Bio-Identical Hormone Optimization and The Unified Theory of Wellness
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Bio-Identical Hormone Optimization and The Unified Theory of Wellness

Ron Rothenberg MD
Aging is a disease which can be prevented or reversed.

We are not prisoners of our genetic destiny.
Chronic Inflammation is the cause and the effect of the diseases of aging.
Balanced hormone optimization decreases chronic inflammation
We age because our hormones decline, our hormones don’t decline because we age.

Treatment of Adult GH deficiency is necessary for healthy adult life and GH Replacement Therapy can prevent and reverse some aspects of aging.
- Testosterone replacement therapy for treatment of testosterone deficiency is safe and provides dramatic benefits in men and women.
- Bio-identical Estrogens/Progestosterone replacement is safe and has dramatic benefits in women.
Progestins are not Progesterone
Equine estrogen is not human
Oral estrogen is not transdermal
Estriol (E3) is an important protective hormone
Many people with “euthyroid” lab values are clinically hypothryoid
Treating “mild” hormone deficiencies can dramatically improve quality of life

- Adrenal fatigue
- Mild Hypothyroidism
- Growth Hormone
- Progesterone
- Testosterone
Bio-Identical hormones

- Treat a “deficiency disease”
- Improve Quality of Life
- Decrease 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 hormone 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
Bio-identical hormones to optimize

- Growth Hormone
- Testosterone for men and women
- DHEA, Pregnenolone, Melatonin
- Estrogens: E1, E2, E3
- Progesterone
- Thyroid: T3, T4
- Cortisol
- Vitamin D

Optimal replacement considers levels and “How do you feel?”
- Eicosanoid hormones
  - Regulated by Lifestyle, Diet, Insulin, Omega 3’s, Endocrine Hormones, Mind-Body connection, Vitamins and Neutraceuticals
- Autocrine
- Paracrine
- Endocrine
- Lifestyle impacts hormone levels and actions
- Lifestyle decreases inflammation
Harmonic Theory of Wellness:
Chronic Inflammation Is the Cause and the Effect of the Diseases of Aging

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Vitamin D
CRP
Red inhibits

Yellow activates
Resveratrol
EPC's

EPA, DHA from Fish Oil
Pain
PGE2: Pain Cancer Skin aging

Angiotensin II

Diabetic Retinopathy

Wellness

ASCVD

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Prostaglandins, Thromboxanes, Leucotrienes, Lipoxins, Hydroxylated Fatty acids

Pain, Vasoconstriction, Atherosclerosis, Plaque formation

COX, LOX are key enzymes for eicosanoid synthesis

Prostacyclin, Vasodilation, PGI2, PGA2 cytoprotective, Blocked by COX2 inhibition

Not all “bad” Eicosanoids are bad

Breast Cancer, Viral replication, LTB4, PGE2, Pain, Lipoxins, Inflammation

Hydroxylated Fatty acids

Atherosclerosis, Cancer
Basics still apply

- Hormone optimization is 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 youthful levels and clinical response - control metabolites when needed
- Advanced treatments are backed up by current medical literature
  - More than any other field of medicine
“Unified Theory of Wellness”

- Chronic Inflammation is the cause and the effect of most illnesses and of the diseases of aging.
- Anti-inflammatory = Wellness
- Hormone optimization is necessary for anti-inflammation
Cytokines, GH, aging, and death

- Age 72-92
- Death associated with higher IL-6: 1.27 x
- TNF alpha: 1.30 x
- Life associated with higher IGF-1: 0.70 x

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
NFkB
Nuclear Factor kappa Beta

- Transcription factor in inflammation
- Lives in cytoplasm and enters nucleus and turns on inflammation genes
Positive regulatory loop

- Inflammatory signals
  - Proinflammatory cytokines
  - Protein kinase C activation
  - Viruses
  - Oxidants

- VCAM
- ICAM
- COX
- LOX

- Amplifying loop
  - NF-κB
  - TNF-α, Interleukin-1β
  - mRNA

- Inflammatory gene

- Inflammatory proteins
  - Receptors
  - Chemokines
  - Adhesion molecules
  - Enzymes
  - Cytokines
Inhibiting NF-kappaB results in apoptosis of abnormal cells and no progress to cancer

NF-kappaB is essential for promoting inflammation-associated cancer

Omega 3’s and NFκB

- EPA inhibits NFκB
- EPA decreases TNF alpha and other pro-inflammatory cytokines
Resveratrol inhibits NFκB


- Turns on Sirtuin genes
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
- Inflammatory cytokines produced by white blood cells and other tissues
- Cytokines cause liver to produce Acute Phase proteins
- Gets animal ready for "combat" with enemies or microorganisms
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

...IS HORMONE THERAPY RIGHT FOR YOU?...

SHOULDN'T YOU BE ASKING A DOCTOR?
I AM A DOCTOR.
Neuroendocrine theory

- We age because our hormones decline, our hormones don’t decline because we age

- Declining hormones increase chronic inflammation
Hormones to Optimize for Wellness and Decreased Inflammation

- Melatonin
- DHEA
- Pregnenolone
- Cortisol
- Thyroid
- Testosterone
- Growth Hormone
- Estrogens
- Progesterone
- Vitamin D
Thyroid

- Treat the patient not the lab test
- Order the right lab test
- Know which is the active hormone, the pro-hormone and the anti-hormone
- “Euthyroid” is not Optimal thyroid
TESTOSTERONE
Andropause is a deficiency disease

- 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.

Andropause is a lethal disease

- Diabetes, Metabolic syndrome
- Brain
- Heart
- Frailty syndrome
- Bone
- Inflammation
- Cancer
High T = Low Mortality

- 10 year prospective study
- 11,606 men – 40-79 years old
- High Endogenous T = low mortality from CV disease and cancer
- Low T predicts CV disease
- High T = no increase in Prostate Cancer
- “Paradoxically” fear of Prostate Ca has keep men from T treatment
41% decrease in chance of dying in men with $T > 564$ compared to 350

For each increase in 173, chance of dying went down 14%

Extrapolating:

Comparing $T 300$ to 1000

57% decrease in chance of dying

This study was of endogenous $T$ not treatment
Prostate CA and Hormones

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

- “There is not now--nor has there ever been a scientific basis for the belief that T causes PC to grow”

- TRT benefits from head to toe
  - Improved mood, cognitive, function, Alzheimer's prevention
  - Improved Body composition, more muscle, less fat, reversal of osteoporosis
  - Improved libido and erectile function
  - Reverses Insulin Resistance and type 2 diabetes
  - Less inflammation, pain, osteo and rheumatoid arthritis

- TRT decreases inflammation
  - CRP, IL-6, TNF alpha decreased
Female Hormones

- Estrogens
- Progesterone
- Testosterone

“Delicate balance between E and P both antagonistic and complimentary”

- Thierry Hertoghe
TRT in Women

- T needed for sense of well being
- Strength especially upper body
- Libido
- Nipple and clitoral sensitivity
- T usually decreased in perimenopausal and menopausal women
- Body composition
- Bone density
- DHEA can increase T in women but not in men
- “Relative Androgen Deficiency” with normal levels
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
Controversies

- Does Bio-identical E and P increase rates of breast cancer and cardiovascular disease?
- Lab tests vs. clinical picture?
- Why not use bio-identical oral E?
- Does she need Progesterone after hysterectomy?
Progesterone = P4
## Antagonism E and P4

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Progesterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid retention</td>
<td>Diuretic</td>
</tr>
<tr>
<td>↑ Sympathetic Energy</td>
<td>↑ Aldosterone blocker</td>
</tr>
<tr>
<td></td>
<td>↑ Parasympathetic Tranquility</td>
</tr>
</tbody>
</table>

- Synthetic “Progestins” are more androgenic lack diuretic and many other beneficial effects of P4
- Block many P4 receptor sites and act as anti-progesterone
Some Problems with WHI

- Wrong Estrogen
  - Premarin is not a human hormone
  - Mostly Equillinn
  - Low Estradiol (E2)
  - No Estriol (E3)

- Wrong “Progesterone”
  - Provera blocks progesterone receptors and is not a human hormone

- Wrong route
  - Oral Estrogens increase inflammation

- Wrong women
  - Older with established CV disease
Oral vs. Transdermal Estrogens

- Oral Estrogens (especially Premarin) increase inflammation as measured by CRP
- Transdermal Estrogens do not

- Decensi A et al. Effect of transdermal estradiol and oral conjugated estrogen on C-reactive protein in retinoid-placebo trial in healthy women Circulation 2002 Sep 3;106(10):1224-8
- Oral CEE
- CRP increased 192%
- IGF-1 decreased 30%

Transdermal E2 decreases IL-6, TNF

- Inflammatory cytokines implicated in autoimmune, cardiovascular, osteoporosis, Alzheimer’s
- E2 may protect above diseases

E3 safe and effective

- Provides some of the protection without the risks associated with stronger estrogens
- Effective at controlling symptoms of menopause:
  - hot flashes
  - Insomnia
  - vaginal dryness
  - frequent urinary tract infections.
E2 protects thru Methoxyestradiols

- Premenopausal women protected against cardiovascular and renal disease
- WHI shows no protection, even worse
- Why “striking disconnect” between basic science and animal studies who consistently show CV protection?

• 2-MeO-E2 has strong antiproliferative, apoptotic, and antiangiogenic action

COMT

CYP 1A1

SULFATES
GLUCURONIDES
FATTY ACID ESTERS

METHOXYESTRADIOLS
e.g. 2-Methoxyestradiol

CATECHOLEESTRADIOLS
e.g. 2-hydroxyestradiol

COMT

CYP 1A1

Multiple Hydroxylated
Metabolites

CYP450s
(1A1, 1B1, 1A2, 3A4)
(Hydroxylases)

Aromatase
(CYP19)

17β-ESTRADIOL

17β-HSD

ESTRONE

Sulfotransferase

Glucuronosyl-
transferase

Sulfates

Glucuronides

Fatty acid esters

TESTOSTERONE

ANDROSTENEDIONE

EAT
Bio-Identical Hormone Replacement in Women

- Balance Estrogens, Progesterone and Testosterone
- Every woman needs a unique balance
- Progesterone protects against breast cancer
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.
- Bioidentical hormones: safer, no increased risk of breast cancer

Progesterone decreases Breast Cancer risk - Campagnoli

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

Estrogen replacement - No increased mortality from cancer

- 23000 women
- Estradiol- (E2 and CEE) and Estriol E3 with or without progestins
- RR- 0.72- Breast Ca mortality
- RR- 0.77 – All cause mortality

Schairer C et al. Epidemiology, Jan 1997, Volume 8 Number 1
Estrogen decreased risk of mortality in patients with Breast CA history

Estrogen Metabolism - Breast

Testosterone → E2 → E2S

Androstenedione → E1

E2, P4 sulfatase inhibitors
E2 aromatase inhibitor

Aromatase

17Beta HSD

Sulfatase

Sulfotransferase

Sulfatase
GROWTH HORMONE
- Exponential decline in GH release after 18-21
- 50% decline every 7 years
- Negative correlation of GH release and BMI
- GH has half life of 15 minutes
- IGF-1 has half life of 15 minutes
- Ternary Complex has half life of 15 hours
IGFBP’s

- 6 IGF Binding Proteins
- Inhibit and Enhance IGF Actions
- IGF-1 + IGFBP-3 + Acid Labile Subunit = Ternary Complex
- Half-Life of Ternary Complex = 15 hours
- IGFBP-3 has independent actions and inhibits cancer through p53
“Life without GH is poor both in quantity and quality.”- R. Savine

- “GH peaks at puberty and begins to decrease at 21.”
- “At age of 60 most adults have total 24-hour secretion rates indistinguishable from those of hypopituitary patients with organic lesions in the pituitary gland.”
- “If IGF-1 of 300 is mean normal for 20-30 almost all > 40 have IGF-1 deficit”

GH deficiency = decreased longevity in humans

- Patients with absent GH-1 gene compared to siblings
- Males, 56 vs. 75 yr (P < 0.0001)
- Females, 46 vs. 80 yr (P < 0.0001)

GHRT for AGHD Improves

- Inflammation
- Brain
- Bone
- Atherosclerosis
- Heart Function
- Immune System
- Body Composition
- Exercise Capacity
- Wound healing
- Well Being
- Quality of Life
- Cosmetic Appearance
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.”

GH and CRP

- GH deficiency = Increased CRP
- GH treatment = Decreased CRP

Andreassen et al. Concentrations of the acute phase reactants high-sensitive C-reactive protein and YKL-40 and of interleukin-6 before and after treatment in patients with acromegaly and growth hormone deficiency. Clin Endocrinol (Oxf). 2007 Aug 28
Know your Inflamm-aging numbers

- CRP < 1
- Fasting Insulin < 7
- Homocysteine < 7
- AA/EPA Ratio < 1.5
- 25-OH-D > 65
- Cytokines
  - IL-6 < 12 pg/l
  - TNF alpha < 8 pg/l
  - IL-1 beta < 15 pg/l
Optimize stem cells

- Optimized hormones and nutraceuticals increase quantity and quality of endogenous adult stem cells


Stem cells optimization through nutraceuticals

- Blueberry
- Green tea
- Vitamin D3
- Carnosine

Resveratrol and stem cells

Unified Theory of Wellness

- Control Inflam-Aging
- Optimize hormones
- 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
Harmonic Theory of Wellness:

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

EPA, DHA from Fish OIL

Pain

PGE2: Pain, Cancer, Skin aging

TXA2, Atherosclerosis

Wellness