ENDOCRINE ASPECTS OF CHRONIC INFECTIONS

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Disclosures

- ❑ I have no relevant financial or non-financial relationships to disclose.

- ❑ All references to off-label or non-FDA approved usage in this presentation will be noted and disclosed.

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HORMONE OPTIMIZATION

- ❑ Resigned psych. res. (Drugs for Sxs!); Disaffected with gen. practice (Drugs for Sxs!)
- ❑ 2004: Bioidentical HRT—remarkable improvements in most patients!
- ❑ Gave fatigued, brain-fogged, achy patients Natural Desicc. Thyroid (NDT=4:1 T4/T3)
- ❑ NDT helped many!, made some worse→Dx: hypocortisolism—dramatic improvements with cortisol (hydrocortisone) and DHEA
- ❑ Realization: Endocrine assoc. guidelines—"the science"→GROSS Underdiagnosis + Undertreatment of hormone deficiencies due to FALSE PARADIGMS.

See Lindner, HH. Hormonerestoration.com

PARADIGMS CONTROL OUR SCIENCES

- Science merely counts, measures and mathematically models the phenomena.
- "The science" is just data. Data must be interpreted. HOW?
- According to Paradigms—ideas, word formulae—definitions, assumptions, theories:
  - Determine what is studied and how; and how results are interpreted
  - Are not correctible by data: Data that doesn't fit is ignored or recategorized.
  - Intergenerational: Students→professors who teach students→professors…
  - Dominate where true causes are obscure or contradict traditional/cherished beliefs
- False/inadequate paradigms must be replaced! (e.g., Copernicus, Darwin)
- Science is incapable of questioning, criticizing or replacing false paradigms!

Humans are ruled by ideas, not facts!

Kuhn T. *The Structure of Scientific Revolutions*, Univ. of Chicago, 1962

ARCHAIC AND FALSE ENDOCRINE PARADIGMS

- ❑ 19th century—Glandular Disease Paradigm: "Endocrine disease"=diseased/damaged primary gland or hypothalamic-pituitary (HP) system; Undamaged=Perfect

- ❑ 20th century—Reference Range Paradigm: "Endocrine disorder"=level above/below 2 S.D.s from mean=middle 95% of symptom-unscreened pop.; "Normal"=Perfect

- ❑ 1970s—TSH-T4 Ref. Range Paradigm: "Hypothyroidism"=thyroid disease=high TSH, and/or low free T4. Rx: Normalize TSH with inactive T4. Normal TSH=Perfect

- ❑ False Simplifications: No attention to signs/symptoms, No clinical judgment!

AND

- ❑ DRUG THINK: Hormones are dangerous drugs, hormone-like drugs are hormones

Impossible to understand hormones or human physiology!
Endocrine association guidelines WRONG.

PHILOSOPHY OVER SCIENCE

- Philosophy: Disciplined use of language to explain the Cosmos and guide our actions
- Judges and replaces paradigms according to philosophical criteria:
  - Logical consistency
  - Consistency with all evidence (including anecdotal)
  - Correspondence with all other knowledge/understanding
  - Explanatory and predictive power
- Uses ALL of the tools available to our intellects:
  - Language: Careful definition of terms: avoidance of *verbal* disagreements
  - Logic: Avoidance of formal/informal fallacies; Word formulas must conform to causality
  - Observation/Experimentation ("the science")
  - Mathematics: quantitative description, analysis, modeling

Philosophy is the full use of our linguistic intelligence; Science is not.

Lindner HH. On the Philosophical Inadequacy of Modern Physics and the Need for a Theory of Space, *Cosmos and History*, 2015;11(2):136-180. Link, henrylindner.net

PHILOSOPHICALLY-VALID ENDOCRINOLOGY

- Correct physiological definitions:
  - Hypothyroidism = insufficient T3 effect in some or all tissues/organs
  - Hypocortisolism = insufficient cortisol effect in some or all tissues/organs
- Incorporate current knowledge: (which is incompatible with the old paradigms)
  - HP system is IMPERFECT: aging, neural inputs, chemicals, mutations, infections, etc.
  - Evolution: All human systems programmed to deteriorate with age (after age 25)
  - Hormone sensitivity varies: SNPs, chemicals, autoimmunity, epigenetic changes, etc.
  - Significant local control of hormone signaling/effects
  - Reference ranges far too broad (2-5x); do not define sufficient or optimal for species or individual
  - Hormones interact: cannot diagnose or treat any “hormone deficiency” in isolation
  - Hormones are NOT DRUGS: Original parts, known actions, No “side effects”, contraindications, etc.
- Clinical diagnosis and treatment: by signs/symptoms first, hormone levels second

FORCED TO DEAL WITH CHRONIC INFECTIONS

- ❑ Daughter: Ticks@10yrs; no rash/illness; slow mental/emotional/physical decline
- ❑ Partial/temporary responses to NDT, testosterone, cortisol, prednisone, T3
- ❑ @25: Initial TBD testing negative. Neurology, Inf. Disease denied chronic infections
- ❑ @27: Proven: Chronic bartonellosis and babesiosis (*B. odocoilei*); Improved with Rx!
- ❑ Realized: Many of my fatigued, disabled patients infected with *B. odocoilei*
- ❑ Gained: Extensive experience with endocrine interventions in chronic infections!
- ❑ Realization: CDC/IDSA guidelines→GROSS Underdiagnosis + Undertreatment of zoonotic parasitic infections due to a FALSE PARADIGM!

ARCHAIC/FALSE INFECTIOUS DISEASE PARADIGM

- ❑ Parasitology: limited to protozoa, helminths, ectoparasites; excludes bacteria!
- ❑ Internal sterility: The bloodstream and tissues of “normal” humans are sterile.
- ❑ Infections are obvious: Fever, ↑WBCs, ESR, +blood cultures, +blood smears
- ❑ Immaculate knowledge: We know everything, our guidelines are “best science”
- ❑ Immaculate tests: Cover all infections, 100% sensitive; Neg. test = No infection
- ❑ Immaculate treatments: Short course of antimicrobials eliminates all organisms.
- ❑ Infections are easy to diagnose and easy to treat!

Impossible to understand zoonotic parasitic infections!
CDC/IDSA guidelines WRONG

PHILOSOPHICALLY-VALID INFECTIOUS DISEASE

- ❑ Our knowledge is rudimentary, still growing
- ❑ *Babesia, Bartonella*, *Borrelia, Mycobacteria,* etc. are parasites; not simple “infections”
- ❑ Evolution: Must study complex parasite-host-vector interactions
- ❑ Variable host response: Symptoms/disability range from minimal to severe
- ❑ Serum tests insensitive: Parasites evade and manipulate the immune system
- ❑ Short courses of antimicrobials do not eradicate most parasites.
- ❑ Parasitic infections can be very hard to diagnose and to treat!

CLINICAL MEDICINE = THINKING MEDICINE

- ❑ "The study and practice of medicine in relation to the actual patient; the art of medicine as distinguished from laboratory science"*
- ❑ "Art" = use of philosophical intelligence, clinical judgment, empathy
- ❑ Treat patients: not lab tests/ranges, guidelines, lawyers, etc.
- ❑ Think: Create and test theories of the cause, Seek to understand physiol./pathophys.
- ❑ Try to help: If tests "normal", consider diagnostic/therapeutic trials (see *House*) Even if a trial fails, it may provide more clues.
- ❑ If patient improves with treatment, continue it and figure out why, If a patient gets worse with treatment, stop it and figure out why

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IMMUNE SYSTEM OVERVIEW

- ❑ Consumes as much Energy as brain, muscles: ≈500kcal/day, more when activated
- ❑ Neuro-endocrine-immune system: Extremely complex, poorly understood
- ❑ Role: Decide how to react to every antigen: Friend or foe, food or poison?
- ❑ Tolerance vs. reaction: Balance between T_{helper} (Th) and T_{reg} lymphocyte activity
- ❑ Th1 cells/cytokines: Kill intracellular parasites, perpetuate autoimmunity (Linked!)
- ❑ Th2 cells/cytokines: Constrain Th1, kill extracellular parasites, promote atopy
- ❑ Need Th1-Th2 balance to control infections, avoid autoimmunity or atopy

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ENDOCRINE SYSTEM OVERVIEW

- Major hormones (controlled by HP system, produced by large glands):
  - Energy-producing (catabolic): Cortisol, T3, sympathetic (adrenaline/noradrenaline)
  - Energy-storing (anabolic): Insulin, estradiol, testosterone, IGF-1, parasympathetic-vagal
- Evolved to respond to short-term injury/inflammation: redirect energy to immune cells, stop energy storage
- Maladaptive response to long-term infection/inflammation→disease/disability:
  - Reduced energy expenditure→Fatigue, cognitive dysfunction, ↓gut function, etc.
  - Reduced uptake of nutrients→vitamin/mineral deficiencies
  - Muscle breakdown
  - Metabolic syndrome (redirection of energy: immune cells have no insulin resistance)
  - Anemia of chronic disease

Straub, Rainer H. Interaction of the endocrine system with inflammation: a function of energy and volume regulation. *Arthritis Res Ther.* 2014;16(1):203. PMID: 24524669
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PARASITES AFFECT IMMUNE AND ENDOCRINE SYSTEMS

- ❑ Parasites persist by evading/suppressing/manipulating the immune system
- ❑ Exposing or killing parasites→↑immune reaction (a.k.a. “herxing”)
- ❑ ↑Cytokines (IFNγ,IL-6,TNF-α, etc.) and chemokines→Chronic inflammation
- ❑ ↑Cytokines alter HP function→↑cortisol, ↓thyroid, ↓gonadal steroids
- ❑ Intravascular parasites (*Babesia*, *Bartonella*) infest brain→inflammation→altered neurotransmission and HP function
- ❑ Some parasites use host hormones to enhance survival/replication
- ❑ Parasites promote autoimmunity: Mimic host mols., expose intracell. ags, break BBB

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LABS IN PARASITIC INFECTIONS

- ❑ CBC, CRP, ESR usually normal, may have ↓CD57 (NK cells), ↑C4a (babesia-specific?)
- ❑ ↑Serum levels of some cytokines, but ↑production/effects often localized
- ❑ ↑Serum cortisol initially (adaptive), but ↓cortisol with time (maladaptive)
- ❑ ↓TSH, free T4 and especially free T3 levels/effects (“euthyroid sick syndrome”)
- ❑ ↓Testosterone levels in men
- ❑ Ovarian dysfunction in women: Irregular menses, amenorrhea, “PCOS”

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HORMONES AFFECT IMMUNE REACTION

- Immune Suppressing
  - Cortisol (most potent)
  - Testosterone (direct effects, ↑'d cortisol levels/effects)
  - Progesterone (direct effects, ↑'d cortisol effects)
- Immune Activating
  - DHEA (direct effects, ↓'d cortisol effects)
  - T3 (energizes immune system, ↓'d cortisol levels/effects)
  - Estradiol (direct effects, ↓'d cortisol effects)
  - Testosterone supplementation—via ↑estradiol and ↑T4-to-T3 conversion

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ESTRADIOL'S COMPLEX EFFECTS

- ❑ Generally immune activating—but also has anti-inflammatory effects
- ❑ Reduces cortisol effects locally by inhibiting 11-beta HSD-1→↓cortisone→cortisol
- ❑ Enhances ACTH-cortisol output if no inflammation, reduces ACTH-cortisol in inflammation (cytokines)
- ❑ Immune Activating at low levels, Suppressing at high levels (ovulation, pregnancy)
- ❑ Stimulates B-cell reaction, antibody production; reduces T-cell reaction
- ❑ Protects from infection; promotes B cell-related autoimmunity

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SEX STEROID SUPPLEMENTATION

- ❑ Infected patients benefit from sex steroid optimization—if tolerated.
- ❑ Testosterone most beneficial: ↑energy, muscle strength, ↓anxiety; can ↓immune reaction
- ❑ For Men (if suboptimal by symptoms/levels):
  - ❑ Testosterone cypionate 200mg/ml: Start with 0.1ml SQ, increase by 0.1ml weekly up to 0.4 or 0.5ml/wk
  - ❑ @2mos: Test bioavailable testosterone@mid-week (4 days), adjust to upper part of youthful ref. range.
- ❑ For Menopausal Women (medical/ethical necessity):
  - ❑ Estradiol: Transdermal—aim for Male Free Estradiol (0.5 to 1.5pg/ml)@midpoint between doses
  - ❑ Progesterone: Transdermal, sublingual or vaginal (↑'ing effectiveness), 100mgs or more daily
  - ❑ Testosterone: Transdermal or injected, test@midpoint, adjust to upper part of Female bioavailable range
- ❑ Infected menopausal women may not tolerate estradiol, some cannot tolerate progesterone.

T3 AND THE INFECTED PATIENT

- If low immune reaction to infection, NDT/T3 may ↑energy, control the infection
- ↑Cytokines→↓TSH, ↓T4-to-T3 conversion (via D1), ↑rT3 = adaptive hypothyroidism
- IF strong immune reaction, NDT/T3 may not be tolerated due to ↑immune function, ↓cortisol levels/effects→↑herxing, fever, tachycardia, etc.
- Sick patients may improve with lowering or stopping NDT/T3 (if HP/thyroid axis intact)
- Wilson's Temp. Syndrome: High-dose SRT3→↑mitochondrial number and function, corrects ATP deficit caused by chronic hypothyroidism, babesiosis, illness, etc. (if tolerated)

NDT/T3 SUPPLEMENTATION

- ❑ TSH helps only to determine cause of hypo/hyper; irrelevant to diagnosis or treatment
- ❑ Avoid T4 monotherapy: Low doses sabotage T3 production, cause hypothyroidism, hypocortisolism
- ❑ NDT and T3 reliably ↑T3 effect even at low doses, also ↑cortisol production and metabolism
- ❑ Consider Trial of NDT for fatigue, hypothyroid sxs, relatively low FT4, FT3—NOT for mild ↑TSH
- ❑ For ill or elderly: Start with 15mgs NDT, ↑every 2 wks to 90mgs NDT; For young/healthy: 30→120mgs
- ❑ Adjust dose by signs/symptoms and FT4/FT3, NOT TSH—If TSH normal, will be low/suppressed
- ❑ On NDT, pre-dose @24hrs: FT4 low in-range, FT3 below mid-range. On T3: Labs useless

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CORTISOL: FOUNDATION OF THE ENDOCRINE SYSTEM

- ❑ Most powerful, misunderstood and feared hormone
- ❑ Our natural "steroid"—affects every tissue/organ in the body, 10% of genes.
- ❑ Secretion is highly responsive: stress, infections, exercise, drugs (amphetamines, SSRIs)
- ❑ Sufficient levels/effects required to cope with stress, inflammation, and infection (↑s by 6x!)
- ❑ Provides glucose, stimulates mitochondria—necessary for energy, mood, cognition
- ❑ Reduces immune reaction: prevents/controls allergies, inflammation, autoimmune disease
- ❑ Counteracted by most other major hormones: estradiol, DHEA, T3, growth hormone
- ❑ Controlled locally: Within cells by 11β-hydroxysteroid dehydrogenases (11βHSD1 and 11βHSD2)—interconvert bioactive cortisol and inactive cortisone.

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SYMPTOMS/SIGNS OF HYPOCORTISOLISM

- ❑ Fatigue—low energy, poor recovery, weakness
- ❑ Cognitive dysfunction—“brain fog”
- ❑ Adrenergic excess—heart pounding, hot flashes, shakiness
- ❑ Inability to cope with stress or exertion, worsened by stress
- ❑ Nausea—↓appetite, poor digestion, diarrhea
- ❑ Aches & pains, muscle stiffness
- ❑ Headaches—tension and migraine
- ❑ Anxiety, irritability and/or depression (atypical)—“nervous breakdown”, “burn-out”
- ❑ Insomnia—frequent awakening
- ❑ Inflammation—↑allergies, autoimmunity
- ❑ Sensitivity to lights, sounds, chemicals
- ❑ Variability—good days/bad days (or weeks)

Mimics and worsens inflammation from chronic infection or autoimmune disease!

ASSESSING CORTISOL STATUS

- ❑ Signs and Symptoms first, saliva/serum cortisol levels second (Clinical Medicine)
- ❑ Clue: Low DHEAS
- ❑ ACTH stimulation test non-physiological, highly insensitive
- ❑ Best Test: 4-sample diurnal saliva cortisol profile (avail at LabCorp, Quest)
- ❑ Physiological saliva cortisol ranges based upon evidence and experience:
  - ❑ Morning: 0.3-0.6 mcg/dL 30 mins after awakening
  - ❑ Noon: 0.1-0.2 mcg/dL Before lunch
  - ❑ Evening: 0.06-0.13 mcg/dL Before dinner
  - ❑ Night: 0.02-0.07 mcg/dL Before bed

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CORTISOL AND THE INFECTED PATIENT

- ❑ Infected/herxing patients usually have a relative hypocortisolism: Saliva levels may be mid-range or high in-range, yet insufficient
- ❑ May need cortisol or prednisone, very ill may need high/frequent doses to:
  - ❑ Feel/function better—to eat, sleep, do activities of daily living
  - ❑ Tolerate antimicrobial treatment—esp. rifampin/rifabutin (↑cortisol metabolism)
  - ❑ Reduce inflammation and tissue damage, control autoimmunity
- ❑ Higher doses reduce TSH, T4-to-T3 conversion→adaptive hypothyroidism
- ❑ Does not prevent parasite eradication IF antimicrobial therapy is sufficient!
- ❑ HP-adrenal axis recovers when infection is eradicated, cortisol tapered

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CORTISOL SUPPLEMENTATION

- ❑ Cortisol/prednisone SAFE long-term at physiological doses with sufficient DHEA
- ❑ Diurnal pattern: Highest dose in AM, e.g., hydrocortisone: 10, 5, 2.5mgs, last dose@dinner
- ❑ Adjust by signs/symptoms—want lowest doses that work to improve quality of life!
- ❑ Bedtime/overnight doses→↑suppression of ACTH/cortisol (AM rise), sometimes needed
- ❑ Inform patients to increase HC dose for ↑stress and activity
- ❑ Suppresses DHEA: Must supplement DHEA to restore balance, may need to ↑HC dose
- ❑ Prednisone for sickest patients: nearly bioidentical, longer-acting, less fluid retention
- ❑ To reduce high glucocorticoid need: Kill more parasites→↓lower load→↓inflammation

DHEA—THE UNKNOWN PROHORMONE

- ❑ From adrenal cortex: Co-secreted with cortisol under ACTH stimulation
- ❑ DHEA+DHEAS (sulfate)—the most abundant steroids in serum (20x cortisol!)
- ❑ DHEA optimal in youth, declines with age, stress, disease
- ❑ Balances/counteracts cortisol effects in tissues, downregulates 11β-HSD1
- ❑ Anabolic: converted to testosterone and estradiol in tissues, ↑s IGF-1
- ❑ All glucocorticoid therapy must include DHEA to prevent or mitigate bone loss, muscle loss, bruising/bleeding, immunosuppression, etc.

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DHEA'S EFFECTS

- ❑ Androgenic: Provides 70% of women's androgens, 50% of serum testosterone
- ❑ Improves fertility and sexual function in women
- ❑ Reduces pain levels—restores β-endorphins, has anti-inflammatory effects
- ❑ Improves immune system function—↑NK cells/cytotoxicity, ↑neutrophil superoxide, ↑dendritic cell maturation (May not be tolerated if infected!)
- ❑ Anti-atherogenic—reduces oxidation of LDL cholesterol, endothelial dysfunction
- ❑ Anti-diabetic—improves insulin sensitivity, mitigates effects of hyperglycemia
- ❑ Neuroprotective—protects hippocampal neurons from glucocorticoid toxicity

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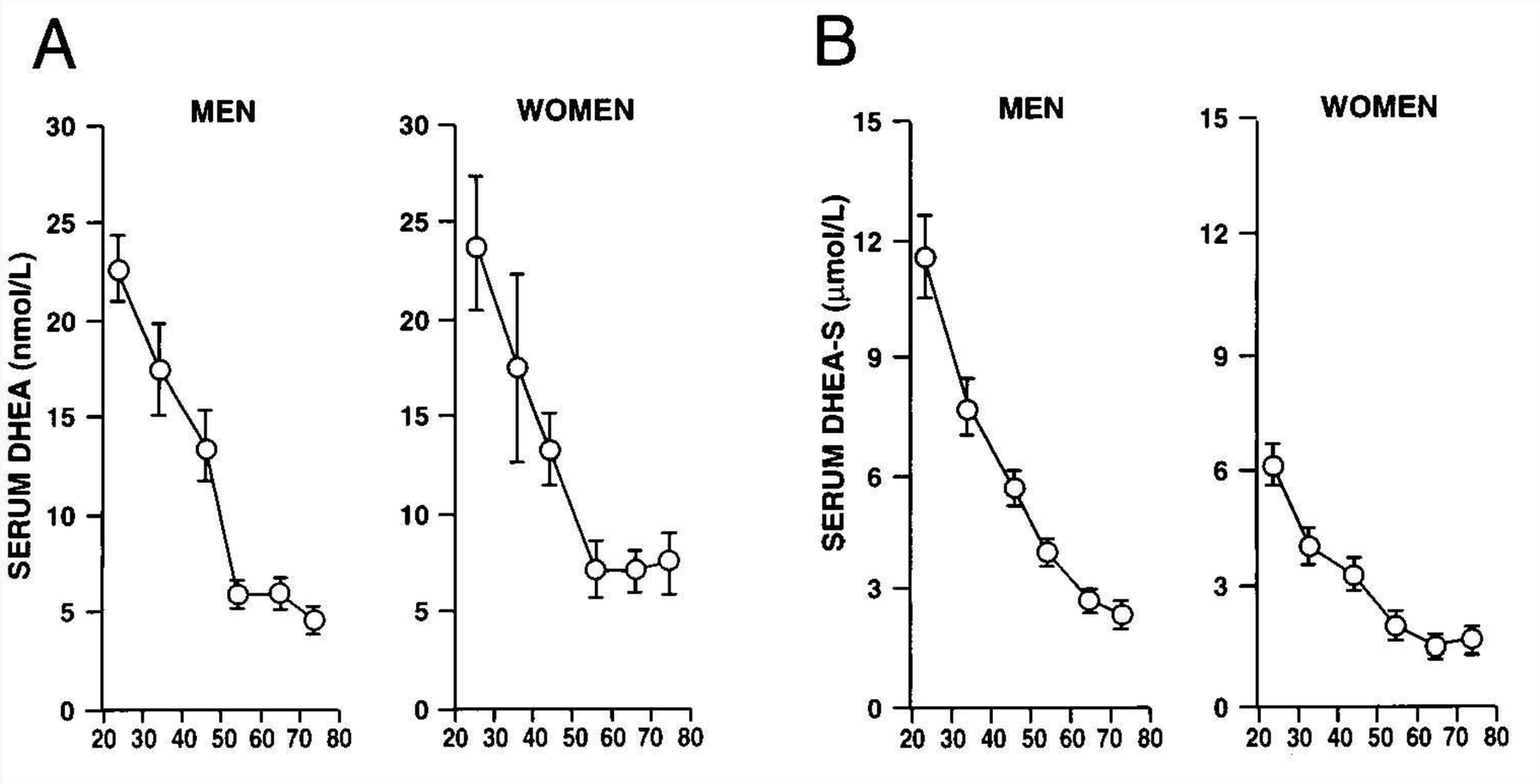
ADRENOPAUSE



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DHEA SUPPLEMENTATION

- ❑ Liver converts swallowed DHEA to inactive DHEAS; poor back-conversion*
- ❑ Use sublingual or vaginal route→more active DHEA into circulation
- ❑ Dose: 6.25 to 25mgs/day for women, 25 to 50mgs/day for men, qd or bid
- ❑ Monitor DHEAS: Goal—high in youthful range@midpoint between doses: (DHEAS ≈200mcg/dl for women, ≈ 400mcg/dL for men).
- ❑ Women may get acne or boils—start low, increase gradually
- ❑ If DHEA not tolerated consider hypocortisolism and/or chronic infection

*Hammer F et al. No evidence for hepatic conversion of dehydroepiandrosterone (DHEA) sulfate to DHEA: in vivo and in vitro st udies. *J Clin Endocrinol Metab.* 2005;90(6):3600-5. PMID: 15755854

HORMONES AND INFECTIONS

- ❑ Chronic infections can resemble and can cause endocrine deficiencies
- ❑ Consider infection if anomalous reactions to NDT, T3, cortisol, DHEA, or estradiol
- ❑ FIRST PRIORITY: Kill the parasites→↓inflammation, ↓symptoms/disability
- ❑ Sex steroid supplementation when indicated, if tolerated
- ❑ NDT/T3 supplementation may help, may hurt infected patient.
- ❑ Glucocorticoids must be accompanied by DHEA and antimicrobials!
- ❑ Consider cortisol or prednisone with DHEA if necessary to treat: disabled/miserable with nausea, headache, fatigue, achiness, brain fog, heart pounding, etc.