The following potential conflict of interest relationships are germane to my presentation.

- **Equipment**: NA
- **Speakers Bureau**: NA
- **Stock Shareholder**: NA
- **Grant/Research Support**: NA
- **Consultant**: NA

Status of FDA devices used for the material being presented:
NA

Status of off-label use of devices, drugs or other materials that constitute the subject of this presentation:
NA
Melatonin

“The Pineal Gland is the seat of the soul”...
....Rene Descartes...1700
Evolutionarily conserved

- Bacteria
- Fungi
- Plants
- Protozoa
- Invertebrates
- Vertebrates
- Man
• Conveys info about day length to organism
• Geomagnetic influences
• Connects life to the cycles of the universe
  • Days
  • Seasons
  • Years
• Maybe it is the “seat of the soul”
Low Melatonin associated with

- Alzheimer's
- CV disease
- Insulin resistance
- Breast cancer
Tryptophan → Serotonin →
Folate, B6

Melatonin - N-acetyl-5-methoxytryptamine

- Secreted by pineal gland
- Produced in darkness, suppressed by light
- Levels decline with aging - 10-15% per decade
- Manages circadian rhythm of inner clock
  - Lowers body temperature
  - Controls sleep wake cycle
Correlation between age and peak levels of plasma melatonin
FIGURE 3
Nighttime melatonin levels in four individuals each in three different age groups
• Scavenges Free radicals
  • Most effective FR scavenger of hydroxyl radical known
    • More than Glutathione or Vitamin E
    • Hydroxyl radical damages mitochondria
  • Protects DNA from Injury
  • Especially in Pharmacologic concentrations
  • Protects against pro-oxidation effect of Fe

• Herrera J et al. Melatonin prevents oxidative stress resulting from iron and erythropoietin administration *Am J Kidney Dis* 2001 Apr;37(4):750-7
The ultimate anti-oxidant?

- Protects lipids, proteins, DNA
- Stimulates glutathione
- Protects mitochondria
- Protects against ischemia-reperfusion injury
- Protects against ionizing radiation

Enhances Immune function

- Inhibits tumor growth
- Counteracts stress induced immunodepression
- Increases in CD4 cells, natural killer cells
- Activates cytokine system when needed
- Decreases pro-inflammatory cytokines
- Increases immune function in winter when there are more environmental stressors
- Nelson RJ Melatonin mediates seasonal changes in immune function *Ann N Y Acad Sci* 2000;917:404-15
- Kriegsfeld LJ In vitro melatonin treatment enhances cell-mediated immune function in male prairie voles *J Pineal Res* 2001 May;30(4):193-8
Aging

• Lengthens Lifespan and Healthspan in mice
• May protect against aging through quenching free radicals or immune system enhancement
78.

• Prolongs survival mice from 23.8 to 28.1 months and preserves aspects of their youthful state
FIGURE 5
Survival in New Zealand Black (NZB) female mice given melatonin in their drinking water
Aging Brain Protection

- Melatonin added to drinking water of mice
- Melatonin prevented mitochondrial impairment associated with aging
Aging Pulmonary Protection

- Melatonin maintained fully functioning lung mitochondria during aging
- Preventive therapy against the hyperoxidative status of the aged lungs, and its use may lead to the avoidance of respiratory complications in the elderly
Exercise - Melatonin

- Strenuous exercise induces inflammatory reactions and high production of free radicals and subsequent muscle damage

- 50km run 2800m ramp

- Increase in TNF-α, IL-6, IL-1,

- Increase in 8-hydroxy-2'-deoxyguanosine (8-OHdG)

- Inflammation and oxidative stress limited by Melatonin before exercise

Melatonin: Analgesic

- Chronobiotic, antioxidant, antihypertensive, anxiolytic and sedative
- Potent analgesic effects in a dose-dependent manner.
- Fibromyalgia, irritable bowel syndrome, migraine
- Mechanism: melatonin receptors, opioid μ-receptors, GABA-B receptors, better sleep
Insulin

• “Daily melatonin administration at middle age suppressed male rat intraabdominal visceral fat and plasma insulin to youthful levels”

• Wolden-Hanson T Daily melatonin administration to middle-aged male rats suppresses body weight, intraabdominal adiposity, and plasma leptin and insulin independent of food intake and total body fat. *Endocrinology* 2000 Feb;141(2):487-97
Cancer

- Inhibits tumor growth in humans
  - Anti-mitotic activity
  - Downregulate activity of receptors
    - Decreased Estrogen binding to cells in breast cancer
  - Enhanced Immune Response
  - Free Radial scavenging
  - Anti-angiogenesis
- Improved outcome in glioblastoma, malignant melanoma, breast cancer
  - Used along with chemo, radiation
  - Large doses used 20-700 mg /day
Blindness and Breast Cancer

- 1392 Blind women
- No Light Perception vs. light perception
- ½ rate of breast cancer
Meta-analysis Cancer/Melatonin

- 10 adjunctive or sole treatment studies of melatonin and solid tumors 1992-2003
- Melatonin reduced the risk of death at 1 year (relative risk: 0.66, P <= 0.56)
- Low adverse effects
- Low cost
- Conclusion: Great potential for melatonin and cancer therapy

Melatonin

- Melatonin levels decreased in migraine and cluster headaches
- Improved pain in migraine and cluster headaches with treatment

Melatonin acts centrally

Melatonin's antinociceptive effects are not via a peripheral site of action but rather a supra-spinal process linked to the central opioidergic system.

Melatonin Decreases Exercise Induced Inflammation

- Exercise increased TNF alpha, IL-6, myeloperoxidase activity and adhesion molecules in mice
- Melatonin down regulated TNF alpha signaling and inflammatory mediators

Melatonin and CRP after MI

- Inverse Correlation

Melatonin and Hypertension

- Free radical scavenging and antioxidant effects
- Preservation of NO availability
- Sympatholytic effect
- Useful in nocturnal hypertension and LVH

Melatonin – CV Hormone

- Vascular Melatonin receptors
- Ventricular Melatonin receptors
  - Anti-adrenergic
- Anti-inflammation prevents atherosclerosis cascade
- Prevents LDL oxidation
- Lowers LDL and raises HDL
MARIA Study

- IV Melatonin used as an adjunct of treatment
- Patients with acute MI undergoing primary Angioplasty
- A unicenter, prospective, randomized, double-blind, parallel-group, placebo-controlled study
- End point- decreased infarct size at 0-72 hours or clinical events in first 90 days ie death
- No published results yet

• Decreases CRP, IL-6, VCAM
• Attenuates tissue damage from reperfusion
• Decreases V Tach and V fib after reperfusion
• Low M in CHD, AMI and Sudden death
• Attenuates cellular a molecular damage from ischemia

Melatonin Cardioprotection

• Both melatonin and resveratrol protect against reperfusion injury
• Melatonin reduces infarct size in mouse model

The Progress of Atherosclerosis

- Foam cells – beginning of fatty streak
- Endothelial cell
- Activated macrophage
- T-cell
- Monocyte
- IL-6
- IL-1
- TNF-α
- Oxidized LDL
- Smooth muscle cells
- ‘Oxidized’ LDL
- Transdermal E2
- Oral E2
- Testosterone
- Transdermal testosterone
- Oral testosterone
- E2
- COMT
- Melatonin
- Epinephrine
- CRP
- SAA
- HDL
- LDL
- P-selectin
- E-selectin
- VCAM-1
- ICAM-1
- MCP-1
- Tissue Inhibitor of MMP (TIMP)
- Epinephrine
- 2-Methoxy E2
- Oral E2
- Melatonin
- Smooth muscle cells
- Foam cells – beginning of fatty streak
- MMP’s
- Stress
- Epinephrine
- E2
- COMT
Melatonin and Alzheimers

- Decreases during aging and patients with AD have a more profound reduction in this hormone.
- Improves sleep, ameliorates sundowning, and slows down the progression of cognitive impairment in Alzheimer patients.
- Protects neuronal cells from Abeta-mediated toxicity via antioxidant and anti-amyloid properties.
Melatonin and Brain

- Neuroprotective in ischemic/reperfusion brain injury
  - Direct and Indirect antioxidant effect
  - Prevention/reversal mitochondrial malfunction
- Reducing Inflammation
- Pro-apoptotic Cell Signaling
Melatonin and TBI

Melatonin and Parkinson’s

• Neuroprotective

Melatonin ADHD

- Genetic mutations in melatonin signaling in ADHD

Melatonin and Bone

• Reverses osteoporosis
• Improves deep sleep and GH release

Melatonin, Hypoxia and Neural stem cells

- Melatonin turns on neural stem cells in setting of neonatal hypoxia

- Jie Fu et al. Melatonin Promotes proliferation and differentiation of neural stem cells subjected to hypoxia in vitro. *J Pin Res* Feb 1 2011
Other Melatonin possibilities

- Female birth control
- Seasonal affective disorder
- Treatment of Alzheimer’s and Parkinson's
- Treatment of CVA
- Treatment/Prevention of Cataracts
- Treatment of Gastric Ulcers and colitis, GERD
Melatonin Replacement Therapy

- No serious adverse effects (NEJM Review)
  - Usually produces drowsiness and decreased sleep latency and increased total sleep
  - Occasional paradoxical stimulation
  - Can produce vivid dreams which are interesting to some and distressing to others
  - Can produce “hangover”
    - This effect usually resolves after a few days
  - Some people “just don’t feel good”
  - Others: well rested, bright eyed and bushy tailed
Melatonin Dose - 1/2 hr before sleep

• Try small dose 0.5 mg at first
• If no unpleasant reaction can increase dose in increments to 3-10 mg
• Time release for people who wake up in middle of night
• Sublingual lozenge or drops for people who have trouble falling asleep
• Some tolerance develops but usually levels off at 3-10 mg
• For some people, less in more and better sleep at low dose 0.3 mg
Jet lag

- Improves recovery and prevents jet lag
- Take 3-6 mg on airplane at the time of bedtime of your destination
- Expose yourself to bright light in AM’s upon arrival
- Take 3-6 mg at bedtime at destination
- Herxheimer A Melatonin for preventing and treating jet lag Cochrane Database Syst Rev 2001;1:CD001520
NEJM Review - Melatonin

- Scavenges free radicals – protects DNA
- Inhibits tumor growth – augments immune response
- Regulates sleep, restores circadian rhythm, improves jet lag
- May protect against aging changes
- Protects against cancer
- But don’t use it……..

Vitamin D Deficiency
The Forgotten Hormone
Vitamin D Deficiency – Kuala Lumpur

- 380 Malay employees from a health screening program of a public university in Kuala Lumpur, > 35 years old, May-July 2010

  Mean 25(OH) Vitamin D
  Men 56 nmol/L = 22.4 ng/dL
  Women 36 nmol/L = 14.4 ng/dL

Associated risks for D Deficiency

- Female
- Clothing style
- Working Indoors
- Age
- BMI
Vitamin D Vocabulary

- Vitamin D3 = Cholecalciferol
- Vitamin D2 = Ergocalciferol
- 25 Hydroxy Vitamin D3 = 25(OH)D3 = 25(OH)D = 25 Hydroxy Cholecalciferol = Calcidiol = Vitamin D blood test = Vitamin D serum level
- 1, 25 Dihydroxy Vitamin D3 = 1,25(OH)2D =
- 1, 25 Dihydroxy Cholecalciferol = Calciatriol
Vitamin D math

- 1 microgram = 40 IU
- 1 milligram = 40,000 IU
- nmol/L divided by 2.49 = ng/mL
- Vitamin D Deficiency: < 20 ng/mL
- Vitamin D Insufficiency < 32 ng/mL
- 25(OH)D reference range 32-100
- 25(OH)D optimal range 50-120
Previtamin D₂ → Vitamin D → 25(OH)D → Liver → Kidney

- Prostate Gland
- Breast
- Colon
- Lung

Immune Cells → 1,25(OH)₂D → Diet → Supplements

- Milk
- Orange Juice

Salmon

Calcium, MuscleBone Health & Regulation of Blood PressureInsulin Production (heart disease and diabetes prevention)

Regulation of Cell Growth (cancer prevention)

Regulation of Immune Function (diabetes type 1, MS, RA autoimmune disease prevention)
**Parathyroid Glands**
- Sense low serum calcium and increase PTH secretion

**Bone**
- Releases calcium and phosphorus

**PTH**
- Increases calcitriol formation
- Decreases excretion of calcium

**Vitamin D**
- Shown as a link to Liver

**Liver**
- Shown as a link to Kidney

**Kidney**
- Shown as a link to Small Intestine
- Increases absorption of dietary calcium

**Increased serum calcium**
• What is one of the cheapest and easiest intervention in medicine that would save the most lives and the most money?
| Serum 25(OH)D, ng/ml | 6  | 8  | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 | 48 | 50 | 52 | 54 | 56 | 58 |
|----------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Studies of Individuals |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cancers, all combined |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Breast Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Ovarian Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Colon Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Non-Hodgkins Lymphoma |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Type 1 Diabetes |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Fractures, all combined |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Falls, women |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Multiple Sclerosis |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Heart Attack (Men) |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Natural Experiments |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Kidney Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Endometrial Cancer |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Rickets |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

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

References:
Vitamin D Pandemic

• Balanced diet or living near equator not sufficient
• Everyone who does not get lots of sun or ingests at least 2000-10,000 IU per day is at high risk for skeletal and non-skeletal consequences
• High rates of Vitamin D Deficiency:
• USA, Mexico, Europe, Middle East, India, Asia, Australia and New Zealand
Vitamin D Deficiency - USA

- All age groups from children to elderly
- Especially African Americans
- USA: Vitamin D Deficiency = 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
Inhibits Cutaneous Vitamin D Production

• Clothing, Cultural Practices
• Sunscreen
• Latitude > 37 in winter, Early and late hours
• Skin pigmentation
• Body fat
• Age: 70 y/o produces 4 x less than 20 y/o
• Drugs
  • Anticonvulsants, corticosteroids, rifampin
Few foods contain vitamin D

- Fatty fish species, :
  - Herring, 85g (3 oz) 1383 IU
  - Salmon, cooked, 3.5 oz 360 IU
  - Sardines, in oil, 1.75 oz, 250 IU
  - Tuna, canned in oil, 3 oz 200 IU
- One whole egg, 20 IU
- Fortified Milk 1 cup 100 IU
- Cod liver oil, 1 Tbs (15 mL) 1,360 IU
Rickets

- Chronic Severe Vitamin D deficiency in children
- Bone deformation due to poor mineralization
- Disrupts chondrocyte maturation and inhibits mineralization of growth plates
- Widening of epiphyseal plates at the end of long bones
- Secondary hyperparathyroidism – phosphaturia and hypophosphatemia
• When rachitic child begins to stand, gravity causes bowing of long bones in lower extremities

• Bowed legs and knocked knees
  • USA
  • 1900 very common in cities
  • 1950 almost eradicated with dietary supplements
  • 2000 increasing cases, especially black children breast fed

• Non D Deficiency forms of rickets due to genetic enzyme deficiencies
Adults with Severe Vitamin D Deficiency

- Secondary hyperparathyroidism
- Increased bone loss
- Decreased BMD
- Osteoporosis
- Increased fragility and fracture risk
Vitamin D Deficiency

- At least 17 varieties of cancer
- Heart disease, stroke, hypertension
- Autoimmune diseases, MS
- Diabetes, type 1 and 2
- Depression
- Chronic pain
- Osteoarthritis
• Osteoporosis
• Muscle weakness
• Periodontal disease
• Childhood bone health
• Infectious disease
• and more
Vitamin D physiology

- Technically not a "vitamin"
- Vitamin D is in a class by itself.
- Its metabolic product, $1,25\text{dihydroxyvitamin D} = \text{calcitriol}$, is a secosteroid hormone that targets over 1000 genes
- Every cell has a vitamin D receptor that responds to $1,25\text{dihydroxyvitamin D}$
Secosteroid hormone
Vitamin D3 = Cholecalciferol
“B” Ring is “Broken”
- Calcitriol - Kidneys via 25(OH)D3-1-hydroxylase
- Most potent steroid hormone
- **First pathway**
  - Calcitriol - kidney - circulates to maintain blood calcium levels
- **Second Pathway**
  - cellular genomic and non genomic effects and that is where all the action is.
- The amazing **health benefits** of vitamin D discovered in the last 10 years are from the second pathway
Calcium metabolism involves several processes:

- **Endocrine** pathway: Vitamin D3 (D3) is converted to 25(OH)D3 in the liver, which is then converted to 1,25(OH)2D3 in the kidney. This hormone helps maintain calcium levels.

- **Autocrine** pathway: 1,25(OH)2D3 is also produced in the periphery, acting locally to regulate cell signals.

- **Gut** pathway: Calcium is absorbed in the gut, regulated by 1,25(OH)2D3, ensuring proper calcium levels in the body.
Serum 25(OH)D by oral intake of vitamin D₃

Rule of thumb: Each 100 IU of vitamin D₃ intake increases serum 25(OH)D by 1 ng/ml

Why are old Vitamin D3 limits wrong

- Can synthesize as much as 26,000 IU per day in the sun
- Lowest intake of Vitamin D3 associated with hypercalcemia – 40,000 IU per day for several months
- 300,000 IU per week produced hypercalcemia and 25(OH)D >400 ng/mL

Hathcock et al. *AJCN* 2007: 85 6-18

**VITAMIN D INTAKE & TOXICITY**

- No toxicity below 30,000 IU/day
- No toxicity below 500 nmol/L (200 ng/mL)
- 15 studies of adults receiving vitamin D supplementation (means)
- 8 studies reporting toxicity (individual values)
Annual high dosage Vitamin D

- 500,000 IU po single dose annually vs placebo
- Falls (RR 1.15) and fractures (RR 1.26) higher in Vitamin D group, esp 1st 3 months
- No toxicity seen
- Sanders, K et al. Annual High-dose Vitamin d and Falls and Fractures in Women. JAMA May 12, 2010, Volume 303
Vitamin D Status in Primates and Early Humans

Winter
43° N Latitude

Serum 25(OH)D nmol/L

Old-World Primates
Humans exposing full skin surface to Sunshine’s UVB

“Normal” Blood Levels when taking 1000 IU/day

Northern People Taking 4000 IU/day

Physiological adult intake

Sources, include Cosman, Osteoporosis Int 2000; Fuleihan NEJM 1999; Scharla Osteoporosis Int 1998; Vieth AJCN 1999, 2000
D deficient girls can’t jump

- Higher 25 OH D3 levels:
  - Improved jump height, velocity and force

- Ward KA et al. Vitamin D status and muscle function in post-menarchal adolescent girls. JCEM 2009 Feb;94(2):559-63
Vitamin D and Depression

- 25OH D3 < 40 nmol/l = 16 ng/ml = Depression
- 20,000 -40,000 IU/wk for 1 year improved

- Hoogendiik WJ et al. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry. 2008 May;65(5):508-12
Vitamin D and Brain

• D insufficiency > 2X dementia, Alzheimer's disease and stroke, and MRI indicators of cerebrovascular disease

• Buell, J et al. 25 Hydroxyvitamin D, dementia and cerebrovascular pathology in elders receiving home services. *Neurology* 2010;74:18-26
1739 Framingham Offspring members
- age: 59 yrs
- follow-up: 5.4 yrs
- 120 individuals developed a CV event
- HR calculated against 25(OH)D values > 15 ng/mL

80% increase in risk
53% increase in risk
25-Hydroxyvitamin D and 1.25-Dihydroxyvitamin D Levels with All-Cause and Cardiovascular Mortality

- Lowest Quartile <17.8ng/mL had a 26% increase in mortality

CHD – Vitamin D Mechanisms

• Reduces blood pressure
• Reduces risk of infection.
• Increases insulin sensitivity.
• Reduces circulating cytokines

Vitamin D and Cardiovascular Diseases

- Vitamin D insufficiency
  - Hypertension
  - Diabetes and metabolic syndrome
  - Left ventricular hypertrophy
  - Heart failure
  - Chronic vascular inflammation

Vitamin D, Type 2 Diabetes, Mechanisms

• Vitamin D replenishment improves glycemia and insulin secretion in patients with type 2 diabetes
• Vitamin D receptors (VDR) and vitamin D-binding proteins (DBP) in pancreatic tissue
• Regulation of plasma calcium levels, which regulate insulin synthesis and secretion
• Direct action on pancreatic beta-cell function.

Annual incidence rate of Type I diabetes, children, by latitude of population centroid, reporting countries.

Source: WHO data

$R^2 = 0.25$

$p < 0.0001$
NEONATAL VIT D & DIABETES

- 10,366 northern Finnish children
- 2000 IU Vit D/d 1st year of life
- prevalence of type I diabetes assessed at age 21
- RR calculated vs. no supplementation

*Hypponen et al., Lancet 2001;358:1500–03
Autoimmune Diseases

• The strongest evidence for a beneficial effect of vitamin D in reducing the risk of autoimmune diseases is for multiple sclerosis (MS) and type 1 diabetes mellitus.

• For MS, the evidence points to the direct and indirect regulation of T cell development and function by vitamin D and cytokine expression.

Cantoma MT et al. D-hormone and the immune system. *J Rheumatol Suppt*. 2005 Sep;76;11-20.

Multiple Sclerosis Prevalence
55 Global Regions

$R^2 = 0.46$

$p < 0.0001$
Vitamin D and Multiple Sclerosis

- 7 million US military personnel.
- The OR for the highest quintile, corresponding to calcidiol levels higher than 99.1 nmol/L, was 0.38 (95% CL, 0.19-0.75; P= 0.006).
- The inverse relation with multiple sclerosis risk was particularly strong for calcidiol levels measured before age 20 years.

Munger KL et al. JAMA 2006 Dec 20;296(23);2832-8.
Molecular Actions of Vitamin D Contributing to Cancer Prevention

- Vitamin D or metabolites have direct inhibitory action on initiation and progression of various cancers
- Renal production of Calcitriol regulates Calcium metabolism with PTH
- Extra-renal production of Calcitriol relates to cancer risk
- Calcitriol is anti-inflammatory and turns off NFkB
- Growth Arrest of malignant cells

SNPs in CYP24A1

- Different cancer risks could be due to SNPs in Vitamin D metabolism

• More CYP 27b1 – less cancer
• More CYP 24 – more cancer
15 Vitamin D-Sensitive Cancers

• Vitamin D-sensitive cancers with strong support after accounting for other factors:
  • Gastrointestinal: Colon, esophageal, gallbladder, gastric, pancreatic, rectal, small intestinal.
  • Urogenital: Bladder, kidney, prostate.
  • Female: Breast, endometrial, ovarian.
Colon cancer mortality rates, males, 1970-94
Harvard Cohort Study, Vitamin D, Cancer

- Giovannucci developed a vitamin D index based on vitamin D from oral intake and UVB production and controlled for other factors.
- Significant inverse correlations with vitamin D were found for colon, esophageal, oral, pancreatic and rectal cancer and leukemia.
- Insignificant inverse correlations were found for bladder, gastric, lung, prostate and renal cancers.
- Male cancer deaths could be reduced by 29% for 1500 IU vitamin D3/day.

US Vitamin D-Sensitive Cancer Deaths

- Digestive system 118,000
- Breast 41,000
- Genital system 51,000
- Urinary system 27,000
- Lymphoma 20,000
- Total 257,000
- 46% of all cancer deaths in the US in 2007

Infectious Diseases

- Calcitriol induces production of human cathelicidin (LL-37) a polypeptide antimicrobial
- LL-37 can fight bacterial and viral infections.

Viral respiratory infections

- 38 ng/ml levels – 2X decrease of acute resp infection with decreased sick days (p<.0001)

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)2D 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.

Prevention of Influenza A Children

- 1200 IU D3/day
- Placebo, double blind, controlled
- Relative Risk getting Influenza A
  - All treated children in study - .58
  - Not previously taking Vitamin D - .36
  - Started preschool > 3 y/o - .36

Treatment with Vitamin D

- Even if treatment is anecdotal or theoretical, at least optimize Vitamin D
- Viral and Bacterial Infections
  - HIV, Hepatitis
- Cardiovascular Disease, Hypertension
- Autoimmune Disease
- Cancer
  - Levels usually low
  - Patients do better in summer
Treatment of Upper Respiratory Viral Disease

- Anecdotal but Safe
- 2000 IU/kg x 3 days
- 150,000 IU per day for 75 kg person

Treatment Summary

- Keep 25(OH) Vitamin D in the top of the reference range 60-100 ng/mL
- No toxicity seen < 150 ng/mL
- Check serum calcium to prove no hypercalcemia
- Optimal dose: 5000-15000 IU of D3 per day
- Weekly dose OK
- Less needed if more sun exposure
Available at the Registration Booth

“Dr. Ron Rothenberg is a talented, innovative, and compassionate doctor. He is setting the trend and is truly blazing holistic medicine for the middle-aged person and those beyond middle-age.”

—William C. Washington, D.C.

“At the age of 58, I have 11% body fat and workout 7 days a week for two hours. My energy is amazing!! I attribute this to the care and hormone treatment I receive at CHL. I can’t imagine my life without their help!! Thank you Dr. Rothenberg and the entire CHL staff.”

—Gary D, San Diego, California

Ron Rothenberg MD. As a pioneer in the field of Preventive and Regenerative Medicine, Dr. Ron Rothenberg, M.D. (age 65) was among the first group of physicians to be recognized for his expertise in this rapidly emerging field. The 10th M.D. in the world to become fully board certified in both the American Board of Anti-Aging and Regenerative Medicine, Dr. Rothenberg founded California HealthSpan Institute in Encinitas, California in 1998 with a commitment to transform our understanding of preventive and regenerative medicine. Challenging traditional medicine’s approach, the California HealthSpan Institute’s mission is to create a paradigm shift in the way we view the decline of fitness, cognition and quality of life treat the cause. California Healthspan now treats and designs custom programs for patients in California and worldwide. (From every continent except Antarctica).

Dr. Rothenberg has always challenged traditional medicine’s ability to embrace paradigms. After graduating from Columbia University, College of Physicians and Surgeons in 1970, Dr. Rothenberg practiced medicine and studied indigenous healing in the Amazon Basin for several years. He then performed his residency in Emergency Medicine at Los Angeles County-USC Medical Center. At the time, the specialty of Emergency Medicine was just Anti-Aging and Regenerative Medicine was not widely recognized by the medical community. Dr. Rothenberg was passionate about the field, and went on to teach and practice Emergency Medicine. He is now the Full Clinical Professor of Preventive and Family Medicine at University of California, San Diego School of Medicine.

To be ready to offer patients the advantages of the new paradigm shift in medicine, California HealthSpan Institute became the first collection center for Neotens in which healthy people could collect and bank their own adult stem cells for future use. As a member of the Neoten Medical Advisory Board, Dr. Rothenberg regularly meets with world leaders in the stem cell field.

Dr. Rothenberg has educated over 25,000 physicians who have attended his continuing education seminars. As the creator and director of the Postgraduate Institute for Preventative and Emergency Physicians at University of California, San Diego, School of Medicine he helped create the specialty of Emergency Medicine by training physicians in this field. He has also lectured worldwide on Preventive and Regenerative Medicine, Hormone Optimization and Stem Cells. In addition to his work in the field of Anti-Aging and Regenerative medicine, Dr. Rothenberg remains an Attending Physician and at Scripps Memorial Hospital in Encinntas, California. With the health and vitality that he had when he was much younger, Ron Rothenberg continues to enjoy his other passions: his wife, his three children, surfing, skiing, mountain hiking, and Baja California.

Guidebook includes Treatment Algorithms and Abstracts