Emergency Medicine to Anti-Aging Medicine What's the connection?

- 1970's: Emergency Medicine Specialty – Not needed (wrong)
- 1990's Anti-Aging Medicine – Not needed (wrong)
- 1/3 Anti-Aging docs (and many leaders in the field) former ED docs

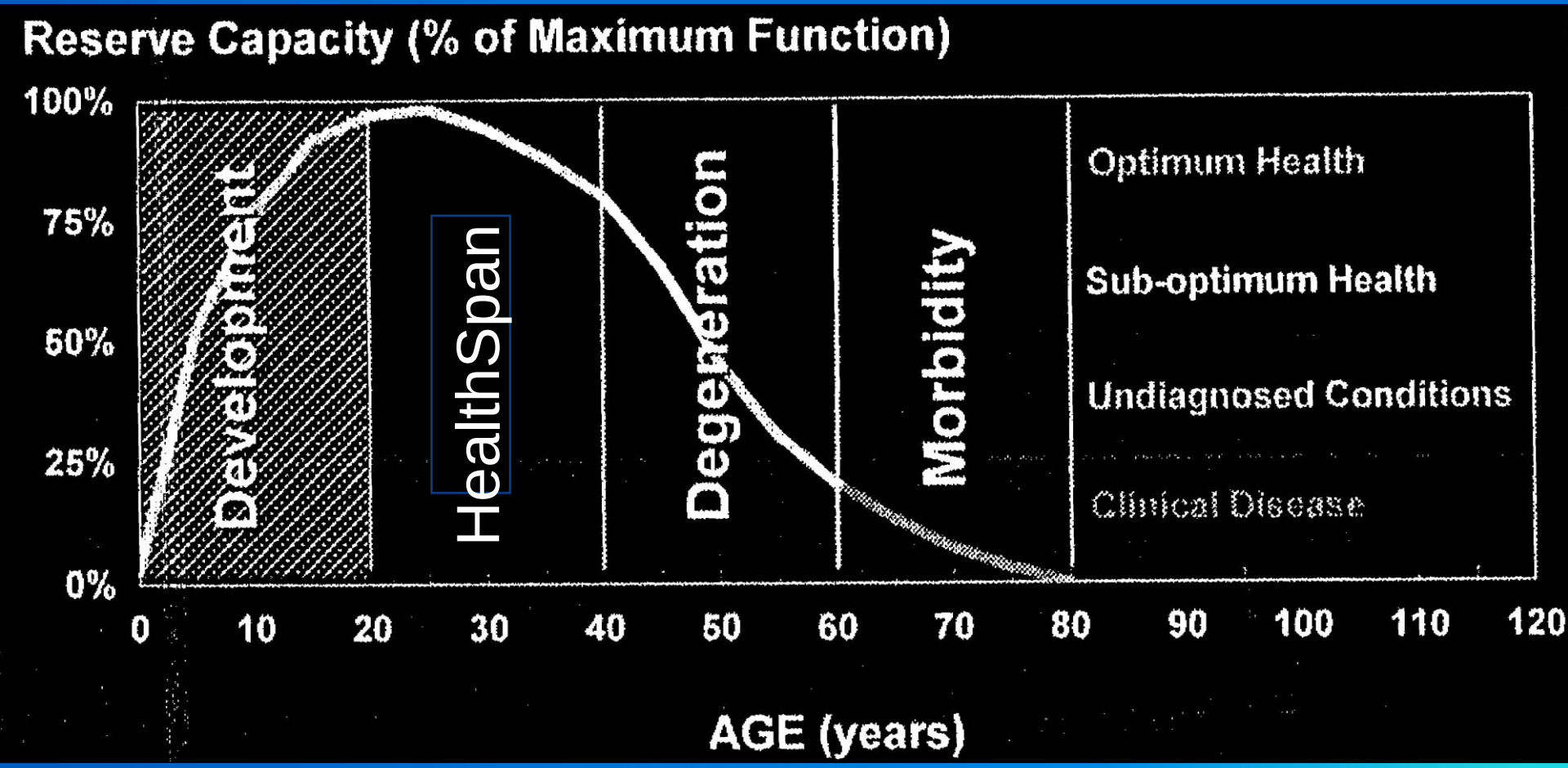
Why?

- Breath and Depth of medical experience
- Exit strategy anyone?
- Personality
  - Quest for acquiring knowledge through research and medical literature
  - Not accepting “conventional wisdom”
  - Cowboy balanced with caution
  - After dealing with acute and chronic illness – how about preventing and modifying for a change

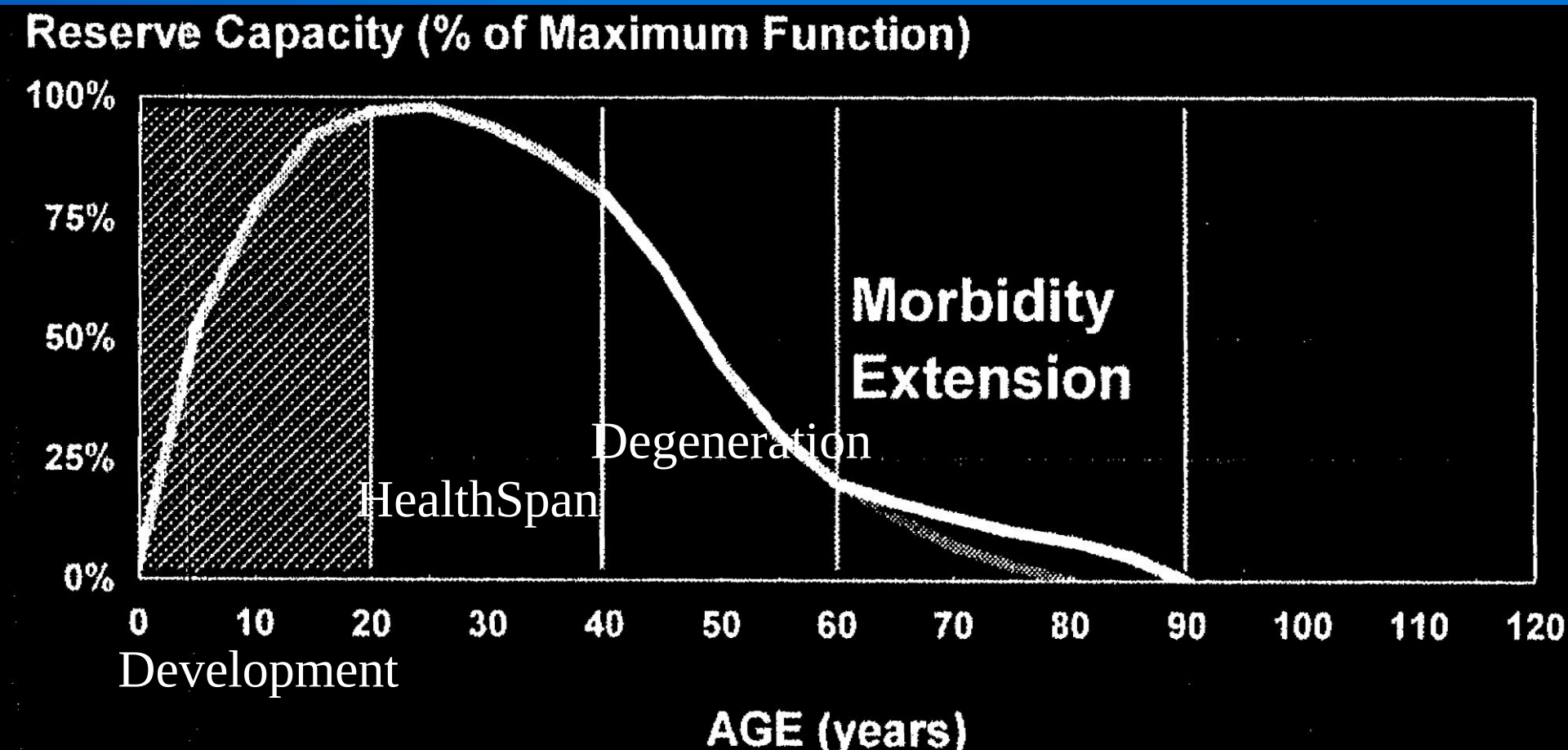
- ED docs know how to make a brief encounter meaningful to our patients
- How bout having hours to get to know our patients?
- How bout not dealing with insurance, hospital politics, and Monday morning quarterbacks?
- Change can be fun
- Both specialties are doing primary care – like it or not
- How bout some follow up?
- Improving health – us and families

- Aging is a disease which can be prevented, controlled and even reversed
- We are not prisoners of our genetic destiny

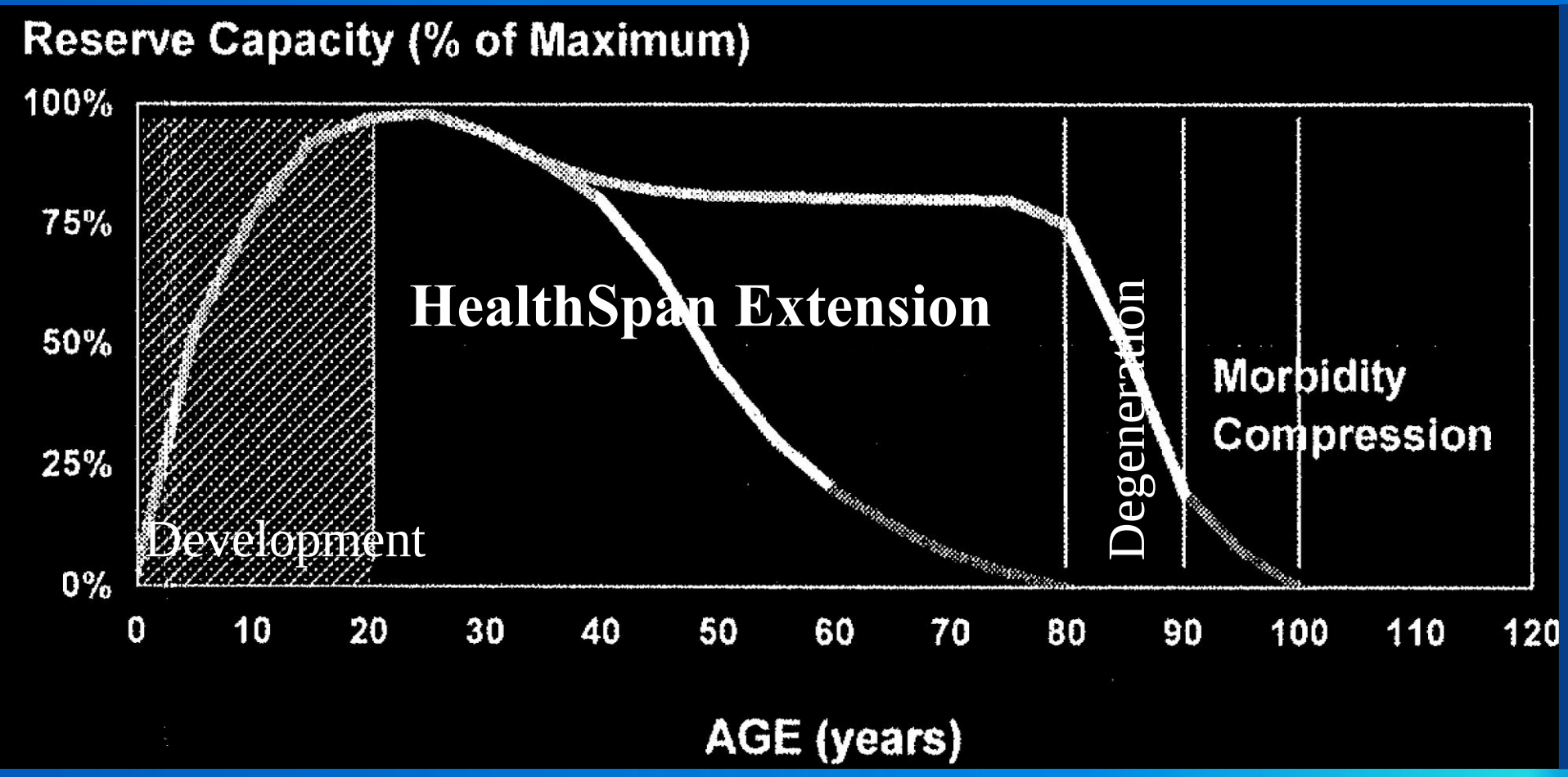
The HealthSpan Curve



“Conventional Medicine” Prolongation of Morbidity

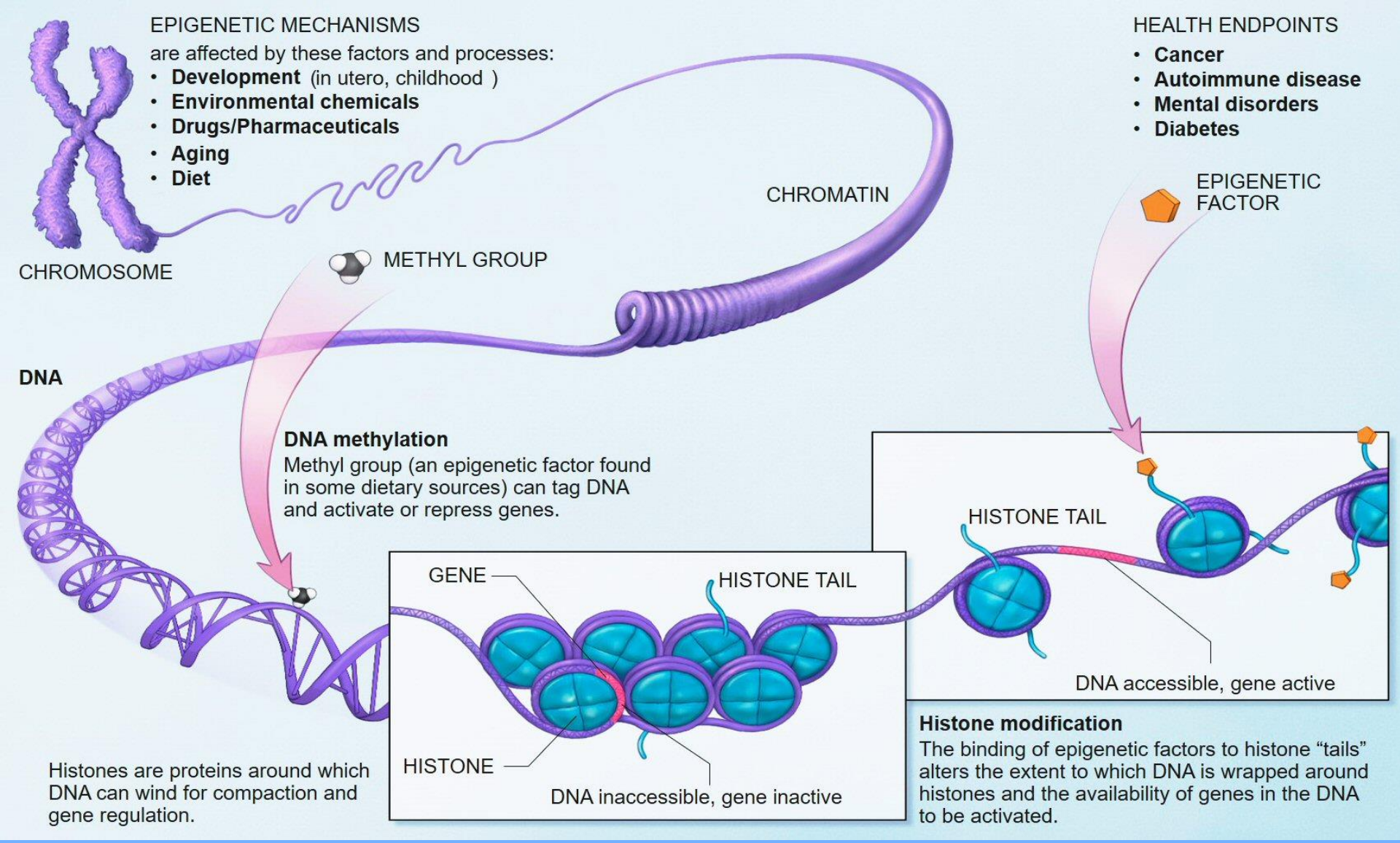


Goal of Preventive/Regenerative Medicine HealthSpan Extension, Morbidity Compression



Epigenetics

- The study of changes in gene expression that do not involve changes to the underlying DNA sequence
- Change in phenotype without a change in genotype
- Epigenetic clock – biomarker of aging
- Measures DNA methylation, histones and other biomarkers



https://upload.wikimedia.org/wikipedia/commons/d/dd/Epigenetic_mechanisms.jpg

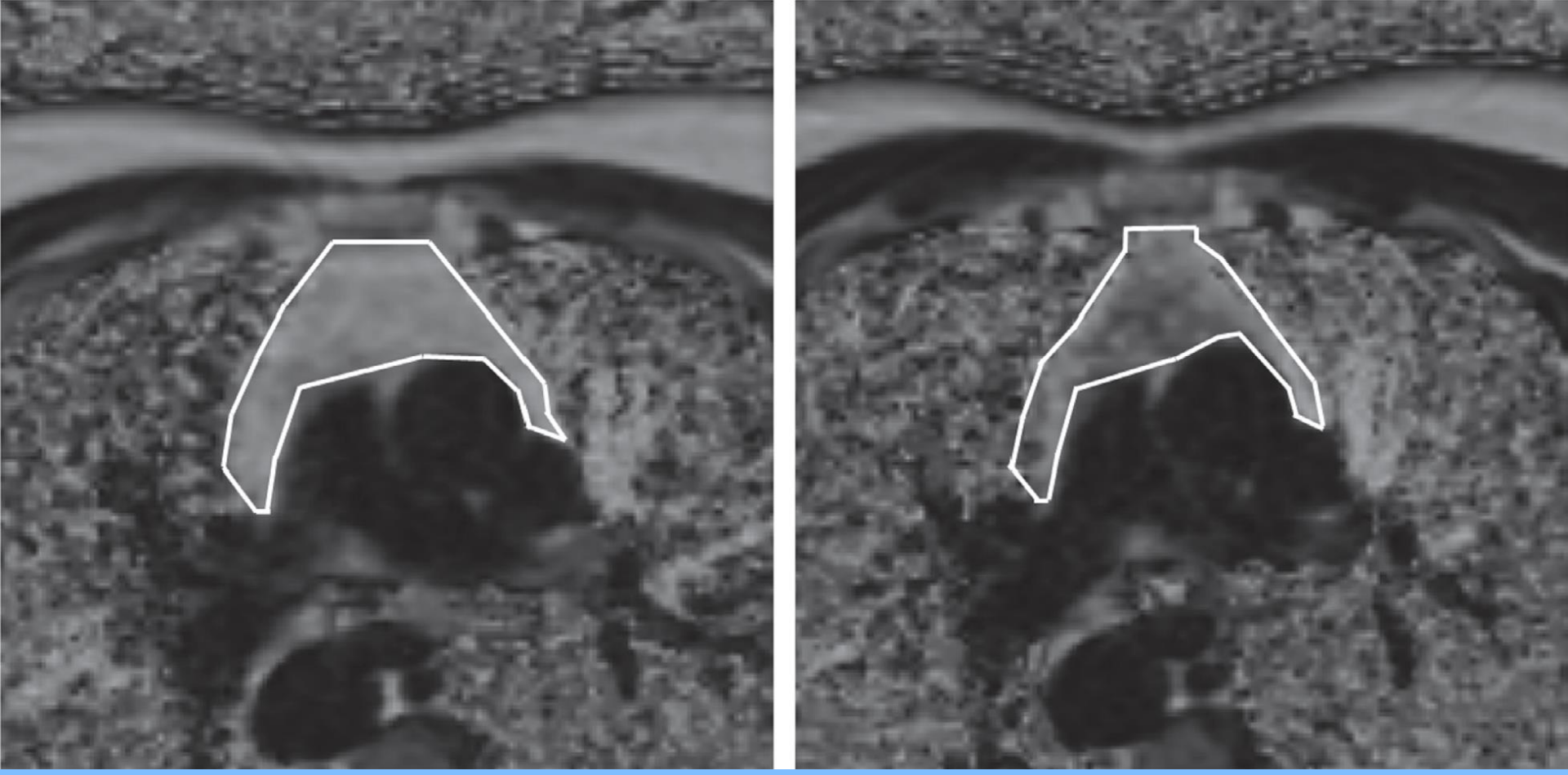
Aging Reversal 2019

- Epigenetic age - Biological age as opposed to chronological age
- Immunosenescence from thymic involution leads to the depletion of critical immune cell populations after the age of ~63
- Linked to age related increases in cancer, infectious disease, autoimmune conditions, inflammation, and all-cause mortality.
- Fahy G et al. Reversal of epigenetic aging and immunosenescent trends in humans. *Aging cell*. August 2019

- TRIIM trial (Thymus Regeneration, Immunorestoration, and Insulin Mitigation): Investigates hGH to prevent or reverse signs of immunosenescence
- hGH has thymotrophic and immune reconstituting effects
- Since hGH can increase glucose and insulin(if no attention to lifestyle) hGH was combined with metformin 500 mg and DHEA 50 mg and zinc
- Fahy G et al. Reversal of epigenetic aging and immunosenescent trends in humans. *Aging cell*. August 2019

Potential problems – did not happen

- PSA, free PSA - improved
- Testosterone no change
- Inflammation – CRP decreased
- Insulin – controlled by Metformin and DHEA
- GFR improved (no lactic acidosis with metformin and renal failure)
- hGH side effects mild (arthralgias) and resolved with dose adjustment

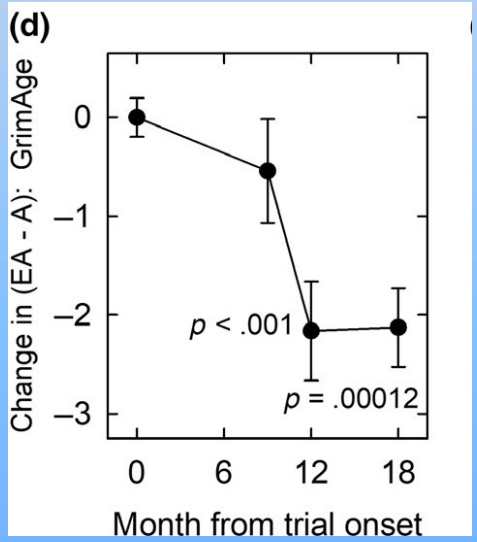


Regeneration of Thymus and Bone Marrow

Fahy G et al. Reversal of epigenetic aging and immunosenescent trends in humans. *Aging cell*. August 2019

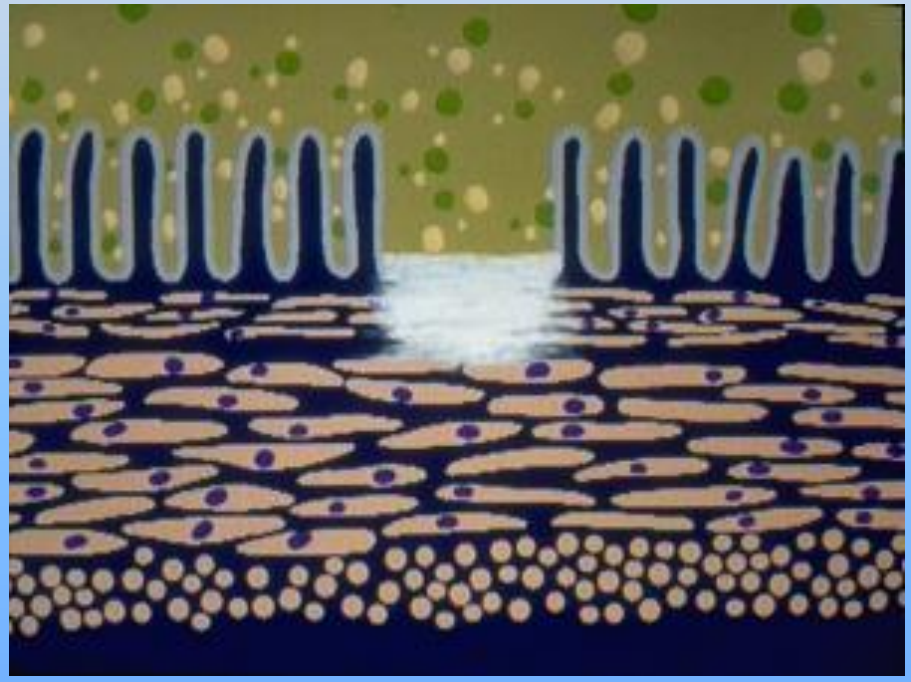
Epigenetic Clock - GrimAge

- 4 Epigenetic clocks including GrimAge showed reversed epigenetic aging
- 2.5 years age reversal after 1 year
- Reversal of immunosenescence



- Lu A et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging* 2019 Jan 21;11(2)
- Fahy G et al. Reversal of epigenetic aging and immunosenescent trends in humans. *Aging cell*. August 2019

- **Chronic Inflammation** is a cause and effect of the diseases of aging

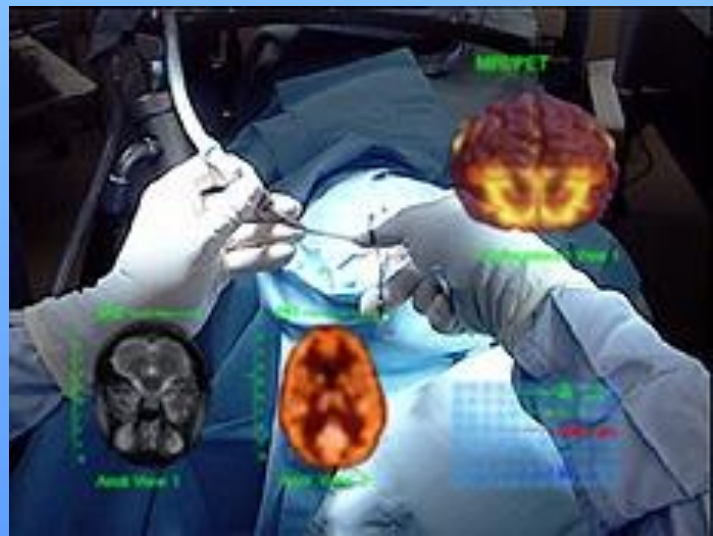


“Unified Theory of Wellness”

- Chronic Inflammation is the cause and the effect of illness and the diseases of aging
- Anti-inflammation through the optimization of lifestyle, nutraceuticals, Hormonal BioIdentity, telomeres and stem cells
- Anti-inflammation = Wellness
- Anti-inflammation = Peak performance, health, happiness
- Anti-inflammation = optimal stem cell function
- Anti-inflammation = telomere optimization

Anti-aging Medicine is:

- Optimal lifestyle
- Inflammation reduction
- Cutting edge technologies to detect, prevent and treat aging related disease
- Scientific and Evidence Based
- Documented in current Peer reviewed medical journals.



What do we do in Anti-Aging medicine?

- Design customized medicine programs
- Advanced lab testing
- Nutrition - personalized
- Exercise
- Stress Reduction
- Nutraceuticals
- Inflammation control
- Optimize Hormonal BioIdentity
- Stem cell treatment
- Telomere testing and optimization

Lifestyle

- 1st treatment in Anti-Aging Medicine
- Diet, Exercise, Stress Reduction
- “Health does not come out of a pill or an injection.” (but can help)
- Improves epigenetics
- Improves telomeres

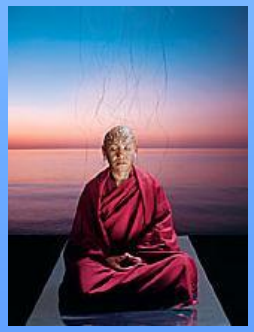
Exercise

- Can be 10-20 years younger than biological age with regular exercise: aerobic, anaerobic, flexibility
- Current data favors sprint type interval training instead of classic “cardio”
- High intensity, low duration, (Gibala M. “The one minute workout”. 2017)
- Exercise promotes longevity and compression of disability into fewer years (Vita, *NEJM* 1998 Apr)
- Increased production of GH
- Increased Sense of Well Being and cognition
- Decreases Inflammation, CRP
- Prevents telomere loss

Stress Reduction

- Lowers inflammation
- Lowers cortisol and protects hippocampus from damage producing cognitive impairment
- Augments anti-cancer, anti-atherosclerosis hormones-- 2-methoxy Estradiol
- Prevents telomere loss

- Zacharia LC et al. Catecholamines abrogate antimitogenic effects of 2-hydroxyestradiol on human aortic vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2001 Nov;21(11):1745-50.
- Okereke O. et al. High phobic anxiety is related to lower leukocyte telomere length in women. *PLoS One.* 2012;7(7)



Hormonal BioIdentity

- Everyone has a unique hormone balance that enables them to function optimally
- As we age adult hormone deficiencies become clinically relevant
- Replacing hormone deficiencies is a major treatment modality
- Optimal lifestyle including nutrition, exercise, and stress reduction is an essential simultaneous component in maintaining your Hormonal BioIdentity.

Bio-Identical hormones

- Defined as hormones atom for atom identical to endogenous hormones
- Treat a “deficiency disease”
- Improve Quality of Life
- Decrease Chronic Inflammation
- Do not increase cancer risk
- Do not increase heart disease risk
- Are a matter of personal choice
- Must be given by the correct route
- Are a “work in progress”

Optimized Hormonal BioIdentity decreases chronic inflammation and slows telomere loss

Bio-identical hormones to consider for optimization

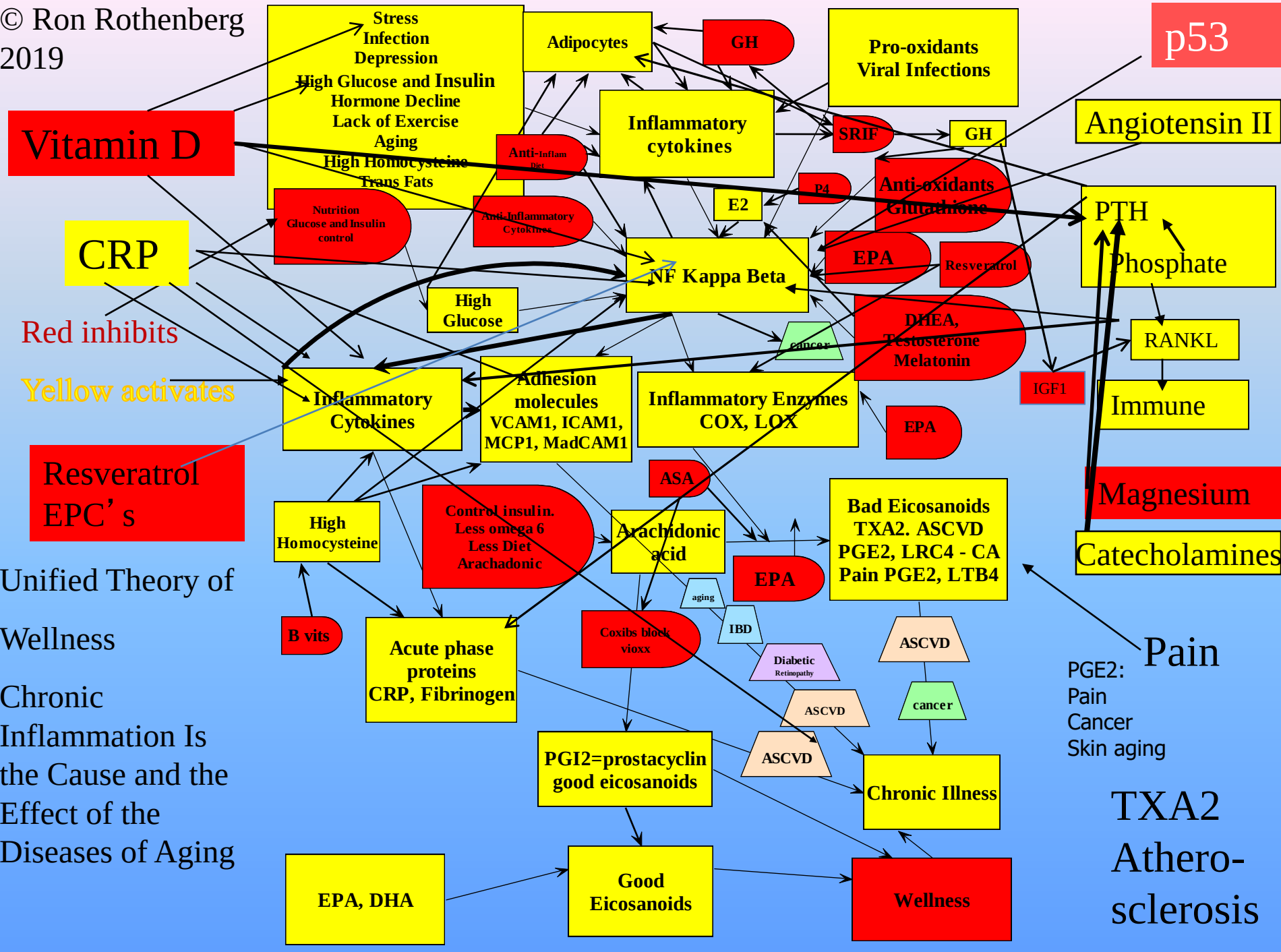
- Vitamin D
- DHEA, Pregnenolone, Melatonin
- Thyroid: T3, T4
- Cortisol
- Testosterone
- Estrogens: E1, E2, E3
- Progesterone
- Growth Hormone
- Optimal replacement considers levels and “How do you feel?”

Hormonal BioIdentity Optimization

- Is a clinical specialty
- Optimal range not reference range
- When lab and clinical do not agree - clinical wins

Evolutionary Biology

- Hormone decline does not serve any positive biological function
- Evolution is blind to events after reproductive age (maybe)



NF-kB

- Nuclear Factor Kappa Beta is central to inflammation, pain, atherosclerosis, cancer, cognitive function and more
- PGE2 can be controlled by NFKB control
- Cytokine amplification pathway
  - IL-6, IL-1beta, TNF-alpha

- Lee KM et al. Spinal NF-kB activation induces COX-2 upregulation and contributes to inflammatory pain hypersensitivity. *Eur J Neurosci*. 2004 Jun;19(12):3375-81.

If a shark bites you, you need inflammation right now

- Blood vessels constrict to stop bleeding
- Fibrinogen and clotting factors increase to stop bleeding
- White blood cells fight infection
- Pain reminds you “Don’t swim with sharks”

- Acute inflammation

  keeps us alive
- Chronic inflammation

  kills us slowly
- Why do we have all this inflammation anyway?

Antagonistic Evolutionary Benefit

- What helped our Paleolithic ancestors make it to reproductive age…is killing us now
- Insulin Resistance – helped store fat and survive famine
- Anti-inflammation resistance – helped survive acute infectious disease and trauma
- Thyroid resistance
  – reverse T3 increased in times of famine or stress

Aging causes inflammation
Youthful hormones protect

- IL-6 proinflammatory cytokine
- Stays low in youth except for trauma, infection, stress
- Testosterone and Estrogens down regulate IL-6 gene expression

- Ershler, WB et al. Age-associated Increased Interleukin-6 Gene Expression, Late-Life Diseases and Frailty. *Annu. Rev. Med*. 2000. 51:245–270

Basics still apply

- Hormone BioIdentity optimization includes the finishing touch on lifestyle: Nutrition, Exercise, Stress Reduction, Anti-oxidants and Nutraceuticals
- Use hormones when necessary to treat a deficiency disease
- Bio-identical
- Titrate to individual BioIdentity and clinical response - control metabolites when needed
- Advanced treatments are backed up by current medical literature

New Thyroid Concepts

- Lab tests lack sensitivity
- TSH not most sensitive test
- “Normal” TSH getting lower all the time
- Free T3 best clue
- Clinical correlation required!
- When all else fails, look at the patient.
- The wide range of “euthyroid” is not “optimal thyroid”

- Patients feel better and lose weight on a T3/T4 combination
- Patients feel best on Porcine Desiccated Thyroid Extract
- Ask your patient if she thinks her thyroid replacement is optimal?
- Potential side effects of bone loss and atrial fib can be monitored and avoided with thyroid optimization
- Cardiovascular benefits of optimal T3

DTE = Desiccated Thyroid Extract = Porcine thyroid vs. Levothyroxine

- Double blind crossover study
- Conclusion:
  - DTE caused more weight loss
  - 50% felt better on DTE
- Conversion factor for = TSH found in this study: 100 micrograms T4 = 88 mg of DTE

- Hoang TD et al. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. *J Clin Endocrinol Metab*. 2013 May;98(5):1982-90.

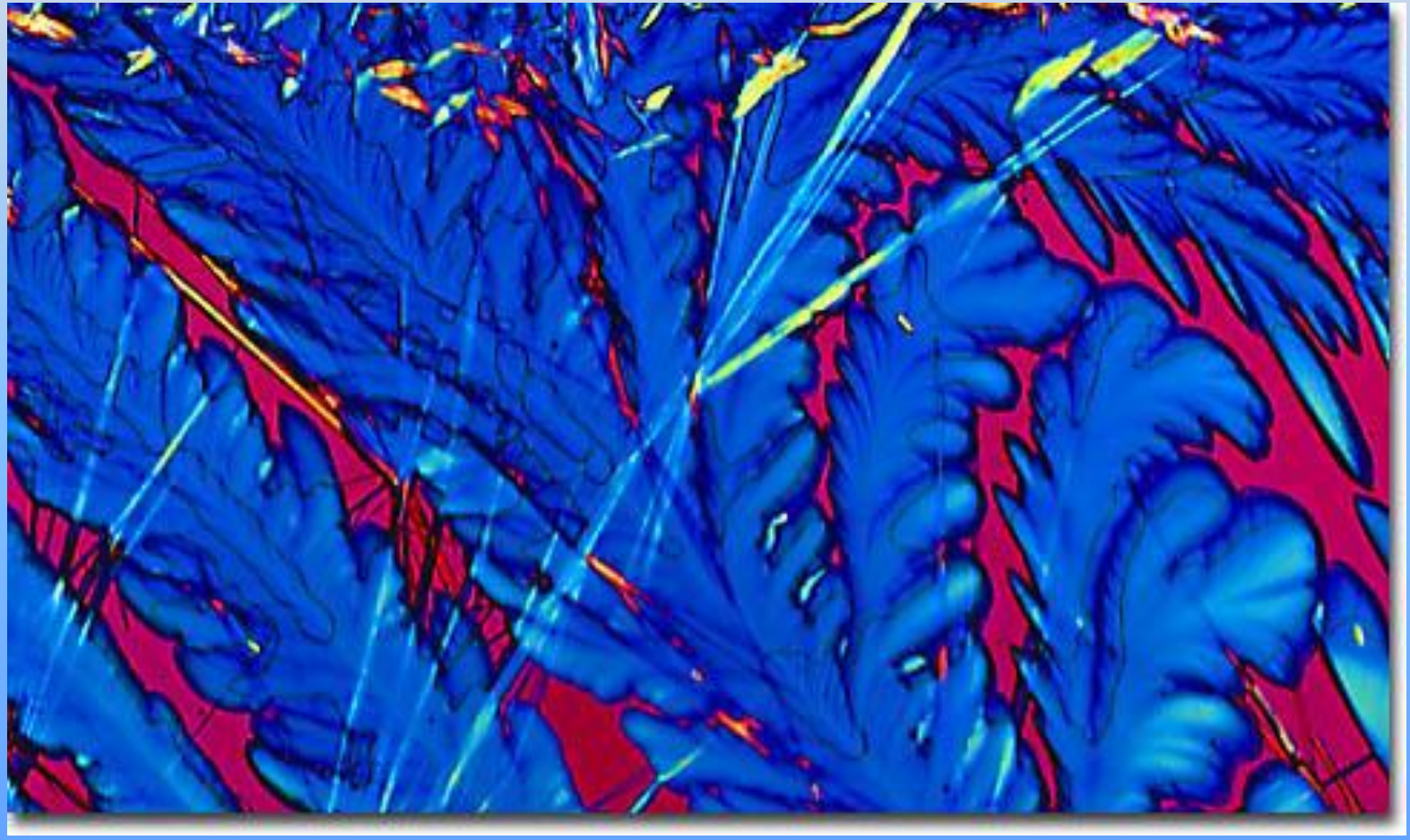
T3 and STEMI

- STEMI
- Borderline or reduced T3
- T3 therapy is safe and improves regional dysfunction in patients with STEMI and NTIS. (Non thyroidal Illness syndrome)
- No side effects, less arrythmias, less tachycardia
- T3 treatment group
  - Less necrosis, better systolic function, increased stroke volume
- Pingitore A *et al*. Usefulness of triiodothyronine replacement therapy in patients with ST elevation myocardial infarction and borderline/reduced triiodothyronine levels (from the THIRST study). *American Journal of Cardiology* 2019 123 905–912.

Cardiovascular benefits of optimal T3

- Lowers CRP - Christ-Crain, 2003
- Lowers Homocysteine – Nedrebo, 1998
- Dilates coronary arteries – Yoneda, 1998
- Anti-arrhythmic:
- V Tach associated with low T3 low ratio of T3/T4 and high reverse T3 – Shimoyama, 1993
- Low fT3 predicts post op AF p=.001 – Cerillo, 2003
- RT3 strongest predictor of mortality in first year post Acute MI - Friberg, 2001
- Higher free T3, greater survival post MI – Pavlou 2003

TESTOSTERONE in men



Testosterone Deficiency

- Half of healthy men between the ages of 50–70 yr will have a Bioavailable Testosterone level below the lowest level seen in healthy men who are 20–40 yr of age

- Korenman SG, Morley JE, Mooradian AD, et al. 1990 Secondary hypogonadism in older men: its relationship to impotence. *J Clin Endocrinol Metab*. 71:963–969.

Testosterone Deficiency is a lethal disease

- Diabetes, Metabolic syndrome
- Brain
- Heart
- Frailty syndrome
- Bone
- Inflammation
- Cancer

True or False?

TT= Testosterone Therapy. TD= Testosterone deficiency

1. The condition of low T does not exist
2. Symptoms of TD do not merit treatment- particularly decreased libido and fatigue
3. TT is risky
4. TT increases risk of VTE e.g. DVT or PE
5. TT increases risk of MI, CVA and death
6. TT causes PCa to develop or become aggressive
7. TT is experimental/investigational
8. T decline is due to normal aging and does not merit treatment

Morgantaler et al. Mayo Clinic Proceedings Consensus Recommendation. 2016 6;91(7)

Testosterone Treatment – 56% less mortality

- 83,000 VA men > 50 y/o low testosterone
- Normalized-TT– treated and test normalized
- Non-normalized-TT– treated and test not normalized
- No TT – not treated

- Sharma, R et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J*. 2015 Aug 6

Normalized-TT vs. No TT Hazard Ratios

- All cause mortality .44 CI .42-.46 p<.00001
- Risk of MI .76 CI .63-.93 p<.00001
- Risk of Stroke .64 CI .43-.96 p<.00001
- Significant but higher hazard ratios
  - Normalized-TT vs. Non-normalized-TT
- No difference
  - Non-normalized-TT vs. No TT

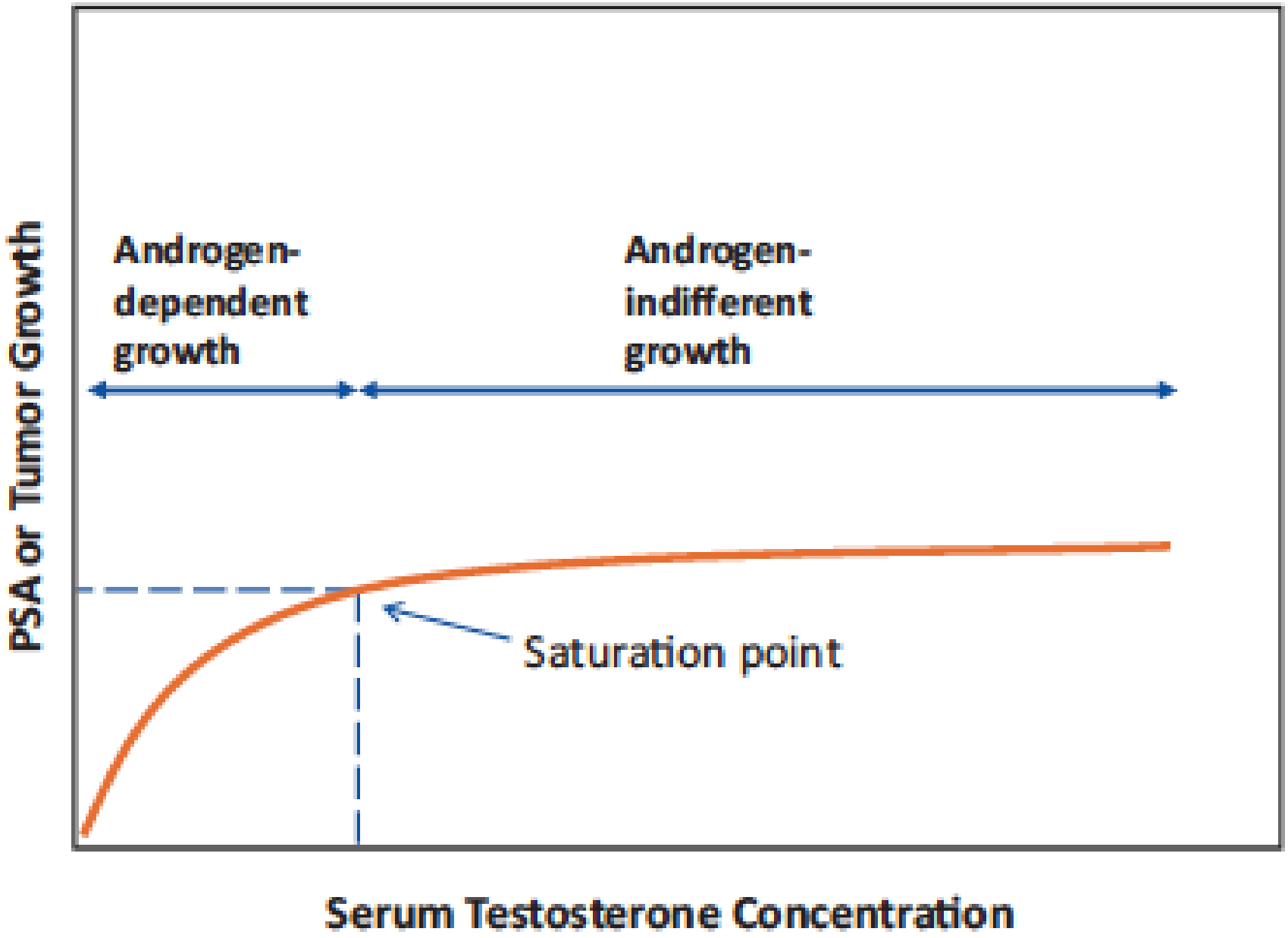
- Sharma, R et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J.* 2015 Aug 6

Testosterone

- Does not increase risk of prostate cancer
- Does not cause existing prostate cancer to grow
- Optimize treatment to match Hormonal BioIdentity

TT and PCa over 20 years

- 1365 men with TT x 20 years
- Screened with PSA and DRE q 6 months
- Abnormal changes with US prostate and biopsy
- Conclusion:
  - No difference in PSA, free PSA and PCa as compared to background
  - All cancer in treatment group localized and curative
  - Testosterone treatment and monitoring may be safer than no treatment
- Feneley MR et al. Is testosterone treatment good for the Prostate? Study of safety during long term treatment. *Journal of Sex Med* 2012; June 6


Androgen-dependent growth
Androgen-indifferent growth
PSA or Tumor Growth
Saturation point
Serum Testosterone Concentration
<100
200
1000

Testosterone in Women

- Functional Androgen Receptors are located in almost all tissues
- Androgen deficiency symptoms
  - Anxiety, irritability, depression
  - Lack of well being, physical fatigue
  - Bone loss, muscle loss
  - Changes in cognition, memory loss
  - Urinary complaints, incontinence
  - Sexual dysfunction

Estradiol

Estrogens

- E1=Estrone
  - May be more than she needs
  - Get some anyway through conversion of E2
- E2=Estradiol
  - Protective Estrogen via catechol and methoxy metabolites
- E3=Estriol
  - Cancer protective, weak

Bioidentical Estrogens and Progesterone

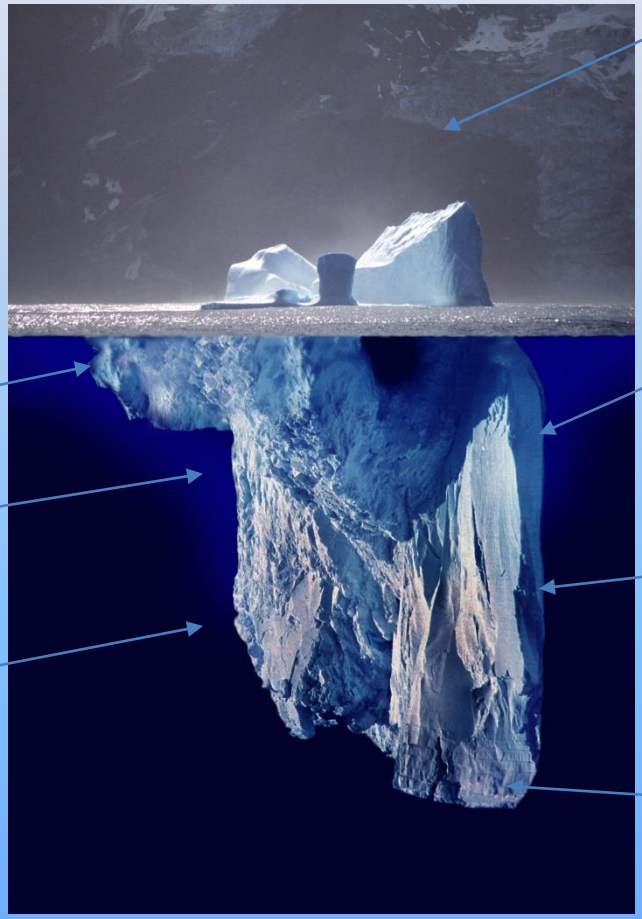
- Do not increase breast cancer risk
- Protect against
  - Cardiovascular disease
  - Cognitive dysfunction
  - Osteoporosis
  - Sexual dysfunction
- Women's Heath Initiative studied Conjugated Equine Estrogen (CEE, horse estrogen) and Medroxyprogesterone acetate (MPA, artificial progesterone)

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 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

Hot Flashes- the Tip of the Iceberg



- (Work by Uwe Kils)http://www.ecoscope.com/iceberg/

Hot Flashes and CVD

- 54 y/o, normotensive, overweight, and postmenopausal
- Hot flashes were positively associated with subclinical atherosclerosis
- More frequent physiologic hot flashes were associated with higher carotid intima media thickness p=.0001
- Thurston, R et al. Menopausal Hot Flashes and Carotid Intima Media Thickness among Midlife Women. *Stroke*. 2016 December ; 47(12): 2910–2915.

Hormonal BioIdentity in Women

- Includes balanced Estrogens, Progesterone and Testosterone
- Every woman needs to reestablish and maintain their unique balance

Omega 3's and NF*k*B

- EPA inhibits NFkB
- EPA decreases TNF alpha and other pro-inflammatory cytokines

- Zhao Y et al. Eicosapentaenoic acid prevents LPS-induced TNF-alpha expression by preventing NF-kappaB activation. J Am Coll Nutr. 2004 Feb;23(1):71-8.

Omega 3 and CV

- VITAL study: 840 mg/day EPA +DHA, 2019
  - a 28% reduced risk for MI
  - 50% reduced risk for fatal MI
  - 17% reduced risk for total coronary heart disease events
  - All significant
- ASCEND study 840 mg/day EPA + DHA, 2018
  - Cardiovascular disease death was significantly reduced by 19%

- Kris-Etherton P et al. Recent Clinical Trials Shed New Light on the Cardiovascular Benefits of Omega-3 Fatty Acids. *Methodist Debakey Cardiovasc J.* 2019 Jul-Sep;15(3):171-178.

- REDUCE-IT 4 g/day EPA (icosapent ethyl) 2019
  - 25% decrease in major cardiovascular events in patients with elevated triglycerides (135-499 mg/dL) who also were taking a statin drug
  - CV death, MI, or stroke in the secondary prevention population: 28% decrease ($P < .001$)
  - CV death or nonfatal MI: 26% decrease ($P < .001$)
  - Fatal or nonfatal MI: 31% decrease ($P < .001$)
  - Urgent or emergent revascularization: 35% decrease ($P < .001$)
  - CV death: 20% decrease ($P < .03$)
  - Hospitalization or unstable angina: 32% decrease ($P < .002$)
  - Fatal or nonfatal stroke: 28% decrease ($P < .01$)

How to evaluate omega 3 level

- Dietary and supplement history
- Omega 3 Index
  - Proportion of EPA +DHA in red cell membrane
  - 8-12% for reduction of CV risk
- AA/EPA ratio.
  - <7 for reduction of CV risk

- Del Gobbo LC et al. Omega-3 polyunsaturated fatty acid biomarkers and coronary heart disease: Pooling project of 19 cohort studies. *JAMA Intern Med*. 2016 Aug 1;176(8):1155-66.

- Tani, S et al. Association of Fish Consumption-Derived Ratio of Serum n-3 to n-6 Polyunsaturated Fatty Acids and Cardiovascular Risk With the Prevalence of Coronary Artery Disease. *Int Heart J.* 2015 May 13; 56(3):260-8.

Melatonin

- Expressed by all life forms bacteria to mammals
- Declines with aging
- Sleep/wake cycle, Jet lag
- Buffers Immune system
- Prolongs lifespan/HealthSpan of animals
- Neuro protective
- Cardio-protective
- Anti-cancer
- Anti-inflammation
- Protects against ionizing radiation

Melatonin and Complementary Treatment Cancer

- Side effect-Fatigue
- 20 mg/day – range 10-40 mg
- Meta-analysis of randomized controlled trials showed
  - Improvement in tumor remission
  - 1-year survival
  - Reduced chemoradiotherapy side effects of neurotoxicity, thrombocytopenia and fatigue
  - Safely increased response rates when added to many forms of standard care
- Stubbe, CE et al. Complementary Strategies for the Management of Radiation Therapy Side Effects. *J Adv Pract Oncol*. 2013 Jul-Aug; 4(4): 219–231.

Blindness and Breast Cancer

- 1392 Blind women
- No Light Perception vs. light perception
- ½ rate of breast cancer

- Flynn-Evans EE et al. Total visual blindness is protective against breast cancer. *Cancer Causes Control*. 2009 Aug 1.

Melatonin -CV

- Coronary heart disease – low melatonin levels
- Protects against ischemia – reperfusion injury
- Anti-arrhythmic
- Anti-inflammatory
- Anti-hypertensive

Melatonin in STEMI (ST segment elevation MI)

- Patients who had developed adverse events during follow-up had significantly lower nocturnal melatonin levels than patients without events. $P < .0001$
  - Cardiac Death, Repeat MI, CHF
- Vasodilator
- Free radical scavenger
- Inhibits oxidation of LDL-C

- Dominguez-Rodriguez A et al. Prognostic value of nocturnal melatonin levels as a novel marker in patients with ST-segment elevation myocardial infarction. *Am J Cardiol*. 2006 Apr 15;97(8):1162-4.

Maria Study Update

- Phase Ⅱ clinical trial
- Multicenter, randomized, controlled clinical trial
- IV and Intracoronary Melatonin in STEMI patients ongoing

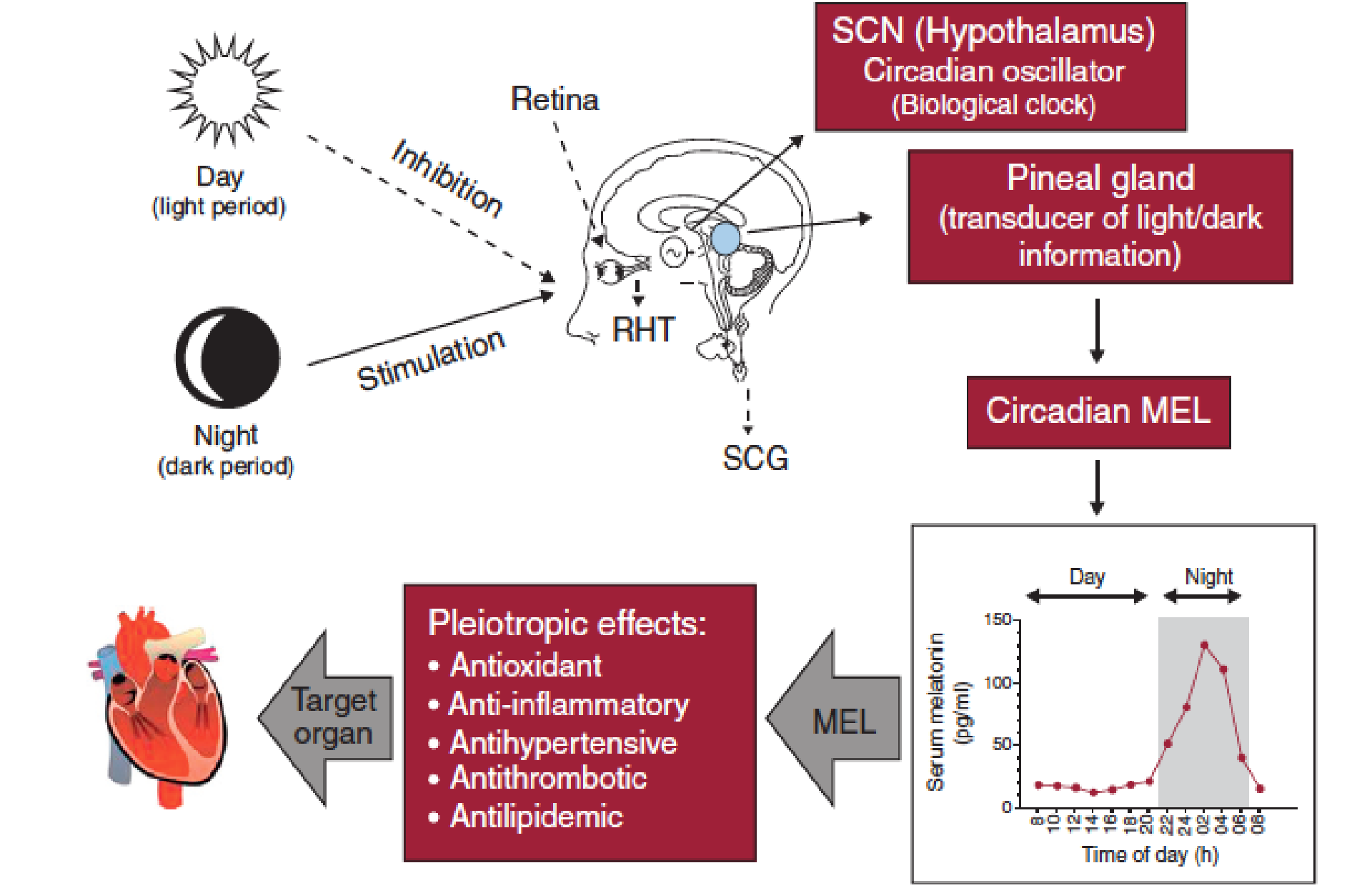
- Alberto Dominguez-Rodriguez et al. Cardioprotection and pharmacological therapies in acute myocardial infarction: Challenges in the current era. *World J Cardiol* 2014 March 26; 6(3): 100-106

MARIA Results

- IV or IC melatonin early within 136 minutes of pain to balloon time
- Significant decrease in infarct size (about ½) $p<.003$
- Dominguez-Rodriguez A et al. Usefulness of Early Treatment With Melatonin to Reduce Infarct Size in Patients With ST-Segment Elevation Myocardial Infarction Receiving Percutaneous Coronary Intervention (From the Melatonin Adjunct in the Acute Myocardial Infarction Treated With Angioplasty Trial). *Am J Cardiol.* 2017 Aug 15;120(4):522-526.

Melatonin and CV

- Alberto Dominguez-Rodriguez, Pedro Abreu-Gonzalez, and Russel J. Reiter.
- Melatonin and Cardiovascular Disease: Myth or Reality? Melatonina y enfermedad cardiovascular: Mito o realidad? *Rev Esp Cardiol*. 2012.

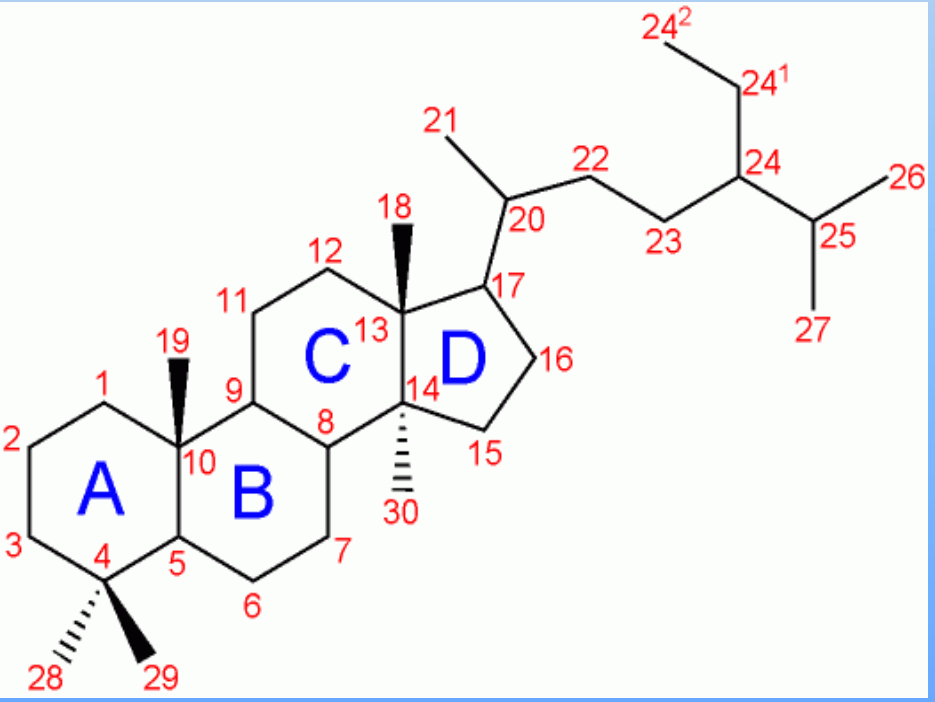


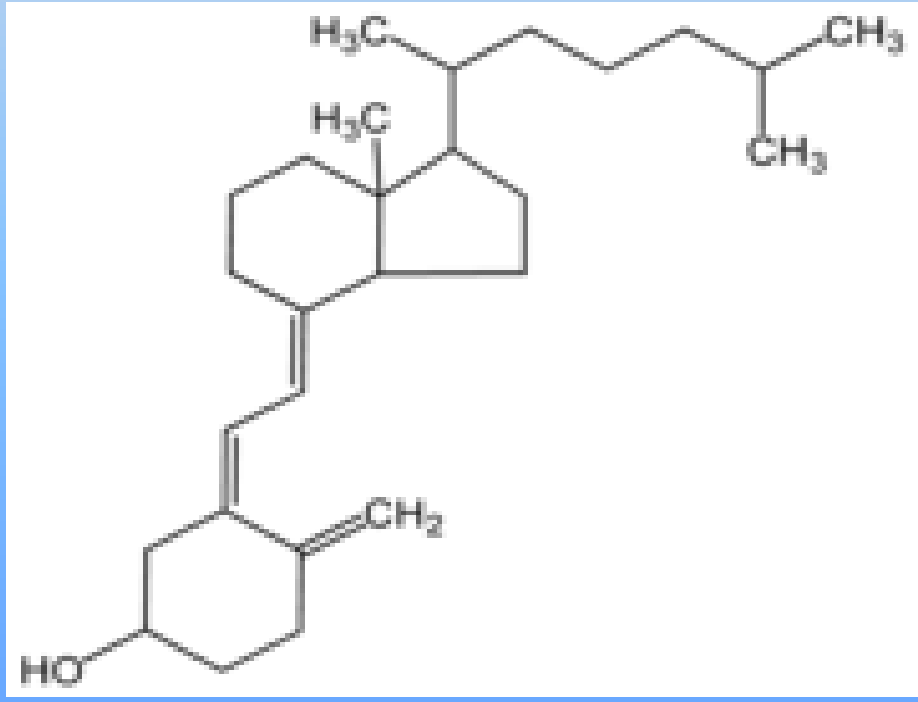
Dominguez-Rodrigues, Abreu-Gonzales, Reiter

Vitamin D

- Benefits from head to toe
- Most are deficient
- Prevention:
  - Cancer
  - Autoimmune disease
  - Cardiovascular disease
  - Viral Infections

Secosteroid hormone
Vitamin D3 = Cholecalciferol
“B” Ring is “Broken”





Vitamin D and inflammation

- Inversely associated with CRP and frailty
- Inhibits NFKB
- 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

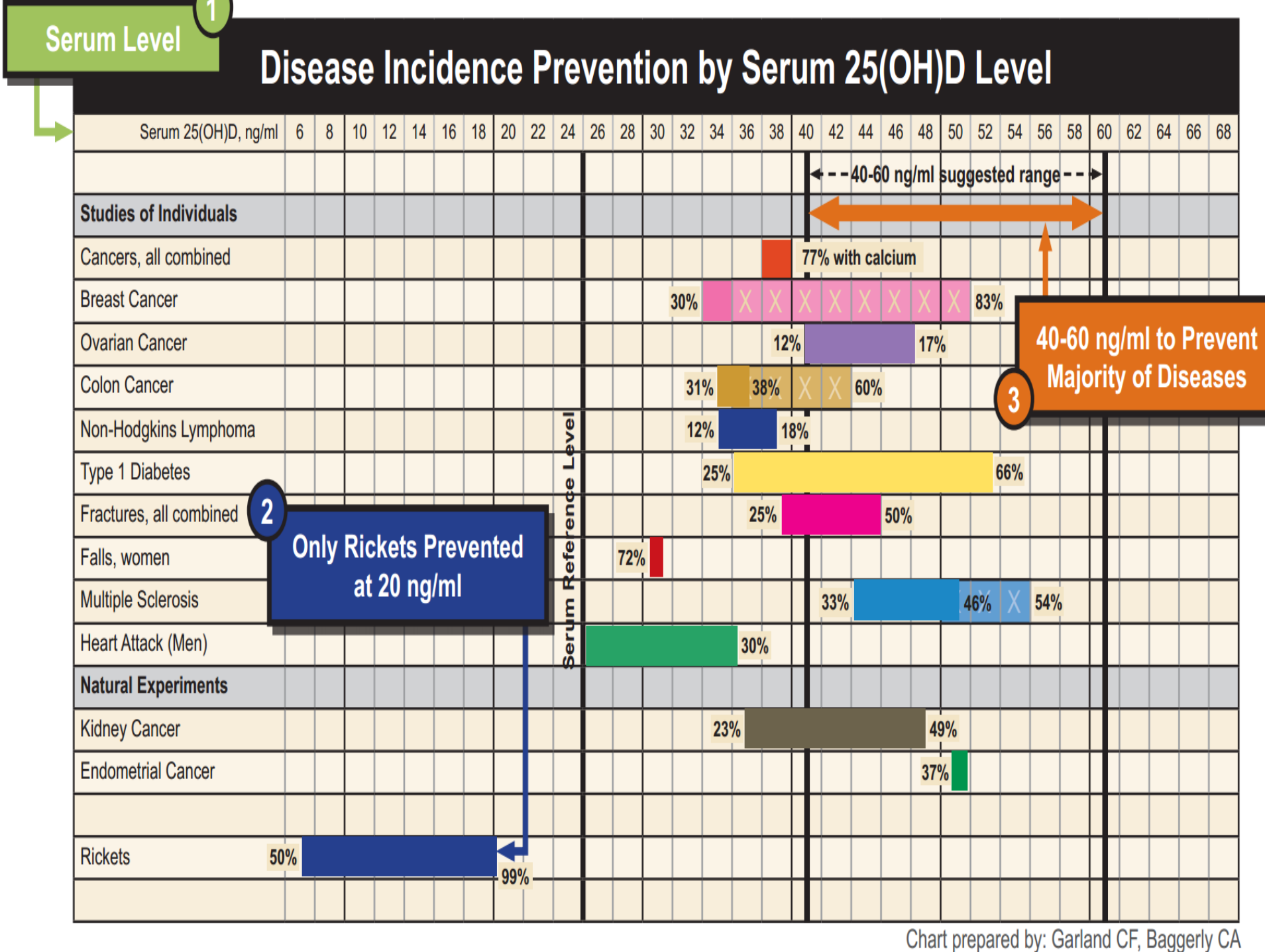


Chart prepared by: Garland CF, Baggerly CA

Vitamin D and cancer mortality

- 6537 cases, 3-10 year follow up
- 25 (OH)D = 54-135 nmol/l = 22-54 ng/ml
- RR =0.87 (95% CI, 0.79-0.96;
- P = 0.005

- Keum N et al. Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. *Ann Oncol.* 2019 May 1;30(5):733-743.

Vitamin D and Cancer Mortality

- Cancer mortality
- RR = 0.81; 95% CI: 0.71-0.93

- Han, J. 25-Hydroxyvitamin D and Total Cancer Incidence and Mortality: A Meta-Analysis of Prospective Cohort Studies. *Nutrients.* 2019 Sep 26;11(10).

Vitamin D and Breast CA

- Serum 25(OH)D levels were inversely significantly associated with breast cancer risk (RR = 0.845, 95% CI = 0.75-0.95).
- Every 10 ng/mL increment in serum 25(OH)D concentration was associated with a significant 3.2% reduction in breast cancer risk.

- Wang D et al. Serum 25-hydroxyvitamin D and breast cancer risk: a meta-analysis of prospective studies. *Tumour Biol.* 2013 Dec;34(6):3509-17.

- Stem cells are the tools of regenerative medicine
- We can use adult autologous stem cells for regenerative medicine now
- We can stimulate endogenous stem cells for self-repair now
- We can induce pluripotency

  in stem cells?

- Acute inflammation activates
- Chronic inflammation inhibits

Optimize stem cells

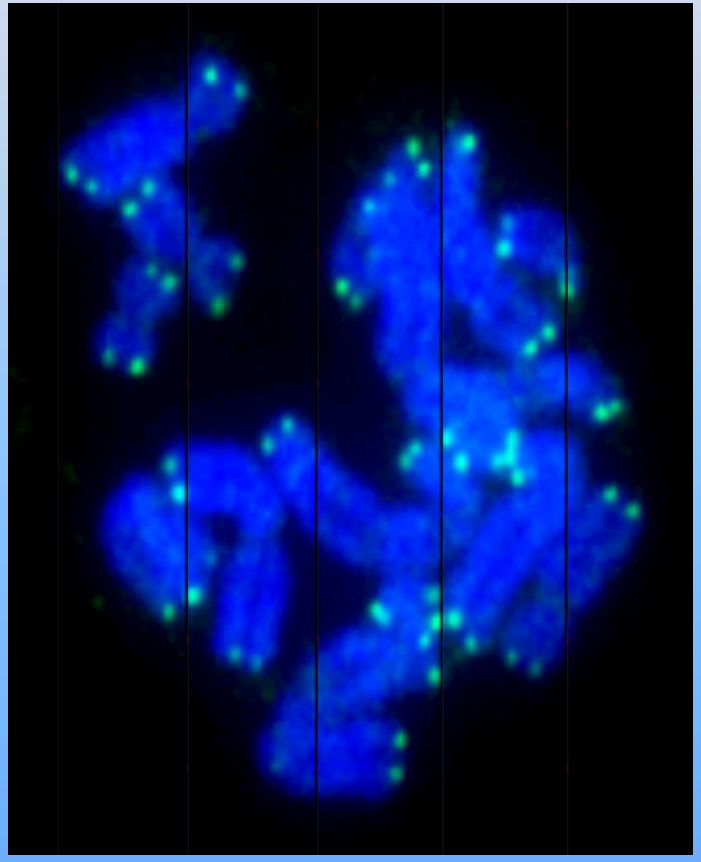
- Optimized hormones and nutraceuticals increase quality and quantity of endogenous adult stem cells
- Combinations of nutrients produce a synergistic effect to promote proliferation of human hematopoietic progenitors.
- Nutrients can act to promote healing via an interaction with stem cell populations.

Stem cells optimization through nutraceuticals

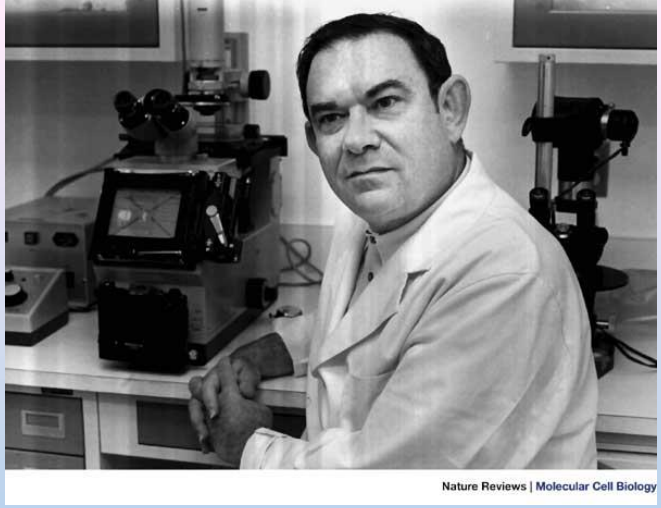
- Blueberry
- Green tea
- Vitamin D3
- Carnosine

- Bickford PC et al. Nutraceuticals synergistically promote proliferation of human stem cells. *Stem Cells Dev*. 2006 Feb;15(1):118-23.

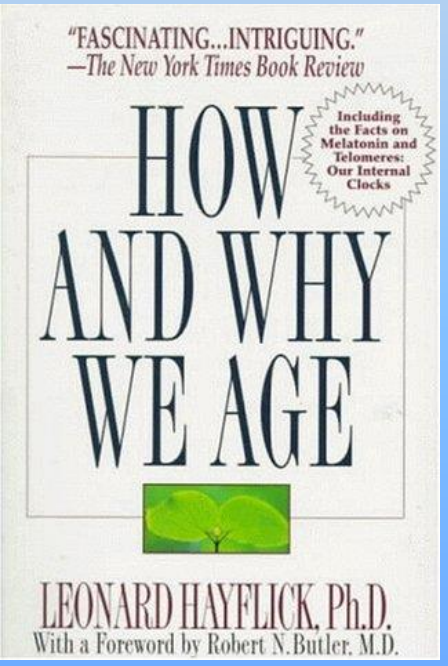
Telomeres

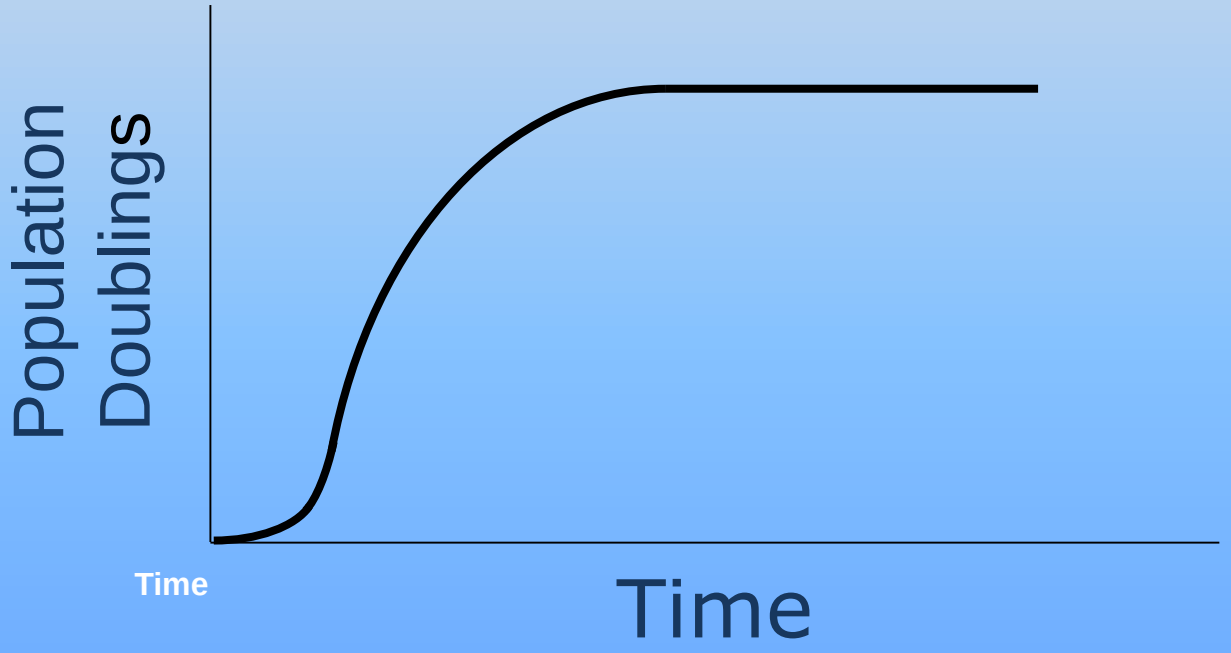


- Region of repetitive nucleotide sequences (TTAGGG) at each end of the chromatid
- Protects the end of the chromosome from deterioration or from fusion with neighboring chromosomes
- Telomeres act as the cellular aging clock.
- Telomere loss is a Major Cause of Cellular Aging



Hayflick Limit





Hayflick L et al. The serial cultivation of human diploid cell strains. *Exp Cell Res.* (1961).25(3):585–621.

Optimized Hormones and Telomere length

- Barbieri, M et al. Higher circulating levels of IGF-1 are associated with longer leukocyte telomere length in healthy subjects. *Mech Ageing Dev.* 2009 Nov-Dec;130(11-12):771-6.
- Kaplan RC et al. Insulin-like growth factors and leukocyte telomere length: the cardiovascular health study. *J Gerontol A Biol Sci Med Sci*. 2009 Nov;64(11):1103-6
- Movérare-Skrtic S et al. Serum insulin-like growth factor-I concentration is associated with leukocyte telomere length in a population-based cohort of elderly men. *J Clin Endocrinol Metab*. 2009 Dec;94(12):5078-84.
- Rastmanesh, R. Potential of melatonin to treat or prevent age-related macular degeneration through stimulation of telomerase activity. *Med Hypotheses*. 2011 Jan;76(1):79-85.

What Can Be Done To Keep Telomeres Long?

- Lifestyle -
  - Nutrition, Exercise, stress reduction, meditation
  - Nutraceuticals
    - Omega 3's, resveratrol, Vitamin D
    - Liu *AJEpid*, 2013, Liu *HumaReprod* 2013
  - Limit inflammation
  - Limit free radial damage
  - Limit toxic environmental exposure
- Restore Youthful hormone levels
- Activate Telomerase with telomerase activation supplement

Telomerase is "Dual Targeted"

- Nucleus -prevents telomere erosion leading to senescence and genomic instability
- Terminally differentiated post mitotic cells
- Mitochondria – has a different function since mitochondrial DNA does not contain telomeric structures.
- Non telomeric activities hTERT in the nucleus:
  - Cell cycle regulation
  - Modulation of cellular signaling and gene expression,
  - Augmentation of proliferative lifespan as well as DNA damage responses
- Mitochondrial hTERT
  - Reduces reactive oxygen species, DNA damage and apoptosis
- Ale-Agha N et al.Cellular functions of the dual-targeted catalytic subunit of telomerase, telomerase reverse transcriptase--potential role in senescence and aging. *Exp Gerontol.* 2014 Aug;56:189-93.

TA-65 and CV function – Harley 2013

- Multivitamin supplement plus TA-65 x 12 months
- Human study
- No significant change in diet or exercise
- Extensive lab testing
- BMD, Dexascan

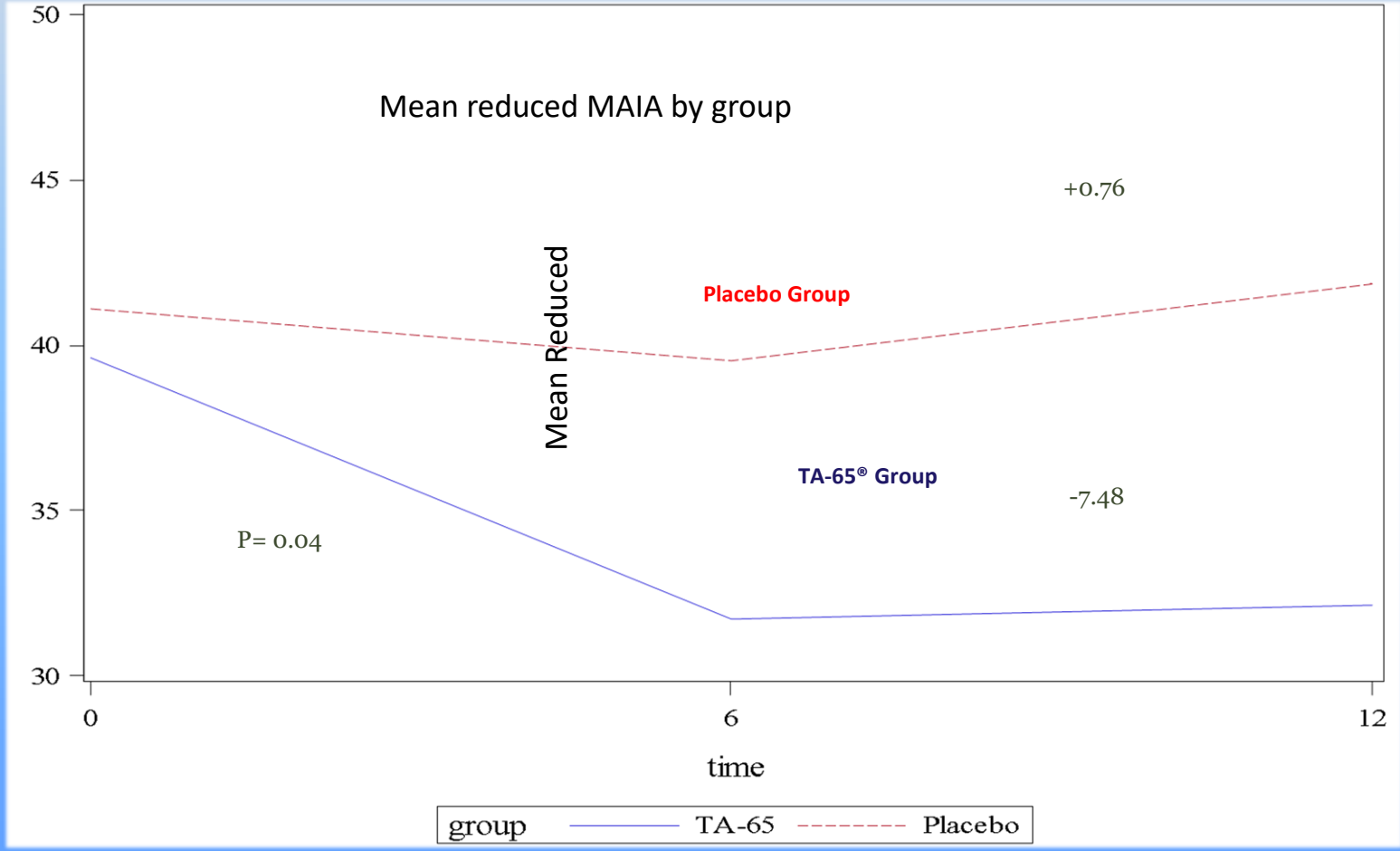
- Harley, C et al. A Natural Product Telomerase Activator as Part of a Health Maintenance Program: Metabolic and Cardiovascular Response. *Rejuvenation Research*. Volume 16, Number 5, 2013

TA-65 and Cardio-Metabolic function – Harley 2013

Fasting glucose	-3.72 mg/dl	p= 0.02
Insulin	-1.32 mIU/ml	p=0.01
Total cholesterol	-13.2mg/dl	p=.002
LDL cholesterol	-11.8 mg/dl	p=.002
Systolic/Diastolic	-17.8/-4.2	p=.007/.001
Homocysteine	-3.6 pmol/L	p=.001
BMD	+2% in spine	p=.003

Evaluation of Telomerase Activator TA-65® for early ARMD (Age Related Macular Degeneration)

Improvements in Eye Function as indicated by MAIA



Effect of TA-65® on Telomere Length in Humans

A Natural Product Telomerase Activator Lengthens Telomeres in Humans: A Randomized, Double Blind, and Placebo Controlled Study. Salvador L, et al. Rejuvenation Res. 2016 Mar 30.

- Randomized, double-blind, placebo controlled study of 97 men and women (50-84 years old)- all CMV+
- First study to show statistically significant lengthening of telomeres ***in humans*** *(3, 6, 9, and 12 months)(p<.005)*

TA-65® Group

Increase in median telomere length

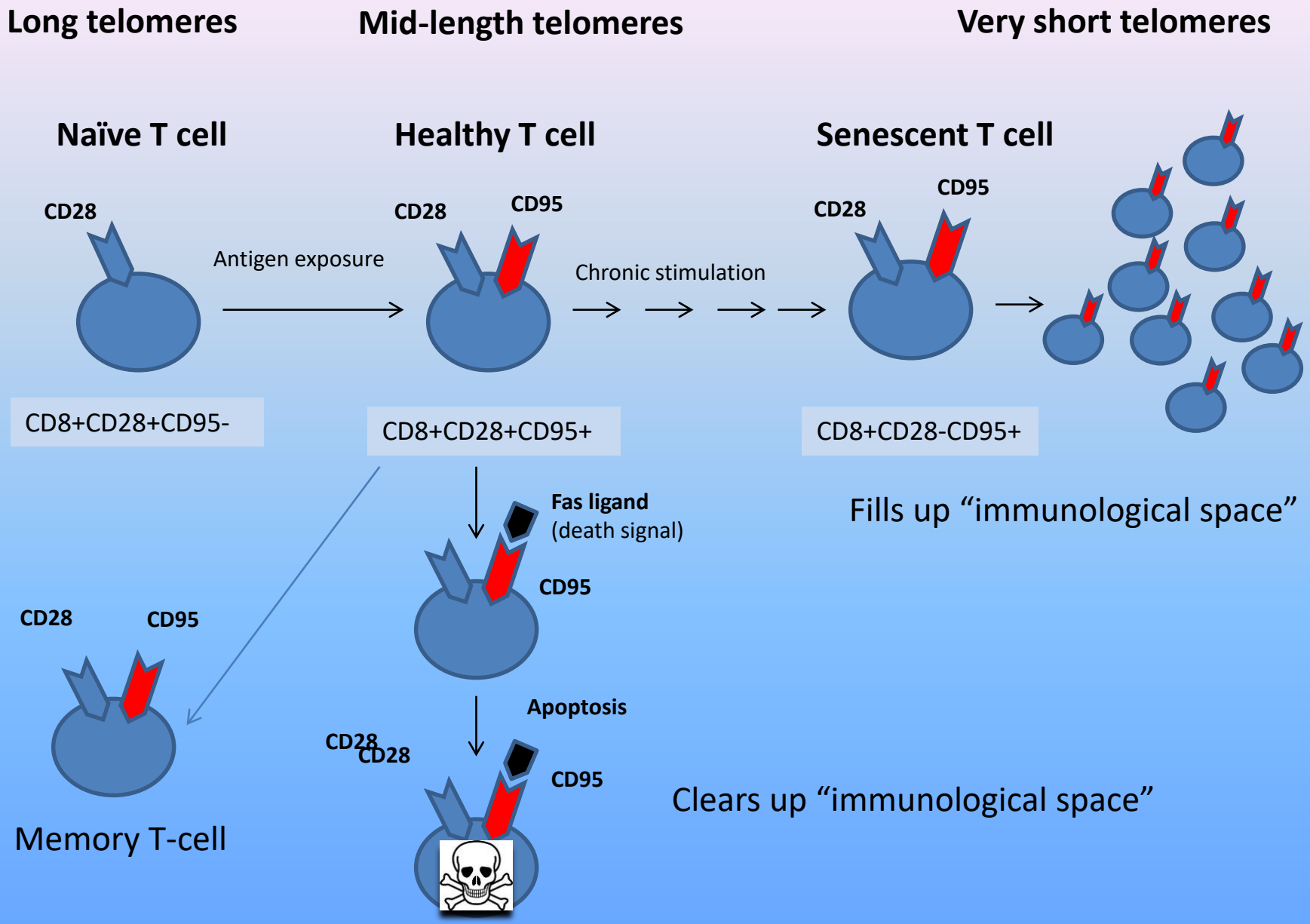
Time (months)	Increase in length (base pairs)
3 months	+384 (± 195) bp *
6 months	+158 (± 164) bp
9 months	+526 (± 167) bp *
12 months	+533 (± 183) bp *

Placebo Group

Decrease in median telomere length

Time (months)	Decrease in length (base pairs)
3 months	-24 (± 106) bp
6 months	none
9 months	-170 (± 106) bp *
12 months	-288 (± 101) bp *

* Statistically significant



Courtesy - Joseph Raffaele MD

- Emergency Medicine and Anti-aging medicine have a lot in common
- Anti-aging can help keep ED docs healthy in their stressful life
- Check your hormone levels and Inflam-aging numbers
- Some anti-aging concepts (thyroid, melatonin) may merge with emergency medicine in the future

BHRT

- Establish each patients unique BioIdentity
- Safe
- Decreases cardiovascular risks
- No increase in breast or prostate cancer risk
- Improved Quality of Life
- Decrease Inflammation
- Improves telomere loss

Know your Inflam-aging numbers

- CRP <1
- Fasting Insulin <7
- Homocysteine <7
- Omega 3 Index >10%
- 25-OH-D 60 -80 ng/dl
- Telomere length < 15 % short
- Cytokines
  - IL-6 <12 pg/l
  - TNF alpha <8 pg/l
  - IL-1 beta <15 pg/l

Hormones Inflam-aging numbers– youthful range

- Testosterone
- Estrogens
- Progesterone
- Thyroid
- DHEAS
- Cortisol
- Growth Hormone/IGF-1

Optimized Hormonal BioIdentity

- Control Inflam-Aging
- Optimize hormones with BHRT
- Optimize stem cells
- Optimize telomeres
- Increased quality of life
- We all have to die sometime
- What will the journey be like?
- Rectangularize
- And if we delay, intervene and reverse the diseases of aging….
- Increased quantity of life as well