

# Hormone Myths vs. Medical Evidence

Ron Rothenberg MD

- 60 year old physician with acute MI, CHF, tachycardia
- TSH 3.5
- Free T4 1.3 (0.70–1.53 ng/dL)
- Free T3 2.1 (2.3–4.2 pg/mL)
- Reverse T3 380 (90–350 pg/mL)
- Would you treat with thyroid?

# Myth: Thyroid is dangerous for the heart

- Hyperthyroidism is associated with atrial fibrillation but....
- Optimizing thyroid
  - Improves lipids
  - Improves CHF
  - Positive inotropic
  - Vasodilatory

- Prevents maladaptive Cardiac Remodeling after acute MI and Rebuilds “Broken Heart”
- Normalizes QT interval
- Improves CRP, Homocysteine
- Improves arterial stiffness and endothelial dysfunction

Asvold BO et al. The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. *Eur J Endocrinol*. 2007 Feb;156(2):181-6.

Razvi Set al. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. *J Clin Endocrinol Metab*. 2008 Aug;93(8):2998-3007

# Symptoms and Signs of low T3 in Cardiovascular disease

- Bradycardia, narrowed pulse pressure, diastolic hypertension most common
- Dyslipidemia
- Endothelial dysfunction
- Elevated CRP and homocysteine
- Fernandez-Real JM et al. Thyroid function is intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects. *JCEM*. 2006 Jun 27

# Low T3 and Death

- Low T3 < 3.1 Free T3
- Low-T3 syndrome is a strong predictor of death in cardiac patients
- Implicated in the poor prognosis of cardiac patients.
- Strongest independent predictor of death > lipids or EF

Iervasi G et al. Low-T3 Syndrome, A Strong Prognostic Predictor of Death in Patients With Heart Disease *Circulation*. 2003;107:708

# Treatment of Dilated Cardiomyopathy and CHF with IV T3

- IV T3 to maintain fT3 in normal range
- fT3 increased and stayed within normal range
- No side effects, no arrhythmias
- Heart rate decreased
- BNP improved
- Improved ventricular performance

Pingitore A et al. Acute effects of triiodothyronine (t3) replacement therapy in patients with chronic heart failure and low-t3 syndrome: a randomized, placebo-controlled study. *J Clin Endocrinol Metab.* 2008 Apr;93(4):1351-8

**Acute MI / Hypertension / Aging / Cardiomyopathies**

Danzi JCEM 4/2008

**Impaired Cardiac Contractility  
(systolic or diastolic dysfunction)**

**Inflammatory Cytokines**

**Congestive Heart Failure**

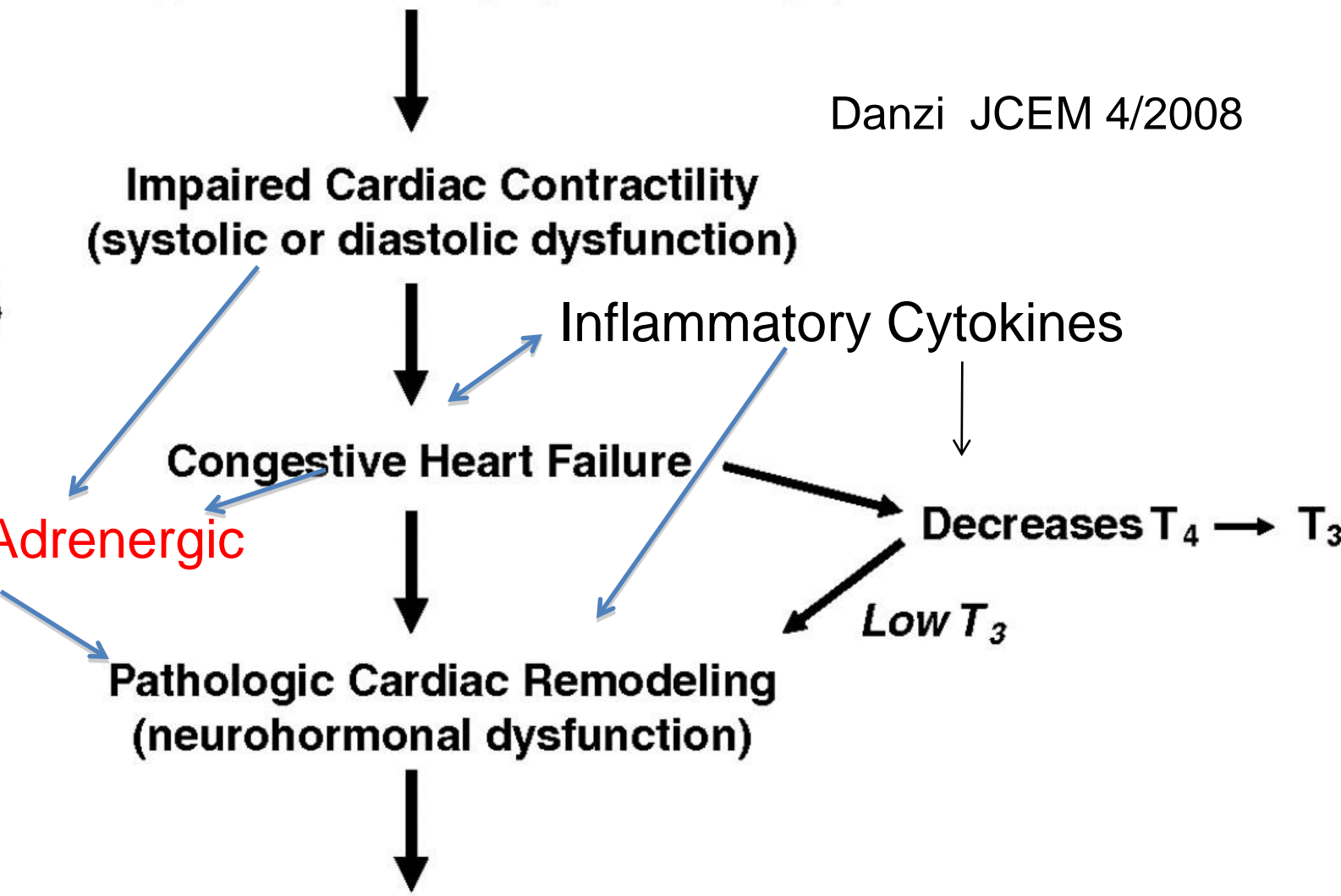
**Decreases  $T_4 \rightarrow T_3$**

**Low  $T_3$**

**Pathologic Cardiac Remodeling  
(neurohormonal dysfunction)**

**Replacement therapy with  $T_3$  will prevent or reverse the process of remodeling and improve cardiac function, neurohormonal signs and symptoms of congestive heart failure**

**Increased Adrenergic**



# Thyroid rebuilds heart after MI

- Maladaptive cardiac remodeling takes place after acute MI

Pantos C et al. Rebuilding the post-infarcted myocardium by activating 'physiologic' hypertrophic signaling pathways: the thyroid hormone paradigm. *Heart Fail Rev.* 2008 Sep 5.

Pantos C et al. Thyroid hormone and "cardiac metamorphosis": potential therapeutic implications. *Pharmacol Ther.* 2008 May;118(2):277-94.

Danzi S et al. Thyroid hormone treatment to mend a broken heart. *J Clin Endocrinol Metab.* 2008 Apr;93(4):1172-4

# Post Ischemic Cardiac Remodeling

- Inflammatory cytokines (TNF alpha) + adrenergic signaling induces fetal like myosin dysfunctional myocardium
- T3 prevents fetal-like pattern of myosin expression
- Post infarct heart rebuilt by preventing fetal myosin
- Wall tension and chamber geometry normalized
- Cellular effects: Positive inotrope, apoptosis limited

# Thyroid and Cardiovascular

- Present use:
  - Measure Free T3 and Reverse T3 in cardiac patients
  - Don't be afraid of Optimizing thyroid
  - Treat mild hypothyroidism by optimizing free T3 to reduce all components of metabolic syndrome
  - Optimize Free T3 in CHF and AMI
  - Don't rely on TSH, look at the patient, look at the active hormone fT3
- Future use:
  - IV T3 in CHF, Acute MI

- 60 year old physician with hx of prostate cancer treated with radical prostatectomy 2 years ago with clinical picture and lab tests of hypogonadism
- Testosterone 350 ng/dL (300-1000)
- Free Testosterone 6 pg/mL (8-24)
- SGBG 40 nmol/L (30-65)
- Estradiol 25 ng/dL (15-50)
- PSA < 0.1 (<4.0)
- Wife concerned about promoting cancer recurrence
- Would you treat patient with Testosterone?

# Myth: Testosterone causes prostate cancer to grow

- Based on one report from 1941
- Saturation model
- No relationship of T, DHT, E2 to prostate Ca
- No reports of PC in men treated with T after radical prostatectomy
- Benefits from head to toe when hypogonadism treated

Morgentaler A. Testosterone and Prostate Cancer: An Historical Perspective on a Modern Myth. *Eur Urol.* 2006 Jul 26

# High T = Low Mortality

- 10 year prospective study
- 11,606 men – 40-79 years old
- High Endogenous T = low mortality from CV disease and cancer
- Low T predicts CV disease
- High T = no increase in Prostate Cancer
- “Paradoxically” fear of Prostate Ca has keep men from T treatment

Khaw KT et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men. *Circulation*. 2007;116:2694-2701

# Prostate CA and Hormones

- 3886 men with prostate cancer, 6438 controls
- No associations were found between the risk of prostate cancer
- Testosterone, calculated free testosterone, dehydroepiandrosterone sulfate, androstenedione, androstenediol, estradiol, calculated free estradiol

Endogenous Sex Hormones and Prostate Cancer: A Collaborative Analysis of 18 Prospective Studies Endogenous Hormones and Prostate Cancer Collaborative Group . *J Natl Cancer Inst* 2008 100: 170-183

# Treating with T after Radical Prostatectomy for PC

- Organ confined PC
- Radical Prostatectomy
- PSA <0.1 after 1 year
- Treated with T
- No recurrences or increase in PSA

Agarwal PK et al. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol.* 2005 Feb;173(2):533-6.

# Prostate CA treated with T

- 84 y/o Gleason 6 PC, total T 400 and free T 7.4, PSA 8.5
- T gel for 21 months , PSA down to 6.2
- Dutasteride added PSA 3.8 at 24 month
  
- Morgentaler A. et al Two years of testosterone therapy associated with decline in prostate-specific antigen in a man with untreated prostate cancer. *J Sex Med.* 2009 Feb;6(2):574-7.

- Raynaud JP et al. Prostate cancer risk in testosterone-treated men. *J Steroid Biochem Mol Biol.* 2006 Dec;102(1-5):261-6
- Khera M et al. The role of testosterone replacement therapy following radical prostatectomy. *Urol Clin North Am.* 2007 Nov;34(4):549-53
- Morgentaler A, Schulman C. Testosterone and prostate safety. *Front Horm Res.* 2009;37:197-203.
- Dobs AS, Morgentaler A. Does testosterone therapy increase the risk of prostate cancer? *Endocr Pract.* 2008 Oct;14(7):904-11

- Same 60 year old physician, known to have a short temper --
- Wife concerned about “roid rage”
- Would you treat patient with Testosterone?

# Myth: Testosterone replacement causes angry aggressive behavior

- Less depression, moodiness (Zitman)
- Higher testosterone men are more sociable and gregarious
- More energy (Zitman)
- TRT (200 mg IM weekly) in hypogonadal men showed less aggression (O'Connor)
- TRT in "eugonadal" men showed no increase in aggression (O'Connor)

- Zitmann M et al. Testosterone and the brain. *Aging Male*. 2006 Dec;9(4):195-9.
- O'Connor DB et al. Exogenous testosterone, aggression, and mood in eugonadal and hypogonadal men. *Physiol Behav*. 2002 Apr 1;75(4):557-66.

# Myth: GH Replacement Therapy is related to cancer risk

- 60 year old physician with clinical and lab picture of adult growth hormone deficiency (AGHD)
- Family history of breast cancer
- Is it safe to treat her for AGHD?

# Does GH cause cancer?

- “Extensive studies of the outcome of GH replacement in childhood cancer survivors show no evidence of an excess of de novo cancers, and more recent surveillance of children and adults treated with GH has revealed **no increase in observed cancer risk .”**

Jenkins PJ et al. Does growth hormone cause cancer? *Clin Endocrinol (Oxf)*. 2006 Feb;64(2):115-21.

# IGF, BPs and Breast CA

- “IGF-I, IGFBP-1, IGFBP-3, and GH levels were not associated with breast cancer risk”

Schernhammer ES et al. Insulin-like growth factor-I, its binding proteins (IGFBP-1 and IGFBP-3), and growth hormone and breast cancer risk in The Nurses Health Study II. *Endocr Relat Cancer*. 2006 Jun;13(2):583-592

# Safety of GH and cancer

- GH treatment of adults with GHD is safe
- “Although there has been some concern about an increased risk of cancer, reviews of existing, well-maintained databases of treated patients have **shown this theoretical risk to be nonexistent**”

Molitch ME. Diagnosis of GH deficiency in adults--how good do the criteria need to be? *J Clin Endocrinol Metab* 2002 Feb;87(2):473-6

# GH Replacement and cancer risk

- “There is no data to suggest that IGF-1 and IGF BP 3 modulate cancer risk in GH treated patients.”
- “Current labeling for GH states that active malignancy is a contraindication”
- “There are no data to support this labeling. Current knowledge does not warrant additional warning about cancer risk”
- No evidence that GH increases cancer recurrence or de novo cancer or leukemia
- Increased risk of cancer in hypopituitary adults

Growth Hormone Research Society

*J Clin Endo Metab*, May 2001

# GH RT and Brain Tumor Recurrence

- Brain tumors most common solid neoplasm in children
- Life expectancy increasing – morbidity increasing – GH deficiency
- GH use increased exponentially
- No increased risk of tumor progression, recurrence or new CNS or non CNS tumor or leukemia
- Bogarin R et al. Growth hormone treatment and risk of recurrence or progression of brain tumors in children: a review. *Childs Nerv Syst.* 2009 Jan 14

# GH and cancer risk

- “Reassuringly, surveillance studies in large cohorts of children and in smaller cohorts of adults indicate that GH is not associated with an increased incidence of tumor occurrence or recurrence.”
- Banerjee I. et al. Growth hormone treatment and cancer risk. *Endocrinol Metab Clin North Am.* 2007 Mar;36(1):247-63.

Myth: Adult Growth Hormone Deficiency is only seen in patients with severe multiple pituitary deficiencies since childhood

- Same 60 year old physician with a history of a concussion after being thrown from her horse one year ago.
- She was comatose for 4 hours. CT showed cerebral contusion.
- What is the relationship between TBI and AGHD?

# GH deficiency after TBI

- GH deficiency, is common among survivors of traumatic brain injury (TBI) tested several months or years following head trauma.
- Moderate-to severe head trauma or mild trauma
- Onset can evolve over years following injury.
- Assessment of the GH-IGF axis is indicated.

Popovic C et al. Hypopituitarism following traumatic brain injury. *Growth Horm IGF Res.* 2005 Jun;15(3):177-84.

- Some degree of hypopituitarism is found in 35-40% of TBI patients
- Untreated TBI induced hypopituitarism contributes to the chronic neurobehavioral problems seen in many head-injured patients

- Patients treated with GH experience significant improvements in concentration, memory, depression, anxiety and fatigue.
- Pituitary failure can occur even in minor head injuries and is poorly recognized.

Rothman MS, The neuroendocrine effects of traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2007 Fall;19(4):363-72.

Behan LA et al. Neuroendocrine disorders after traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2008 Jul;79(7):753-9

- AGHD is common and often not recognized after TBI and other brain insults
- Evaluate all TBI, CVA and SAH patients within a year for AGHD
- Treat if deficiency disease exists

# GHRT - TBI

- Cognitive impairments partially reversible in TBI with GHD/GHI
- High W et al. Effect of Growth Hormone Replacement Therapy on Cognition after Traumatic Brain Injury. *J Neurotrauma*. 2010 Jun 25.

Myth: Progesterone treatment is only for menopausal women with a uterus who are being treated with estrogens

- What other hormone therapy could have helped our current patient when she was thrown from her horse?

# Progesterone and TBI

- Progesterone given after traumatic brain injury (TBI) has been shown to reduce the initial cytotoxic surge of inflammatory factors
- Decreases NFkB
- Decreases inflammatory eicosanoids
  - IL1-beta, TNF-a

Pettus EH et al. Progesterone treatment inhibits the inflammatory agents that accompany traumatic brain injury. *Brain Res.* 2005 Jul 5;1049(1)

He, J et al. Progesterone and allopregnanolone reduce inflammatory cytokines after traumatic brain injury. *Exp Neurol.* 2004 Oct;189(2):404-12.

# Allopregnanolone (AP alpha) turns on neuronal stem cells

- Neuroactive progesterone metabolite
- 3 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one
- Increase proliferation of neuroprogenitor cells (NPCs) derived from the rat hippocampus
- Increase human neural stem cells (hNSCs) derived from the cerebral cortex.

Wang JM et al. The neurosteroid allopregnanolone promotes proliferation of rodent and human neural progenitor cells and regulates cell-cycle gene and protein expression. *J Neurosci*. 2005 May 11;25(19):4706-18.

# AP alpha and Brain Regeneration

- Decline of neurosteroids: neurodegeneration and increased risk of Alzheimer's disease
- Alzheimer's: greater reduction in  $Ap\alpha$
- Alzheimer's mice treated with  $Ap\alpha$ 
  - maintains the regenerative ability of the brain,
  - modifies progression of AD related pathology
  - reverses learning and memory deficits

Wang JM et al. Regenerative potential of allopregnanolone. *Brain Res Rev.* 2008 Mar;57(2):398-409.

# ProTECT: A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury

- Animal studies show neuroprotection with progesterone
- Randomized, placebo-controlled, clinical trial in 100 patients to evaluate the safety and potential efficacy of progesterone in patients with traumatic brain

Wright DW et al. *Ann Emerg Med*. Volume 20:10 October 2006

# Progesterone - TBI

- 230 patients with GCS  $\leq 8$
- Progesterone 1 mg/kg IM BID x 5 days vs. placebo
- Significant improvement in GCS and functional outcome 6 months post treatment

Xiao G et al. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. *Crit Care*. 2008;12(2):R61

# Progesterone TBI

- Glasgow coma score 4-12
- Well tolerated
- P4 IV drip over 3 days – 37 mg/kg = 2500-3500mg
- 30 day mortality cut in half
- 30 days post injury
  - Severe brain (GCS 4-8) injury survivors in both groups had poor Glasgow outcome score
  - Moderate brain injury (GCS 9-12) survivors more likely to have moderate or good Glasgow outcome score
  - 0/7 in placebo group,
  - 10/18 in P4 group  $p=.02$

# Progesterone TBI

- The idea that Progesterone is just a female reproductive hormone is outdated
- Stein DG et al. Progesterone in the clinical treatment of acute traumatic brain injury. *Expert Opin Investig Drugs*. 2010 Jul;19(7):847-57.

- What “Vitamin” would augment the protective effect of Progesterone on TBI?

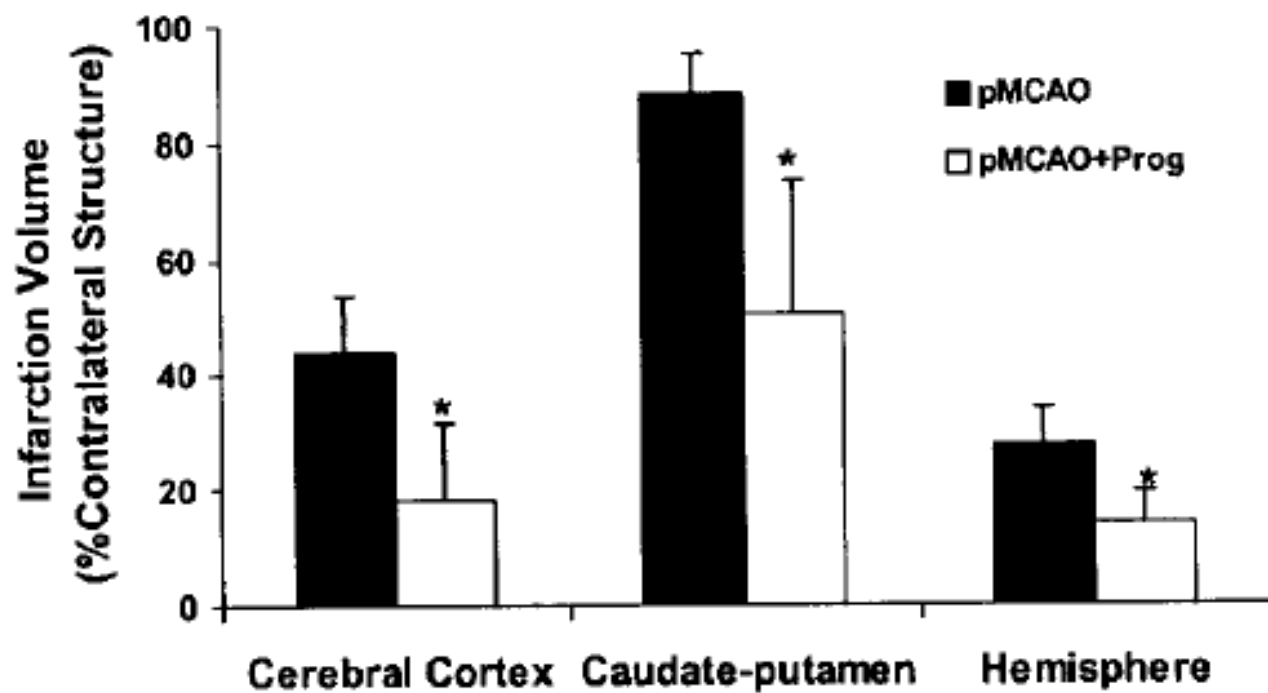
- Cekic M et al. Combination treatment with **progesterone and vitamin D hormone** may be more effective than monotherapy for nervous system injury and disease. . *Front Neuroendocrinol.* 2009 Jul;30(2):158-72.

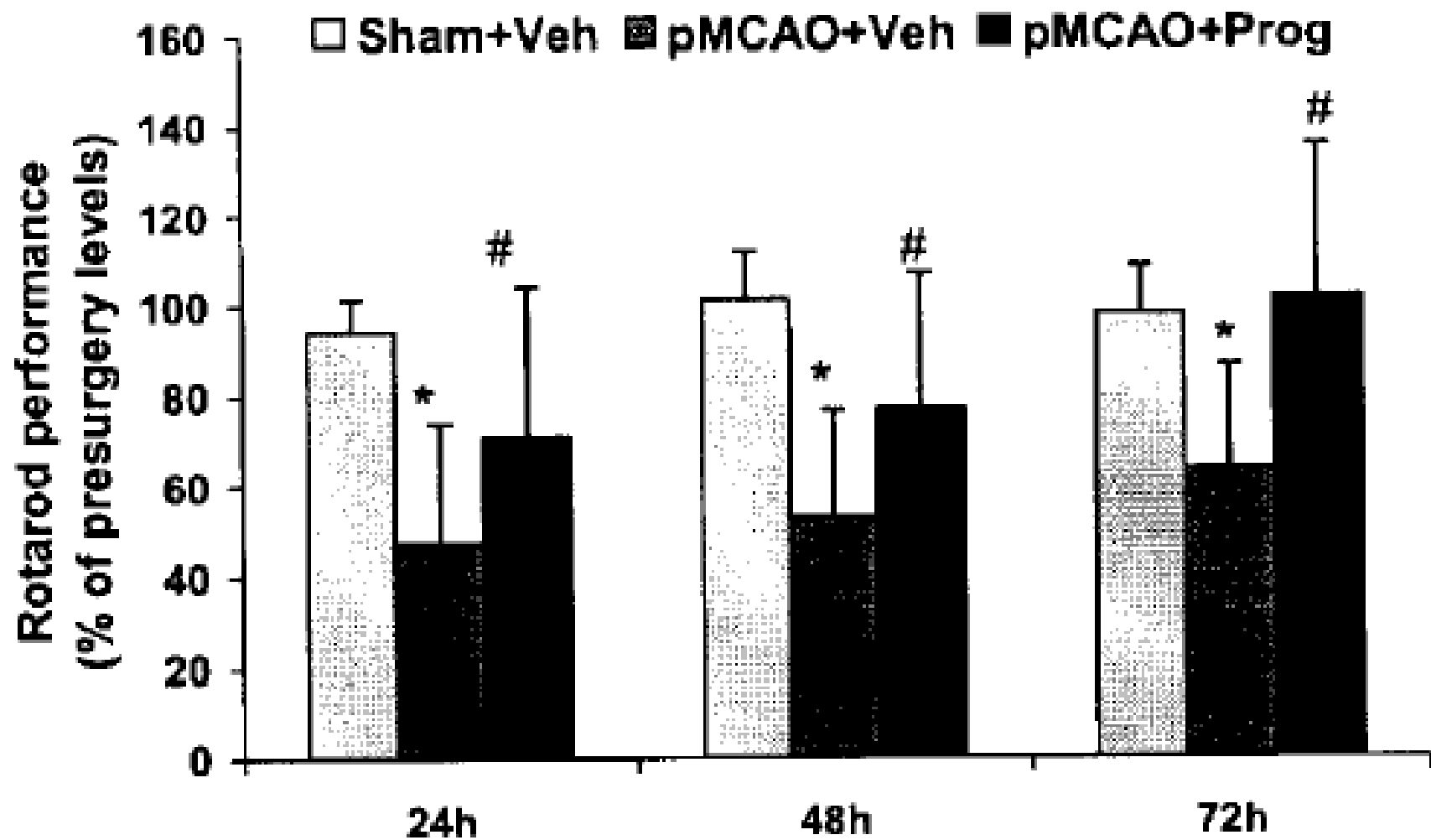
- Same 60 year old physician, different scenario
- Sudden onset of left hemiplegia
- Eyes deviating to the right
- No expressive aphasia
- Confabulates

# Progesterone and CVA

- Sayeed I et al. Progesterone inhibits ischemic brain injury in a rat model of permanent middle cerebral artery occlusion. *Restor Neurol Neurosci*. 2007;25(2):151-9
- Ishrat T et al. Effects of progesterone administration on infarct volume and functional deficits following permanent focal cerebral ischemia in rats. *Brain Res*. 2009 Feb 27;1257:94-101.

- Sayeed I et al. Allopregnanolone, a progesterone metabolite, is more effective than progesterone in reducing cortical infarct volume after transient middle cerebral artery occlusion. *Ann Emerg Med*. 2006 Apr;47(4):381-9.

**A****pMCAO****pMCAO+PROG****B**



# Progesterone Mechanisms in cerebral resuscitation p CVA

- Cytoprotection
- Increased Cerebral Blood Flow
- Crosses BBB and enters ischemic tissue
- Reperfusion not needed since effective in permanent occlusion model of stroke
- P4 and metabolites are vasodilators and may improve blood flow to ischemic area

# Progesterone Mechanisms in cerebral resuscitation p CVA

- Attenuates excitatory amino acid (glutamate)
- P4 and Ap $\alpha$  modulate GABA receptor function and counteract excitotoxic mechanisms
- MPA is not neuroprotective
- Critically important to use only bio-identical progesterone
- Improves cerebral edema

# Myth: Progesterone = Progestin

- 60 year old physician is concerned that if you treat her with progesterone there may be increased cancer and ischemic heart disease risks because of the results of the Women's Health Initiative study

# Endocrine Society Statement

- "...in the subgroup of women starting MHT between ages 50 and 59 or less than 10 years after menopause, congruent trends suggested additional benefit including reduction of overall mortality and coronary artery disease."
- Santen, R et al. Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement. JCEM July 2010 Vol 95 supp 1 number 7

# Results from the E3N cohort study- Fournier 2007

- 80,377 postmenopausal women
- No increase or decrease in breast cancer in women on E2 and Progesterone. **RR 1.0**
- E2 plus MPA (Provera) had RR of **1.69** or 69% increase in risk of breast cancer.
- Progestins are not Progesterone

Fournier A. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat.* 2007 Feb 27

# Progesterone decreases Breast Cancer risk - Campagnoli

- Synthetic progestins increase BC risk
- Progesterone decreases BC risk
- Higher P4 in pregnancy 50% reduction in risk
- Higher P4 during menstrual cycle premenopausal, 78% reduction in risk

Campagnoli C et al. Pregnancy progesterone and progestins in relation to breast cancer risk. *Journal of Steroid Biochemistry and Molecular Biology* 97 (2005)441-450

- 60 year old physician from San Diego, with family history of colon cancer and autoimmune disease. She is taking a multivitamin with 1000 IU of Vitamin D3
- 25 OH Vitamin D3 level - 34 ng/dL (33-105)
- Should she increase her Vitamin D3 dose?
- How much?

# Vitamin D Myths

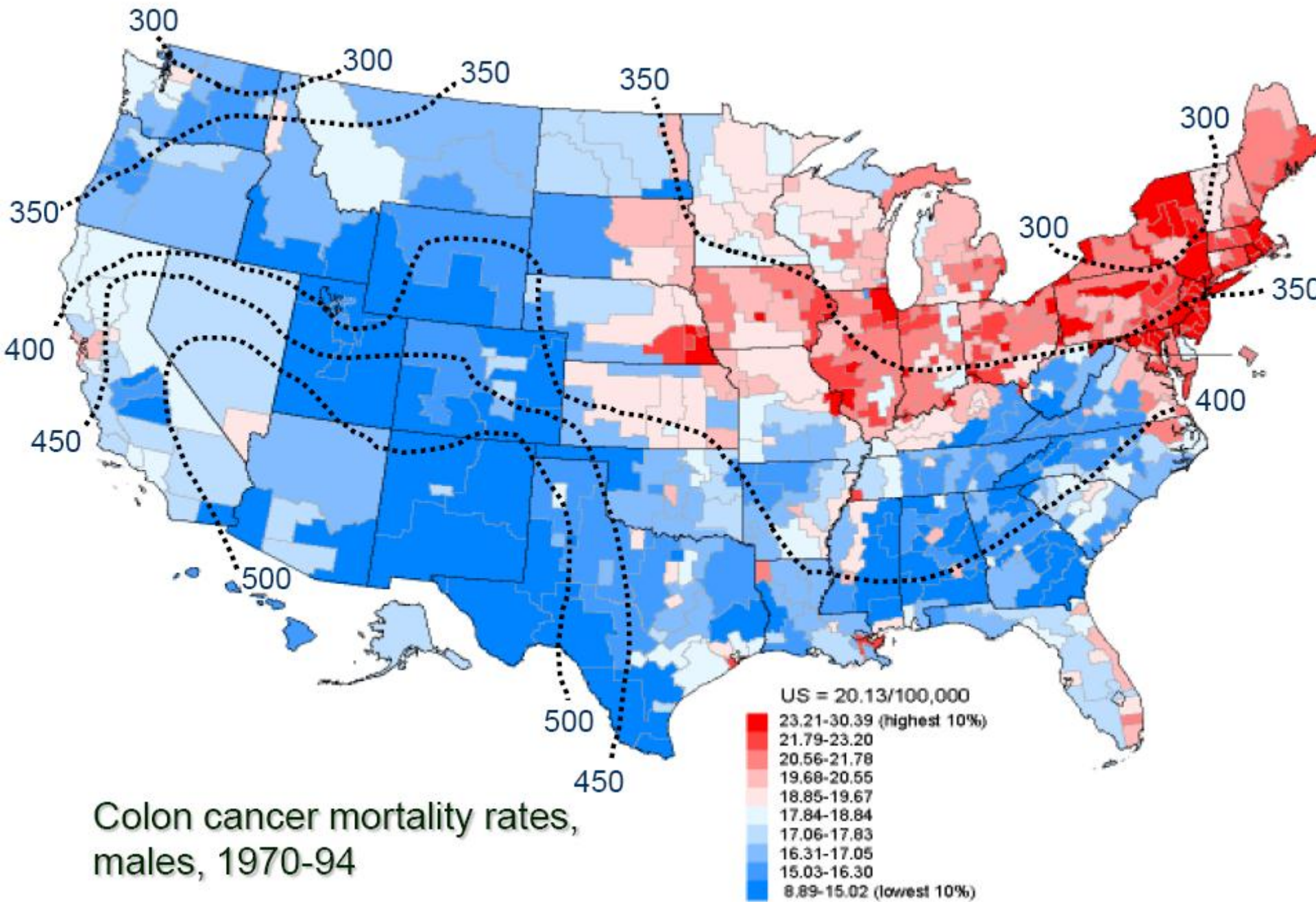
- Vitamin D is a vitamin
- The only function of Vitamin D is calcium regulation
- 1000 IU per day is more than enough
- Most people in the USA get adequate amounts
- Extreme care must be taken to avoid toxicity

- 15 minutes in the sun per day produces adequate Vitamin D
- All you need is a balanced diet
- Vitamin D does not prevent cancer
- Vitamin D does not prevent auto-immune disease
- Vitamin D does not prevent AMI and heart disease
- The cause of clinical influenza is the influenza virus transmitted from the sick to the well
- The only way to prevent H1N1 influenza is the new vaccine

# Vitamin D Deficiency - USA

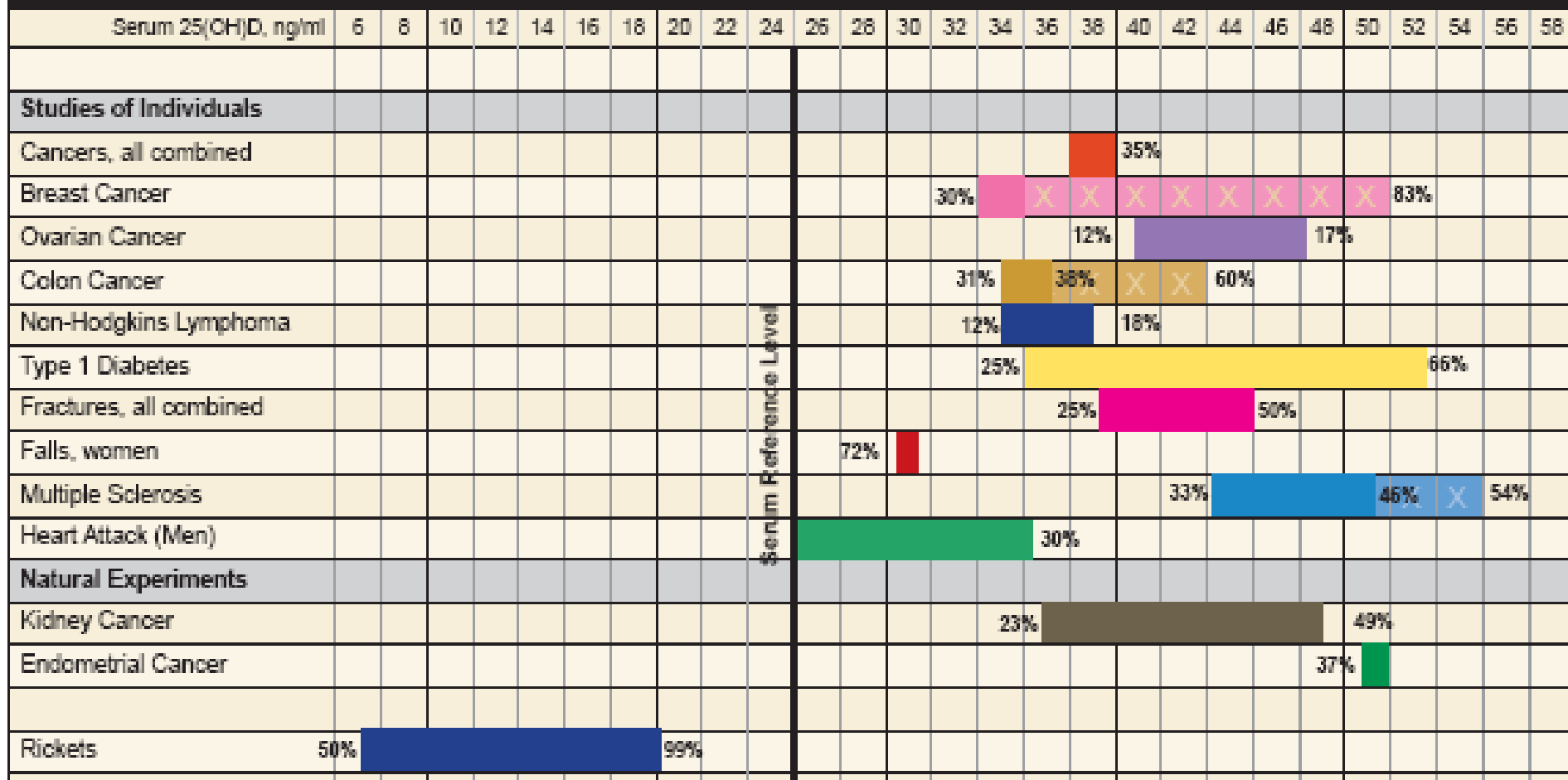
- All age groups from children to elderly
- Especially African Americans
- USA: Very Low 25(OH)D = Calcidiol <20 ng/mL
  - 36% - age 18-29
  - 42% - African American women 15-49
  - 41% - Outpatients 49-83
  - 57% - Inpatients
- Europe: 28-100% of healthy adults

Holick, MF. High Prevalence of Vitamin D Inadequacy and Implications for Health. *Mayo Clinic Proc.* 2006;81(3):353-373



Colon cancer mortality rates,  
males, 1970-94

# Disease Incidence Prevention by Serum 25(OH)D Level



\*\*All percentages reference a common baseline of 25 ng/ml as shown on the chart.

References:

All Cancers: Lappe JM, et al. Am J Clin Nutr. 2007;85:1586-91. Breast: Garland CF, Gorham ED, Mohr SB, Grant WB, Garland FC. Breast cancer risk according to serum 25-Hydroxyvitamin D: Meta-analysis of Dose-Response (abstract). American Association for Cancer Research Annual Meeting, 2008. Reference serum 25(OH) D was 5 ng/ml. Garland, CF, et al. Amer Assoc Cancer Research Annual Mtg, April 2008,. Colon: Gorham ED, et al. Am J Prev Med. 2007;32:210-6. Diabetes: Hyppönen E, et al. Lancet 2001;358:1500-3. Endometrium: Mohr SB, et al. Prev Med. 2007;45:323-4. Falls: Broe KE, et al. J Am Geriatr Soc. 2007;55:234-9. Fractures: Bischoff-Ferrari HA, et al. JAMA. 2005;293:2257-64. Heart Attack: Giovannucci et al. Arch Intern Med/Vol 168 (No 11) June 9, 2008. Multiple Sclerosis: Munger KL, et al. JAMA. 2006;296:2832-8. Non-Hodgkin's Lymphoma: Purdue MP, et al. Cancer Causes Control. 2007;18:989-99. Ovary: Tworoger SS, et al. Cancer Epidemiol Biomarkers Prev. 2007;16:783-8. Renal: Mohr SB, et al. Int J Cancer. 2006;119:2705-9. Rickets: Arnaud SB, et al. Pediatrics. 1976 Feb;57(2):221-5.

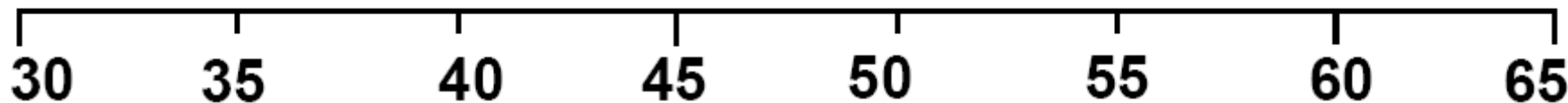
# Estimated Proportion of Conditions Preventable by Specified Range of Serum 25(OH) D Level

**50% | Falls, women**

**50% | All fractures combined**

**Multiple sclerosis**  
50%  60%

50%  **Type 1 Diabetes** 80%



**Serum 25(OH)D, ng/ml**

# Estimated Proportion of other Conditions Preventable by Specified Range of Serum 25 (OH) D Level

Diabetes:

Hypponen E et al. *Lancet* 2001 2001; 358:1500-3.

Multiple Sclerosis:

Munger KL et al. *Jama*. 2006;296:2832-8.

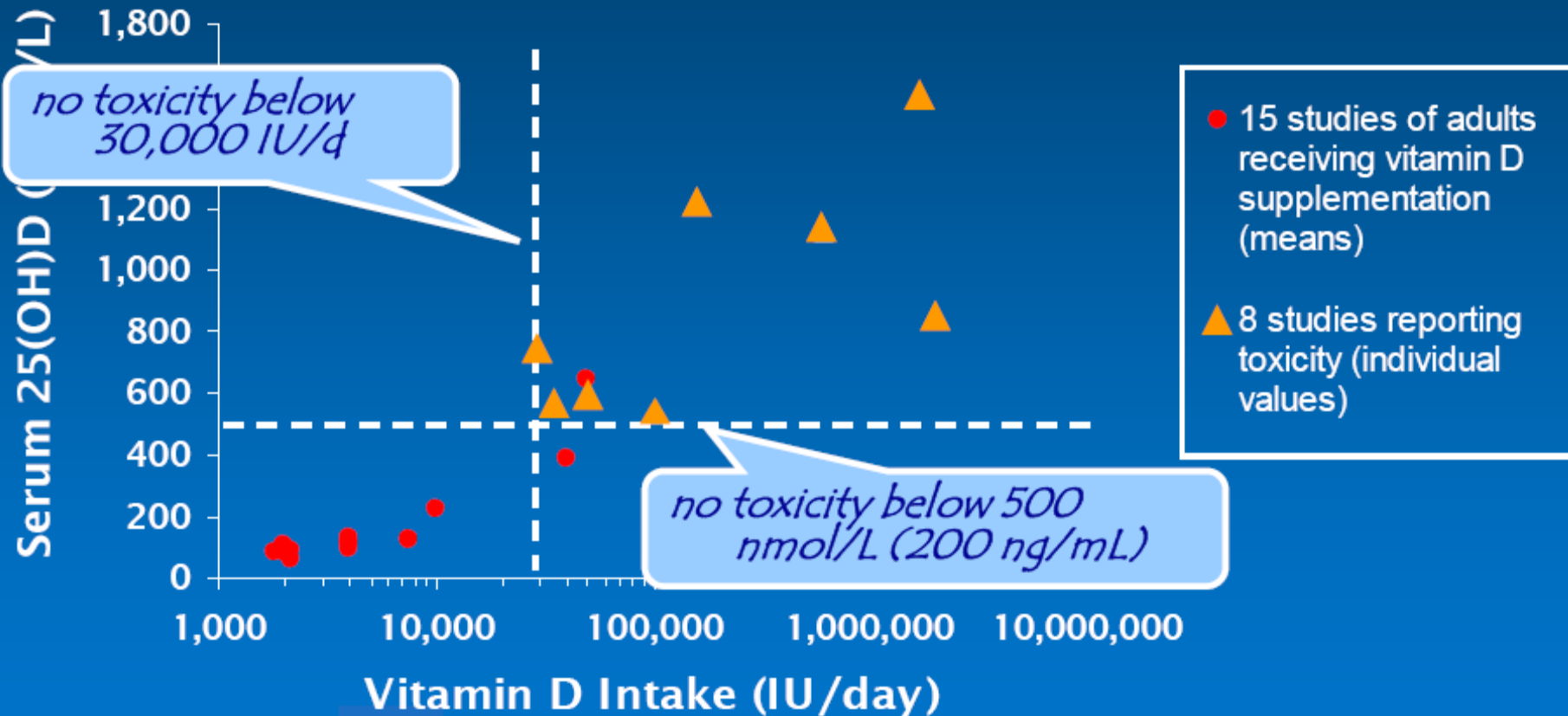
Fractures:

Bischoff-Ferrari HA et al. *Jama*.2005;293:2257-64

Falls:

Broe KE et al. *J American Geriatric Society*  
2007;55:234-9.

# VITAMIN D INTAKE & TOXICITY\*



# Vitamin D and inflammation

- Inversely associated with CRP and frailty
- Inhibits NF $\kappa$ B

Boxer RS et al. The Association Between Vitamin D and Inflammation with the 6-Minute Walk and Frailty in Patients with Heart Failure. *J Am Geriatr Soc.* 2008 Jan 5

Szeto FL et al. Involvement of the vitamin D receptor in the regulation of NF-kappaB activity in fibroblasts. *J Steroid Biochem Mol Biol.* 2007, March

# Vitamin D and Risk for AMI

- 18,000 men 45-75 without CV disease
- 10 year follow up
- Adjusted for confounding variables
- 25 (OH) < 15 ng/mL 2.5 x risk
- 15-30 ng/mL 2.0 x risk
- > 30 ng/mL 1.0

Giovannucci E al. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med*. 2008 Jun 9;168(11):1174-80.

# Problems with influenza as infectious disease from sick to well

- Why is influenza seasonal and where is virus between epidemics?
- Why in the winter in temperate areas and rainy season in tropics?
- Why explosive and stop abruptly?
- Why are epidemics in similar latitudes concurrent?
- Why is secondary attack rate so low?
- Why did epidemics spread rapidly before modern transportation
- Why does inoculation of sero-negative humans fail to cause consistent illness?
- Why no change in mortality despite vaccines?

# “The snot study”

- Donors: 1-3 day of disease
  - Collected mucous secretions of mouth, nose, bronchi mixed together
  - 1cc of the “stuff” sprayed into 10 volunteers throat and eye. No got sick.
  - Recipients: Navy volunteers. None had flu the year before
- 
- Rosenau MJ. Experiments to determine mode of spread of influenza. *JAMA* 1919, 73:311-313

# Influenza and Vitamin D

- Seasonal Variation – winter
- 1,25(OH)<sub>2</sub>D acts as an immune system modulator
- Prevents excessive expression of inflammatory cytokines and increases the 'oxidative burst' potential of macrophages
- Dramatically stimulates the expression of potent anti-microbial peptides, which exist in neutrophils, monocytes, natural killer cells, and in epithelial cells lining the respiratory tract.

Canell J et al. Epidemic influenza and vitamin D. *Epidemiol Infect.* 2006 Dec;134(6):1129-40.

# Vitamin D and H1N1

- H1N1 outbreak at Central Wisconsin Center (CWC)
- Patients (275) with disabilities monitored and supplemented with vitamin D.
- 2 cases of H1N1 in residents, 103 staff members=0.73% of residents were affected, as compared to 7.5% of staff  
 $P < 0.001$
- John Cannell, MD President Vitamin D Council 585 Leff St, San Luis Obispo, CA 93422

# Vitamin D and infectious disease

- Cannell JJ, Zasloff M, Garland CF, Scragg R, Giovannucci E. [On the epidemiology of influenza.](#) Virol J. 2008 Feb 25;5:29.
- Grant WB, Garland CF. [The role of vitamin D3 in preventing infections](#) Age Ageing. 2008 Jan;37(1):121-2.
- Rosenau MJ. [Experiments to determine mode of spread of influenza.](#) JAMA 1919, 73:311-313

# Vitamin D3 Treatment

- Keep 25(OH) Vitamin D optimal at 60-80 ng/mL
- No toxicity seen < 150 ng/mL
- Check serum calcium to prove no hypercalcemia if large doses used
- Optimal dose: 5000-15000 IU of D3 per day
- Weekly dose OK
- Less needed if more sun exposure

# Myth: Hormones don't actually change the process of aging

- Hormones and neuropeptides promote stem cell stimulation and changes in biomarkers of aging
- You can “grow your own stem cells”

# Endothelial Progenitor cells (EPCs)

- Stem cells that reside in the adult bone marrow or circulate in the blood
- Differentiate and mature into endothelial cells.
- Identified by stem-cell markers (CD34, CD133)
- EPCs decrease with age and are a measurement of vascular senescence and a biomarker of aging

- Impact vascular health by modulating vascular repair and function.
- Repair endothelial injury and protect against atherothrombosis
- EPC number predict vascular events better than conventional risk factors
- Higher numbers associated with decreased risk of CV death
- Werner N et al. Endothelial progenitor cells correlate with endothelial function in patients with coronary artery disease. *Basic Res Cardiol.* 2007 Nov;102(6):565-71.

Shantsila E et al. Endothelial progenitor cells in cardiovascular disorders. *J Am Coll Cardiol.* 2007 Feb 20;49(7):741-52.

# Improving quantity and quality of EPC's and other endogenous stem cells

- Growth Hormone
- Testosterone
- Estradiol
- Controlling CRP
- Controlling Homocysteine
- Exercise
- Antioxidants

# Improving quantity and quality of EPC's and other endogenous stem cells

- Nutraceuticals
  - Fish Oil
  - Red wine
  - Resveratrol
  - Green tea
  - Blueberries
  - Carnosine
  - L-arginine
  - Gingko

# Myth: The brain and the penis are not connected

- Higher number/function EPC's
  - Better cognitive and erectile function
- EPC's - the link between cerebral vascular function and erectile function
- Interaction between NO, ROS, TNF-alpha, adhesion markers, fibrinolytic factors may be regulated by EPC's
- Traish AM et al. The brain, the penis and steroid hormones: clinical correlates with endothelial dysfunction. *Curr Pharm Des.* 2008;14(35):3723-36

# EPCs = Biomarker Aging

## Increase

- GH/IGF-1
- E2 → Telomerase
- Testosterone
- Antioxidants →
- Exercise
- Red Wine, Resveratrol
- L-Arginine
- Blueberries, Green Tea
- Carnosine
- Fish Oil
- Fucoidan
- Gingko → Telomerase

## Decrease

- Inflammation
- Inflammatory Cytokines
- CRP
- ROS

**Vitamin D**

**CRP**

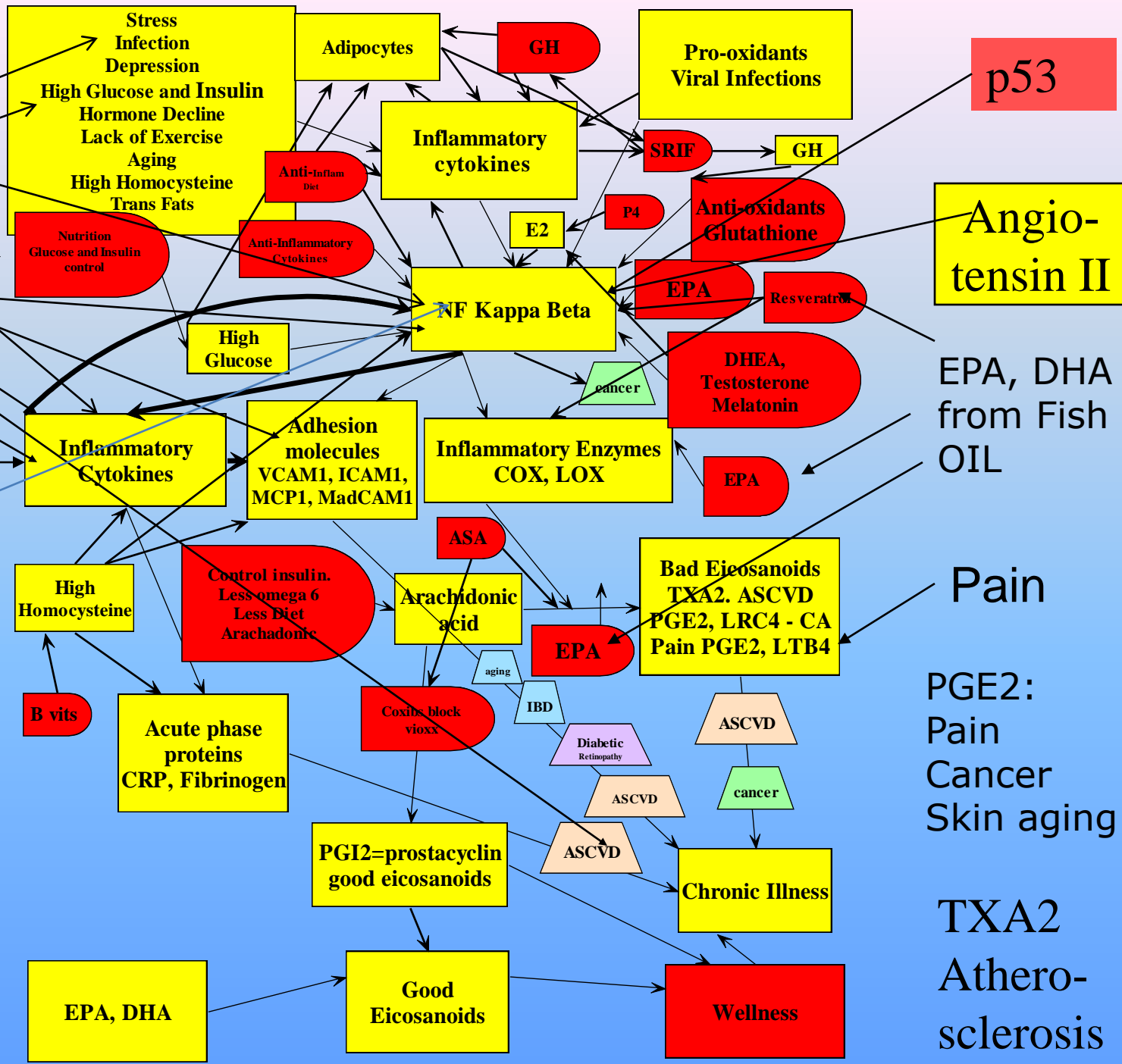
**Red inhibits**

**Yellow activates**

**Resveratrol  
EPC's**

**Unified Theory  
of Wellness:**

**Chronic  
Inflammation  
Is the Cause  
and the Effect  
of the Diseases  
of Aging**



**p53**

**Angio-  
tensin II**

**EPA, DHA  
from Fish  
OIL**

**Pain**

**PGE2:  
Pain  
Cancer  
Skin aging**

**TXA2  
Athero-  
sclerosis**