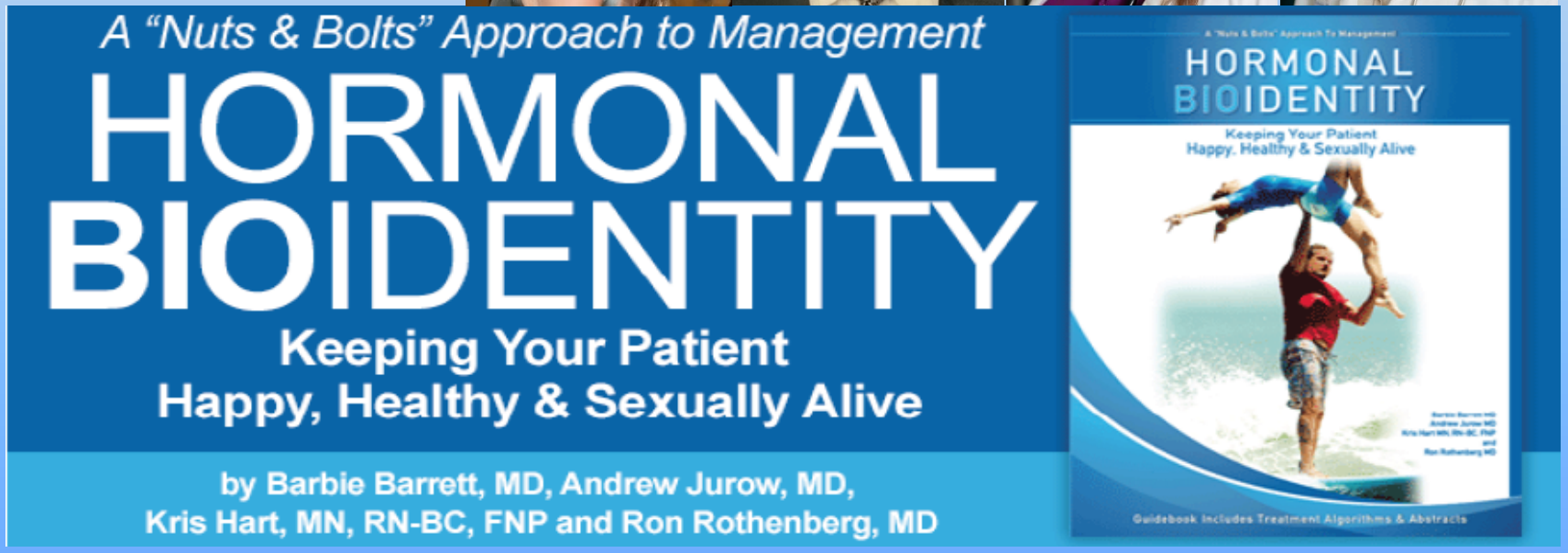
Hormonal BioIdentity

Ron Rothenberg MD

- Now available at UCP or Amazon

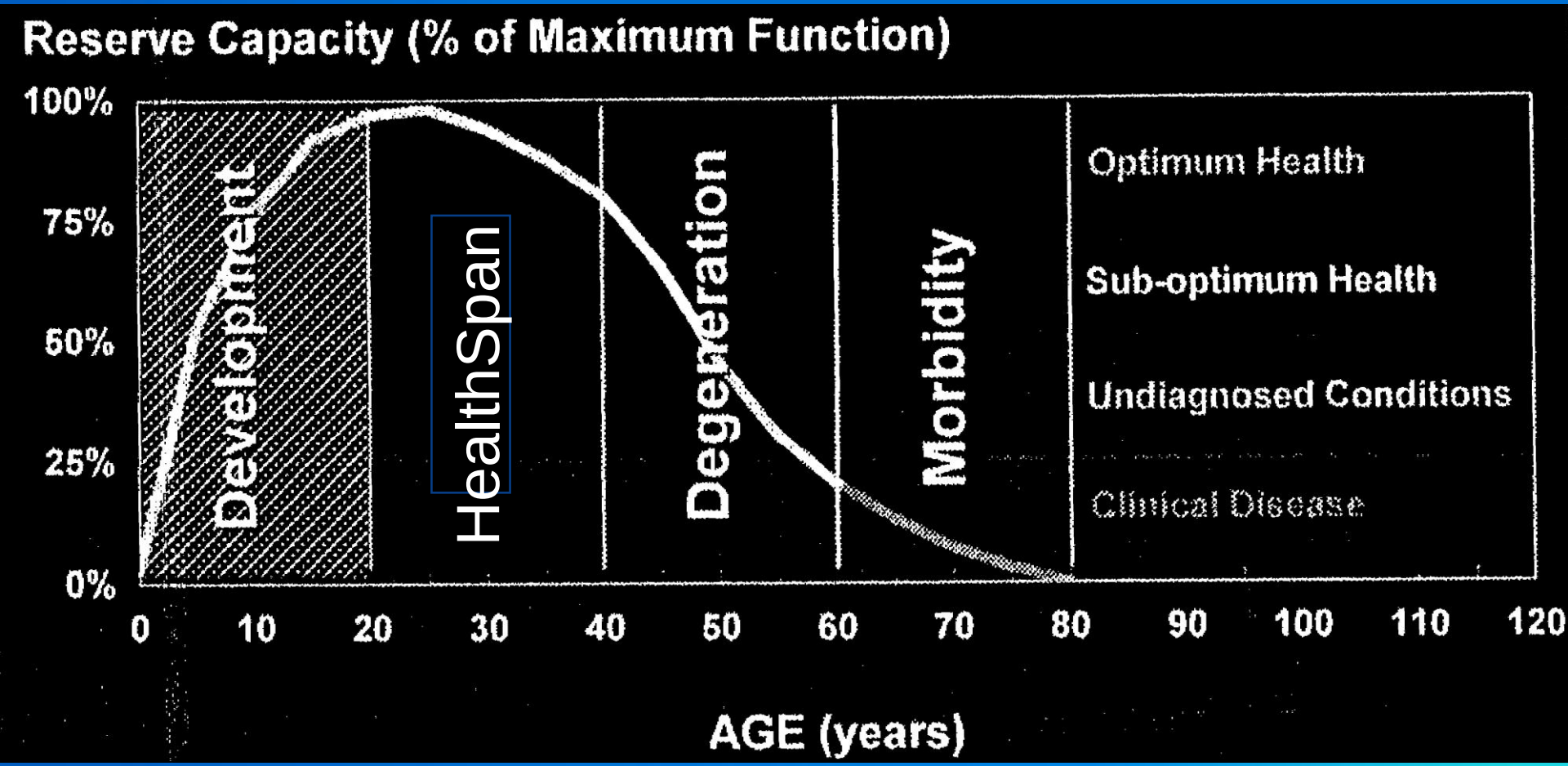


Hormonal BioIdentity

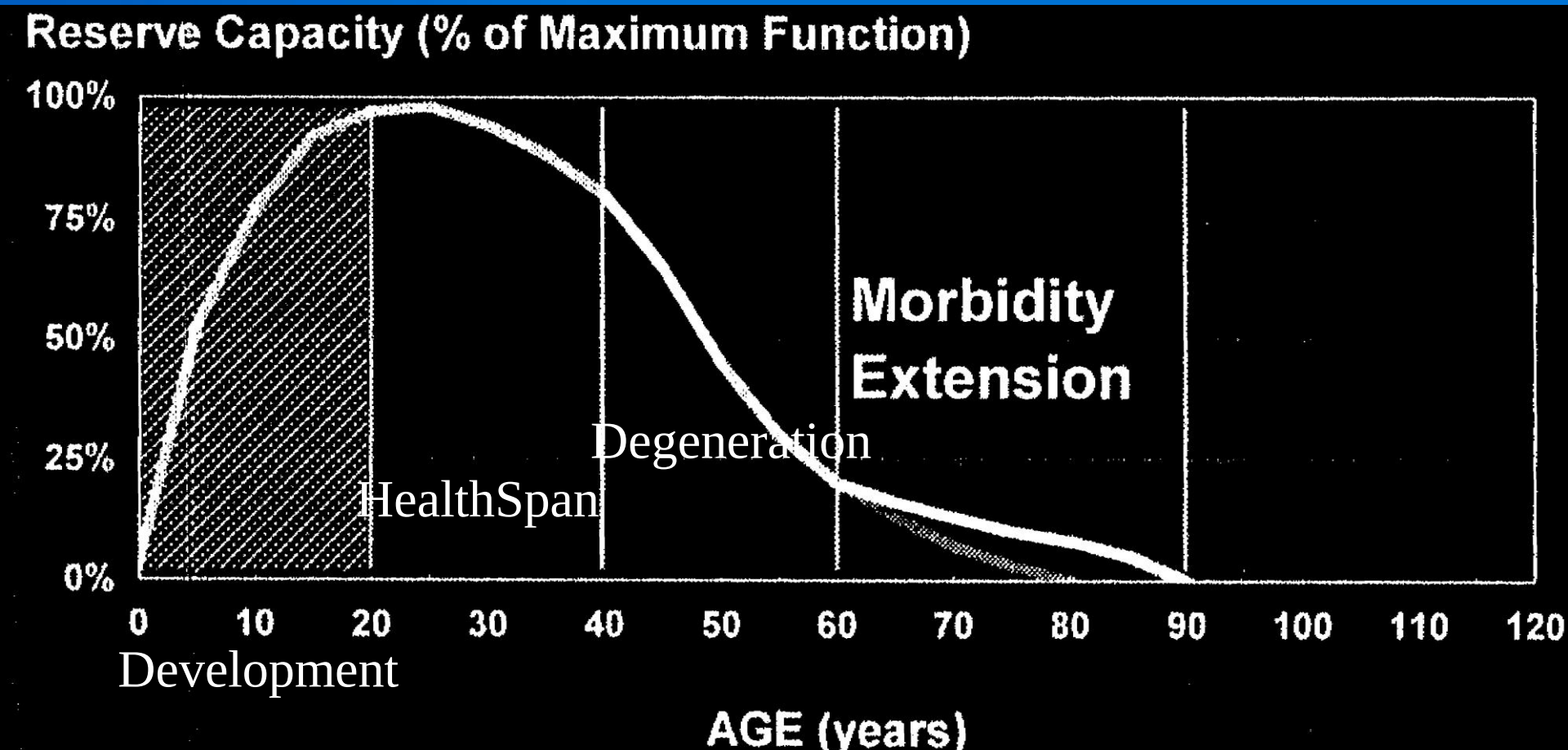
- Everyone has a unique hormone balance that enables them to function optimally
- As we age adult hormone deficiencies become clinically relevant
- Replacing hormone deficiencies is a major treatment modality
- Optimal lifestyle including nutrition, exercise, and stress reduction is an essential simultaneous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

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

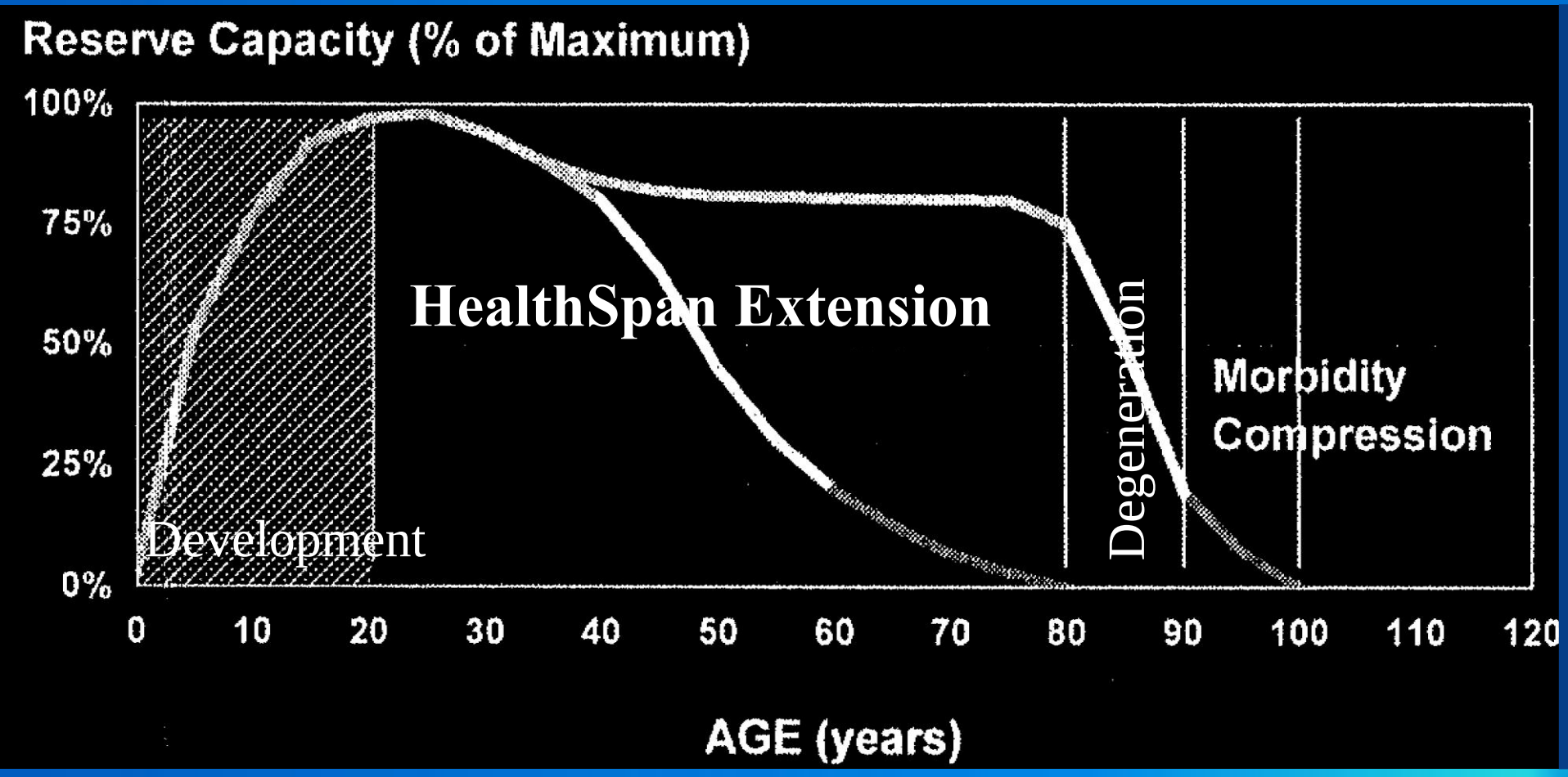
The HealthSpan Curve



“Conventional Medicine” Prolongation of Morbidity

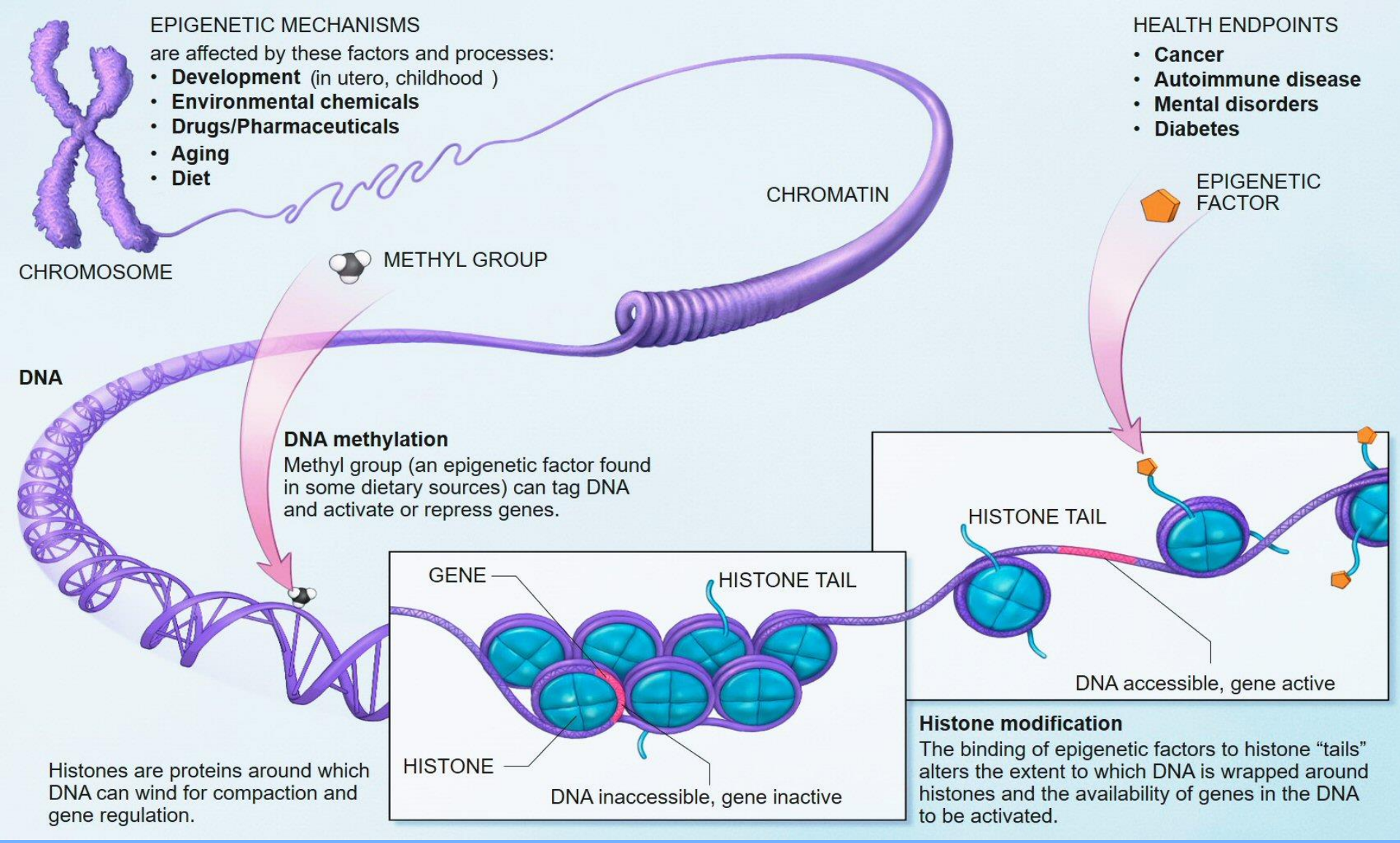


Goal of Preventive/Regenerative Medicine HealthSpan Extension, Morbidity Compression



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 — which in turn affects how cells read the genes.
- Epigenetic clock – biomarker of aging
- Measures DNA methylation, histones and other biomarkers



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

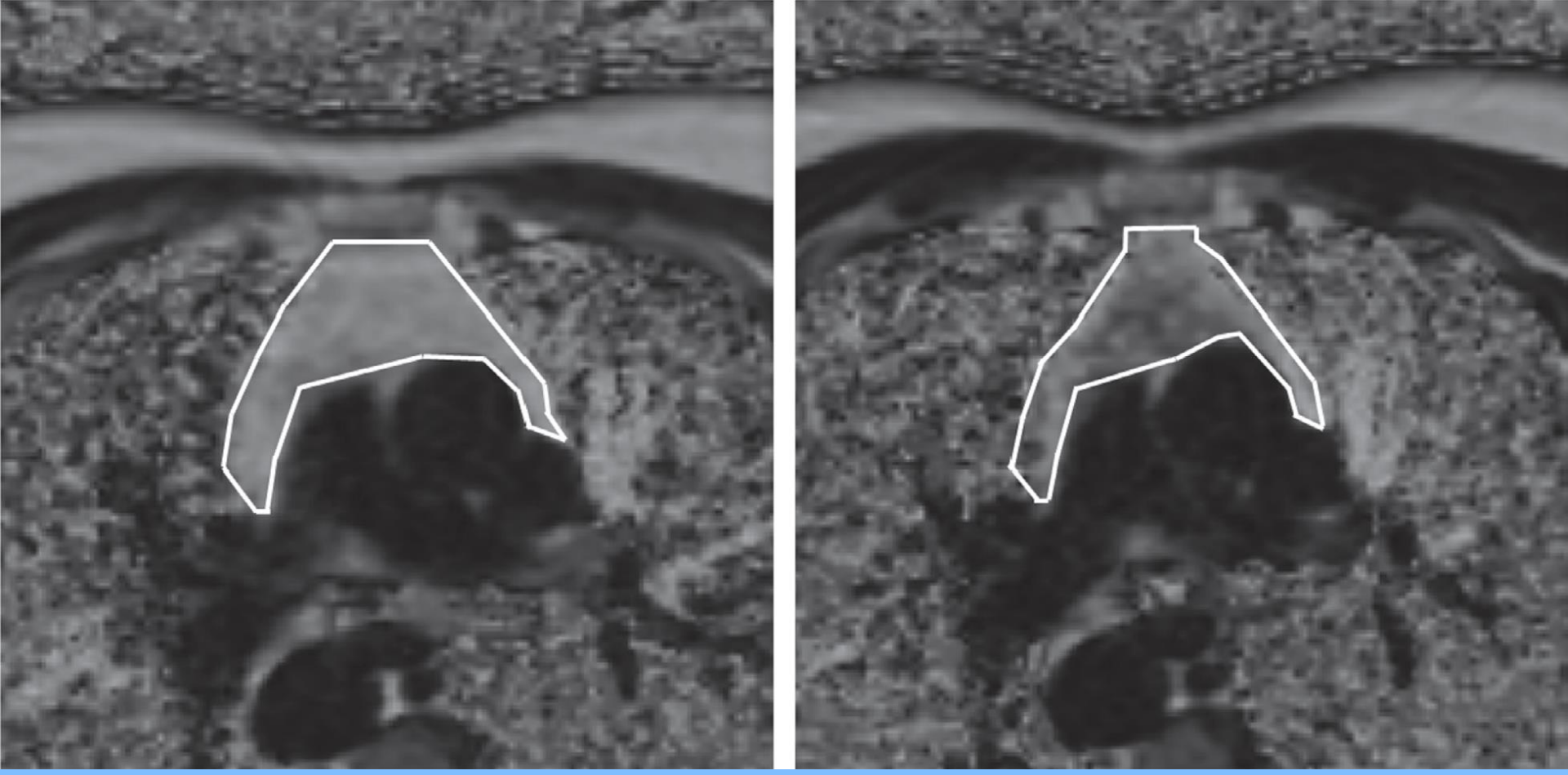
Aging Reversal 2019

- Epigenetic age - indication of biological age as opposed to chronological age
- Immunosenescence from thymic involution →
- Depletion of critical immune cell populations after the age of ~63
- Linked to age related increases in cancer, infectious disease, autoimmune conditions, generalized inflammation, and all-cause mortality.
- TRIIM trial (Thymus Regeneration, Immunorestoration, and Insulin Mitigation): hGH to prevent or reverse signs of immunosenescence in 51-65 year-old healthy men.
- hGH has thymotrophic and immune reconstituting effects
- Since hGH can produce increased glucose and insulin(if no attention to lifestyle) hGH was combined with metformin 500 mg and DHEA 50 mg

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

Concerns

- 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

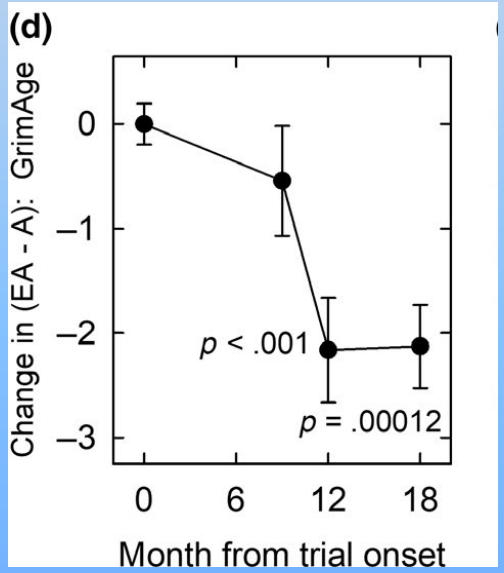


Regeneration of Thymus and Bone Marrow

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

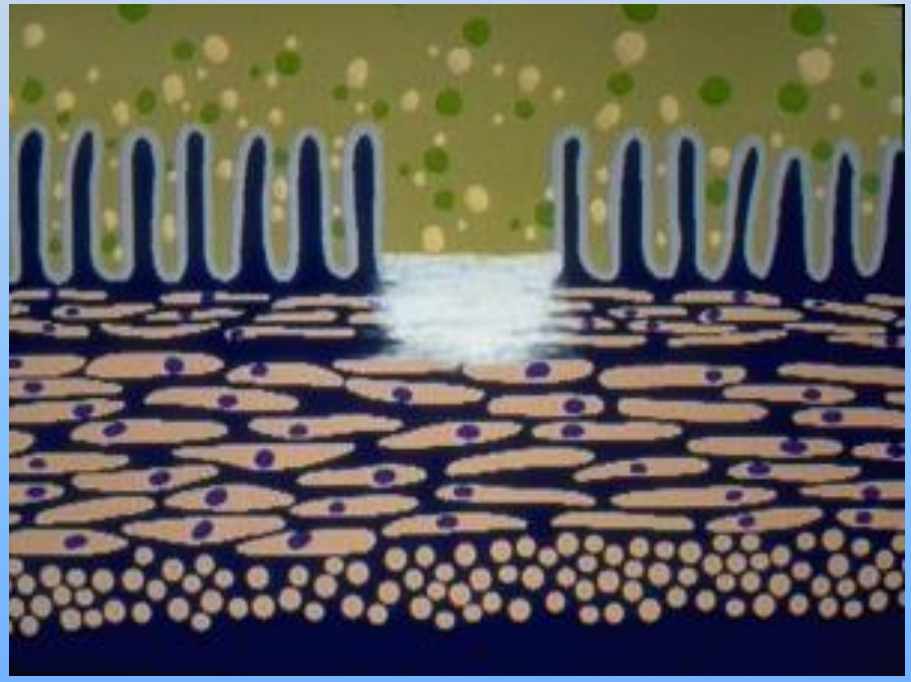
Epigenetic Clock - GrimAge

- 4 different epigenetic clocks – all 4 Epigenetic clocks including GrimAge showed reversed epigenetic aging – 2.5 years after 1 year
- Reversal of immunosenesence



- 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

Lifestyle

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

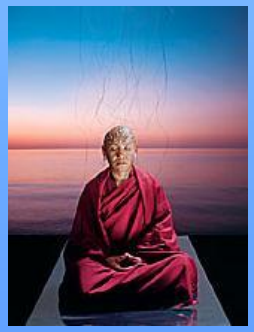
Exercise

- 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)



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”

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?”

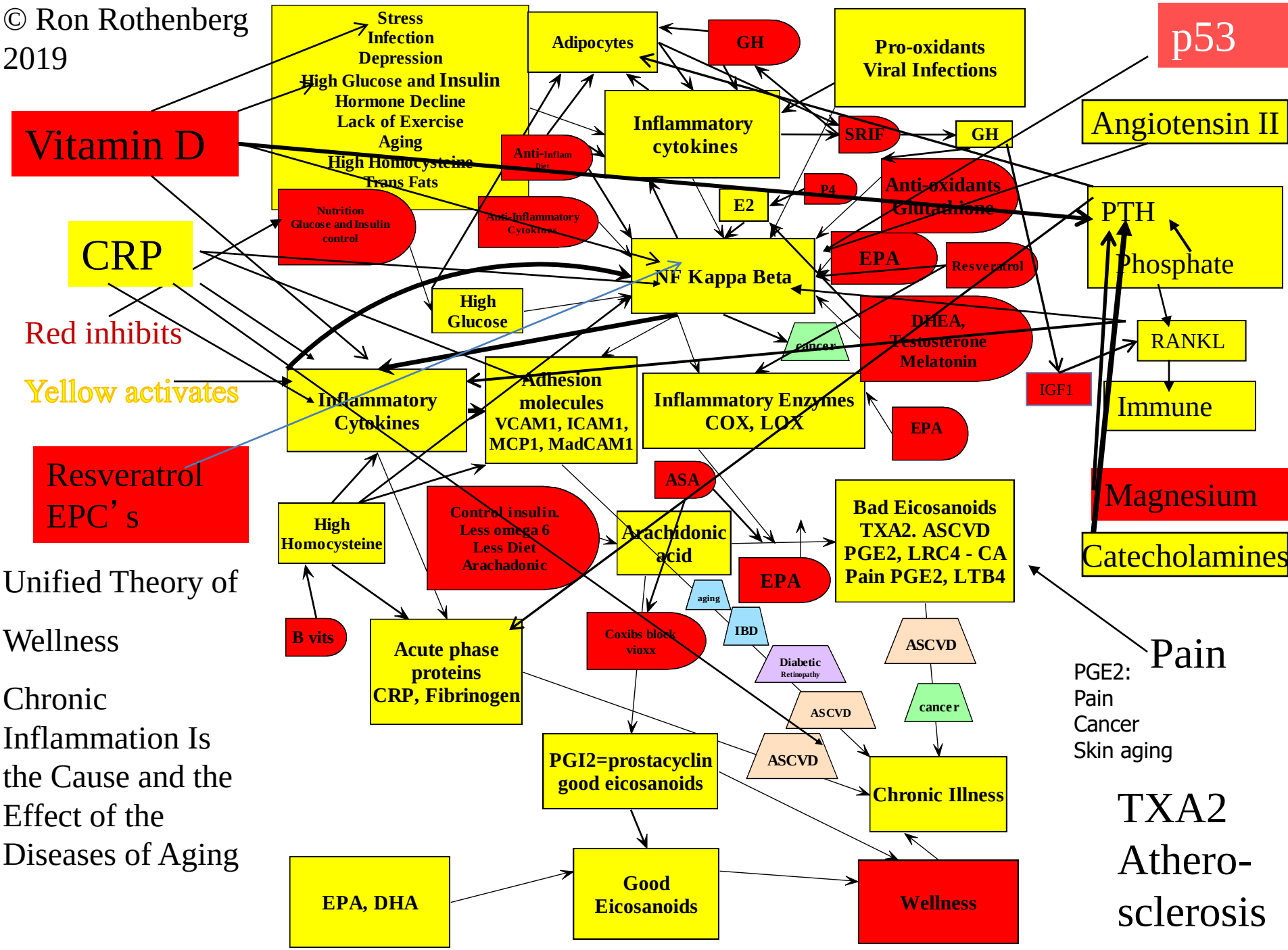
Hormonal BioIdentity Optimization

- 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)

- Eicosanoid hormones
  - Regulated by Lifestyle, Diet, Insulin, Omega 3’ s, Endocrine Hormones, Mind-Body connection, Vitamins and Nutraceuticals
- Autocrine
- Paracrine
- Endocrine
- Lifestyle impacts hormone levels and actions
- Lifestyle decreases inflammation



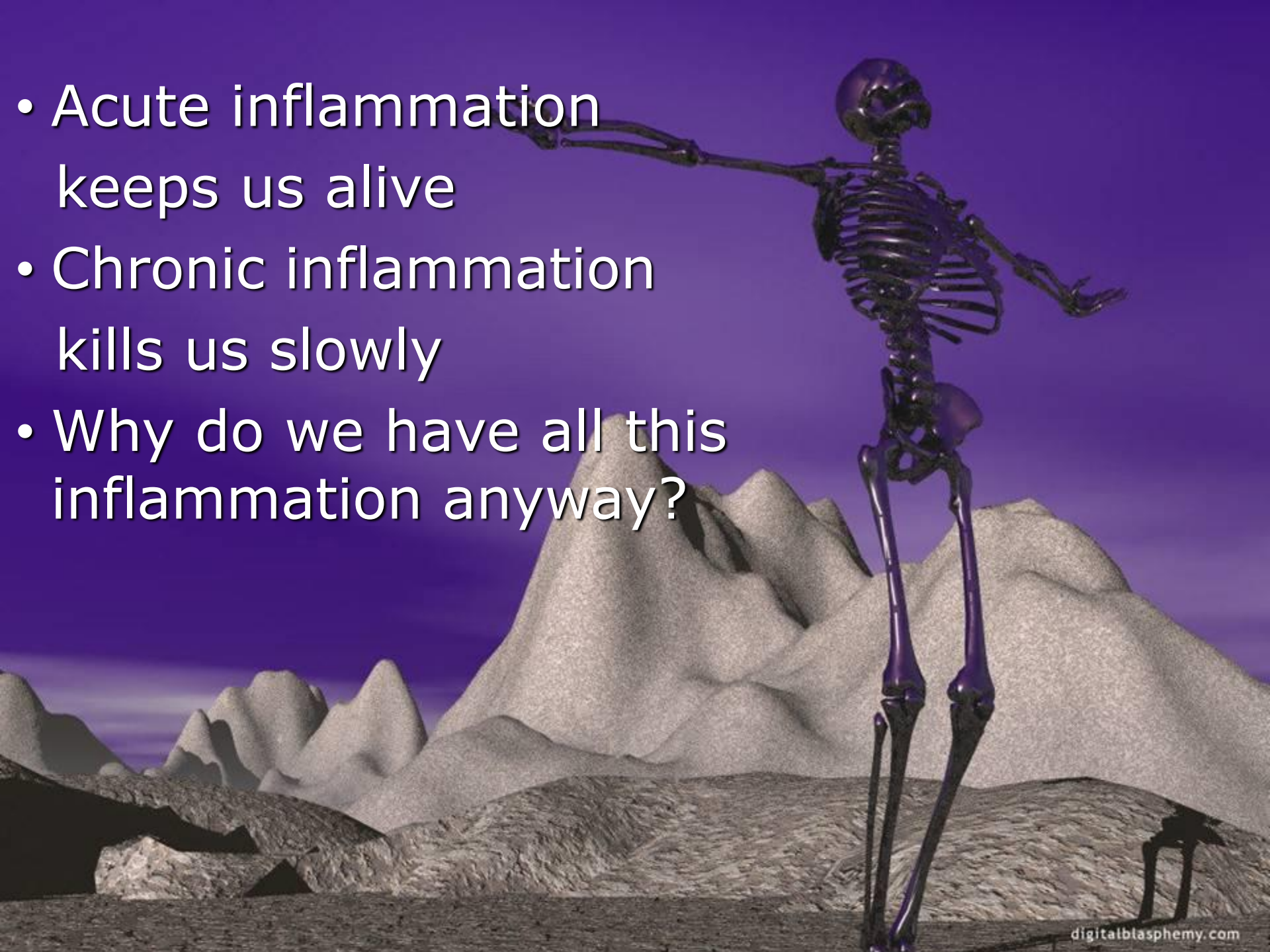
Unified Theory of

Wellness

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

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?

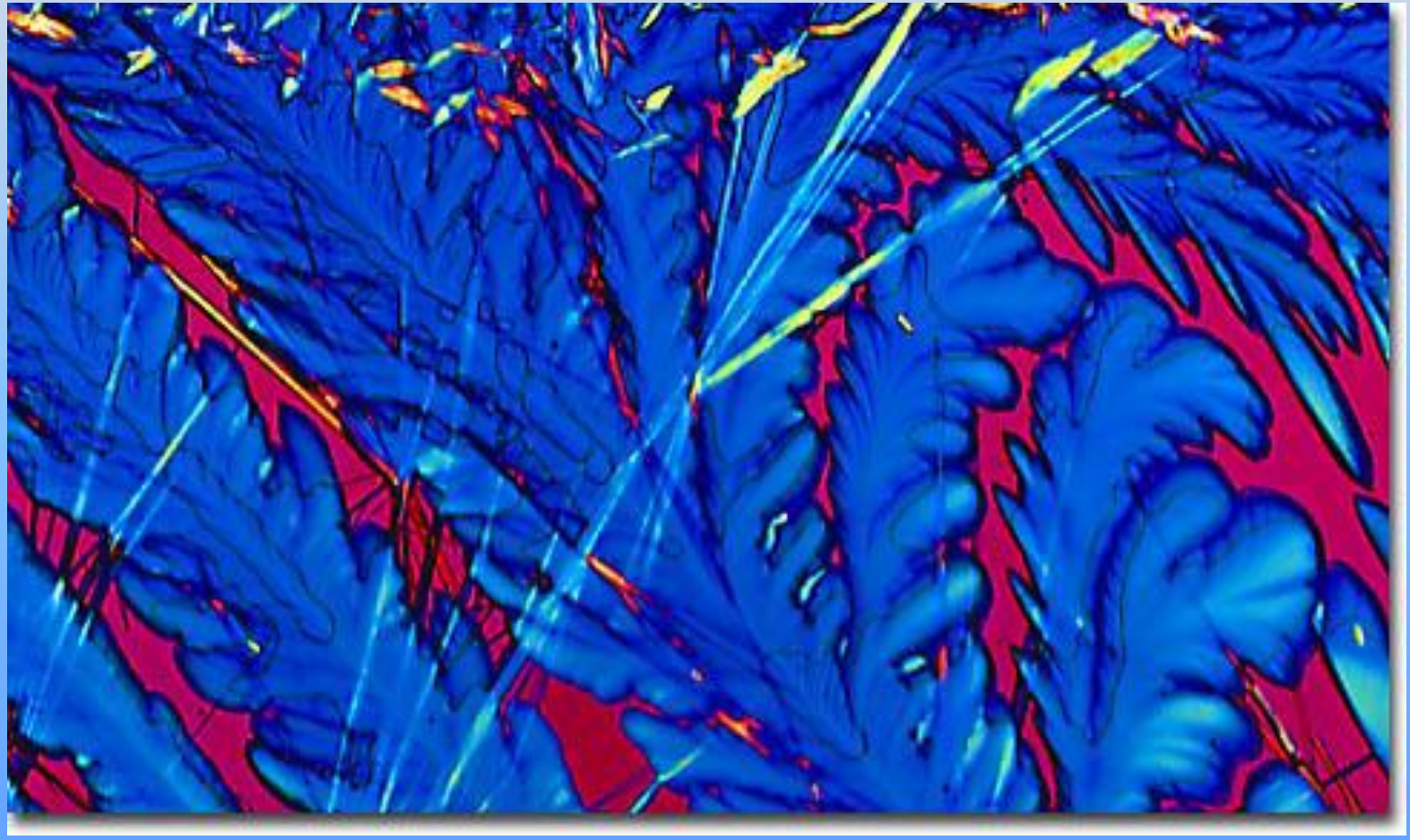
Antagonistic Evolutionary Benefit

- 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

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

TESTOSTERONE in men



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 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

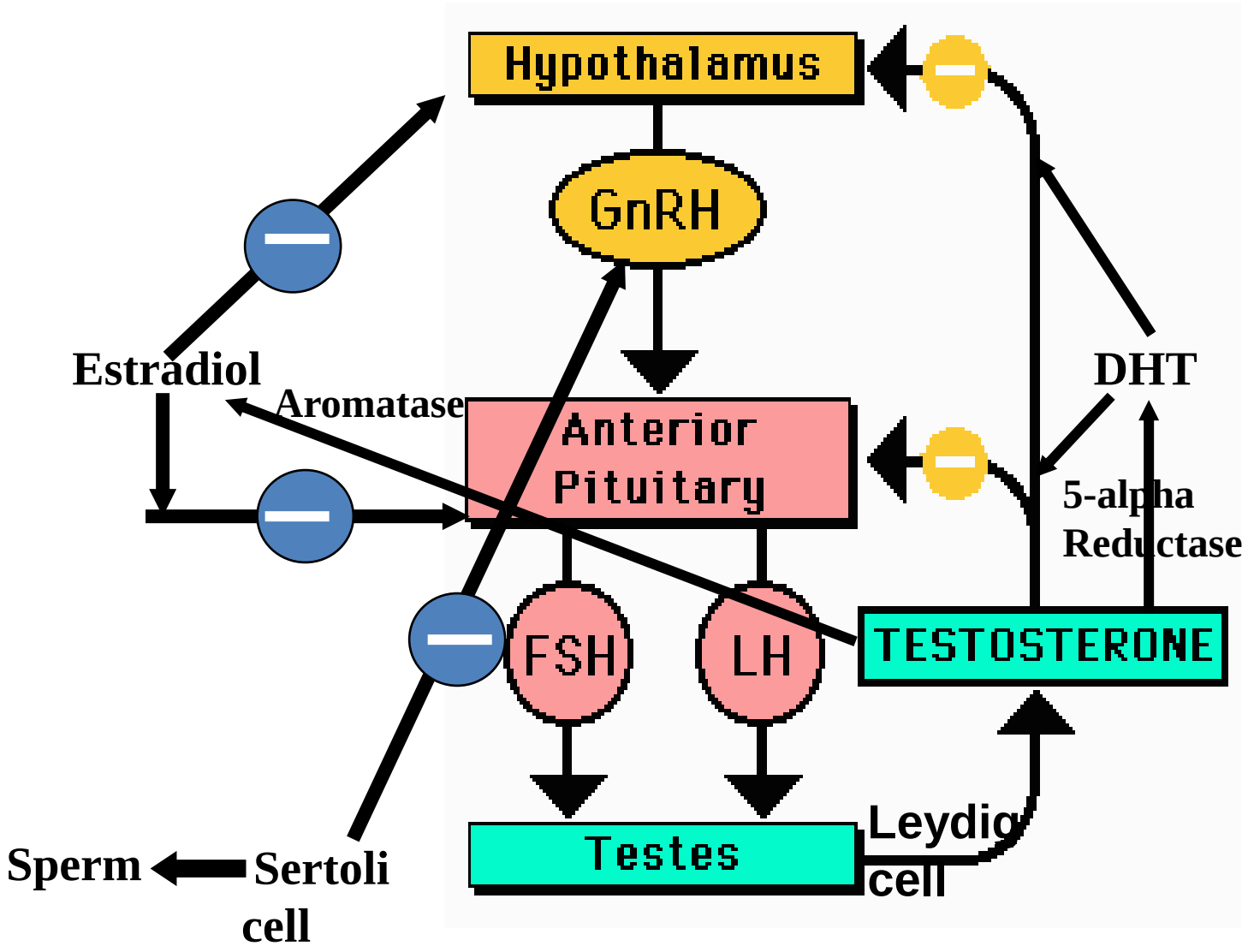
Testosterone

- Does not increase risk of prostate cancer
- Does not cause existing prostate cancer to grow
- Optimize treatment to match Hormonal BioIdentity
- See testosterone today and testosterone and prostate cancer tomorrow

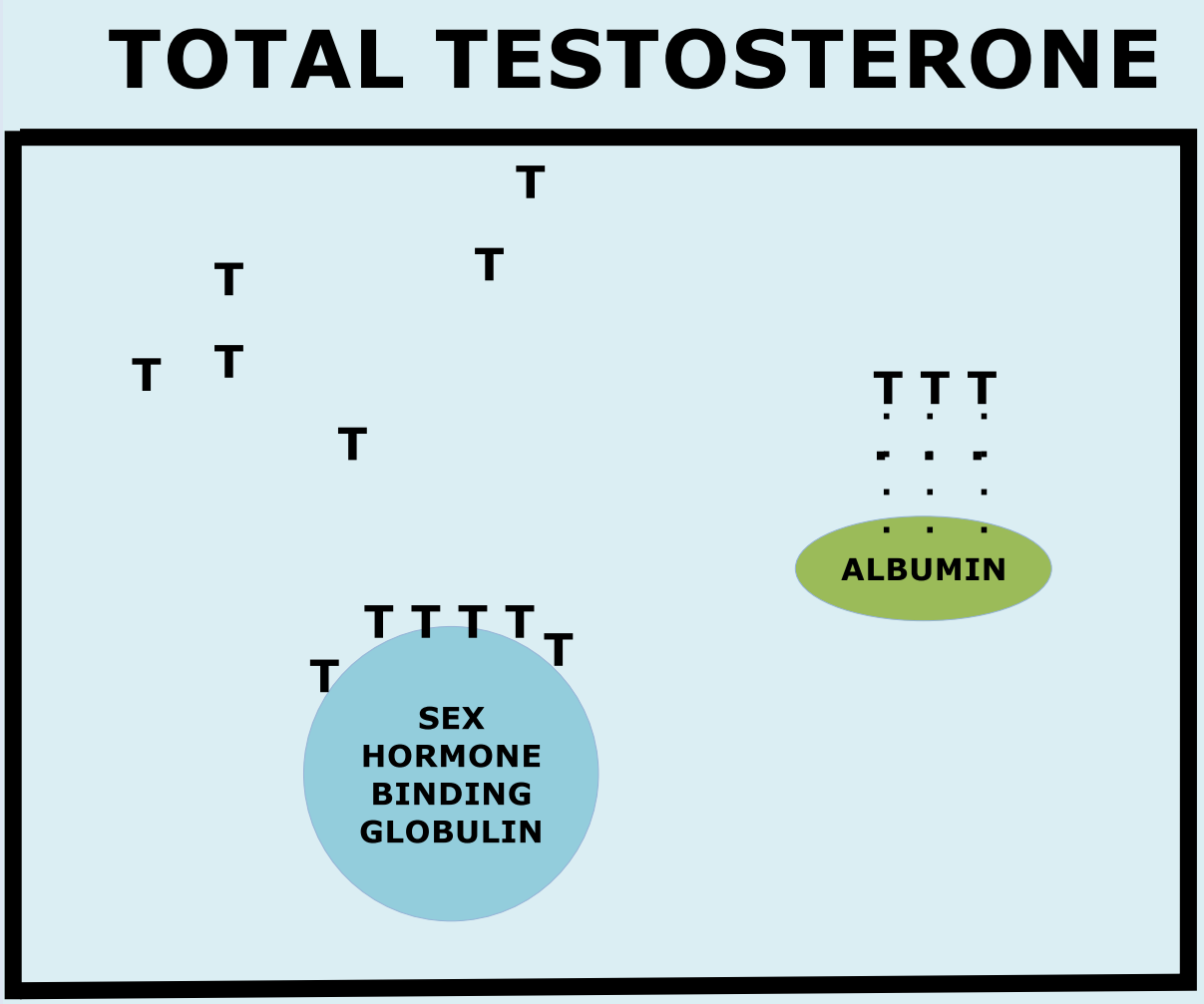
Normalized-TT vs. No TT Hazard Ratios

- 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

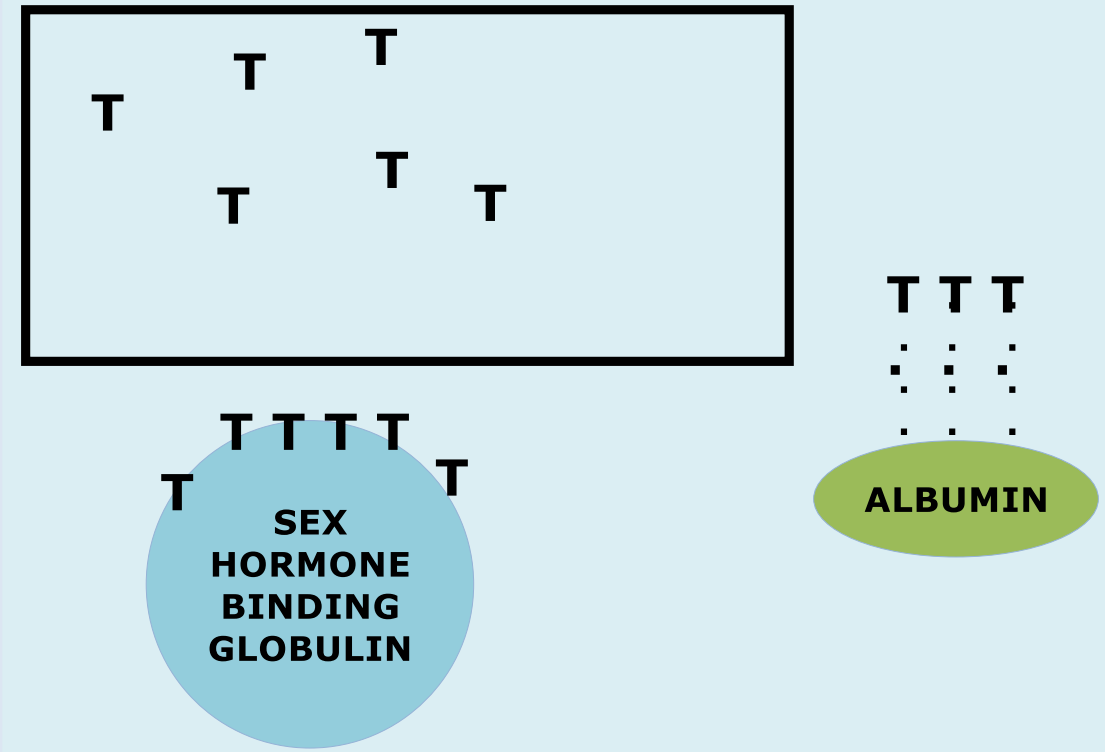
- Sharma, R et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J.* 2015 Aug 6


Hypothalamus
GnRH
Estradiol
Aromatase
Anterior Pituitary
DHT
5-alpha Reductase
FSH
LH
TESTOSTERONE
Testes
Leydig cell
Sperm
Sertoli cell

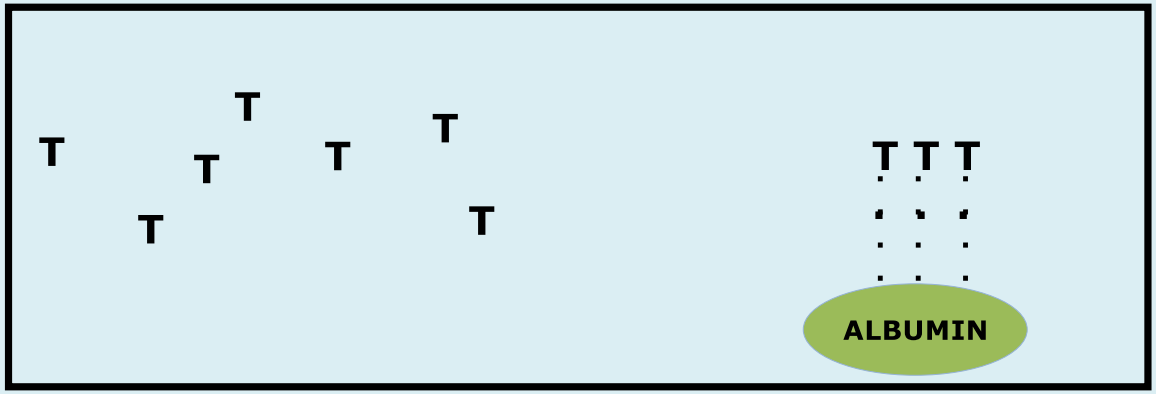
TOTAL TESTOSTERONE

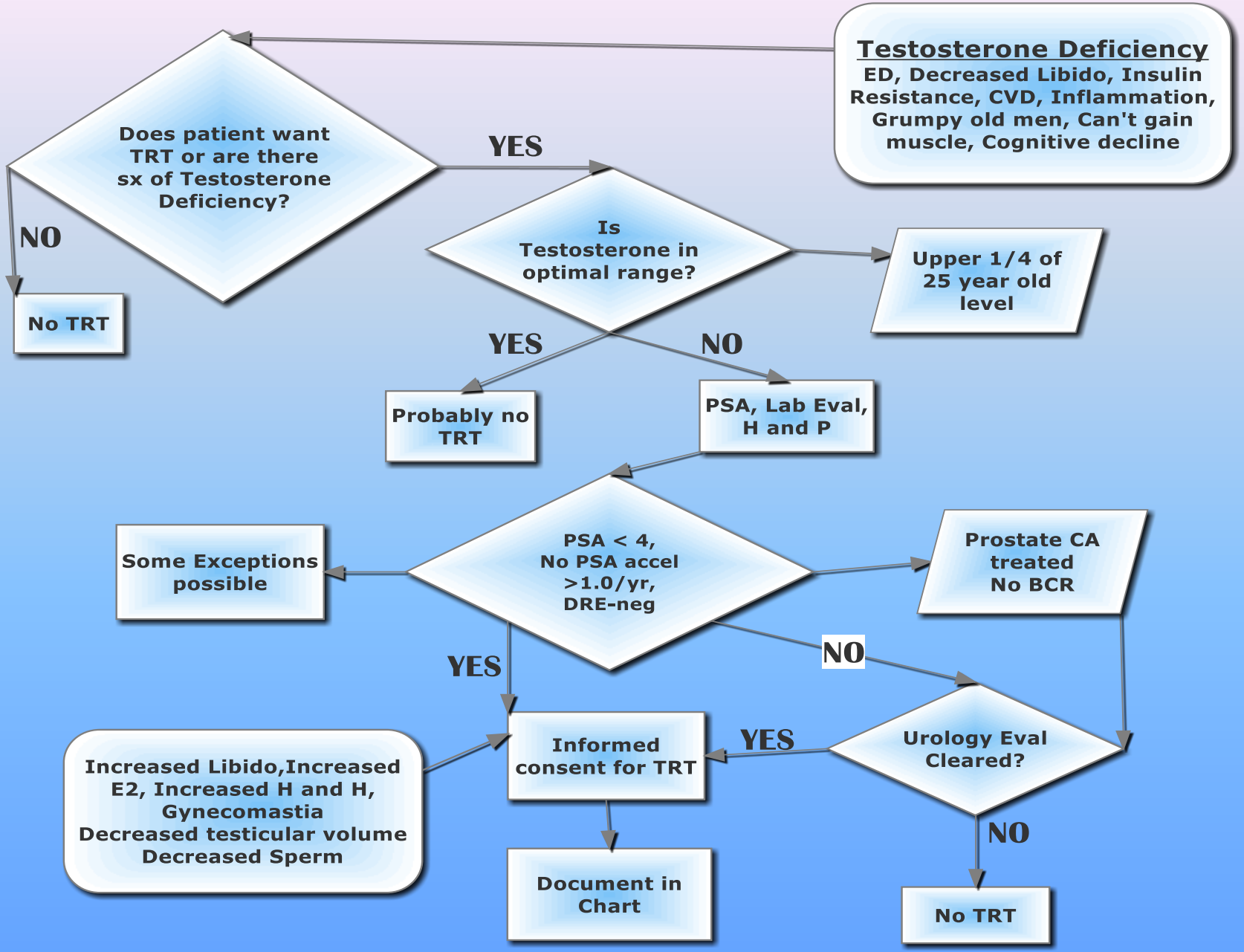


FREE TESTOSTERONE



BIOAVAILABLE TESTOSTERONE




Testosterone Deficiency
ED, Decreased Libido, Insulin Resistance, CVD, Inflammation, Grumpy old men, Can't gain muscle, Cognitive decline
Does patient want TRT or are there sx of Testosterone Deficiency?
YES
NO
No TRT
Is Testosterone in optimal range?
Upper 1/4 of 25 year old level
YES
NO
Probably no TRT
PSA, Lab Eval, H and P
PSA < 4, No PSA accel >1.0/yr, DRE-neg
Some Exceptions possible
Prostate CA treated No BCR
YES
NO
Increased Libido,Increased E2, Increased H and H, Gynecomastia Decreased testicular volume Decreased Sperm
Informed consent for TRT
YES
Urology Eval Cleared?
Document in Chart
NO
No TRT

Its not a numbers game

- 50 yo man with sx of test deficiency
- Testosterone total 300
- Treated with testosterone cypionate 100 mg weekly or
- Testosterone cream 100 mg per day

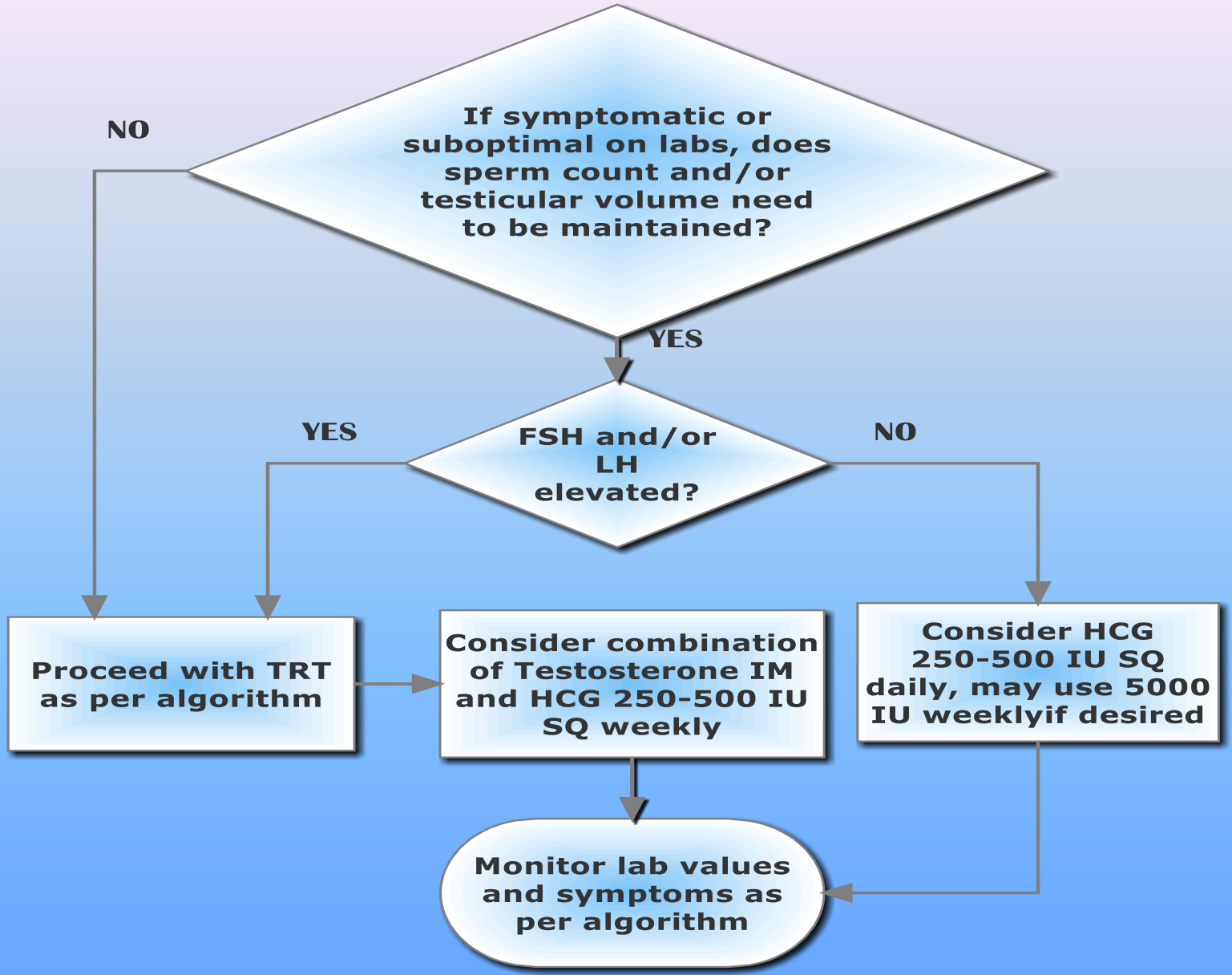
- Follow up labs
  - Testosterone 500 – clinically feels great OK
  - Testosterone 1100 – clinically feels great. OK
  - Testosterone >1500- clinically feels great – explore reasons

Fertility

- Baseline sperm analysis and possible freezing
- If FSH/LH relatively high HCG may not work

Fertility – Management Options

- HCG:
  - Weekly method: 2000-5000 units subq per week. Can divide Into 2 doses per week
  - Daily method: 250 units per day = 1750 units per week
  - Combined method: T SubQ once a week and HCG 250 units on day 5 and 6
- Clomiphene
- May maintain or increase sperm count as above


If symptomatic or suboptimal on labs, does sperm count and/or testicular volume need to be maintained?
NO
YES
FSH and/or LH elevated?
YES
NO
Proceed with TRT as per algorithm
Consider combination of Testosterone IM and HCG 250-500 IU SQ weekly
Consider HCG 250-500 IU SQ daily, may use 5000 IU weeklyif desired
Monitor lab values and symptoms as per algorithm

Hematocrit/Hemoglobin Elevated

- Phlebotomy or Donate a unit of blood every 3-6 months

DHT

- Measure or not
- 5ARI’s
- Zinc, Saw Palmetto, Progesterone?

LUTS treatment options

- Treatment options
- Saw Palmetto + beta sitosterol
- PDE5i’s
- Avoid 5-alpha-reductase inhibitors
- Possibly alpha blockers
- Innovative procedures

- Sudeep et al. A double blind, placebo-controlled randomized comparative study on the efficacy of phytosterol-enriched and conventional saw palmetto oil in mitigatingbenign prostate hyperplasia and androgendeficiency *BMC Urology* (2020) 20:86

5-alpha reductase inhibition

- Neuroactive steroids - 5-allo-pregnenolone needed for neuronal repair and memory
- Inhibition of 5-alpha-reductase by finasteride inhibits hippocampal neurogenesis
- Contributes to the pathophysiology of depression and memory loss
- Neurosteroids are potent endogenous modulators of the GABA receptor

- Traish AM et al. 5- alpha-reductases in human physiology: an unfolding story. *Endocr Pract*. 2012 Nov-Dec;18(6):965-75.

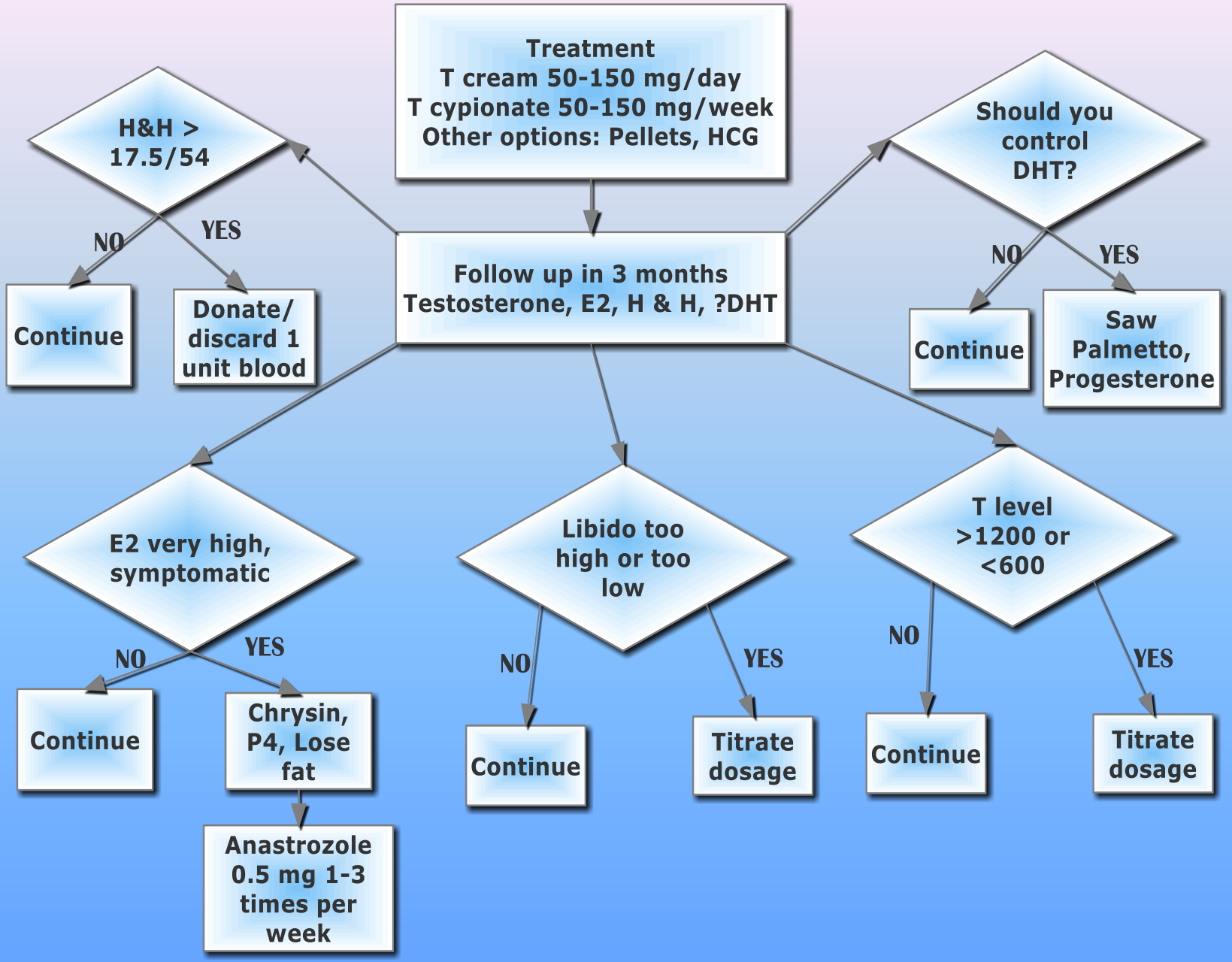
Estradiol - men

- Don’t have to micromanage
- Men need estradiol for libido, erections, fat loss, holding onto bone
- Approaches
  - Don’t measure?
  - Clinically- nipple sensitivity, gynecomastia
  - If very high – 80-100 Consider anastrazole

Guys Need Estrogen Too

- Higher testosterone, greater muscle size and strength
- Higher estrogen, less Fat
- Higher testosterone and higher estrogen, better libido and erection function

- Finkelstein JS et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med*. 2013 Sep 12;369(11):1011-22

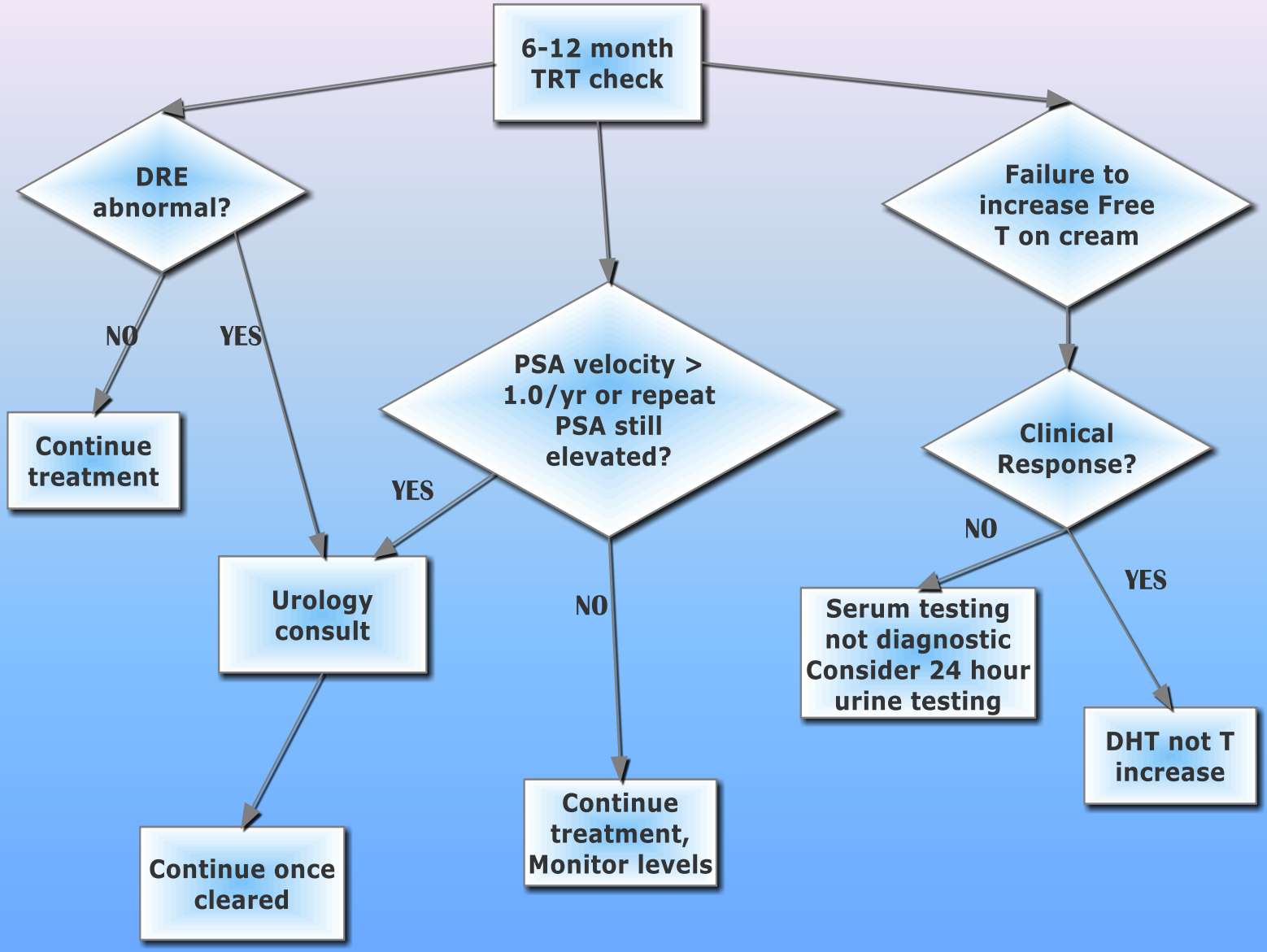

Treatment
T cream 50-150 mg/day
T cypionate 50-150 mg/week
Other options: Pellets, HCG
Follow up in 3 months
Testosterone, E2, H & H, ?DHT
H&H > 17.5/54
NO
YES
Continue
Donate/ discard 1 unit blood
Should you control DHT?
NO
YES
Continue
Saw Palmetto, Progesterone
E2 very high, symptomatic
NO
YES
Continue
Chrysin, P4, Lose fat
Anastrozole 0.5 mg 1-3 times per week
Libido too high or too low
NO
YES
Continue
Titrate dosage
T level >1200 or <600
NO
YES
Continue
Titrate dosage

PSA

- If you get a PSA you don’t like, repeat and avoid the activities that can falsely elevate the PSA, and save unnecessary biopsy

False causes of an elevated serum PSA

- Digital rectal examination (DRE) elevations of 0.26 to 0.4 ng/mL
- Ejaculation - up to 0.8 ng/mL, return to normal within 48 hours
- Bacterial prostatitis – 6-8 weeks after symptoms resolve.
- Asymptomatic prostatic inflammation
- Acute urinary retention -decrease by 50 percent within one to two days following resolution.
- https://www.uptodate.com/contents/screening-for-prostate-cancer


6-12 month TRT check
DRE abnormal?
NO
YES
Continue treatment
Urology consult
Continue once cleared
PSA velocity > 1.0/yr or repeat PSA still elevated?
YES
NO
Continue treatment, Monitor levels
Failure to increase Free T on cream
Clinical Response?
NO
YES
Serum testing not diagnostic Consider 24 hour urine testing
DHT not T increase

Most Reliable PCa Test to Date

"

	Positive	Negative
Cancers	30	3
Controls	3	30
Sensitivity, %	91	
Specificity, %	91	

- Cornu, JN et al. Olfactory detection of prostate cancer by dogs sniffing urine: a step forward in early diagnosis. *Eur Urol.* 2011 Feb;59(2):197-201.

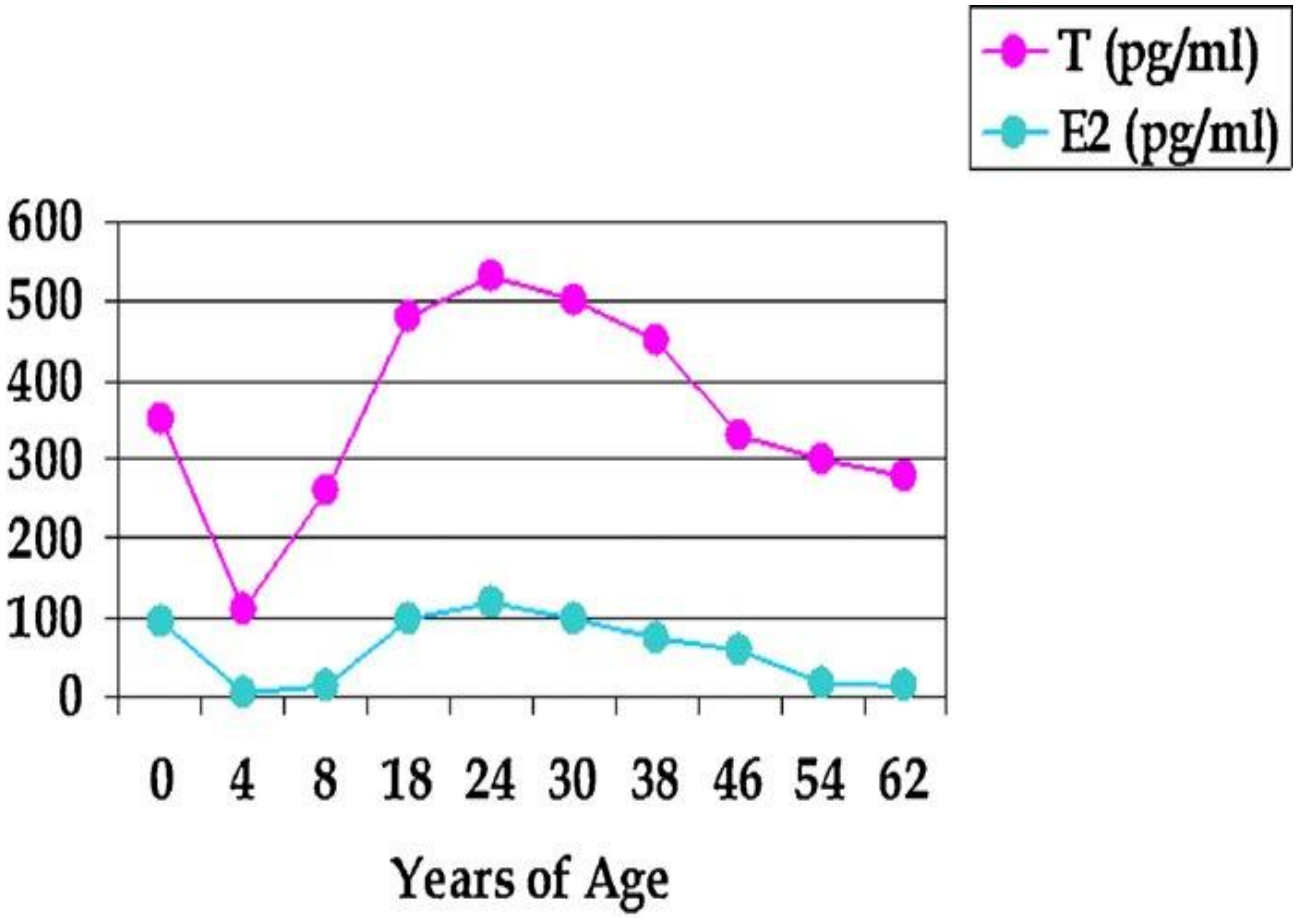
TT - Full Circle

- 1940s - many symptomatic benefits of TT i.e. improved angina pectoris and peripheral vascular disease.
- Huggins and Hodges (Cancer Res 1941;1:293-297) testosterone activated prostate cancer (PCa) - next 70 years.
- Radioimmunoassay in the 1970s shifted the diagnosis of TD from clinical to blood test results.
- The fear of PCa was the primary obstacle to the adoption of TT for decades.
- Testosterone Trials (2016) - high-quality evidence of multiple benefits of testosterone therapy, nearly all of which had been recognized by clinicians by 1940.
- Morgentaler A, Traish A. The History of Testosterone and the Evolution of its Therapeutic Potential. *Sex Med Rev* 2018 Apr 13.

Testosterone is Essential for female physiology

- Functional AR 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

Testosterone is the most abundant biologically active hormone in women

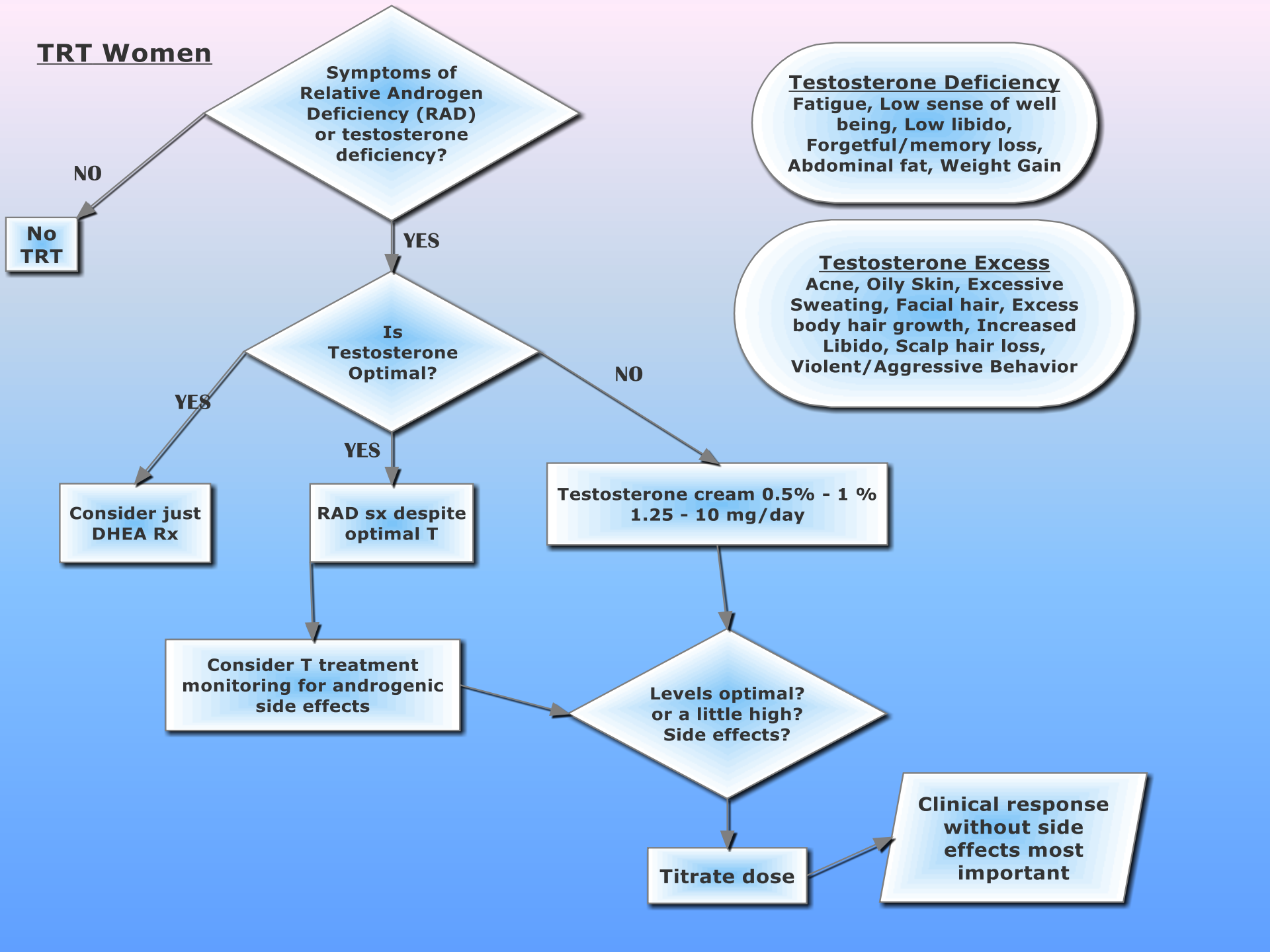


Glaser RL, Dimitrakakis C. Testosterone therapy in women: myths and misconceptions. *Maturitas*. 2013 Mar;74(3):230-4

CHOIICE study: BHRT

- Cardiovascular biomarkers- CRP, Fibrinogen + other clotting factors, fasting glucose, triglycerides, BP and health outcomes were favorably impacted
- Transdermal Biest, Progesterone, Testosterone and DHEA

- Stephensen, K et al. The effects of compounded bioidentical transdermal hormone therapy on hemostatic, inflammatory, immune factors, cardiovascular biomarkers, quality – of-life measures; and health outcomes in postmenopausal women. *Int J Pharm.Compd*. 2013 Jan-Feb 17(1) 74-85.


TRT Women
Symptoms of Relative Androgen Deficiency (RAD) or testosterone deficiency?
NO
No TRT
YES
Is Testosterone Optimal?
YES
Consider just DHEA Rx
YES
RAD sx despite optimal T
NO
Testosterone cream 0.5% - 1 % 1.25 - 10 mg/day
Consider T treatment monitoring for androgenic side effects
Levels optimal? or a little high? Side effects?
Titrate dose
Clinical response without side effects most important
Testosterone Deficiency
Fatigue, Low sense of well being, Low libido, Forgetful/memory loss, Abdominal fat, Weight Gain
Testosterone Excess
Acne, Oily Skin, Excessive Sweating, Facial hair, Excess body hair growth, Increased Libido, Scalp hair loss, Violent/Aggressive Behavior

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
- AA/EPA Ratio <1.5
- 25-OH-D 60 -90
- 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 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

The Various Types of Hypothyroidism: A Review

- ***B.J. Barrett, M.D., M.S., FACEP, FAAAAM***
- ***Clinical Associate Professor***
- ***Department of Emergency Medicine Stanford University***

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Off-Label Usage: None

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- Lena Wapen P.A.
- Desiree Rozzi, B.S.
- Robert Fuller, EMTP

New Thyroid Concepts

- Replacing T3 + T4 = better quality of life than just T4
- Many factors decrease T4 to T3 conversion including
  - Dieting, Stress
  - Zinc, selenium and iodine deficiency
  - Amiodarone, beta blockers, phenytoin and other drugs
- T3 and T 4 doses should be every 12 hours

New Thyroid concepts

Fix the gut first

T3 is needed for fat loss

T3 protects against arrhythmias

T3 decreases with stress or dieting

T3 is active hormone and T4 is pro-hormone

T4 does not necessarily convert to adequate T3

Reverse T3 reverses T3

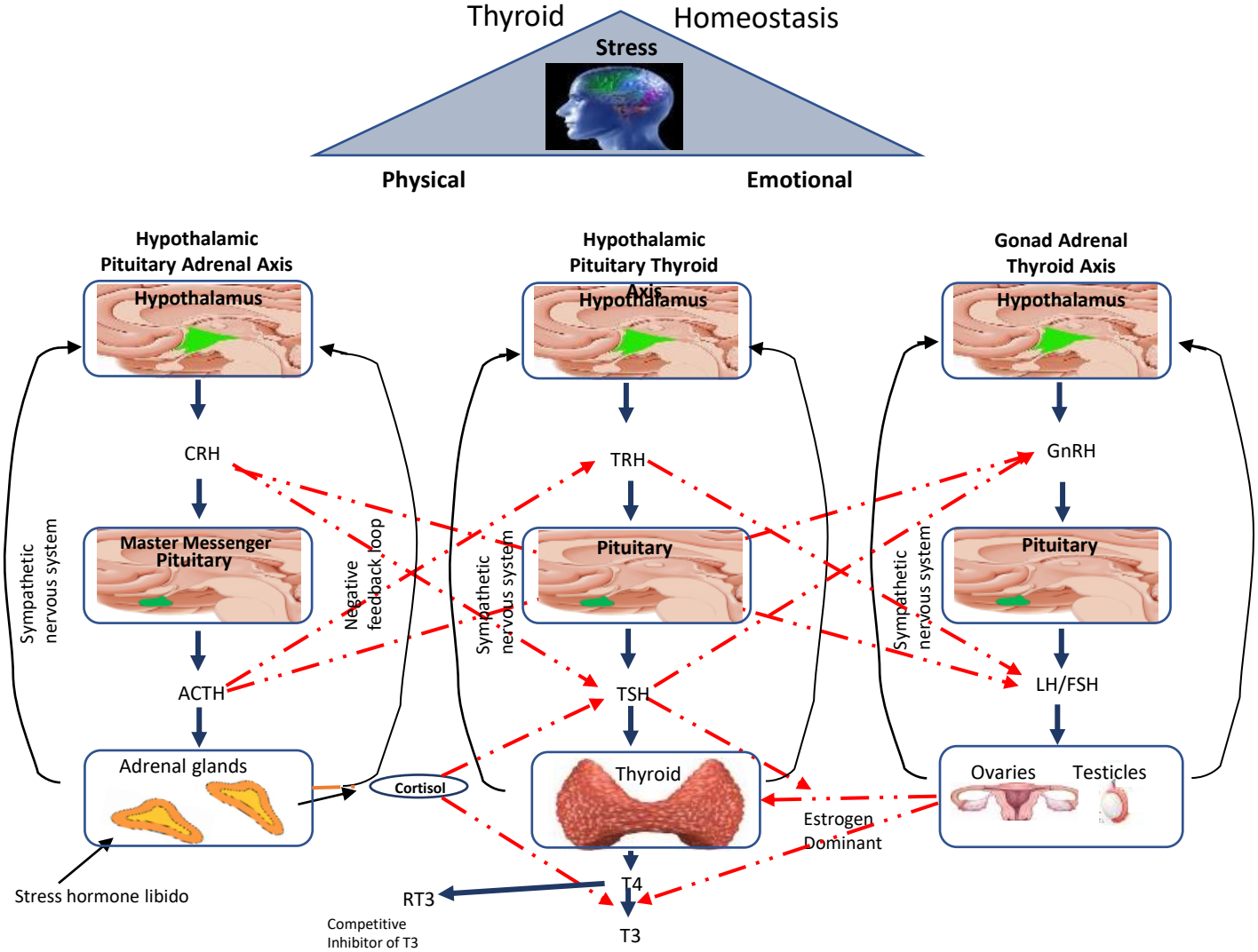
Hashimoto's without hypothyroidism?

New Thyroid Concepts

- Lab tests lack sensitivity
- TSH not most sensitive test
- “Normal” TSH getting lower all the time
- Free T3 to reverse T3 ratio is the best indicator
- When all else fails, look at the patient.
- The wide range of “euthyroid” is not “optimal thyroid”
- Naltrexone ⬇ thyroid inflammation and autoimmune response
- Covid 19 and Thyroid

What do you want to order?

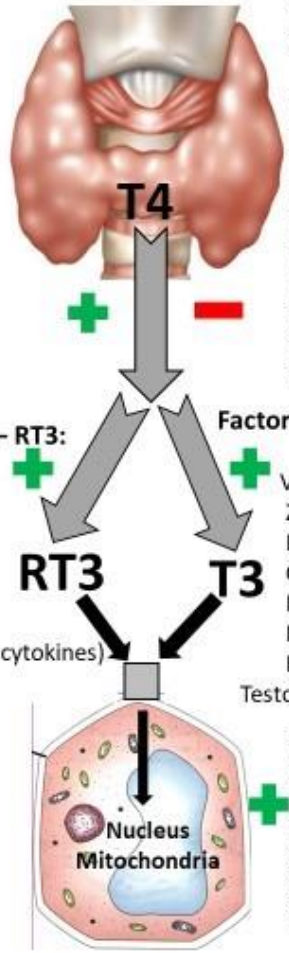
- CBC, CMP, Vit D, Ferritin
- TSH = 0.4-4.5 milliunits/L
  Not the most sensitive test
- Total T_4, Free T_4
- Free T_3, *T3/RT3 ratio*
- Total T_3, 80-230
- Reverse T_3
- Thyroid antibodies
  - Antithyroglobulin antibody
  - Antimicrosomal antibody
  - Antithyroperoxidase (anti-TPO) antibody
- GI effects study/intestinal biome
- Iodine
- Cortisol


Thyroid
Homeostasis
Stress
Physical
Emotional
Hypothalamic Pituitary Adrenal Axis
Hypothalamic Pituitary Thyroid Axis
Gonad Adrenal Thyroid Axis
Hypothalamus
Hypothalamus
Hypothalamus
CRH
TRH
GnRH
Master Messenger Pituitary
Pituitary
Pituitary
ACTH
TSH
LH/FSH
Adrenal glands
Thyroid
Ovaries
Testicles
Cortisol
Estrogen Dominant
Stress hormone libido
RT3
Competitive Inhibitor of T3
T4
T3
Sympathetic nervous system
Negative feedback loop
Sympathetic nervous system
Sympathetic nervous system

Factors That Affect Thyroid Function

Factors that contribute to thyroid hormone production:

Iron
Tyosine
Vitamin D
Vitamin B3
Vitamin C
Iodine
Zinc Selenium
Vitamin B2
Vitamin B6



Factors that inhibit thyroid hormone production:

Hypothalamus dysfunction
Poor T4-T3 conversion
Increased formation of reverse T3
Thyroid receptor block
Inhibition of thyroid stimulating hormone inactivation
Fluorides and other halogens that act as antagonists to iodine
Stress, infection, trauma, radiation, advanced age, medications, toxins

Factors that increase conversion of T4 – RT3:

Stress (increased nuclear factor B)
Sleep deficit
Trauma
Gluten
Dairy bad fats
Inflammation (oxidation, elevated cortisol & cytokines)
Leptin resistance
Obesity
Fibromyalgia
Toxins (pesticides alcohol)
Infections
Night shift workers
Liver and Kidney malfunction
Diabetes
Medications

Factors that increase conversion of T4 to T3:

Vitamins A, B and E
Zinc
Rehmannia
Coleus
Insulin
Melatonin
Estrogen domianance
Selenium
Potassium
Ashwaganda
Growth hormones
Glucagon
Tyrosine
Testosterone (decrease the concentration of TGB)

Factors that improve cellular sensitivity thyroid hormones:

Vitiamin A
Optimum diet
Outdoor activity
Zinc
Healthy lifestyle
Insulin sensitivity
Exercise
Younger age
Disease-free state

Differences between T_4 and T_3

- The thyroid secretes about 80 mcg of T_4, but only 5 mcg of T_3 per day.
- T_3 has a much greater biological activity (about 10x) than T_4
- An additional 25 microg/day of T_3 is produced by peripheral monodeiodination of T_4

Diagnosis of Hypothyroidism

Elevated TSH, or...

- Clinical symptoms
- Free T3 below optimal range
- Free T4, TSH often normal

Basal Body Temperature

97.8 – 98.2 Degrees = Normal

Less than 97.8 indicates sub optimal metabolism

A = Adjunct contribution only

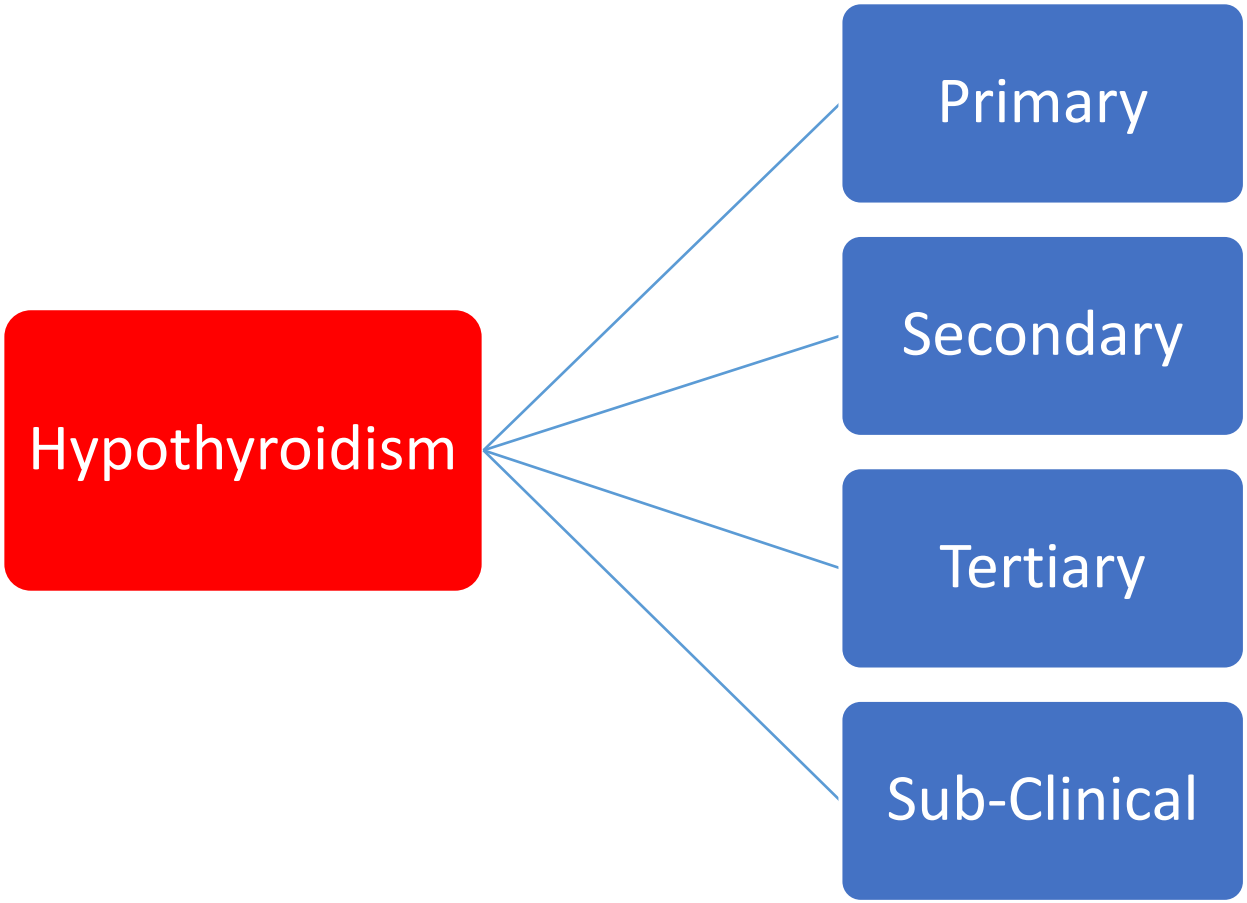
A = Awakening

A = Axillary

A = Alarm

A = Average of 3 days

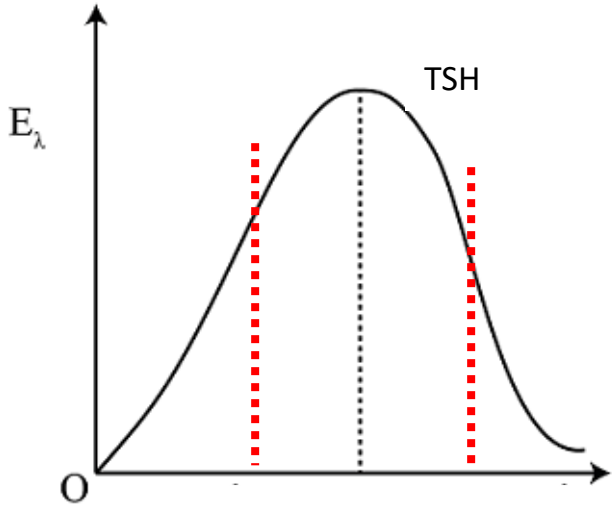
Classification



Causes of Hypothyroidism

- Failure of Pituitary control – low TSH
  - Secondary (central) hypothyroidism
- Failure of Hypothalamic control – low TRH
  - Tertiary hypothyroidism
- Thyroid failure – Primary hypothyroidism
  - Most common
- Conversion failure of T4 to T3
- Receptor uptake failure – thyroid resistance
  - “Type 2” hypothyroidism like ‘Type 2” diabetes
- Adrenal Insufficiency
  - Lowered cortisol affects thyroid production, conversion and receptor uptake

- Continuum between euthyroid and hypothyroid
- Continuum between normal and elevated TSH
- Distinction between normal and elevated TSH is arbitrary



Hyperthyroidism

Nonintentional weight loss

Palpitations, tachycardia,

Thyroid stare/gaze

Anxiety, nervousness

Tremor or restlessness

Insomnia fatigue weakness

Increased appetite

Goiter/ enlarged thyroid

Hair loss

Skin flushing

Tongue wasting

Hypothyroidism

Family history of hypothyroidism
Nonintentional weight gain

Bradycardia

Body temperature greater than 98.2 Fahrenheit

Brain fog, poor memory

Cold intolerance

Slow movements, exercise intolerance

Facial edema periorbital edema

Thick tongue

Fatigue and weakness

Constipation

Dry or coarse skin decreased skin turgor

In females increase infertility or miscarriage, menstrual irregularities
Hair loss, fine brittle hair and nails

Follicular hyperkeratosis of extremities

Carotenodermia (not diet associated) palms and soles

Bilateral delayed at Achilles tendon return

Dyslipidemia

Loss of lateral aspect of eyebrows

More Hypothyroidism

- Hypothyroid children now survive and pass on genes (better sanitation, antibiotics)
- Attracted to hypothyroid mate (same low activity lifestyle) and reproduce….
- Environmental toxicity with heavy metals and other toxins.
- More autoimmune thyroiditis
- Under diagnosed

Thyroid - Adrenal

- Treat adrenal fatigue nutritionally or with bio-identical physiological hydrocortisone replacement
- Low thyroid output is a stress situation and increased cortisol is the response
- When treated with only T4 and lack of T3 conversion – stress situation can get worse
- This “works for a while” and eventually leads to adrenal fatigue

Adrenals and Stress Response

- Acute stress-
  - Increased norepinephrine
  - Increased epinephrine
  - Increased cortisol
  - Disruption of circadian release of cortisol

- Chronic Stress – Decreased cortisol
  - Increased CVD
  - Elevated Blood Pressure and Heart rate
  - Elevated Glucose

Thyroid tests

- Free T3 –Normal 2.3-4.3 pg/mL
  - Optimal Upper quartile
  - 3.5-4.3 pg/mL
- Reverse T3 –Normal 90-350 pg/mL
  - Optimal Lower quartile
  - < 200 pg/mL
- Conversion factor
  - T3 pg/ml x 1.54 = T3 pmol/L

What TSH is normal?

- In Americans
  - Mean TSH
    - 1.5 without known thyroid disease
    - 1.4 whole population
  - TPO positive
    - 13% whole population
    - 11% without known thyroid disease

Hollowell JG et al. Serum TSH, T(4), and thyroid antibodies in the United States population (NHANES III). *J Clin Endocrinl Metab* 2002 87(2)489-499.
Biondi B. The normal TSH reference range: what has changed in the last decade?. *J Clin Endocrinol Metab*. 2013;98(9):3584-3587. doi:10.1210/jc.2013-2760

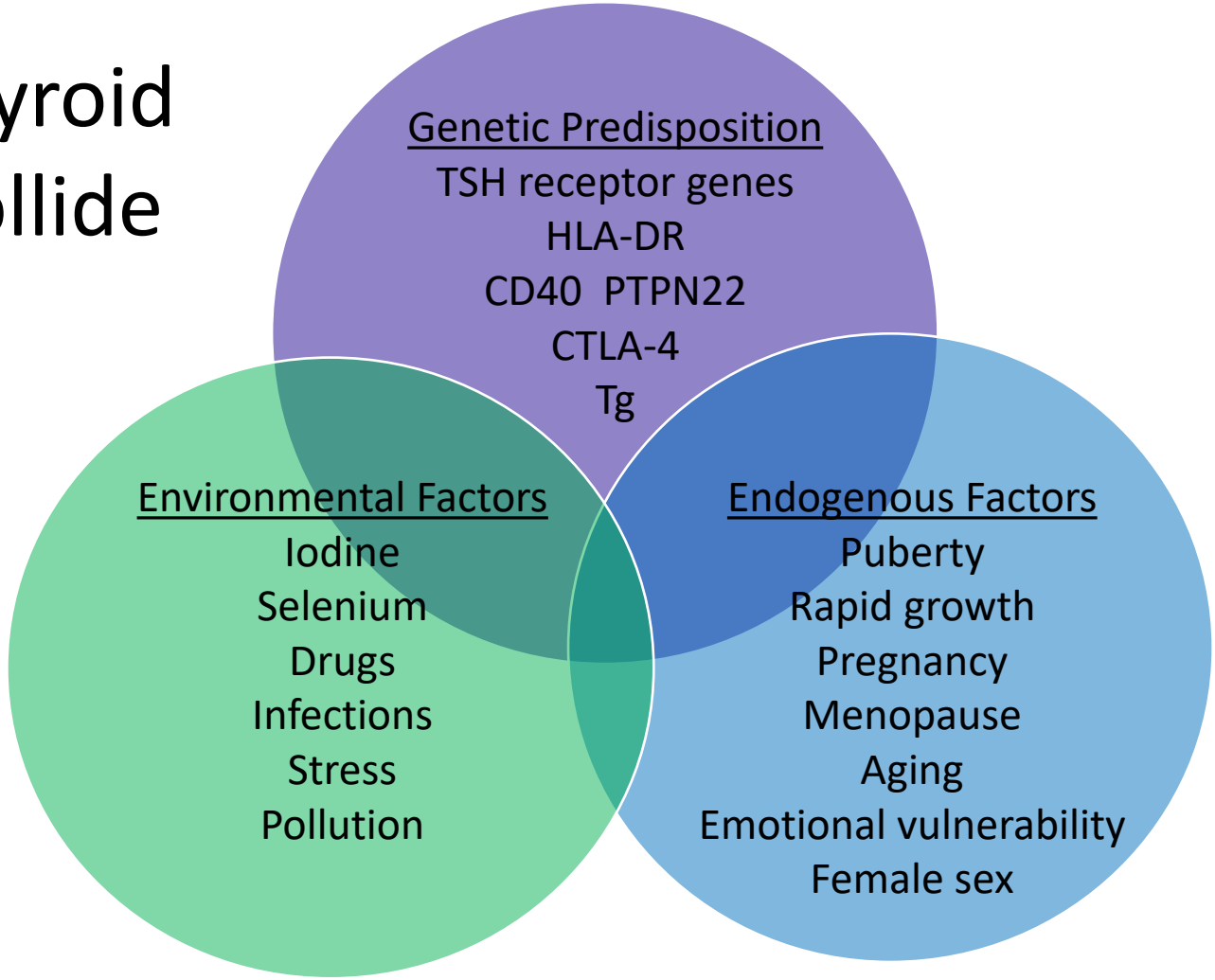
What TSH is optimal?

- .1 - 1.0
- Happiest, best cognitive function, best lipids, least adipose
- No adverse effects, no atrial fib, no bone loss
- Increased longevity with low normal thyroid function tests

Anti-thyroid Antibodies

- Anti thyroid peroxidase (TPO)
  - Positive in 90% HT and 70% GD
  - Incidence of positive TPO in“Subclinical” autoimmune disease incidence much higher
- Thyrotropin Receptor Antibody (TRAbs)
  - Positive in 70-100% GD
- Thyroglobulin antibodies (Tg Abs)
  - Positive in 70% HT and 30% GD
- These antibodies can be present in non-thyroid autoimmune disease
- Sensitivity and Specificity is low

Thyroid Collide



Modulation of TPO levels

- Treat hypothyroidism with T3, T4
- Selenium 200 mcg/day - 2 brazil nuts daily
- Optimize Iodine and Vitamin D
- Reduce inflammation/gut mediated response
  - Gluten free diet
  - Omega 3
  - Probiotics
  - Control Homocysteine
  - Treat Mercury toxicity

Reverse T3

- Fatigue
- Difficulty losing fat
- Brain Fog
- Muscle aches
- Increased with chronic illness CF/FM
- Increased with yo-yo dieting
- Increased with heavy metals, infections, mental and physical stress

How do you get less reverse T3?

- Increase activity of D2 and D1 or decrease D3
  - Eliminate physical and mental stress
  - Treat with thyroid
  - GH increases D2 and D1 activity
  - Treat Selenium deficiency
  - Treat Iodine deficiency

T3 vs T4

- Arguments against T3
- Short half life, high then low levels
- "desiccated porcine thyroid" has 20% T3, humans produce 10% T3
- Lab tests not better on combo T3, T4

Other T3 options

- Liothyronine
  - 5, 25, 50 mcg
  - “Playing with T3 option”
- Compounded extended release T3
  - 7.5mcg, 10mcg, 12.5mcg, 22.5mcg, 37.5mcg
- T3
  - Short half life - 18 hours
  - Give BID or extended release
- T4 half life – 6.7 days

Williams Textbook of Endocrinology, 2003

Conversion Guide

(Immediate Release Capsules, Sustained Release Capsules, +/- Conversion Co-Factors)*		(Thyroid Tablets)	(Levothyroxine Tablets)	(Thyroid Tablets)	(Liothyronine Tablets)	(Liotrix Tablets)
Compounded		Desiccated, Porcine	Synthetic	Desiccated, Porcine	Synthetic	Synthetic
T4 (4.2)	T3 (1)	T4/T3	T4	T4/T3	T3	T4/T3
7.6 mcg	1.8 mcg				5 mcg	
9.5 mcg	2.25 mcg	¼ grain (15 mg)	25 mcg (0.025mg)	¼ grain (16.25 mg)		¼ grain (12.5/3.1 mcg)
19 mcg	4.5 mcg	½ grain (30 mg)	50 mcg (0.05mg)	½ grain (32.5 mg)		½ grain (25/6.25 mcg)
28.5 mcg	6.75 mcg		75 mcg (0.075mg)	¾ grain (48.75 mg)		
33.44 mcg	7.92 mcg		88 mcg (0.088mg)			
38 mcg	9 mcg	1 grain (60 mg)	100 mcg (0.1mg)	1 grain (65 mg)	25 mcg	1 grain (50/12.5 mcg)
42.56 mcg	10.08 mcg		112 mcg (0.112mg)			
47.5 mcg	11.25 mcg		125 mcg (0.125mg)	1 ¼ grain (81.25 mg)		
52.06 mcg	12.33 mcg		137 mcg (0.137mg)			
57 mcg	13.5 mcg	1 ½ grain (90 mg)	150 mcg (0.15mg)	1 ½ grain (97.5 mg)		
66.5 mcg	15.75 mcg		175 mcg (0.175mg)	1 ¾ grain (113.75 mg)		
76 mcg	18 mcg	2 grain (120 mg)	200 mcg (0.2mg)	2 grain (130 mg)	50 mcg	2 grain (100/25 mcg)
85.5 mcg	20.25 mcg			2¼ grain (146.25 mg)		
95 mcg	22.5 mcg			2 ½ grain (162.5 mg)		
114 mcg	27 mcg	3 grain (180 mg)	300 mcg (0.3mg)	3 grain (195 mg)		3 grain (150/37.5 mcg)
152 mcg	36 mcg	4 grain (240 mg)		4 grain (260 mg)		
190 mcg	45 mcg	5 grain (300 mg)		5 grain (325 mg)		

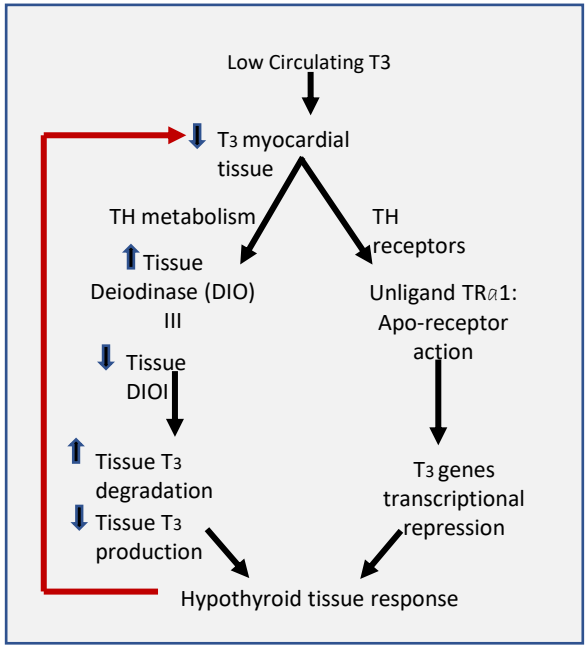
http://thecompounder.com/wp-content/uploads/2015/07/thyroid.png

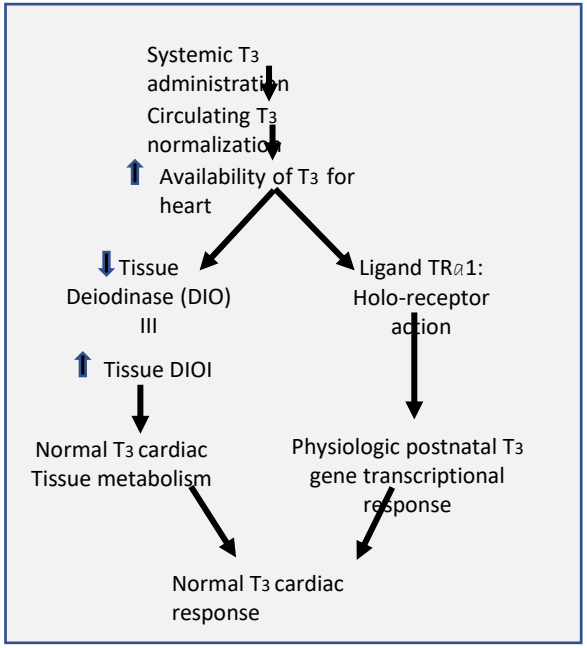
Low Dose Naltrexone

- Immune system modulator
- Low doses of this opioid antagonist (1-5 mg QD) decrease glial inflammatory response
- Increase endorphin function
- Improves T 4 conversion to active T 3
- Lowers thyroid antibodies
- Increases T regulatory cytokines and modulates TGF=b thus reducing Th-17
- Prescribe with Vitamin D and probiotics

Toljan K. 2018https://www.ncbi.nom.nih.gov>pmc
Hortoff, Kent MD. 2019
https://Indresearchtrust.org

T3 and Cardiac Health



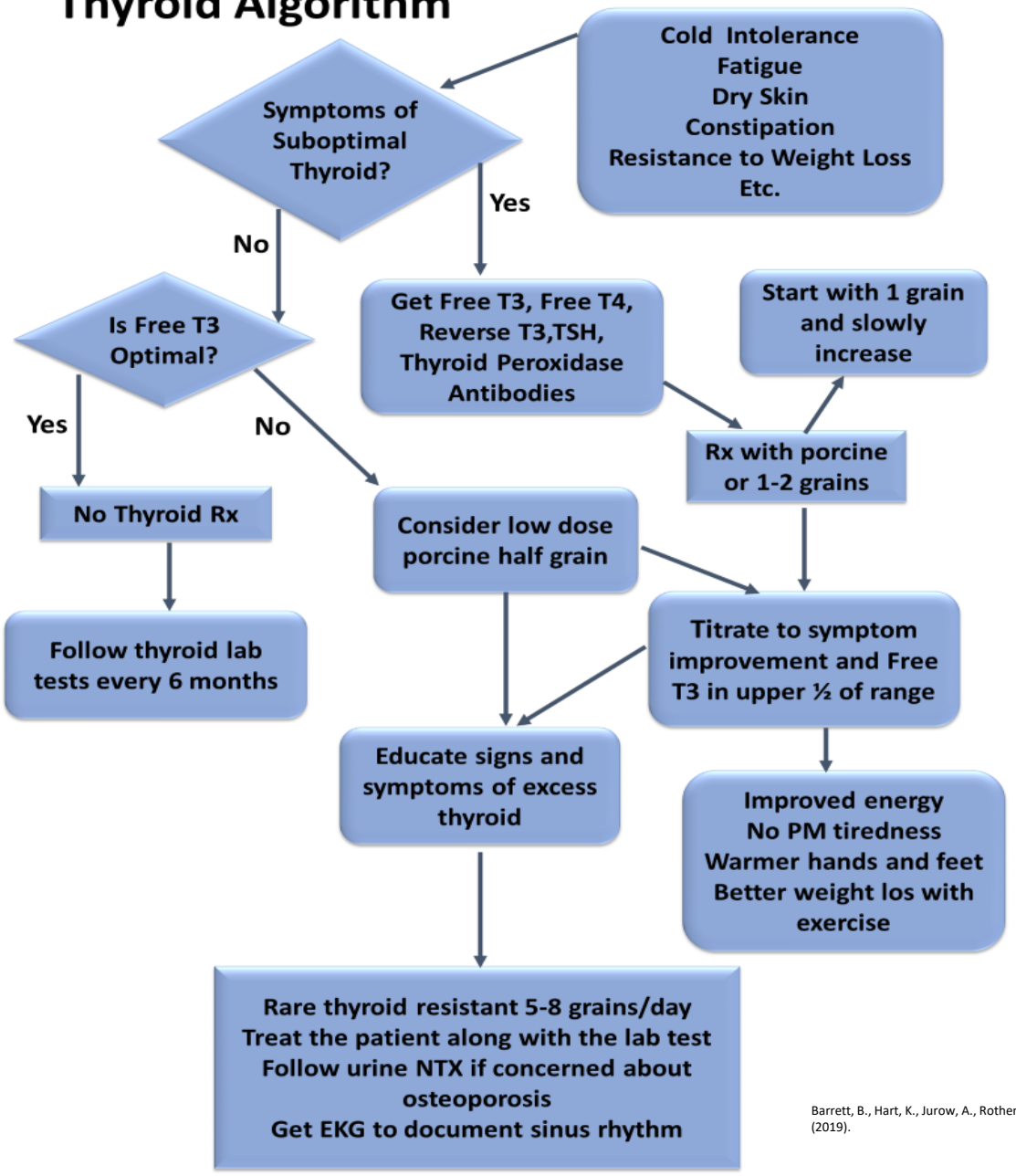


Does thyroid replacement cause osteoporosis?

- Most studies – No
- Premenopausal – No
- Postmenopausal – Probably not
- Prove it for yourself – follow urine NTx
- Suppressive therapy
- No decrease in BMD in pre or post menopausal women or men

Gorres G et al. Bone mineral density in patients receiving suppressive doses of thyroxine for differentiated thyroid carcinoma *Eur J Nucl Med* 1996 Jun;23(6):690-2

Thyroid Algorithm

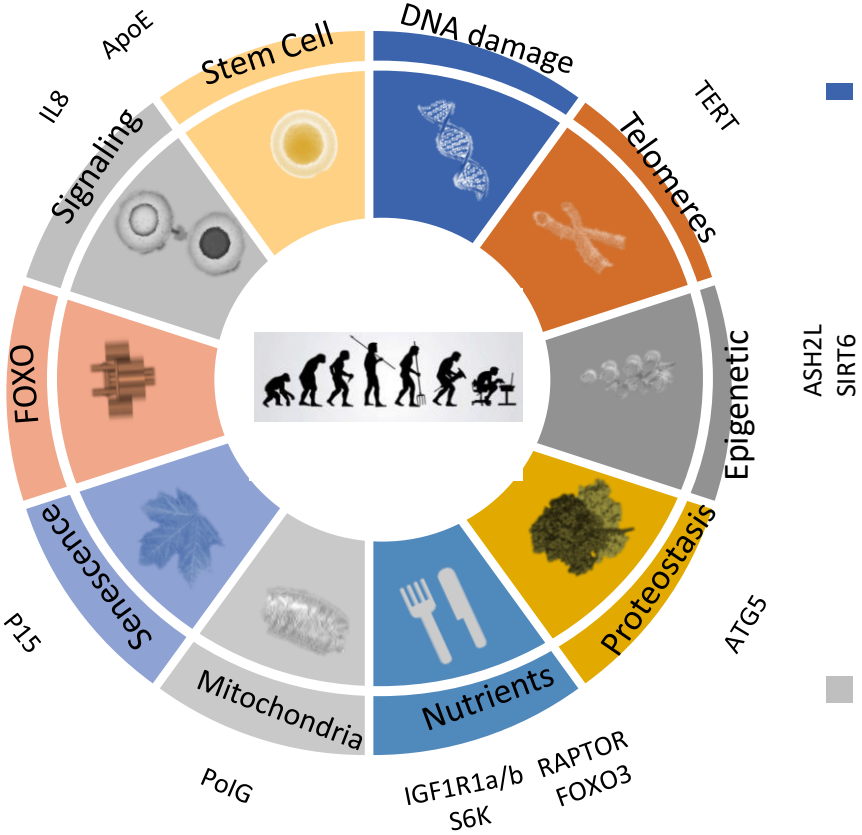


Barrett, B., Hart, K., Jurow, A., Rothenberg, R,; Hormonal BioIdentity (2019).

A platform to study aging and age-related disease genes in vertebrates

CRISPR/Cas9

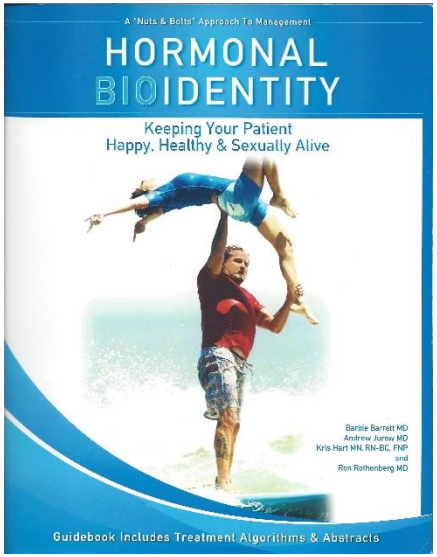
Stable line
F0 chimeras
In eggs



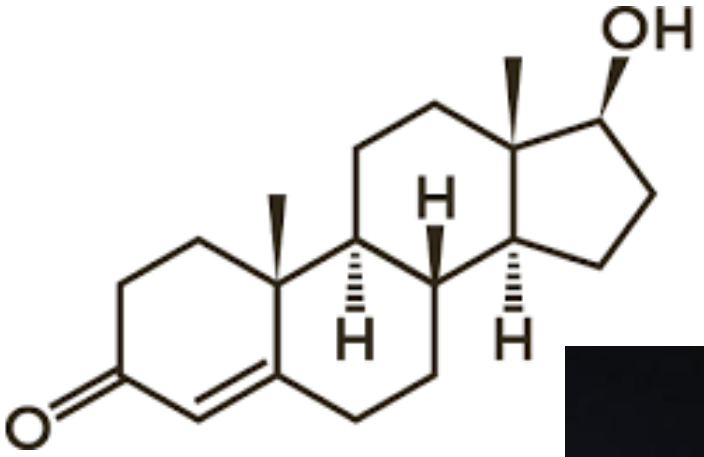
Modified from Lopez-Otin C. el at Cell (2013)

Gene Editing

Female Hormones



- ***B.J. Barrett, M.D., M.S., FACEP, FAAAAM***
- ***Clinical Associate Professor***
- ***Department of Emergency Medicine Stanford University***

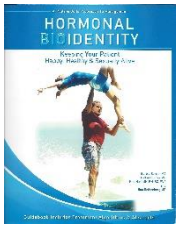


Not Just For Men!

Female Hormones

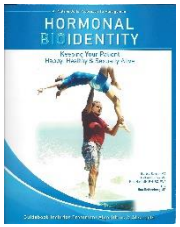
- **Estrogens**
- **Progesterone**
- **Testosterone**

- **Delicate harmony between E and P both antagonistic and complimentary**



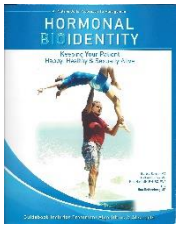
Female hormones

- Deficiencies can start years before menopause in Peri-menopause
  - Low libido due to low testosterone
  - Poor sleep, anxiety, PMS symptoms due to low progesterone
- At menopause ovaries no longer produce estrogen and progesterone

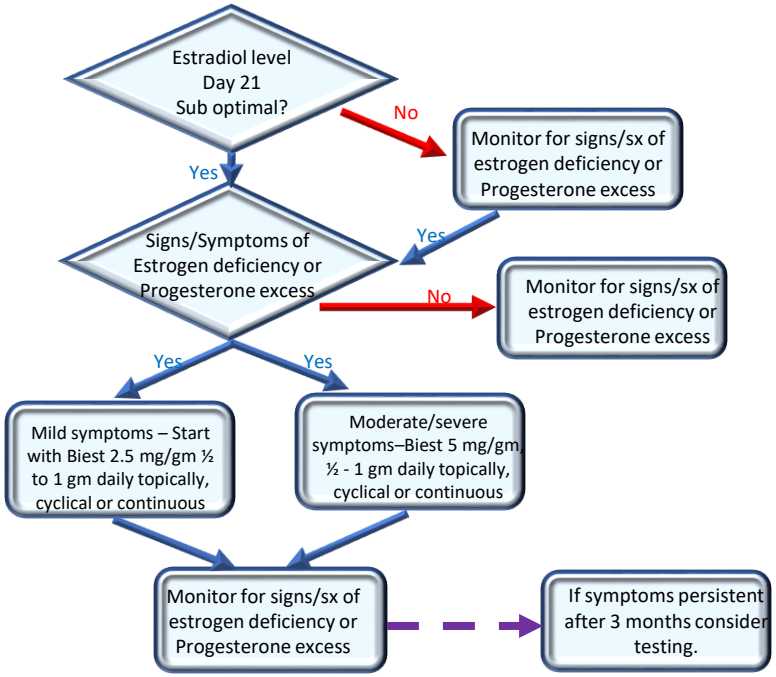


Estrogen deficiency

- **Depressed mood**
- **Decreased concentration**
- **Decreased sexual desire or libido**
- **Vaginal dryness**
- **Excessive daytime sleepiness**
- **Stress incontinence and UTI's**
- **Osteoporosis, Cardiovascular disease, Dementia**
- **Vasomotor symptoms: hot flashes, night sweats**

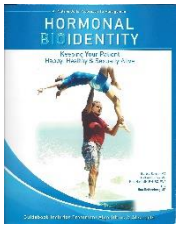


Estrogen Replacement



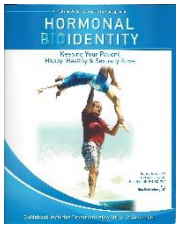
Estrogen Deficiency / Progesterone Excess

Hot Flashes
Night Sweats
Foggy Thinking
Forgetfulness
Fatigue
Palpitations
Depression
Decreased Libido
Vaginal Dryness
Decreased Energy
Excessive Daytime Sleepiness
Etc..



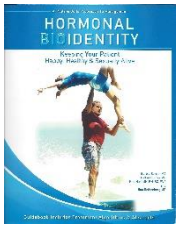
Progesterone deficiency

- **Insomnia**
- **Agitation**
- **Irritability, aggressiveness**
- **Anxiety, anger**
- **Weight gain**
- **Water retention**
- **Headaches**
- **Swollen or tender breasts**

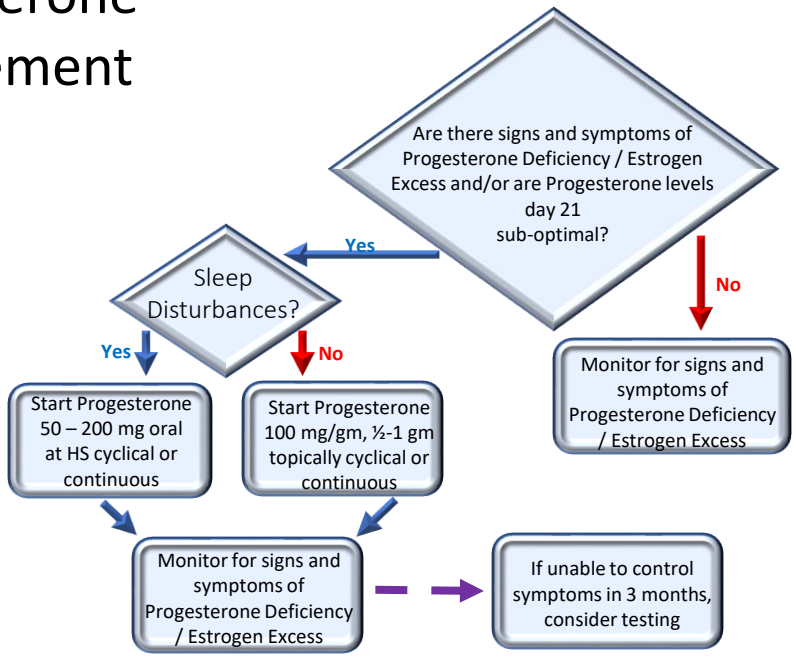


Progesterone deficiency

- **Bloating**
- **Spotting or breakthrough bleeding**
- **Mood swings**
- **Joint pain**
- **Menorrhagia**
- **Endometriosis**
- **Fibrocystic breasts**
- **Insomnia**



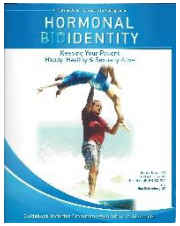
Progesterone Replacement



Progesterone Deficiency / Estrogen Excess

Agitation	Water Retention
Anxiety	Sleep Disturbances
Bloating	Breakthrough Bleeding
Mood	Heavy Menstrual Bleeding
Swings	Swollen, Tender Breast
Joint Aches	

Etc



WHI

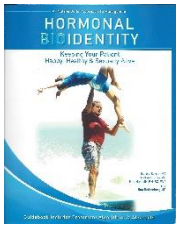
- THE WRONG GROUP OF PEOPLE

  (TOO LONG AFTER MENOPAUSE)

- THE WRONG HORMONE

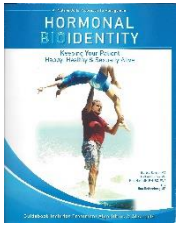
  (SYNTHETIC)

- THE WRONG ROUTE OF ADMINISTRATION (ENTEROHEPATIC METABOLISM)



WHI

- THE PROBLEMS ASSOCIATED WITH THE WHI ARE INCREASINGLY BEING RECOGNIZED. THESE INCLUDE: THE POPULATION STUDIED … THE EFFECT OF DURATION OF EXPOSURE, AND THE INTERPRETATIONS PROVIDED BY VARIOUS EXPERTS. MANY WOMEN NEED AND WANT HORMONE THERAPY.



12TH WORLD CONGRESS OF GYN ENDOCRINOLOGY. LEON SPEROFF MD. 2006
Langer RD, Hodis HN, Lobo RA, Allison MA. Hormone replacement therapy - where are we now? Climacteric. 2021 Feb;24(1):3-10. doi: 10.1080/13697137.2020.1851183. Epub 2021 Jan 6. PMID: 33403881.

GAUGING PREGNANCY RISK WITH NO HUMAN DATA, PAGE 12

ELSEVIER

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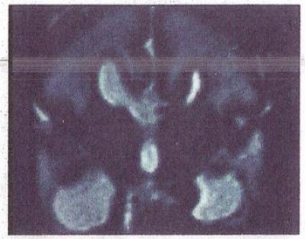
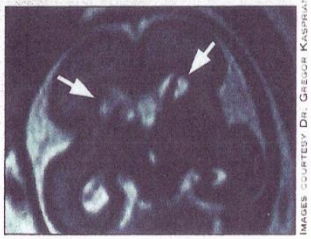




IMAGES COURTESY DR. GREGOR KASPRIAN

This coronal T2 image (top) of a fetus diagnosed with an aberrant pulmonary vein shows agenesis of the corpus callosum, abnormal and retarded gyration, malrotation of both hippocampi, and associated signal abnormalities of the developing white matter at 28 weeks. The brain of a fetus (bottom) with Fallot's tetralogy shows bilateral germinolytic cysts in the caudothalamic groove at 25 weeks.

Fetal Cardiac, Brain Defects Are Linked

BY AMY ROTHMAN SCHONFELD
Contributing Writer

NEW ORLEANS — Fetal MRI echo-planar sequences in three orthogonal section planes), brain pathology was found in 33 cases (59%), said Dr. Kasprian, a radiologist at the Medical University of

INSIDE

Induction Effect
Declines in mean birth weight and gestational age are linked to an increase in labor induction.
PAGE 6

Preterm Triggers
Low HDL cholesterol and high homocysteine levels may be keys to preterm delivery.
PAGE 10

Trump the Triad
Education and professional teamwork can prevent the female athlete triad.
PAGE 16

HT May Benefit Postmenopausal Cognition, Memory

Three new studies contradict past results.

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

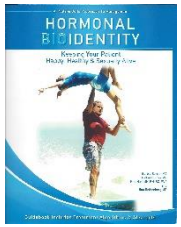
CHICAGO — Hormone therapy might preserve cognition and memory in postmenopausal women, and even attenuate some of the cognitive deficits that occur in Alzheimer's disease, new research suggests.

Controversy exists over the possible cognitive benefits of hormone therapy in older women, Dr. Mary Tierney said at the International Conference on Alzheimer's Disease. "While preclinical and observational studies have shown a positive effect of estradiol on the brain and cognitive function, randomized controlled trials using conjugated equine estrogens have shown no treatment effects in women at risk for Alzheimer's disease, or in women who have the illness."

These concerns, plus her own hypothesis that the "minidoses" of hormones used in many randomized trials might be too low to offer protection benefit, prompted Dr. Tierney of the Sunnybrook Health Sciences Centre, Toronto, and her colleagues to undertake a new study. The 2-year trial randomized 142 women aged 61-87 years to either placebo or to 1 mg estradiol daily plus 0.35 mg progestin 3 days per week.

The primary outcome was the

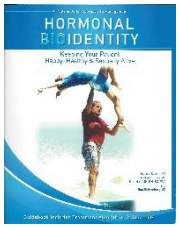
See **Cognition** *page 6*



Results from the E3N cohort study- Fournier 2007.

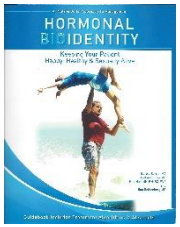
- **80,377 postmenopausal women**
- **No increase or decrease in breast cancer in women on E2 and Progesterone. RR 1.0**
- **E2 plus MPA (Provera) had RR of 1.69 or 69% increase in risk of breast cancer.**
- **This proves that "bio-identical" hormones are safer**

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 (P4) 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

Campagnoli C, Pasanisi P, Castellano I, Abbà C, Brucato T, Berrino F. Postmenopausal breast cancer, androgens, and aromatase inhibitors. Breast Cancer Res Treat. 2013 May;139(1):1-11. doi: 10.1007/s10549-013-2505-2. Epub 2013 Apr 10. PMID: 23572296.

"**Such an important book.** Groundbreaking and carefully researched, it will help women feel more comfortable taking estrogen, leading to healthier, longer lives for many."
—Patricia T. Kelly, PhD, author of *Assess Your True Risk of Breast Cancer*

Estrogen Matters

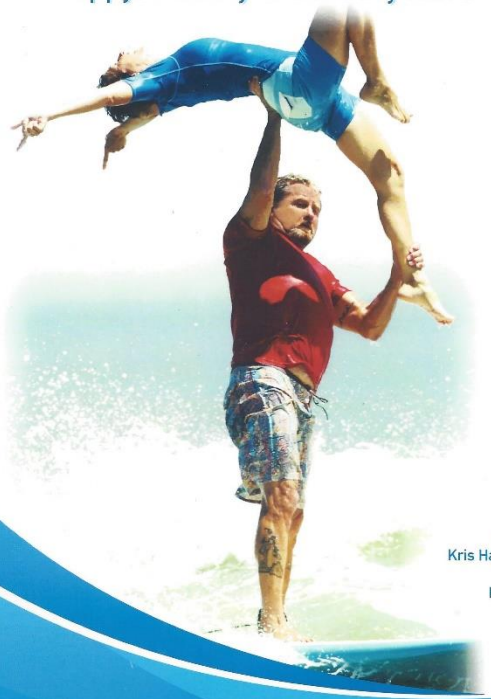
Why Taking Hormones in Menopause Can Improve Women's Well-Being and Lengthen Their Lives—Without Raising the Risk of Breast Cancer

Avrum Bluming, MD, and Carol Tavris, PhD

A "Nuts & Bolts" Approach To Management

HORMONAL BIOIDENTITY

Keeping Your Patient Happy, Healthy & Sexually Alive



Barbie Barrett MD
Andrew Jurow MD
Kris Hart MN, RN-BC, FNP
and
Ron Rothenberg MD

Guidebook Includes Treatment Algorithms & Abstracts

Contact Information:

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Associate Professor, Department of Emergency Medicine
Stanford University & Medical Center

Barretter@aol.com

Diagnosis & Prescribing Growth Hormone for Adult Growth Hormone Deficiency Syndrome

Andrew H. Jurow, M.D.,M.S.
Palo Alto Medical Foundation

Growth Hormone Synthesis

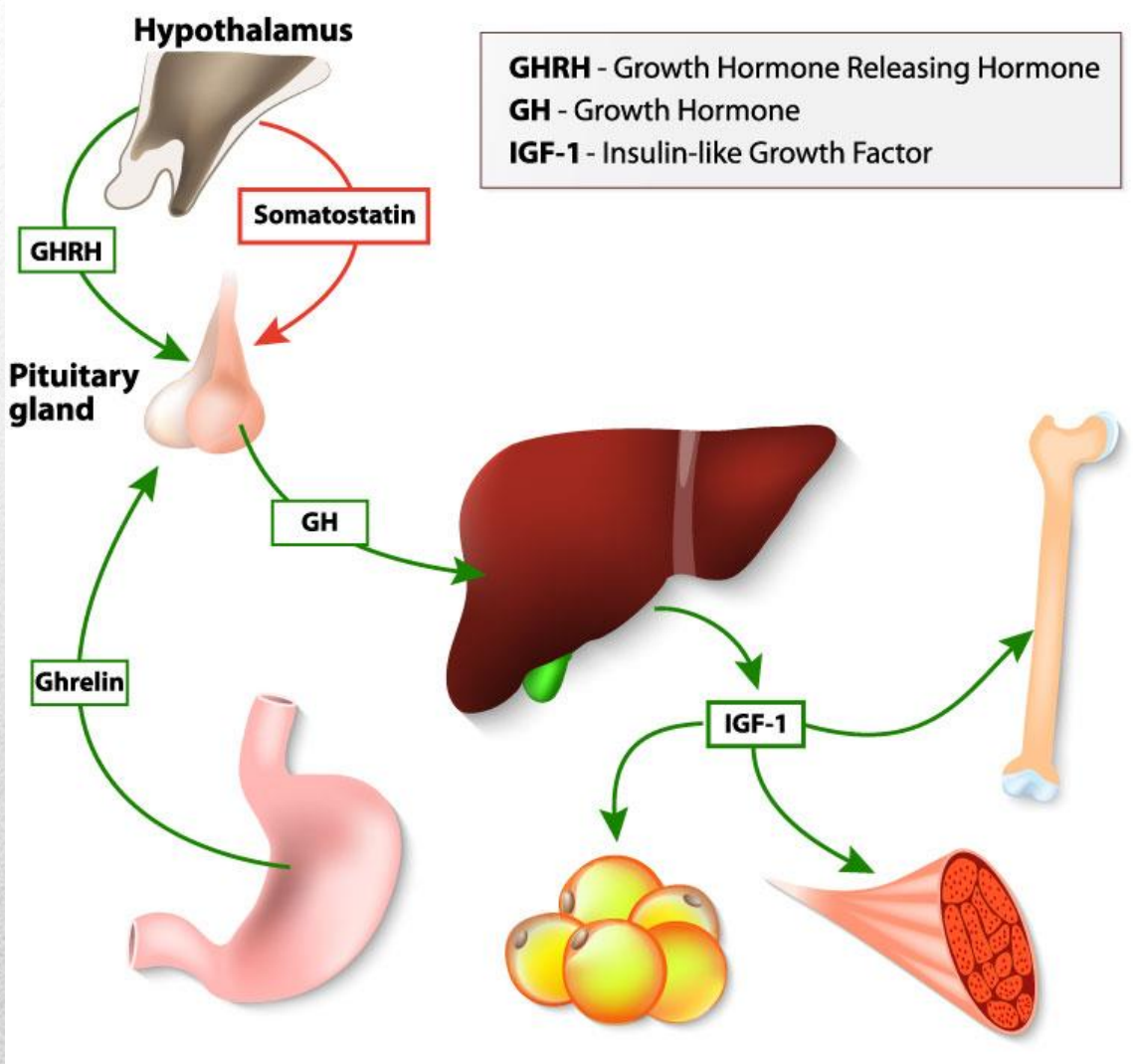
Growth Hormone is a 191 amino acid polypeptide

Synthesized, stored and secreted by cells of the anterior pituitary gland.

Regulated by a combination of GHRH(Growth Hormone

Releasing Hormone) and GHIH(Growth Hormone Inhibiting factor)

Stimulated by a variety of physiologic factors, i.e. sleep, exercise, free fatty acid concentration.


Hypothalamus
GHRH - Growth Hormone Releasing Hormone
GH - Growth Hormone
IGF-1 - Insulin-like Growth Factor
Somatostatin
GHRH
Pituitary gland
GH
Ghrelin
IGF-1

Growth Hormone Prescriptions

Not Approved in Some Countries for “Anti-Aging”
Those against its use say HGH doesn’t work

And yet it is banned for use in athletes as a performance enhancing substance.

US Federal Law, 21 U.S.C. 333(e) GH is the only legal
Drug that is banned for off label use for two indications: *Anti-aging and athletic performance*

If it doesn't work, why ban it??

Physiology GH

- What data on GH Replacement Therapy (GHRT) is in the medical literature in the past few years?
- Does GHRT increase the risk of cancer?
- Are there significant side effects to GHRT?
- What are the practical aspects of GHRT based on medical literature and clinical experience?
- GH and inflammation, stem cells?

Syndrome of Adult Growth Hormone Deficiency (AGHD)

- Increased fat mass
- Decreased lean body mass
- Decreased muscle strength
- Decreased exercise performance
- Decreased cardiac capacity
- Decreased bone mineral density and increased risk of fractures

Reed ML et al. Adult growth hormone deficiency - benefits, side effects, and risks of growth hormone replacement. *Front Endocrinol (Lausanne).* 2013 Jun 4;4:64.

Syndrome of AGHD

- Atherogenic lipid profile
- Thin dry skin
- Psychosocial problems and decreased quality of life
  - Fatigue
  - Depression
  - Anxiety
  - Impaired sleep
  - Social isolation

Reed ML et al. Adult growth hormone deficiency - benefits, side effects, and risks of growth hormone replacement. *Front Endocrinol (Lausanne)*. 2013 Jun 4;4:64.

Is GHRT a “Fountain of Youth”?

- No
- Since we are on a “programmed course of destruction”, GHRT is a way to help to maintain Quality of Life.
- Treat if patient has AGHD
- Risk/Benefit analysis
- Work in Progress

Rothenberg, R. Quality of Life Improves with GH Therapy. Anti-Aging Medical News, Summer-fall 2002. p 34.

AGHD

- Neurocognitive decline

GH Replacement

- Improved memory, alertness and concentration

GH and the brain

- GH exerts profound effects on CNS
- Improves
  - Cognitive capabilities
  - Memory
  - Alertness
  - Motivation, Work Capacity
- GH receptors present in the brain
  - Hypothalamus, choroid plexus, hippocampus
- GH crosses BBB

Nyberg F. Growth Hormone in the Brain: Characteristics of Specific Brain Targets for the Hormone and Their Functional Significance. *Front Neuroendocrinol* 2000 Oct;21(4):330-348

GH and Brain Injury

- GH deficiency common among survivors of Traumatic Brain Injury tested several months or years following head trauma.
- Mild or Moderate-to severe head trauma.
- Onset can evolve over years following injury.
- Assessment of the GH-IGF axis is indicated.

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

GH and Brain Injury (cont.)

- Some degree of hypopituitarism is found in 35-40% of Traumatic Brain Injury(TBI) patients.
- Untreated TBI induced hypopituitarism contributes to the chronic neurobehavioral problems seen in many head-injured patients.
- Subjects 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.

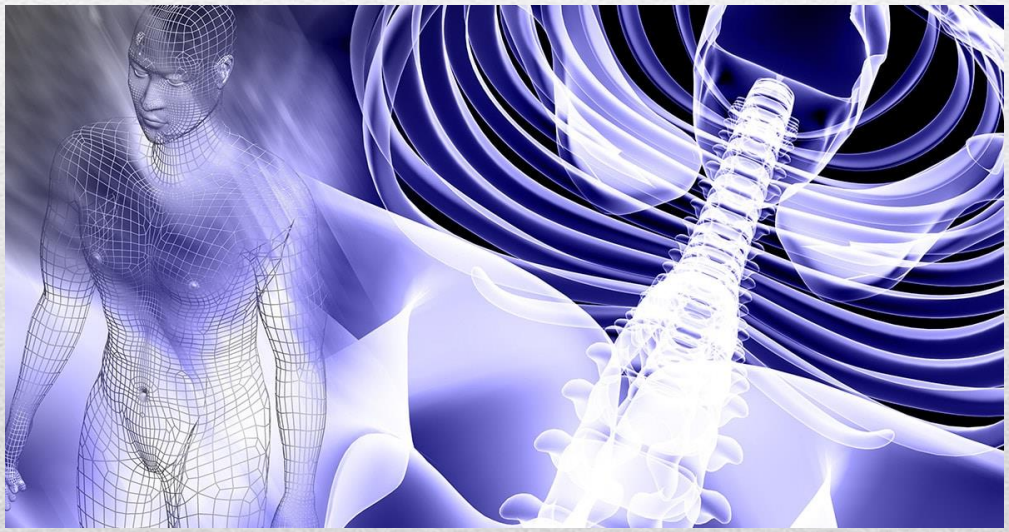
Popovic V et al. Hypopituitarism following traumatic brain injury. *Growth Horm IGF Res.* 2005 Jun;15(3):177-84.

AGHD Replacement

- Reduced bone density

GH

- Reversal of osteoporosis



Logobardi, *J Endocinol Invest*, May 1999 Bone density significantly improved with GH therapy

GH and Bone

- Increases formation and strength of cortical bone.
- Synergistic effect with exercise
- Lower IGF in Hip Fx patients

H. Oxlund, et al Growth Hormone and Mild Exercise in Combination Markedly Enhance Cortical Bone Formation and Strength in Old Rats *Endocrinology*, April 1998, p. 1899-1904 Vol. 139, No 4

Colao A. Bone loss is correlated to the severity of growth hormone deficiency in adult patients with hypopituitarism. *J Clin Endocrinol Metab* 1999 Jun;84(6):1919-24

Hedstrom M. Hip fracture patients, a group of frail elderly people with low bone mineral density, muscle mass and IGF-I levels. *Acta Physiol Scand* 1999 Dec;167(4):347-50

AGHD Replacement

- Increased CV deaths

GH

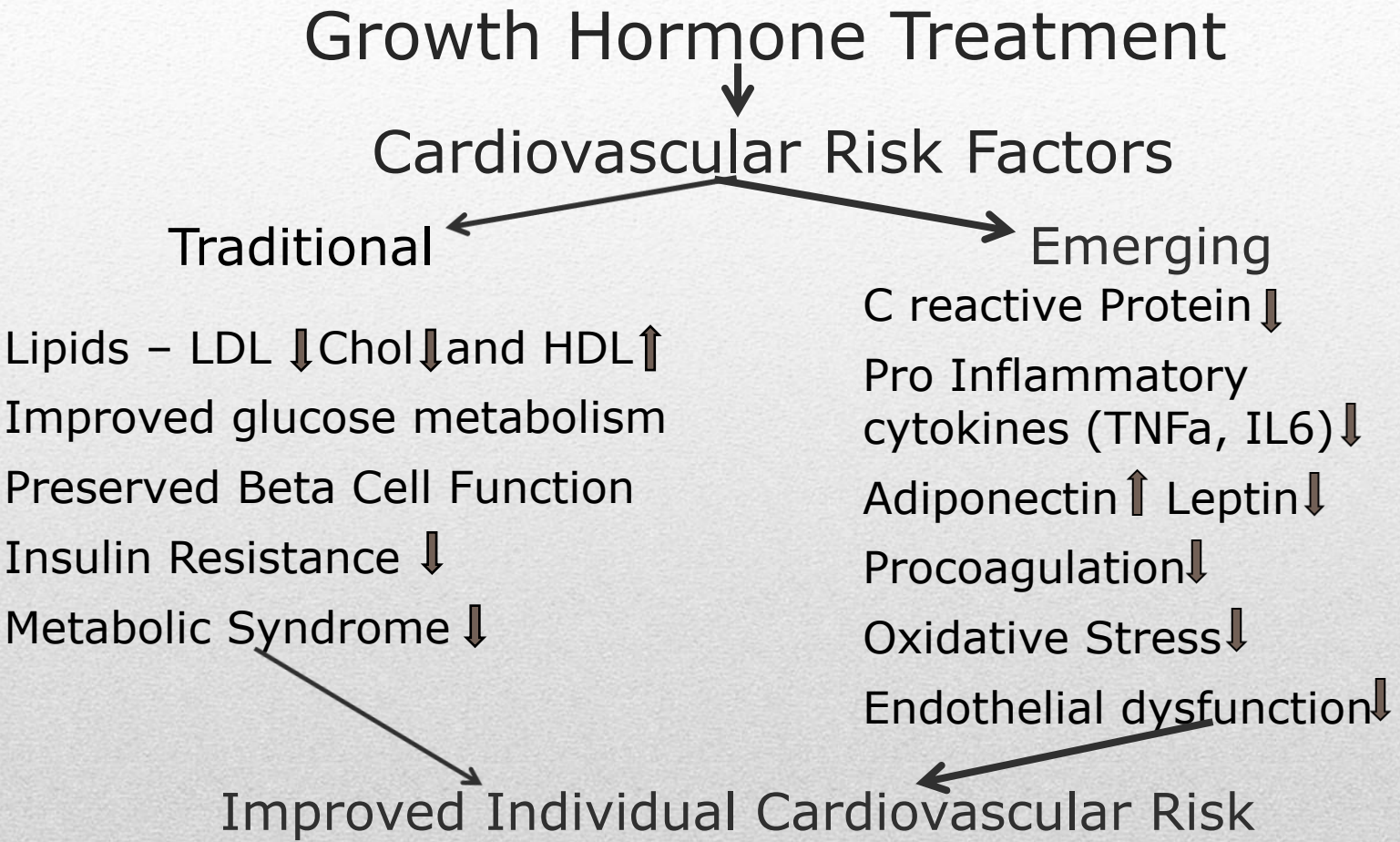
- Increased CV function
- Improves lipid profile?
- Reverses atherosclerosis
- Reduced carotid intima thickness
- Improves dilated cardiomyopathy

Gibney et al. The effects of 10 years of GH in adult GH deficient patients
J Endocrin Metab 1999 August

GH improves traditional and emerging cardiovascular risk factors

Decrease in LDL, increase in HDL, may not effect Triglycerides.
Synergistic with Statin?
Reduced inflammation – CRP, Reduce IL-6, TNF-alpha, reduced endothelial dysfunction(reduced asymmetrical dimethylarginine – ADAMA.)
Little data on long term cardiovascular mortality outcomes.

Gazzaruso C et al. Cardiovascular risk in adult patients with growth hormone (GH) deficiency and following substitution with GH--an update. J Clin Endocrinol Metab. 2014 Jan;99(1):18-29.


Growth Hormone Treatment
Cardiovascular Risk Factors
Traditional
Emerging
Lipids – LDL ⇓ Chol ⇓ and HDL ⇑
Improved glucose metabolism
Preserved Beta Cell Function
Insulin Resistance ⇓
Metabolic Syndrome ⇓
C reactive Protein ⇓
Pro Inflammatory cytokines (TNFa, IL6) ⇓
Adiponectin ⇑ Leptin ⇓
Procoagulation ⇓
Oxidative Stress ⇓
Endothelial dysfunction ⇓
Improved Individual Cardiovascular Risk

GH/IGF-1 and Immune System

- Connection between neuroendocrine and immune systems
  - Aging, stress and nutrition effect GH/IGF-1
  - IGF-1 needed for lymphocyte maturation and function
  - IGF-1 restores age-related thymic involution in rodents
  - IGF-1 restores damaged immune system
- Decline in T and B cells are restored by GH

Clark R. The somatogenic hormones and insulin-like growth factor-1: stimulators of lymphopoiesis and immune function. Endocr Rev. 1997 Apr;18(2):157-7

Burgess W et al. The immune-endocrine loop during aging: role of growth hormone and insulin-like growth factor-I. Neuroimmunomodulation 1999 Jan-Apr;6(1-2):56-68

AGHD

- Abnormal Body fat and distribution

GH Replacement

- Increased Lean body mass and Decreased abdominal fat
- Decreased abdominal fat by up to 50%

IGF-1 and Fitness

- IGF-1 is correlated with:
  - Body composition
  - Cardiovascular Health
  - Fitness – aerobic, muscular endurance
  - Improved health and fitness outcomes

Nindl BC et al. Circulating IGF-I is associated with fitness and health outcomes in a population of 846 young healthy men. *Growth Horm IGF Res*. 2011 Jun;21(3):124-8

GH and Body Composition

- GH deficiency:
  - Abnormal body composition
  - Increased adipose mass and decrease in muscle mass
  - Insulin resistance and decreased muscle strength
- Long term GH replacement normalized these abnormalities

Christiansen, J. Effects of GH upon body composition.. Growth Hormone in Adults , 1996, Cambridge University Press

AGHD Replacement

- Impaired physical performance

GH

- Increased exercise capacity

Johansson, J. Psychosocial and CNS effects.. Growth Hormone in Adults 1996, Cambridge University Press

AGHD Replacement

- Chronic fatigue, depression

GH

- Sense of well being
- Improved Quality

Gibney et al. The effects of 10 years of GH in adult GH deficient patie*J Endocrin Metab* 1999 August

GH and Quality of Life

- GH deficient adults
- 9 year follow up, n-61, part of randomized double-blind study
- GH RT improved Quality of Life
- Improved (all significant p values)
  - Energy
  - Vitality
  - Anxiety
  - Depression
  - Well-being
  - Self-control

Gilchrist FJ et al. The effect of long-term untreated growth hormone deficiency (GHD) and 9 years of GH replacement on the quality of life (QoL) of GH-deficient adults. *Clin Endocrinol* (Oxf) 2002 Sep;57(3):363-70

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.

GH and Cancer

- *Swerdlow et al.(2002);* showed a link but no information on IGF-1,IGFBP-3 levels. Given high dose HGH.
- *Reed ML, et al. (2013);* a majority of series show no link to cancer.
- *Ali S, et al. Gerontology 2014;* " the evidence linking GH and cancer is weak."

GH and Cancer (cont.)

- There is no evidence that GH replacement in adults increases the risk of *de novo* or recurrent malignancy
- Long-term surveillance of adult GHRT has not demonstrated increased cancer risk or mortality

Reed ML. et al (2013)

Growth Hormone – Adverse Effects

- Report of Adverse Events
- No difference GH treated vs untreated
  - Death
  - Cancer
  - Recurrence
  - Diabetes
  - Cardiovascular events

Hartman ML et al. Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients. *J Clin Endocrinol Metab*. 2013 Mar;98(3):980-8.

Diagnosis of GH Deficiency

- Phenotype – Clinical
- Provocation tests
  - L-arginine, GHRH, Insulin, Glucagon
  - Inconsistent, Impractical, Potentially dangerous
  - Macimorelin – oral, few side effects-expensive
- IGF-1
  - Optimal range 250-400ng/ml
  - Do not need to “chase” IGF-1

GHD Phenotype

- Increased truncal and visceral fat
- Decreased lean mass
- Osteopenia, glucose intolerance associated with insulin resistance
- Lipid profile consistent with increased atherogenic risk
- Decreased exercise capacity
- Altered cardiac structure and function
- Diminished quality of life.

Frohman LA. Controversy about treatment of growth hormone-deficient adults: a commentary. *Ann Intern Med* 2002 Aug 6;137(3):202-4

GH deficiency

- Hypertension
- Fractures
- Dyslipidemia
- Obesity
- Type 2 Diabetes
- Poor Quality of Life
- GH Treatment improved above

.

Abs, R et al. Isolated growth hormone (GH) deficiency in adult patients: baseline clinical characteristics and responses to GH replacement in comparison with hypopituitary patients. A sub-analysis of the KIMS database. *Growth Horm IGF Res*. 2005 Oct;15(5):349-59

GH Controversy

- Can Dx of AGHD be made without a stimulation test on the basis of clinical picture and IGF-1?
- Endocrine literature supports this idea
- Growth Hormone package insert has deleted the requirement for a stimulation test.

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
Savine R. Growth hormone replacement for the somatopause. *Horm Res* 2000;53 Suppl 3:37-41Savine R. et al.

Dx AGHD

- Suspect in Brain Injuries (TBI, SAH, Tumors)
- Suspect in Cranial Irradiation
- Suspect in hypopituitarism
- Normal IGF-I levels do not rule out severe GHD
- Very low IGF-I levels in patients highly suspected for GHD – skip provocative tests

Ghigo E et al. Diagnosis of adult GH deficiency. *Growth Horm IGF Res*. 2008 Feb;18(1):1-16.

- **Dose Related Effects of Growth Hormone**
- Higher doses of growth hormone increased insulin resistance but decreased waist circumference better endothelial function
- Small(30) Placebo Controlled Study Short Term Follow-up

"Titrating Growth Hormone Dose to High-Normal IGF-1 Levels Has Beneficial Effects …Despite Causing Insulin Resistance." Van Bunderen, Meijer, Lips, et. Al. Front. Endocrinol. Feb 2021.Vol11 Article 6129173

GH decreases Insulin Resistance

"Low-dose GH treatment combined with dietary restriction resulted not only in a decrease of visceral fat but also in an increase of muscle mass with a consequent improvement of the insulin resistance observed in obese type 2 diabetic patients."

Nam SY et al. Low-dose growth hormone treatment combined with diet restriction decreases insulin resistance by reducing visceral fat and increasing muscle mass in obese type 2 diabetic patients. *Int J Obes Relat Metab Disord* 2001 Aug;25(8):1101-7

GH RT Algorithm

- Possible plan
  - Everything in this field is controversial
  - Many different approaches
- "Work in Progress"
  - Changes are continuously necessary
- Women need higher doses than men for same IGF-1 and clinical results
- Average male dose 0.4 mg/day
- Average female dose 0.6 mg/day

Should you use GH for anti-aging?

- Improving physical function in healthy older population is high priority in medicine.
- Frailty leads to disability
- AGHD accelerates aging phenotype
- GH and Testosterone promote muscle protein synthesis when combined - greater efficacy than in either hormone alone.

Giannoulis MG, Martin FC, Nair KS, Umpleby AM, Sonksen P. Hormone replacement therapy and physical function in healthy older men. Time to talk hormones? *Endocr Rev*. 2012;33(3):314

- The evidence indicates unequivocally that it is possible to influence at least some components of this aging process favorably by hormone replacement with GH and T.
- Published data indicate that interventions with replacement HRT with Testosterone and GH in healthy older men is safe.
- GH Therapy improves
  - CVD and metabolic syndrome(most studies)
  - Muscle mass strength and physical function
  - Bone mineral density
  - Mood, QOL, cognition

Giannoulis MG, Martin FC, Nair KS, Umpleby AM, Sonksen P. Hormone replacement therapy and physical function in healthy older men. Time to talk hormones? *Endocr Rev*. 2012;33(3):314

Growth Hormone Treatment for Improved Health

80 Healthy Men (ages 65-80). Randomize, double blind, placebo controlled.

Lean body mass increase

Total body fat decrease

Increase Mid thigh muscle and aerobic activity

Improved age-Related Quality of Life Questionnaire.

Best with HGH and Testosterone combined group.

NO major adverse effects.

J Clin Endocrinol Metab, 2006 Feb;91(2):477-84. Epub 2005 Dec 6.

Growth Hormone Treatment for Improved Health

19,153 subjects.

Meta-analysis in adults with hypo-Pituitarism.

Decrease in all cause mortality.

Less pronounced in females(estrogen replacement?)

J. Clin Endocrinol Metab Apr 2015. Pappachan, JM et al.

2229 Treatment Group.

No increase in mortality.

No increase in cancer

J. Clin Endocrinol Metab.2011 Oct;96(10):3151-9

GROWTH HORMONE REVERSES AGING

TRIIM (Thymus Regeneration, Immunorestoration and Insulin Mitigation) Trial

First clinical use of Epigenetic “clock” to verify increase in biological age

1.5-2.0 years less than expected aging after 2 year study – effect increased toward end of study.

TRIIM STUDY

Treatment "cocktail"

- Growth Hormone
- Metformin
- DHEA
- Vitamin D
- Zinc

Well constructed but study issues:

- Nine patients
- No controls
- Study drugs were individualized for patients no static dosing

Stanford / UCLA study Fahy, Brooke, Watson, Good, Vasanawala, et al. Aug 2019 "Aging Cell"

HGH Adverse Press

"Growth drugs don't fight aging, researchers find the costly hormone shots can have serious side effects, according to a roundup of studies."

January 16, 2007;Thomas H. Maugh II |LA Times Staff Writer

HGH –Adverse Press

31 studies, 220 patients given HGH for at least 2 weeks.

Results:

Decrease in 2.1 kgms(4.6Lbs) of fat mass

Increase in 2.1 kgms of Lean Body Mass

Decrease in Cholesterol

Liu et, al Annals of Int Med 2007

Often quoted to support reason not to use HGH

HGH – Adverse Press (cont.)

Side Effects listed as “Adverse Events”

- Soft tissue edema
- Arthralgia's
- Carpal Tunnel
- Alteration of Glucose Metabolism

HGH – Adverse Press (cont.)

Although published under Stanford University Moniker.

It was an incomplete selection of studies.

It averaged 7 (seven) patients per study.

They excluded any study that listed a disease process including Adult Growth Hormone Deficiency

Doses not listed but not physiologic.

Side effects are dose related and rare with proper use.

Their ”report” showed it worked!

Mobilized 4.2kg of fat/muscle and decreased Cholesterol

HGH– Adverse Press

"It's hard to understand the unusual degree of emotional involvement that physicians and researchers exhibit when it comes to the discussion of growth hormone"

Barrett, Jurow, Hart, Rothenberg, Hormonal Bioidentity. 2019

Points to Remember when Ordering Growth Hormone

Diagnosis of AGHD needs to be on the Rx

- Replacement available through UCP – cost effective option
- Diagnosis: Replacement of endogenous GH in adults with GH deficiency. Document AGHD
- Baseline IGF1 levels and symptoms in your chart.
- GH can only be used for AGHD or indications in package insert.
- GH can be used for children with growth hormone deficiency and without GHD for short stature.

Hormone Lab Testing and the Office Visit

Kris Hart MN, RN-C
Family Nurse Practitioner

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 preventive/ regenerative medicine programs
- Advanced lab testing
- Nutrition - personalized
- Exercise
- Stress Reduction
- Nutraceuticals
- Inflammation control
- Optimize Hormonal BioIdentity
- Telomere testing and optimization

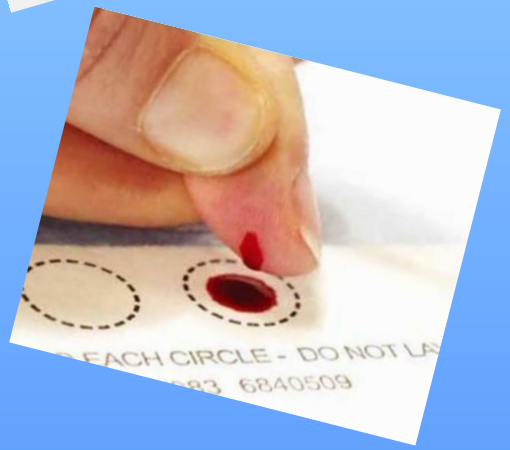
Basic Rules of Testing

- Establish a baseline prior to initiating therapy.
- Follow up to evaluate for safety and management.
- Be consistent with testing- testosterone dose, menstrual cycle, type of testing, etc.
- Start with a reasonable amount of testing. You can always do more.
- Listen to your patient--When there is a discrepancy between a lab test and the patient's symptoms, the patient will always win.

When to order?

- Before first visit
- In women who are still cycling, mid luteal phase 19-21(if 28 day cycle) gives the most information
- At 3-6 month intervals after initiating treatment for the first year, then annual
- Whenever symptoms don't make sense

What Testing to Use?



- Serum testing measures single point of reference for hormone levels. Measures circulating bound and unbound hormone levels as well as other reference levels needed for patient assessment.
- Dried blood spot similar to serum testing, but can be done at home.
- Saliva measures biologically active free forms of hormone as they diffuse into saliva.
- Urine measures active metabolites and ratios of hormones over a 24 hour period.
- Spot dried urine tests now available as well with improved compliance

What is Normal?

- "Normal range" is an unsatisfactory yardstick for decisions.
  - *Sylleptic ambiguity* - "normal=healthy"
  - *Circuitous reasoning* -"normal population" being "free from disease"
  - *Emotional overtones* - not "normal" is "abnormal," and needs to be corrected
- The best dividing lines between the "normal" and the "diseased" depends on
  - The disease under consideration
  - Distributions/sizes of the normal and diseased groups
  - Costs of making the wrong decision.
- Sunderman, W. Current concepts of "normal values" "reference values" and "discrimination values" in clinical chemistry. *Clinical Chemistry,* 1975 Vol. 21, No 13.

Serum Testing

What to order initially

- CBC
- Comprehensive Metabolic Panel
- Cholesterol panel
- Homocysteine, C-Reactive Protein
- Insulin, A1C
- Hormone Levels
- Vitamin Levels
- Cancer Screens
- Urine NTX

BASELINE LABORATORY TESTS

- CBC (85025)
- Comprehensive Metabolic Panel (80053)
- Cholesterol Profile -(fasting) (80061, 83704)
- Homocysteine (fasting) (83090)
- Cardio C-Reactive Protein (fasting) (86141)
- Fasting Insulin (83525)
- Hemoglobin A1C (83036)
- Magnesium (83735)
- Selenium (84255)
- Vitamin B12 (82607)
- Vitamin D, 25 Hydroxy (82306)
- CoQ10 (82491)
- Urinalysis (87086, 87088)

Lipid Panel with expanded Lipoprofile

- Cholesterol, Triglycerides, HDL, LDL
- Non HDL Cholesterol
- Lipoprotein (a)
- Particle Size or LDL-P number
  - May want to expand with PLAC2, MPO or other cardiac testing if history/risk found
  - Helps to identify if aggressive management and cardiac imaging is needed such as coronary calcium score

Hormone Serum Levels

- Estradiol (82670
- Progesterone (84144)
- Free & Total Testosterone (84402,84403)
- SHBG (84270)
- DHT (82651)
- DHEA Sulfate (82627)
- IGF1 (Somatomedin C) (84305)
- IGFBP3 (83520)
- FSH (83001)
- LH (83002)
- Free T3, Free T4 (84443, 84439)
- Reverse T3 (84442) TSH (84481)
- TPO (86376), Thyroglobulin Abs (86800)

Possible ICD 10 Codes

- Fatigue - R53.83
- Hyperlipidemia – E78.5
- Hypertension – I10
- Hypothyroid - E03.9
- Impaired Fasting Glucose - R73.01
- Insomnia - F51.02
- Menorrhagia – N92.4
- Menopause Symptomatic N95.1
- Testosterone Deficiency – E29.1
- Management of Chronic Disease -

What is “Optimal”

- Every Patient has their own “optimal level” that works for them
- Optimal levels usually fall in the reference range from whatever lab you are using
- Trend labs over time and correlate with clinical symptoms to find the “optimal” levels for each patient

Visit Overview

- The Office Visit
  - Preparation- lab testing, costs, time involved
  - Environment - relaxed
- Physician or Nurse Practitioner Contact
  - Patient Centered Communication
  - Body Language/Nonverbal Tone
- Team approach to developing the plan
  - Patient and family
  - Physician / Nurse Practitioner
  - Nutritionist
- The Bill
- Follow up

The Interview

- Get to know your patient- "Tell me the story of your life…"
  - What made them come to see you- personal goals Where were they born
  - Where did they grow up
  - What do they do – occupation
  - Do they travel
  - Are they married
  - Do they have children or pets
  - Do they have hobbies or other interests

  All will give you information on who they are and their belief systems

Exam

- Hands on completion of what you should already suspect from history
- Complete vital signs including O_2 saturation, height and weight
- Full exam on all including
  - Thyroid
  - Breasts
  - DRE on men
  - Optional pelvic exam on women with pap smear if indicated

Formulate the Plan

- From lab, history and exam identify deficiencies and their Hormonal BioIdentity
- Assess patient compliance and financial concerns
- Shared Decision Making and a team approach to create medication and supplement plan specific to your patient

- Give patient a written list and guidelines for medication management and usage and put in journal
- Send them home with supplements and arrange to have the prescriptions shipped to them within a couple days
- Have nurse go over everything and answer all questions regarding the medication schedule

Follow up, Follow up, Follow up

- Two week follow up phone call or office visit scheduled to review information from initial visit
- Lab evaluations routinely at 3 months, special testing as indicated
- Phone follow up prescheduled for general or same day scheduled for urgent issues
- Follow up by nutritionist, aesthetician and acupuncture if needed
- Contact information given for everyone on the team with 24 hour turn around goal for email questions

Remember

- Listen to your patients
- Be consistent in testing (menstrual cycle time, last testosterone dose)
- Treat the patient first not the lab test
- Look for trends
- Repeat tests that do not make sense
- Check the units of measure, they change from one lab to another

Goal of the Visit

- Happy, healthy patients
- Early detection and intervention
- Motivated to optimize their health
- Partnering in their future goals
- Family involvement if desired
- Trust
- Rectangularization of their lifespan with increased quality and possibly quantity of life

- Now available at UCP or Amazon