

# **Bioidentical Hormone Replacement as the “Standard of Care”**

*Hormone Myths vs. Scientific Evidence*

**William Clearfield D.O.  
9550 S. McCarran Blvd, Ste. B  
Reno, NV 89523  
775 359 1222  
drbill@rejuvenatereno.com**

# Objectives

1. Review the AMA Position Papers on Bioidentical Hormone Replacement
2. Present the Scientific Evidence for BHRT as the "Standard of Care."
3. Provide A Succinct Reference Source Utilizing the Latest Peer Reviewed Scientific Literature to Counter the Position Paper, "No Credible Evidence Exists on the Value of Bioidentical Hormones."

# **AMA: "No Credible Evidence Exists on the Value of Bioidentical Hormones."**

- **Current evidence does not support the use of testosterone in older men with low testosterone levels.**
- **Evidence of the value of testosterone as an antiaging therapy does not exist.**
- **Current evidence fails to support the efficacy of hGH as an anti aging therapy**
- **The long term use of estrogens with or without progestins cause more risks than benefits.**
- **The long term use of estrogens for the prevention of chronic conditions in postmenopausal women is not recommended**
- **DHEA as an antiaging supplement shows neither meaningful benefit nor serious adverse effects**

# Mayo Clinic

**No evidence currently suggests that custom CBHT formulations offer clinically relevant benefits.**

[Julia A. Files](#), MD, [Marcia G. Ko](#), MD, and [Sandhya Pruthi](#), MD, Bioidentical Hormone Therapy, *Mayo Clin Proc.* 2011 Jul; 86(7): 673–680.

PMCID: PMC3127562

# American Association of Clinical Endocrinologists

For women who cannot control severe vasomotor symptoms, lifestyle changes should be implemented first.

Pharmacologic therapy:

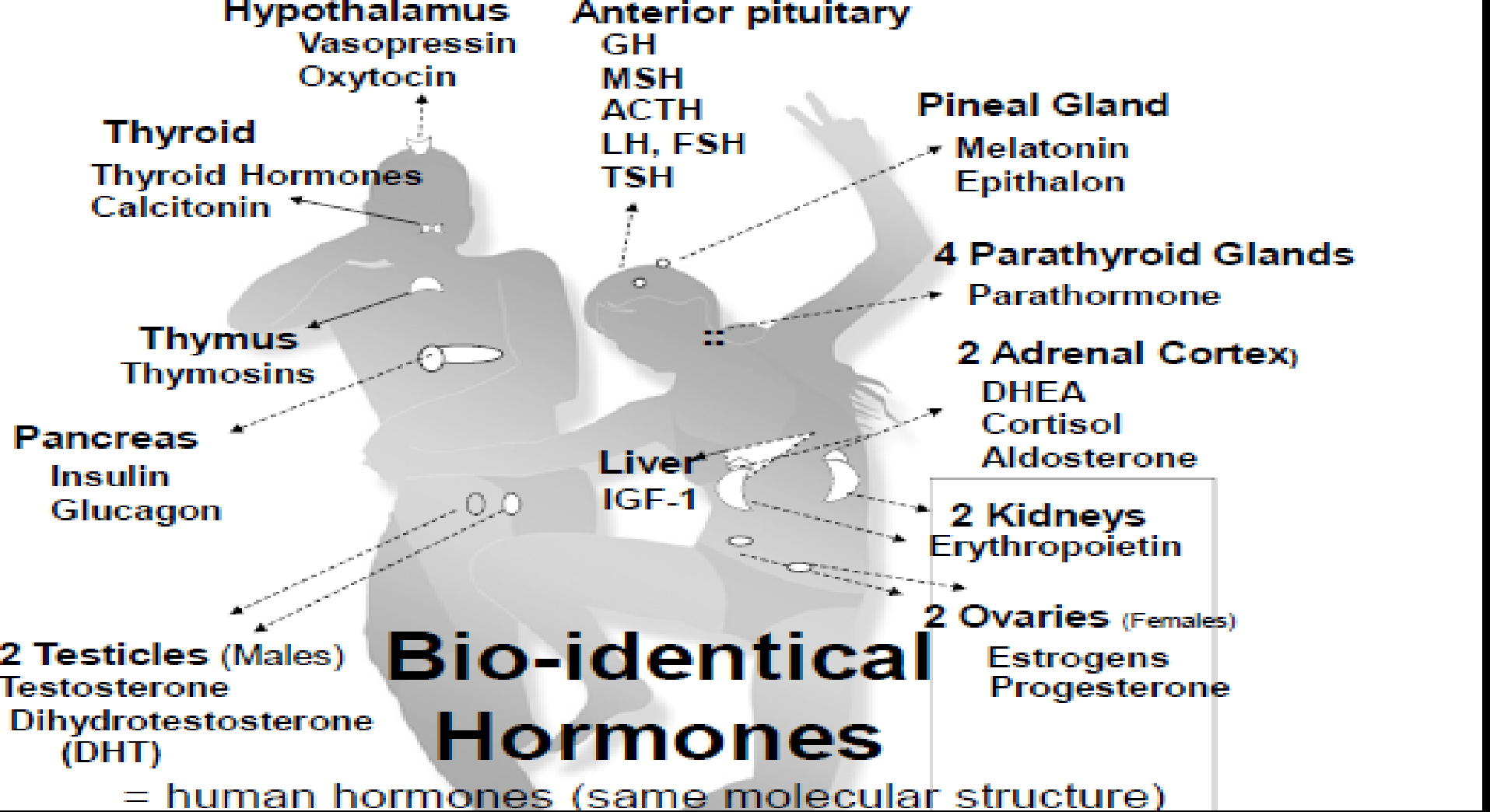
a. Antidepressants-Venlafaxine (**Effexor**)

b. Antidepressants intolerant

i. **Clonidine (Catapres)**

ii. **Megestrol (Synthetic Progesterone)**

iii. **Gabapentin**



**Hypothalamus**  
Desmopressin Vasopressin  
Oxytocin

**Thyroid**  
Thyroid hormones  
Calcitonin

**Thymus**  
Thymosins

**Pancreas**  
Insulin  
Glucagon

**2 Testicles**  
Nandrolone  
Stanozolol  
Testosterone  
Mesterolone  
Dihydrotestosterone (DHT)

**Anterior pituitary**  
GH  
Melanotan II (MSH)  
ACTH  
LH, FSH  
TSH

**Liver**  
Longacting  
IGF-1 (R3)  
IGF-1

**Pineal Gland**  
Melatonin  
Epithalon

**4 Parathyroid glands**  
Parathormone

**2 Adrenal cortex**  
DHEA  
Methyl/prednisolone  
Dexamethasone  
(Cortisol)  
Fludrocortisone  
Aldosterone

**2 Kidneys**  
Erythropoietin

**2 Ovaries**  
Ethinylestradiol  
Conjugated estrogens  
Estrogens  
Medroxyprogesterone  
/Cyproterone  
Norethisterone  
/Levonorgestrel  
Progesterone

# Non-Bio-identical Hormones

= synthetic derivatives of human hormones (different molecular structure)

**True or False?**

**There Are No FDA Approved "Bioidentical Hormones."**

**True or False?**

**There is no FDA Indication for Testosterone Use in Women.**



# Just For Fun: "FDA Approved Treatment With "Credible Evidence" of Therapeutic Efficacy

## 1. Rofecoxib (Vioxx)

- Maker: Merck
- Recalled: 2004 (after five years on the market)
- Financial damage: nearly \$6 billion in litigation-related expenses alone
- 140,000 incidents of premature coronary artery disease

## 2. Cerivastatin (Baycol)

- Maker: Bayer
- Hyperlipidemia
- Recalled: 2001 (after four years on the market)

# Just For Fun: "FDA Approved Treatment With "Credible Evidence" of Therapeutic Efficacy

## 3. Oxycontin-Pain Relief

- a. **Side Effects**-Highly Addictive, Easy Accommodation. Patients quickly need larger and larger doses to achieve same level of relief. Leading drug of abuse from 2004 on. 29,600 drug related fatalities due to overdose
- b. **Costs**-\$38.5 Billion for abuse treatment, medical complications, productivity loss (minus mortality), and criminal justice. **Premature Death Cost \$63 B Life Years Lost 29**
- c. **Sales- \$36 B Fine-\$600 million**

August 14, 2015: [FDA Approves Oxycontin for Children as Young as 11](#)

**OxyContin sales put Purdue's Sackler family on Forbes rich list**

# **"Ed Begley, Jr. Rule"**

**"Don't get your information from me, folks, or any newscaster. Get it from people with PhD's after their names."**



# The AMA vs. Testosterone

- **Current evidence does not support the use of testosterone in older men with low testosterone levels.**
  
- **Evidence of the value of testosterone as an antiaging therapy does not exist.**

Executive Summary of the AMA House of Delegates 2009 Annual Meeting: Council on Science and Public Health Report. The use of hormones for “anti aging”: A review of efficacy and safety. *Report 5 of council on science and public health (A-09)*. 2009:1-17.

SECTIONS HOME SEARCH

# The New York Times

The Opinion Pages OP-ED CONTRIBUTOR

## Don't Ask Your Doctor About 'Low T'

By JOHN LA PUMA FEB 3, 2014

SANTA BARBARA, Calif. — A FUNNY thing has happened in the United States over the last few decades. Men's average testosterone levels have

EMAIL FACEBOOK TWITTER

CBSNews.com / CBS Evening News / CBS This Morning / 48 Hours / 60 Minutes / Sunday Morning / Face The Nation

SUBSCRIBE LOG IN

U.S. Department of Health & Human Services

# FDA U.S. Food and Drug Administration

Protecting and Promoting Your Health

A to Z Index Follow FDA FDA Voice Blog

Home Food Drugs Medical Devices Radiation-Emitting Products Vaccines, Blood & Biologics Animal & Veterinary Cosmetics Tobacco Products

## Drugs

Home Drugs Drug Safety and Availability

### Drug Safety and Availability

Log In Search

## FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products

View and print full Drug Safety Communication (PDF - 36KB)

Safety Announcement References

01/31/2014 The U.S. Food and Drug Administration (FDA) is evaluating the cardiovascular safety of testosterone products.

CBS Evening News with SCOTT PELLEY

By JONATHAN LAPOOK CBS NEWS January 29, 2014, 7:16 PM

## Testosterone supplements linked to heart attacks in new study



60 NEWS MINUTES

FOLLOW

### FROM CBS NEWS

- Senate takes extending benefits 48:04 VIEW
- Subway to found in y 32:09 VIEW
- Jay Leno Tonight 25:08 VIEW
- Leonard lung dis 23:39 VIEW
- Snipe transf attack 22:20 VIEW

# Forbes

New Posts Popular Lists Video

Larry Husten, Contributor

I'm a medical journalist covering cardiology news.

+ Follow (187)

PHARMA & HEALTHCARE | 1/31/2014 @ 4:27PM | 568 views

## FDA Evaluating Safety Of Testosterone Products

1 comments, 1 called-out + Comment Now + Follow Comments

The FDA said today that it was evaluating the cardiovascular safety of testosterone products. The investigation is prompted by two recent published studies that found a significant increase in cardiovascular events in men who received testosterone therapy.

The FDA said it had not concluded that testosterone is unsafe but recommended that "health care professionals should consider whether the benefits of FDA-approved testosterone treatment is likely to exceed the potential risks of treatment." Testosterone is approved for use only in men who lack or have low testosterone levels in conjunction with an associated medical condition.

Larry Husten Contributor + Follow (187)

I cover cardiology news for CardioExchange, a social media website for cardiologists published by the New England Journal of Medicine. I was the editor of TheHeart.Org from its inception in 1999 until December 2008. Following the purchase of TheHeart.Org by WebMD in 2005, I became the editorial director of WebMD

+ show more

The author is a Forbes contributor. The opinions expressed are those of the writer.

LARRY HUSTEN'S POPULAR POSTS

- Case Closed: Multivitamins Should Not Be Used 79,627 views
- Resveratrol and Fraud 55,513 views
- Another One Bites the Dust: Diovan Patent Expires But Generic Valsartan Is MIA 48,121 views
- Study Finds Sodium-Potassium Ratio Strongly Tied to Mortality and CV Disease 42,408 views
- Link To Prostate Cancer Brings More Bad News For Fish Oil Story 42,082 views

MORE FROM LARRY HUSTEN

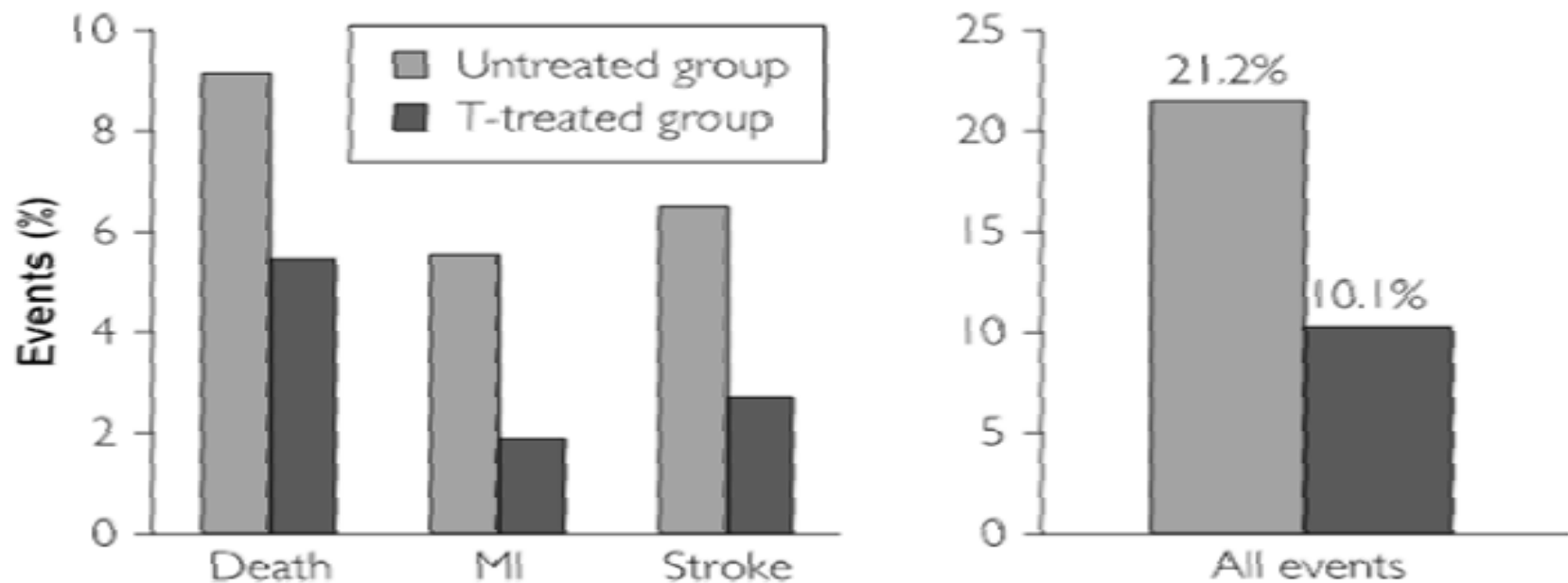
# Current Evidence does not Support the Use of Testosterone in Older Men with Low Testosterone levels.

- Risk of non-fatal MI greater in the 3 months after testosterone Rx.
- ICD-9 study, patients not seen or interviewed
- No information on preparation, dose or interval of usage or if even used
- No info on fatal MI or cardiovascular mortality or all cause mortality
- No information on testosterone serum levels before or after therapy

# Facts: Testosterone and Heart Disease

- **Low testosterone levels are associated with increased mortality, atherosclerosis, and incident coronary artery disease;**
- **Mortality is reduced by one half in testosterone-deficient men treated with testosterone therapy compared with untreated men;**

# Morgantaler vs Vigen



Morgantaler, A et al. Testosterone Therapy and Cardiovascular Risk: Advances and Controversies. *Mayo Clin Proc.* February 2015;90(2):224-251



# Conclusional: Delusional?

A Predetermined Outcome?

With T 10% w Event vs. Without T 21% Events = T Caused Events?

With T 5% Deaths vs. Without T 9% Deaths = T Caused Deaths?



# Testosterone and Heart Disease-Study Retracted

1. Authors improperly excluded 1132 men from analysis. Corrected to 128 subsequently.
  - a. (Error rate 89%)
- 2. 100 women were identified among the study group.**
3. Original group of 1132 individuals, meaning that one out of eleven “men” in the study were actually women.
4. More than 160 leading testosterone researchers and 29 medical societies from around the world joined ASG called for retraction of the study following revelation of the data errors, asserting that the magnitude and quality of the errors rendered the study "no longer credible."

# Myth: Testosterone Causes Prostate Cancer

Based on one report from 1941

- No relationship of T, DHT, E2 to prostate Ca
- No reports of PC in men treated with T after radical prostatectomy
- Benefits from head to toe when hypogonadism treated
- Morgentaler A. Testosterone and Prostate Cancer: An Historical Perspective on a Modern AMA. Eur Urol. 2006 Jul 26

# Myth: Testosterone Causes Prostate Cancer

- 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**

Endogenous Sex Hormones and Prostate Cancer: A Collaborative Analysis of 18 Prospective Studies Endogenous Hormones and Prostate Cancer Collaborative Group . **J Natl Cancer Inst** 2008 100: 170-183 51

- **Conclusion- Testosterone therapy in hypogonadal men does not increase the risk of prostate cancer.**

# Myth: Testosterone Causes Prostate Cancer

- “No compelling evidence at present suggests that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases this risk.
- **In fact it should be recognized that prostate cancer becomes more prevalent exactly at the time in a man's life when testosterone levels decline.”**

Rhoden E et al. “Medical Progress: Risks of Testosterone Replacement Therapy and Recommendations for Monitoring.” **N Engl J Med** 2004; Jan 29; 350:482-492

• Bassil et al, “The benefits and risks of testosterone replacement therapy: a review,” **Therapeutics and Clinical Risk Management** 2009; 5 427-448

• Morgentaler A Testosterone therapy and prostate risks: where's the beef? **Can J Urol.** 2006 Feb;13 Suppl 1:40-43

# Testosterone and Depression

**T has Antidepressant effect in Depressed Patients, esp. those w Hypogonadism.**

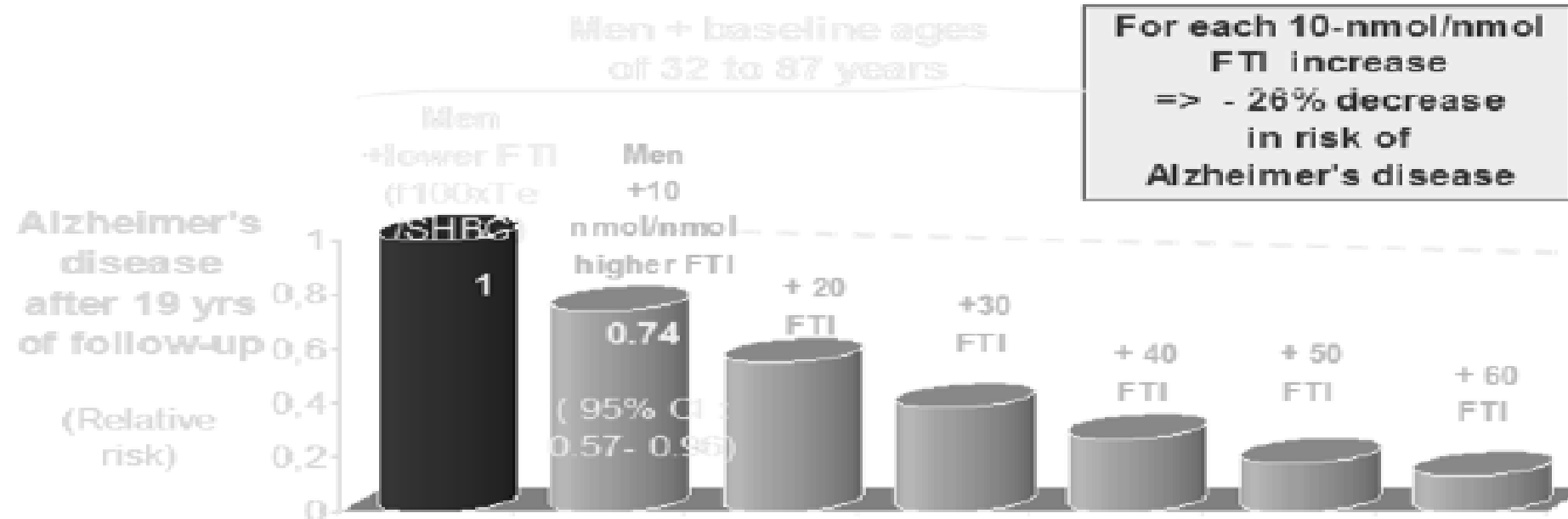
Zarrouf, FA, Artz S., F=Griffith J, et al. Testosterone and Depression: Systematic review and meta-analysis. *J. Psychiatric Pract.* 2009 Jul;15(4):289-305.

**Testosterone and Growth Hormone Improve Body Composition and Muscle Performance in Older Men**

Supplemental T produced significant gains in lean mass, strength and aerobic endurance with significant reductions in whole body and trunk fat. GH further enhances outcome

Sattler FR, Castaneda-Sceppa C, Binder EF, et al. Testosterone Growth Hormone Improve Body Composition and Muscle Performance in Older Men. *J. Clin Endocrinol Metabol.* 2009 Jun;94(6):1991-2001.

# ↑ Free & Total Testosterone ⇒ ↓ Alzheimer's D.



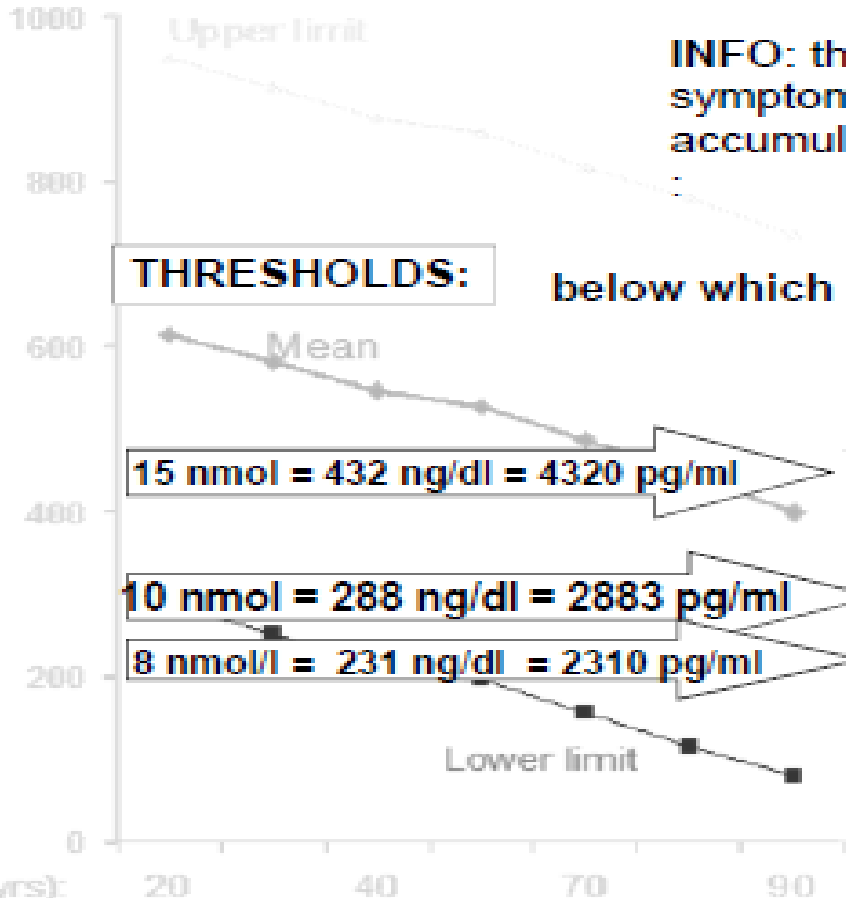
**Figure:** Increases in the FTI were assoc. w/ a decreased risk of Alzheimer's disease. Calculated free testosterone conc. were lower in men who developed Alzheimer disease, & this difference occurred before diagnosis

n = 574 men followed for a mean of 19.1 years (range, 4 - 37 years)

Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, Resnick SM. Free testosterone and risk for Alzheimer disease in older men. *Neurology*. 2004 Jan 27;62(2):188-93

**↓ Serum Testost. within ref. range => ↓ vigor, libido, depression, type 2 diabetes, erectile dysfunction**

**Serum Total testosterone in apparently healthy men (ng/dl)**  
 (Mohr BA; Clin Endocrinol (Oxf). 2005 Jan;62(1):64-73)



**INFO:** the prevalence of psychosomatic symptoms & metabolic risk factors accumulated with ↓ androgen levels

**THRESHOLDS:**

below which risk factors sign. increased

15 nmol = 432 ng/dl = 4320 pg/ml

10 nmol = 288 ng/dl = 2883 pg/ml

8 nmol/l = 231 ng/dl = 2310 pg/ml

- Loss of vigor
  - Loss of libido
  - Depression & Diabetes mellitus type 2 (also in nonobese men)
  - Erectile dysfunction
- Many levels within the ref range

N = 434 consecutive male patients aged 50-86 yr

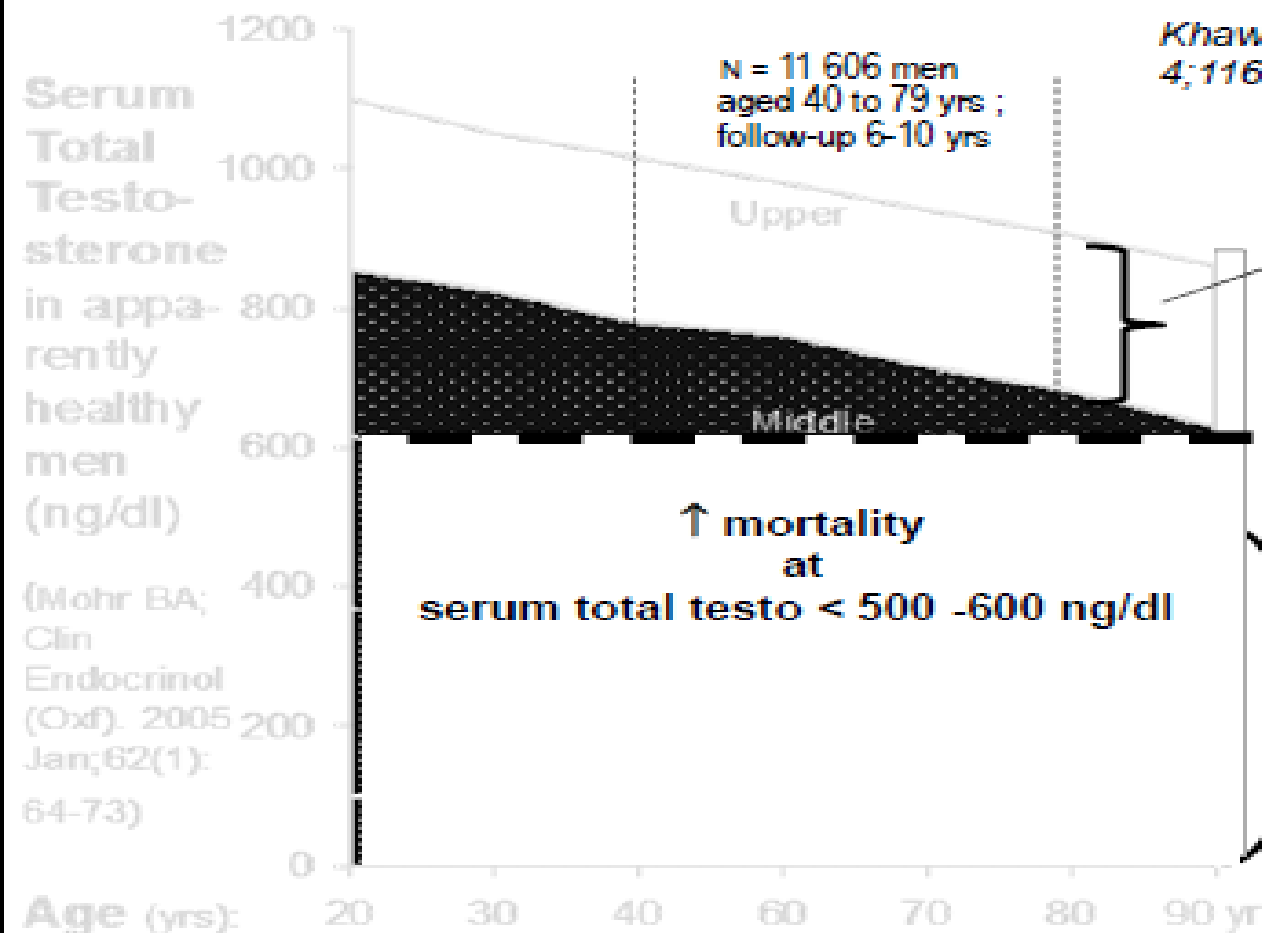
Zitzmann M, et al. J Clin Endocrinol Metab. 2006 Nov;91(11):4335-43



# ↑ serum testosterone => ↓ Mortality

Khaw KT. *Circulation*. 2007 Dec 4;116(23):2694-701 Cambridge UK

N = 11 606 men  
aged 40 to 79 yrs ;  
follow-up 6-10 yrs



**SAFER** when serum testo is in highest quartile

A man needs to have a serum testo > ± 600 ng/dl

Insufficient testosterone levels => Men die quicker

# Testosterone Novelties

- 1. Dry Eye Disease**-0.3% Testosterone with 0.5% Progesterone in cyclodextrin base. Dawson, T.L., Testosterone eye drops: “A novel treatment for dry eye disease,” *Ophthalmology Times*, November 15, 2015
- 1. Chronic Pain in Fibromyalgia**-White, H.,Robinson T.; “A novel use for testosterone to treat central sensitization of chronic pain in fibromyalgia patients,” *International Immunopharmacology*, [Volume 27, Issue 2](#), August 2015, Pages 244–248
- 1. Chronic Non Radicular Low Back Pain**-Dubick MN, Ravin TH, Michel Y, Morrisette DC; Use of localized human growth hormone and testosterone injections in addition to manual therapy and exercise for lower back pain: a case series with 12-month follow-up, *Dove Press*, 23 June 2015 [Volume 2015:8](#) Pages 295—302

## Myth: “No Credible Evidence Exists on the Value of Bioidentical Hormones.”

- **Current evidence fails to support the efficacy of hGH as an anti aging therapy.**

Executive Summary of the AMA House of Delegates 2009 Annual Meeting: Council on Science and Public Health Report. The use of hormones for “anti aging”: A review of efficacy and safety. *Report 5 of council on science and public health (A-09)*. 2009:1-17.

Yet: **Rudman D**, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE. Effects of human growth hormone in men over 60 years old. *N Engl J Med*. 1990 Jul5;323(1):1-6

- 8.8 percent increase in lean body mass
- 14.4 percent decrease in adipose-tissue mass
- 1.6 percent increase in average lumbar vertebral bone density (P less than 0.05 in each instance).
- Skin thickness increased 7.1 percent.

# **Myth: GH Deficiency is Only Seen in Patients with Severe Multiple Pituitary Deficiencies since Childhood**

**Patients treated with GH experience significant improvements in concentration, memory, depression, anxiety and fatigue.**

**Pituitary failure can occur even in minor head injuries and is poorly recognized.**

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

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

**AGHD is common and often not recognized after TBI and other brain insults.**

- Evaluate all TBI, CVA patients within a year for AGHD. Treat if deficiency disease exists.

**GH replacement therapy improves cognition and QoL in TBI patients with GHD, especially in those with severe disabilities.**

Kozlowski O et al. Growth hormone replacement therapy in patients with traumatic brain injury. Neurotrauma. 2013 Jan 16.

# “Current evidence fails to support the efficacy of hGH as an anti aging therapy.”

1. GH-therapy of GH-deficient men **reverses early atherosclerotic changes**, namely the increased thickness of the intima media of the common carotid artery & the carotid bifurcation in 11 GH-deficient men (24-49 yr old) (Pfeifer M et al, J Clin Endocrinol Metab, 1999, 84 : 453-457)
2. **Decrease in Oxidative Stress (free radical formation) by 50%** Evans LM, Davies JS, Anderson RA, Ellis GR, Jackson SK, Lewis MJ, Frenneaux MP, Rees A, Scanlon MF. The effect of GH replacement therapy on endothelial function and oxidative stress in adult growth hormone deficiency. Eur J Endocrinol. 2000 Mar;142(3):254-62. Section of Endocrinology, Diabetes and Metabolism, University Hospital of Wales, Cardiff, UK.
3. **Increases thyroid & androgen activities, but decreases cortisol.** 1) Vierhapper H, Nowotny P, Waldhausl W. Treatment with growth hormone suppresses cortisol production in man. Metabolism 1998 Nov;47(11):1376-8 ; 2) Rodriguez-Arnan J, Perry L, Besser GM, Ross RJ. Growth hormone treatment in hypopituitary GH deficient adults reduces circulating cortisol levels during hydrocortisone replacement therapy. Clin Endocrinol (Oxf) 1996 Jul;45(1):33-7 ; 3) Weaver JU, Thaventhiran L, Noonan K, Burrin JM, Taylor NF, Norman MR, Monson JP. The effect of growth hormone replacement on cortisol metabolism and glucocorticoid sensitivity in hypopituitary adults. Clin Endocrinol (Oxf) 1994 Nov;41(5):639-48 ; 4) Carani C, Granata AR, De Rosa M, Garau C, Zarrilli S, Paesano L, Colao A, Marrama P, Lombardi G. The effect of chronic treatment with GH on gonadal function in men with isolated GH deficiency. Eur J Endocrinol 1999 Mar;140(3):224-30 ; 5) Belgorosky A, Martinez A, Domene H, Heinrich JJ, Bergada C, Rivarola MA .High serum sex hormone-binding globulin (SHBG) and low serum non-SHBG-bound testosterone in boys with idiopathic hypopituitarism: effect of recombinant

# All Mortality with GH Use Decreased Post MI by Minimum 300%

Mortality => ↑↑ in GH deficient patients,  
normalized by GH therapy

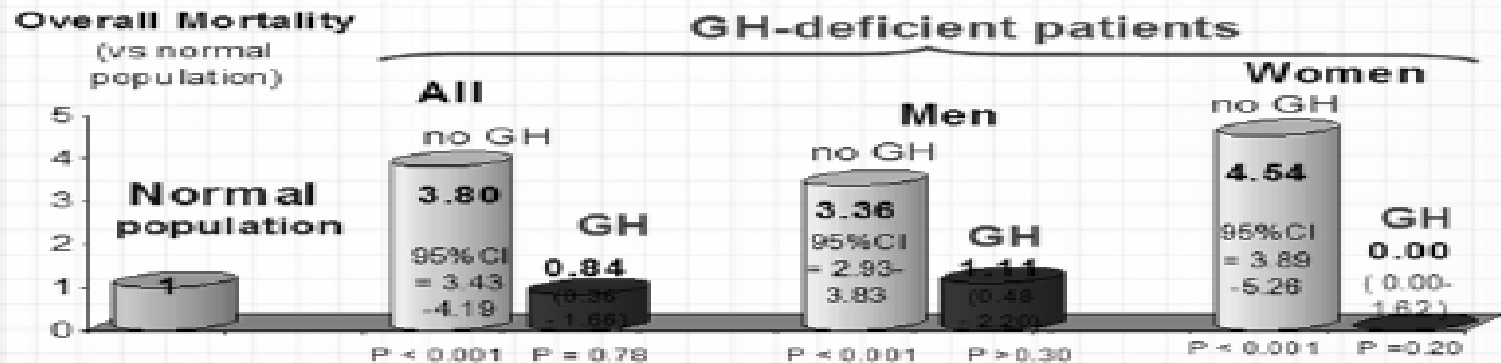


Figure: Overall mortality & the rate of myocardial infarctions were increased in hypopituitary patients without GH replacement, GH replacement normalized the risk.

J. Svensson, B.-Å. Bengtsson, T. Rosén, A. Odén, G. Johannsson. Malignant Disease and Cardiovascular Morbidity in Hypopituitary Adults with or without Growth Hormone Replacement Therapy. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3306-12

“Current evidence fails to support the efficacy of hGH as an anti aging therapy.”

# **GH Improves Nutrition, QOL and CV Risk**

Feldt-Rasmussen B, Lange M, Sulowicz W, Gafter U, Lai KN, Wiedemann J, Christiansen JS, El Nahas M; APCD Study Group. Growth hormone treatment during hemodialysis in a randomized trial improves nutrition, quality of life, and cardiovascular risk. *J Am Soc Nephrol.* 2007 Jul;18(7):2161-71

**Rudman D**, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE. Effects of human growth hormone in men over 60 years old. *N Engl J Med.* 1990 Jul5;323(1):1-6

Colao A, Di Somma C, Spiezia S, Savastano S, Rota F, Savanelli MC, Lombardi G. Growth hormone treatment on atherosclerosis: results of a 5-year open, prospective, controlled study in male patients with severe growth hormone deficiency. *J Clin Endocrinol Metab.* 2008 Sep;93(9):3416-24

# GH, Longevity, and Efficacy of hGH as an Anti Aging Therapy

1. Increases albumin and prolongs survival in patients with chronic liver failure
2. Reduces neoplastic disease, modifies age-related pathology, increases life span
3. HGH is not associated with any increase in mortality.

Li N, Zhou L, Zhang B, Dong P, Lin W, Wang H, Xu R, Ding H. Recombinant human growth hormone **increases albumin and prolongs survival in patients with chronic liver failure**: a pilot open, randomized, and controlled clinical trial. *Dig Liver Dis.* 2008 Jul;40(7):554-9

Sonntag WE, Carter CS, Ikeno Y, Ekenstedt K, Carlson CS, Loeser RF, Chakrabarty S, Lee S, Bennett C, Ingram R, Moore T, Ramsey M. Adult-onset growth hormone and insulin-like growth factor I deficiency **reduces neoplastic disease**, modifies age-related pathology, and **increases life span**. *Endocrinology.* 2005;146(7):2920-32

Khansari DN, Gustad T. Effects of long-term, low-dose growth hormone therapy on immune function and life expectancy of mice. *Mech Ageing Dev.* 1991 Jan;57(1):87-100

Bengtsson BA, Koppeschaar HP, Abs R, Benmarker H, Hernberg-Stahl E, Westberg B, Wilton P, Monson P, Feldt-Rasmussen U, Wuster C. **Growth hormone replacement therapy is not associated with any increase in mortality**. KIMS Study Group. *J Clin Endocrinol Metab.* 1999;84(11):4291-2



# **Myth: GH Deficiency is Only Seen in Patients with Severe Multiple Pituitary Deficiencies since Childhood**

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

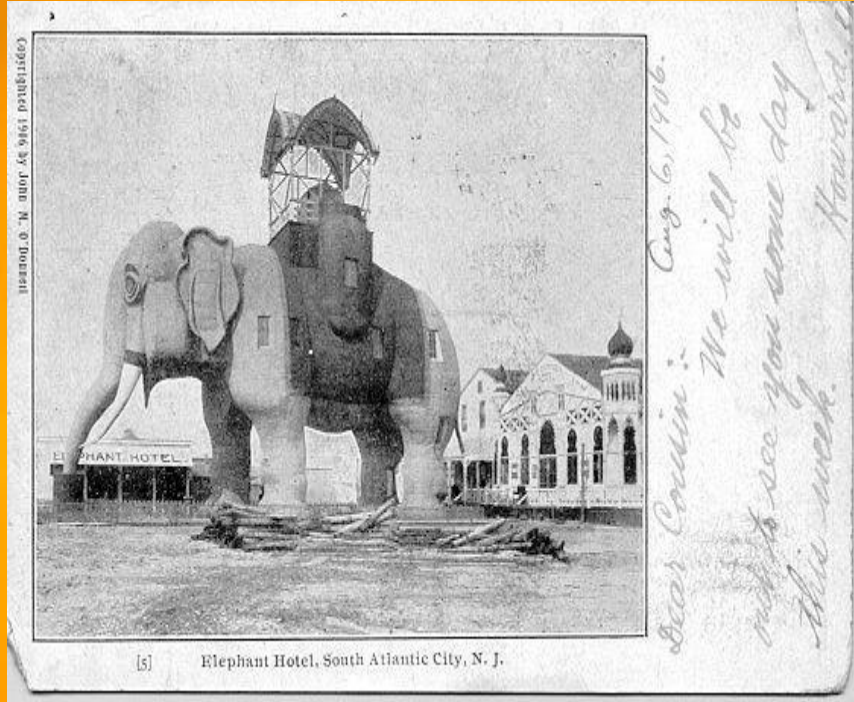
Popovic C et al. Hypopituitarism following traumatic brain injury. Growth Horm IGF Res. 2005 Jun;15(3):177-84.

# Myth: “No Credible Evidence Exists on the Value of Bioidentical Hormones.”

- The long term use of estrogens with or without progestins cause more risks than benefits.
- The long term use of estrogens for the prevention of chronic conditions in postmenopausal women is not recommended

Executive Summary of the AMA House of Delegates 2009 Annual Meeting: Council on Science and Public Health Report. The use of hormones for “anti aging”: A review of efficacy and safety. *Report 5 of council on science and public health (A-09)*. 2009:1-17.

# The Elephant In The Room: Estrogen Causes Cancer



AMA: Estrogen Use in Postmenopausal Women=

**DON'T CROSS THE  
STREAMS**

**IT WOULD BE VERY, VERY  
BAD**

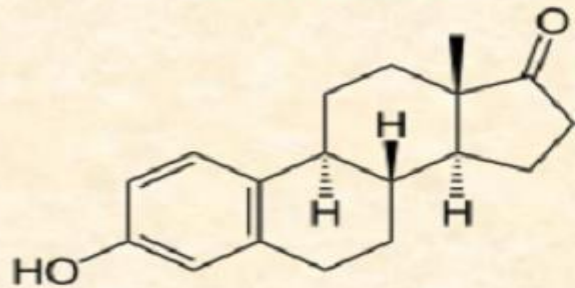
# 2002 WHI Study—“HRT” is Dangerous!

- ✦ Premarin<sup>®</sup> alone given to older postmenopausal women caused adverse effects in the first year (strokes, blood clots)
  - ◆ Oral estrogens cause blood clots, transdermal estradiol does not
- ✦ Adding Provera<sup>®</sup> (Prempro<sup>®</sup>) caused more adverse effects (breast cancers, heart attacks, dementia)
  - ◆ Provera increases breast cancer and vascular inflammation. Progesterone does neither.
- ✦ Thousands of lawsuits pending; drug companies running a legal-protection propaganda campaign to paint all “hormones” as equally dangerous!

# Premarin<sup>®</sup>

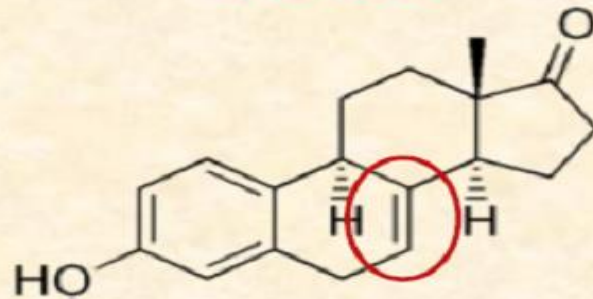
## Conjugated Equine Estrogens

Human



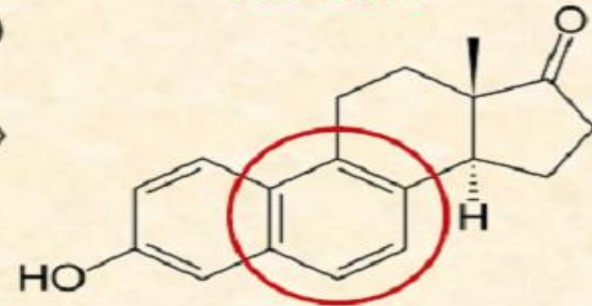
Estrone

Horse



Equilin

Horse



Equilenin

CEE contains at least 10 estrogens, only 3 are human; also contains horse androgens and progestins.

Klein R The Composition of Premarin. 1998 Int J Fertil 43:223

# Women Killers and Hormones

- ✦ Cardiovascular disease (CVD), osteoporosis, dementia and breast cancer are all rare before menopause.
  - ✦ The first 3 are clearly related to estradiol deficiency ; breast cancer is related to progesterone deficiency.
  - ✦ Early removal of ovaries increases risk of heart disease, osteoporosis, and dementia.
- Parker WH, Womens Health (Lond Engl). 2009 Sep;5(5):565-76
- ✦ **Youthful hormone levels protect** women from these diseases.

# Estradiol Restoration

- ✦ Protects against heart disease, dementia and osteoporosis.
- ✦ Improves insulin sensitivity—prevents diabetes
- ✦ Eliminates hot flashes, restores sleep
- ✦ Restores cognitive function and mood
- ✦ Maintains thickness, fullness of skin and hair
- ✦ Maintains genital/pelvic health-helps with vaginal lubrication, incontinence, bladder infections
- ✦ Protects against colon cancer and macular degeneration



# Estradiol vs. Cardiovascular Disease

- ✦ Prevents the oxidation of LDL
- ✦ Improves lipid profile
- ✦ Reduces lipoprotein (a)
- ✦ Reduces blood pressure
- ✦ Improves endothelial function
- ✦ Reduces plaque formation
- ✦ Improves insulin sensitivity

# Myth: E2 Replacement Increases Risk of Clots

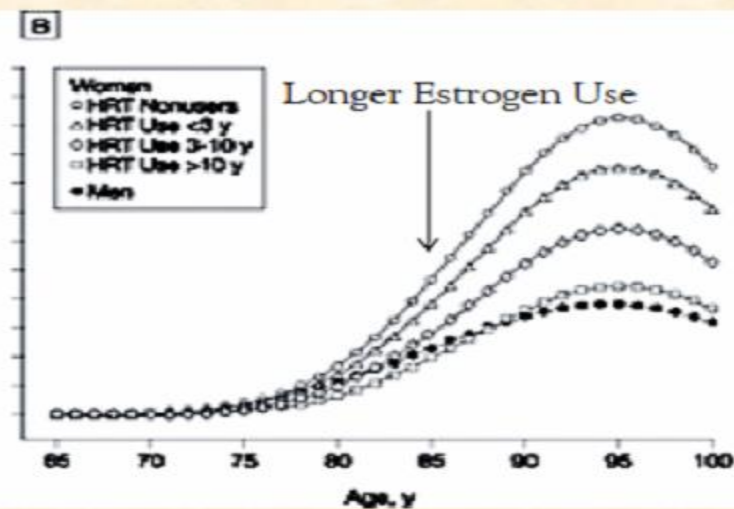
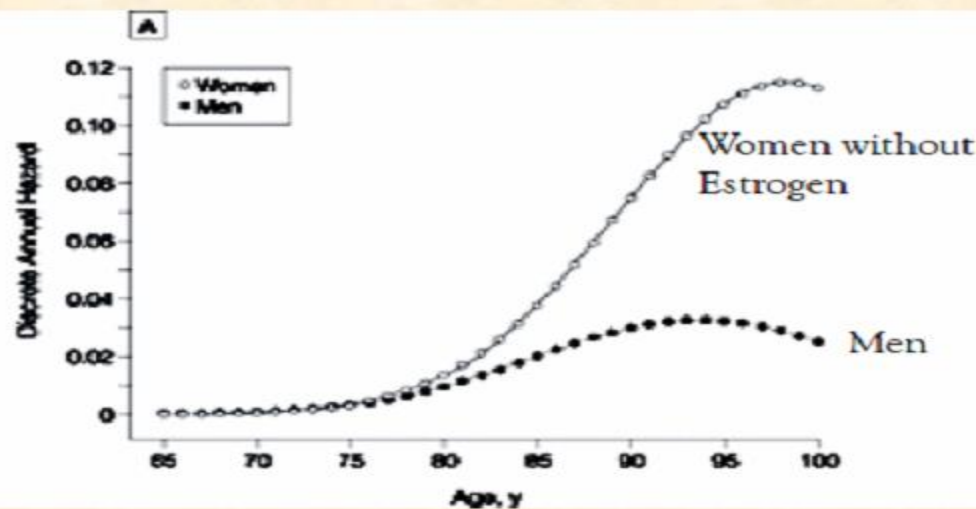
Transdermal E2 does not increase risk of VTE like oral E2

- Cardioprotective, decreased risk of AMI, Decreased risk of T2DM
- Internal Carotid Artery lumen widens by 224% when patient administered Estradiol > 6 months.

(Jonas HA et al, Ann Epidemiol, 1996, 6 (4) : 314-23)

- Mueck AO. Et al. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. Climacteric. 2012 Apr;15 Suppl 1:11-7

# Estrogen Replacement Prevents Alzheimer's Disease



72% used Premarin<sup>®</sup> only


Zandi PP, et al., Cache County Study. JAMA. 2002 Nov 6;288(17):2123-9.

RR 0.46 in Kawas C, The Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517-1521

RR 0.65 Paganini-Hill A, Arch Intern Med 1996;156:2213-2217.

RR 0.4, Tang M-X, Lancet 1996;348:429-432.

# Hormonal Influence on Breast Cancer Risk



Estrogen Excess



Oxidation of E1, E2



Lack of clearance

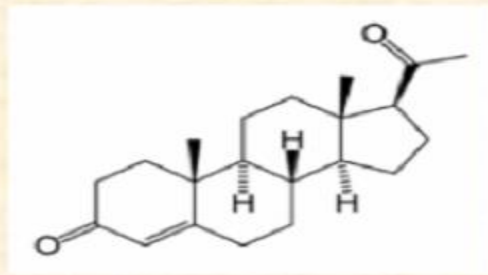
# Estrogen Dominance

- ✦ Allergies
- ✦ Autoimmune diseases
- ✦ Anxiety, moodiness
- ✦ PMS
- ✦ Bloating, fluid retention
- ✦ Fibrocystic breasts
- ✦ Heavy periods
- ✦ Endometriosis
- ✦ Breast cancer
- ✦ Ovarian cancer
- ✦ Uterine cancer
- ✦ Gallstones

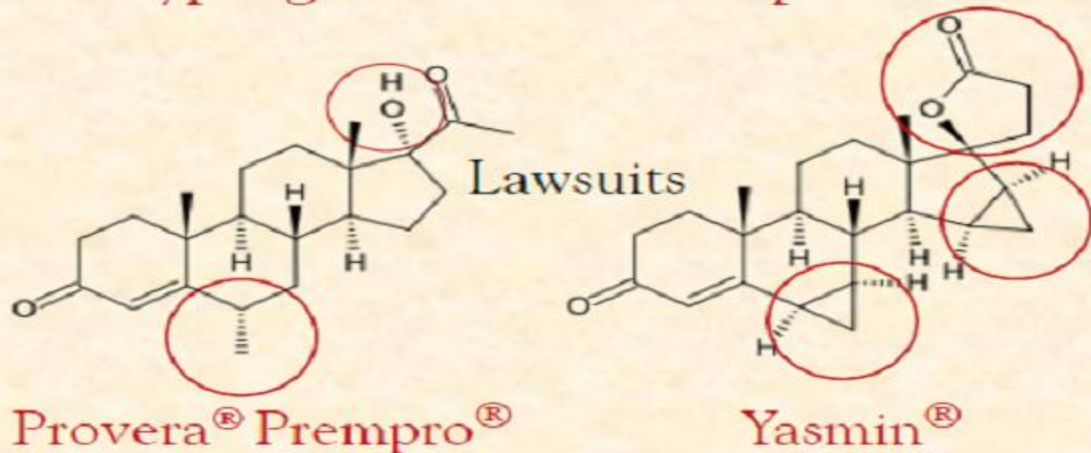
**Progesterone** is the only effective treatment  
for **estrogen dominance**

# Progestins $\neq$ Progesterone

Progesterone  $\neq$  Medroxyprogesterone Drosiprenone



$\neq$



## Confusion:

Progestins are often called “progesterone”, in the media and in scientific papers!

Scientific studies show that:

**Provera<sup>®</sup>**

≠

**Progesterone**

- Causes birth defects
- Can cause depression
- Insomnia, irritability
- Fluid retention
- Raises blood sugar
- Counteracts estrogen-induced arterial dilation
- Worsens lipid profile
- Causes heart attacks
- Increases estrogenic stimulation of breasts
- Causes breast cancer

- Maintains pregnancy
- Improves mood
- Improves sleep
- Diuretic
- No effect on blood sugar
- Maintains estrogen-induced arterial dilation
- Improves lipid profile
- No evidence of ↑ CVD
- Reduces estrogenic stimulation of breasts
- Prevents breast cancer

# Who Needs Progesterone Supplementation?

- ✦ Irregular menstrual cycles
- ✦ No periods—**amenorrhea**
- ✦ Heavy bleeding
- ✦ Fibrocystic breast disease
- ✦ **Endometriosis/adenomyosis**
- ✦ Every woman in **menopause**



# Novel Use of Progesterone: CVA, DM, BP and TBI

1. Progesterone inhibits ischemic brain injury
2. Progesterone reduces infarct volume and improves functional deficits following cerebral ischemic event.
3. Micronized P4 reduces risk of T2DM, does not increase risk of VTE, reduces BP
4. Dose: 8 mg/kg Progesterone best clinical results

• Sayeed I et al. Progesterone inhibits ischemic brain injury in a rat model of permanent middle cerebral artery occlusion. *Restor Neurol Neurosci*. 2007;25(2):151-9

• Ishrat T et al. Effects of progesterone administration on infarct volume and functional deficits following permanent focal cerebral ischemia in rats. *Brain Res*. 2009 Feb 27;1257:94-101

Yousuf S et al. Progesterone in transient ischemic stroke: a dose response study. *Psychopharmacology (Berl)*. 2014 Sep;231(17):3313-23

# **Does Estrogen Cause Breast Cancer?**

**“Pimp” Question for the day:**

**What is the LARGEST study ever done, exploring  
hormone use and breast cancer occurrence?**

**What did it show?**

# **Does Estrogen Cause Breast Cancer?**

**If you said “Women’s Health Initiative”**

**Then you are listening to gossip and propaganda**

**Open A Book, Your Eyes and Pay Attention**

# E3N Vs. WHI

**WHI – no Bioidentical hormone used**

**E3N – (+)Bioidentical and CEE + Progestins were used**

**# of women receiving “hormone” treatment**

**• WHI = 13,816 E3N = 29,420**

**Estrogen alone (CEE) both studies showed increase risk**

**Progestin's in both studies showed GREATER risk**

**BHRT when used in balanced combo – no increased risk**

# WHI

**Vs.**

# E3N

**# of women receiving “hormone” treatment**

**WHI = 13,816**

**WHI – no Bioidentical hormone used**

**•Estrogen alone (CEE) both studies showed increase risk**

**Progestin’s in both studies showed GREATER risk**

**# of women receiving “hormone” treatment**

**E3N = 29,420**

**E3N – Bioidentical and CEE + Progestins used**

**Estrogen alone (CEE) both studies showed increase risk**

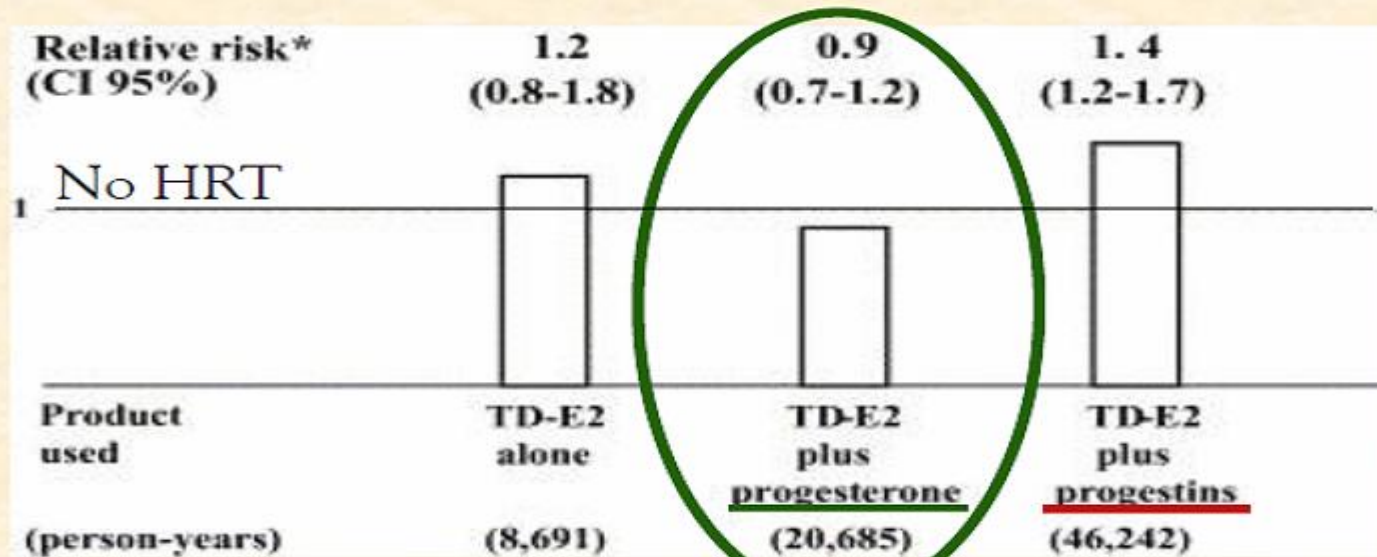
**Progestin’s in both studies showed GREATER risk**

**BHRT When Used in Balanced Combo – no increased risk**

# E3N-EPIC Study

TD-E2 = transdermal estradiol

Cohort study  
55,000 women  
8 years f/u  
c/w WHI--  
16,000, 6 yr. f/u



Int J Cancer. 2005 Apr 10;114(3):448-54

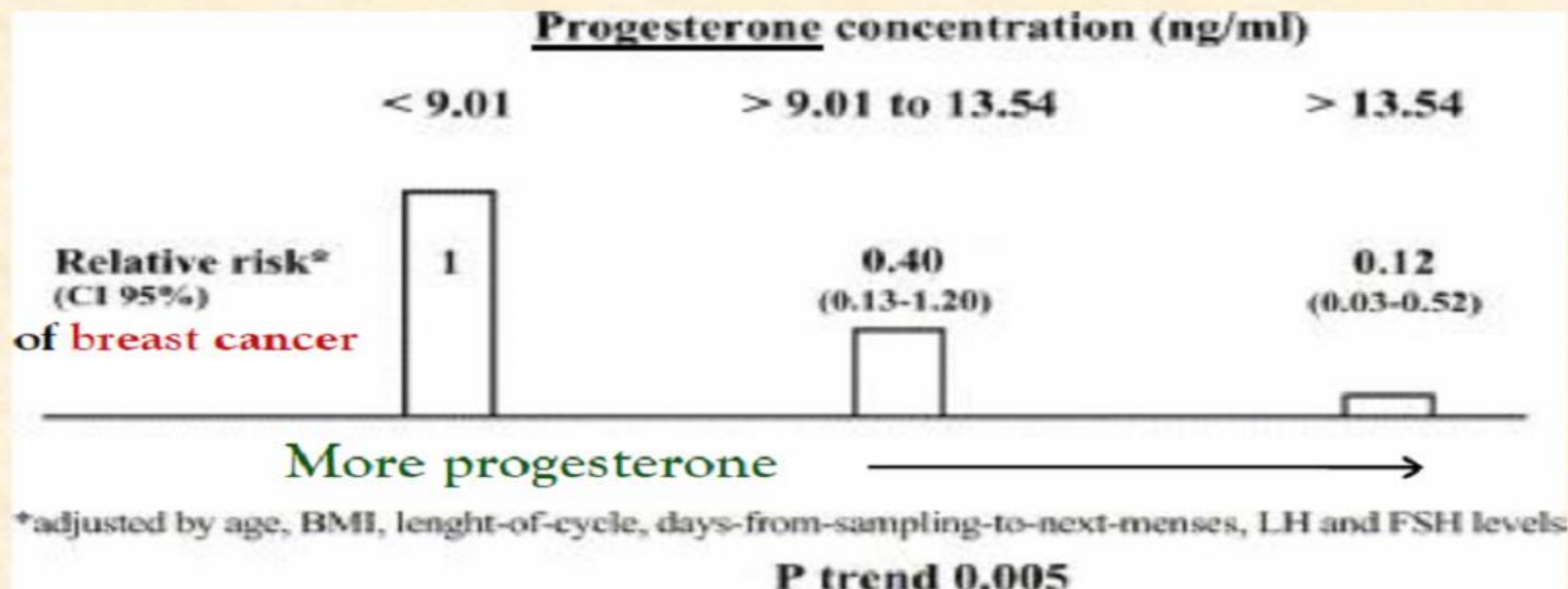
**E2 plus progesterone: no increased risk of breast cancer!**

*Similar study: estradiol + progesterone 0.4; estradiol + synthetic progestin 0.94*

*Espié, Gynecol Endocrinol. 2007 Jul;23(7):391-7.*

## Progesterone vs. Breast Cancer in menstruating women

6,000 women  
5 yr. F/U



**Higher progesterone = lower risk of breast cancer**

**Estrogen, Progesterone and Breast Cancer**

**Never, Ever, Never, Ever Use Estrogen  
without Progesterone**

•

**Never, Ever**

**You All Have to Pinky Swear**



**PINKY**

**SWEAR**

# Myth: The Women's Health Initiative Saved Lives by Demonstrating the Dangers of HRT.

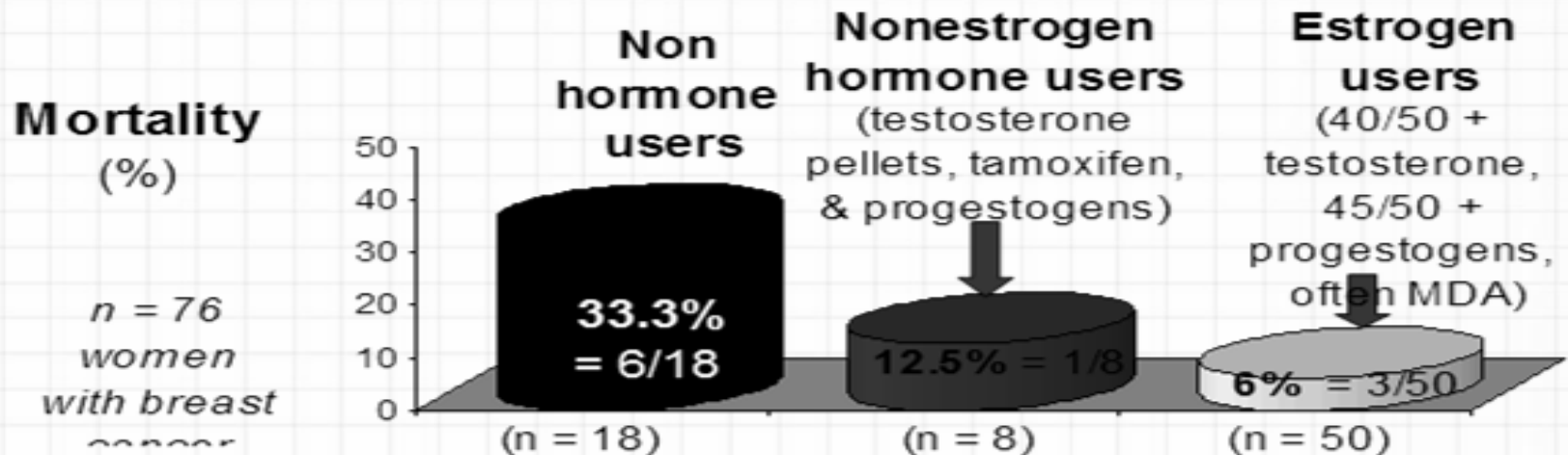
**10 years of randomized treatment**

- Oral HRT (estradiol, norethindrone) early after menopause
- Significantly reduced risk of mortality, heart failure, myocardial infarction

**Without any apparent increase in risk of:** Cancer, venous thromboembolism and stroke.

- Schierbeck et al Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ 2012;345

# HRT after breast cancer => ↓ mortality



n = 76 women with breast cancer

Follow-up: 6 mo. to 10 yrs (mean = 4 yrs 2.5 mo.)      Follow-up: 2 to 11 yrs (mean = 6.0 yrs)      Follow-up 6 mo. to 32 yrs (mean = 6 yr 11.3 mo)

**Figure:** Estrogen replacement does not seem to increase either recurrences or mortality rates. Adding progestogens may even reduce recurrences. **Women with early breast cancer should be offered hormone replacement after full explanation (risks, benef.,controv.)**

Natrajan PK, Soumakis K, Gambrell RD Jr. Estrogen replacement therapy in women with previous breast cancer. *Am J Obstet Gynecol.* 1999;181(2):288-95. Georgia, USA

# Case Hx.-Breast cancer in remission x 2 years

(+) Hormone Sx Do you give hormones? Other options?

- Black cohosh
- Siberian rhubarb extract

Sweedish Sunflower Seeds

- Gabapentin, Clonidine, Paroxetine, Citalopram

Hormone options might include

- Vaginal Estriol to address dryness
- Progesterone to modulate estrogen receptors

# Interventions to Improve Estrogen Balance

- Cruciferous vegetables = DIM & Allium (garlic, onion)
- Iodine – promotes Cyp-1A1 enzyme
- Flax seed meal – lignans (never OIL)
- High Protein Diet, Exercise
- Omega 3 fatty acids, NAC, ALA
- Folic acid, B6, B12 support pathway and promote COMT
- Soy – always organic, whole (not fractionated)
- Kudzu - isoflavone (daidzein)

# **Estrogen Use in the Presence of Breast Cancer**

**Estradiol is not completely contraindicated if Remission x2 years, (-)  
Mammo and clearance pathways have been evaluated**

**Durna, Wren, et al. Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. MJA 2002; 177: 347–351**

**Peters, Fodera, et al. Estrogen replacement therapy after breast cancer: a 12-year follow-up. Ann Surg Oncol. 2001 Dec;8(10):828-32.**

**O'Meara, Rossing, et al. Hormone Replacement Therapy After a Diagnosis of Breast Cancer in Relation to Recurrence and Mortality. Journal of the National Cancer Institute, Vol. 93, No. 10, May 16, 2001**

# Testosterone: For Males Only?

**Testosterone- T** is the most abundant active sex steroid in women throughout the female lifespan.

- Helps maintain muscle and bone strength, restores sex drive and libido.
- Improves overall feeling of well being, reduces “bad” cholesterol.
- Testosterone replacement leads to increase bone and muscle mass.
- Testosterone Deficiency leads to dry eyes, pale faces, thinning of inner 1/3 of eyebrow.

# Myth: Testosterone's Only Role in Women is Sex Drive and Libido

Pre and post-menopausal women, and aging men, experience symptoms of androgen deficiency:

Dysphoric mood (anxiety, irritability, depression)

Sexual dysfunction

Lack of well being

Urinary complaints, incontinence

Physical fatigue

Hot flashes,

Rheumatoid complaints, pain,

Breast pain

Bone loss and Muscle loss

Changes in cognition, Memory loss, Insomnia

**Fact: Testosterone is essential for women's physical and mental health and wellbeing.**



# More Myths: Testosterone and Women

1. **Myth: Testosterone masculinizes females** **Fact:** T does not have a masculinizing effect on females.
2. **Myth: Testosterone causes hoarseness and voice changes.** **Fact:** There is no evidence that T causes hoarseness or irreversible vocal cord changes in women.
3. **Myth: Testosterone causes hair loss.** **Fact:** T increases scalp hair growth in women
4. **Myth: Testosterone causes liver damage.** **Fact:** Non-oral T does not adversely affect the liver or clotting factors.
5. C.J. Wolf, A. Hotchkiss, J.S. Ostby, G.A. LeBlanc, L.E. Gray, Effects of prenatal testosterone propionate on the sexual development of male and female rats: a dose-response study, *Toxicological Sciences*, 65 (2002), pp. 71–86
6. F. Nordenskjöld, S. Fex, Vocal effects of danazol therapy, *Acta Obstetrica et Gynecologica Scandinavica*, 63 (1984), pp. 131–132
7. V. Matilainen, M. Laakso, P. Hirsso, P. Koskela, U. Rajala, S. Keinänen-Kiukaanniemi, Hair loss, insulin resistance, and heredity in middle-aged women. A population-based study, *European Journal of Cardiovascular Risk*, 10 (2003), pp. 227–231
8. D.J. Handelsman, A.J. Conway, C.J. Howe, L. Turner, M.A. Mackey, Establishing the minimum effective dose and additive effects of depot progestin in suppression of human spermatogenesis by a testosterone depot, *Journal of Clinical Endocrinology & Metabolism*, 81 (1996), pp. 4113–4121

# Myth: Testosterone Increases the Risk of Breast Cancer

- 1268 pre and postmenopausal women
- 142/100,000 treatment groups
- 390/100,000 control groups

## Fact: More than double the Risk of Breast Cancer W/O Testosterone

- $P < 0.001$
- Glaser and Dimitrakakis. Reduced Breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: a prospective, observational study. *Maturitas* 2013 Dec;76(4): 342-9

# Myth: “No Credible Evidence Exists on the Value of Bioidentical Hormones.”

- **DHEA as an antiaging supplement shows neither meaningful benefit nor serious adverse effects**

Executive Summary of the AMA House of Delegates 2009 Annual Meeting: Council on Science and Public Health Report. The use of hormones for “anti aging”: A review of efficacy and safety. *Report 5 of council on science and public health (A-09)*. 2009:1-17.

# **DHEA as an Antiaging Supplement shows Neither Meaningful Benefit nor Serious Adverse Effects**

**DHEA => Builds and protects against cortisol catabolism.**

**Decreases visceral & subcutaneous fat in elderly persons.**

**Reduces serum low density lipoprotein levels and body fat.**

**Improved Bone Density**

**Symptoms Relieved: Fatigue, Dry Eyes, Dry Skin**

**Regulates mood, Supports the immune system, Improves Insulin Sensitivity**

Nestler JE, Barlascini CO, Clore JN, Blackard WG. Dehydroepiandrosterone reduces serum low density lipoprotein levels and body fat but does not alter insulin sensitivity in normal men. J Clin Endocrinol Metab. 1988;66(1):57-61

Jankowski CM, Gozansky WS, Kittelson JM, Van Pelt RE, Schwartz RS, Kohrt WM. Increases in bone mineral density in response to oral dehydroepiandrosterone replacement in older adults appear to be mediated by serum estrogens. J Clin Endocrinol Metab. 2008 Dec;93(12):4767-73

# **DHEA as an Antiaging Supplement shows Neither Meaningful Benefit nor Serious Adverse Effects**

**DHEA: Reduces of atherosclerotic plaques; Inhibits Platelet Aggregation (Similar to Aspirin)**

**Inhibits Free Radical Formation-inhibits nuclear factor-kappaB-dependent transcription**

**Improves Sexual Function**

**Improves Skin Tone, Reduce Vulvar Vaginal Atrophy Postmenopausal With No Systemic Side Effects**

Gordon GB, Bush DE, Weisman HF. Reduction of atherosclerosis by administration of dehydroepiandrosterone. A study in the hypercholesterolemic New Zealand white rabbit with aortic intimal injury. *J Clin Invest.* 1988 Aug;82(2):712-20

Jesse RL, Eoesser K, Eich DM, Zhen Y, Hess M, Nestleer JE. Dehydroepiandrosterone Inhibits Human Platelet Aggregation in vitro and in vivo. *Ann NY Acad Sci.* 1995;774:281-90

Iwasaki Y, Asai M, Yoshida M, Nigawara T, Kambayashi M, Nakashima N. Dehydroepiandrosteronesulfate inhibits nuclear factor-kappaB-dependent transcription in hepatocytes, possibly through antioxidant effect. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3449-54

Labrie, et al. *Menopause*, Sept-Oct 2009

## **DHEA as an Antiaging Supplement shows Neither Meaningful Benefit nor Serious Adverse Effects**

### **Low levels associated with:**

- All cause mortality, Cardiovascular mortality, Obesity, Type 2 diabetes**
- Immune dysfunction, Autoimmune disease, Cancer, Hypertension, CV Disease**
- Depression and loss of well-being, Low libido, Erectile dysfunction, Osteoporosis**

Ohlsson C et al. Low Serum Levels of Dehydroepiandrosterone Sulfate Predict All-Cause and Cardiovascular Mortality in Elderly Swedish Men. *J Clin Endocrinol Metab.* 2010 Jul 7.

# **DHEA and Well-Ness (DAWN) Study.**

**Cognitive, life satisfaction and sexual function evaluated**

- **Healthy, normal cognitive**
- **Double blind placebo controlled with 50 mg daily of DHEA**
- **Increased testosterone (60%) and estrogen (40%) in women, not men**
- **No adverse effects**

• Kritz-Silverstein, D et al. Effects of DHEA supplementation on cognitive Function and Quality of Life: The DHEA and Well- Ness (DAWN) Study. J Am Geriatric Soc. 2008 July; 56(7):

# 7 Keto DHEA

**Weight loss without side effects (kalman)**

- **Improves Immune function; Useful in Raynaud's, Autoimmune Dx.**
- **Improves lipids**
- **Improves memory in rats**
- **Dose: 50-200 mg in AM**

Ihler G et al. 7-oxo-DHEA and Raynaud's phenomenon. Med Hypotheses. 2003 Mar;60(3):391-7.



# Myth: “No Credible Evidence Exists of the Value of Bioidentical Hormones.”

- **No evidence of long term cognitive changes in therapeutic doses of “anti aging hormones”**

Executive Summary of the AMA House of Delegates 2009 Annual Meeting: Council on Science and Public Health Report. The use of hormones for “anti aging”: A review of efficacy and safety. *Report 5 of council on science and public health (A-09)*. 2009:1-17.

Insulin

Vaso-  
pressin

Thyroid

IGF-1

Hormone Therapies

that

↑ **Life span**

**Scientific Evidence**

Cortisol

Growth  
hormone

Aldo-  
sterone

Oxytocin

Testo-  
sterone

Estrogens

DHEA

# No Evidence of Long Term Changes with Therapeutic Doses of “Anti Aging Hormones”

1. **Vitamin D**-Infections Dx Protection, CV Disease Risk (<25=2.5x risk), IBS, Ovarian Cancer, Dementia, Keloids
2. **Melatonin**-Free Radical Scavenger, Delays Aging, Anti-inflammatory, inhibits Tumor Growth, Hypertension, Neuroprotective
3. **Telomeres**-Deterioration accelerates aging, Anti neoplastic, Can restore organ function with Telemerase
4. **Pregnenolone, Estrogen, Progesterone, Testosterone, DHEA, Thyroid**-Lessen and/or prevent Psychiatric Disorders including Schizophrenia
5. **Aldosterone**-Hearing Loss, Balance, Tinnitus

## **Do You Agree? There is **No Credible Evidence Exists on the Value of Bioidentical Hormones.****

- **Current evidence does not support the use of testosterone in older men with low testosterone levels.**
- **Evidence of the value of testosterone as an antiaging therapy does not exist.**
- **The long term use of estrogens with or without progestins cause more risks than benefits.**
- **The long term use of estrogens for the prevention of chronic conditions in postmenopausal women is not recommended**
- **Current evidence fails to support the efficacy of hGH as an anti aging therapy**
- **DHEA as an antiaging supplement shows neither meaningful benefit nor serious adverse effects**

# References Cited

In this Presentation 108 Peer Reviewed Studies Are Cited Refuting AMA Paper

In My Thyroid Module (available upon request) we cite 25 studies from peer reviewed medical journals.

**A Grand Total of 133 “Non Credible” Evidence Published In Journals  
Endorsed by A Multitude of Mainstream Medical Societies**

**“Don't get your information from me, folks, or any newscaster. Get it from people with PhD after their names.”**



## **Do You Agree?**

**Myth: There are no studies on bioidentical hormones.**

**Reality: Do you have the Scientific Evidence for BHRT as the “Standard of Care?”**

**Reality: Do You Now Have A Succinct Reference Source to the Age Old Refrain “My Doctor Says BHRT is No Good For Anything.”**

# **You're At The Watering Hole: DRINK!**

**Remaining Slides Contain References to:**

**Vitamin D**

**Melatonin**

**Telomeres**

**Sex Hormones and Psychiatric Disorders**

**Aldosterone**



**Lucy and I Thank You For Inviting Us Today!**



# Fact: Vitamin D and Infectious Disease

**Vitamin D is an Effective in Preventing and Aborting the Spread of Influenza**

**Calcitriol induces production of human cathelicidin (LL-37) a polypeptide antimicrobial**

**LL-37 can fight bacterial and viral infections.**

- Cannell JJ, Zasloff M, Garland CF, Scragg R, Giovannucci E. On the epidemiology of influenza. *Virology*. 2008 Feb 25;5:29.
- Grant WB, Garland CF. The role of vitamin D3 in preventing infections *Age Ageing*. 2008 Jan;37(1):121-2.
- Rosenau MJ. Experiments to determine mode of spread of influenza *JAMA* 1919, 73:311-313
- Mookherjee N et al. Cathelicidins and functional analogues as antiseptics molecules. *Expert Opin Ther Targets*. 2007 Aug;11(8):993-1004.

# Fact: Vitamin D and Infectious Disease

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

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

Study: 1200 IU D<sub>3</sub>/day; Placebo, double blind, controlled

- Relative Risk getting Influenza A
- All treated children in study - .58 Not previously taking Vitamin D - .36 Started preschool > 3 y/o - .36

• Urashima M et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* March 10, 2010;71:10

# Fact: Vitamin D and Cardiovascular Disease

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

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

# No Evidence of Long Term Changes with Therapeutic Doses of “Anti Aging Hormones”

## Vitamin D References

Cannell JJ, Zasloff M, Garland CF, Scragg R, Giovannucci E. On the epidemiology of influenza. *Virology*. 2008 Feb 25;5:29.

Grant WB, Garland CF. The role of vitamin D3 in preventing infections. *Age Ageing*. 2008 Jan;37(1):121-2.

Rosenau MJ. Experiments to determine mode of spread of influenza. *JAMA* 1919, 73:311-313

Urashima M et al. Randomized trial vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* March 10, 2010;71:004.

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

Cannell, JJ. Vitamin D3 Treatment for Irritable Bowel Disease, <https://www.vitamindcouncil.org/blog/vitamin-d3-treatment-for-irritable-bowel-syndrome/>

[Sprake EF, Grant VA, Corfe BM. Vitamin D3 as a novel treatment for irritable bowel syndrome: single case leads to critical analysis of patient-centred data. \*BMJ Case Rep\*. 2012 Dec 13;2012.](#)

[Zhang X1, Nicosia SY, Bai W](#), Vitamin D receptor is a novel drug target for ovarian cancer treatment. [Curr Cancer Drug Targets](#). 2006 May;6(3):229-44.

G.Y. Zhang; T. Cheng; Q. Luan; T. Liao; C.L. Nie; X. Zheng; X.G. Xie; W.Y. Gao, Vitamin D: A Novel Therapeutic Approach for Keloid, *in vitro* Analysis *The British Journal of Dermatology*. 2011;164(4):729-737.

# **Myth: Melatonin is Only for Sleep**

**Fact: Manages circadian rhythm of inner clock-Controls sleep wake cycle**

**Low Melatonin associated with:**

- **Alzheimer's**
- **CV disease**
- **Insulin resistance**
- **Cancer**
- **Infectious disease**
- **Immune dysfunction**

# **Fact: Melatonin is a Potent Free Radical Scavenger**

- 1. More effective than Glutathione or Vitamin E**
- 2. Protects Lipids, Protein, DNA, and against pro-oxidation effect of Fe**
- 3. Protects DNA, Mitochondria from Injury,**
- 4. Protects Against Ionizing Radiation**
- 5. Aids Reperfusion of Ischemic Tissue**
- 6. Inhibits tumor growth**
- 7. Counteracts stress induced immunosuppression**
- 8. Increases in CD4 cells, natural killer cells; Activates cytokine system,**
- 9. Decreases pro-inflammatory cytokines**

# **Fact: Melatonin Delays Aging**

**Stimulates under basal immunosuppressive conditions**

**Anti-inflammatory under exacerbated immune response**

**Inflammation or autoimmune conditions.**

**Binds Free Radicals (Antioxidant)**

**Prolonged survival mice from 23.8 to 28.1 months; preserved youthful state**

Pierpaoli W, Regelson W. Pineal control of aging: effect of melatonin and pineal grafting on aging mice. Proc Natl Acad.

Carrillo-Vico A et al. Melatonin: buffering the immune system. Int J Mol Sci. 2013 Apr 22;14(4):8638-83.



# **Fact: Melatonin Delays Aging, Decreases Visceral Fat**

## **Melatonin prevented mitochondrial impairment associated with aging**

Carretero, M et al. Long-term melatonin administration protects brain mitochondria from aging. *Journal of Pineal Research*. 47(2):192-200, September 2009.

## **Daily melatonin administration at middle age suppressed male rat**

**intraabdominal visceral fat and plasma insulin to youthful levels.”**

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

# Melatonin as an Analgesic

**Chronobiotic, antioxidant, antihypertensive, anxiolytic and sedative**

- **Potent analgesic effects in a dose dependent manner.**
- **Fibromyalgia, irritable bowel syndrome, migraine**
- **Mechanism: melatonin receptors, opioid  $\mu$ -receptors, GABA-B receptors, better**

**sleep**

• **Wilhelmsen M et al. Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies. J Pineal Res. 2011 Apr 18**

# Melatonin and Cancer

- **Inhibits tumor growth in humans; Anti-mitotic activity, Downregulate activity of receptors**
- **Decreased Estrogen binding to cells in breast ca; Enhanced Immune Response, Free Radical scavenging, Anti-angiogenesis**
- **Improved outcome in glioblastoma, malignant melanoma, breast cancer**
  - **Used along with chemo, radiation, Protects against chemo/radiation toxicity**
  - **Large doses used 20-700 mg /day**

# Melatonin and Cancer

370 patient, with advanced solid CA, 20 mg orally at bedtime

- Chemotherapy alone vs chemo/melatonin
- Significant regression rate and survival in combination group
- Lissoni P. Biochemotherapy with standard chemotherapies plus the pineal hormone melatonin in the treatment of advanced solid neoplasms. Pathol Biol (Paris). 2007 Apr-May;55(3-4):201-4

10 adjunctive or sole treatment studies of melatonin and solid tumors 1992-2003

- Melatonin reduced the risk of death at 1 year Relative risk: 0.66
- Conclusion: Great potential for melatonin and cancer therapy

Mills Edward et al. Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis Journal of Pineal Research. 39(4):360-366, November 2005.

# Melatonin Facts

**Protects Against:**

**Hypertension**

**B-Amyloid Formation**

**Stimulates Neural Stem Cell Proliferation in Hypoxic State**

**Counteracts Neurodegenerative Processes of Brain**

Simko, F et al. Potential roles of melatonin and chronotherapy among the new trends in hypertension treatment. *Journal of Pineal Research*. 47(2):127-133, September 2009

Escames, G et al. The Role of Mitochondria in Brain Aging and the Effects of Melatonin *Current Neuropharmacology*, 2010, 8, 182-193

# Melatonin Administration

**1. Low dose lozenge -2-3 hours before sleep: 0.3 mg SL**

**1. Combine 1-2 hours before bedtime:**

**Melatonin 3-30 mg**

**Magnesium Taurate 200-400 mg**

**Vitamin D 2000-5000 IU**

# **AMA: “No Credible Evidence Exists of the Value of Bioidentical Hormones.”**

**Fact: Hormone optimization prevents Telomere shortening**

## **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

# Telomeres

**Telomere length is dynamic and results from balance between:**

- Erosion (Blackburn, 1991)**
- Oxidative stress (Von Zglinicki, 2000)**
- Restoration through telomerase activity, (Greider and Blackburn, 1985)**
- Telomere length remains a key feature that indicates the viability of a cell.**



# Telomeres

## Protects genomic integrity

- Prevents chromosome fusion
- Prevent genomic instability
- Necessary for cellular replication
- Protection from cellular senescence
- Protection from DNA mutations that can lead to cancer

• Sahin E, Depinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. *Nature*. 2010 Mar 25;464(7288):520

# Telomeres

Reverses some aspects of aging in old mice

- Brain, spleen and reproductive organs were rejuvenated
- Resulting in increased neurons and new viable sperm cells.
- Sense of smell returned.
- None of the mice developed cancer.

- Jaskelioff M et al. Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. *Nature*. 2011 Jan 6;469(7328):102-6.

# Telomere Length Determines Cellular Age

**Somatic cells– Make up > 99% of the cells in the adult body – Have little or no telomerase and telomeres shorten as we age**

- **Telomere Length Shortening:**

- **Conception: Telomeres start out 15,000 base pairs (bp) long.**

- **By Birth the embryo has divided so many times that telomere length is down to 10,000 bp.**

- **Over the rest of our lifetime we lose another 5,000 to 7,000 bp.**

- **When telomere length gets to 3-5,000 bp, the genome is no longer protected from mutations, the cell can no longer divide, becomes senescent, metabolism slows down, and the cell dies.**

**Senescence-Associated Secretory Phenotype - inflammation**

# Telomeres Shorten When Cells Divide

**"Short telomeres appear to be associated with increased risks for human bladder, head, neck, lung, and renal cell cancers"**

- **Fraternal twins with the shortest telomeres had a three times greater risk of death during the follow-up period than their co-twins with the longest telomere measurements**

- **Wu X et al. Telomere Dysfunction: A Potential Cancer Predisposition Factor (2003) J National Cancer Inst. 2003 Aug 20;95(16)1211-18.**
- **Johansson, S et al. Telomere length predicts survival independent of genetic influences (2007) Aging Cell, 2007. 130**

# Chronic Diseases are Telomere Syndromes?

- **Short telomeres are involved with almost all the diseases associated with aging**
- **Root cause of the disease?**

Calado RT et al. Telomere diseases N Engl J Med. 2009 Dec 10;361(24): 2353-65. 131

# What Can Be Done To Limit Telomere Shortening?

## 1. Limit inflammation

- a. Limit free radical damage
- b. Limit toxic environmental exposure

## 2. Restore Youthful Hormone Levels

## 3. Activate Telomerase

## 4. Lifestyle – Nutrition, Exercise, stress reduction, meditation

## 5. Nutraceuticals-Omega 3's, resveratrol, Vitamin D

# Limit Inflammation

## Mediterranean Diet = Longer Telomeres

- **Conclusion** In this large study, greater adherence to the Mediterranean diet was associated with longer telomeres.  $P < .004$

Marta Crous-Bou et al. Mediterranean diet and telomere length in Nurses' Health Study: population based cohort study BMJ 2014; 349

## Exercise-VO<sub>2</sub>max associated with telomere length (3x/wk)

- Østhus IB et al. Telomere length and long-term endurance exercise: does exercise training affect biological age? A pilot study. PLoS One. 2012;7(12).
- Kim JH et al. Habitual physical exercise has beneficial effects on telomere length in postmenopausal women. Menopause. 2012Oct;19(10):1109-15.

# Limit Inflammation

**Stress Reduction**-Correlations between improvements in psychological distress, eating behavior, and metabolic health and increases in telomerase activity.

- Telomerase activity may be in part regulated by levels of both psychological and metabolic stress.
- Changes in stress, eating, and metabolic factors are related to changes in telomerase activity in a randomized mindfulness intervention pilot study.

Daubenmier J et al Psychoneuroendocrinology. 2012 Jul;37(7):917-28.



# Limit Inflammation

## Cortisol and Telomeres

Greater cortisol responses to acute stressor associated with shorter telomeres

- Long-term consequences of frequent high stress reactivity include accelerated telomere shortening.

Tomiyama AJ et al. Does cellular aging relate to patterns of allostasis? An examination of basal and stress reactive HPA axis activity and telomere length. *Physiol Behav.* 2012 Apr 12

## Depression associated with shortened telomeres.

- Shorter telomeres persist in individuals with lifetime depression
- CD8+ cytotoxic T cells and CD20+ B cells are particularly affected in depression.

Alexander Karampatziakis et al. Telomere shortening in leukocyte subpopulations in depression. *BMC Psychiatry* 2014, 14:192

# Hormones and Telomeres

Androgen and Estrogen increase telomerase activity

- No effect from Cortisol
- Tamoxifen decreases telomerase activity

Rodrigo T. Calado et al. Sex hormones, acting on the TERT gene, increase telomerase activity in human primary hematopoietic cells. *Blood*. Sep 10, 2009; 114(11): 2236–2243

# Lengthen Telomeres

**Activate Telomerase** – an endogenous enzyme that stabilizes telomere length by adding DNA repeats (TTAGGG ) onto the telomeric ends of the chromosomes, compensating for the erosion of telomeres when cells divide.

# Therapeutic Uses of Hormones in Psychiatry

- Journal “Psychiatric Annals” devoted entire issue in 2000;30(2)1-76
  - Reviewed Male Hypogonadism and Therapeutic Implications in Psychiatry
  - Effects of Estrogens on Mood and Cognition in Aging Women
  - The role of DHEA in Psychiatry
  - Use of Thyroid Hormones in Mood Disorders
  - Antigluccorticoid Medication for the Treatment of Depression

## Severe hearing loss

=> -50 % serum aldosterone within ref. range

**SUBJECTS:** 47 healthy men & women, ages of 58 & 84

**RESULTS:** people + severe hearing loss =>

- average about 1/2 serum aldosterone as their counterparts with normal hearing.
- aldosterone levels found in all the participants = considered normal
- direct link between blood levels of aldosterone & the ability of people to hear normally as they age. Depressed hormone levels => hurt hearing both in the inner ear & the part of the brain used for hearing

"The inner ear is es.sensitive to any disruption in potassium levels," said Robert D. Frisina, Ph.D., professor of Otolaryngology at the University of Rochester Medical Center and an adjunct professor at Rochester Institute of Technology. "We know that **potassium levels in the inner ear seem to decrease as we age and that these falling levels play a role in age-related hearing loss**, and we also know that **blood levels of aldosterone generally decrease with age.**"

**Need More Info?**

**Dr. William Clearfield**

**Ph:775 359 1222**

**Fax:888 977 3503**

**[doctrbil9@gmail.com](mailto:doctrbil9@gmail.com)**

**See Us at OMED on Oct 8, 2017 in Philadelphia  
We will be presenting a 1 day workshop on BHRT**