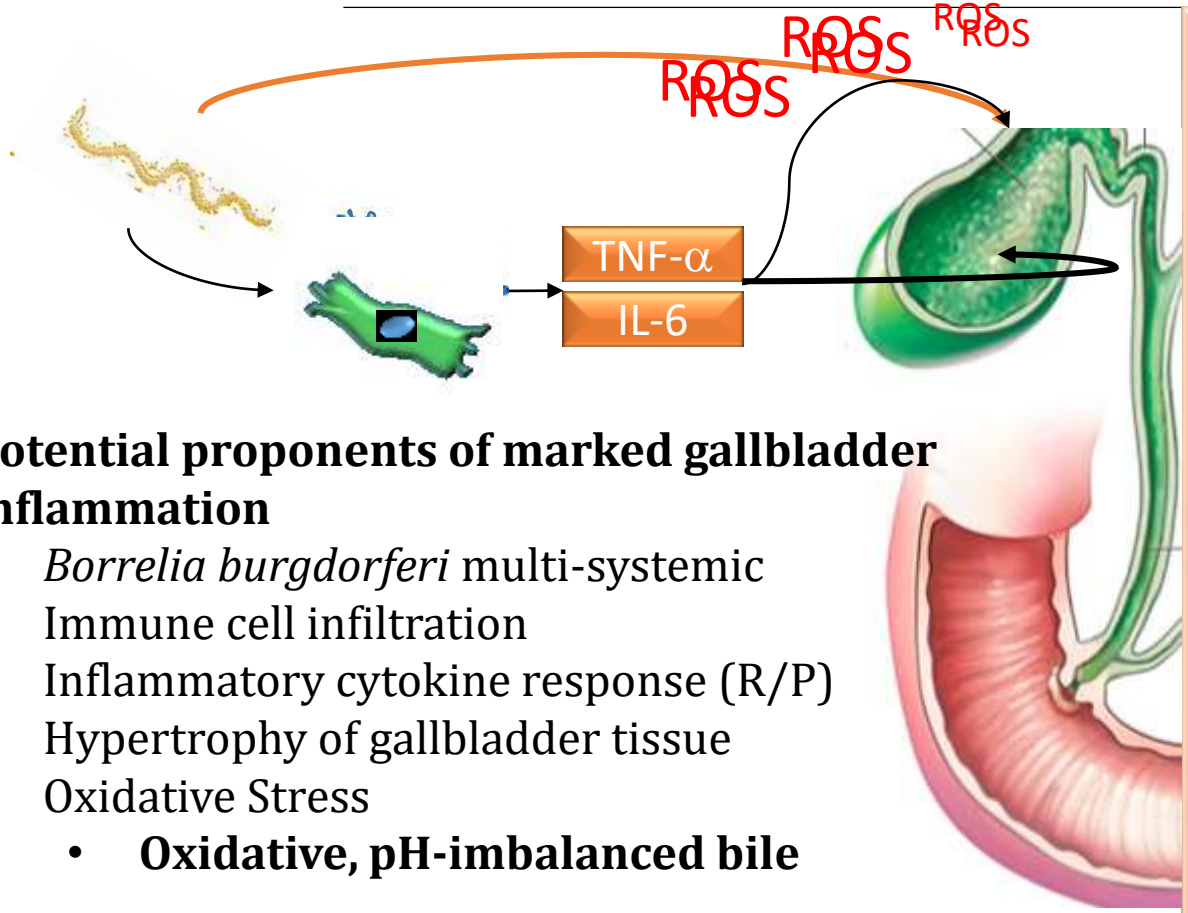
Subacute Acalculous Cholecystitis

Subacute Acalculous Cholecystitis is a clinically undefined and unrecognized disease in surgical literature.



- Slow-onset form of acalculous-type gallbladder inflammation
- Takes months to propagate into noticeable inflammation through physical examination
- Clinically unique presentation mounted by extended periods of pain post-examination (Jemsek sign).
- Establishes prior to or during antibiotic exposure
- Stark symptom remission and increased treatment efficacy after removal.

Subacute Acalculous Cholecystitis



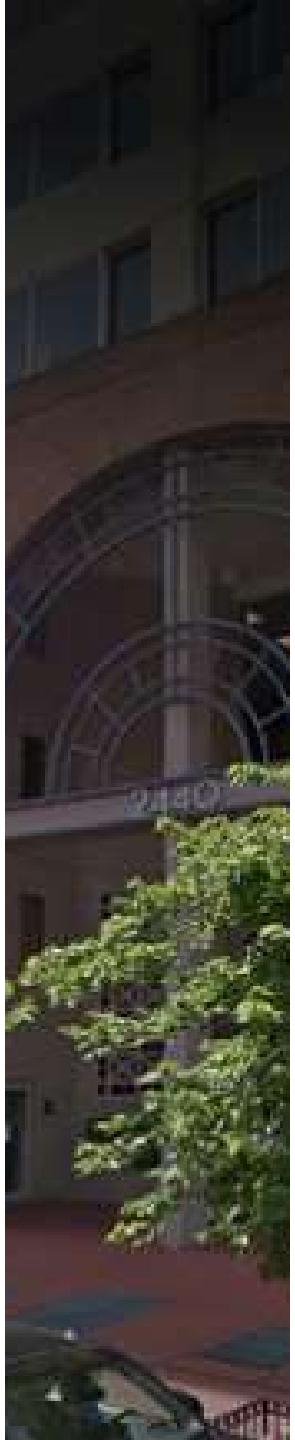
Potential proponents of marked gallbladder inflammation

- *Borrelia burgdorferi* multi-systemic
- Immune cell infiltration
- Inflammatory cytokine response (R/P)
- Hypertrophy of gallbladder tissue
- Oxidative Stress
  - **Oxidative, pH-imbalanced bile**

Subacute Acalculous Cholecystitis, we believe, may be contributed to **both direct and indirect effects** of Lyme Borreliosis Complex.

1. **Direct -** Borrelia infiltration of tissue and subsequent action on resident and peripheral immune cells

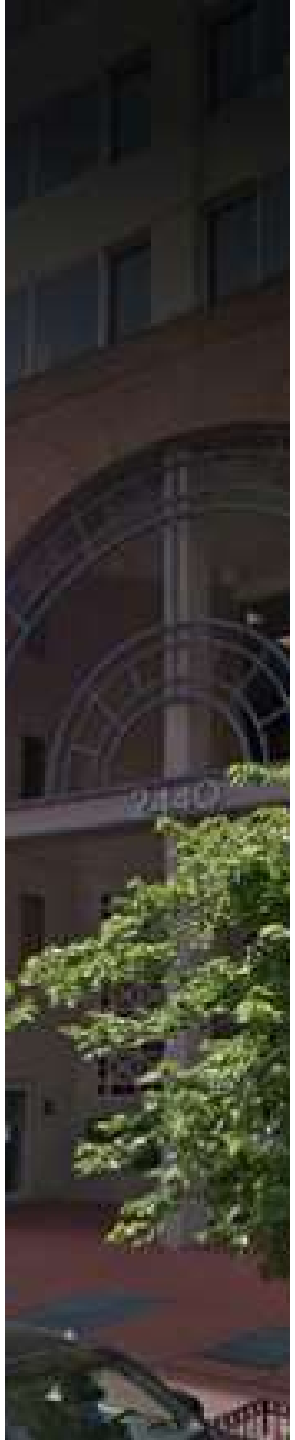
2. **Indirect -** Borrelia impact on peripheral immune cells generating inflammatory cytokines which generate oxidative radicals which contribute to hypertrophy of gallbladder tissue as well as producing oxidative "**HOT" bile**.



Perimenstrual Volatility

Perimenstrual cycles tend to present a variety of endrocrinologically-defined complications that **contribute to volatility** in LBC disease progression and therapeutic intervention.

- Contributions of the inverse relationship between **estrogen and prostaglandins**
- **Hyper-inflammatory state** presumably mediated through prostaglandin interactions. Derived from arachidonic acid (EPA/DHA).
- Prostaglandin interaction with afferent nerve fiber endings contributing to **pain.**
- Damage to pituitary gland through oxidative stress and inflammatory cytokines
  - Inflammation **confounds release of FSH and LH** which causes major variation in menstruation patterns



Perimenstrual Volatility and Pelvic Inflammatory Issues

Major increase in inflammatory and pain-sensitizing hormones prior to menses.

- Prostaglandins (PGF2a and PGE2)
- Vasopressin
- Leukotrienes

Anaerobic metabolites produced during this ischemic period in the endometrium are proposed to **stimulate Type C neurons which contribute to pain (POEMS).**

Endometriosis as a potential outcome of infection and impediment towards treatment efficacy.

Pelvic floor dysfunction – inappropriate contraction (painful)

Overall **hormonal fluctuations** paired with the release and rise of **inflammatory cytokine mediators** contributes to LBC pathogenesis and impairs treatment efficacy.

Motor Neuron Predominant Presentation

Generalised motor neuron disease as an unusual manifestation of *Borrelia burgdorferi* infection FREE

B HEMMER, F X GLOCKER, R KAISER, C H LÜCKING

1. Department of Neurology and Cl

2. Department of Neurology and Cl

Acta Clin Belg. 2009 May-Jun;64(3):225-7.

Motor neuron disease features in a patient with neuroborreliosis and a cervical anterior horn lesion.

De Cauwer H[1], Declerck S, De Smet J, Matthyssen P, Pelzers E, Eykens L, Lagrou K.

Dr Fi

Immunologic reactivity against Borrelia burgdorferi in patients with motor neuron disease.

Halperin JJ[1], Kaplan GP, Brazinsky S, Tsai TF, Cheng T, Ironside A, Wu P, Delfiner J, Golightly M, Brown RH, et al.

Author information

Abstract

Of 19 unselected patients with the diagnosis of amyotrophic lateral sclerosis (ALS) living in Suffolk County, New York (an area of high Lyme disease prevalence), 9 had serologic evidence of exposure to Borrelia burgdorferi; 4 of 38 matched controls were seropositive. Eight of 9 seropositive patients were male (8 of 12 male patients vs 2 of 24 controls). Rates of seropositivity were lower among patients with ALS from nonendemic areas. All patients had typical ALS; none had typical Lyme disease. Cerebrospinal fluid was examined in 24 ALS patients--3 (all with severe bulbar involvement) appeared to have intrathecal synthesis of anti-B burgdorferi antibody. Following therapy with antibiotics, 3 patients with predominantly lower motor neuron abnormalities appeared to improve, 3 with severe bulbar dysfunction deteriorated rapidly, and all others appeared unaffected. There appears to be a statistically significant association between ALS and immunoreactivity to B burgdorferi, at least among men living in hyperendemic areas.

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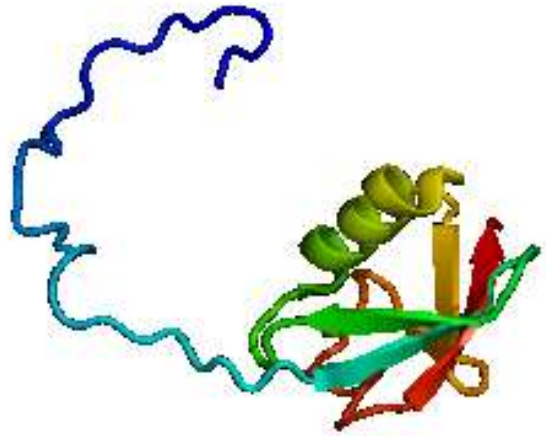
[Indexed for MEDLINE]

ny, axonal neuropathy, stroke,
orreliosis with cervical myelitis
areses and atrophies as well
of a meningoencephalitis.
ease, in all neurological

Motor Neuron Predominant Presentation

The neuropathological involvement of *Borrelia burgdorferi* models similarities to motor neuron predominant presentations in amyotrophic lateral sclerosis (ALS)

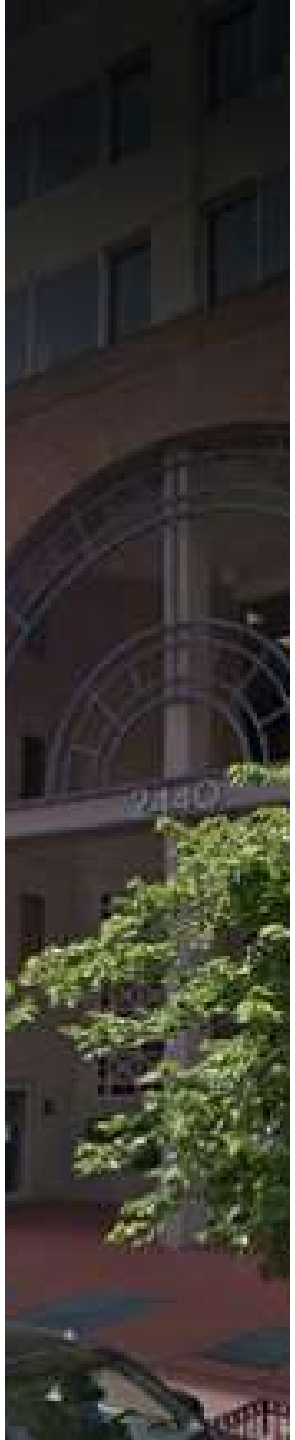
- Borrelia known to **target lower brainstem and the upper cervical roots**
  - Focal muscles weakness and/or bulbar onset
  - Difficulty swallowing
  - Wasting in the upper torso – overall muscle weakness and fatigue

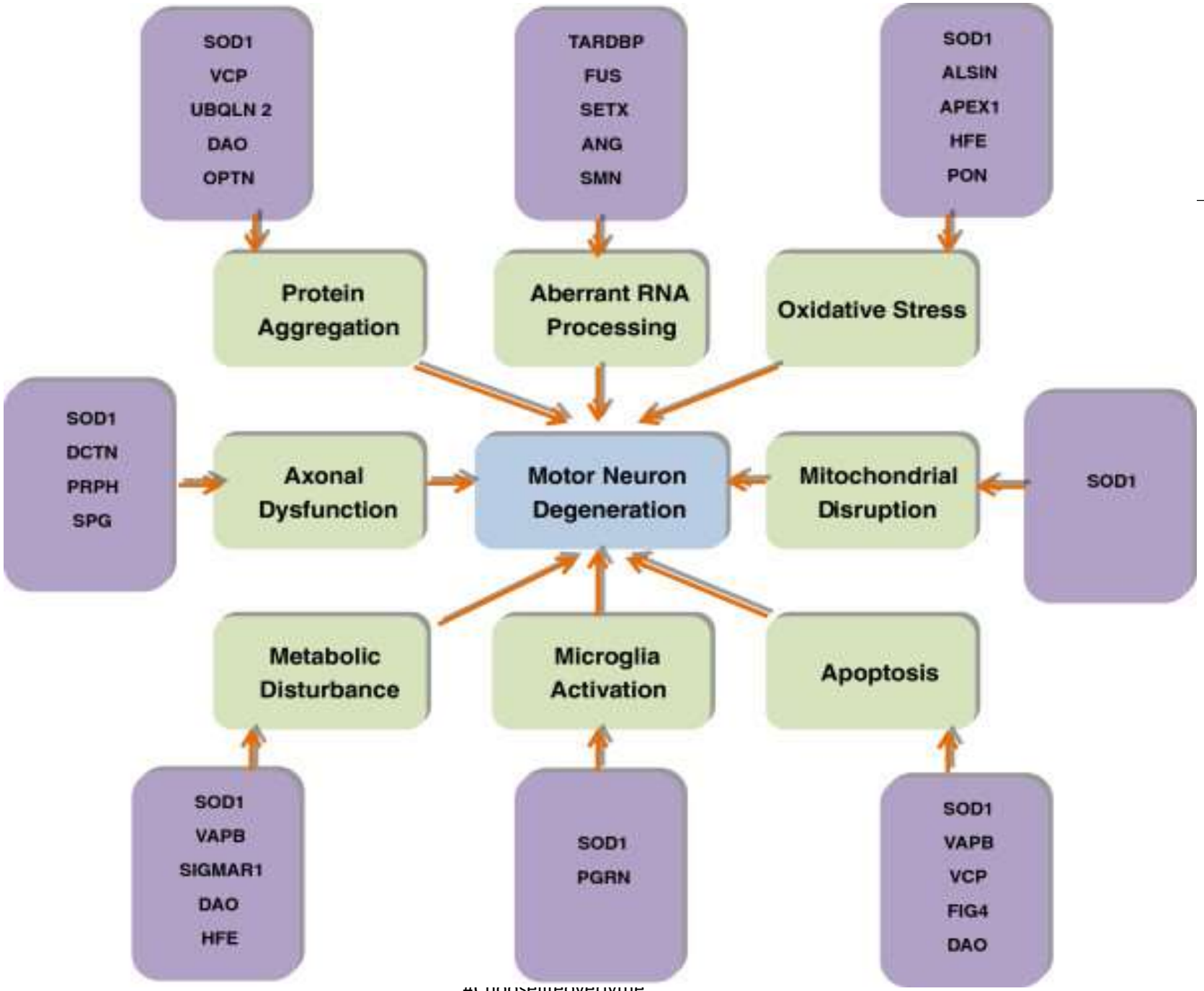


- Potential genetic profile mutation of **UBQLN2 gene** which may contribute to build-up of ubiquitin-immunoreactive (ub-ir) cytoplasmic inclusions in susceptible individuals (*familial lineage)*

Retroviruses – HERV-K?

"It can be speculated that the spirochete Borrelia burgdorferi has the ability to induce an immune reaction that specifically affects motor neurons. This reaction may mimic different, non-curable diseases, such as spastic spinal paralysis, spinal muscle atrophy, and amyotrophic lateral sclerosis." (Hemmer et al., 1997)





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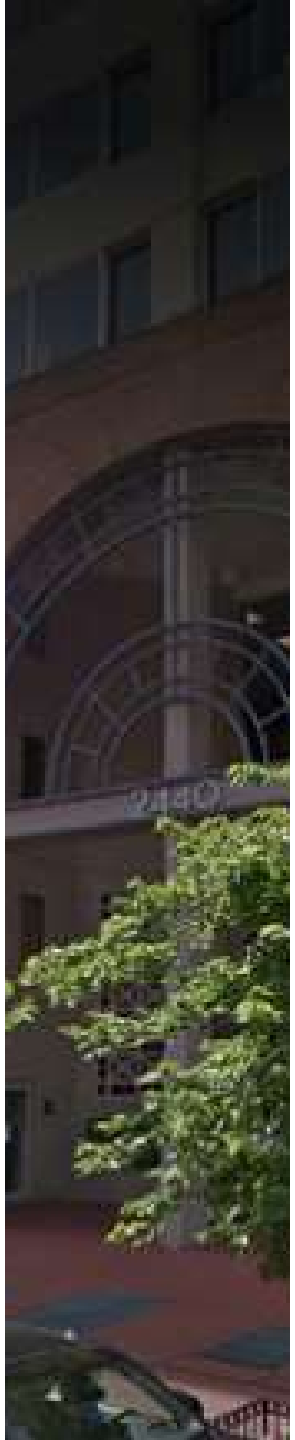
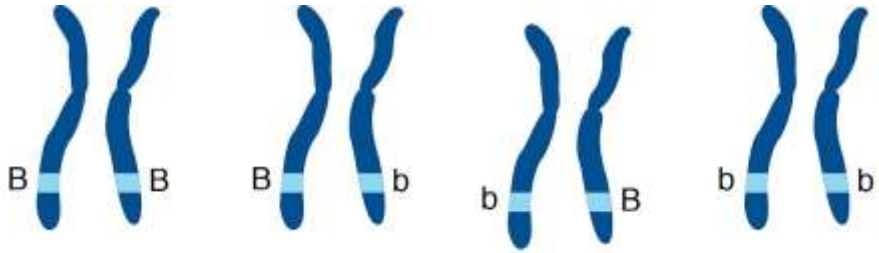


Methylation Pathway Disruption

There are at least two major contributing factors to methylation pathway disruption that we focus on:

- **Significant genetic mutations that contribute to methylation cycle dysfunction.**
  - COMT
  - MOA
  - **MTFHR**
  - CBS
  - Etc…

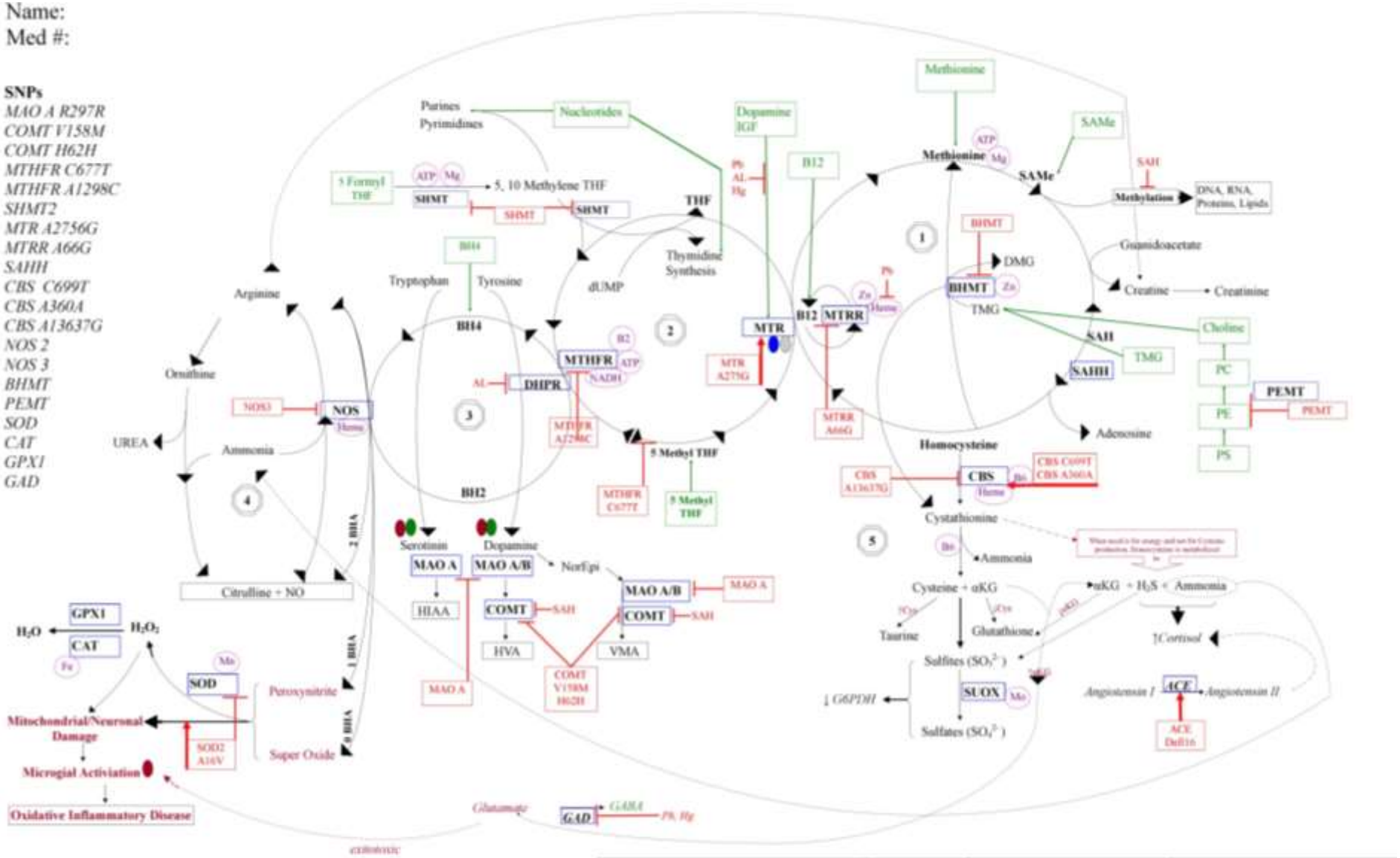


- **DNA methylation and epigenetic modulation as a product of oxidative stress due to inflammatory load in the creation of free-oxidative and nitrogen radicals.**

Methylation Map

Name:
Med #:

SNPs
MAO A R297R
COMT V158M
COMT H62H
MTHFR C677T
MTHFR A1298C
SHMT2
MTR A2756G
MTRR A66G
SAHH
CBS C699T
CBS A360A
CBS A13637G
NOS 2
NOS 3
BHMT
PEMT
SOD
CAT
GPX1
GAD



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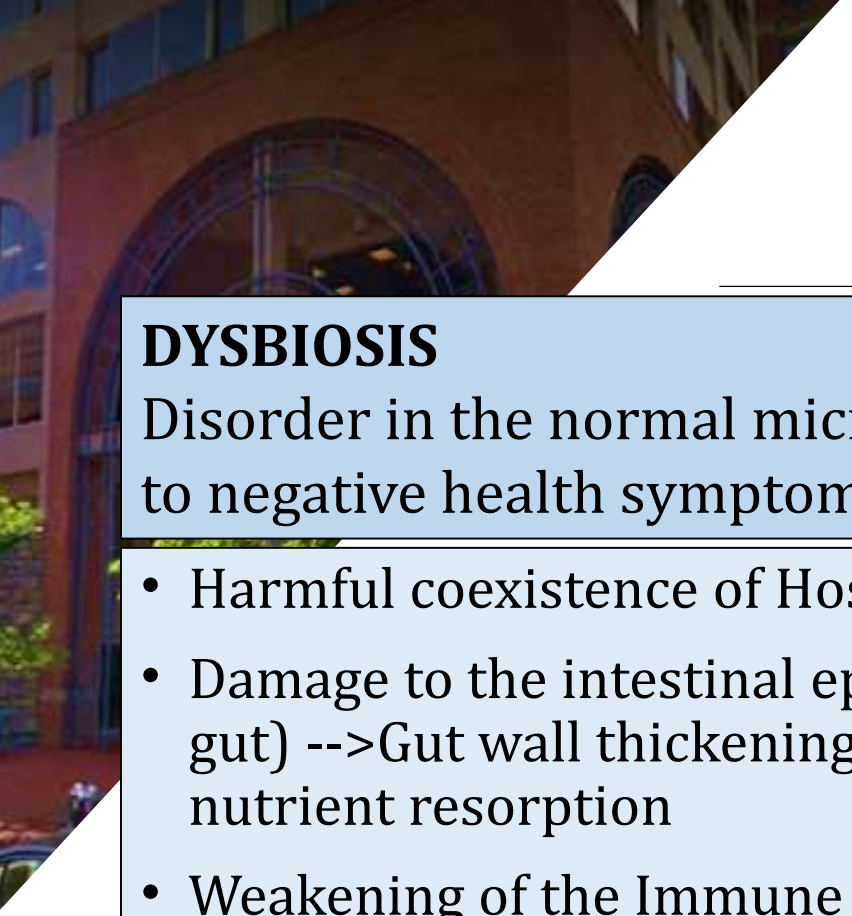
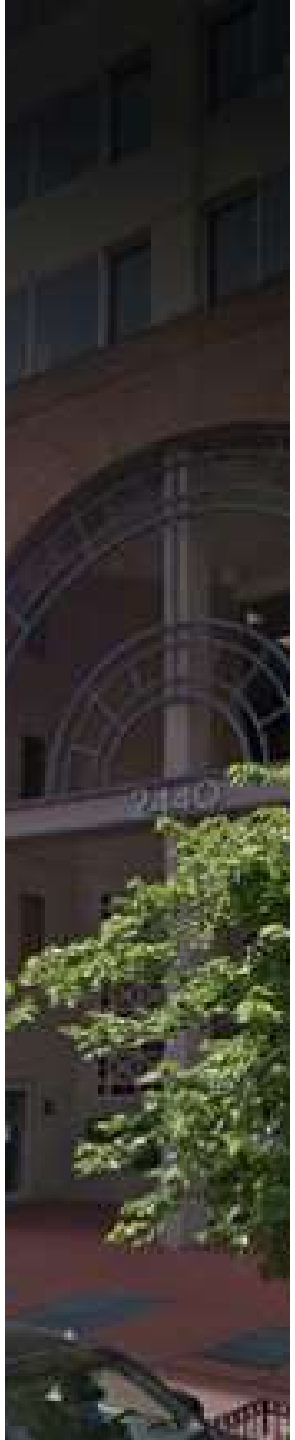


Severe Dysbiosis

DYSBIOSIS

Disorder in the normal microbial distribution/quotient in the digestive system resulting to negative health symptoms; Catastrophic disruption of indigenous microflora

- Harmful coexistence of Host & Microflora
- Damage to the intestinal epithelium (leaky gut) -->Gut wall thickening and reduced nutrient resorption
- Weakening of the Immune System
- Unprocessed Antigen and Allergen exposure: Increases food sensitivity and non-specific immune reactions.
- Unrecognized/Unclassifiable Parasitosis
- Increase Histamine and other Biogenic Amine production through bacterial decarboxylation.
- Increased gas production (H_2S, NH_3, CH_4, CO_2)
- Acceleration of cell turnover – increased energy need
- Vitamin deficiencies



Other Reasons for Relapse

Other major players contributing to treatment failure or relapse:

- Cervical instability syndrome
- Unrecognized Stressors (including toxic relationships)
- Severe Mast Cell Disorder - Histamine
- Leaky gut
- Unresolved intestinal parasitosis
- Sphincter of Oddi
- Chronic cerebrospinal venous insufficiency (CCSVI)
- Median arcuate ligament syndrome (MALS)
- Spontaneous CSF Leaks
  - Dural Tears and CSF Venous Fistulas
- Severe Periodontal Disease
- Paradoxical reactions to neurotropics/psychotropics
- Cyclical vomiting syndrome
- Superior mesenteric artery syndrome
- Yeast Overgrowth
- Hyperammonemia
- Chronic Sinusitis

Challenges and Opportunities in LBC Rx

Review of Goals and Approach to Rx

a) The primary goal of LBC Rx is immune restoration of immune competence

b) Stabilize oxidative stress and limit cellular damage

c) Stabilize neuropsychiatric and multi-systemic chaos

- ELF
- POEMS

Challenges and Opportunities in LBC Rx

Review of Goals and Approach to Rx

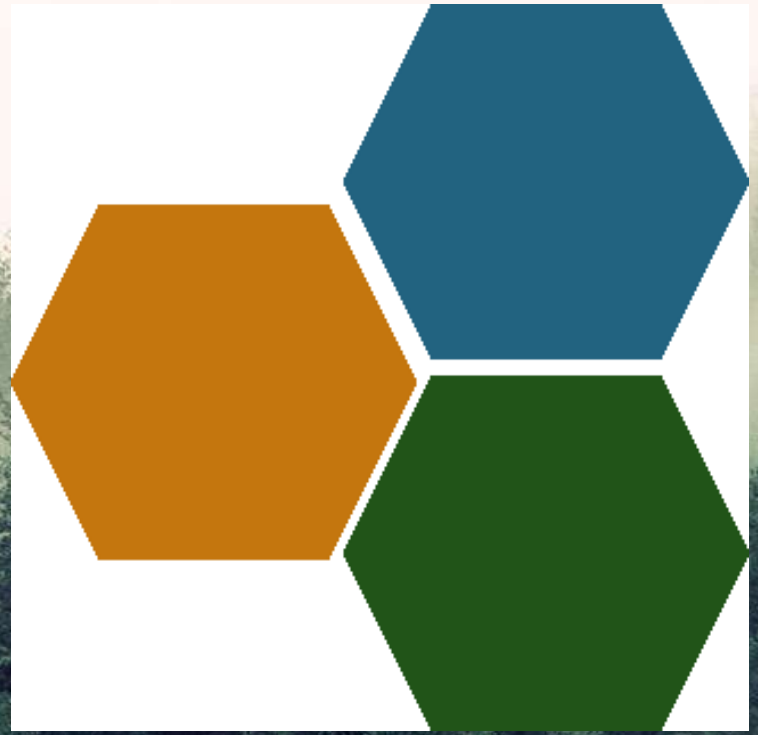
d) Recognize Major Obstacles to LBC remission

- e.g. **The Big 6**

e) Design Rx program to create 'Balance' in the effectiveness and continued killing of LBC pathogens while managing intense reactivity (Herxheimer) – Overwhelming oxidative stress inhibits Immune Restoration

“The greatest enemy of knowledge, is not ignorance but the illusion of knowledge”

Stephen Hawking



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