# Classical and Integrative Medical Approaches in Chronic Lyme Disease: New Paradigms in Diagnosis & Treatment

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# Investigative Treatment Protocols for Lyme Disease and Multiple Co-infections

**Immune dysregulation:**
**ANA+, HLA DR4 +**
**Plaquenil**
**?Herbs / CAM tx**

**Tetracyclines**

**Cleocin & Quinine**
**Mepron&Zithromax**
**Lariam**
**Artemesia**
**Malarone**

**Candida: Nystatin, Diflucan, Acidophilus**
**?Leaky Gut**
**?Food Allergies**
**?El syndrome, Heavy metal toxicities**
**?Multiple chemical sensitivities**
**Hormonal d/f**

**Borrelia burgdorferi**

**Ehrlichia/Anapl.**

**Babesia**

**Bartonella**

**Viruses**

**? Mycoplasma**
**? Chlamydia**

**Cell Wall:**
**Penicillin / Cephalosporins**

**Cyst: Flagyl/Plaquenil**

**Macrolides / Ketolides**

**Rifampin**

**Septra/Bactrim**

**Quinolones**

**?Neurotoxins**
**?HBOT**
**?Heat Therapy**
**?IV Glutathione**

**Anti-Virals**

Therefore, drug regimens which are effective against multiple organisms simultaneously and penetrate intracellularly and into the CNS may be necessary to achieve significant clinical improvement.

"Virtually all human diseases result from the interaction of genetic susceptibility factors and modifiable environmental factors, broadly defined to include infections, chemical, physical, nutritional, and behavioral factors"

Office of Genetics and Disease Prevention, CDC

# Chronic Lyme Disease: Differential Diagnosis

1. Infections:

   a) Bacterial: Lyme disease, Ehrlichiosis, Bartonella, Mycoplasma, Chlamydia, RMSF, Typhus, Tularemia, Q-Fever, Tick paralysis…

   b) Parasites: Babesiosis and other piroplasms, filiariasis, amebiasis, giardiasis…

   c) Viruses: EBV, HHV-6, HHV-8, CMV, St Louis Encephalitis, W Nile, Powassan encephalitis and other viral encephalopathies

   d) Candida and other fungi

# Chronic Lyme Disease: Differential Diagnosis

- 2)Immune dysfunction
- 3)Inflammation
- 4)Toxicity: Multiple Chemical Sensitivity, Environmental Illness, Heavy Metals, Mold and Neurotoxins (external and internal biotoxins)
- 5)Allergies: foods, drugs, environmental…
- 6)Nutritional & Enzyme Deficiencies/ functional medicine abnormalities in biochemical pathways
- 7)Mitochondrial dysfunction

# Chronic Lyme Disease: Differential Diagnosis

- 8)Psychological: stress, PTSD, abuse, depression, anxiety, OCD…
- 9)Endocrine abnormalities: thyroid, GH, adrenal, sex hormones, pituitary, Vit D def
- 10)Sleep disorders: Acute and Chronic (OSA, Medications, Pain, Nocturia, Depression/Anxiety, RLS…
- 11)Autonomic Nervous System (ANS) Dys(f)

# Chronic Lyme Disease: Differential Diagnosis

- 12)Gastrointestinal: Leaky Gut, Candida, Dysbiosis, Celiac Disease, Colitis, Cancer…
- 13)Elevated LFT's: ?AB's, ETOH, Hepatitis, Hemochromatosis, Wilsons disease, α-1AT deficiency, chemicals (carbon tet,drugs)…
- 14)Drug use/Addiction
- 15)Deconditioning: Need for PT/Exercise program..

# I: Infections In Chronic Lyme Disease

- 1)Bacterial :

  a)Borrelia burgdorferi: Combine drugs to address all 3 forms of Bb simultaneously 2º to the ability of the organism to shift between different forms, go dormant, and evade immune surveillance. Continue treatment until the patient is 2 months symptom free

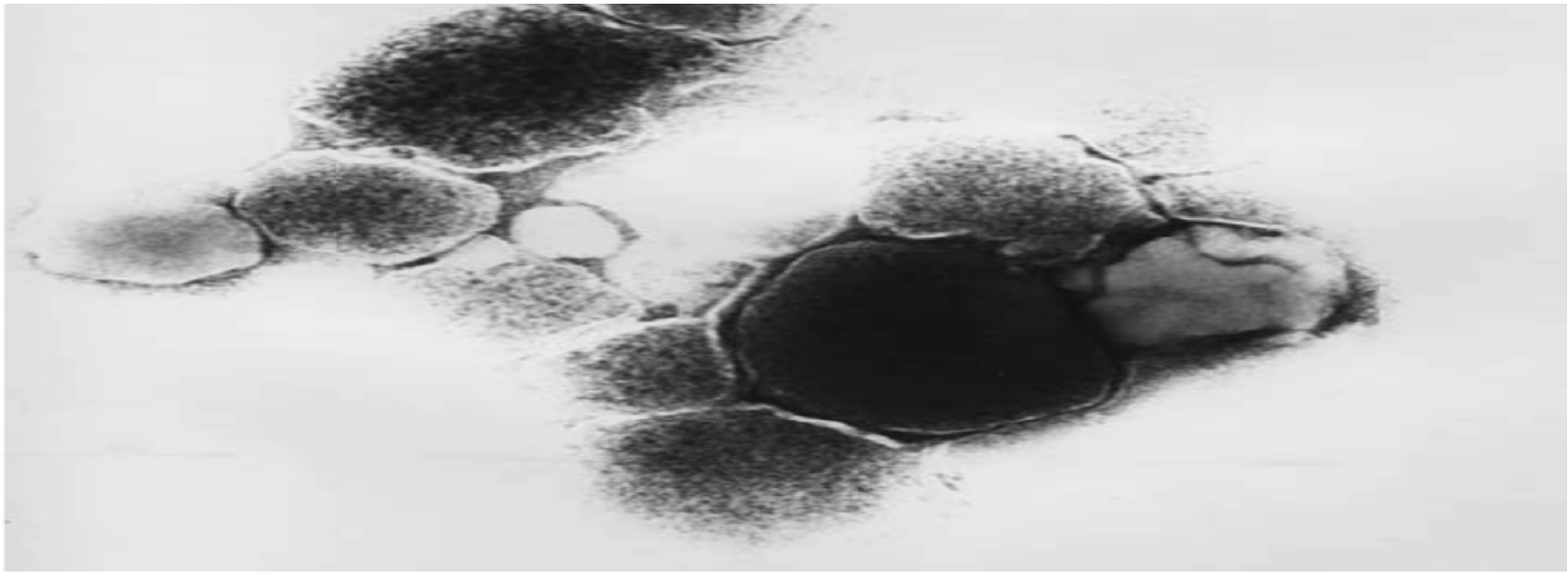
  -Cell Wall forms →Amoxicillin, Augmentin, Ceftin ,Cedax, Omnicef, IM Bicillin, IV Rocephin, IV Claforan, IV Vancomycin, IV Primaxin…

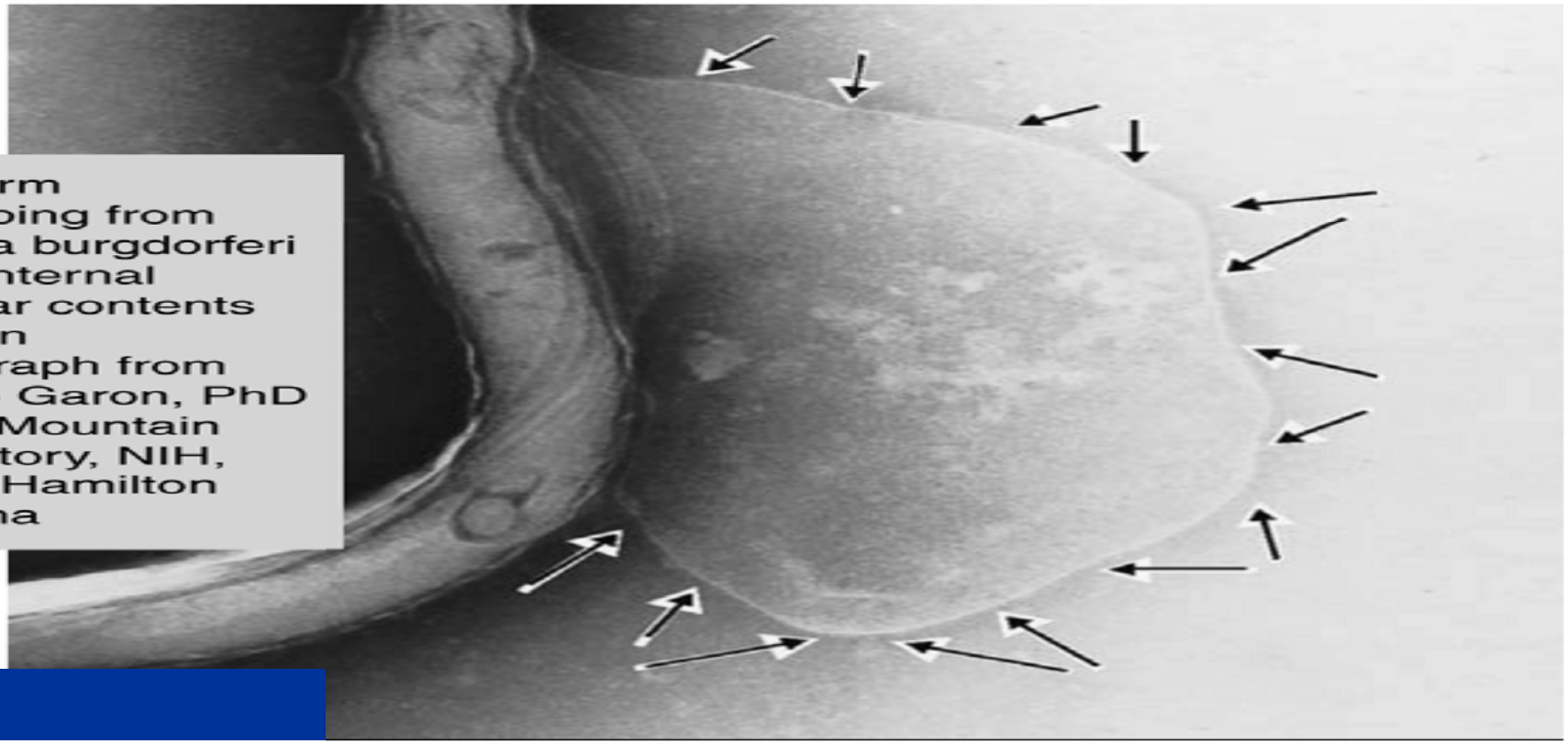
  -Cystic forms ( L-forms, spheroplasts, CWD forms..) → Plaquenil (hydroxychloroquine), GSE, Flagyl (metronidazole), Tindamax (tinidazole)

  -Intracellular forms → tetracyclines (doxycycline, minocycline, tetracycline HCL), macrolides (azithromycin, clarithromycin), quinolones (Cipro, Levaquin, Avelox), Rifampin…

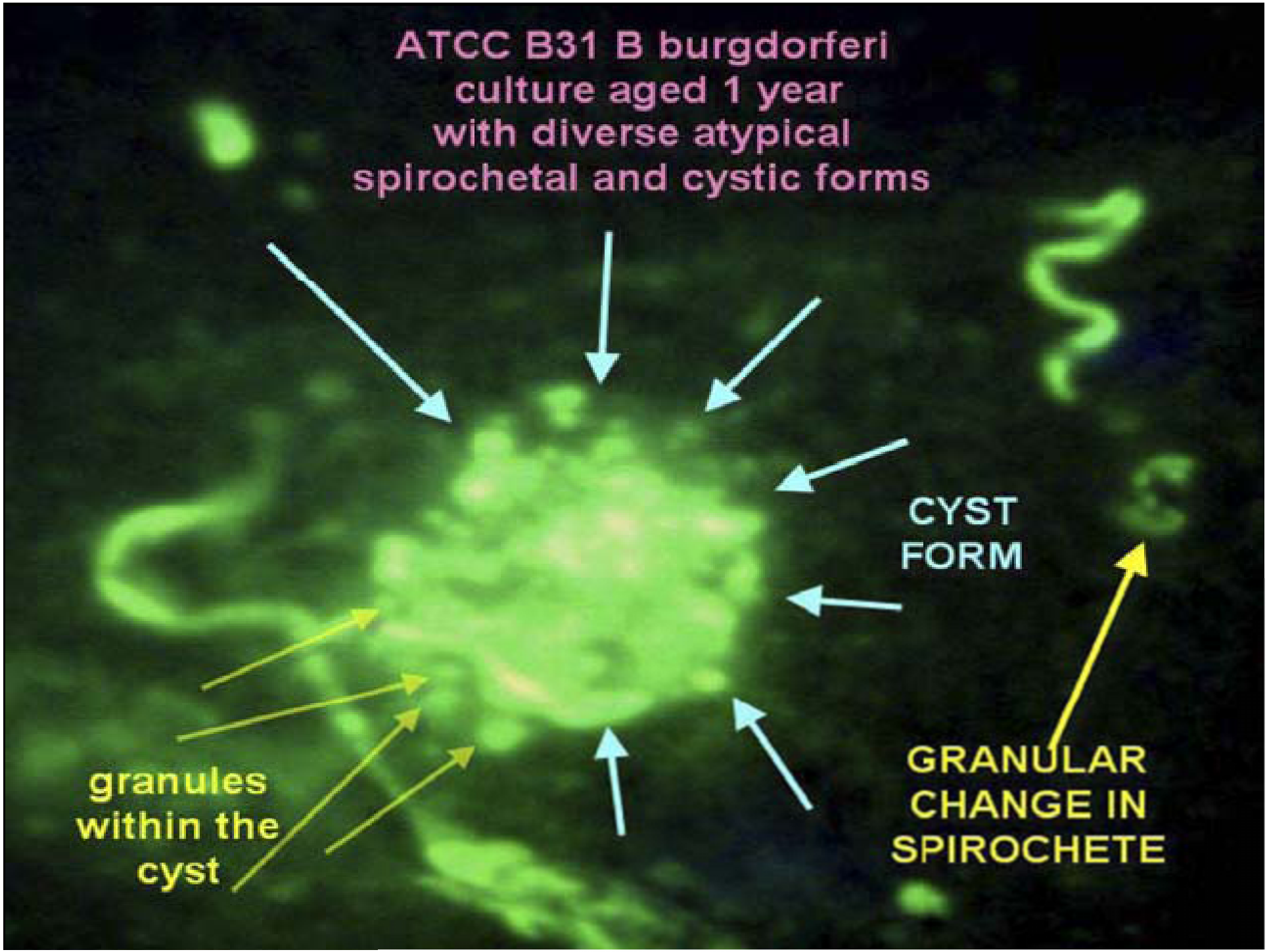
# Persistence of Lyme Borreliosis: Atypical Forms/Cystic Forms

- Preac-Mursic, V et al, Formation and Cultivation of Borrelia burgdorferi Spheroplast-L-form Variants, Infection 24 (1996);No 3:218-26
- Brorson,O et al, Transformation of cystic forms of Borrelia burgdorferi to normal, mobile spirochetes, Infection 25 (1997); No 4:240-45.
- Alban PS et al, Serum-starvation induced changes in protein synthesis and morphology of Borrelia burgdorferi, Microbiology (2000), 146:119-27
- Brorson, O et al, A rapid method for generating cystic forms of Borrelia burgdorferi, and their reversal to mobile spirochetes, APMIS, 106 (1998):1131-41





Cyst form developing from Borrelia burgdorferi Note: Internal floccular contents Electron micrograph from Claude Garon, PhD Rocky Mountain Laboratory, NIH, NIAID, Hamilton Montana


ATCC B31 B burgdorferi
culture aged 1 year
with diverse atypical
spirochetal and cystic forms
CYST
FORM
granules
within the
cyst
GRANULAR
CHANGE IN
SPIROCHETE

# Treatment Relapses and Failures with Short-term Therapy

- Logigian (1990) : After 6 mo's of therapy, 10/27 patients treated with IV AB's relapsed or had treatment failure.
- Pfister (1991) : 33 patients with neuroborreliosis were treated with IV AB's. After a mean of 8.1 months 10/27 were symptomatic and borrelia persisted in the CSF in 1 pt
- Shadick (1994) : 10/38 pts relapsed (5 with IV) within 1 year of treatment, and had repeated AB treatment
- Asch (1994) : 28% relapsed w/ major organ involvement 3.2 years after initial treatment
- Valesova (1996) :10/26 relapsed or progressed at 36 mo
- Trieb (1998) : >50% pts symptomatic after 4.2/+/- 1.2 yrs
- Shadick (1999) : 69/184 (37%) report a previous relapse

# Benefit of Longer treatment Regimes for Disseminated Lyme Disease

1. Wahlberg,P. et al, Treatment of late Lyme borreliosis. J Infect, 1994. 29(3): p255-61 → 31% improved w/ 14 d Rocephin, 89% improved w/ Rocephin + 100d of Amox and Probenecid, 83% improved w/ Rocephin, then 100 days of cephadroxil
2. Donta, ST., Tetracycline therapy for chronic Lyme disease. Clin Infect Dis, 1997. 25 Suppl 1: p.S52-6.

   → 277 pts with chr LD treated between 1-11 mo: 20% cured, 70% improved, 10% treatment failure

# Benefit of Longer treatment Regimes for Disseminated Lyme Disease

3. Oksi, J et al., Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. Eur J Clin Microbiol Infect Dis, 1998. 17(10) :p 715-9

→ 30 pts w/ chr Lyme treated for 100 d, 90% w/ good or excellent responses

4. Oksi, J., et al. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med, 1999. 31(3):p.225-32

→ 32/165 pts w/ disseminated Lyme treated for 1 or more months of AB's showed that even > 3 mo of treatment may not eradicate the spirochete, longer term therapy may be necessary

# Infections in Chronic Lyme Disease

- 1)Bacterial:

  b)Ehrlichiosis: tetracyclines (doxy, minocycline)
  or rifampin for allergic/intolerant patients

  c)Bartonella, Mycoplasma, Chlamydia, RMSF,
  Typhus, Tularemia, Q-fever (Coxiella)…

  →these are all intracellular co-infections, and are difficult to completely eradicate from the intracellular compartment. Consider 2 intracellular drugs simultaneously to improve clinical outcomes (doxycyline w/ macrolide, macrolide + rifampin, tetracycline + quinolone…) and use Plaquenil to alkalize the intracellular compartment to achieve better intracellular killing (Maurin et al. Phagolyosomal Alkalinization and the Bactericidal Effect of Antibiotics. J. Infect Dis1992; 166:1097-1102)

  If one regimen of an intracellular combo fails, rotate the regimen to another double intracellular regimen, and consider treating other co-infections not addressed (Babesiosis, viruses..)

# Infections In Chronic Lyme Disease

- 2) Parasites: Babesiosis/Piroplasmosis

- Classical Treatment options: Mepron (atovaquone) and a macrolide (Zithromax, Biaxin) +/- Septra, Malarone, Larium (mefloquine), Cleocin and Quinine or Biaxin , ?Riamet..

-CAM: Artemisinin (wormwood): anti-malarial, antiparasitic, antiviral, anti-tumor. Modified form of Artemesinin, artesunate, has been found effective for Babesia in vitro. Complete inhibition of B. equi and caballi occurred at 0,2 and 1.0 mcg/ml respectively.

-Dosage: 500mg/d x30-40 days for malaria, ? Best dosage for Bab

-In malaria, effective dose is 500-1000mg 1st day, then 500 mg/day x4 days (but relapse rate = 39%)

If the dosage is increased to 800 mg/day, relapse rate ↓ to 3%

In China they use 800-1600mg/d x 3 days, repeated in 2 wks

-Side effects: GI at high dose: ↓ apetite, N+, V+, diarrhea

-Contraindications: Pregnancy

# Artemesia: Scientific References


- Eckstein-Ludwig, U. et al. Artemesinins target the SERCA of Plasmodium falciparum, Nature 2003;424(6951):957-61
- Gordi et al. Artemesinin pharmacokinetics and efficacy in uncomplicated malarial patients treated with two different dosage regimens, Antimicrobial Agents Chemother 2002;46(4):1026-31
- Wong, J. et al. Therapeutic equivalence of a low dose artemesinin formulation in falciparum malaria patients, Journal of Pharmacy and Pharmacology 2003;55(2):193
- Jung, M. et al. Recent advances in artemesinin and its derivatives as antimalarial and antitumor agents, Curr Med Chem 2004;11(10):1265-84
- Hatimi, S. et al. In vitro evaluation of antileishmania activity of Artemesia herba Asso, Bull Soc Pathol Exot 2001; 94(1):29-31
- Kim, J. et al. In vitro antiprotozoal effects of artemesinin on Neospora caninum, Vet Parasitol 202;103(1-2):53-63

# CHRONIC PERSISTENT BABESIOSIS AFTER ACUTE TREATMENT WITH CLEOCIN AND QUININE, AND ATOVAQUONE AND AZITHROMYCIN

**12th International Scientific Conference on Lyme Disease, April 1999, New York City**
**Dr Richard Horowitz 4232 Albany Post Road Hyde Park, N.Y. 12538**

Persistent parasitemia after acute babesiosis was described by Krause (NEJM 7/98, Vol 339, 160-165) when patients were given Cleocin and Quinine (C+Q), and an experimental regimen with Atovaquone and Azithromycin (M+Z) was noted to possibly cure human babesiosis. Horowitz described significant clinical improvement in a cohort of chronic Lyme patients co-infected with babesia when given Atovaquone + Azithromycin, but relapses were seen at the completion of therapy, and PCR studies were needed to elucidate the eradication rate of the organism (Horowitz, R.I.: Atovaquone and Azithromycin therapy: A new treatment protocol for Babesiosis in co-infected Lyme patients, in Abstracts of the 11th International Scientific Conference on Lyme disease, NYC, NY April 1998). This report describes PCR + RNA evidence of persistent parasitemia with both antibiotic regimens.

## CHRONIC PERSISTENT BABESIOSIS AFTER ACUTE TREATMENT WITH CLEOCIN AND QUININE, AND ATOVAQUONE AND AZITHROMYCIN

**Results:**

72 of 189 serum specimens were PCR positive, and 38 of 58 specimens were RNA positive. 33 charts were analyzed among patients who received one or more courses of M+Z or C+Q and remained PCR and/or RNA positive post treatment. PCR testing and RNA testing remained positive up to 9 months and 5 months respectively, with several patients who were both IFA and PCR negative turning PCR positive after treatment. The majority of patients clinically improved while on the regimens but relapsed shortly after the antibiotics were stopped, with flares occurring often during treatment. Only 4 out of 27 patients became PCR/RNA negative post treatment. Crossing over from one regimen to the other was generally ineffective as PCR/RNA values remained positive, except in 2 cases. M+Z was better tolerated than C+Q, and lab values generally remained within normal limits with both regimens, with an occasional mild elevation of liver functions.

# Infections in Chronic Lyme Disease

- 3)Viruses: EBV, CMV, HHV6 & 8, W. Nile, Powassan encephalitis and other viral encephalitis

  -ex HHV6→there is a link to CFS/FM. Causes roseola in childhood & nearly 100% of adults are exposed. Can reactivate later in life 2º to immunol/envir factors→ can lead to hepatitis, meningoencephalitis.. ?cofactor in Autism, ADD, MS, FM, CFS

  -Classical treatment: antivirals (Valtrex, Famvir, acyclovir, gancyclovir..) ? Valcyte (ongoing trial at Stamford University by Dr Montoya)

  -CAM: Transfer factors (colostrum), mushroom derivatives that increase NK cells and T cells (1-3 and 3-6 B glucan..). Another scientifically proven compound is Olive leaf extract and its active component oleuropein. This was found by researchers at Upjohn labs to be virucidal against many viruses including herpes, influenza A, coxsackie and others.

  Juven B. et al. Sudies on the Mechanism of Antimicrobial Action of Oleuropein. Jnl of Applied Bacteriology 35 (1970), 559-567

# I: Infections in Chronic Lyme Disease

- 4)Candida and other fungi: ? Yeast syndrome→ yeast overgrowth in the intestinal tract leads to fermentation of dietary sugars and starches. Can be 2º to antibiotic use for Lyme disease

  Symptoms include: fatigue, HA's, dizziness, brain fog, abdominal pain with bloating, muscle and joint pain..& may overlap with classic Lyme symptoms

  Testing: Stool CDSA, Genova Diagnostics w/ sensitivity to fungal agents. Metametrix Organix test

  Classical treatment: Diflucan (fluconazole), Sporanox, Oral Nystatin

  CAM: High dose probiotics (acidophilus), Saccharomyces boulardii, Candibactin, Caprylic Acid, Berberain, Oregano oil, Garlic, Pau D'Arco

# II: Immune Dysregulation and Lyme

- Blebs are shed particles containing partial DNA, frequently plasmids.

-Radolf JD et al. Analysis of Borrelia burgdorferi membrane architecture by freeze-fracture electron microscopy. Journal of Bacteriology. Jan 1994;176(1):21-31

-Garon CF; Dorward DW; Corwin MD. Structural features of Borrelia burgdorferi-the Lyme disease spirochete: silver staining for nucleic acids. Scanning Electron Microscopy. 1989 3:109-115

- Highly stimulatory to the immune system

-Whitmire WM; Garon CF. Specific and nonspecific responses of murine B cells to membrane blebs of Borrelia burgdorferi. Infection & Immunity, 1993 61:1460-1467

- Intra-cellular blebs convert host cells into targets for the immune system

-Beerman C; Wunderli-Allenspach H et al. Lipoproteins from Borrelia burgdorferi applied in liposomes and presented by dendritic cells induce CD8(+) T-lymphocytes in vitro. Cell Immunology May 2000;201 (2):124-131

# II: Immune Dysregulation and Lyme

- Positive ANA, RF and other autoimmune markers (Plaquenil)
- Increased severity with genetic HLA markers (HLA DR2, 4)
- Elevated pro-inflammatory cells:

  -IL-6, TNF-α, IFN gamma

  - Propensity to excessive proinflammatory response in Lyme borreliosis. Kisand et al, APMIS. 2007 Feb; 115(2):134-41
  - Interleukin-6 is expressed at high levels in the CNS in Lyme neuroborreliosis. Pachner et al. Neurology 1997 Jul;49(1)c147-52
  - INF-gamma alters the response of Bb activated endothelium to favor chronic inflammation. J. Immunol. 2007 Jan 15;178(2):1172-9
- Decreased anti-inflammatory cells: IL-10
- Abnormal helper/suppressor cell ratio (CD4/CD8).
- Both Lyme and ASD have immune dysregulation, and it is known that systemic infections (Bb, viruses..) with associated inflammation can affect chronic neurodegeneration

Perry et al. Nature Reviews Immunology 7, 161-167 (Feb 2007)

# Mycoplasma Infections May Contribute to Immune Dysregulation in Chronic Lyme Disease

- **Discussion: (**con't) Mycoplasmas have been shown to interact non-specifically with B-lymphocytes resulting in the modulation of immunity promoting autoimmune reactions and rheumatoid diseases (Simecka et.al. Clin. Infect. Dis. 1993;17(Suppl 1):5176-5182). Mycoplasmal infections also increase proinflammatory cytokines including IL-1,2, and 6 (MJhlradt et.al. Infect. Immunol. 1991;58:1273-1280), and have been found in the joint tissues of patients with rheumatological diseases suggesting their pathogenic involvement (Furr et.al. Ann. Rheumatol. Dis. 1994;53;183-184). Further studies therefore need to be done to elucidate the role of mycoplasmal infections in Lyme Disease patients with chronic persistent symptomatology.

# III: Role of Inflammatory Mediators in Neurotoxicity

- Inflamm processes are involved in the neurotoxicity of AD and other CNS diseases. Microglia are activated by B amyloid & proinflamm cytokines. Activated microglia in turn release proinflamm cytokines (IL-1-β, IL-6, TNF-α) that may lead to neuronal death and dys(f) by a variety of mechanisms, including:

1) Enhancement of glutamate-induced excitotoxicity

2) Inhibition of long term potentiation, which limits (f) plasticity after neuronal injury

3) Inhibition of hippocampal neurogenesis

Recent studies have reported ↑ TNF-α levels in the CSF of AD pts, and a single nucleotide polymorphism in the TNF-α gene is associated w/ earlier onset AD

Lyme dx pts are known to have ↑ levels of IL-1, 6, & TNF-α. ?Role of these proinflamm cytokines w/ CNS LD

& ? Role of Actos/LDN to modulate levels of TNF-α/cytokines

# Role of Inflammatory Mediators and NO/ONOO Cycle in Illness

- A Common Etiologic Mechanism for CFS, MCS, FM, PTSD and ?CLD : Dr Martin Pall, Professor of Biochemistry and Basic Medical Sciences, Wash State Univ.
- Above illnesses share many sx in common
- Illnesses can be initiated by a variety of factors (viral, bacterial, physical or emot trauma, exposure to VOS's , pesticides…)
- These diverse stressors can all ↑ NO, and several can ↑ NMDA receptor activity & ↑ NO & its oxidant product peroxynitrite

# Role of Inflammatory Mediators and NO/ONOO Cycle in Illness

- NO → ↑ peroxynitrite → ↑ oxidative stress → stimulates NF-κB → ↑ production of iNOS (nitric oxide synthetase) → ↑ NO in a vicious cycle
- NF-κB → ↑ IL-1, IL-6, IL-8, TNF-α, IFNγ which may contribute to symptoms and signs of these varied illnesses
- Testing for immune dys(f): Autoimmune panel (ANA, RF, ESR, ss +ds DNA, Sjogrens AB's), Immunoglobulin levels and subclasses, HLA classes..
- Classical therapy: immune modulators (Plaquenil, DMARD's), drugs w/antiinflamm effect (macrolides, tetracyclines), IVIG for decreased immunoglob's
- CAM Therapy: focus on down-regulation of NO/ONOO cycle biochemistry with subsequent ↓ of inflammatory markers: Antioxidants, CoQ10, B vit's, α-lipoic acid, Mag++, Zn++, omega 3 FA's, glutathione precursors,…

# Role of Inflammatory Mediators and Cytokines in JH rxns

- Jarish-Herxheimer/Flare protocols:

-Alkalize: lemons/limes, Alka-Seltzer gold 4x per day (or Na bicarb) x 1-2 days and increase fluids

-Burbur or Parsley 10 drops q 10 min x 1-2 hours

-LDN: start 2mg HS, work up to 4.5 mg HS w/Pekana drainage remedies 15 drops each 3x/day

-Glutathione: IV 2g, oral, PR, dermal

# IV: Toxicity and Chronic Lyme Disease

- Environmental toxins: Multiple Chemical Sensitivity (MCS), Environmental Illness (E.I.) due to exposure to a multitude of chem's in the environment (PCB's, dioxins, plastics, heavy metals, TCE, VOS's..) We will focus on 3 major categories:
- 1)Heavy Metals
- 2)Mold
- 3)Biotoxins 2º to Lyme and associated co-infections/ External toxin exposure

# Magnitude of Exposure to Toxins

1. Pesticides: EPA office of Prevention, Pesticides, & Toxic substances
   - 1999 > 4 billion lbs. of pesticides produced
2. EPA: 1982 National Adipose Tissue Survey
   - 100% of Americans: benzene, xylene, toluene, styrene, dioxin, PCBs
     - These are some of the most potent cancer causing chemicals known to mankind
3. CDC: 2005, 6.5 million dollar study. Discovered 116 different toxins in over 50% patients studied (13 heavy metals, 14 combustion byproducts, 10 pesticides

# Toxicity Associated Symptoms & Conditions

- Headaches
- Mineral imbalances (zn & ca)
- Kidney dysfunction
- Fertility problems
- Abnormal pregnancy outcome
- Immune system depression
- Multiple chemical sensitivities
- Fibromyalgia
- Recurrent yeast infections
- Tinnitus
- Contact dermatitis
- Learning disorders
- Cancer
- Panic attacks
- Memory loss
- Parkinson's disease
- Broad mood swings
- Fatigue
- Chronic fatigue syndrome
- Muscle weakness
- Unusual response to meds or supplements
- Increasing sensitivity to exogenous exposures: odors, medications, etc.
- Worsening of symptoms after anesthesia or pregnancy

# OVERLAPPING SX OF HEAVY METALS AND TBD'S

| SYMPTOMS | HEAVY METAL | LD/CO-INFX |
|---|---|---|
| Fatigue | ✓ | ✓ |
| FMS sx | ✓ | ✓ |
| Joint pain | ✓ | ✓ |
| Paresthesias | ✓ | ✓ |
| Cognitive d/f | ✓ | ✓ |
| Ataxia / Incoordination | ✓ | ✓ |
| Abd sx | ✓ | ✓ |
| Urinary sx | ✓ | ✓ |
| Visual sx | ✓ | ✓ |
| Auditory sx | ✓ | ✓ |
| Psych sx | ✓ | ✓ |
| Wt loss | ✓ | ✓ |
| ↑ Suscept to infection | ✓ | ✓ |

| MERCURY | | |
|---|---|---|
| Sources | Biochemistry | Clinical Symptoms |
| - Mining and Chemical Industries<br>- Fish/Shellfish<br>- Dental work and medical treatment (thimerasol) | -SH binding<br>-Oxidative stress<br>-Penetrates nerves and binds to cysteines on Ach receptors resulting in neurologic dysfunction.<br>-retrograde axonal transport<br>-Denervation of nerve fibers similar to the pathology of MS, and Hg can leak into the BBB and reduce nerve conduction velocity and VEP | -CFS, FMS, joint pain<br>-metallic taste, changes in vision & hearing<br>-tremors, ataxia<br>-cognitive dysfunction, depression, irritability<br>-renal and GI disturbances<br>-weight loss<br>-increased susceptibility to infections<br>-peripheral neuropathy<br>-autoimmunity |

# LEAD

| Sources | Biochemistry | Clinical Symptoms |
|---|---|---|
| -Drinking water<br>-Dinnerware with lead glazing<br>-Paint products<br>-Soil around older homes painted with lead based paints are still contaminated with lead | -SH binding<br>-Alters calcium-mediated cellular processes<br>-Reduces nerve conduction velocity in peripheral nerves<br>-Interferes in the heme biosynthetic pathway leading to anemia | -Fatigue<br>-Encephalopathy with impaired concentration, short-term memory deficits, insomnia, anxiety, depression, irritability, decreased IQ<br>-Elevated BP, chronic renal failure, anemia<br>- Abd colic, peripheral nerve dysfunction, reproductive dysfunction |

# DMSA

- Heavy metals accumulate x years → leaves the blood → no longer measurable there → start compartmentalizing.
- DMSA diffuses into and effectively competes with tissue binding sites → releases metals from sequestered sites in tissues.
- Rationale for provocation test w/ chelating agent
  - Toxic metals accumulate in non-exchange pools in specific tissues.
  - DMSA disturbs the body stores of toxic metals & binds to them, so a certain quantity will redistribute into the blood as a stable complex → eliminated in the urine
  - Do a 6 hour urine DMSA challenge (30 mg/kg 1x dose)

# Levels of heavy metals post provocation w/ 6 hour urine DMSA challenge: ↑ Hg, ↑Pb, ↑As, ↑Cd

## URINE TOXIC METALS

DOCTOR'S DATA INC

CLIENT#: 26262
DOCTOR: Richard Horowitz, MD

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Hyde Park, NY 12538 U.S.A.

### POTENTIALLY TOXIC METALS

| METALS | RESULT µg/g CREAT | REFERENCE RANGE | WITHIN REFERENCE RANGE / ELEVATED / VERY ELEVATED |
|---|---|---|---|
| Aluminum | < dl | < 35 | |
| Antimony | < dl | < 5 | |
| Arsenic | 130 | < 100 | |
| Beryllium | < dl | < 0.5 | |
| Bismuth | < dl | < 30 | |
| Cadmium | 3.9 | < 2 | |
| Lead | 42 | < 15 | |
| Mercury | 13 | < 3 | |
| Nickel | < dl | < 12 | |
| Platinum | < dl | < 2 | |
| Thallium | 0.9 | < 14 | |
| Thorium | < dl | < 12 | |
| Tin | 3.3 | < 6 | |
| Tungsten | < dl | < 23 | |
| Uranium | < dl | < 1 | |

### CREATININE

| | RESULT mg/dL | REFERENCE RANGE | 2SD LOW 1SD LOW MEAN 1SD HIGH 2SD HIGH |
|---|---|---|---|
| Creatinine | 12 | 60- 160 | |

### SPECIMEN DATA

Comments:
Date Collected: 3/11/2003
Date Received: 3/14/2003
Date Completed: 3/15/2003

Method: ICP-MS
<dl: less than detection limit
Provoking Agent: DMSA

Collection Period: Timed
Volume:
Provocation: POST

Toxic metals are reported as µg/g creatinine to account for urine dilution variations. **Reference ranges are representative of a healthy population under non-challenge or non-provoked conditions.** No safe reference levels for toxic metals have been established.

V10.00

# Importance of Detoxifying Heavy Metals

- 15-20 % of CLD pts improve sx of fatigue, myalgias, arthralgias, and neuro-cognitive sx with detoxification of heavy metals
- ? Responsible for AI overlap in certain CLD pts (Hg)
- Heavy metal burden may lead to mineral deficiencies (Mag++, Zn) and has an effect on immune (f), oxidative stress, and inflammatory cytokines
- Testing: 6 hr urine DMSA challenge to Doctors Data. Use 30mg/kg 1x as a loading dose
- Treatment: Chelation using DMSA 100-200 mg Q3rd night with Algas (10 drops) and Chlorella (split cell, 7 tab's) w/ 600 mg NAC, Med Caps DPO (B vitamins, NAC, α-lipoic acid..), DMPS, EDTA

  Replace minerals the next day (MTV w/ Ca, Mag, Zn)

# IV: Toxicity and Lyme Disease

- Apart from heavy metal toxicities, the most common toxic exposures include external toxins (PCB's, Dioxins, Plastics and plasticizers, Pesticides, VOS's..) and mold exposure →

  -CDC 2003: 6.5 million $ study w/ 2500 patients: found 116 different pollutants (13 heavy metals, 14 combustion byproducts, 10 pesticides) One of those toxins TCE, was responsible for a leukemia outbreak in Woburn, MA, and frequently causes learning disabilities, paresthesias...

- Testing: Accuchem labs, Texas; Stachybotris titers
- Other toxins may result from exposure to bacteria and viruses, ie biological effects of these agents in our bodies ( Bb tox 1, Quinolinic Acid…)

# Role of Endogenous Exotoxins

- Quinolinic Acid (Quin) is a neurotoxic metabolite of the L-tryptophan-kynurenine pathway that activates the NMDA receptor class of excitatory AA receptors to produce excitotoxic lesions. Lyme dx pts have been shown to have ↑ levels of Quinolinic acid. ? Role in CNS dx ?Role for IV GSH & antioxidant therapies

1) -Oxidative stress as a mechanism for quinolinic acid-induced hippocampal damage: protection by melatonin and deprenyl W.M.H. Behan, et al. British Jnl Pharm (1999) 128, 1754-1760
2) -Enhanced neuronal damage by co-administration of quinolinic acid and free radicals, and protection by adenosine A2A receptor antagonists W.M.H Behan et al. British Jnl Pharm (2002) 35, 1435-1442
3) -Neuroprotective effects of the mGlu5R antagonist MPEP towards quinolinic acid-induced striatal toxicity: involvement of pre- and post-synaptic mechanisms and lack of direct NMDA blocking activity. Popoli et al. Jnl of Neurochemistry 2004, 89, 1479-1489
4) -Quinolinic Acid Is Extruded from the Brain by a Probenecid-Sensitive Carrier System: A Quantitative Analysis. Morrison et al, Jnl of Neurochemistry 1999, 72, 2135-2144

# Glutathione

- IV GSH has been shown to be effective in a subset of resistant Lyme patients, implying a need to include a detoxification regime in the treatment plan.
- Detox protocols would include Mag++, NAC, GLY, α lipoic acid, DIM, sulforaphane glucosinalate, diet w ↑ prot, crucif veg's
- IV GSH also addresses heavy metal burden, but it is unclear which chem's/toxins are being removed w/ treatment. Since GSH may have an effect within min's in select pts to improve CNS (f), is there an effect on removing inflamm cytokines & Quinolinic acid?

# Intravenous Glutathione: A Novel Approach for Treating Resistant Symptoms in Chronic Lyme Disease

## Background:

Chronic Lyme Disease must be seen in the light of multiple tick borne diseases, including HME, HGE, Babesiosis, Mycoplasma infections, and Bartonella henselae. The mechanisms responsible for ongoing symptoms have been hypothesized to be secondary to persistent Borrelial infection, occult and/or resistant co-infections, autoimmune mechanisms, and/or other neurotoxins.

Among known toxins, heavy metals such as mercury and lead have been found in Lyme disease patients with a small percentage of patients (10-15%) reporting improvement in resistant symptoms (fatigue, joint aches, cognitive dysfunction) with removal of the corresponding heavy metals (Horowitz, Abstract 16th International Lyme Conference, June 2003).

A novel approach to remove toxins from the body involves Glutathione (GSH) (Perlmutter, 2000). GSH is an endogenous peptide made in the liver, which plays an important role in various metabolic functions including its role as an antioxidant and in Phase II liver detoxification of various chemicals. A trial of GSH was therefore undertaken to determine its role in patients with Lyme Disease with chronic resistant symptoms.

## Method:

118 patients with Lyme Disease were given IV GSH over a 5-10 minute period. 80 patients were given 1000mg of GSH and 38 patients were given 2000mg of GSH. The GSH was stored in a refrigerator and protected from direct light until patient administration. Patients' symptoms scores before and after treatment with GSH (0-100% self reported scale) were recorded after a 30-minute interval.

## Results:

Among 80 patients given 1000mg GSH, 36% (29/80) had no clinical improvement (0% improvement on self-reported scale), 40% (32/80) had a mild clinical improvement (1 to 10% improvement), 6% (5/80) had moderate clinical improvement (11 to 20% improvement), and 18% (14/80) had marked clinical improvement (21 to 60% improvement in clinical symptom scores). Mean improvement in symptoms after 30 minutes of 1000mg of GSH administration was 9%.

Among 37 patients given 2000mg of GSH, 27% (10/37) had no clinical improvement, 46% (17/37) had mild clinical improvement, 16% (6/37) had moderate clinical improvement, and 11% (4/37) had marked clinical improvement. Mean improvement in symptoms after 30 minutes of 2000mg of IV GSH was 9.5%.

Improvements from a single dose of IV GSH lasted from several hours to 2-3 days before patients experienced a relapse in symptoms. There were no significant adverse effects from GSH except for transient nausea & rare pressure like feelings and paresthesias. One patient had a vagal event with needle insertion (before GSH administration) and 2 patients experienced a flare up of Lyme symptoms after injection, which subsequently resolved.

## Intravenous Glutathione: A Novel Approach for Treating Resistant Symptoms in Chronic Lyme Disease

Results: (cont'd)

There were also 8 chronic Lyme Disease patients who underwent a 1-2 month GSH trial, with doses ranging from 400mg IV 3x/wk to 2000mg per day. These patients generally comprised a group of difficult to treat "non-responders". There were no adverse side effects from longer-term use of GSH. Among that group, 1 patient out of 8 had no clinical response, and the other 7 patients had sustained positive clinical improvements ranging from 10% to 35%, with a mean improvement of 20%. These patients reported consistent improvements in cognitive functioning, energy, headaches, muscle strength, muscle pain, and joint pain.

# Discussion:

Patients who experienced the most significant benefit from Glutathione were often patients who had failed multiple antibiotic regimens in the past and were considered treatment resistant. Several patients who had significant neurologic dysfunction with dysarthria, incoordination, and muscle weakness experienced a rapid and dramatic improvement in symptoms with a single dose of IV GSH.

Metabolic functions of GSH include DNA synthesis and repair, protein synthesis, prostaglandin synthesis, amino acid transport, enzyme activation, prevention of oxidative cell damage, enhancement of immune system function, and metabolism of toxins and carcinogens (Annals of Pharmacotherapy: Glutathione in Health & Disease: pharmacotherapeutic issues:1995 Dec., Vol. 29, 1263-1273). Since patients reported improvement in fatigue, joint pain, muscle pain, mood swings, headaches, balance, dizziness, speech problems, and cognitive difficulties within 30 minutes of administration, GSH may be acting to metabolize toxins in the short term, and may have an effect on prostaglandins, interleukins, oxidative stress & immune modulation in the long term. Alternatively, the rapid initial improvement in symptoms may be a placebo response due to the novelty of trying a new treatment approach; however, the sustained response among patients given longer term treatments suggests that something other or in addition to a placebo response is in effect.

# Modulators of Phase I Metabolic Pathways of the Liver Cytochrome P450

- Ellagic Acid
- Watercress glucosinolates
- Green Tea Catechins
- Silymarin

# Upregulation of Phase II Metabolic Pathways of the Liver

**Glutathione Conjugation**
- Glutathione
- NAC
- Ellagic Acid
- Watercress
- Silymarin

**Sulfation**
- Sodium Sulfate
- MSM
- Cysteine
- Alpha Lipoic Acid

**Amino Acid Conjugation**
- Glycine

**Glucuronidation**
- Preventium
- Artichoke Leaf

**Acetylation**
- Pantothenic Acid
- Magnesium
- Vitamin B6

**Methylation**
- Folate
- Vitamin B12
- Vitamin B6

Prostaglandins
Leukotrienes
Petroleum Distilates

Estrogen
Testosterone
Thyroxine
Cortisol
Adrenaline
Melatonin
DHEA

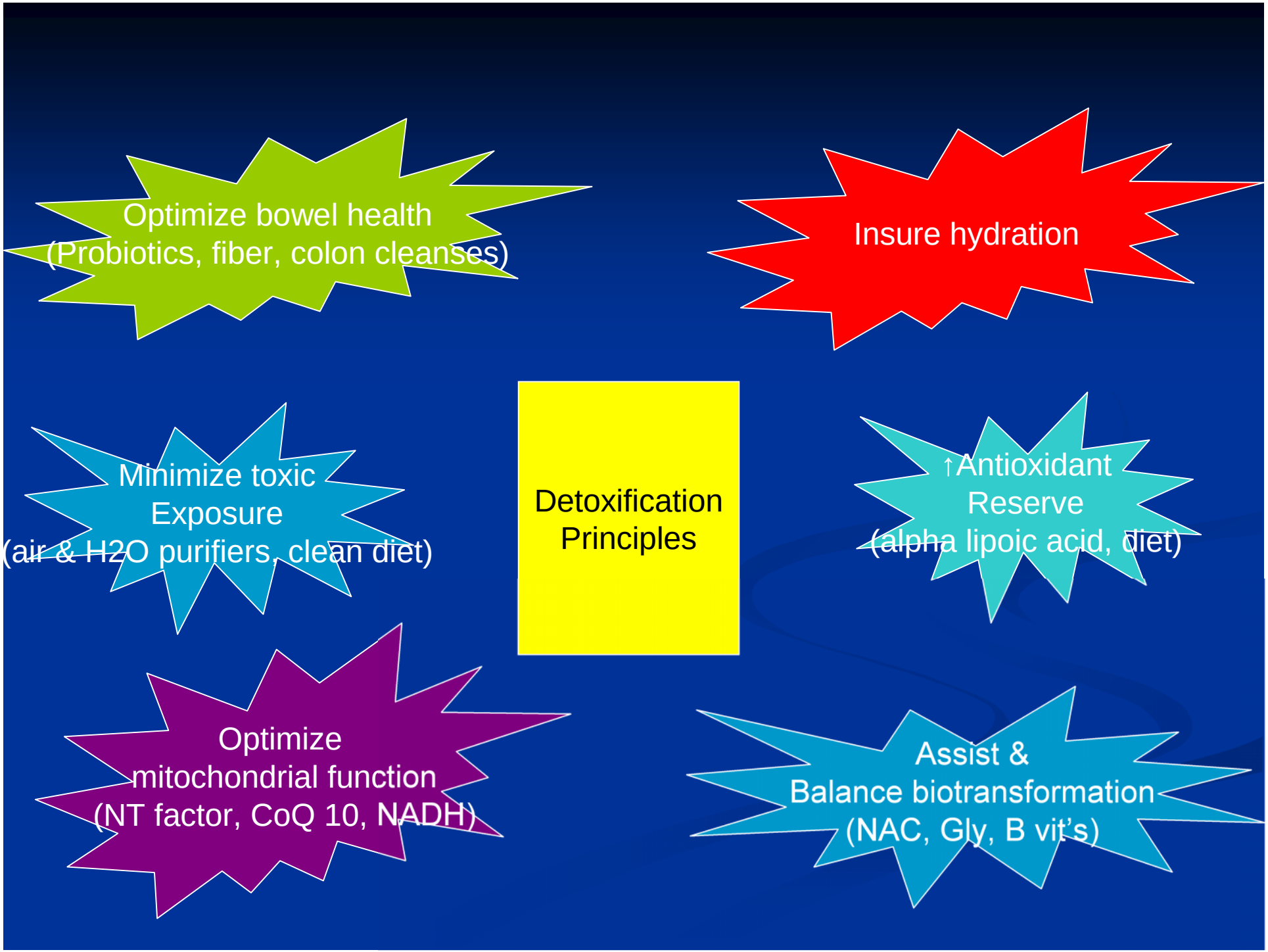
Bile Acids

PABA

Estrogen
Fat Soluble Vitamins
Steroid Hormones
Pesticides (DDT)

Histamine

Estrogen
Mercury
Lead
Cadmium
Dopamine
Epinephrine


Optimize bowel health
(Probiotics, fiber, colon cleanses)
Insure hydration
Minimize toxic
Exposure
(air & H2O purifiers, clean diet)
Detoxification
Principles
↑Antioxidant
Reserve
(alpha lipoic acid, diet)
Optimize
mitochondrial function
(NT factor, CoQ 10, NADH)
Assist &
Balance biotransformation
(NAC, Gly, B vit's)

# Detoxification/Chelation/Nutritional Supplementation

- Detoxification: Skin (saunas), Colon (probiotics, fiber, ?Questran, cleanses), Kidneys (↑fluids), liver ( vit's, min's, herbs to ↑ phase I & II detox pathways)
- Chelation : 6 hr urine DMSA challenge, then using oral (DMSA, DEPEN..), rectal (EDTA), transdermal (DMPS, GSH), or IV (DMPS, EDTA) to remove heavy metals, replacing minerals. A recent study at the HVHAC found that 100mg DMSA Q 3rd night x mo's to be safe & effective, w/ ALA, chlorella, NAC, replacing vit/min's
- Nutritional Supplementation : Focus on using NAC, Glycine, DIM, Sulforaphane glucosinalate, Med Caps DPO, α lipoic acid, MTV w/ min's (Mag++, Zn+..)
- Effect of Toxins on an Individual: Notion of Toxic load/ individual susceptibility/genetics

# V: Allergies and CLD

- Food allergies are frequently seen in the general population, especially to common allergens such as wheat, dairy, corn, nuts, shellfish, food dyes and additives, etc. It may present as an immediate hypersensitivity reaction (IgE), or delayed hypersensitivity reaction (IgG)
- Allergies are a common complaint of indiv's with CFS & FM, and are frequently seen in E.I. Syndrome
- They may be related to Candidiasis and a leaky gut, and should prompt investigation into these 2 diagnoses
- Common manifestations: fatigue, headaches, allergic rhinitis, eczema, asthma, irritability, concentration prob's
- Testing: local IGE (Quest, expanded food allergy profile), or IgG (Metametrix 90 food allergy panel)
- Treatment: Classical: Avoidance, rotation diets, Immuniz's
- Treatment: CAM: plus treat underlying Candida or leaky gut if present, use enzyme therapy, ?NAET, NMT….

# VI: Nutritional & Enzyme deficiencies

- Digestive disorders which are common in CFS may stem from an enzyme deficiency
- Enzyme deficiencies → poor digestion of proteins, carbohydrates, and fats → deficiency of vital nutrients necessary for proper cellular function
- Detoxification reactions of environmental chemicals require an ongoing supply of essential vitamins, minerals, AA's, fatty acids and phytonutrients to be effective. The higher the toxic load, the more likely nutritional deficiencies will be present in an individual

# Effect of Mineral Deficiencies on Biochemical (f)

- Mag++ → Nec in appx 300 detox enzymes in the body. Deficiency results in muscle spasm, tremors, anxiety, Raynauds phen, arrhythmias,
- Cu+ → SOD (free radicals), polyphenol oxidase (detox chem's), tyrosinase & dopa oxidase (neurotransmitters), Cytochrome C oxidase (energy)
- Zn++ → Nec in > 90 enzymes (alcohol dehydrogenase, Phase I rxn, converts alcohols → aldehydes. If low, biochem bottleneck, with shift to chloral hydrate and toxic brain symptoms)

-Older pts gen have signif lower level of plasma Zn, ↑ levels of inflammatory cytokines and IL 10, and ↑ plasma oxidative stress. Compared to the placebo gp, Zn supplemented gp had ↓ incidence of infections, ↓ TNF-α, & ↓ plasma oxidative stress markers (NIH funded study)

Am J Clin Nutr 2007; 85: 837-844

# VI: Nutritional & Enzyme deficiencies

- Testing: serum minerals (Mag++, Zn..), RBC minerals (Mag++), AA & FA analysis, ION test/ Organix test (Metametrix labs) to test functional biochemical pathways
- Lipid peroxides, sulfates, nitrates (Metametrix) to check free radical exposure (important in CNS disease, ALS…), detox pathways, NO pathway (indirect)
- Treatment: Replace vit's, minerals, AA's, EFA's, enzymes (plant or pancreatic w/amylase, lipase, proteases)
- CAM: ? Role of enzymes between meals for viral inf's/ inflammation

-Morley, J.E. et al. Nutritional Modulation of Neural Function. UCLA Forum in Medical Sciences 28 (San Diego, CA: Academica Press, 1988)

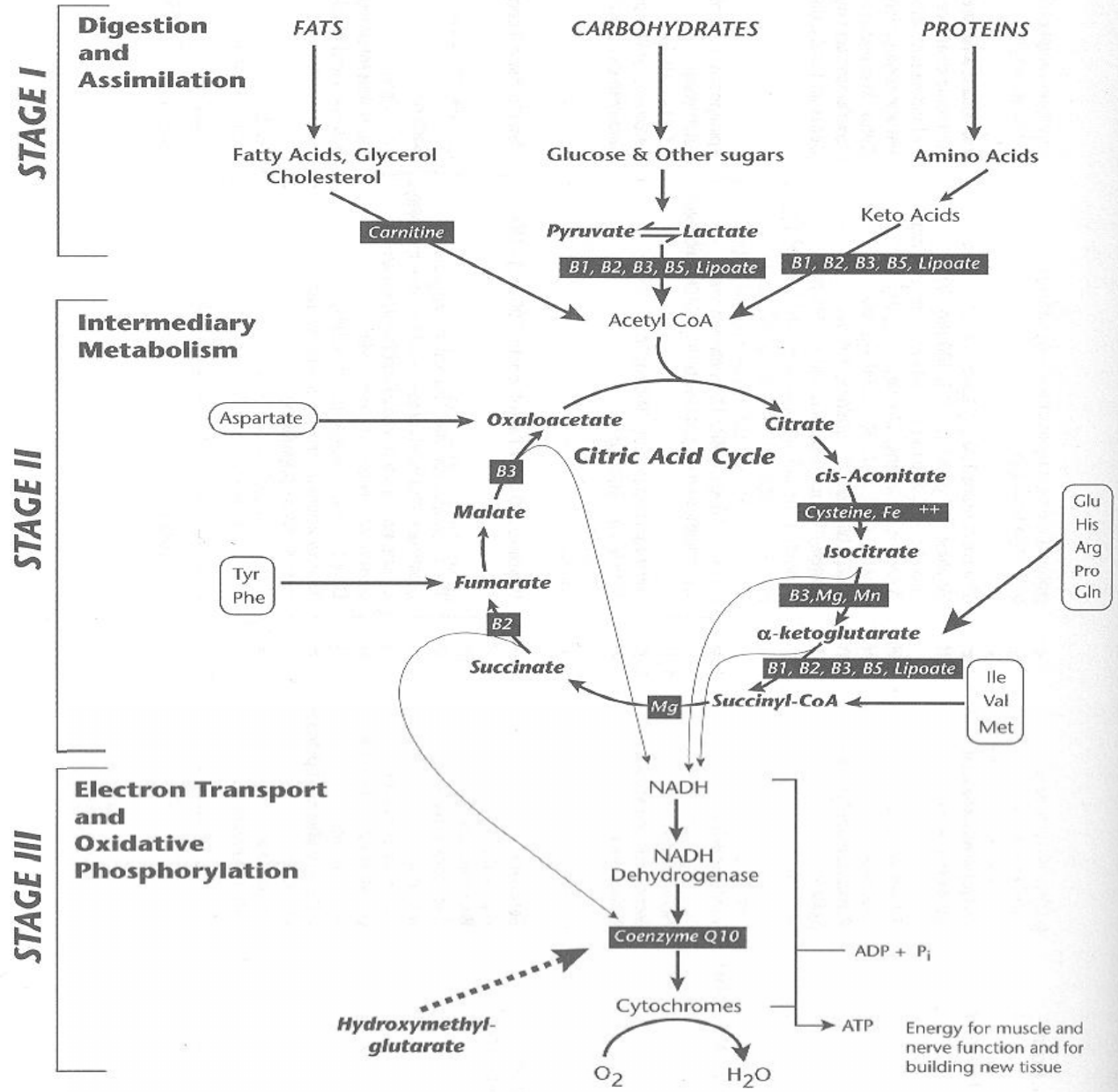
-Jaeger, C.B, et al. "Polymer Encapsulated Dopaminergic Cell Lines as 'Alternative Neural Grafts' Progress in Brain Res 82 (1990), 41-6

# VII: Mitochondrial Dysfunction

- Mitochondrial membrane components are especially susceptible to free radical damage, as they are exposed to molecular 02 which is constantly utilized for ATP production, and have high concentrations of molecules that are easily oxidized (unsaturated fatty acids).
- Certain nutrients are essential for proper mitoch (f) and energy production, ie CoQ10, NADH, L-carnitine, essential phospholipids, α-keto glutarate
- Testing: lipid peroxides, Organix test (Metametrix) may provide indirect evidence through nutritional deficiencies, free radical exposure
- Treatment: NT factors (gycosylated phospholipids), CoQ10, NADH, L-carnitine

-Laboratory Evaluations in Molecular Medicine: Nutrients, Toxicants, and Cell Regulators. J. Alexander Bralley, PHD. IAMM, Norcross, GA

-Seidman, M. Polyunsaturated PC in NT factor improves mitochondrial function. Anti Aging Med Nov 2001


STAGE I
Digestion and Assimilation
FATS
CARBOHYDRATES
PROTEINS
Fatty Acids, Glycerol Cholesterol
Glucose & Other sugars
Amino Acids
Keto Acids
Carnitine
Pyruvate ⇌ Lactate
B1, B2, B3, B5, Lipoate
B1, B2, B3, B5, Lipoate
Acetyl CoA
STAGE II
Intermediary Metabolism
Aspartate
Oxaloacetate
Citrate
Citric Acid Cycle
B3
Malate
cis-Aconitate
Cysteine, Fe ++
Isocitrate
Glu
His
Arg
Pro
Gln
Tyr
Phe
Fumarate
B3,Mg, Mn
α-ketoglutarate
B2
Succinate
B1, B2, B3, B5, Lipoate
Mg
Succinyl-CoA
Ile
Val
Met
STAGE III
Electron Transport and Oxidative Phosphorylation
NADH
NADH Dehydrogenase
Coenzyme Q10
ADP + Pi
Cytochromes
ATP
Hydroxymethyl-glutarate
O2
H2O
Energy for muscle and nerve function and for building new tissue

# VIII: Psychological Factors In CLD

- Many patients with CLD have overlapping psychological dys(f), ie history of depression, anxiety, OCD, PTSD with abuse (physical, emotional, sexual)
- Lyme and associated co-infections will cause previous psychological patterns to intensify, or cause new patterns to emerge (ie psychosis, manic-depressive disorder..)
- Health care providers should ask about previous psych hx, and refer for counseling/psychiatric help.
- Treatment: Medications (SSRI's, buproprion, Remeron, anxiolytics,), Stress reduction (yoga, meditation, TaiChi)

  CAM: Herbs (SJW, Valerian, Kava Kava L-theanine), Cognitive processing therapy (PTSD), Journey work (Brandon Bays), ?EFT…

# IX: Endocrine Abnormalities

- Hypothalamic-pituitary axis may be affected → check FSH, LH, GH and IGF1, TSH & ACTH levels, DHEA/Cortisol, sex hormones
- Impt to test full TFT's (new range TSH 0.5-2.5; 1 or less may be necessary for significant clinical improvement) with thyroid AB's,T3, T4, rT3, T3/rT3 ratio. Consider TRH stimulation test= Gold standard.

  A poorly functioning thyroid converts T4 to rT3 (can be w/ stress, fasting, illness, increased cortisol) & leads to low T3 syndrome
- "Normal" ranges may not be applicable
- ? Xenoestrogens/toxins blocking receptor sites→ certain pts need to have hormone levels at the higher range of "normal" to have clinical improvement

# Endocrine Problems Among Lyme Patients : Adrenal Fatigue

- Adrenal fatigue: A spectrum disorder in between Addison's and Cushing's disease
- Etiology: Any form of chronic stress (physical, emotional, psychological, environmental, infectious, in combination)
- Symptoms: fatigue, non-regenerative sleep, salt craving, hypoglycemia, ↓ libido,

  low BP/ postural hypotension, depression/irritability, ↓ memory/focus, ↑ time to recover from illness, injury, or trauma
- Associated Diseases: CFS, Fibromyalgia, alcoholism, RA, Chronic allergies/asthma

# Laboratory Testing for Adrenal Fatigue

- Problems w/ blood testing: population used to standardize the tests may have included many people w/ some level of adrenal fatigue, & lab tests are defined & standardized based on statistical norms, not physiologically optimal norms
- 24 hr urinary cortisol test → if levels are in the bottom 1/3 of "Normal" range, suspect ↓ adrenal (f)
- Blood tests: do not measure tissue levels
- ACTH Challenge: + if cortisol levels < 2x ↑
- DHEA/Cortisol salivary testing: measures tissue levels, reliable marker. Labs: Aeron, Metametrix, Genova, Diagnostek.
- Consider adrenal suppl's (B vit's, Vit C, rhodiola, licorice..) and low dose Cortef for replacement if ↓ levels

# X: Sleep Disorders

- Impaired sleep correlates directly with impaired immune functioning

  -Sleep and the immune system. Int J Immunopharmacol 1995;17:649-54

  -Sleep, neuroimmune and neuroendocrine functions in fibromyalgia and chronic fatigue syndrome. Adv Neuroimmunol 1995;5:39-56

  -Adv Management of sleep disorders in fibromyalgia. Rheum Dis Clin North Am. 2002;28:53-65

- Sleep disorders are commonly associated with chronic inflammatory diseases and chronic age/stress disorders, such as RA, FM, and CFS.

  -Lorton D et al. Neuroimmunomodulation. 2006;13(5-6):357-74. Epub 2007 Aug 6

  -M. Haack, et al. J Pain; April 2004, Supplement 1, Vol 5, no 3

- Chronic sleep restriction leads to elevations in IL-6 and pain symptoms in healthy volunteers.

  -M. Haack, et al. J Pain; April 2004, Supplement 1, Vol 5, no 3

# X: Sleep Disorders

- Causes: Obstructive Sleep apnea, Medications, Caffeine, Nocturia, Depression/Anxiety, RLS..
- Evaluation: Sleep Study if unresponsive to standard treatment regimens
- Treatment : Activating Agents in the AM, Sleep promoting agents in the PM, especially those that encourage stage 3/stage 4 REM sleep (Lyrica, Trazadone, Gabitril, Seroquel, Xyrem)
- CAM: check neurotransmitter levels. Balance neurotransmitters with 5-HTP, to increase GABA. Valerian root, L-theonine also useful

# X: Sleep Disorders, Normalizing the Amplitude of Circadian Rhythm

- Activating Agents (AM)
  - Modanifil (Provigil)
  - Stimulants
  - Bupropion (Wellbutrin)
  - Noradrenergic Agents
  - SSRI's
  - Activating Atypicals
  - Thyroid
- Sleep Promoting (PM)
  - Pregabilin (Lyrica)
  - Trazadone
  - Gabitril
  - Seroquel
  - Xyrem
  - Non-Benzos: Ambien, Lunesta, Sonata
  - Benzodiazepines
  - Mirtazipine (Remeron)
  - Doxepin, Elavil
  - Melatonin, Ramelton

# XI: Autonomic Nervous System Dysfunction

- The ANS involves elements of the CNS (brain & spinal cord), and PNS, sensory motor branches, which is controlled by the hypothalamus. It regulates automatic body functions such as breathing, heart rate, and digestion.
- The Parasympathetic nervous system: ↓ heart rate, and BP, but increases gastric secretion and intestinal activity
- The Orthosympathetic nervous system is associated with arousal and stress, increases heart rate, BP and muscle tension and regulates the contraction and expansion of blood vessels.

# XI: Autonomic Nervous System Dysfunction

- Certain Chronic Lyme disease patients will complain of fatigue, dizziness, & concentration problems despite classical therapies. BP will be low on exam (< 90/60), with associated tachycardia (> 100 BPM) at rest.
- Testing: Tilt table test, blood pressure log with home readings
- Treatment: salt (minimum 3-4 grams/day), increase fluids (3 liters +), consider Florinef, Cortef, and/or B blockers if inadequate response

# XII: Gastointestinal Disorders

- Celiac disease: one of several malabsorption syndromes, due to gluten sensitivity. Clinical features include muscle wasting, small stature, weight loss, paresthesias, muscle cramps, diarrhea. Look for laboratory evidence of malabsorption: ↓ albumin, chol, Ca++, Mag++, B12, w/ macrocytic anemia, ↓ Fe, K+
- Testing: Antigliadin AB, TTG, avoid gluten as therapeutic trial
- Other GI: Crohns, UC, parasites, Candida/Leaky gut/dysbiosis, other malabsorption syndromes

# XIII: Elevated LFT's

- Patients frequently present with ↑ LFT's at some point during treatment.
- Etiologies: Tick-borne disorders - (Ehrlichiosis/Anaplasmosis, Q-Fever, Babesia..), antibiotics, ETOH use, Hepatitis, Hemochromatosis, Wilson's disease, Autoimmune, hyperlipidemia, chemical or drug exposure
- Testing: ANA, Hep B, C screen, Fe-TIBC/Ferritin, Ceruloplasmin levels, α-antitrypsin levels, tick-borne panel, lipid levels..
- Treatment: Treat symptomatically if above etiologies ruled out. CAM: Milk thistle (silymarin), Hepa #2 (TCM), NAC, alpha lipoic acid..

# XIV: Drug Use/ Addiction
# XV: Deconditioning

- Some CLD patients present with severe pain, and may be on chronic NSAID's & high dose narcotics to control pain.
- Narcotics may interfere with deep, regenerative sleep, and rebound pain and headaches may result which becomes part of a chronic symptom complex which is difficult to treat. Consider a pain management specialist for resistant pain and detox program if appropriate.
- Patients need to be placed on a regular exercise program once their physical condition permits. Start slow and refer to PT/OT if overlapping muscle weakness and fine motor coordination are affected.

# Role of Integrative Therapies in CLD

- HVHAC has seen over 11,000 CLD pts over the last 20 years. Antibiotics are useful in treating the underlying infections, but do not clinically appear to completely eradicate the infections as the vast majority of patients relapse upon discontinuation of antibiotics. Therefore CAM therapies have been investigated as an alternative to antibiotics.
- Success in treating patients requires addressing the 3 I's: Infection, Immunity, and Inflammation while investigating other overlapping etiologies responsible for ongoing sx (hormones, heavy metals, neurotoxins, viruses, parasitic infections, leaky gut, food allergies, autoimmunity….)

# Herbal/CAM therapies used for Chronic Lyme Disease

- Buhner protocol (Samento, Andrographis, Japanese knotwood..)
- Schart protocol (Diflucan/ Pen)
- Zhang protocol (TCM → Coptis, HH, Circ P)
- Homeopathic protocols (Ledum, syphilitic and malarial nosodes)
- Salt & Vit C protocol
- Rife machines

-None of these have been scientifically validated by large controlled studies

# Cowden Protocol Results

- Full Cowden protocol, no AB's : N=50

  → 70% had improvement in sx (scale -3 to +3), median at 2 (moderate improvement) w/ 6/50 (12%) w/ mild improvement, 14/50 (28%) w/ moderate improvement, and 15/50 (30%) w/ significant improvement. There was also a 35% overall improvement (scale 0-100%)

- Limited Cowden protocol, no AB's : N= 32

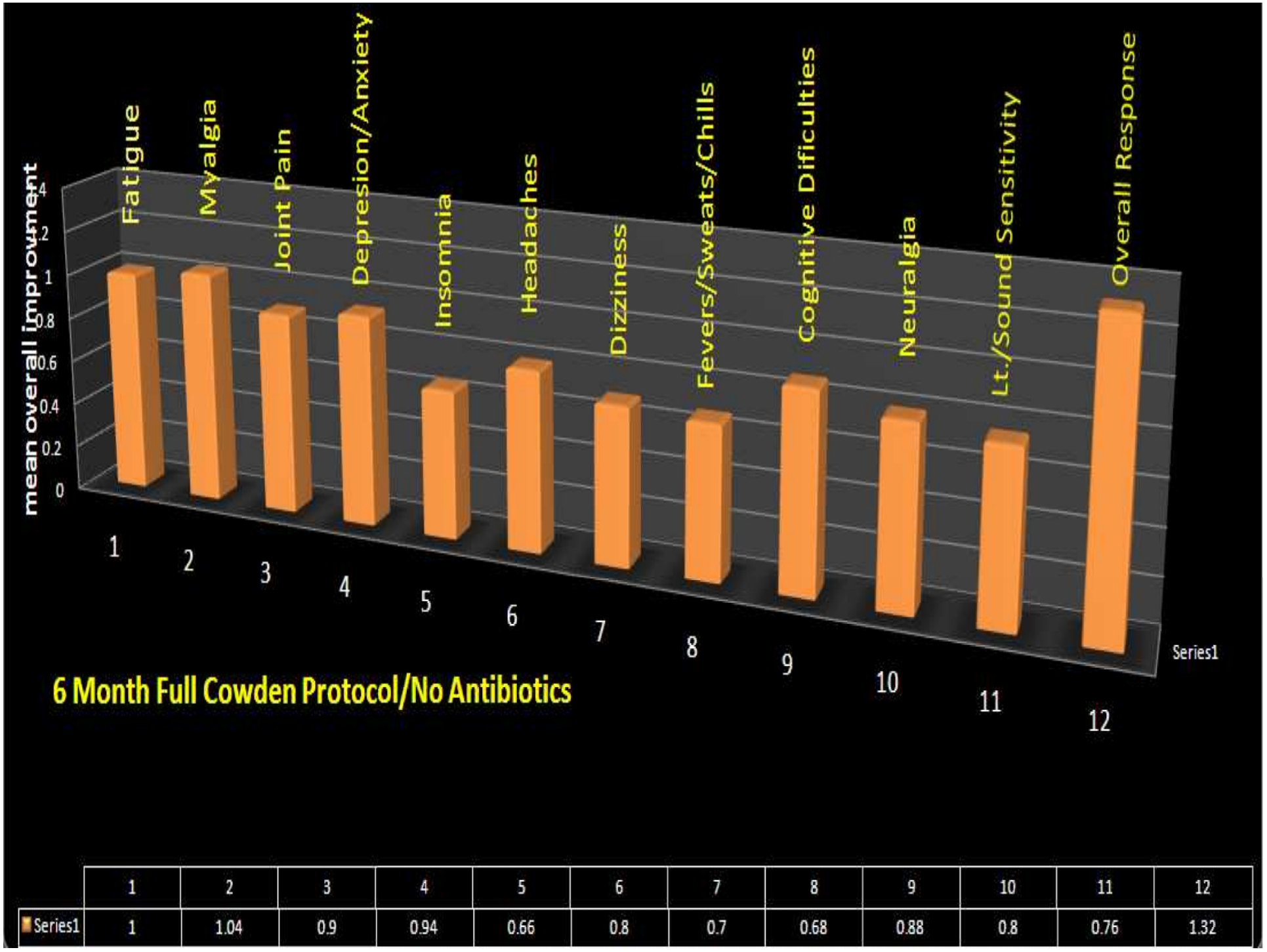
  → 72% had improvement in sx (scale -3 to +3), median at 2 (moderate improvement) w 6/32 (19%) w/ mild improvement, 11/32 (34%) w/ moderate improvement, and 7/32 (22%) w/ significant improvement. There was also a 13.7% overall improvement (scale 0-100%)

- Full Cowden protocol, w/ AB's : N=13

  → 77% had improvement in sx (scale -3 to +3), median at 1 (mild improvement) w/ 8/13 (62%) w/ mild improvement,1/13 (8%) w/ moderate improvement, and 2/13 (15%) w/ signif improvement. There was also a 12.7% overall improvement in sx (scale 0-100%)

- Limited Cowden protocol, w/ AB's : N=37

  → 66% had improvement in sx (38% mild improvement, 28% moderate to signif improvement), median at 1 (mild improvement) w/ 1.5% overall improvement (scale 0-100%)




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Series1 | 1 | 1.04 | 0.9 | 0.94 | 0.66 | 0.8 | 0.7 | 0.68 | 0.88 | 0.8 | 0.76 | 1.32 |

# Putting It Together: Integrating Classical and CAM therapies

- Herbs can be added at any time during an antibiotic protocol to address inflammation and elevated cytokines (andrographis, polygonum/resveratrol, smilax, stephania, samento…) and to ↓ the number of antibiotics used, especially if there is GI intolerance
- Once a patient has achieved a significant level of improvement, consider rotation onto an herbal protocol, and maintain for at least 1 year (relapses were seen with the Cowden protocol < 6 months).
- Controlled clinical trials need to be done to evaluate the role of different herbal medicines in Chronic Lyme Disease. It is not known at this time which combination of herbs in different clinical circumstances may yield the safest and most efficacious results.

# Putting It Together: Integrating the 15 Differential Diagnoses into a Comprehensive Treatment Plan

- Chronic Lyme Disease is a symptom complex of borreliosis and multiple co-infections with associated inflammation and immune dysfunction. Treat the 3 "I's" simultaneously
- Treating all 3 forms of Bb, co-infections, hormonal abN's, heavy metals and neurotoxins, sleep d/o, psychiatric issues, and nutritional deficiencies are the most commonly found abN's at the HVHAC that have the greatest impact on regaining health
- Evaluate all 15 differential diagnostic categories and prioritize those that most need to be addressed early on in the illness

# Putting It Together: Chronic Infections and Neurobiological Effects

- These agents create inflammation through various pathways (IL-1, IL-6, TNF-α, NO and its metabolites) which creates free radicals and oxidative stress which damages cell membranes, mitochondria, and nerve cells
- Some infectious agents produce neurotoxins (Quinolinic Acid..) which affect nerve cells
- Autoimmunity may also result from antibodies cross reacting with our own tissue antigens
- Mitigating these effects requires treating the 3 I's (infection, immune issues, inflammation) while supporting detox pathways and eliminating environmental triggers (heavy metals) which ↑ inflammation as well as addressing ALL issues found during the evaluation of 15 differential diagnoses

“Wisdom is the marriage of knowledge and experience bound by compassion.”