Dzugan PhysioLogic

Workshop

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Bioidentical Hormones in Clinical Practice:
How to do? Potential problems and safety.

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The practical aspects of Hormonorestorative therapy

W.W.W.

What? When? Where?

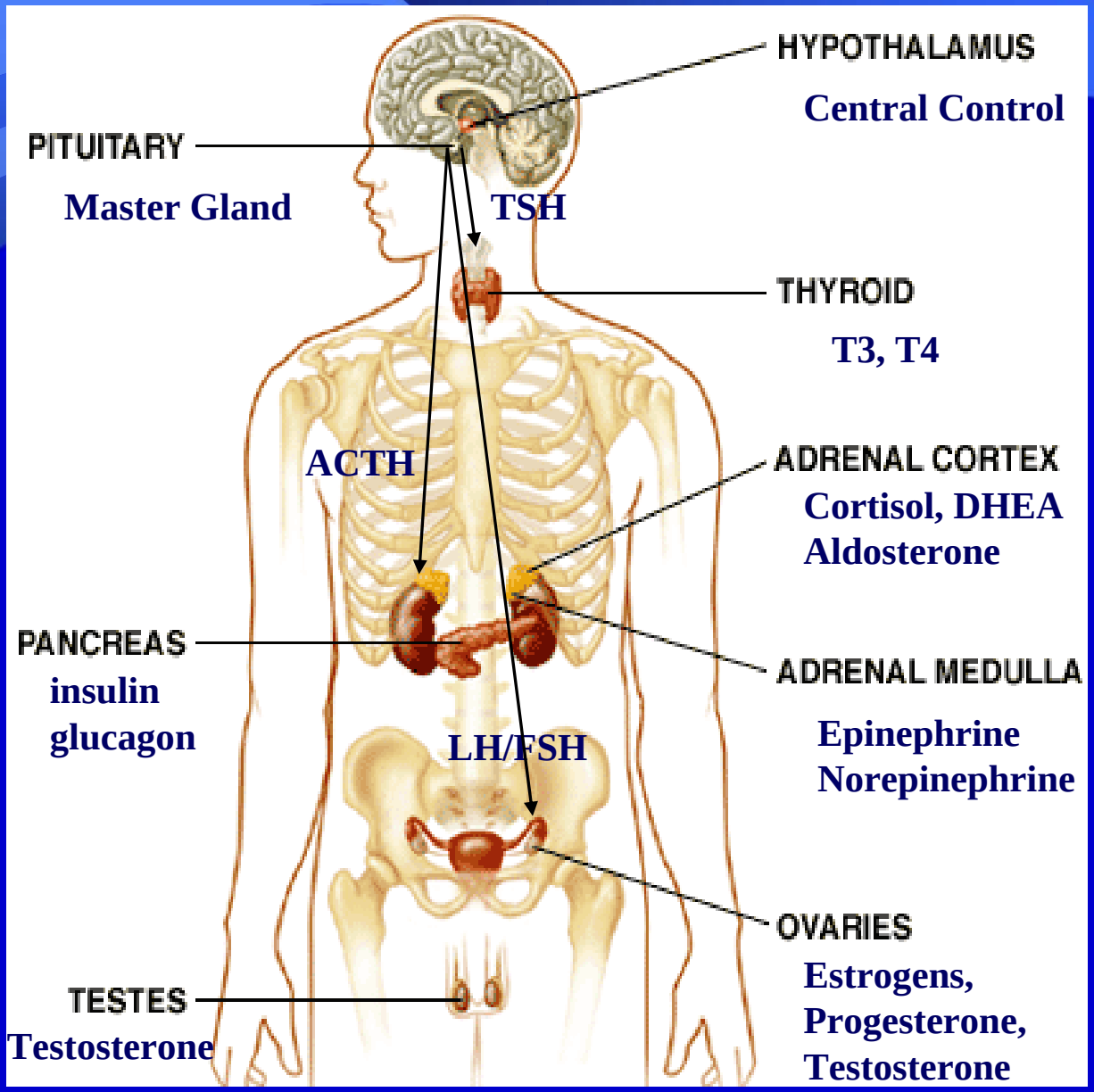
The practical aspects of Hormonorestorative therapy

W.W.W.

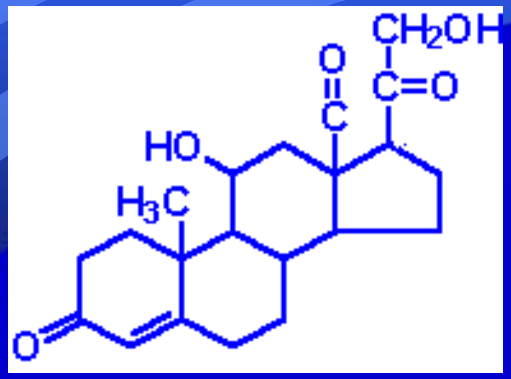
Basic information

What are Hormones?

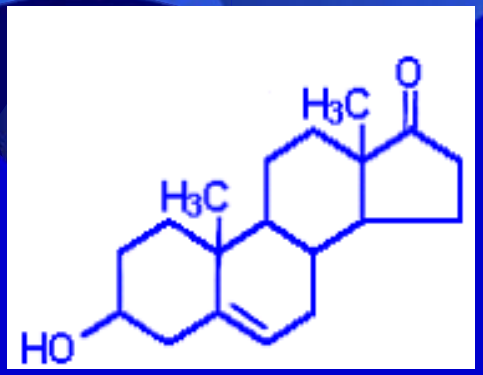
- The most powerful molecules in biology
- Parts of our integrated neuro-endocrine-immune system
- Travel via blood to all cells
- Control cells' proliferation, differentiation, protein synthesis, metabolic rate, etc.
- Optimal levels and effects are essential for health and quality of life


HYPOTHALAMUS
Central Control
PITUITARY
Master Gland
TSH
THYROID
T3, T4
ACTH
ADRENAL CORTEX
Cortisol, DHEA
Aldosterone
PANCREAS
insulin
glucagon
ADRENAL MEDULLA
Epinephrine
Norepinephrine
LH/FSH
OVARIES
Estrogens,
Progesterone,
Testosterone
TESTES
Testosterone

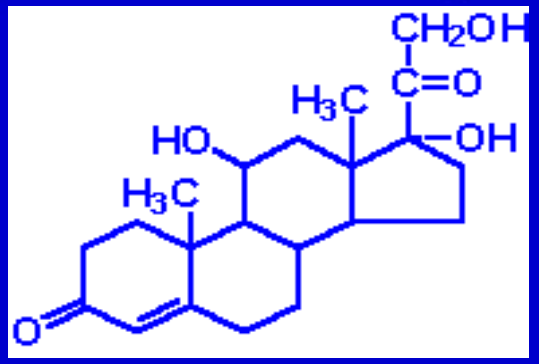
Steroid Hormones



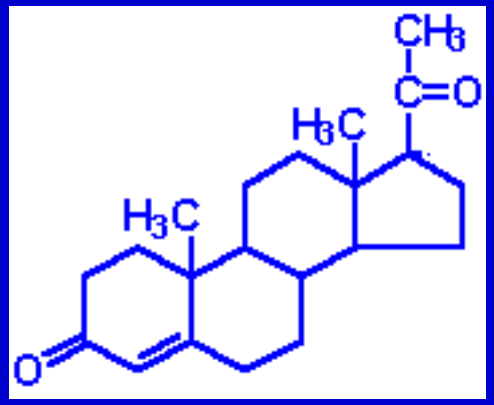
Aldosterone



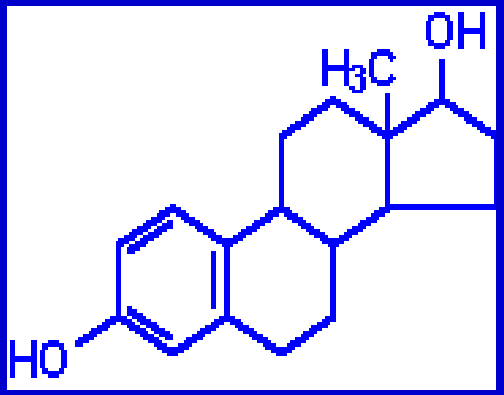
DHEA



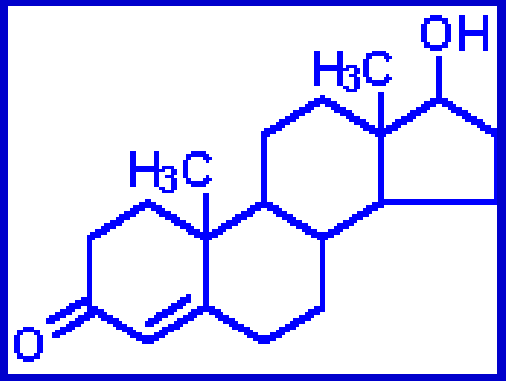
Cortisol



Progesterone



Estradiol



Testosterone

Bioidentical Hormones are not Drugs

- correct molecular structure - same action at receptors, same metabolism and elimination.
- proper dose determined by blood tests
- non-toxic:
  - no side effects, only effects
  - no interactions with drugs
  - no allergic reactions
- safe in youthful physiological levels/balance
- negative effects?? – only with excessive dose, wrong delivery method, or imbalance with other hormones

“Hormone deficiency diseases” require the proper prevention and treatment of these “diseases” is a hormone restoration.

Bioidentical Hormone Restoration

If a hormone is low, restore optimal levels!

- **type 1 Diabetes: bioidentical insulin**
- **hypothyroidism: bioidentical T4 and T3 (Armour Thyroid)**
- **growth hormone deficiency: bioidentical GH**
- **adrenal insufficiency: cortisol (hydrocortisone)**

But… menopause, andropause, autoimmune disease, etc…

non-bioidentical: Premarin, Provera, methyltestosterone, etc?!!!!

How do we diagnose deficiency?

How do we decide which dose is right?

What do we do about deficiencies due to aging?

Reference Ranges

- normal ranges are not optimal ranges
- include 95% of tested population of the same aging group
- persons were not screened for optimal health
- only few tests use diagnostic ranges (glucose, cholesterol)
- physicians assume that all ranges are diagnostic, but it is not the case
- hormonal ranges are huge!

  pregnenolone 10- 230 (female) and 10-200 (man)

  DHEAS 65-380 (female) and 280-640 (man)

"Normal result" ⟶ diagnosis: no hormonal deficiency ⟶ Rx: drugs

- **Optimal range based on healthy persons and on physiological research**
- **Individualized diagnosis and treatment must be used!**

Kratzsch J, Fiedler GM, Leichtle A, Brügel M, Buchbinder S, Otto L, Sabri O, Matthes G, Thiery J. New reference intervals for thyrotropin and thyroid hormones based on National Academy of Clinical Biochemistry criteria and regular ultrasonography of the thyroid. Clin Chem. 2005 Aug;51(8):1480-6. Epub 2005 Jun 16.

Hormonal physiology

- we are born with hormones
- our hormone levels elevate at puberty
- the level of hormones is stable between age 20-30
- hormones gradually decline after age 35
- hormonal decline leads to loss of normal physiology control or body surveillance

Hormonal physiology (cont.)

- loss of surveillance control leads to symptoms and disease
- loss of surveillance is hormonally driven
- loss of surveillance can be hormonally corrected
- hormonorestoration is a key to successful systemic therapy of diseases of aging treated with traditional therapy

Hormonorestorative therapy

In 1996 we employed the term hormonorestorative therapy (HT) into our practice for the regimen that was used for our patients.

Hormonorestorative therapy **is the multi-hormonal therapy with the use of a chemically identical formula to human hormones** and is administered in physiologic ratios and dosages that simulate the natural human production cycle and allows to restore the optimal level of hormones.

The goal of hormonorestorative therapy:

to restore vital forces that control the optimal physiology to treat the patient, not the illnesses that have befallen them

- most diseases represent a manifestation of a long established derangement of vital forces
- the derangement of the vital force had happened due to a deficit of the surveillance control system resulting in an abnormality of hormonal metabolism
- **the vital force is hormonal health and physiological balance**

Safety of hormones

- hormonorestorative therapy is designed to restore your hormonal levels to the optimum

- nothing negative is yet to be published on the bio-identical hormones that we use

Terminology confusion:

- **HRT** - mainly used in the context of estrogen or estrogen/progestin replacement therapy
- **natural HRT**
  - not clear; is it “natural” for human being or “natural” for nature?
  - natural means not human-made
  - may refer to phytoestrogens or equine estrogens (natural for horse)
- the term “**bio-identical to the human hormones**” is unambiguous, but just “**bio-identical hormones**” is confusing

Terminology confusion:

- the term “bioidentical HRT” refers to the use of hormones that are exact copies of endogenous human hormones, including estriol, estradiol, and progesterone, as opposed to synthetic versions with different chemical structures or nonhuman versions

Terminology confusion:

- Bioidentical hormones are also often referred to as "natural hormones," which can be confusing because bioidentical hormones are synthesized, while some estrogens from a natural source, such as equine urine, are not considered bioidentical because many of their components are foreign to the human body

Definitions:

- **Bioidentical hormones** have a chemical structure identical to human hormones but are chemically synthesized, such as progesterone, estriol, and estradiol.

- **Nonbioidentical hormones** are not structurally identical to human hormones and may either be chemically synthesized, such as MPA, or derived from a nonhuman source, such as CEE.

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (Estradiol, Estriol, and Progesterone) safer or more efficacious than commonly used synthetic versions in Hormone Replacement Therapy? Postgrad Med 2009;121(1):1-13.

Definitions:

- **Nonbioidentical hormones are not identical in STRUCTURE or ACTIVITY to the hormones naturally produced within the body.**

Terminology confusion (cont.):

"Bios" from Greek - LIFE

"Anthropos" (Greek) - meaning HUMAN

Maybe the term **anthropo-identical hormones is better**? It is a more restrictive term than bio-identical.

- **"anthropo-identical restoration"** means that:
- ✓ the chemical structure of the hormones employed is identical to human hormones
- ✓ normal ratios between hormones inside of each hormonal group is maintained

Problems with conventional HRT

- the majority of studies were performed with only one or two agents
- no physiological cyclicity
- standard dose (CEE/MPA or other HRT were not designed to be optimal for the physiological/endocrinological status of all women over the age of 50)
- no bio-identical restoration attempted (different estrogens or progestins are not recognized in the same way in all cells and do not have equivalent function)
- serum hormonal levels not used clinically

Problems with conventional HRT (cont.)

- mostly, oral route of administration (in 2003, an estimated 80% of prescriptions dispensed in the US for HRT were estrogen +/- progestin formulation delivered orally, and the majority of these contained CEE as the estrogen component)
- ignorance of anamnesis vitae (the average age of the participants at entry was 63 (with nearly 70% between ages of 60 and 79) and, for a majority of the women, estrogen deficiency had been present for more than a decade)

Turgeon JL, Carr MC, Maki PM, et al. Complex actions of sex steroids in adipose tissue, the cardiovascular system, and brain: Insights from basic science and clinical studies. Endocr Rev. 2006 Oct;27(6):575-605.

Premarin (conjugated equine estrogens) is derived from the urine of pregnant horses and comprised of at least 10 different estrogens, as well as some androgens and progestins. Most prominent estrogen that is unique to the horse is equilin.
The common **synthetic progestins** used in HRT can be divided into those structurally related to progesterone (MPA and nomegestrol) or testosterone (norethindrone and levonorgestrel)

Bioidentical hormones

- not too long ago, the gold standard of insulin therapy was insulin derived from pigs. Today, that type of insulin is not available because bioidentical human insulin, which is more effective, is used.
- today, bioidentical hormones seem more effective and more safe for patients
- because the use of bioidentical hormones in women is in its infancy, few clinical trials have been conducted on that topic
- until the results of such studies have been published, little valid information on the use of bioidentical hormones will be available

Conventional HRT vs bioidentical

- one major reason for a lack of conclusive data is that, until recently, progestogens were lumped together because of a commonly held belief that different forms of progestogens would have identical physiological effects and risks, because they all mediate effects via the same (progesterone) receptor

- this view also applies to the different forms of estrogen, which are commonly grouped together and referred to as estrogen replacement therapy

The practical aspects of Hormonorestorative therapy

W.W.W.

What?

Basic Hormonorestorative therapy

HT includes a combination of several bio-identical hormones:

- pregnenolone
- dehydroepiandrosterone (DHEA)
- triestrogen (women)
- progesterone
- testosterone
- compounded/Armour thyroid
- melatonin
- hydrocortisone
- aldosterone

Basic Hormonorestorative therapy

- it is clear as to what we should use when we talk about the majority of hormones with the exception of estrogens and progesterone

Crucial Remarks

New Paradigm: Physiology optimization based on Endocrinology restoration

- HPA control and endocrine glands deteriorate with age
- deterioration of body surveillance system decreases a regulation of hormones for optimal physiology
- hormonal deficiencies or imbalances are dangerous for health
- the restoration of optimal hormonal levels is crucial for:
  - treatment of diseases related to error of physiology
  - prevention of disease
  - improvement of quality of life

Crucial Remarks

- due to a natural decline in production, estrogens restoration is medically necessary for optimal body function
- estrogens restoration is safe if route of administration is transdermal and accompanied by progesterone
- pregnenolone, DHEA, cortisol, progesterone, testosterone and aldosterone (if necessary) must be restored to youthful levels

Age - Hormones

- at menopause, the levels of estrogen, progesterone, and testosterone, which are the principal hormones normally secreted by the premenopausal ovary, decrease markedly
- the level of progesterone decreases first as a result of the decline in ovarian function that can begin during the third decade of life in women
- that decrease of progesterone is followed by a decline in estrogen and finally in testosterone

Hargrove JT, Eisenberg E. Menopause. Med Clin North Am. 1995 Nov;79(6):1337-56.

Age – Hormones (cont.)

- by the age of 50 years, women experience a 30% decrease in the level of estrogen, and during menopause a sharp decrease and fluctuations in the estrogen level occur.
- in contrast, a decrease of up to 75% in the level of progesterone occurs in women from the age of 35 to 50, after which the progesterone level continues to decrease.

Reiss U. Natural Hormone Balance. New York:Pocket Books (Simon & Schulster); 2001:6

Crucial Remarks (cont.)

- problems caused by hormone substitution have not been seen after hormonorestoration
- it is hard to comprehend the viewpoint of those who oppose bioidentical restoration with all the evidence presented in favor of the contrary

We restore not just sex hormones!

- and… “sex hormones” are not just Sex Hormones
- physiology requires ALL hormones for the normal growth and function of all organs and systems:

  - nervous system
  - cardiovascular system
  - immune system
  - integumentary system
  - skeletal system
  - muscular system
  - endocrine system
  - etc

Not Just “Sex Hormones”

- estrogens, progesterone, testosterone and DHEA are required for the function, growth, and maintenance, of all tissues in both sexes!
- maintain brain function and health - neurosteroids affect mood, cognition, memory, pain, etc.
- maintain the immune system

Not Just "Sex Hormones" (cont.)

- maintain connective tissue: skin, hair, bone, muscle
- improve insulin sensitivity: prevent diabetes, fatty liver
- reduce blood pressure - improve endothelial function
- prevent atherosclerosis (plaques in arteries)

Hormones decline with aging

- we are genetically programmed to die
- hormones start to decline after age 30
- cardiovascular diseases, cancers, diabetes type II, etc. occur when hormones declined
- these diseases frequently develop in individuals with low level of hormones – normal level of steroid hormones protect people from this conditions
- cardiovascular diseases, breast cancer, and osteoporosis are rare before menopause – they are clearly associated with a hormonal imbalance

The goal of hormonorestorative therapy is:

- treatment of diseases
- prevention of disease
- improvement of quality of life!

Our body needs hormones for the optimal health.

The partial restoration of hormone deficiencies can lead to imbalances and could be a harmful.

Cortisol

- irrational fear of cortisol supplementation
- one of the basic agent of the hormonal system
- bioidentical hormone with anti-inflammatory effect
- stress, inflammation, and diseases require more cortisol
- excess of cortisol can be cause of hypertension, diabetes type II, osteoporosis, obesity
- deficiency of cortisol is the cause of fatigue, inflammation, aches and pain, depression, anxiety, hypoglycemia, insomnia, etc.
- prevents and controls autoimmune diseases and allergies

Cortisol (cont.)

- **stressful/inflammatory conditions activate the immune system and subsequently the hypothalamic-pituitary-adrenal (HPA) axis through the central and peripheral production of cytokines such as IL-6 and TNF-alpha.**

- **a relative adrenal hypofunction has been recently claimed to play a causative role in the pathogenesis of autoimmune/inflammatory diseases such as rheumatoid arthritis (RA) and polymyalgia rheumatica (PMR).**

Cutolo M, Foppiani L, Minuto F. Hypothalamic-pituitary-adrenal axis impairment in the pathogenesis of rheumatoid arthritis and polymyalgia rheumatica. J Endocrinol Invest. 2002;25(10 Suppl):19-23.

Cortisol (cont.)

- the clinical and biochemical improvement observed after glucocorticoid therapy in patient with rheumatoid arthritis (RA) and polymyalgia rheumatica (PMR) , may be attributed to a direct dampening of pro-inflammatory factors as well as to the restoration of the steroid milieu.

- given its multifaceted properties, including the ability to counteract the negative side effects of glucocorticoids, the therapeutical administration of DHEA might be considered in these pathologies, provided its safety is proved.

Cutolo M, Foppiani L, Minuto F. Hypothalamic-pituitary-adrenal axis impairment in the pathogenesis of rheumatoid arthritis and polymyalgia rheumatica. J Endocrinol Invest. 2002;25(10 Suppl):19-23.

Cortisol Deficiency

- fatigue
- depression
- aches & pains
- anxiety, irritability
- can’t cope with stress or exertion
- insomnia - frequent awakening
- severe PMS, PMDD
- hypoglycemia
- allergies, autoimmune diseases
- variability: good days, bad days

Cortisol (cont.)

- **women have a lower production of cortisol than men and that explains why women have a much greater incidence of chronic fatigue syndrome, fibromyalgia, depression, anxiety, and autoimmune diseases**

Vierhapper H, Nowotny P, Waldhäusl W. Sex-specific differences in cortisol production rates in humans. Metabolism. 1998 Aug;47(8):974-6.

Takai N, Yamaguchi M, Aragaki T, Eto K, Uchihashi K, Nishikawa Y. Gender-specific differences in salivary biomarker responses to acute psychological stress. Ann N Y Acad Sci. 2007 Mar;1098:510-5.

Cortisol (cont.)

- **circadian rhythms are driven by biological clocks and are endogenous in origin. Therefore, circadian changes in the metabolism or secretion of endogenous glucocorticoids are certainly responsible in part for the time-dependent changes observed in the inflammatory response and arthritis.**

- **the right timing (early morning) for the glucocorticoid therapy in arthritis is fundamental and well justified by the circadian rhythms of the inflammatory mechanisms**

Cutolo M, Sulli A, Pizzorni C, Secchi ME, Soldano S, Seriolo B, Straub RH, Otsa K, Maestroni GJ. Circadian rhythms: glucocorticoids and arthritis. Ann N Y Acad Sci. 2006 Jun;1069:289-99.

Cortisol (cont.)

- **rheumatic diseases are associated with hypofunctioning of the hypothalamic-pituitary-adrenal (HPA) axis, low cortisol response to ACTH stimulation, and relative adrenal insufficiency**

Johnson EO, Kostandi M, Moutsopoulos HM. Hypothalamic-pituitary-adrenal axis function in Sjögren's syndrome: mechanisms of neuroendocrine and immune system homeostasis. Ann N Y Acad Sci. 2006 Nov;1088:41-51.

Demir H, Tanriverdi F, Ozoğul N, Caliş M, Kirnap M, Durak AC, Keleştimur F. Evaluation of the hypothalamic-pituitary-adrenal axis in untreated patients with polymyalgia rheumatica and healthy controls. Scand J Rheumatol. 2006 May-Jun;35(3):217-23.

Chikanza IC, Petrou P, Kingsley G, Chrousos G, Panayi GS. Defective hypothalamic response to immune and inflammatory stimuli in patients with rheumatoid arthritis. Arthritis Rheum. 1992 Nov;35(11):1281-8.

Cutolo M, Foppiani L, Minuto F. Hypothalamic-pituitary-adrenal axis impairment in the pathogenesis of rheumatoid arthritis and polymyalgia rheumatica. J Endocrinol Invest. 2002;25(10 Suppl):19-23.

Cortisol (cont.)

Cutolo M, Sulli A, Pizzorni C, Secchi ME, Soldano S, Seriolo B, Straub RH, Otsa K, Maestroni GJ. Circadian rhythms: glucocorticoids and arthritis. Ann N Y Acad Sci. 2006 Jun;1069:289-99.

Gudbjörnsson B, Skogseid B, Oberg K, Wide L, Hällgren R. Intact adrenocorticotropic hormone secretion but impaired cortisol response in patients with active rheumatoid arthritis. Effect of glucocorticoids. J Rheumatol. 1996 Apr;23(4):596-602.

Mastorakos G, Ilias I. Relationship between interleukin-6 (IL-6) and hypothalamic-pituitary-adrenal axis hormones in rheumatoid arthritis. Z Rheumatol. 2000;59 Suppl 2:II/75-9.

Kebapcilar L, Bilgir O, Alacacioglu A, Yildiz Y, Taylan A, Gunaydin R, Yuksel A, Karaca B, Sari I. Impaired hypothalamo-pituitary-adrenal axis in patients with ankylosing spondylitis. J Endocrinol Invest. 2010 Jan;33(1):42-7. Epub 2009 Jul 20.

Rules for Cortisol Restoration

- **safe in physiologic dose**
- **must be used with other steroid hormones that also need to be optimized**
- **must replace DHEA to prevent bone loss, increased blood sugar, abdominal fat, etc.**
- **must maintain thyroid/cortisol balance**

William McK Jefferies. Safe Uses of Cortisol. Charles C. Thomas Publisher; 2nd edition (September 1996)

Menopause – androgens deficiency

- **testosterone concentration of a woman of 40 would be about half that of a woman of 21**

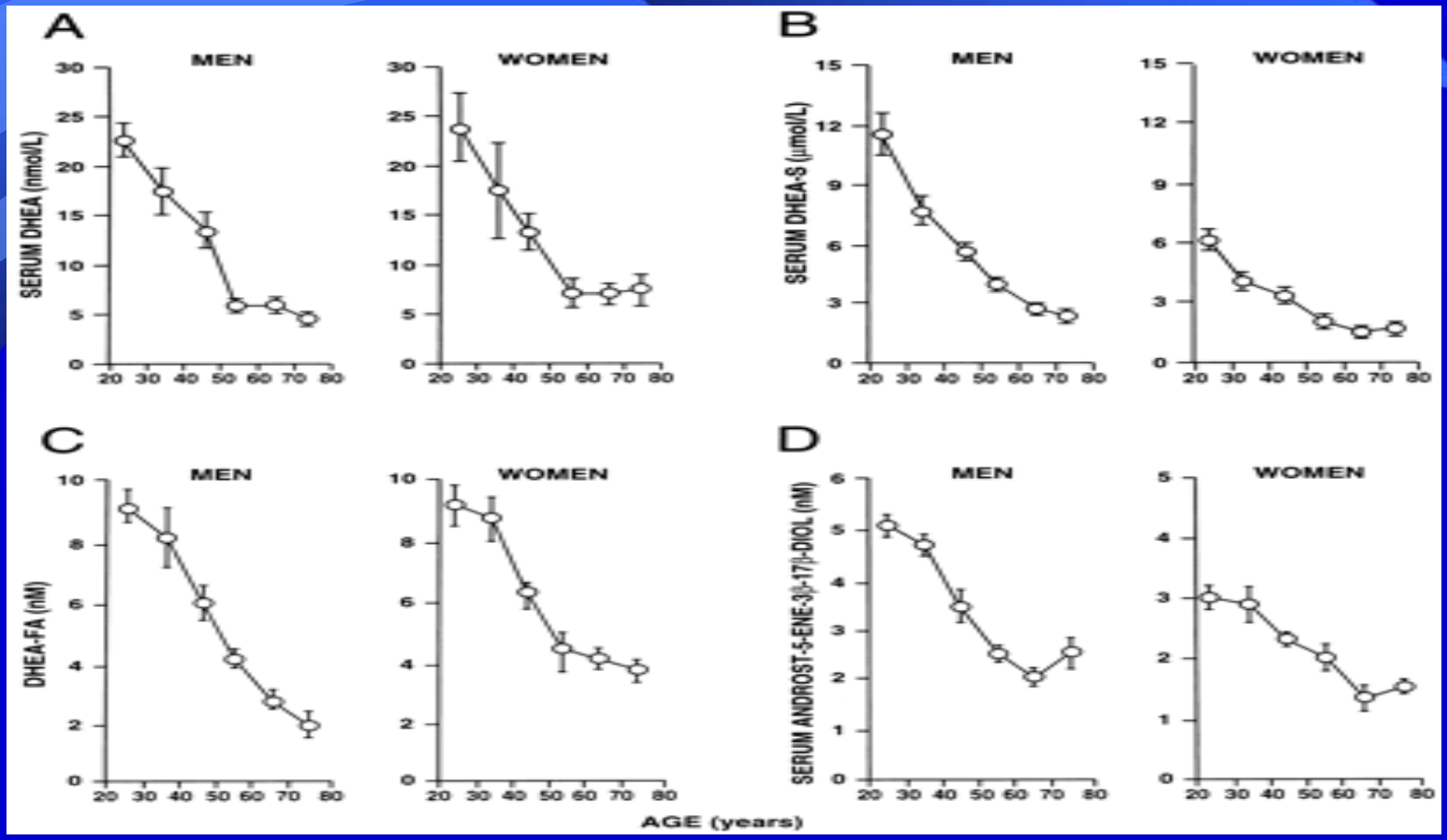
Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. J Clin Endocrinol Metab. 1995 Apr;80(4):1429-30.

Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. Menopause. 2003 Sep-Oct;10(5):390-8.

- **menopausal ERT decreases serum androgen levels, decreasing DHEA- sulfate and testosterone by 23% and 42%, respectively**

Casson PR, Elkind-Hirsch KE, Buster JE, Hornsby PJ, Carson SA, Snabes MC. Effect of postmenopausal estrogen replacement on circulating androgens. Obstet Gynecol. 1997 Dec;90(6):995-8.

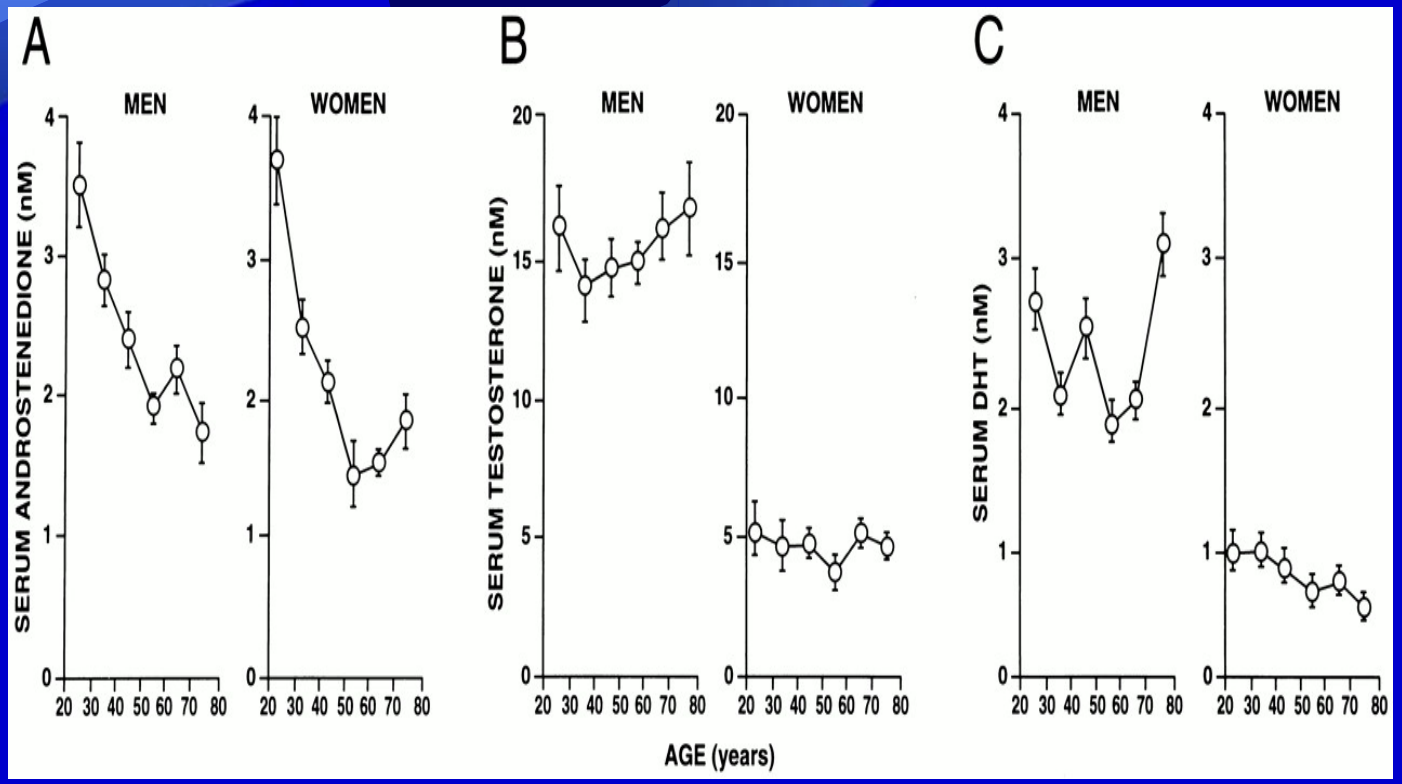
DHEA and DHEAS production during aging



In the 50- to 60-yr-old group, serum DHEA decreased by 74% and 70% from its peak values in 20- to 30-yr-old men and women, respectively.

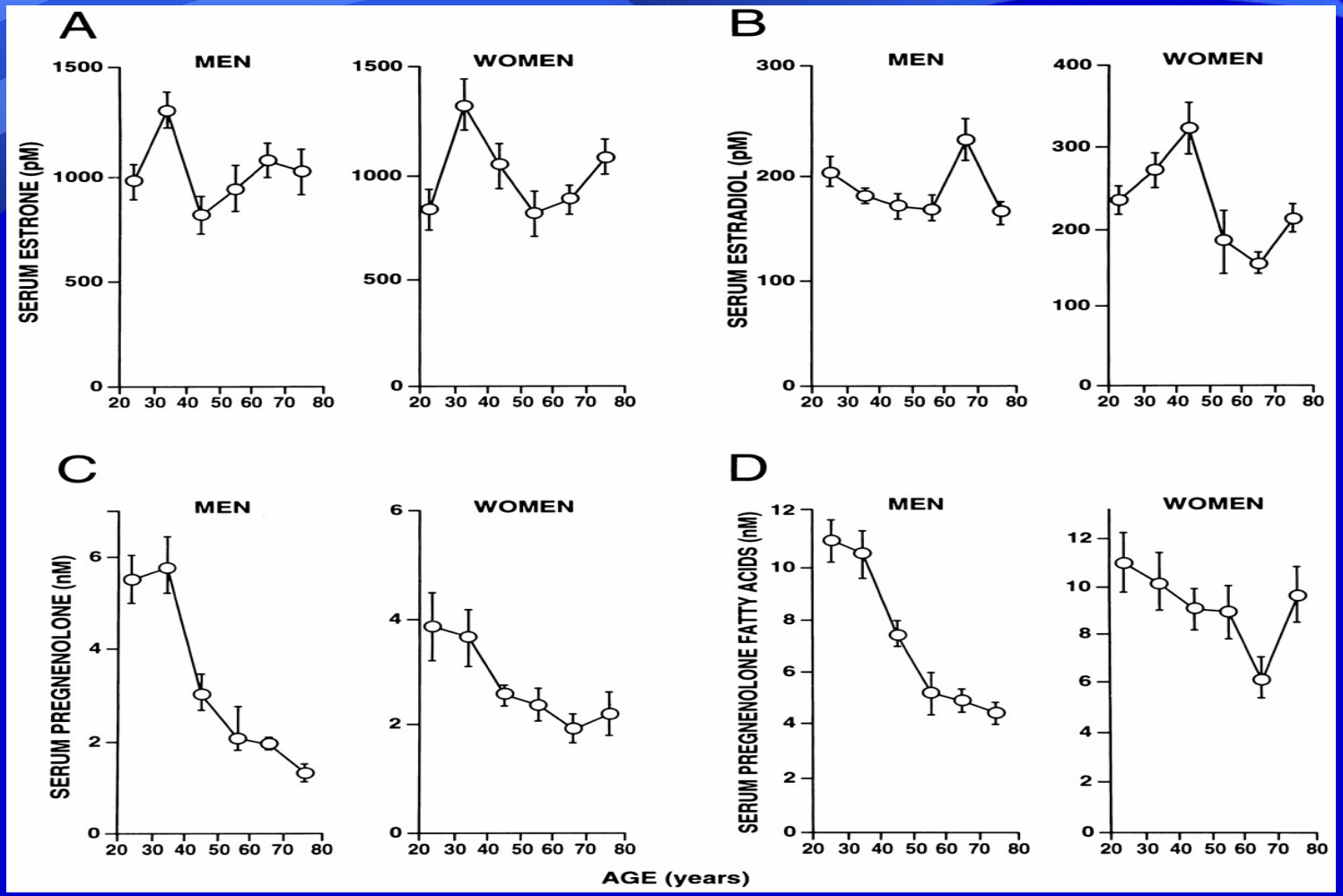
Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab. 1997Aug;82(8):2396-402.

Effect of age (20–30 yr old *vs*. 70–80 yr old) on serum concentration of 4-dione (A), testosterone (B), and DHT (C) in men and women.



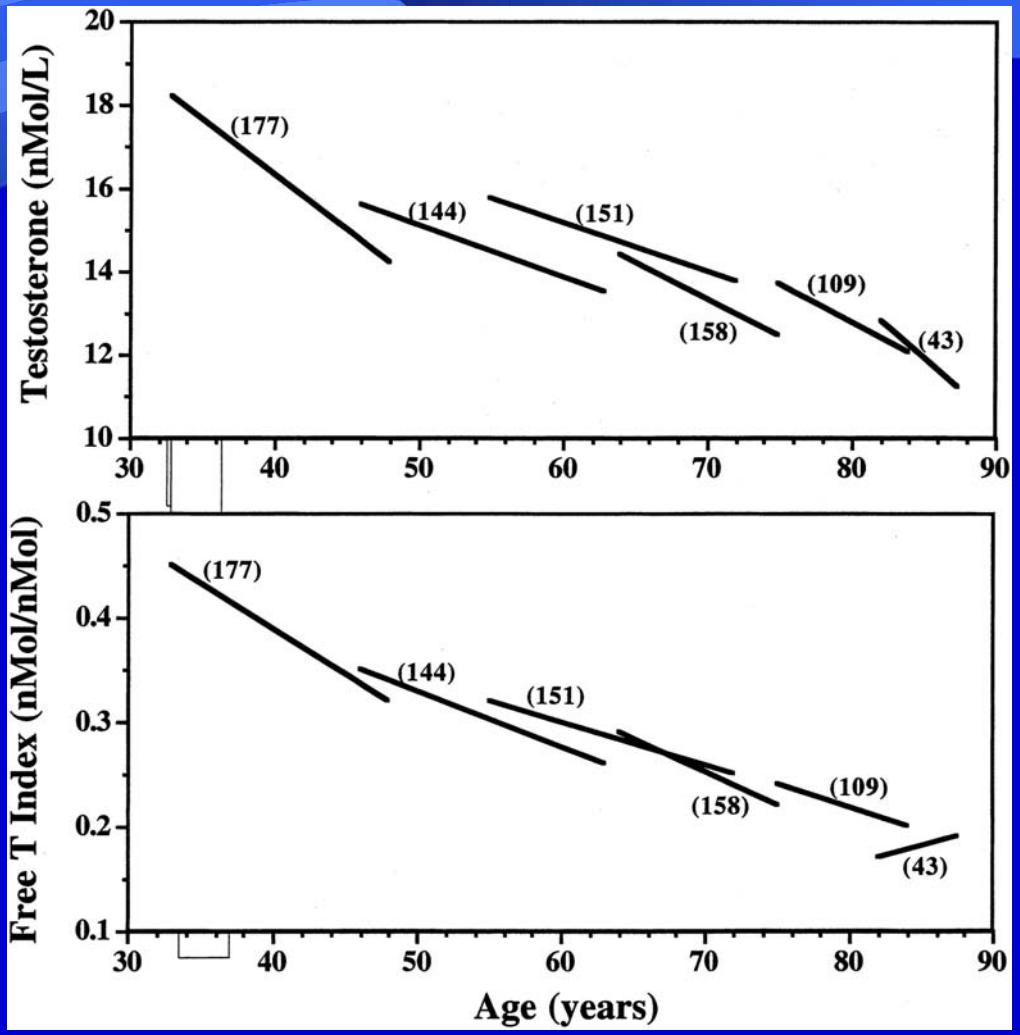
Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab. 1997Aug;82(8):2396-402.

Effect of age (20–30 yr old *vs*. 70–80 yr old) on serum concentration of E1 (A), E2 (B), pregnenolone (C), and pregnenolone-fatty acid esters (D) in men and women.



Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab. 1997Aug;82(8):2396-402.

Effects of aging on date-adjusted T and free T index

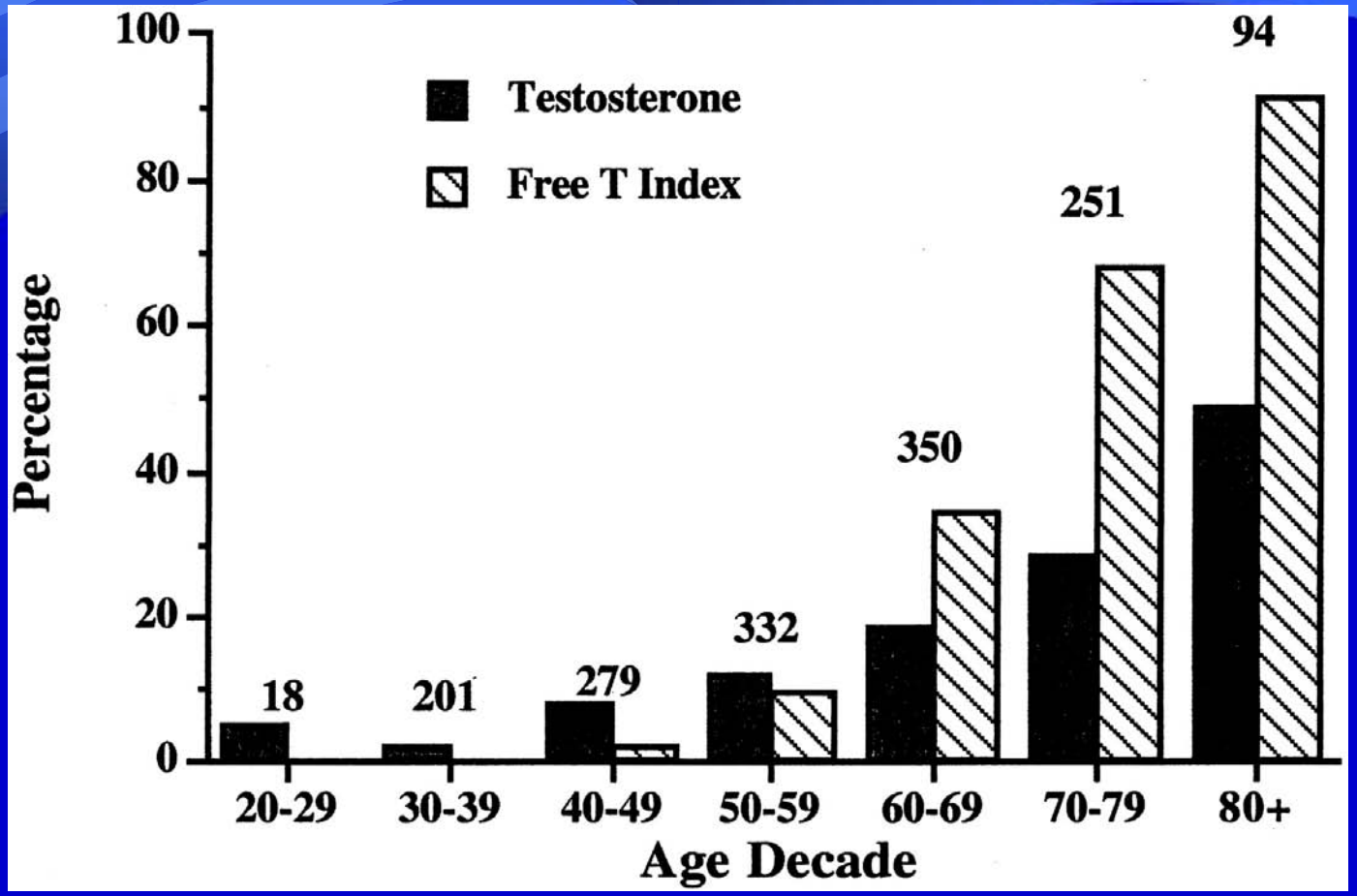


Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001 Feb;86(2):724-31.

Calculation of Testosterone Free Index (TFI)

TFI = (Total Testosterone / SHBG) x100

Hypogonadism in aging men



Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001 Feb;86(2):724-31.

DHEA

- most abundant steroid hormone
- source for testosterone and estrogens
- level declines with age, stress and disease
- low level associates with increased risk of disease and mortality
- has anabolic effect
- improves immunity
- improves sexual function
- balances a cortisol effect

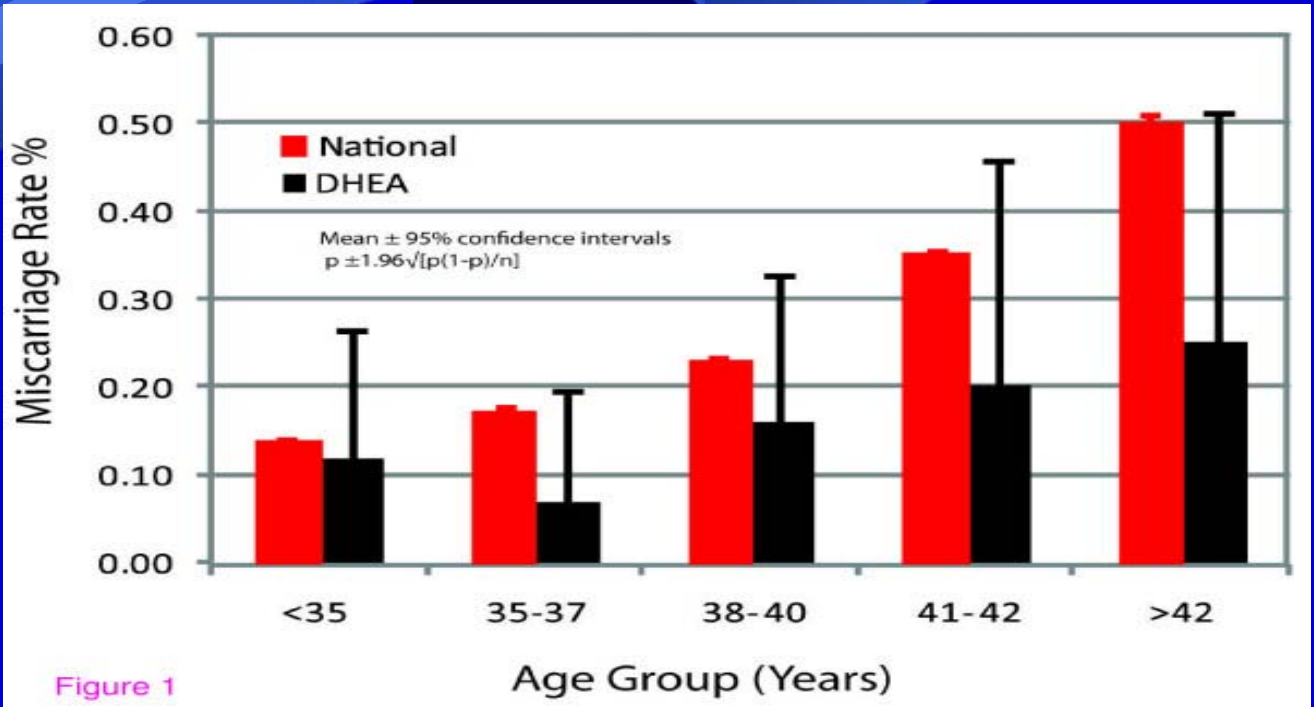
Barad D, Brill H, Gleicher N. Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. J Assist Reprod Genet. 2007 Dec;24(12):629-34.

DHEA (cont.)

- reduces abdominal fat
- decreases pain
- restores endorphins level
- reduces inflammation through the regulation of IL-6, TNF-alpha, and IL-2)
- prevents oxidation of LDL
- improves fertility in older women

Barad D, Brill H, Gleicher N. Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. J Assist Reprod Genet. 2007 Dec;24(12):629-34.

Comparison of miscarriage rates at all ages between DHEA supplemented infertility patients and 2004 national U.S. IVF outcome data



- **reduction in miscarriages after DHEA supplementation exceeds all expectations**

Gleicher N, Ryan E, Weghofer A, Blanco-Mejia S, Barad DH. Miscarriage rates after dehydroepiandrosterone (DHEA) supplementation in women with diminished ovarian reserve: a case control study. Reprod Biol Endocrinol. 2009 Oct 7;7:108.

Androgens Restoration

- beneficial effects on bone mass
- increases in muscle mass
- improves well-being and mood
- improves sexual function
- maintains pelvic health
- improves insulin sensitivity

Miller KK, Biller BM, Schaub A, Pulaski-Liebert K, Bradwin G, Rifai N, Klibanski A. Effects of testosterone therapy on cardiovascular risk markers in androgen-deficient women with hypopituitarism. J Clin Endocrinol Metab. 2007 Jul;92(7):2474-9. Epub 2007 Apr 10.

Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. Menopause. 2003 Sep-Oct;10(5):390-8.

Androgens Restoration (cont.)

- **opposes estradiol-induced breast stimulation and reduces risk of breast cancer**

Somboonporn W, Davis SR; National Health and Medical Research Council. Testosterone effects on the breast:
implications for testosterone therapy for women. Endocr Rev. 2004 Jun;25(3):374-88.

Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. Menopause. 2004 Sep-Oct;11(5):531-5.

Zhou J, Ng S, Adesanya-Famuiya O, Anderson K, Bondy CA. Testosterone inhibits estrogen-induced mammary
epithelial proliferation and suppresses estrogen receptor expression. FASEB J. 2000 Sep;14(12):1725-30.

Androgens Restoration (cont.)

- estradiol and testosterone were more effective in increasing bone mineral density in the hip and lumbar spine than estradiol alone. Significantly greater improvement in sexuality was observed with combined therapy

Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas. 1995 Apr;21(3):227-36.

Miller BE, De Souza MJ, Slade K, Luciano AA. Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. Menopause. 2000 Sep-Oct;7(5):318-26.

Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang HM, Nolan J. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. J Reprod Med. 1999 Dec;44(12):1012-20.

Androgens Restoration (cont.)

- in men, testosterone has been demonstrated to have beneficial fibrinolytic effects and beneficial effects on blood vessel endothelium, in blood sugar and insulin metabolism, and in maintaining coronary artery circulation

- restoring a physiologic level of testosterone to women not only can improve quality of life in terms of sexual libido, sexual pleasure, and sense of well-being but also can build bones - and may be a key to protecting cardiovascular health

Rako S. Testosterone deficiency: a key factor in the increased cardiovascular risk to women following hysterectomy or with natural aging? J Womens Health. 1998 Sep;7(7):825-9.

Androgens Restoration (cont.)

- **in postmenopausal women decreased T level is associated with CAD**

Kaczmarek A, Reczuch K, Majda J, Banasiak W, Ponikowski P. The association of lower testosterone level with coronary artery disease in postmenopausal women. Int J Cardiol. 2003 Jan;87(1):53-7.

Rules for the hormones use

- if hormones are missing, replace and restore it!
- if they are present but insufficient, optimize it!
- optimal levels improve health
- anthropo-identical structure
- anthropo-identical must be a Standard of Care the same approach as to insulin, T4, growth hormone, cortisol, oxytocin, etc.
- use nutrients that assist with physiology optimization: saw palmetto, zinc, magnesium, probiotics, etc.

Menopause – estrogen deficiency

- hot flashes
- vaginal dryness
- irritability
- anxiety, depression
- insomnia
- fatigue
- aches and pains
- incontinence
- poor short-term memory
- Alzheimer's disease
- osteoporosis
- spine and hip fractures
- loss of teeth
- wrinkles, dry skin
- cardiovascular diseases
- cancer

Estrogen Restoration

- controls hot flashes
- maintains pelvic health
- improves cognitive function
- improves mood
- restores sleep
- maintains thickness and fullness of skin and hair
- protects against colon cancer
- protects against macular degeneration
- prevents atherosclerosis, hypertension
- improves insulin sensitivity
- prevents osteoporosis
- prevents osteoarthritis
- improves memory

Estrogens

- when discussing estrogen it is important to note that “estrogen” is an umbrella term for many different estrogens including estriol, estrone, and estradiol

- all three of these estrogens are produced in the body and have physiological effects

Estrogens

Trends in female physiology

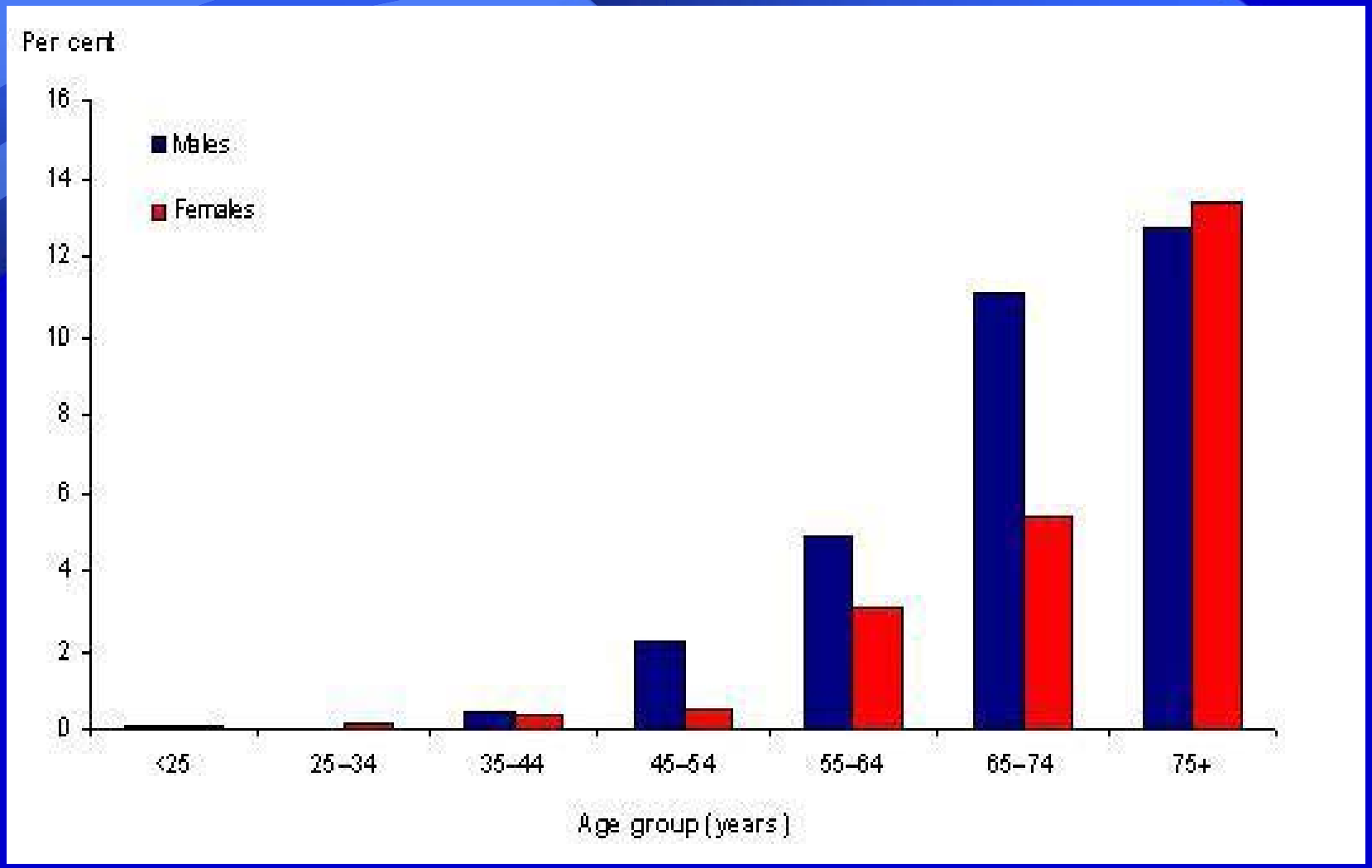
- females born with a fixed numbers of oocytes
- the number of oocytes decrease during aging – it cause of decreased production of estrogen and progesterone starting as early as age 30
- perimenopause characterized by infrequent ovulation and low progesterone because number of functional oocytes progressively decline
- ovarian failure leads to menopause

Female hormones and major illnesses

- **coronary heart disease, dementia, osteoporosis, hip fracture, stroke, Parkinsonism, cognitive impairment, depression, anxiety and breast cancer are associated with the estrogen deficiency and all rare before menopause**
- **the first 3 diseases are clearly associated with estrogen deficiency and breast cancer – with progesterone deficiency**
- **youthful hormone levels protect women from these diseases**
- **early removal of ovaries increases risk of heart disease, osteoporosis, and dementia.**

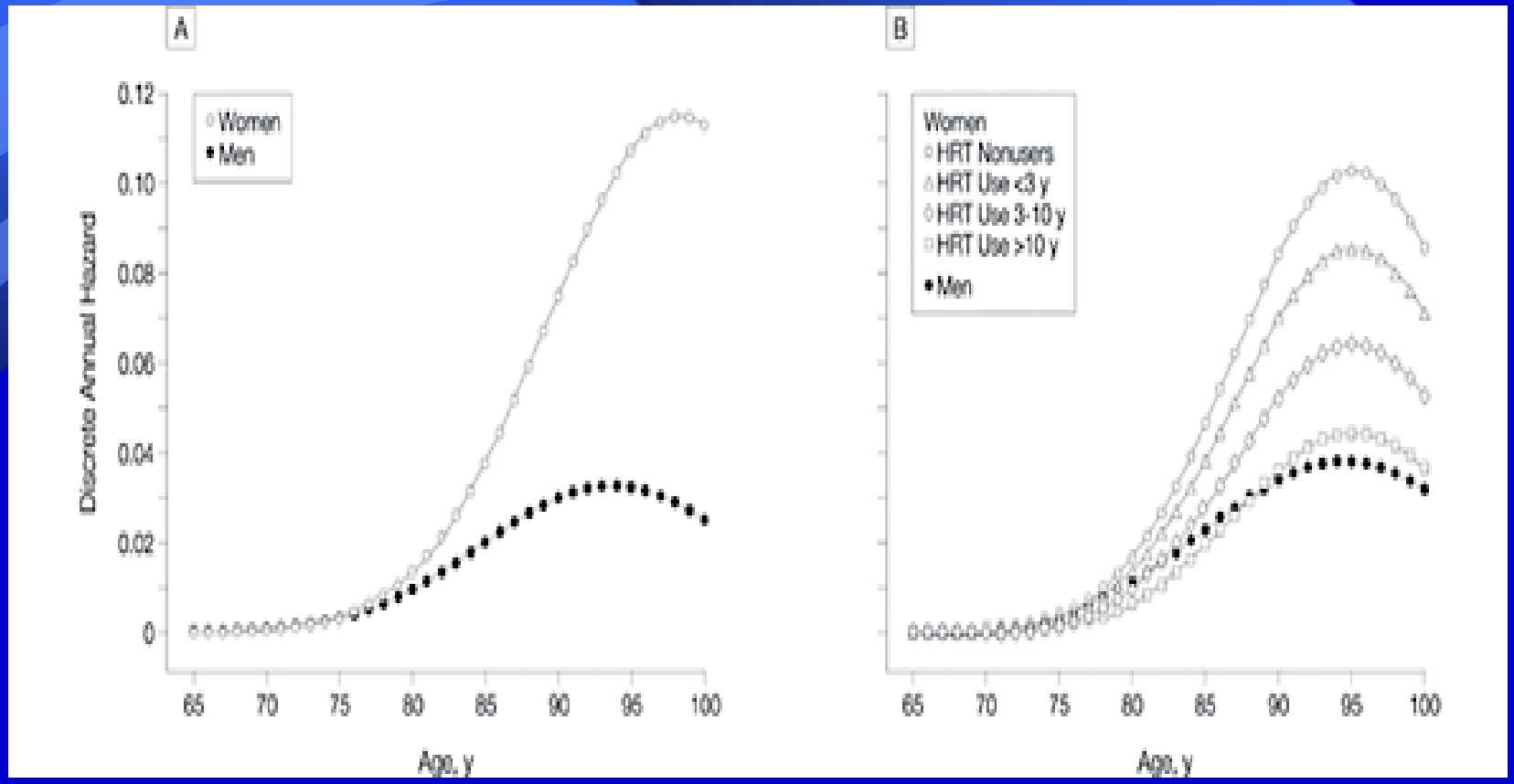
Parker WH, Jacoby V, Shoupe D, Rocca W. Effect of bilateral oophorectomy on women's long-term health. Womens Health (Lond Engl). 2009 Sep;5(5):565-76.

Coronary Heart Disease during aging



AIHW Heart, stroke and vascular diseases, Australian facts 2004.
http://www.aihw.gov.au/publications/cvd/hsvd04/hsvd04.pdf

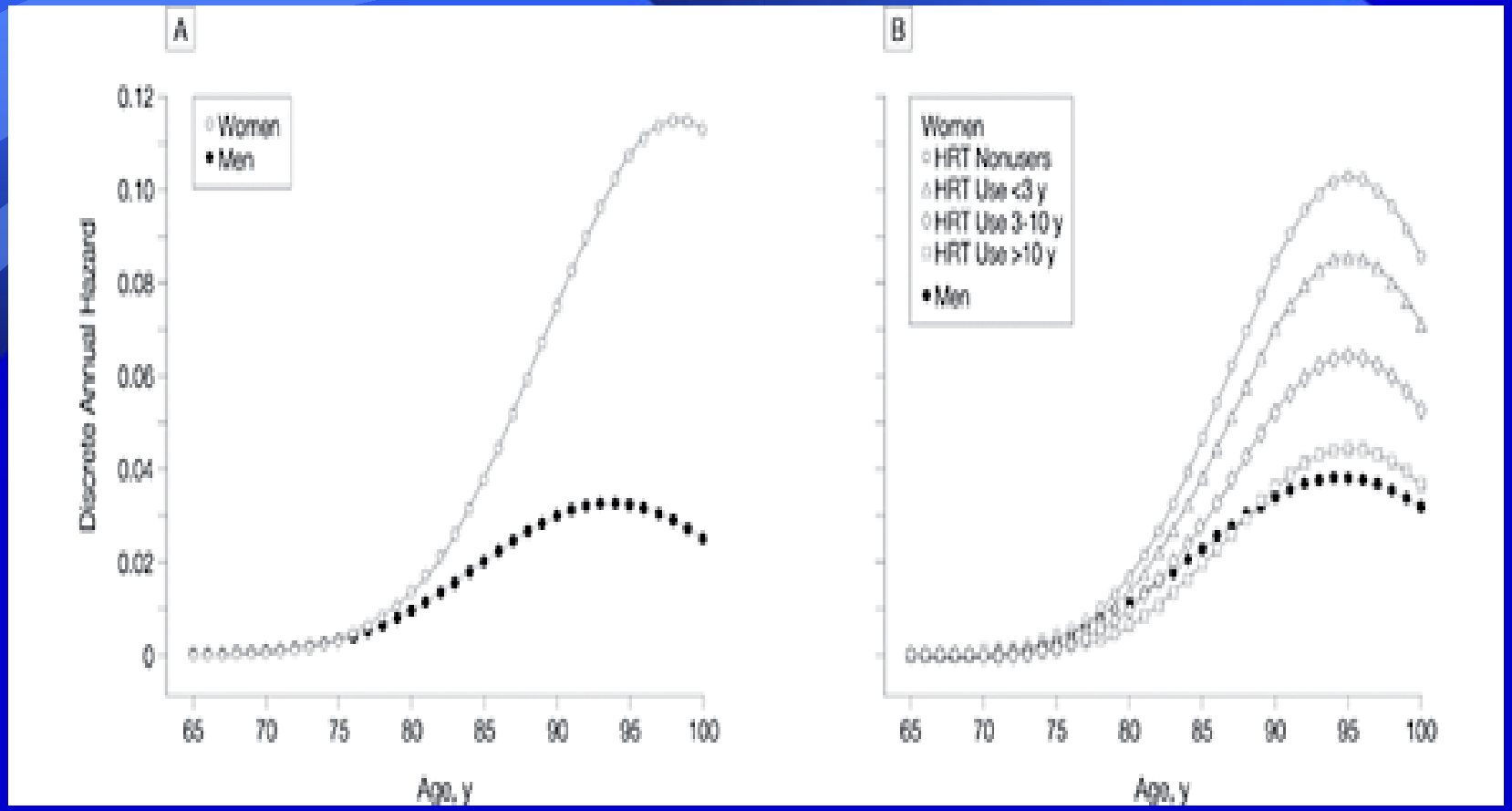
Estimated Discrete Annual Hazard of Alzheimer Disease for Men and Women by Age, and by Duration of Hormone Replacement Therapy Use



Zandi PP, Carlson MC, Plassman BL, Welsh-Bohmer KA, Mayer LS, Steffens DC, Breitner JC; Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA. 2002 Nov 6;288(17):2123-9.

Kawas C, Resnick S, Morrison A, Brookmeyer R, Corrada M, Zonderman A, Bacal C, Lingle DD, Metter E. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology. 1997 Jun;48(6):1517-21.

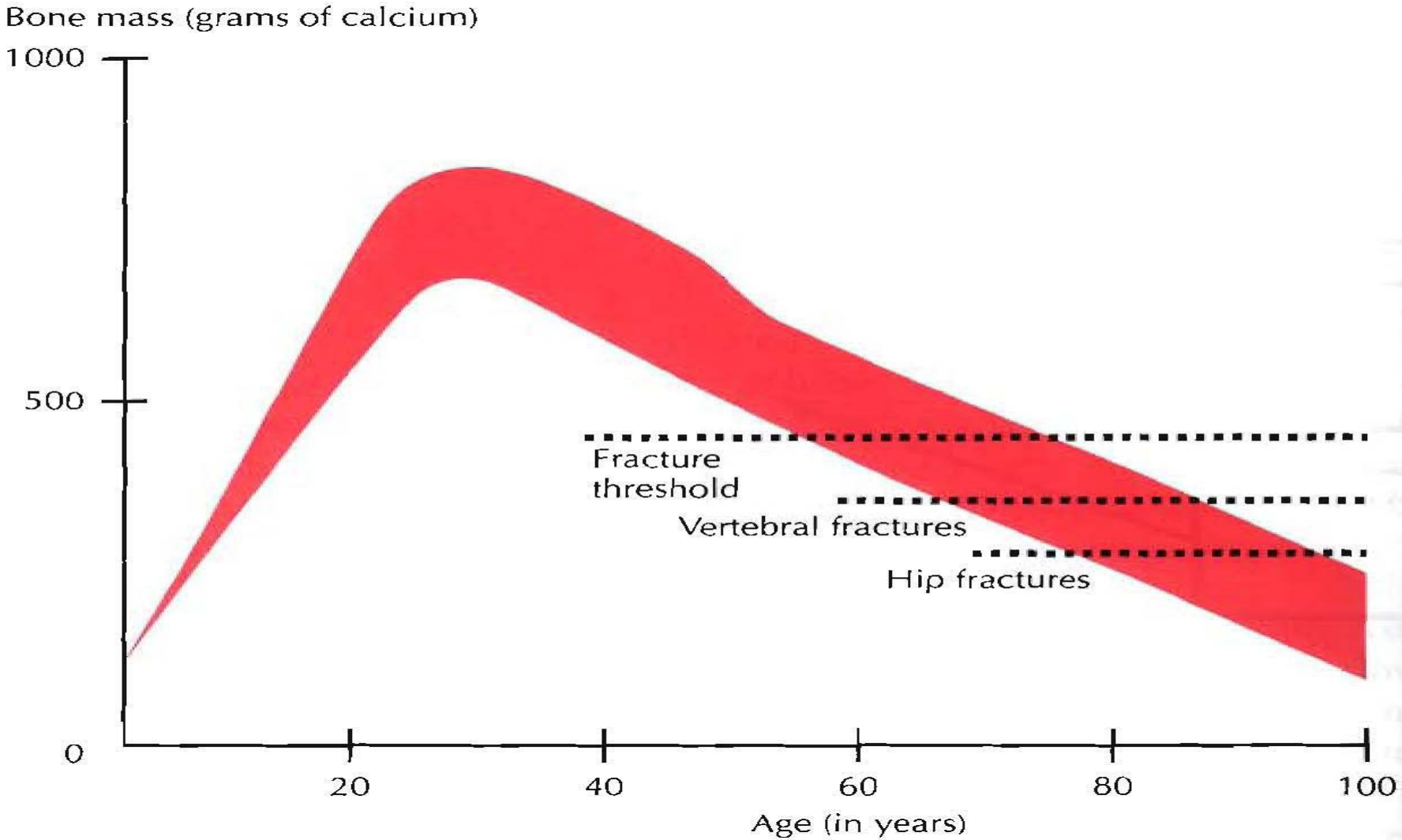
Estimated Discrete Annual Hazard of Alzheimer Disease for Men and Women by Age, and by Duration of Hormone Replacement Therapy Use (ref. cont.)



Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med. 1996 Oct 28;156(19):2213-7.

Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, Andrews H, Mayeux R. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet. 1996 Aug 17;348(9025):429-32.

Changes in Women's Bone Mass with Age



Speroff L, Fritz M. Clinical Gynecologic Endocrinology and Fertility, Lippincott Williams & Wilkins; Seventh edition (September 2, 2004)

Osteoporosis

- **5% bone loss each year for first 5 years in menopause – 25% due to loss of estrogen!**
- **20 yrs. post menopause - 50% reduction in trabecular bone, 30% in cortical bone**
- **50% of women >65 yrs. old have spinal compression fractures**

Speroff L, Fritz M. Clinical Gynecologic Endocrinology and Fertility, Lippincott Williams & Wilkins; Seventh edition (September 2, 2004)

- **Vitamin D3 and vitamin K2 are essential for bone health**

Iwamoto J, Takeda T, Ichimura S. Treatment with vitamin D3 and/or vitamin K2 for postmenopausal osteoporosis. Keio J Med. 2003 Sep;52(3):147-50.

Osteoporosis

- **estrogens prevent resorption of old bone while testosterone, progesterone, DHEA, and growth hormone build a new bone**

Raisz LG, Wiita B, Artis A, Bowen A, Schwartz S, Trahiotis M, Shoukri K, Smith J Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. J Clin Endocrinol Metab. 1996 Jan;81(1):37-43.

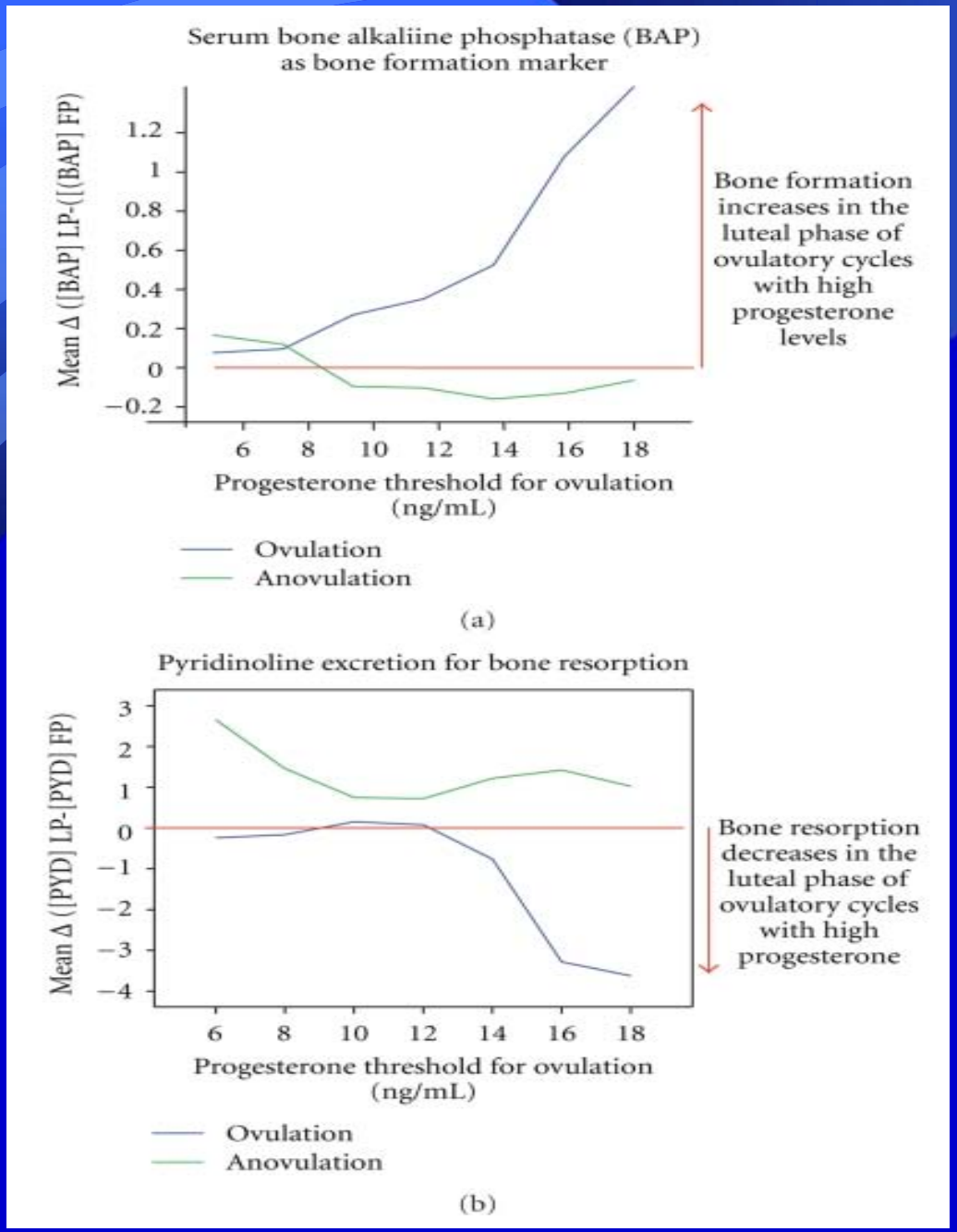
Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang HM, Nolan J. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. J Reprod Med. 1999 Dec;44(12):1012-20.

Seifert-Klauss V, Prior JC. Progesterone and bone: actions promoting bone health in women. J Osteoporos. 2010 Oct 31;2010:845180.

McCormick RK. Osteoporosis: integrating biomarkers and other diagnostic correlates into the management of bone fragility. Altern Med Rev. 2007 Jun;12(2):113-45.

Labrie F, Luu-The V, Bélanger A, Lin SX, Simard J, Pelletier G, Labrie C. Is dehydroepiandrosterone a hormone? J Endocrinol. 2005 Nov;187(2):169-96.

- **Bisphosphonates (Fosamax, Actonel, Boniva) stop bone remodeling, suppress bone formation – increase non-traumatic fractures after >5yrs**
- **Hormone restoration including Vit. D-3 increases bone density better than bisphosphonates and preserves normal bone remodeling**



Estradiol (E2) and progesterone (P4) collaborate within bone remodelling on resorption (E2) and formation (P4).

Progesterone prevents bone loss in pre- and possibly perimenopausal women; progesterone co-therapy with antiresorptives may increase bone formation and BMD

Seifert-Klauss V, Prior JC. Progesterone and bone: actions promoting bone health in women. J Osteoporos. 2010 Oct 31;2010:845180.

Estrogens

- Estradiol (E2) is the predominant estrogen produced in pre-menopausal women while estrone (E1) is the primary estrogen produced after menopause
- in the body, estradiol is reversibly oxidized to estrone and both estradiol and estrone can be converted to estriol
- the potency of E2 is 12 times that of E1 and 80 times that of E3.

Lorentzen J. Hormone Replacement Therapy: part 2 Estrogen Defined. IJPC 2001 Nov-Dec;5(6):460-461

Estrogens

- in the literature, there is scant data regarding serum estriol values in non-pregnant, premenopausal women

- in the conventional medical practice, it is believed that estriol has no significant job in non-pregnant women compared to other estrogens

Estrogens

- the result of Dr. J. Wright study showed that serum estriol was always significantly higher than the sum of estrone and estradiol and less fluctuating

- he concluded that estriol is probably a significant estrogen component

Wright JV, Schliesman B, Robinson L. Comparative measurements of serum Estriol, Estradiol, and Estrone in non-pregnant, premenopausal women: A preliminary investigation. Altern Med Rev 1999;4(4):266-270.)

Estrogens

- reference values are available for serum estrone and estradiol, but serum estriol levels are listed in reference books for only pregnant women

- research on estriol to date had been focused on concentrations in pregnant women

Wright JV, Schliesman B, Robinson L. Comparative measurements of serum Estriol, Estradiol, and Estrone in non-pregnant, premenopausal women: A preliminary investigation. Altern Med Rev 1999;4(4):266-270.)

Problem with Estriol

- prior to the 1970s, the technology was not sophisticated enough to accurately analyze estriol in non-pregnant patients

- by the time estriol could be analyzed accurately, researchers had already conclusively demonstrated that estriol was a much weaker hormone than estradiol and estrone; therefore, it was believed to be of no known consequence

Wright JV, Schliesman B, Robinson L. Comparative measurements of serum Estriol, Estradiol, and Estrone in non-pregnant, premenopausal women: A preliminary investigation. Altern Med Rev 1999;4(4):266-270.)

Estriol

- Dr. J. Wright developed a solid-phase competitive-binding radio-immunoassay (RIA) procedure for estriol

- The data showed that the estriol in every case was at least three times as great as the concentration of estradiol and estrone combined. The average EQ for the population was 8.9. With estriol circulating at nearly 10 times the concentration of estrone and estradiol, it appears that there must be unknown significant biological activity for this “weaker” hormone.

Wright JV, Schliesman B, Robinson L. Comparative measurements of serum Estriol, Estradiol, and Estrone in non-pregnant, premenopausal women: A preliminary investigation. Altern Med Rev 1999;4(4):266-270.

E3:E2:E1

Subject number	Day of cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Estrogen quotient (Estriol)/[(Estradiol)+(Estrone)]
1	10	233	52.5	21.2	3.2
2	10	186	43.4	14.4	3.2
3	10	1254	188.8	55.0	5.1
4	10	329	40.4	23.4	5.2
5	10	369	43.9	20.4	5.7
6	10	700	30.9	68.0	7.1
7	10	374	35.9	15.1	7.3
8	10	429	25.3	33.1	7.3
9	10	941	86.7	32.5	7.9
10	10	736	21.5	70.6	8.0
11	10	1616	61.2	127.4	8.6
12	10	726	61.7	52.5	6.4
13	10	826	22.6	39.1	13.4
14	10	1614	57.9	144.4	8.0
15	10	771	11.3	35.4	16.5
16	10	1700	30.7	58.6	19.0
17	11	595	15.1	35.9	11.7
18	11	2408	156.8	121.9	8.6
19	12	961	32.8	71.6	9.2
20	12	1161	71.2	27.3	11.8
21	12	1271	22.2	72.0	13.5
22	14	685	24.6	43.4	10.1
23	14	988	31.1	65.8	10.2
24	14	212	23.7	12.5	5.9
25	14	1412	183.4	54.7	5.9
26	14	1146	17.4	68.6	13.3
				Average	8.9
				Standard deviance	3.9

Estrogen excretion (in mcg/day) in women and men of various ages

Estrogens	Women Age 18-41		Postmeno-pausal Women	Men	
	Proliferative phase	Secretory phase		Age 20-48	Age 45-65
Estriol	7	16	3	3	6
Estrone	5	7	2	4	6
Estradiol	2	4	1	1	2

Data from Brown in: Clinical Endocrinology I. Astwood EB (editor). Grune & Stratton, 1960.

Estriol

- estriol has been used for decades without reported safety concerns and is a component of medications approved for use worldwide

- the FDA has acknowledged that it is unaware of any adverse events associated with the use of compounded medications containing estriol

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (Estradiol, Estriol, and Progesterone) safer or more efficacious than commonly used synthetic versions in Hormone Replacement Therapy? Postgrad Med 2009;121(1): 73-85.

Estriol

- when estriol is given together with estradiol, the estradiol-specific stimulation to cells is decreased[203]

- experimental studies suggest that estriol has a protective effect against radiation-induced cancer of the breast[204]

Estrogen receptors

- Estrogen effects are mediated through 2 different estrogen receptors: estrogen receptor-alpha (ER-α) and estrogen receptor-beta (ER-β).[106–111]

- Estrogen receptor-α promotes breast cell proliferation, while ER-β inhibits proliferation and prevents breast cancer development via G2 cell cycle arrest.[106,112–117]

Estriol

- because of its differing effects on ER alpha and ER beta, we would expect that estriol would be less likely to induce proliferative [potential cancerous growth] changes in breast tissue and to be associated with a reduced risk of breast cancer."[205]

Estriol and the risk of breast cancer

- Estradiol equally activates ER-α and ER-β, while estrone selectively activates ER-α at a ratio of 5:1.[118,119]

- In contrast, estriol selectively binds ER-β at a ratio of 3:1.[118,119] This unique property of estriol, in contrast to the selective ER-α binding by other estrogens,[107,118–121] imparts to estriol a potential for breast cancer prevention,[59,122–125] while other estrogens would be expected to promote breast cancer.[106,112–115,126]

Estriol and the risk of breast cancer

- CEE components are potent downregulators of ER-β receptors.[114] Whether this activity is unique to CEE is unclear, but it could potentially increase carcinogenic properties.

- Conjugated equine estrogens also contains at least one particularly potent carcinogenic estrogen, 4-hydroxy-equilenin, which promotes cancer by inducing DNA damage.[127–131]

Estriol and the risk of breast cancer

- Because of differing effects on ER-α and ER-β estriol is less likely to induce proliferative changes in breast tissue and is associated with a reduced risk of breast cancer.[40,59,80,103–105,122–125,132–144]

Estriol and the risk of breast cancer

- acting alone, estriol is a weak estrogen, but when given with estradiol, it functions as an antiestrogen[135]
- estriol and/or tamoxifen, as opposed to other estrogens, prevented the development of breast cancer in rats after the administration of carcinogens[123,124]

Estriol and the risk of breast cancer

- in a large study of more than 30 000 women the use of estrogen-only HRT increased the risk of breast cancer compared with that in nonusers

- the addition of a synthetic progestin further increased breast cancer risk while the use of an estriol-containing preparation was not associated with the risk of breast cancer that was seen with other preparations[144]

Estriol and uterine cancer

- the increased risk of uterine cancer in users of non-bioidentical estrogen is well-established in the scientific literature[206-208]

- in contrast, the use of topical lower-potency estriol is not associated with an increased risk of uterine cancer[209]

Estriol and progesterone during pregnancy

- Estriol and progesterone levels dramatically increase during pregnancy (an approximate 15-fold increase in progesterone and a 1000-fold increase in estriol), and postpartum women continue to produce higher levels of estriol than nulliparous women.[136]

Estriol and progesterone during pregnancy

- an increased exposure to progesterone and estriol during and after pregnancy confers a significant long-term reduction in the risk for breast cancer[40,103–105,136–141]

Estriol in postmenopausal women

- urinary estriol levels in postmenopausal women show an inverse correlation with the risk for breast cancer in many studies[125,132–134,142,143,146]

The facts on Estriol

- the FDA has not received a single report of an adverse event in more than 30 years of estriol use

- Estriol is also the subject of a US Pharmacopeia monograph. The FDA Modernization Act of 1997 clearly indicated that drugs with a US Pharmacopeia monograph could be compounded.

The facts on Estriol

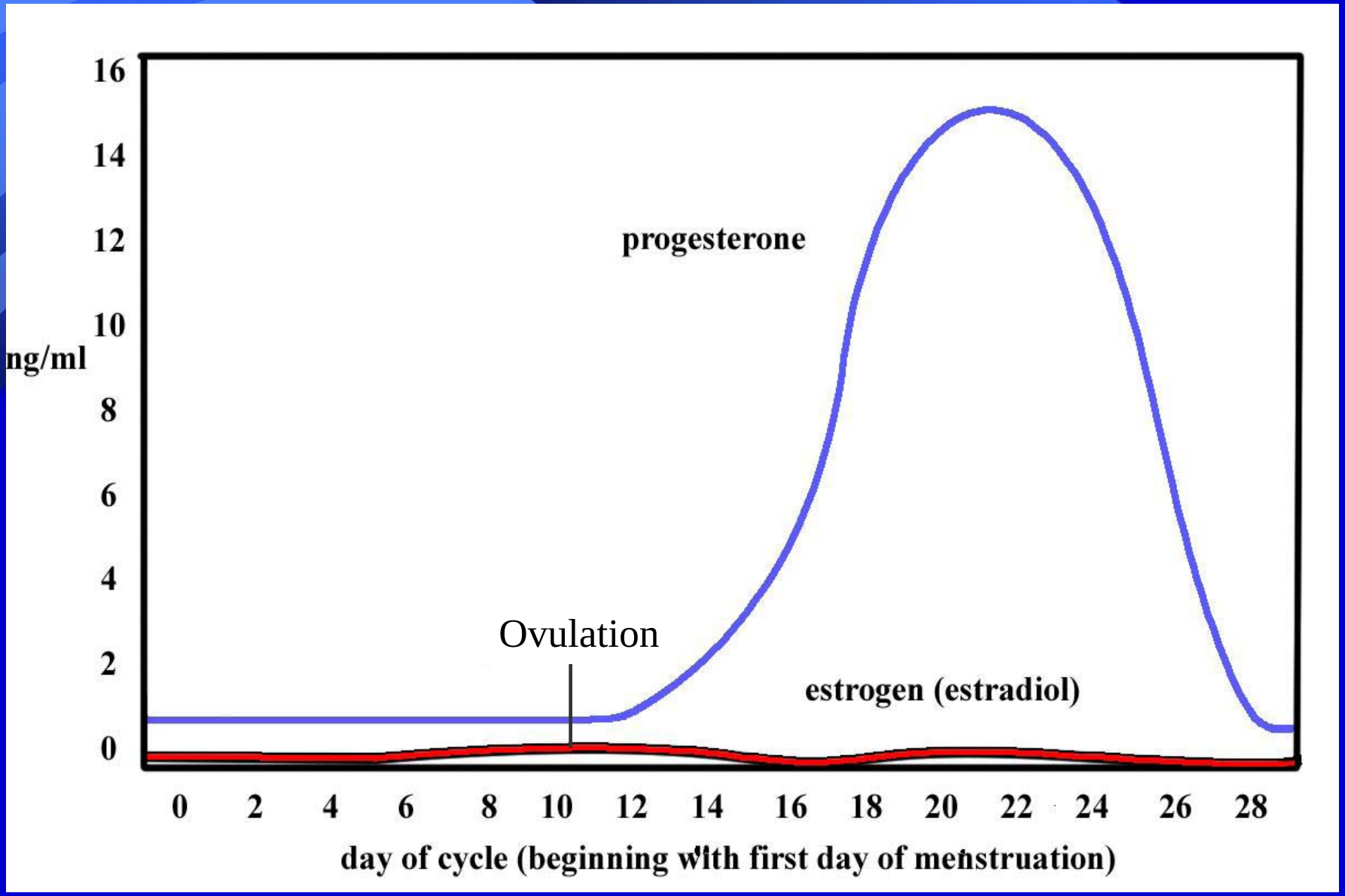
- It appears that the FDA took action, not because estriol is at least as safe and effective as current estrogens on the market, but in response to what was considered unsupported claims that estriol was safer than current forms of estrogen replacement and because there is no standardized dose.

- Estriol has unique physiologic properties associated with a reduction in the risk of breast cancer, and combining estriol with estradiol in hormone replacement preparations would be expected to decrease the risk for breast cancer.

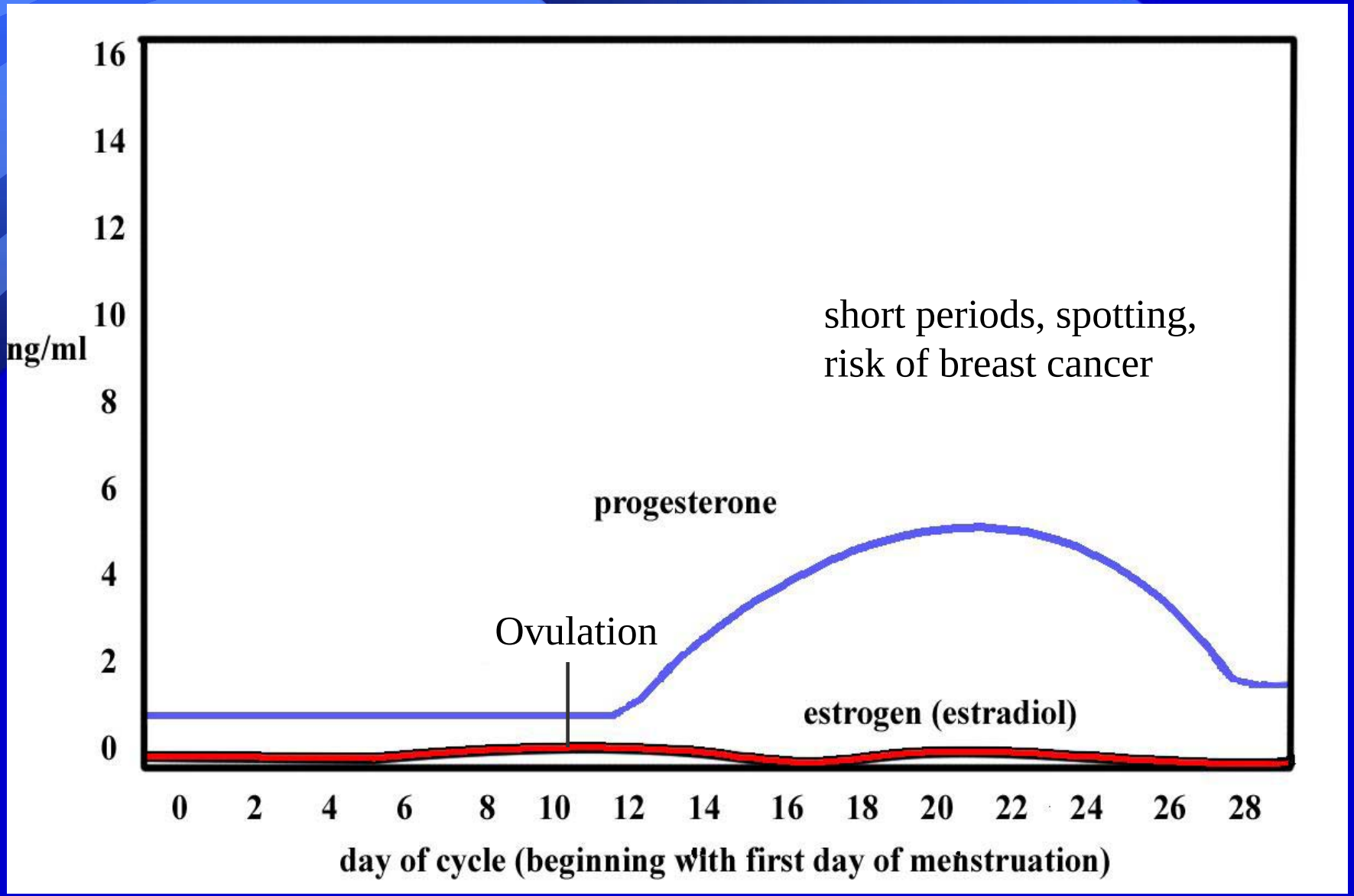
Progesterone - aging

- **oocytes during aging have a poor quality**
- **estrogen dominance begins as early as age 30 because progesterone production reduces during luteal phase**

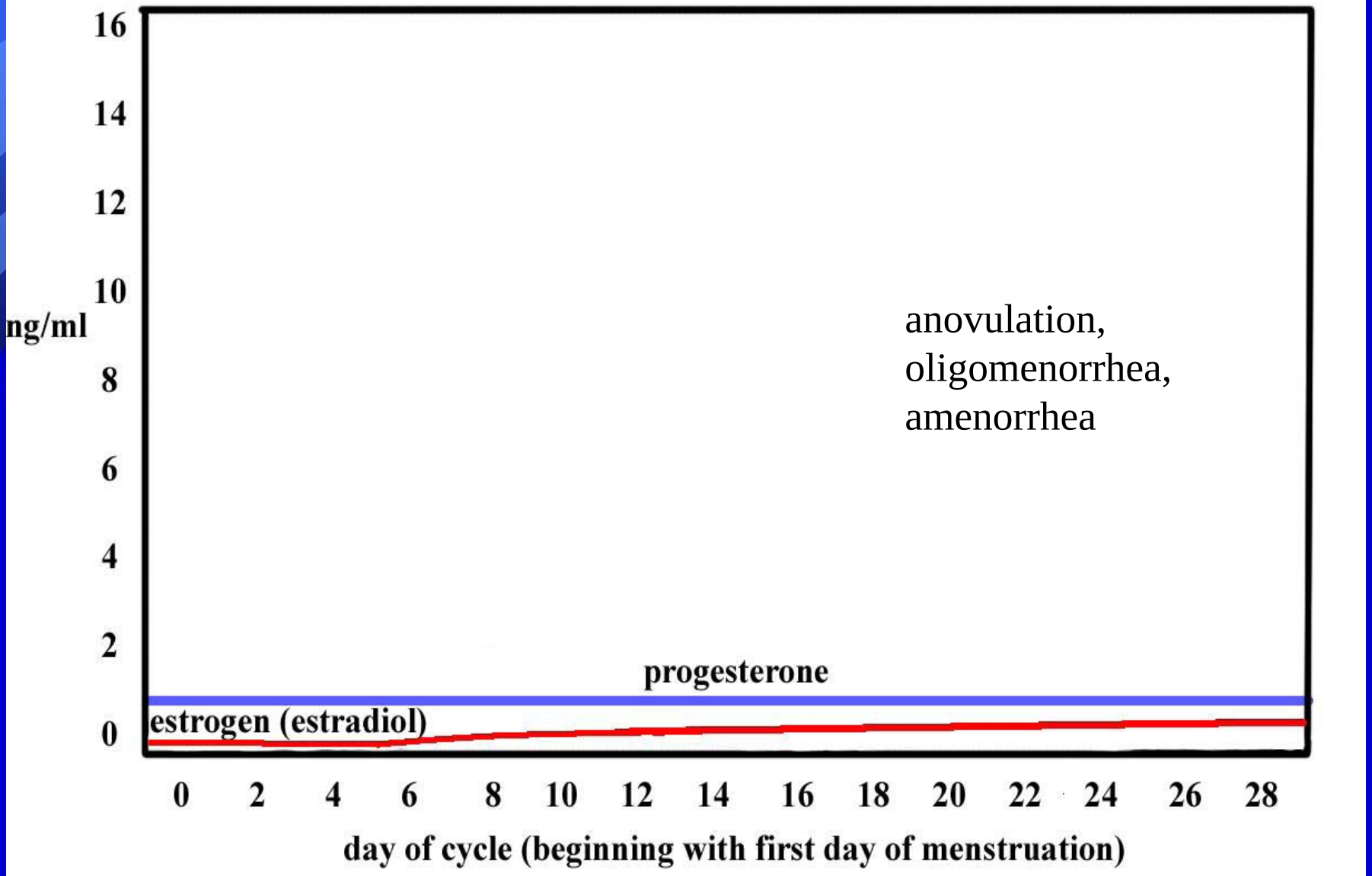
Physiologic progesterone dominance (young age)



Estrogen dominance (perimenopause)



Estrogen dominance (perimenopause)



Problem with progesterone

- the number one problem in women's health care today is the lack of knowledge about progesterone among the general public and medical professionals

- in fact, many physicians and pharmacists erroneously believe that progesterone and progestins are the same substances and that those terms can be used interchangeably

Problem with progesterone (cont.)

- progesterone is a member of a class of drugs called progestogens
- progesterone is the only bioidentical progestogen
- synthetic progestogens are called progestins

Progesterone is not progestin

- progesterone facilitates pregnancy and then helps to sustain that pregnancy to term
- the use of medroxyprogesterone acetate (MPA, Provera) however, is contraindicated in pregnant women because it is teratogenic
- progesterone is an important precursor in the biosynthesis of cortisol, aldosterone, and the other sex hormones, but MPA cannot be converted to those substances

Progesterone is not progestin (cont.)

- the difference in progesterone and MPA is also clearly evident when their side-effect profiles are compared:
  - ✓ the most common side effect of progesterone is sedation
  - ✓ on the other hand, MPA often produces fluid retention, breast tenderness, weight gain, depression, and headache
- obviously, MPA is *not* progesterone

Progesterone is not progestin (cont.)

- progesterone exerts many effects on the cardiovascular system that are not produced by progestins. For example:

- the natriuretic (and thus diuretic) effects due to its mineralocorticoid activity

Corvol P, Elkik M, Feneant ME, et al. Effect of progesterone and progestins on water and salt metabolism. In: Progesterone and progestins. New York: Raven Press;1983

Landau RL, Lugibihl K. The catabolic and natriuretic effects of progesterone in man. Recent Prog Horm Res. 1961;17:249-92.

- 200 mg of progesterone is equivalent to about 25 to 50 mg of spironolactone

Kuhl H. Pharmacokinetics of oestrogens and progestogens. Maturitas. 1990 Sep;12(3):171-97.

Progesterone is not progestin (cont.)

- **it is antihypertensive**

Rylance PB, Brincat M, Lafferty K, De Trafford JC, Brincat S, Parsons V, Studd JW. Natural progesterone and antihypertensive action. Br Med J (Clin Res Ed). 1985 Jan 5;290(6461):13-4.

Armstrong JG. Hypotensive action of progesterone in experimental and human hypertension. Proc Soc Exp Biol Med. 1959 Nov;102:452-5.

- **decreases sympathetic vascular tone without significantly altering blood pressure**

Tollan A, Oian P, Kjeldsen SE, Eide I, Maltau JM. Progesterone reduces sympathetic tone without changing blood pressure or fluid balance in men. Gynecol Obstet Invest. 1993;36(4):234-8.

Progesterone is not progestin (cont.)

- **progesterone promotes bone formation and inhibit bone resorption**

Prior JC. Progesterone as a bone-trophic hormone. Endocr Rev. 1990 May;11(2):386-98.

- **progesterone enhances mineral deposition and bone formation rates**

Schmidt IU, Wakley GK, Turner RT. Effects of estrogen and progesterone on tibia histomorphometry in growing rats. Calcif Tissue Int. 2000 Jul;67(1):47-52.

- **progesterone was linked with the reversal of osteoporosis. Topical progesterone cream was administered for 3 years to 100 postmenopausal women, most of whom had previously experienced at least one osteoporotic fracture.**

Lee JR.Osteoporosis reversal with transdermal progesterone. Lancet. 1990 Nov 24;336(8726):1327.

Progesterone is not progestin (cont.)

- a synthetic progestin or progesterone is usually prescribed only when needed to protect against endometrial cancer caused by ERT
- therefore, neither synthetic progestin nor progesterone is given to women who have undergone hysterectomy
- this practice must be questioned, because after a complete hysterectomy, when the production of estrogen and progesterone is greatly reduced, only estrogen is typically prescribed for the patient
- there are several reasons for which every woman, regardless of whether she has an intact uterus, should receive bioidentical progesterone as part of treatment with ERT

Low Progesterone/normal Estrogens

- Allergies
- Autoimmune diseases
- Anxiety, irritability
- Insomnia
- Depression
- Bloating and edema
- Fibrocystic breasts
- Uterine fibroids

- Breast cancer
- Ovarian cancer
- Uterine cancer
- Thyroid dysfunction
- Gallbladder disease
- Menorrhagia
- Migraines
- Seizures

Restoration of progesterone is the key in physiology optimization

Progesterone vs Progestins

Somatic effects

- the effect of progesterone compared with MPA included a 30% reduction in sleep problems, a 50% reduction in anxiety, a 60% reduction in depression, a 30% reduction in somatic symptoms, a 25% reduction in menstrual bleeding, a 40% reduction in cognitive difficulties, and a 30% improvement in sexual function

- overall, 65% of women felt that HRT combined with progesterone was better than the HRT combined with MPA

Fitzpatrick LA, Pace C, Witta B. Comparison of regimens containing oral micronized progesterone of medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey. J Womens Health Gend Based Med. 2000;9(4):381–387.

Progesterone vs Progestins

Somatic effects

- in a randomized study comparing HRT with MPA or progesterone in women with no mood disorders such as depression or anxiety, Cummings and Brizendine found significantly more negative somatic effects but no differences in mood assessment with synthetic hormones

- these negative effects included increased vaginal bleeding and increased breast tenderness with a trend for increased hot flashes with the use of MPA compared with progesterone

Cummings JA, Brizendine L. Comparison of physical and emotional side effects of progesterone or medroxyprogesterone in early postmenopausal women. *Menopause. 2002;9:253–263.*

Progesterone vs Progestins

Physiologic effects

- synthetic progestins have potential antiapoptotic effects and may significantly increase estrogen-stimulated breast cell mitotic activity and proliferation[7-21]

- in contrast, progesterone inhibits estrogen-stimulated breast epithelial cells[16, 22-28]

Progesterone vs Progestins

Physiologic effects

- Progesterone also downregulates estrogen receptor-1 (ER-1) in the breast,[27–29] induces breast cancer cell apoptosis,[30,31] diminishes breast cell mitotic activity,[7,16,22–24,26–28,31,32] and arrests human breast cancer cells in the G1 phase by upregulating cyclin-dependent kinase inhibitors and downregulating cyclin D1.[23,32]

- Synthetic progestins, in contrast, upregulate cyclin D121 and increase breast cell proliferation.[7–21]

Progesterone vs Progestins

Physiologic effects

- Progesterone consistently demonstrates antiestrogenic activity in breast tissue.[7,16,22,24–29,31–34]
- Synthetic progestins may also increase the conversion of weaker endogenous estrogens into more potent estrogens.[7,40–45]

Progesterone vs Progestins

Physiologic effects

- 3 subclasses of progesterone receptors (PR) have been identified: PRA, PRB, and PRC, each with different cellular activities.[48–52]

- In normal human breast tissue, the ratio of PRA:PRB is approximately 1:1.[50,53] This ratio is altered in a large percentage of breast cancer cells and is a risk for breast cancer.[50,53,54]

Progesterone vs Progestins

Physiologic effects

- In contrast to progesterone, synthetic progestins alter the normal PRA:PRB ratio,[55–57] which may be a mechanism by which synthetic progestins increase the risk for breast cancer.

- Synthetic progestins and progesterone have a number of differences in their molecular and pharmacological effects on breast tissue, as some of the procarcinogenic effects of synthetic progestins contrast with the anticarcinogenic properties of progesterone.[8,16,22,24–26,31,33,40,58–70]

Progesterone vs Progestins

Risk for breast cancer - progestins

- synthetic progestins have been clearly associated with an increased risk for breast cancer[7,8,58,71–98]
- The Women's Health Initiative (WHI), a large randomized clinical trial, demonstrated that a synthetic progestin, MPA, as a component of HRT significantly increased the risk for breast cancer.[71–74]

Progesterone vs Progestins

Risk for breast cancer - progestins

- higher doses of testosterone-derived synthetic progestins and progestin-only regimens increase the risk for breast cancer[8,75–77,80,91]

- synthetic progestin use increased the risk for breast cancer by approximately 25% for each 5 years of use compared with estrogen[82]

Progesterone vs Progestins

Risk for breast cancer - progestins

- The Nurses' Health Study found that, compared with women who never used hormones, use of unopposed postmenopausal estrogen from ages 50 to 60 years increased the risk for breast cancer to age 70 years by 23%.

- The addition of a synthetic progestin to the estrogen replacement resulted in a tripling of the risk for breast cancer.[98]

Progesterone vs Progestins

Risk for breast cancer - progestins

- there is a significant increase in breast cancer of 2% per year for the estrogen-only group and a 4% increase per year if a synthetic progestin was used in addition to the estrogen

- higher doses of progestin increased the risk for breast cancer, and use of a progestin-only preparation doubled the risk for breast cancer[77]

Progesterone vs Progestins

Risk for breast cancer - progesterone

- progesterone and synthetic progestins have generally indistinguishable effects on endometrial tissue

- but…there is significant evidence that progesterone and synthetic progestins have differing effects on breast tissue proliferation

Progesterone vs Progestins

Risk for breast cancer - progesterone

- large-scale observational trials[58,59] and randomized placebo control primate trials[16] do show significant differences between progesterone and synthetic progestins

- in contrast to the demonstrated increased risk for breast cancer with synthetic progestins,[7,8,58,71–98] studies have consistently shown a decreased risk for breast cancer with progesterone[22,23,25,60,61,66–70,99–101]

Progesterone vs Progestins

Risk for breast cancer - progesterone

- women who used progesterone in combination with estrogen, the increased risk for breast cancer was eliminated with a significant reduction in breast cancer risk compared with synthetic progestin use[59]

Progesterone vs Progestins

Risk for breast cancer - progesterone

- progesterone inhibited breast cancer cell proliferation at higher estrogen levels, but that synthetic progestins had the potential to stimulate breast cancer cell proliferation when combined with the synthetic estrogens equilin or 17-alpha-dihydroequilin, which are major components of CEE[24]

Progesterone vs Progestins

Risk for breast cancer - progesterone

- the risk for breast cancer was significantly increased if synthetic progestins were used, but was reduced if progesterone was used

- there was a significant difference in the risk for breast cancer between the use of estrogens combined with synthetic progestins versus estrogens combined with progesterone[58]

Progesterone vs Progestins

Risk for breast cancer - progesterone

- significantly increased proliferation was found with the combination of estrogen and MPA in both lobular and ductal tissue, but was not seen with the combination of estrogen and progesteron[102]

- the induction rate, multiplicity, and size of estrogen-induced mammary tumors were significantly reduced by simultaneous administration of either tamoxifen or progesterone[25]

Progesterone vs Progestins

Risk for breast cancer - progesterone

- estrogen increased cell proliferation rates by 230%, but progesterone decreased cell proliferation rates by 400%
- progesterone, when given with estradiol, inhibited the estrogen-induced breast cell proliferation[22]
- randomized, double-blind study showed that progesterone eliminated estrogen-induced breast cell proliferation[23]

Progesterone vs Progestins

Risk for breast cancer - progesterone

- a prospective epidemiological study demonstrated a protective role for progesterone against breast cancer[99]

- the premenopausal risk for breast cancer was 5.4 times higher in women who had low progesterone levels compared with those with normal levels

Progesterone vs Progestins

Risk for breast cancer - progesterone

- there were 10 times as many deaths from cancer in the low progesterone group compared with those with normal progesterone levels[99]
- women with low progesterone have significantly worse breast cancer survival rates than those with more optimal progesterone levels[100,101]

Progesterone vs Progestins

Risk for breast cancer - progesterone

- Progesterone was inversely associated with breast cancer risk for the highest versus lowest tertile.[61] Other case control studies also found such a relationship.[66–70]

Progesterone vs Progestins

Risk for cardiovascular diseases

- the WHI study demonstrated that the addition of MPA to Premarin® (a CEE) resulted in a substantial increase in the risk of heart attack and stroke[71–73]
- this outcome with MPA is not surprising because synthetic progestins produce negative cardiovascular effects and negate the cardioprotective effects of estrogen[71,73,148–172]

Progesterone vs Progestins

Risk for cardiovascular diseases

- progesterone, in contrast, has the opposite effect because it maintains and augments the cardioprotective effects of estrogen, thus decreasing the risk for heart attack and stroke[148-151,153,155,157,162,165,167,173–178]

Progesterone vs Progestins

Risk for cardiovascular diseases

- a number of studies have shown that coronary artery spasm, which increases the risk for heart attack and stroke, is reduced with the use of estrogen and/or progesterone[149–151,174,179,180]

- the addition of MPA to estrogen has the opposite effect, resulting in vasoconstriction[149–151,174]

Progesterone vs Progestins

Risk for cardiovascular diseases

- when estradiol was given with progesterone, the coronary arteries were protected against induced spasm. However, the protective effect was lost when MPA was used instead of progesterone[149]

Progesterone vs Progestins

Risk for cardiovascular diseases

- none of the animals treated with bioidentical progesterone experienced vasospasm, while all of those treated with MPA showed significant vasospasm[151]

- progesterone protectes against coronary hyperreactivity, while MPA has the opposite effect and induces coronary constriction[150]

Progesterone vs Progestins

Risk for cardiovascular diseases

- the CEE and progesterone combination resulted in a 50% reduction in atherosclerotic plaques in the coronary arteries[175]
- when MPA was combined with the CEE, almost all the cardioprotective effect (atherosclerotic plaque reduction) was reversed[152]

Progesterone vs Progestins

Risk for cardiovascular diseases

- several studies have shown that progesterone by itself,[167,177,181] or in combination with estrogen,[152,175,177] inhibits atherosclerotic plaque formation

- synthetic progestins, in contrast, have a completely opposite effect: they promote atherosclerotic plaque formation and prevent the plaque-inhibiting and lipid-lowering actions of estrogen[152,164,166]

Progesterone vs Progestins

Risk for cardiovascular diseases

- transdermal estradiol, when given with or without oral progesterone, has no detrimental effects on coagulation and no observed increased risk for venous thromboembolism (VTE)[161,182–184]

Progesterone vs Progestins

Risk for cardiovascular diseases

- this result is in contrast to an increased risk for VTE with CEE, with or without synthetic progestin, which significantly increases the risk for VTE, whether both are given orally (eg, oral estrogen and oral synthetic progestin),[71,73,160,171] as transdermal estrogen and oral synthetic progestin,[161] or both estrogen and synthetic progestin given transdermally[185,186]

Progesterone vs Progestins

Risk for cardiovascular diseases

- progesterone is a competitive inhibitor of aldosterone, which is generally a desirable effect[189]
- no changes in blood pressure are observed with progesterone in normotensive postmenopausal women, but a slight reduction in blood pressure is shown in hypertensive women[190,191]

Progesterone vs Progestins

Conclusion

- based on both physiological results and clinical outcomes, current evidence demonstrates that bioidentical hormones are associated with lower risks than their nonbioidentical counterparts

- until there is evidence to the contrary, current evidence dictates that bioidentical hormones are the preferred method of HRT

Summary on progesterone

- the number one problem in women's health care today is the lack of knowledge about progesterone among the general public and medical professionals
- in fact, many physicians and pharmacists erroneously believe that women who had a hysterectomy do not need progesterone?!
- in fact, progesterone is not just a hormone for the uterus. Our body needs progesterone because of the following reasons:

1. progesterone protects a body from estrogen dominance;
2. it protects a breast from breast cancer, fibroids, and cysts;
3. progesterone exerts many effects on the cardiovascular system;

Summary on progesterone (cont.)

4. it has the natriuretic (and thus diuretic) effectis due to its mineralocorticoid activity;

5. it is antihypertensive;

6. progesterone is an important precursor in the biosynthesis of cortisol, aldosterone, and the other sex hormones;

7. decreases sympathetic vascular tone without significantly altering blood pressure;

8. progesterone promotes bone formation and inhibits bone resorption;

9. progesterone enhances mineral deposition and bone formation rates;

Summary on progesterone (cont.)

10. progesterone was linked with the reversal of osteoporosis;
11. progesterone is a natural immune modulator;
12. progesterone calms down the CNS;
13. it is a natural antidepressant and tranquilizer;
14. progesterone improves female libido;
15. it boosts thyroid action;
16. helps use body fat, rather than store it.

There are several more reasons for which every woman, regardless of whether she has an intact uterus, should receive bioidentical progesterone as part of the treatment of hormonorestoration.

Testosterone Restoration for Men

- improves mood and sociability
- restores energy and ambition
- improves cognition, probably protects against Alzheimer's disease
- increases libido and sexual performance
- increases muscle and bone mass
- reduces abdominal fat, improves insulin sensitivity, lowers blood pressure - counteracts metabolic syndrome (Syndrome X)

Haider A, Gooren LJ, Padungtod P, Saad F. Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate. Exp Clin Endocrinol Diabetes. 2010 Mar;118(3):167-71. Epub 2009 May 26.

Testosterone and the Heart

- **low testosterone levels correlate with coronary artery disease and stroke**
- **hyperestrogenemia and hypotestosteronemia have been observed in association with myocardial infarction (MI) and its risk factors**

Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb. 1994 May;14(5):701-6.

Zhao SP, Li XP. The association of low plasma testosterone level with coronary artery disease in Chinese men. Int J

Cardiol. 1998 Jan 31;63(2):161-4.

English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have Lower levels of androgens than men with normal coronary angiograms. Eur Heart J. 2000 Jun;21(11):890-4.

Jeppesen LL, Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS, Winther K. Decreased serum testosterone in Men with acute ischemic stroke. Arterioscler Thromb Vasc Biol. 1996 Jun;16(6):749-54.

Testosterone and the Heart (cont.)

- testosterone dilates coronary arteries—improves angina
- testosterone levels showed a negative significant correlation with thoracic aortic intima media thickness
- testosterone decreases fibrinogen levels

Demirbag R, Yilmaz R, Ulucay A, Unlu D. The inverse relationship between thoracic aortic intima media Thickness and testosterone level. Endocr Res. 2005;31(4):335-44.

Testosterone and the Heart (cont.)

- **testosterone increases heart muscle size, strength**
- **androgen deprivation therapy with GnRH agonists was associated with an increased risk of diabetes, incident CHD, myocardial infarction, sudden cardiac death, and stroke**

Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2010 Jan 6;102(1):39-46. Epub 2009 Dec 7.

Testosterone and Prostate

- **lower testosterone levels increase the risk of prostate cancer**

Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. Urology. 2006 Dec;68(6):1263-7.

- **low testosterone associated with more aggressive prostate cancers**

Slater S, Oliver RT. Testosterone: its role in development of prostate cancer and potential risk from use as hormone replacement therapy. Drugs Aging. 2000 Dec;17(6):431-9.

Testosterone and Prostate (cont.)

- there is an absence of scientific data supporting the concept that higher testosterone levels are associated with an increased risk of prostate cancer
- specifically, no increased risk of prostate cancer was noted in
  1) clinical trials of testosterone supplementation,
  2) longitudinal population-based studies, or
  3) in a high-risk population of hypogonadal men receiving testosterone treatment
- moreover, hypogonadal men have a substantial rate of biopsy-detectable prostate cancer, suggesting that low testosterone has no protective effect against development of prostate cancer

Morgentaler A. Testosterone replacement therapy and prostate risks: where's the beef? Can J Urol. 2006 Feb;13 Suppl 1:40-3.

Testosterone and Prostate (cont.)

- **testosterone is a prostate growth factor, but does not promote prostate cancer.**
- **prostate cancer growth can be *temporarily* slowed only by eliminating all testosterone from the body.**

Abraham Morgentaler. *Testosterone for Life: Recharge Your Vitality, Sex Drive, Muscle Mass, and Overall Health.* McGraw-Hill; 2008

Testosterone and Women

esterified estrogens plus methyltestosterone (E + A) in surgically menopausal women:

- **prevent loss of bone in the spine and hip and increase BMD**
- **improve well-being and sexual interest**
- **decreases LDL**

Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang HM, Nolan J. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone Mineral density, symptoms and lipid profiles. J Reprod Med. 1999 Dec;44(12):1012-20.

Testosterone and Women (cont.)

- E2 alone increased mammary epithelial proliferation by approximately six fold and increased mammary epithelial estrogen receptor (ER alpha) mRNA expression by approximately 50%
- testosterone reduced E2-induced proliferation by approximately 40% and entirely abolished E2-induced augmentation of ER alpha expression.
- combined estrogen/androgen hormone replacement therapy might reduce the risk of breast cancer associated with estrogen replacement

Zhou J, Ng S, Adesanya-Famuiya O, Anderson K, Bondy CA. Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. FASEB J. 2000 Sep;14(12):1725-30.

Testosterone and Women (cont.)

- endogenous androgens normally inhibit mammary epithelial proliferation (MEP)
- small, physiological dose of T to standard estrogen therapy almost completely attenuates estrogen-induced increases in MEP
- the increased breast cancer risk associated with estrogen treatment could be reduced by T supplementation

Dimitrakakis C, Zhou J, Wang J, Belanger A, LaBrie F, Cheng C, Powell D, Bondy C. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. Menopause. 2003 Jul-Aug;10(4):292-8.

Testosterone and Women (cont.)

- testosterone reduces mammary epithelial estrogen receptor (ER) alpha and increases ER beta expression, resulting in a marked reversal of the ER alpha/beta ratio

- that treatment with a balanced formulation including all ovarian hormones may prevent or reduce estrogenic cancer risk in the treatment of girls and women with ovarian failure

Dimitrakakis C, Zhou J, Wang J, Belanger A, LaBrie F, Cheng C, Powell D, Bondy C. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. Menopause. 2003 Jul-Aug;10(4):292-8.

Testosterone and Women (cont.)

- testosterone may serve as a natural endogenous protector of the breast and limit mitogenic and cancer-promoting effects of estrogen on mammary epithelium
- androgen action is antiproliferative and proapoptotic despite the potential for testosterone and dehydroepiandrosterone to be aromatized to estrogen

Somboonporn W, Davis SR; National Health and Medical Research Council. Testosterone effects on the breast: implications for testosterone therapy for women. Endocr Rev. 2004 Jun;25(3):374-88.

Testosterone and Women (cont.)

- **addition of testosterone to conventional hormone therapy for postmenopausal women does not increase and may indeed reduce the hormone therapy-associated breast cancer risk - thereby returning the incidence to the normal rates observed in general, untreated population**

Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone In addition to usual hormone therapy. Menopause. 2004 Sep-Oct;11(5):531-5.

Zhou J, Ng S, Adesanya-Famuiya O, Anderson K, Bondy CA. Testosterone inhibits estrogen-induced mammary
epithelial proliferation and suppresses estrogen receptor expression. FASEB J. 2000 Sep;14(12):1725-30.

Male Andropause

- testosterone levels decline slowly in men - just getting old
- fatigue, reduced mental function
- passivity and moodiness - loss of drive, ambition
- loss of muscle, increased abdominal fat
- increased blood sugar and blood pressure
- loss of libido, spontaneous erection, and eventually erectile function

Controversial issues: hormones - cancer

- **female – disorder of hormonal/menstrual cycle can lead to cancer in female organs (breast, uterus, ovaries)**
- **estradiol stimulates growth of female organs necessary for reproduction; maintain female health and quality of life**
- **estradiol promotes cancer if not balanced with progesterone and androgens**
- **progesterone stops proliferation and promotes maturation and differentiation**

Controversial issues: hormones – cancer (cont.)

- **progesterone has anti-estrogenic action in uterus and breast**
- **decreases synthesis of estradiol receptors**
- **increases conversion of estradiol to estrone by inducing 17β-hydroxysteroid dehydrogenase Type 2**
- **decreases conversion of estrone to estradiol by inhibiting 17β-hydroxysteroid dehydrogenase Type 1**
- **increases sulfation (inactivation) of estrogens**

Williams Text. of Endocrinology, 10thEd., p. 612

Controversial issues: ERT – breast cancer

- **Current use of HRT is associated with an increased risk of incident and fatal breast cancer; the effect is substantially greater for oestrogen-progestagen combinations than for other types of HRT**

Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003 Aug 9;362(9382):419-27.

Controversial issues: ERT – breast cancer

- **DHEA and testosterone can be converted into estrogens and increase risk of breast cancer unless progesterone is restored**

Kaaks R, Berrino F, Key T, Rinaldi S, Dossus L, Biessy C, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). J Natl Cancer Inst. 2005 May 18;97(10):755-65.

Testosterone – breast cancer

- **the normal ovary produces abundant testosterone in addition to estradiol (E2) and progesterone, but usually only the latter two hormones are "replaced" in the treatment of ovarian failure and menopause**
- **endogenous androgens normally inhibit estrogen-induced mammary epithelial proliferation (MEP) and thereby may protect against breast cancer**
- **addition of a small, physiological dose of T to standard estrogen therapy almost completely attenuates estrogen-induced increases in MEP**

Testosterone – breast cancer (cont.)

- **increased breast cancer risk associated with estrogen treatment could be reduced by T supplementation**

Dimitrakakis C, Zhou J, Wang J, Belanger A, LaBrie F, Cheng C, Powell D, Bondy C. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. Menopause. 2003 Jul-Aug;10(4):292-8.

Dimitrakakis C, Zhou J, Bondy CA. Androgens and mammary growth and neoplasia. Fertil Steril. 2002 Apr;77 Suppl 4:S26-33.

Zhou J, Ng S, Adesanya-Famuiya O, Anderson K, Bondy CA. Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. FASEB J. 2000 Sep;14(12):1725-30.

Testosterone – breast cancer (cont.)

- **in rodent breast cancer models, androgen action is antiproliferative and proapoptotic despite the potential for testosterone and dehydroepiandrosterone to be aromatized to estrogen**

- **testosterone may serve as a natural endogenous protector of the breast and limit mitogenic and cancer-promoting effects of estrogen on mammary epithelium**

Somboonporn W, Davis SR; National Health and Medical Research Council. Testosterone effects on the breast: implications for testosterone therapy for women. Endocr Rev. 2004 Jun;25(3):374-88.

Testosterone – breast cancer (cont.)

- **the addition of testosterone to a common estrogen/progestogen regimen was found to inhibit the stimulatory effects of hormones on breast cell proliferation**

von Schoultz B. Androgens and the breast. Maturitas. 2007 May 20;57(1):47-9.

Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. Menopause. 2004 Sep-Oct;11(5):531-5.

Testosterone – breast cancer (cont.)

- **testosterone and DHT inhibit *in vitro* growth of breast cancer cells**

Ortmann J, Prifti S, Bohlmann MK, Rehberger-Schneider S, Strowitzki T, Rabe T. Testosterone and 5 alpha-dihydrotestosterone inhibit in vitro growth of human breast cancer cell lines.Gynecol Endocrinol. 2002 Apr;16(2):113-20.

- **clinical data showing that androgenic compounds induce an objective remission after failure of antiestrogen therapy as well as those indicating that the antiproliferative action of androgens is additive to that of antiestrogens**

Labrie F, Simard J, de Launoit Y, Poulin R, Thériault C, Dumont M, Dauvois S, Martel C, Li SM. Androgens and breast cancer. Cancer Detect Prev. 1992;16(1):31-8.

Testosterone and Prostate cancer

- **lower testosterone levels increase the risk of prostate cancer**
- **no scientific data supporting the concept that higher testosterone levels are associated with an increased risk of prostate cancer**
- **no increased risk of prostate cancer was noted in clinical trials of testosterone supplementation**
- **low testosterone associated with more aggressive prostate cancer**
- **testosterone is a prostate growth factor, but does not promote prostate cancer**

Hormones – breast cancer

- **unopposed estradiol promotes breast cancer**
- **some progestins increase risk of the breast cancer**
- **progesterone prevents breast cancer**
- **testosterone and DHEA may increase risk of breast cancer if estradiol and progesterone are low**
- **DHEA and testosterone prevent breast cancer if estradiol is optimal**
- **estrogen restoration is safe if given with progesterone, testosterone, and DHEA**

Testosterone and Prostate

Few Remarks:

- young men with naturally high testosterone and low estrogen levels are almost completely immune to prostate diseases
- the fall in testosterone and rise in estrogen – almost exactly parallels the rise in prostate diseases
- common sense tells you nothing gets better when you cut a man's testicles off – whether you use scalpel or prescription drugs (like Lupron or Casodex)

Few Remarks (cont.):

- youthful levels of all the androgens including DHEA, androstenedione, testosterone are important to good prostate health
- when men are low in testosterone the prostate receptor must accept dihydrotestosterone (DHT) instead of testosterone

Androgens and risk of prostate cancer:

- review done collectively by six international clinics used the Norwegian Cancer Registry to study the frozen blood serum and medical records over 28,000 men
- they found the higher the testosterone level the less prostate cancer and the longer their life
- neither testosterone, dihydrotestosterone (DHT), nor DHT metabolite 3 alpha, 17 beta-androstanediol glucuronide were associated with the risk of developing prostate cancer

Vatten LJ, Ursin G, Ross RK, Stanczyk FZ, Lobo RA, Harvei S, Jellum E. Androgens in serum and the risk of prostate cancer: a nested case-control study from the Janus serum bank in Norway. Cancer Epidemiol Biomarkers Prev. 1997 Nov;6(11):967-9.

Androgens and risk of prostate cancer (cont.):

- they concluded that the popular idea that testosterone promotes prostate cancer in any way is completely unsupported by research.
- this is the second largest prostate cancer study in history and results are simply inarguable based on ***28,000 men***

Vatten LJ, Ursin G, Ross RK, Stanczyk FZ, Lobo RA, Harvei S, Jellum E. Androgens in serum and the risk of prostate cancer: a nested case-control study from the Janus serum bank in Norway. Cancer Epidemiol Biomarkers Prev. 1997 Nov;6(11):967-9.

Low testosterone – Prostate cancer

- **a high prevalence of biopsy-detectable prostate cancer was identified in men with low total and free testosterone levels despite normal PSA levels and results of digital rectal examination**

Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA. 1996 Dec 18;276(23):1904-6.

History of androgen deprivation therapy

- in 1941 Huggins and Hodges reported that marked reductions in T by castration or estrogen treatment caused metastatic pCA to regress, and administration of exogenous T caused pCA to grow

- remarkably, this latter conclusion was based on results from only one patient

Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. Eur Urol. 2006 Nov;50(5):935-9. Epub 2006 Jul 27.

History of androgen deprivation therapy (cont.)

- for this reason, it has been considered taboo to offer testosterone replacement therapy (TRT) to any man with a prior history of PCa, even if all objective evidence suggests he has been cured
- the fear has been that higher testosterone levels would "awaken" dormant cells and cause a recurrence
- thus, US Food and Drug Administration-mandated language in all testosterone package inserts states that testosterone is contraindicated in men with a history of, or suspected of having, PCa.

Morgentaler A. Testosterone therapy for men at risk for or with history of prostate cancer. Curr Treat Options Oncol. 2006 Sep;7(5):363-9.

History of androgen deprivation therapy (cont.)

- although there is little modern experience with administration of testosterone in men with known history of PCa, there is a varied and extensive literature indicating that TRT does not pose any increased risk of PCa growth in men with or without prior treatment

- for instance, the cancer rate in TRT trials is only approximately 1%, similar to detection rates in screening programs, yet biopsy-detectable PCa is found in one of seven hypogonadal men

Morgentaler A. Testosterone therapy for men at risk for or with history of prostate cancer. Curr Treat Options Oncol. 2006 Sep;7(5):363-9.

History of androgen deprivation therapy (cont.)

- moreover, PCa is almost never seen in the peak testosterone years of the early 20s, despite autopsy evidence that men in this age group already harbor microfoci of PCa in substantial numbers

- the growing number of PCa survivors who happen to be hypogonadal and request treatment has spurred a change in attitude toward this topic, with increasing numbers of physicians now offering TRT to men who appear cured of their disease

Morgentaler A. Testosterone therapy for men at risk for or with history of prostate cancer. Curr Treat Options Oncol. 2006 Sep;7(5):363-9.

History of androgen deprivation therapy (cont.)

- publications have now reported no prostate-specific antigen (PSA) recurrence with TRT in small numbers of men who had undetectable PSA values after radical prostatectomy
- although still controversial, there appears to be little reason to withhold TRT from men with favorable outcomes after definitive treatment for PCa
- monitoring with PSA and digital rectal examination at regular intervals is recommended

Morgentaler A. Testosterone therapy for men at risk for or with history of prostate cancer. Curr Treat Options Oncol. 2006 Sep;7(5):363-9.

History of androgen deprivation therapy (cont.)

- historical perspective reveals that there is not now - nor has there ever been-a scientific basis for the belief that T causes pCA to grow.
- discarding this modern myth will allow exploration of alternative hypotheses regarding the relationship of T and pCA that may be clinically and scientifically rewarding

Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. Eur Urol. 2006 Nov;50(5):935-9. Epub 2006 Jul 27.

Conventional medical wisdom

- it has been part of the conventional medical wisdom for six decades that higher testosterone in some way increases the risk of prostate cancer
- this belief is derived largely from the well-documented regression of prostate cancer in the face of surgical or pharmacological castration
- however, there is an absence of scientific data supporting the concept that higher testosterone levels are associated with an increased risk of prostate cancer

Morgentaler A. Testosterone replacement therapy and prostate risks: where's the beef? Can J Urol. 2006 Feb;13 Suppl 1:40-3.

Conventional medical wisdom (cont.)

- Specifically, no increased risk of prostate cancer was noted in:

1)clinical trials of testosterone supplementation,
2)longitudinal population-based studies, or
3)in a high-risk population of hypogonadal men receiving testosterone treatment

- moreover, hypogonadal men have a substantial rate of biopsy-detectable prostate cancer, suggesting that low testosterone has no protective effect against development of prostate cancer

- these results argue against an increased risk of prostate cancer with testosterone replacement therapy

Morgentaler A. Testosterone replacement therapy and prostate risks: where's the beef? Can J Urol. 2006 Feb;13 Suppl 1:40-3.

What are the risks for middle-aged men?

- with increased recognition of the benefits of testosterone (T) therapy for middle-aged men, there has been a concomitant reexamination of the historical fear that raising T will result in more prostate cancer (PCa)

- studies have failed to show increased risk of PCa in men with higher serum T, and supraphysiologic T fails to increase prostate volume or prostate-specific antigen in healthy men

Morgentaler A. Testosterone and prostate cancer: what are the risks for middle-aged men? Urol Clin North Am. 2011 May;38(2):119-24. Epub 2011 Apr 13.

What are the risks for middle-aged men? (cont.)

- this apparent paradox is explained by the Saturation Model, which posits a finite capacity of androgen to stimulate PCa growth

- modern studies indicate no increased risk of PCa among men with serum T in the therapeutic range

Morgentaler A. Testosterone and prostate cancer: what are the risks for middle-aged men? Urol Clin North Am. 2011 May;38(2):119-24. Epub 2011 Apr 13.

Testosterone therapy in men with untreated prostate cancer

- testosterone therapy in men with untreated prostate cancer was not associated with prostate cancer progression in the short to medium term
- the longstanding prohibition against testosterone therapy in men with untreated or low risk prostate cancer or treated prostate cancer without evidence of metastatic or recurrent disease merits reevaluation

Morgentaler A, Lipshultz LI, Bennett R, Sweeney M, Avila D Jr, Khera M. Testosterone therapy in men with untreated prostate cancer. J Urol. 2011 Apr;185(4):1256-60. Epub 2011 Feb 22.

TRT and PIN

- after 1 year of TRT men with prostatic intraepithelial neoplasia (PIN) do not have a greater increase in PSA or a significantly increased risk of cancer than men without PIN
- these results indicate that TRT is not contraindicated in men with a history of PIN

Rhoden EL, Morgentaler A. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. J Urol. 2003 Dec;170(6 Pt 1):2348-51.

Testosterone level – Prostate Cancer

- high grade prostate cancer is associated with low serum testosterone levels
- the men with low levels averaging only 2.8 ng/ml had the fastest growing malignancies and died faster
- the men with high levels averaging 4.1 ng/ml had the slowest growing malignancies and lived the longest
- why aren't we using testosterone supplements for prostate cancer?

Schatzl G, Madersbacher S, Thurridl T, Waldmüller J, Kramer G, Haitel A, Marberger M. High-grade prostate cancer is associated with low serum testosterone levels. Prostate. 2001 Apr;47(1):52-8.

Testosterone level – Prostate Cancer (cont.)

- **patients with a pretreatment level of testosterone less than 300ng/ml had the most rapid progression**

Ishikawa S, Soloway MS, Van der Zwaag R, Todd B. Prognostic factors in survival free of progression after androgen deprivation therapy for treatment of prostate cancer. J Urol. 1989 May;141(5):1139-42.

Testosterone level – Prostate Cancer (cont.)

- **the results showed that serum testosterone in patients with BPH and PCA (cancer) was lower than that of the (healthy) control group**

Li S et al. Hubei Yike Daxue Xeubao, V. 19, 1998, pp.241-2, 247

Testosterone level – Prostate Cancer (cont.)

- serum concentrations for DHEA-S and testosterone were comparable between PC and control patients
- the lower the testosterone the worse the diseases rates

Schatzl G, Reiter WJ, Thürridl T, Waldmüller J, Roden M, Söregi S, Madersbacher S. Endocrine patterns in patients with benign and malignant prostatic diseases. Prostate. 2000 Aug 1;44(3):219-24.

Testosterone level – Prostate Cancer (cont.)

- at the University of Washington a progressive, innovative and free thinking doctor named Richmond Prehn actually said that we should consider giving androgen supplements to reduce the growth of prostate cancer!
- he showed that earlier studies proved low testosterone levels led to a far worse prognosis than in men with higher testosterone level

Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. Cancer Res. 1999 Sep 1;59(17):4161-4.

Testosterone level – Prostate Cancer (cont.)

- the healthy men had testosterone levels of 636 ng/ml, the men with BPH had 527, and the cancer patients only 473
- yet doctors tried to deny their own data since it didn't fit into their bias!!!" these data suggest there are no measurable differences in serum testosterone levels among men who are destined to develop prostate cancer and those without the disease"!
- how can there be "no measurable differences" between levels of 636 ng in healthy men and only 473 ng in cancer patients?!

Carter HB, Pearson JD, Metter EJ, Chan DW, Andres R, Fozard JL, Rosner W, Walsh PC. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. Prostate. 1995 Jul;27(1):25-31.

Testosterone level – Prostate Cancer (cont.)

- at the University of Utah a very unusual study was done with 214 pairs of identical twins
- such rare studies are exceedingly accurate due to biological equality of the twins
- they found the higher the testosterone the smaller the prostate glands, and the lower the testosterone the larger the prostate glands
- prostate volume correlated inversely with age adjusted serum testosterone level

Meikle AW, Stephenson RA, Lewis CM, Middleton RG. Effects of age and sex hormones on transition and peripheral zone volumes of prostate and benign prostatic hyperplasia in twins. J Clin Endocrinol Metab. 1997 Feb;82(2):571-5.

Testosterone level – Prostate Cancer (cont.)

- **the analysis of serum testosterone levels revealed that the higher the pretreatment serum testosterone level, the greater the survival rate**

Chodak GW, Vogelzang NJ, Caplan RJ, Soloway M, Smith JA. Independent prognostic factors in patients with metastatic (stage D2) prostate cancer. The Zoladex Study Group. JAMA. 1991 Feb 6;265(5):618-21.

Testosterone level – Prostate Cancer (cont.)

- **patients with prostate cancer and low free testosterone had more extensive disease**

Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? J Urol. 2000 Mar;163(3):824-7.

Testosterone level – Prostate Cancer (cont.)

- **low testosterone, indicating androgen independence, and a younger age, seem to result in a more aggressive disease and a poorer prognosis in advanced prostate cancer**

Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. Am J Clin Oncol. 1997 Dec;20(6):605-8.

Testosterone level – Prostate Cancer (cont.)

- **low serum testosterone in men with newly diagnosed prostate cancer is associated with higher tumor microvessel and androgen receptor density as well as with higher Gleason score, suggesting enhanced malignant potential**

Schatzl G, Madersbacher S, Haitel A, Gsur A, Preyer M, Haidinger G, Gassner C, Ochsner M, Marberger M. Associations of serum testosterone with microvessel density, androgen receptor density and androgen receptor gene polymorphism in prostate cancer. J Urol. 2003 Apr;169(4):1312-5.

TRT– Prostate

- **there were no ill effects on prostate size, symptoms or prostate specific antigen level during 9 weeks intervention with either intramuscular testosterone, transdermal testosterone**

Kenny AM, Prestwood KM, Raisz LG. Short-term effects of intramuscular and transdermal testosterone on bone turnover, prostate symptoms, cholesterol, and hematocrit in men over age 70 with low testosterone levels. Endocr Res. 2000 May;26(2):153-68.

TRT– Prostate (cont.)

- these findings suggest that exogenous testosterone in middle-aged and older men with some clinical features of age-related androgen deficiency can retard or reverse prostate growth and that elevated plasma LH may be a useful index of severity of age-related androgen deficiency

Pechersky AV, Mazurov VI, Semiglazov VF, Karpischenko AI, Mikhailichenko VV, Udintsev AV. Androgen administration in middle-aged and ageing men: effects of oral testosterone undecanoate on dihydrotestosterone, oestradiol and prostate volume. Int J Androl. 2002 Apr;25(2):119-25.

TRT– Prostate (cont.)

- 86 men with BPH were given testosterone propionate injections. After three to six weeks of injections, 69 of the men were described as “completely cured”

Kook N. J Int Coll Surg. 1944;7:129.

TRT– Prostate (cont.)

- Dr. Georges Debled has treated more than 2000 men with testosterone over the past two decades. In a group of this size, statistically we would expect at least 50-60 would develop prostate cancer. According to Dr. Debled, prostate cancer has occur in none of these men

- Dr. Wright clinical experience with natural testosterone is not as extensive as Dr. Debled's, it's been very similar; every man who's reported back to Dr. Wright has been pleased with results

Wright JV. Maximize your vitality and potency. 1999

DHT– Prostate

- Dr. de Lignieres: 5 alpha-reductase inhibitors may only be useful in the short term. In the long run, they may be potentially harmful
- by blocking the conversion of testosterone to DHT, they force testosterone down to aromatase-estradiol pathway – thus shifting the hormonal balance in favor of estrogen
- don’t forget that, in addition to prostate problems, elevated estrogens relative to androgens in the human male have also been associated with sexual dysfunction, CVD, and other serious chronic illnesses

de Lignieres B. Transdermal dihydrotestosterone treatment of 'andropause'. Ann Med. 1993 Jun;25(3):235-41.

DHT– Prostate (cont.)

- DHT also inhibits aromatase activity, potentially reducing the level of estradiol. This would tend to shift the estrogen:DHT ratio back in a safer direction
- daily percutaneous DHT treatment suggested that high plasma levels of DHT (> 8.5 nmol/l) effectively induced clinical benefits while slightly but significantly reducing prostate size

de Lignieres B. Transdermal dihydrotestosterone treatment of 'andropause'. Ann Med. 1993 Jun;25(3):235-41.

Testosterone and ED

- hypogonadism (low serum testosterone) is commonly associated with erectile dysfunction (ED)
- however, many urologists may lack appreciation of the relative merits of treating hypogonadism compared with oral phosphodiesterase inhibitors for sexual dysfunction
- testosterone-replacement therapy (TRT) may be the best treatment for men with ED when the presentation includes diminished libido or other sexual symptoms or when non-sexual symptoms such as depressed mood, decreased sense of vitality, and increased fatigue also exist

Lazarou S, Morgentaler A. Hypogonadism in the man with erectile dysfunction: what to look for and when to treat. Curr Urol Rep. 2005 Nov;6(6):476-81.

Testosterone and ED (cont.)

- the health benefits of TRT also include improvements in body composition, bone density, cognition, and sense of well-being
- thus, there may be good reasons to use TRT as first-line therapy for the man with ED
- concerns regarding prostatic and cardiovascular risks of TRT have not been supported by the literature

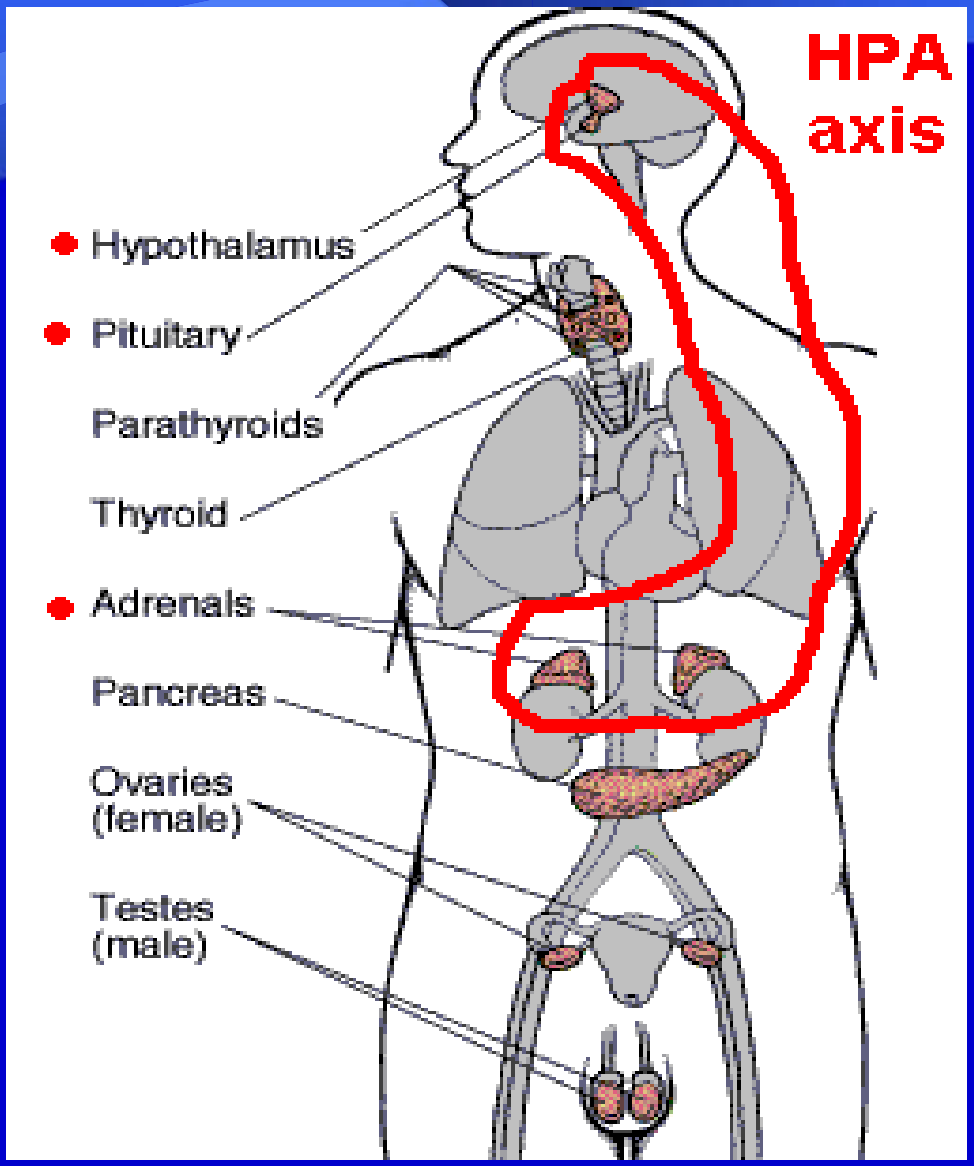
Lazarou S, Morgentaler A. Hypogonadism in the man with erectile dysfunction: what to look for and when to treat. Curr Urol Rep. 2005 Nov;6(6):476-81.

Testosterone and ED (cont.)

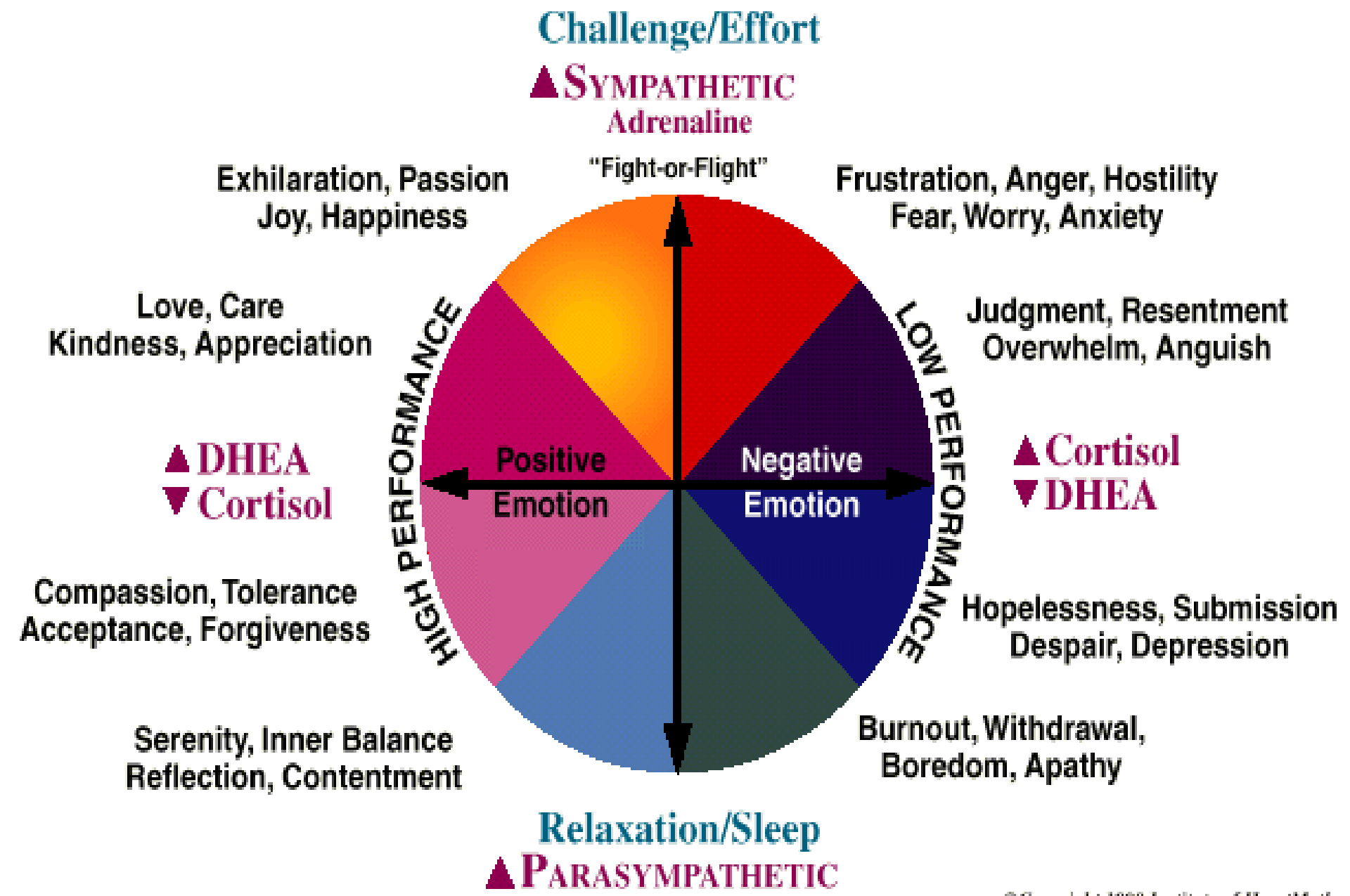
- nevertheless, men receiving TRT must be monitored at regular intervals with digital rectal examination and blood testing for prostate-specific antigen
- hematocrit or hemoglobin also should be obtained regularly due to the risk of erythrocytosis

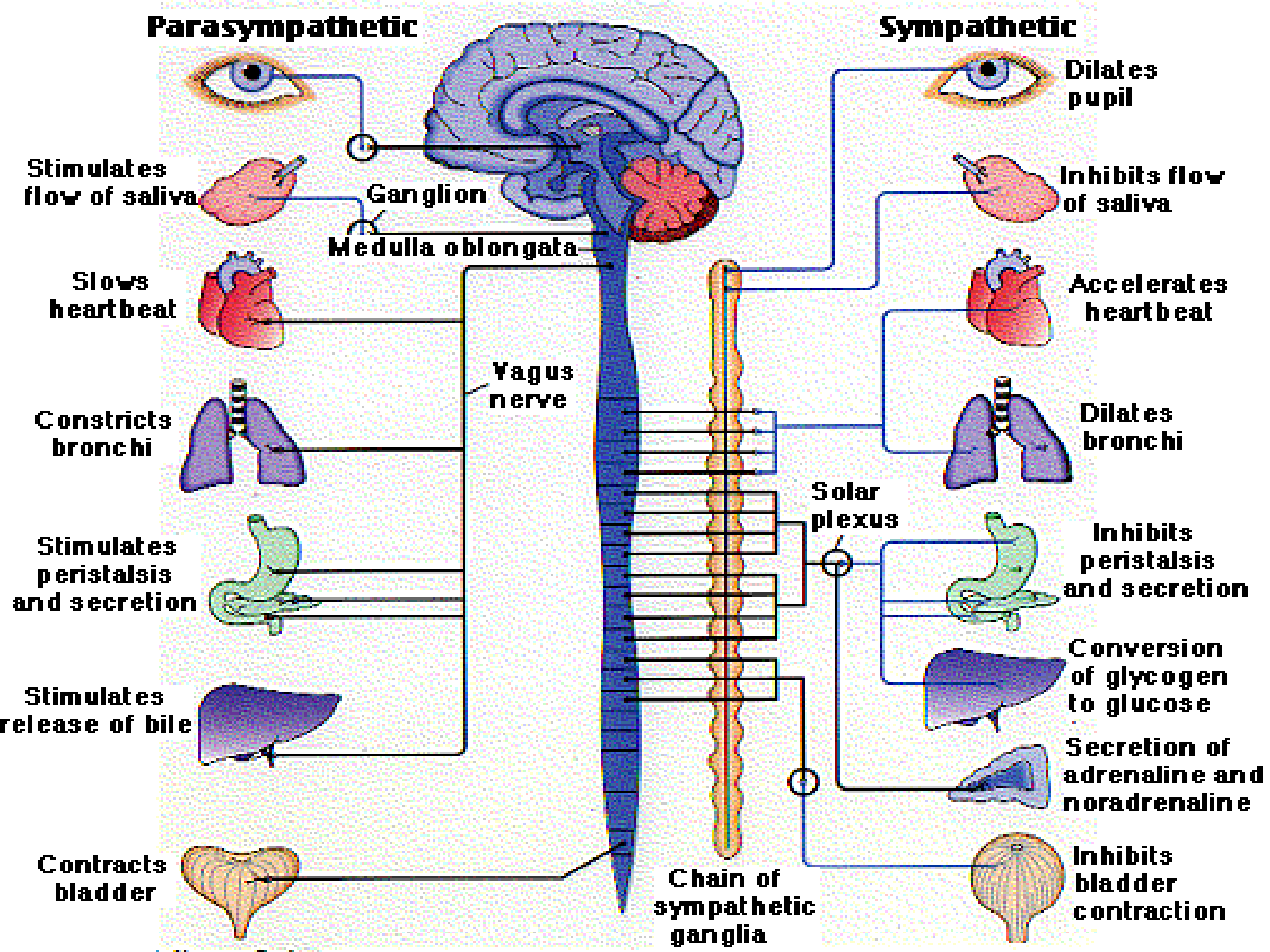
Lazarou S, Morgentaler A. Hypogonadism in the man with erectile dysfunction: what to look for and when to treat. Curr Urol Rep. 2005 Nov;6(6):476-81.

The team-work of our glands



Stress, Emotion and Physiological Activation




Parasympathetic
Sympathetic
Dilates pupil
Stimulates flow of saliva
Ganglion
Medulla oblongata
Inhibits flow of saliva
Slows heartbeat
Accelerates heartbeat
Vagus nerve
Constricts bronchi
Dilates bronchi
Solar plexus
Stimulates peristalsis and secretion
Inhibits peristalsis and secretion
Conversion of glycogen to glucose
Stimulates release of bile
Secretion of adrenaline and noradrenaline
Contracts bladder
Chain of sympathetic ganglia
Inhibits bladder contraction

Delivery systems for hormones:

Oral

1. Capsules

- pregnenolone
- DHEA
- melatonin
- aldosterone

2. Tablets

- hydrocortisone
- whole thyroid (Armour thyroid)

3. Troche

- progesterone (200 mg/troche)

4. Drops

- Tri-Est – 5 mg/ml (E3:E2:E1- 80:10:10)
- progesterone - 50 mg/ml
- testosterone - 50 mg/ml

Topical

Gels (micronized)

- Tri-Est gel – (E3:E2:E1 – 90:7:3) – 1.25-2.5 mg/ml
- progesterone 5-10% – 50-100 mg/ml
- testosterone 5-10% – 50-100 mg/ml

Parenteral

Subcutaneus

- HGH (human growth hormone)
- HCG (human chorionic gonadotropin)

Estrogens formulations:

BI-EST

Biest is a combination of two estrogens: estriol and estradiol. It is most commonly found in a ratio of 80:20, estriol to estradiol.

TRI-EST

Triest is a combination of three estrogens: estriol, estradiol and estrone. It is most commonly found in a ratio of 80:10:10, estriol, estradiol, and estrone.

This combination is very popular and contains all of the three major circulating estrogens. It is slightly weaker in its effect when compared

to biest. However, this can be compensated for by increasing the strength or by slightly changing the ratios.

topical gels/creams:

- contain highly lipophilic molecules with low molecular weight that better absorbed through the skin. This is called "transdermal" administration
- the better absorption is obtained with the use of "trans-mucosal" administration if hormones are rubbed into a mucous membrane surface (inner surface of labia or intravaginally).
- may use adipose tissue as a reservoir
- facilitate individualized dose of prescription[200-202]

Standard approach to hormonal treatment

- youthful levels of hormones increase risk of heart attacks and cancers in aging patients
- the low level of hormones is body adaptation that allows us to increase longevity

Such “misunderstanding” is perfect for pharmaceutical companies:

Rx drugs for every symptom caused by the hormonal deficiency

Against standard approach to hormonal treatment

- **coronary heart disease, high blood pressure, diabetes type II, different cancers, autoimmune diseases, etc., occur years after hormone deficiencies were established and registered more frequent in individuals with lower levels**

- **studies on hormonorestorative therapy did not show any harm**

Transdermal Bases

Comparison of Transdermal Bases			
Base Name	**Penetrating Ability**	**Uses**	**Notes**
Pluronic Lecithicin Organogel (PLO)	++++	Penetration of water soluble, large molecules, and drugs for systemic absorption.	Lipodermal system of drug delivery. The standard of transdermal bases.
Lipoderm Gel	++++	Same as PLO, except in some chemically sensitive patients. More cosmetically acceptable.	Liposomal delivery, can be refrigerated
Anhydrous Gel	+++	Slightly less penetrating than PLO. Not as greasy as PLO.	Good for alcohol soluble drugs. Does not contain water.
Vanpen Cream	+++	Use for more lipophyllic drugs, and more cosmetically acceptable.	May not be used as vaginal cream.
Aladerm Cream	++	An occlusive emulsion base used for absorption into, rather than through the skin.	Contains 20% urea.

http://kenmorerx.com/transdermal.aspx

Dosage

- the recommended doses to different patients during HT varied significantly and were determined by clinical data and serum hormonal levels during serial testing
- doses were individually selected during HT to produce physiologic serum levels typical for healthy individuals between the age of 20 and 30 for both genders
- we administered hormones in doses sufficient to restore the optimal level that was defined as level of hormones in one third of highest normal range for all steroid hormones (except of estradiol/total estrogen for men) from the testing laboratory

Basic Lab – Serum: *Additional Lab:* (if needed)

- CBC
- chemistry panel
- lipid profile
- homocysteine
- pregnenolone
- DHEA Sulfate
- total testosterone
- total estrogen
- progesterone
- cortisol
- vitamin D-3
- TSH, T3, T4
- serotonin
- prolactin
- aldosterone
- melatonin
- dopamine
- free testosterone
- DHT
- SHBG
- IGF-1
- PSA *(men)*

Saliva test:

- saliva test was suggested when physicians tried to find a noninvasive, nonstressful, convenient, simple, and unexpensive method of measuring various hormones that can be correlated with hormonal levels in the blood
- the concentrations of hormones in saliva are very low[220]
- the concentration of conjugated steroids, thyroid hormones, and protein hormones such as choriogonadotropin in saliva does not reflect their concentration in plasma in any clinically useful way[215]
- salivary concentrations of unconjugated steroids reflect those for free steroids in serum although concentrations may differ because of salivary gland metabolism[221]

Saliva test:

- the diagnostic value of salivary oestradiol, progesterone, testosterone, dehydroepiandrosterone and aldosterone testing is compromised by rapid fluctuations in salivary concentrations of these steroids[221]
- accuracy of testosterone levels achieved by the salivary method is questionable in individuals whose actual testosterone levels are low[222]
- saliva does not produce accurate results in children with lower levels of testosterone and estrogen[223]
- salivary testosterone measurements in children do not have proven sensitivity and specificity and cannot be generally recommended for clinical use[223]
- multiple samples are required to obtain reliable information, and at present the introduction of these assays into routine laboratory testing is not justified[221]

Saliva test:

- significant reduction in salivary flow rate was observed in patients with primary thyroid insufficiency and peripheral neurpathy secondary to Diabetes Mellitus[225]

- saliva progesterone levels were very high and variable in the progesterone cream groups compared to the placebo group and presented a paradox to the usual relationship observed between plasma and saliva progesterone in premenopausal women[227]

- salivary concentrations of unconjugated steroids reflect those for free steroids in serum although concentrations may differ because of salivary gland metabolism[221]

- results do not support the routine use of salivary testosterone levels in postmenopausal women[226]

Saliva test:

- significantly poorer salivary function was found in autoimmune diseases (they are not rare in aging patients) that makes saliva testing useless[216,217]
- there is a poor correlation between the concentration of estrogens and progesterone in the blood and saliva both in physiological and pathological pregnancy[218]
- salivary cortisol response parallels that of total plasma cortisol, but the relative change in cortisol levels from the basal value is greater in saliva than in plasma[219]
- Another problem is dry mouth. Dry mouth is a common complaint among older adults, and the aging process is erroneously considered by many to be the primary cause. Salivary gland hypofunction and common complications related to this problem can mislead doctors when they evaluate saliva test.[219]

Saliva test:

- Between 50% and 60% of patients with parkinsonism suffer from severe drooling (sialorrhoea). Sialorrhoea is leading to storage of saliva in the anterior part of the mouth[228]
- The measurement of the salivary level is a valuable clinical tool for some hormones (e.g. cortisol, oestriol, progesterone), is of little value for others (e.g. cortisone, dehydroepiandrosterone sulphate, thyroxine, pituitary hormones) and for many others the saliva/plasma relationship is not yet sufficiently understood to assess the value of the salivary measurement[224]
- measurements of salivary hormone levels will usually only be of value if they reflect the plasma level of the hormone and the relationship between the saliva and plasma levels of many hormones[224]

Urine test:

- the major role of the kidney in steroid metabolism is the elimination of metabolites
- metabolites circulate in free form and are readily eliminated by the kidney
- depending on the steroid, up to 98% may be protein bound; protein binding effectively restricts glomerular filtration
- metabolic processing of active hormone also occurs in the kidney, but, this is a minor process[213]
- because of the minor role played by the kidney in inactivating steroid hormones, the metabolic pathways involved have not been studied as intensively as those in the liver[214]

Dry Blood Spot:

- **Advantages** of using dry blood spot samples-compared with venipuncture include the relative ease and low cost of sample collection, transport, and storage[232]
- **Disadvantages** include requirements for assay development and validation as well as the relatively small volumes of sample

Dry Blood Spot:

- there are advantages for patients to take samples at home but these must be weighed against potential problems with the sampling technique
- some assays appear to work very well whilst others suffer from poor recovery because of adsorption of the analyte onto the filter paper
- calibration of assays and the problems with matrix matching of standards are also important issues that need to be addressed before an assay can be used routinely[235]

Dry Blood Spot:

- despite the increasing popularity of DBS-LC-MS/MS, the method has its limitations in assay sensitivity due to the small sample size
- sample quality is often a concern
- whereas most analytes may be stable on DBS, unstable compounds present another challenge for DBS as enzyme inhibitors cannot be conveniently mixed during sample collection[234]
- improvements on the chemistry of DBS card are desirable

DBS – Dry Blood Spot
LC - Liquid chromatography
MS/MS -mass spectrometry

Dry Blood Spot:

- major the use of dried blood spot samples in population-level research is subject to some limitations[229]
- the majority of standard laboratory protocols require the use of serum or plasma, meaning that protocols using dried blood spot samples have to be developed and verified independently
- in addition, clinical, diagnostic analyte values are nearly always based on protocols using serum or plasma, and because of differences in sample composition, these may not be directly comparable to analyte values derived from dried whole blood spot samples

Dry Blood Spot:

- in cases where such comparison with serum or plasma values is desired, correction factors can be applied to dried blood spot analyte values, but these correction factors are method specific, and the relationship between serum/plasma values and dried blood spot values can be population specific as well[230]
- Preanalytical variability associated with dried blood spot collection (i.e., blood spot serum volume)[231] and transport (sample degradation)[229] has also been identified as a problem associated with the method in some cases

Dry Blood Spot:

- correspondence of serum to blood spot measures is high, with blood spot hormone levels explaining an average of 88.60% of the variance in serum gonadal hormones in females, but only 46.20% in males[233]
- there is a need in formulas converting hormone levels in blood to hormone levels in serum

Dry Blood Spot, Cholesterol and TRG:

- the collection of blood samples by finger pricks from subjects living in places with limited resources and transportation to a distant laboratory will be useful for screening with a wider reach
- however, the suitability of dried blood for the screening of cholesterol and triglycerides needs evaluation under field conditions
- blood collection in the field is difficult in a developing country such as India where technical expertise in remote places may be limiting
- dried blood would be of great utility in remote locations where facilities for centrifugation are not accessible[236]

Dry Blood Spot, Cholesterol and TRG:

- there is a reasonably good correlation between dried blood and serum for total cholesterol and triglyceride measurement
- unlike in controlled laboratory conditions, the collection and transportation of blood on filter paper in the field were beset with several caveats
- the following shortcomings were noted in the collection of blood spots:
  - spots were too small in some instances and disks could not be punched out for extraction
  - blood was spotted twice at the same spot in some samples

Dry Blood Spot, Cholesterol and TRG:

- filters were not dried properly prior to putting inside the resealable bags
- the Ziploc bags were not closed tightly; as a result, moisture entered inside
- filter papers were not labeled properly

- because of the aforementioned factors, the coefficient of variation in dried blood measurement was high, which is likely to affect the value of the assay in screening

Dry Blood Spot, Cholesterol and TRG:

- for the dried blood approach to be successful in field conditions, variations in measurements due to these factors would need to be minimized

- a more rigorous training of field staff and preparation and circulation of an instruction manual with pictorial representations of do's and don'ts may help in minimizing these preanalytical variations[236]

Dry Blood Spot, Cholesterol and TRG:

- because temperature and humidity conditions vary in different parts of the country, these may also have an important bearing on the quality of blood spots
- minimization of preanalytical variations with proper collection and storage of blood would be an important determinant for the success of mass screening of total cholesterol and triglycerides using dried blood for risk factor assessment[236]

Latest Serum Lab “chaos”:

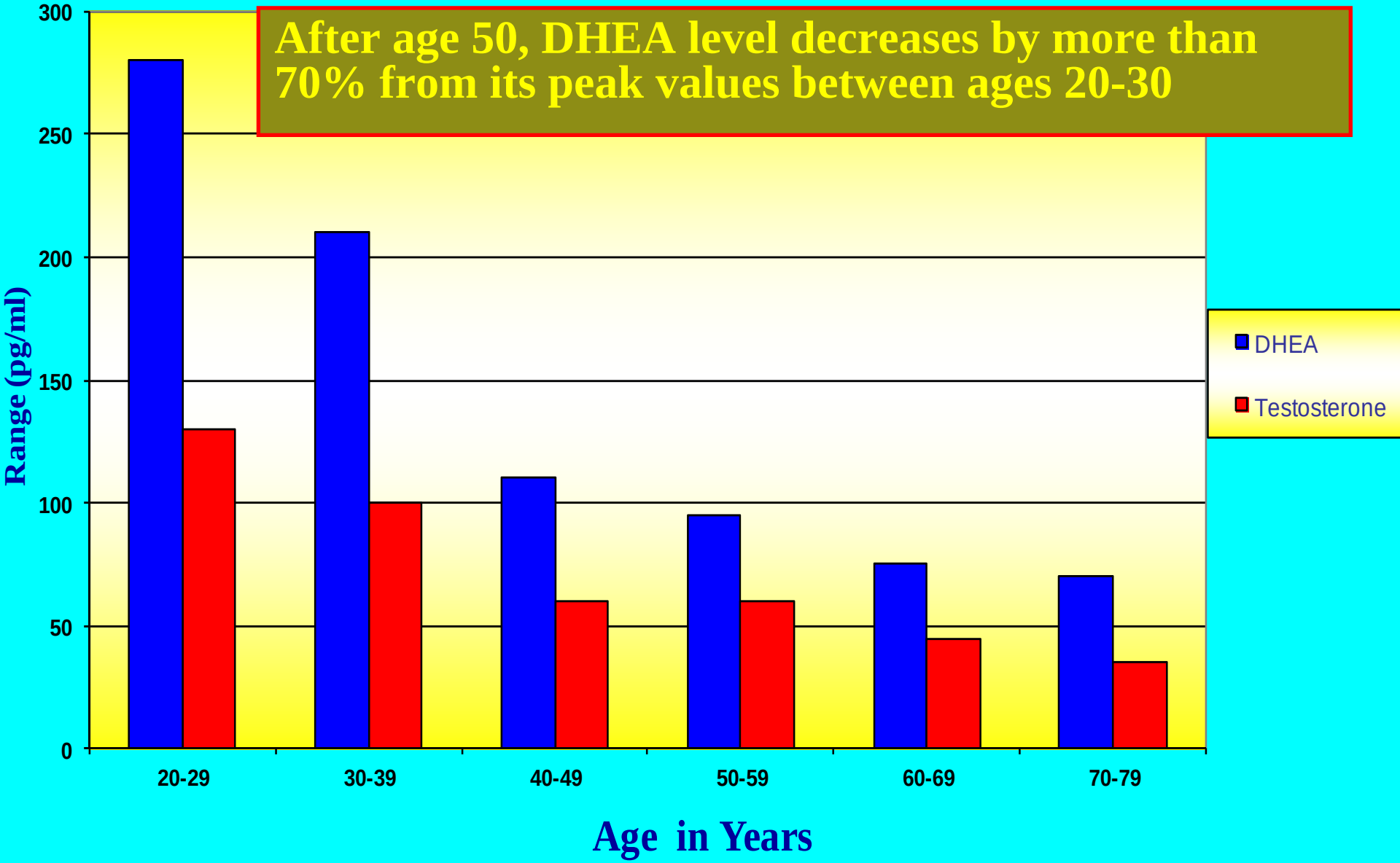
- total estrogen in female

BP, 53 yo

- Estradiol - 117.8 pg/mL
- Estrone - 794 pg/mL
- Total Estrogens 496 pg/mL

- total testosterone in female, progesterone in male

Ranges for DHEA and testosterone



Bio-identical Hormone Restoration

If a hormone is low, restore optimal levels!

- **type 1 Diabetes: bioidentical insulin**
- **hypothyroidism: bioidentical T4 and T3 (Armour Thyroid)**
- **growth hormone deficiency: bioidentical GH**
- **adrenal insufficiency: cortisol (hydrocortisone)**

Bio-identical Hormone Restoration (cont.)

- **proper fit in receptors**
- **normal elimination**
- **monitor therapy with blood tests!**

No side effects, but effects!

But… menopause, andropause, autoimmune disease, etc
Non-bioidentical: methyltestosterone, Premarin, Provera, etc?!!!!

Few rules for HT:

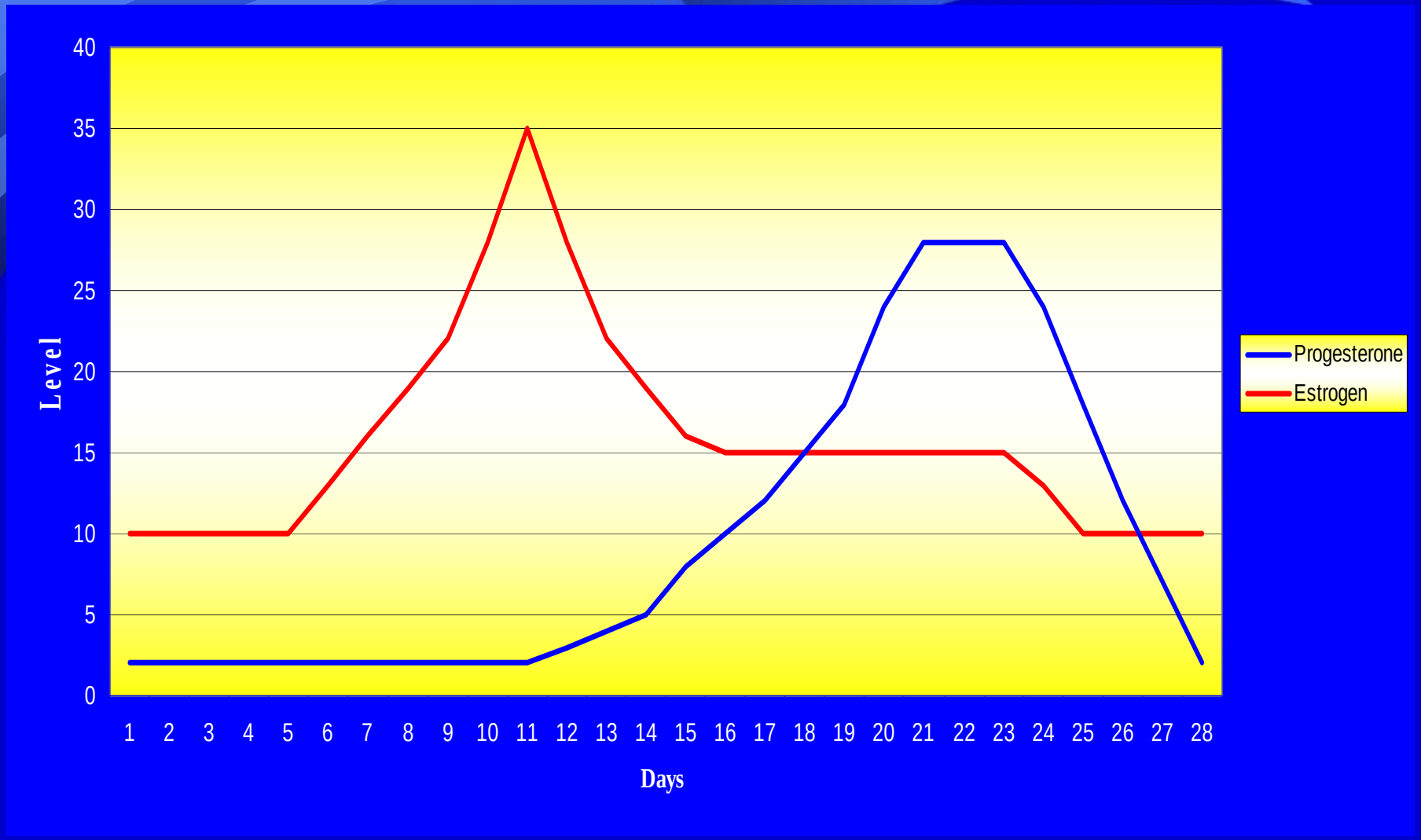
- **bio-identical structure of hormones**
- **individually modified doses**
- **cyclical manner**
- **larger dose in the morning**
- **treatment control by serum hormonal level**
- **mono- or bi-hormonal therapy is usually inadequate**
- **multi-hormonal therapy is optimal**

Bio-identical Hormone Restoration (cont.)

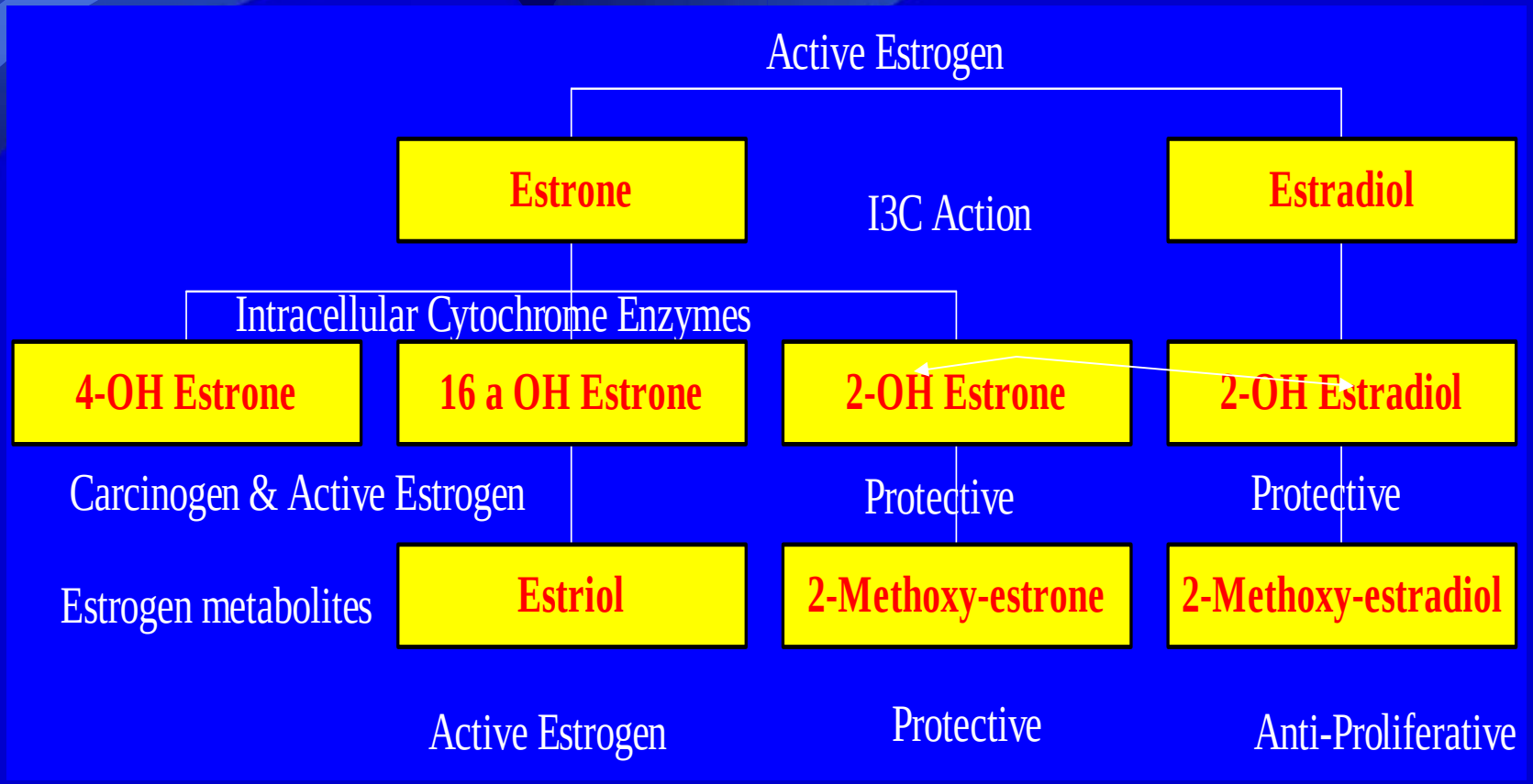
bio-identical restoration must be used instead of non-bio-identical substitution in all cases

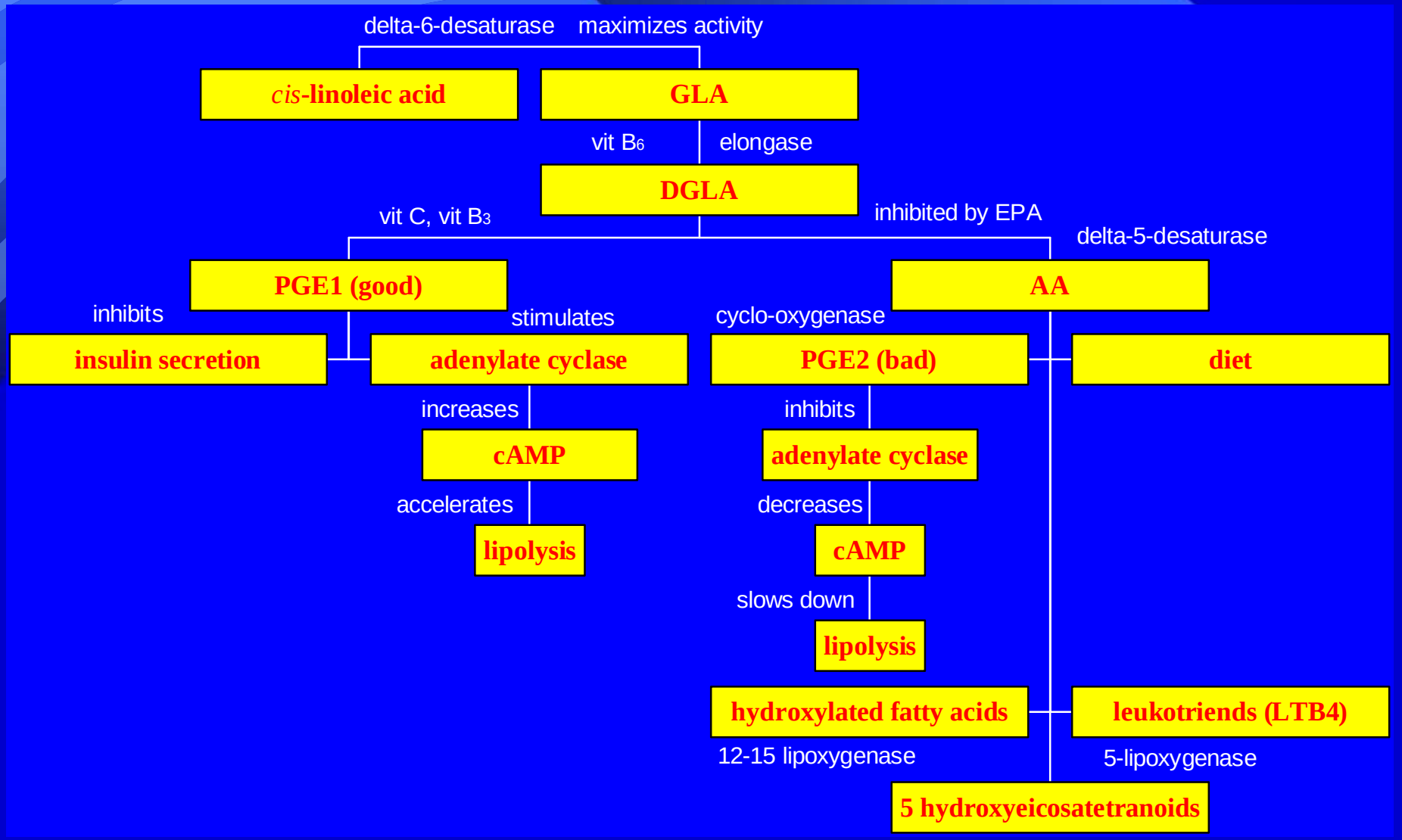
Estrogen and progesterone levels

(during a 28-days menstrual cycle)

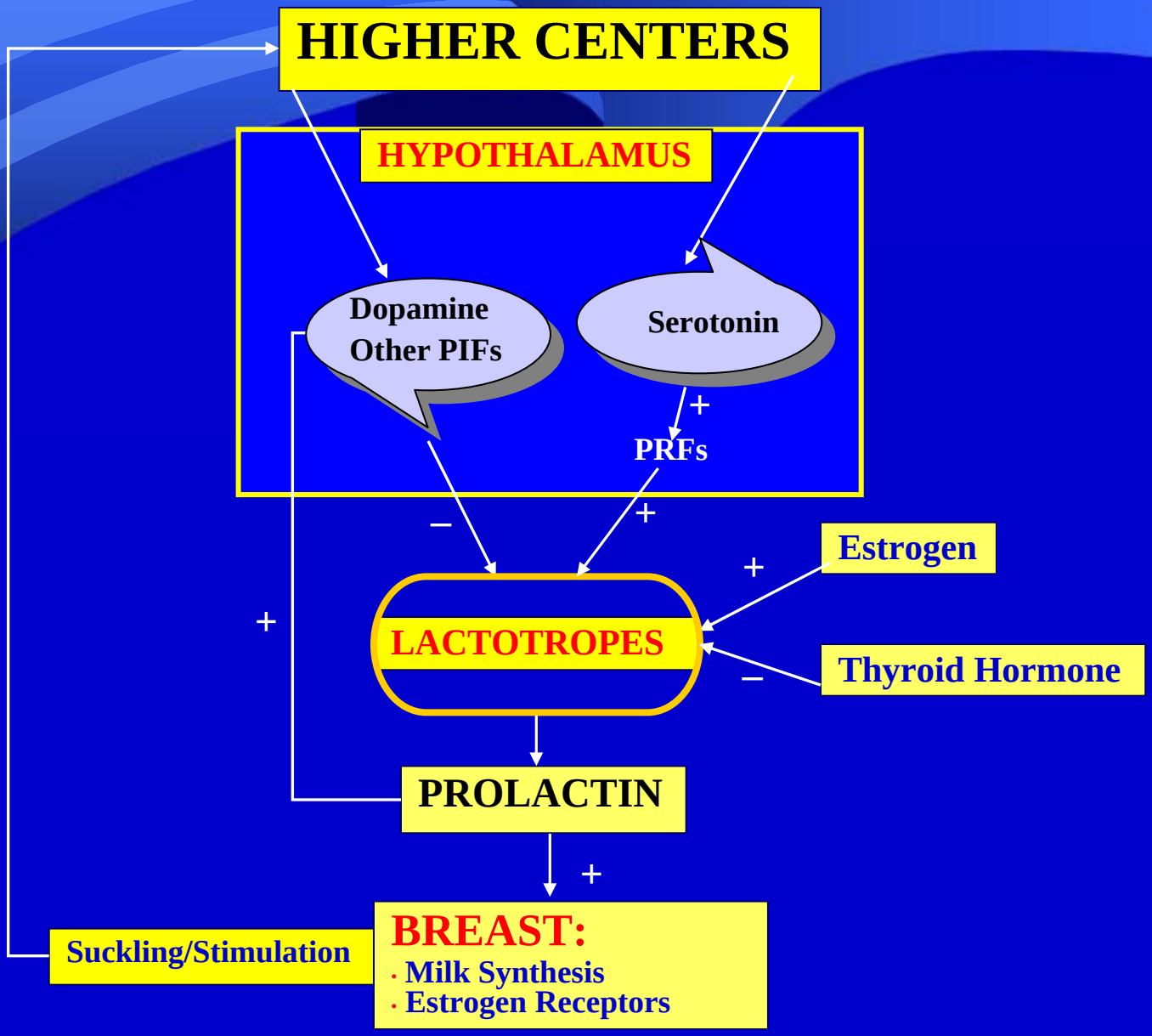


Estrogen Metabolism




delta-6-desaturase
maximizes activity
cis-linoleic acid
GLA
vit B6
elongase
DGLA
vit C, vit B3
inhibited by EPA
delta-5-desaturase
PGE1 (good)
AA
inhibits
stimulates
cyclo-oxygenase
insulin secretion
adenylate cyclase
PGE2 (bad)
diet
increases
inhibits
cAMP
adenylate cyclase
accelerates
decreases
lipolysis
cAMP
slows down
lipolysis
hydroxylated fatty acids
leukotriends (LTB4)
12-15 lipoxygenase
5-lipoxygenase
5 hydroxyeicosatetranoids

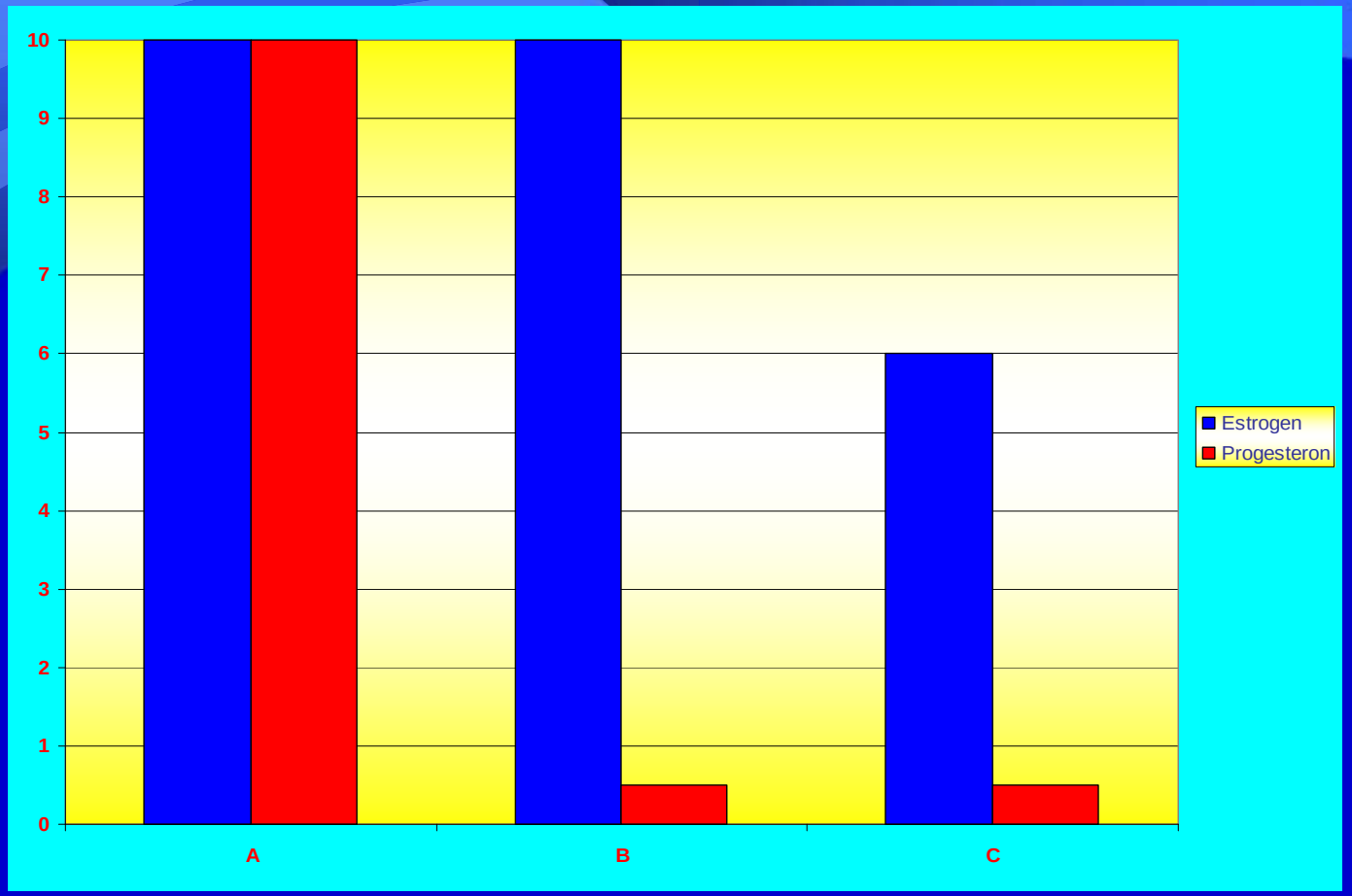
Control of Prolactin Synthesis and Secretion



Age and Breast Cancer[210]

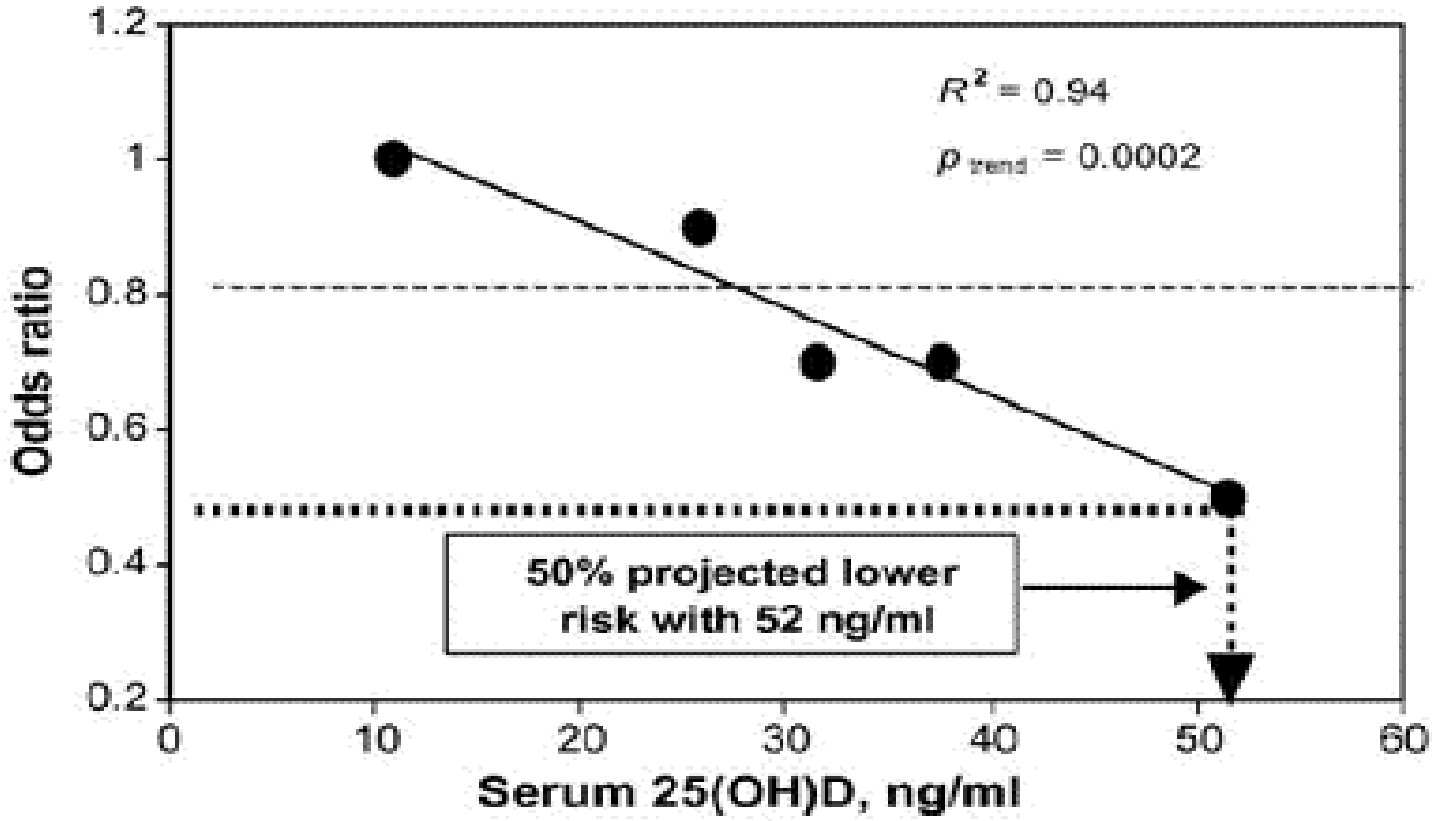
Risk of Developing Breast Cancer by Age126	
By age **25:**	1 in 19,608
By age **30:**	1 in 2,525
By age **40:**	1 in 217
By age **45:**	1 in 93
By age **50:**	1 in 50
By age **55:**	1 in 33
By age **60:**	1 in 24
By age **65:**	1 in 17
By age **70:**	1 in 14
By age **75:**	1 in 11
By age **80:**	1 in 10
By age **85:**	1 in 9

Estrogen/progesterone ratio during aging



- **A** = balance of estrogen and progesterone during the secretory phase of a normal menstrual cycle
- **B** = relative production of estrogen and progesterone during an anovulatory premenopausal menstrual cycle
- **C** = relative production of estrogen and progesterone after menopause

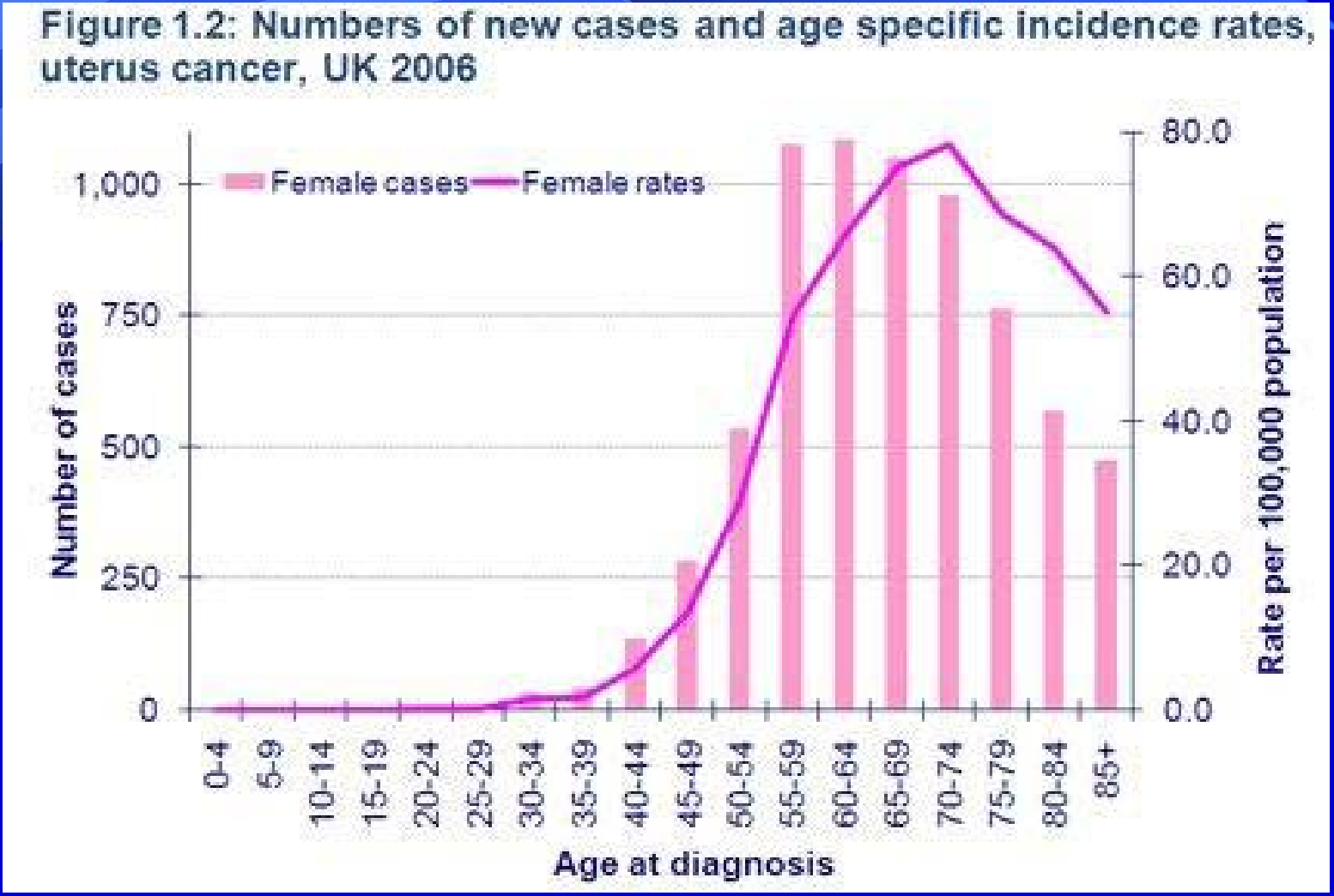
Vitamin D - Breast Cancer



Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, pooled analysis.

Source: Garland CF, et al. Vitamin D and prevention of breast cancer: Pooled analysis, J Steroid Biochem Mol Biol. 2007;103:708-11

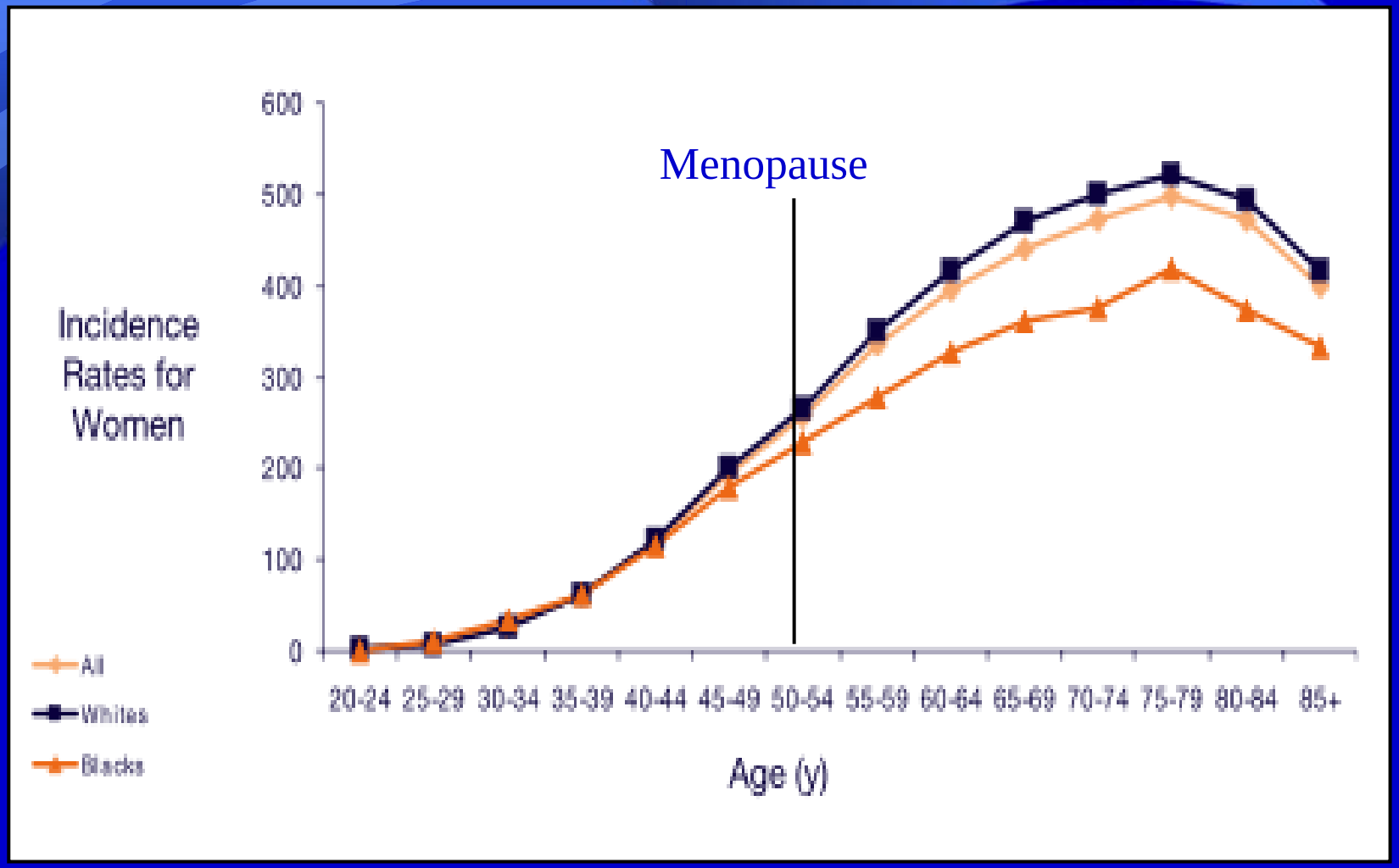
Age - Uterine Cancer



Cancer Research UK 2006

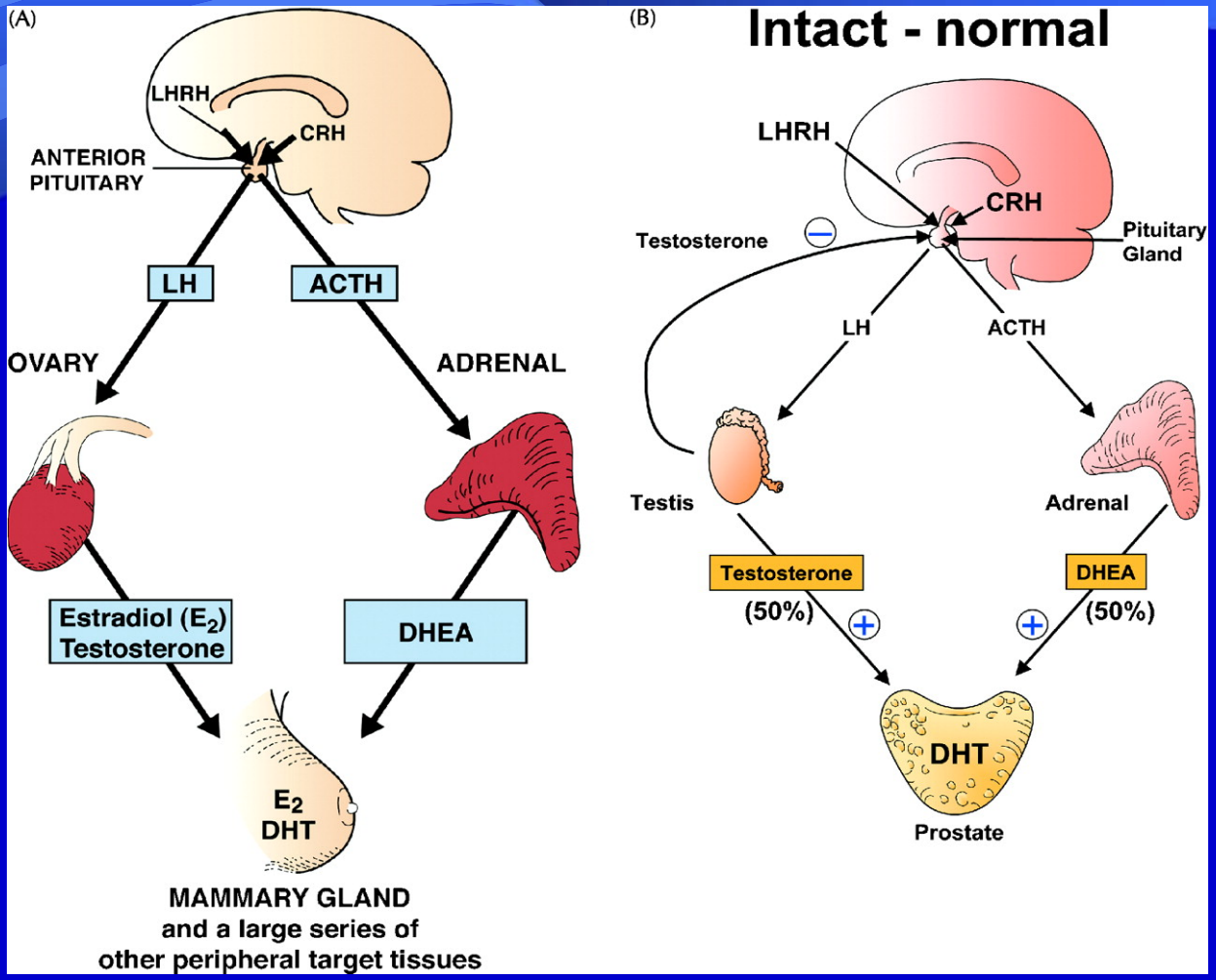
Breast Cancer Rate during Aging

Low/no progesterone increases risk of breast cancer



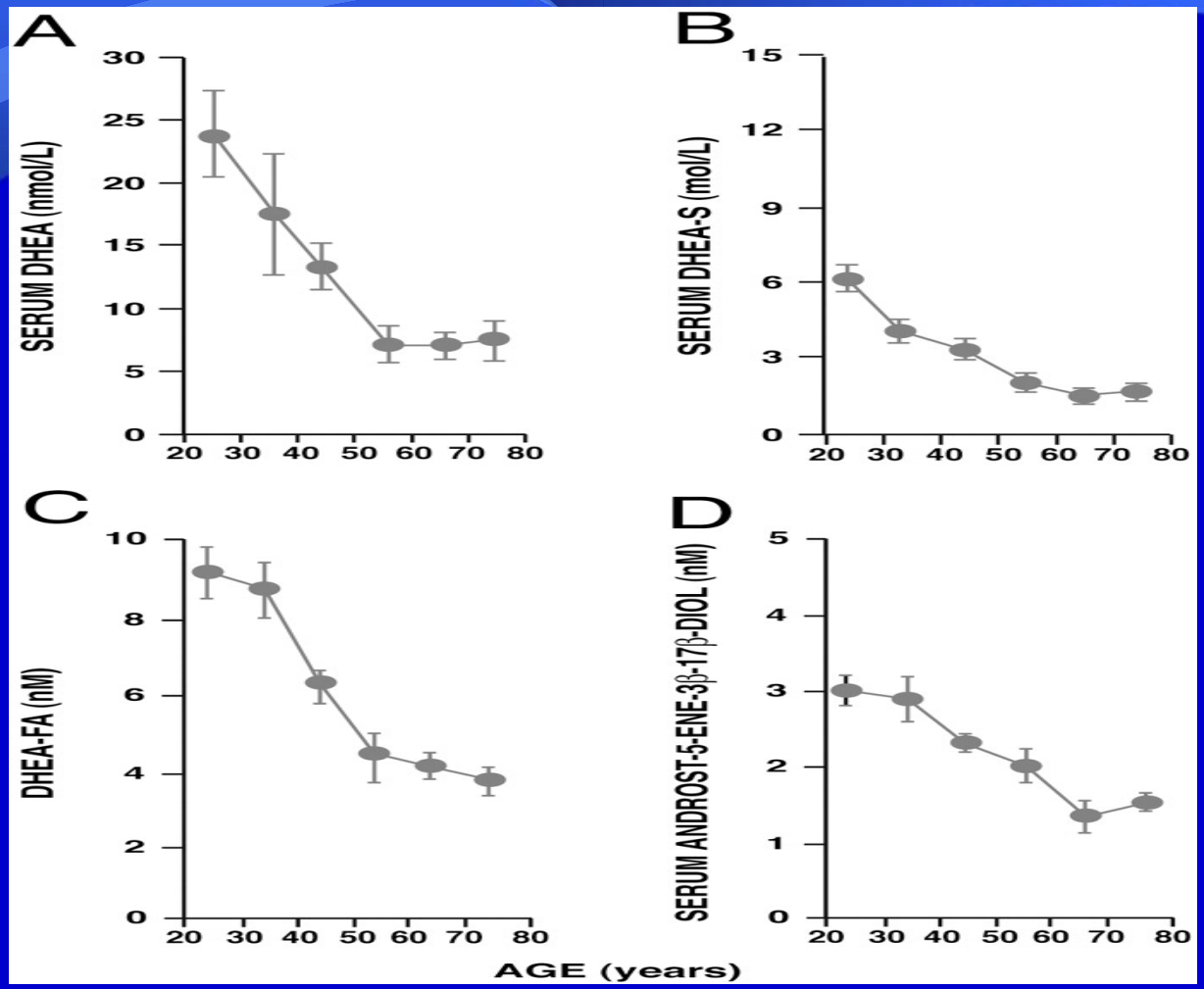
National Cancer Institute. *SEER cancer statistics review 1975-2002*. Table IV-3.

Schematic representation of the role of ovarian and adrenal sources of sex steroids in premenopausal women and the role of testicular and adrenal sources of androgens in 60-year-old men



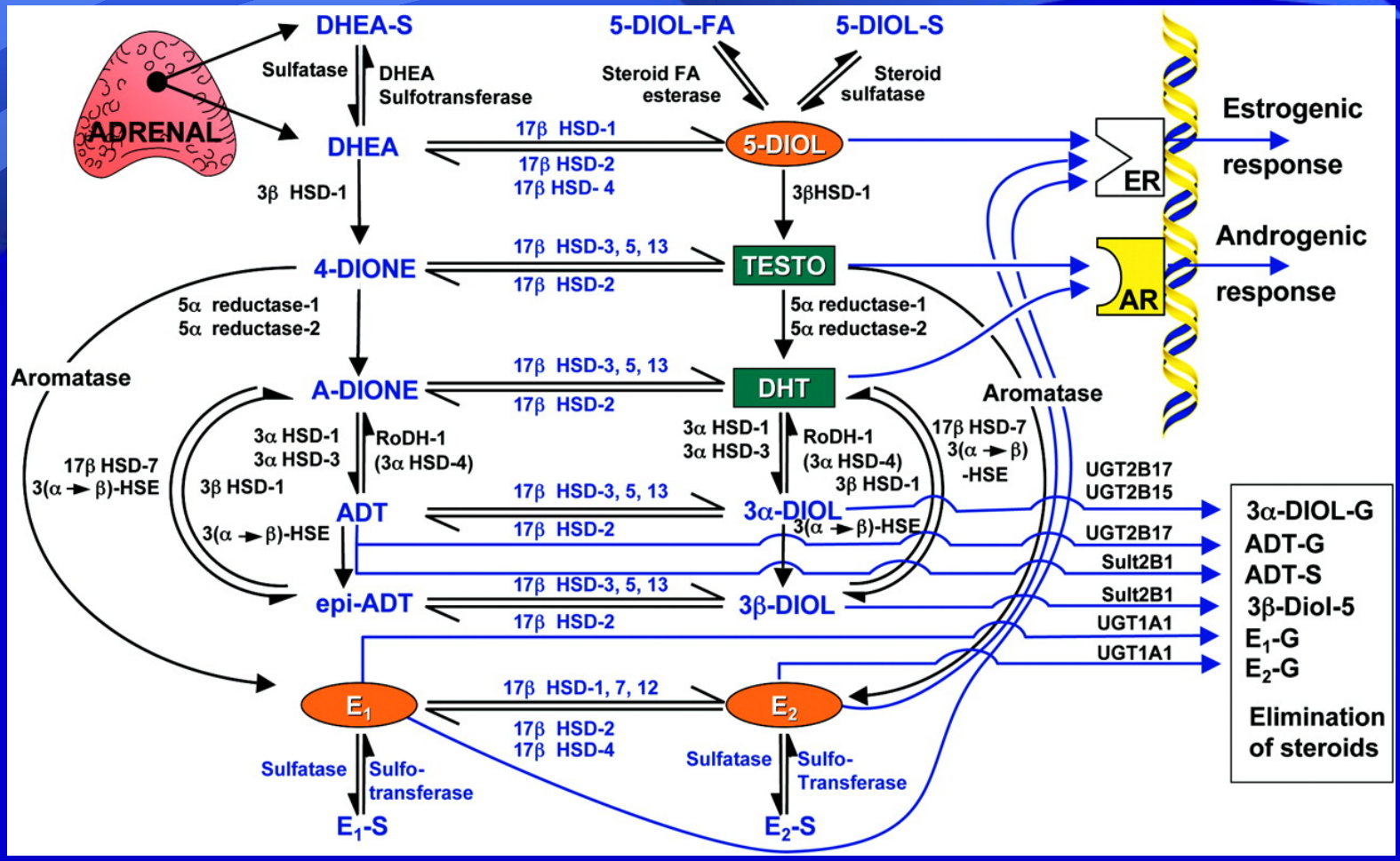
Labrie F, Luu-The V, Bélanger A, Lin SX, Simard J, Pelletier G, Labrie C. Is dehydroepiandrosterone a hormone? J Endocrinol. 2005 Nov;187(2):169-96.

Effect of age (20-30 to 70-80 years old) on serum concentration of (A) DHEA, (B) DHEA-S, (C) DHEA-fatty acid esters (DHEA-FA) and (D) androst-5-ene-3{alpha},17{beta}-diol (5-diol) in women



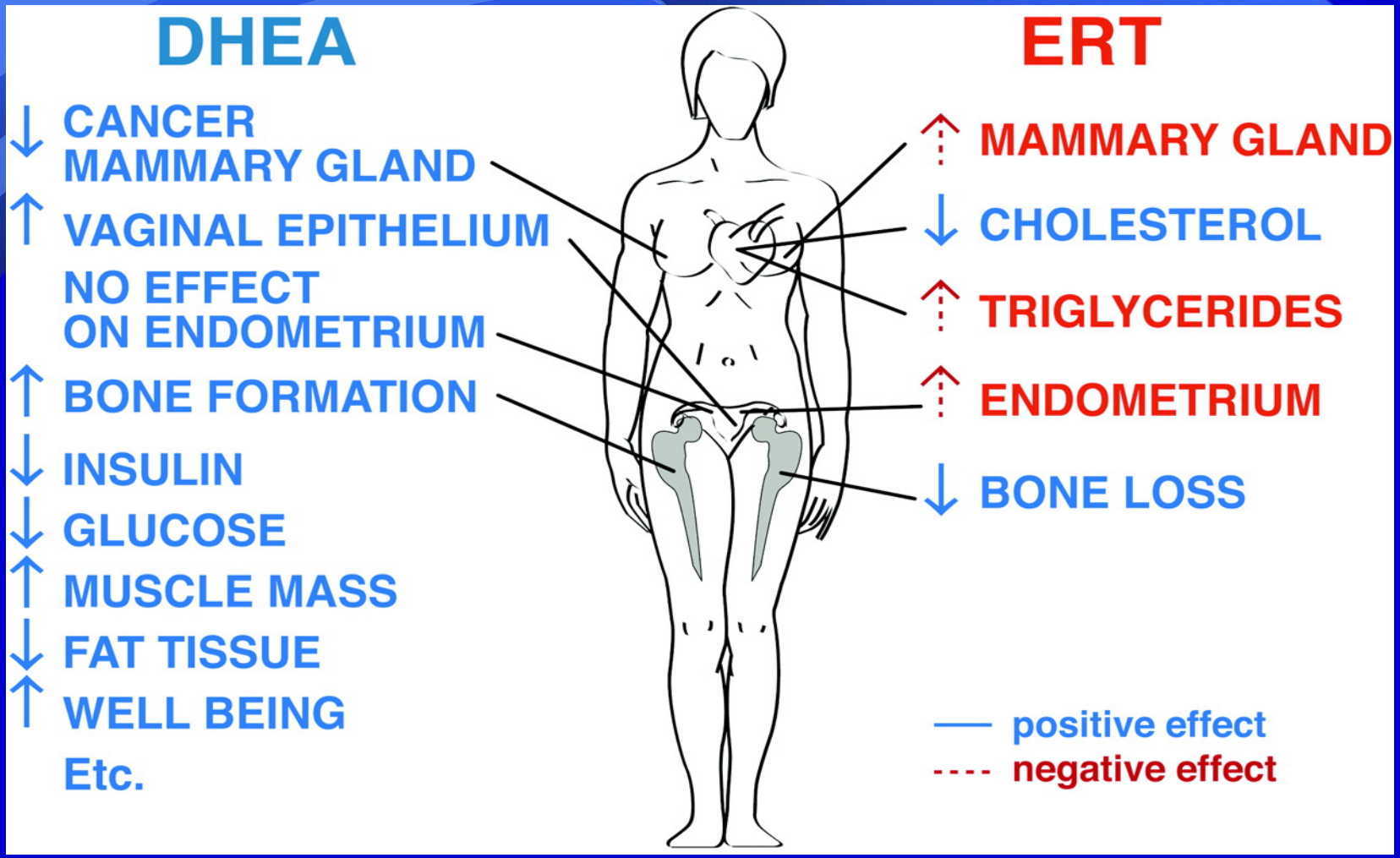
Labrie F, Luu-The V, Bélanger A, Lin SX, Simard J, Pelletier G, Labrie C. Is dehydroepiandrosterone a hormone? J Endocrinol. 2005 Nov;187(2):169-96.

Human steroidogenic and steroid-inactivating enzymes in peripheral intracrine tissues



Labrie F, Luu-The V, Bélanger A, Lin SX, Simard J, Pelletier G, Labrie C. Is dehydroepiandrosterone a hormone? J Endocrinol. 2005 Nov;187(2):169-96.

Comparison of the effects of standard ERT (estrogen) and DHEA on parameters of menopause



Labrie F, Luu-The V, Bélanger A, Lin SX, Simard J, Pelletier G, Labrie C. Is dehydroepiandrosterone a hormone? J Endocrinol. 2005 Nov;187(2):169-96.

Potential Problems with Bio-identical Hormones

- **excessive dose**
- **lack of balance with other hormones**
- **nonphysiological delivery: formulations, route, cycle, and timing**

Significant adverse effects from bioidentical hormone use ?!!!

- **there is widespread public belief that bioidentical hormones are both efficacious and cause less harm than conventional hormones**

MacLennan AH, Wilson DH, Taylor AW. The escalating cost and prevalence of alternative medicine. *Prev Med* 2002; **35**: 166–173.

Significant adverse effects from bioidentical hormone use ?!!! (cont.)

This case report illustrates significant adverse effects from bioidentical hormone use:

- healthy 59-year-old woman, presented in 2003 with poor libido. Baseline T was < 0.5 nmol/L (nl 0.5–2.5)

- in July 2007 routine endocrine testing demonstrated elevated plasma testosterone (37.9 nmol/L) and muscle hypertrophy on clinical examination

- Mrs LM, presented at age 60 with an 18-month history of acne and facial hair requiring two-weekly electrolysis

- three years prior to presentation when testosterone cream (compounding pharmacy, 0.1 mg/mL) was commenced daily for low libido

- examination revealed a lean woman with mild acne, facial hair and significant clitoromegaly (grade 2/4). Plasma androgen levels were as follows: total testosterone (T) 33 nmol/L (nl 0.5–2.5).

Ogilvie CM, Levenberg R, Milsom SR. Bioidentical testosterone cream: a rare cause of postmenopausal virilisation. Aust N Z J Obstet Gynaecol. 2009 Feb;49(1):116-7.

Safety: HRT vs bioidentical Hormones

- proponents for bioidentical hormones claim that they are safer than comparable synthetic and nonhuman versions of HRT

- according to the FDA and the Endocrine Society, there is little or no evidence to support claims that bioidentical hormones are safer or more effective

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (Estradiol, Estriol, and Progesterone) safer or more efficacious than commonly used synthetic versions in Hormone Replacement Therapy? Postgrad Med 2009;121(1):1-13.

Safety: HRT vs bioidentical Hormones

Published papers were analysed from PubMed/MEDLINE, Google Scholar, and Cochrane databases

- patients report greater satisfaction with HRTs that contain progesterone compared with those that contain a synthetic progestin

- bioidentical hormones have some distinctly different, potentially opposite, physiological effects compared with their synthetic counterparts, which have different chemical structures

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (Estradiol, Estriol, and Progesterone) safer or more efficacious than commonly used synthetic versions in Hormone Replacement Therapy? Postgrad Med 2009;121(1):1-13.

Safety: HRT vs bioidentical Hormones

- both physiological and clinical data have indicated that progesterone is associated with a diminished risk for breast cancer, compared with the increased risk associated with synthetic progestins

- synthetic progestins have a variety of negative cardiovascular effects, which may be avoided with progesterone.

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (Estradiol, Estriol, and Progesterone) safer or more efficacious than commonly used synthetic versions in Hormone Replacement Therapy? Postgrad Med 2009;121(1):1-13.

Safety: HRT vs bioidentical Hormones

- Estriol has some unique physiological effects, which differentiate it from estradiol, estrone, and CEE

- Estriol would be expected to carry less risk for breast cancer, although no randomized controlled trials have been documented

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (Estradiol, Estriol, and Progesterone) safer or more efficacious than commonly used synthetic versions in Hormone Replacement Therapy? Postgrad Med 2009;121(1):1-13.

Safety: HRT vs bioidentical Hormones

- however, we could say that almost all women on the planet undergo a "controlled trial" during 9 months of pregnancy when estirol levels increase almost 1000 times more than during normal periods

Safety: HRT vs bioidentical Hormones

- physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their synthetic and animal derived counterparts

- until evidence is found to the contrary, bioidentical hormones remain the preferred method of HRT

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (Estradiol, Estriol, and Progesterone) safer or more efficacious than commonly used synthetic versions in Hormone Replacement Therapy? Postgrad Med 2009;121(1):1-13.

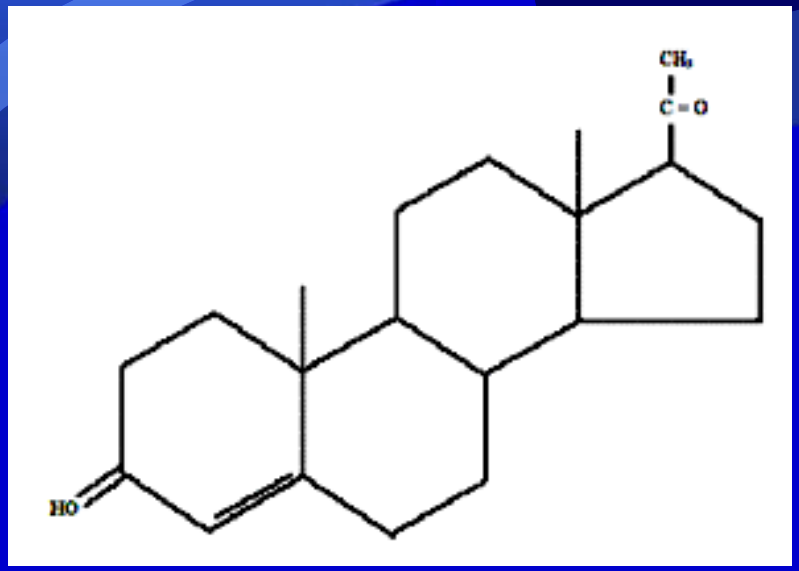
We Must Remember

Bioidentical Hormones

are

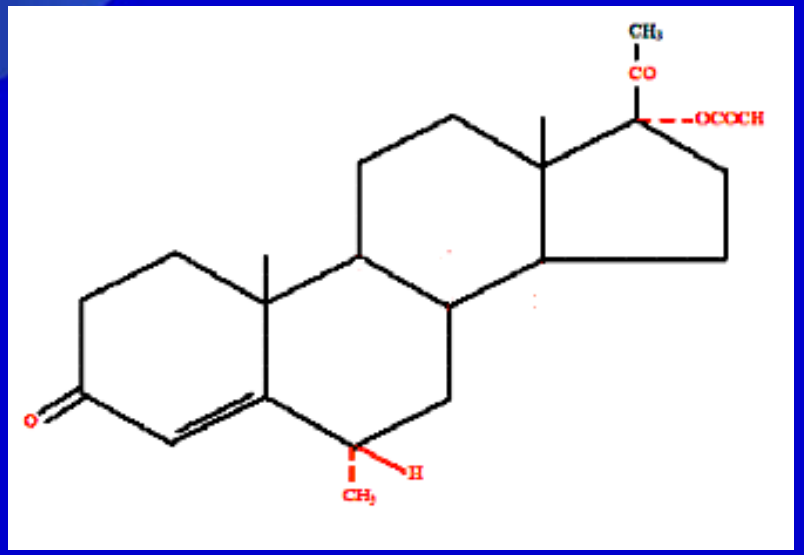
NOT SYNTHETIC DRUGS!

Natural Hormones



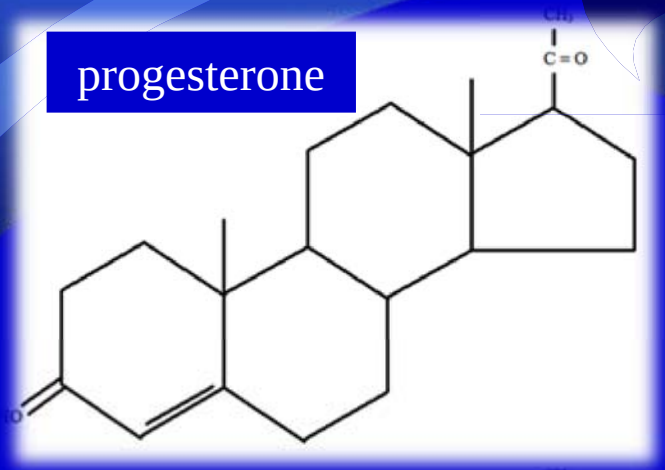
The Progesterone in YOUR BODY

A Drug



A Drug used to replace Progesterone in your body

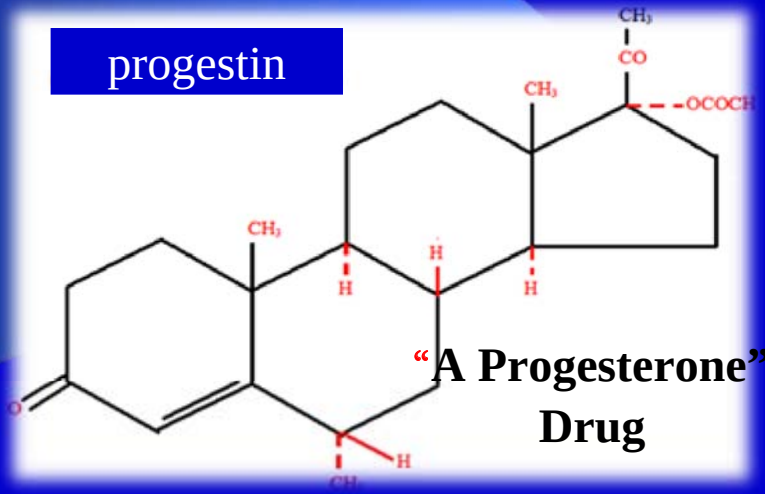
progesterone



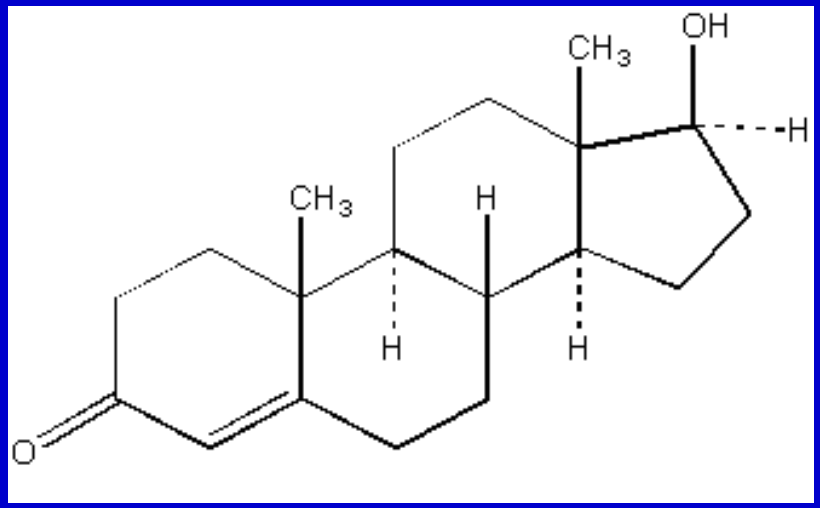
The Progesterone in YOUR BODY

≠

progestin



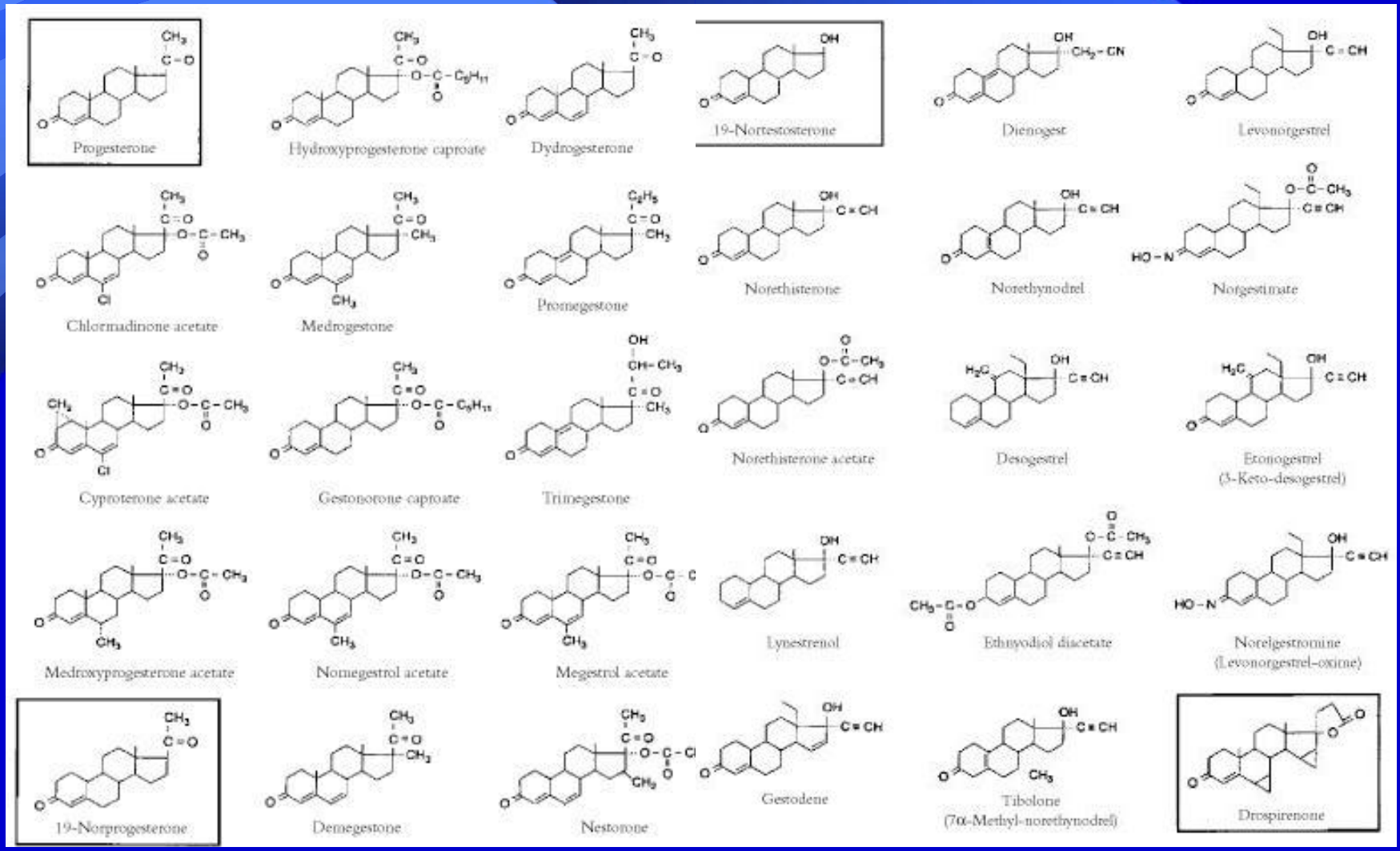
“A Progesterone” Drug



Testosterone!!!!

Natural Hormones!

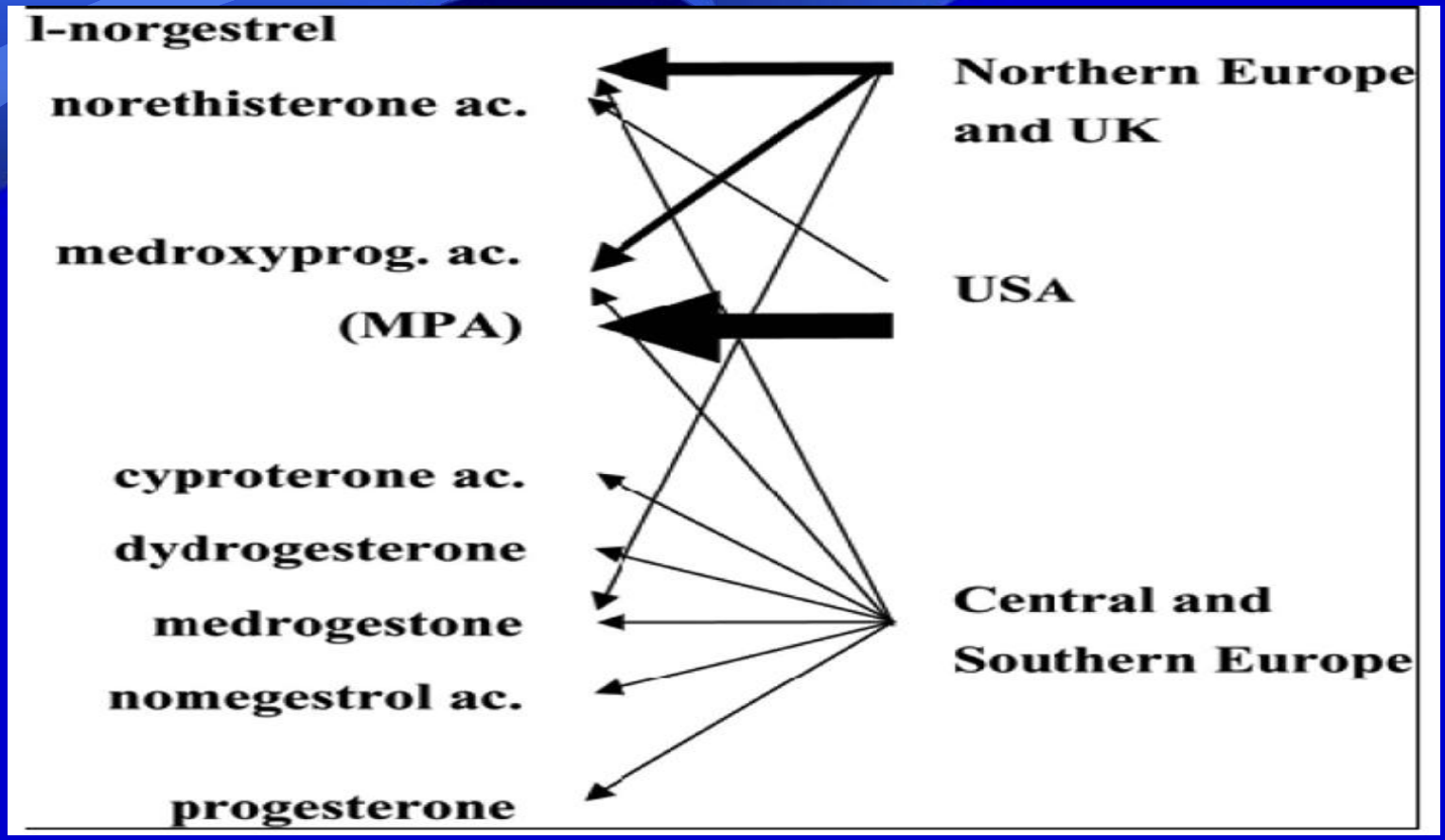
Progestin "Theater"



- **progestins have androgenic, estrogenic, glucocorticoid, and progestational effects**

Kuhl H. Pharmacology of estrogens and progestogens:influence of different routes of administration. Climacteric. 2005 Aug;8 Suppl 1:3-63.

Progestins used in HRT in different countries



Campagnoli C, Clavel-Chapelon F, Kaaks R, Peris C, Berrino F. Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. J Steroid Biochem Mol Biol. 2005 Jul;96(2):95-108.

Origin of Confusion -

Substitution of Hormones

Why are most doctors saying that HRT is dangerous?

Hormone Replacement Therapy (HRT) in fact is:

Hormone Substitution Therapy (HST)!!!

Hormone Substitution Therapy

- **Estradiol and estrone were substituted by conjugated equine estrogens (Premarin)**
- **Progesterone was substituted by medroxyprogesterone acetate (Provera) and other progestins - all are called progesterone!!!**
- **Testosterone was substituted by methyltestosterone**
- **Patented drugs are not human hormones!**
- **Majority of doctors don't know the difference!**
- **Human hormones cannot be patented, no profits**

- Premarin was approved in 1942
- the first human steroid hormone progesterone was synthesized in 1940. It was poorly absorbed orally
- progesterone was altered to make progestins – drugs that could be patented
- HRT uses molecules that have hormone-like effects
- terminology confusion: HRT, ERT, bioidentical hormones, natural hormones, etc

Hormone Substitution Therapy

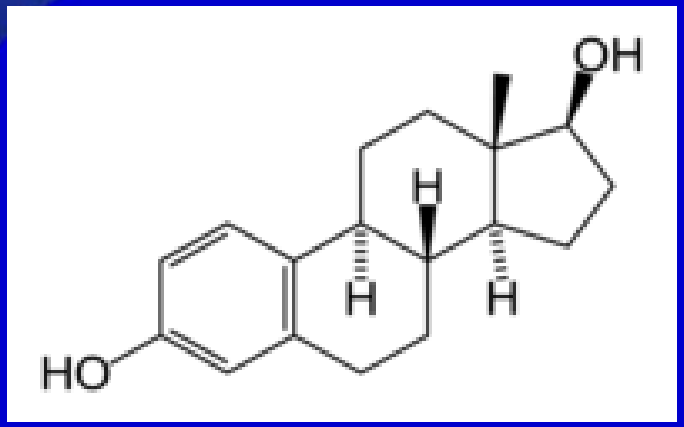
- **in both peripheral and cerebral vasculature, synthetic progestins caused endothelial disruption, accumulation of monocytes in the vessel wall, platelet activation and clot formation, which are early events in atherosclerosis, inflammation and thrombosis**

- **natural progesterone or estrogens did not show such toxicity**

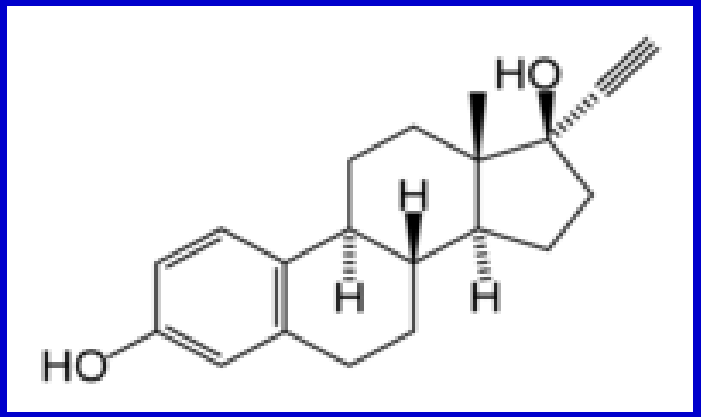
Thomas T, Rhodin J, Clark L, Garces A. Progestins initiate adverse events of menopausal estrogen therapy. Climacteric. 2003 Dec;6(4):293-301.

Hormone Substitution Therapy

Estradiol



Ethinyl Estradiol (EE)



- **EE cannot be inactivated by normal oxidation**
- **EE does not interact with estrogen beta-receptors**
- **EE is much more potent than E2**
- **EE is more thrombogenic than estradiol**

Premarin

- in the 1970s it was believed that Premarin only consisted of 10 estrogens
- advancements in technology have revealed that the original 10 estrogens make up less than 40% of the hormonal content of Premarin
- using modern analytical techniques, today over 200 individual components have been identified, including androgens and progestins

Klein R. The composition of Premarin. Int J Fertil 1998;43(4):223.

Hudson T. Women's Health Update: Use of Hormone Replacement Therapy. http://www.townsendletter.com/Oct_2002/womenshealth1002.htm

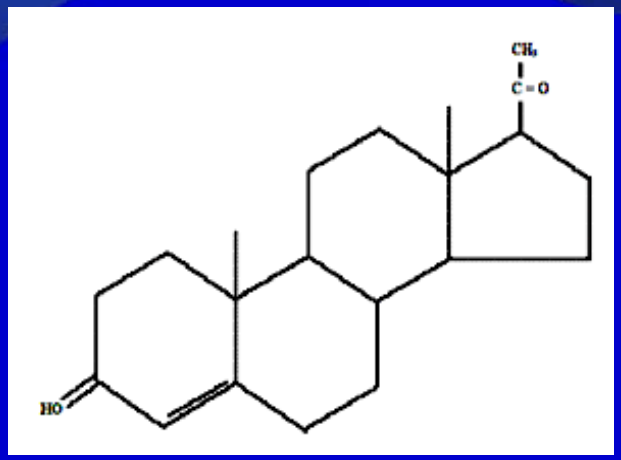
Premarin (cont.)

- different estrogens produce various effects in different tissues. This can explain the problems with conjugated equine estrogens vs natural bio-identical estradiol, estrone and estriol.
- the major forms of estrogen in Premarin are estrone (>50%), equilin (15-25%) and equilenin; there is a profound distinction between a non bio-identical hormone and a bio-identical hormone because a complex content of CEE
- majority of doctors think that Premarin is mainly estradiol!

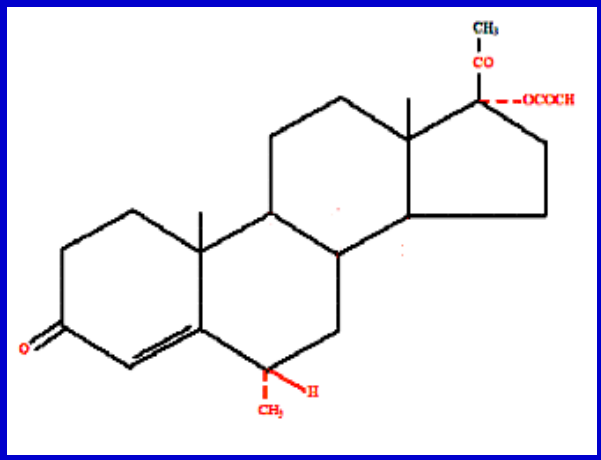
Klein R. The composition of Premarin. Int J Fertil 1998;43(4):223.

Hudson T. Women's Health Update: Use of Hormone Replacement Therapy. http://www.townsendletter.com/Oct_2002/womenshealth1002.htm

Progesterone



Progestin



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

Progesterone

- maintains pregnancy
- improves mood
- improves sleep
- diuretic
- no effect on blood sugar
- improves lipid profile
- no evidence of increased CVD
- reduces estrogenic stimulation of breasts
- prevents breast cancer

Medroxyprogesterone Acetate (Provera)

- causes birth defects
- can cause depression
- insomnia, irritability
- fluid retention
- raises blood sugar
- worsens lipid profile
- causes heart attacks
- increases estrogenic stimulation of breasts
- causes breast cancer

French Study

“The hypothesis of progesterone …decreasing the proliferative effect of estradiol in the postmenopausal breast remains highly plausible and (progesterone) should be, until the coming of new evidences, the first choice for symptomatic postmenopausal women.”

Modena MG, Sismondi P, Mueck AO, Kuttenn F, Lignières B, Verhaeghe J, Foidart JM, Caufriez A, Genazzani AR; TREAT. New evidence regarding hormone replacement therapies is urgently required transdermal postmenopausal hormone therapy differs from oral hormone therapy in risks and benefits. Maturitas. 2005 Sep 16;52(1):1-10.

Rationale for the use of progesterone in ALL women receiving Estrogen Replacement Therapy

- to prevent symptoms of estrogen dominance
- to protect against endometrial cancer
- to decrease the risk of breast cancer
- to reduce the risk of osteoporosis
- to improve cardiovascular benefits
- to improve brain function
- to improve sexual function

Progesterone use requires women with:

- irregular menstrual cycles
- heavy bleeding
- no menses—amenorrhea
- fibrocystic breast
- endometriosis
- fibroids
- menopause

WHI Study - "HRT" is Dangerous!

- Premarin 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 (Prempro) caused more adverse effects (breast cancers, heart attacks, dementia)
- progesterone does not
- drug companies running a propaganda campaign to say that all hormones as equally dangerous!

Pharma Pressure

American Congress of Obstetricians and Gynecologists (ACOG) October 31, 2005
"…compounded bioidentical hormones should be considered to have the same safety issues as those hormone products that are approved by the FDA… hormone therapy does not belong to a class of drugs with an indication for individualized dosing" (????)

The Endocrine Society October 2006
"…all estrogen-containing hormone therapies, "bioidentical" or "traditional," would be expected to carry essentially the same risks and benefits (as those products used in the WHI study).

North American Menopause Society July 2008
"…the generalized benefit-risk ratio data of commercially available HT products should apply equally to BHT."

ACOG, The Endocrine Society, and NAMS are all funded by Pharmaceutical corporations that make the hormone substitutes.

Doctors assume that these are unbiased experts!

Conventional Medicine is Pharmaceutical Medicine

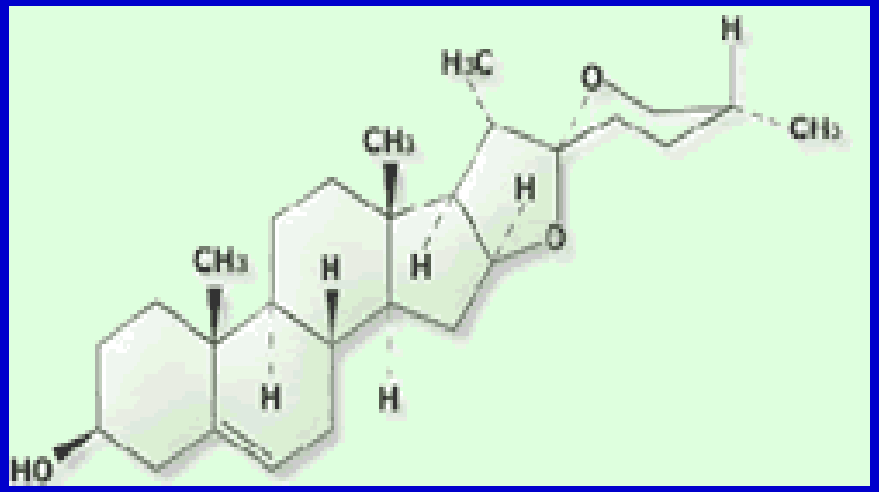
- pharmaceutical corporations fund medical schools, journals, organizations, research
- bioidentical molecules cannot be patented
- Pharma agenda: sell more high-profit drugs

Conventional Medicine is Pharmaceutical Medicine (cont.)

- Pharma influence: Label hormone-related symptoms and disorders as syndromes to be treated with drugs (depression, fatigue, fibromyalgia, anxiety, impotence, PMS, osteoporosis, insomnia, etc.)
- doctors follow pharma-funded guidelines
- hormone and nutrient deficiencies misunderstood, underdiagnosed and undertreated

Source for hormones

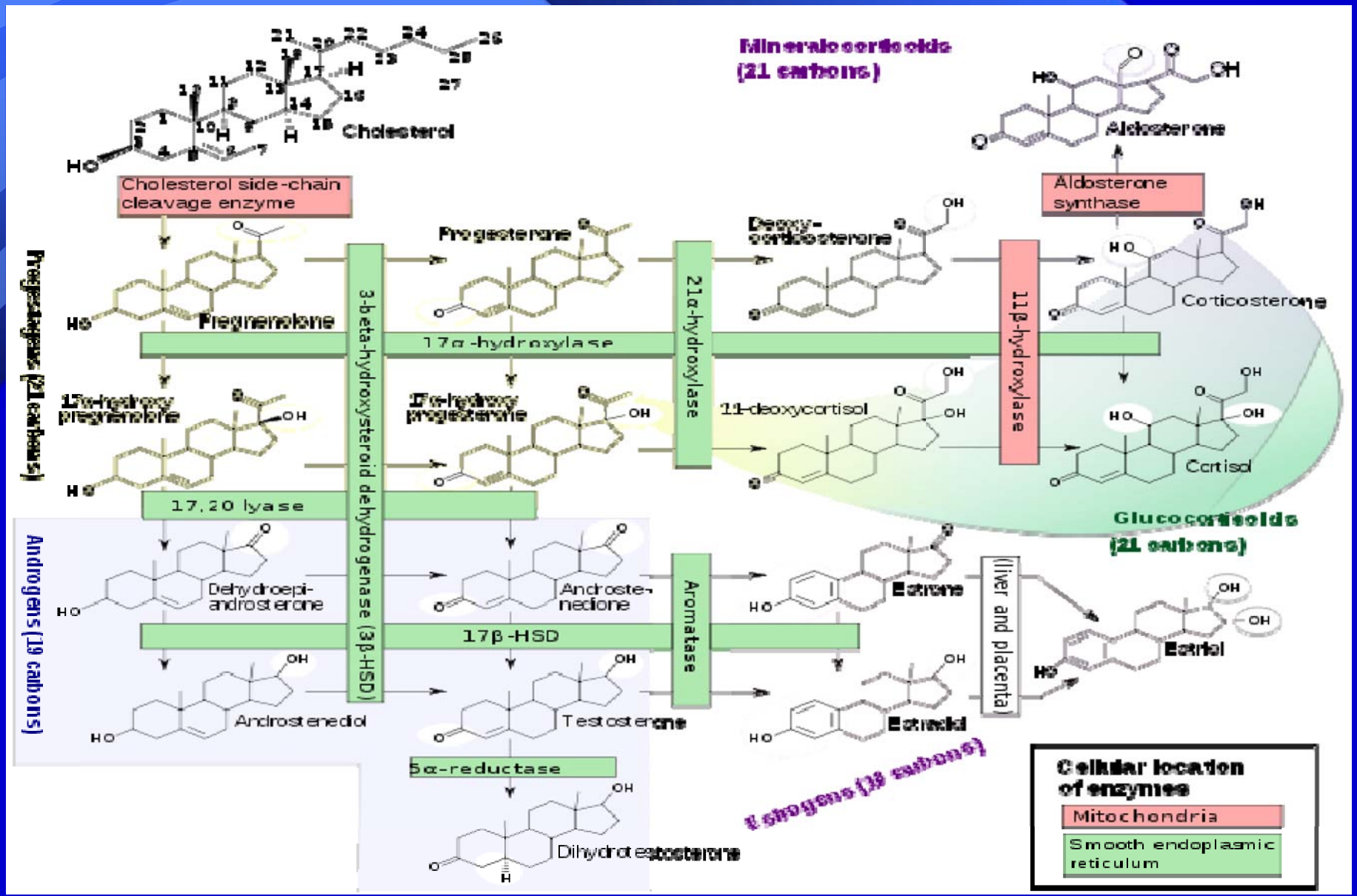
- all bioidentical steroid hormones (and substitutes too) are chemically synthesized from diosgenin (from wild Mexican yams and soy)

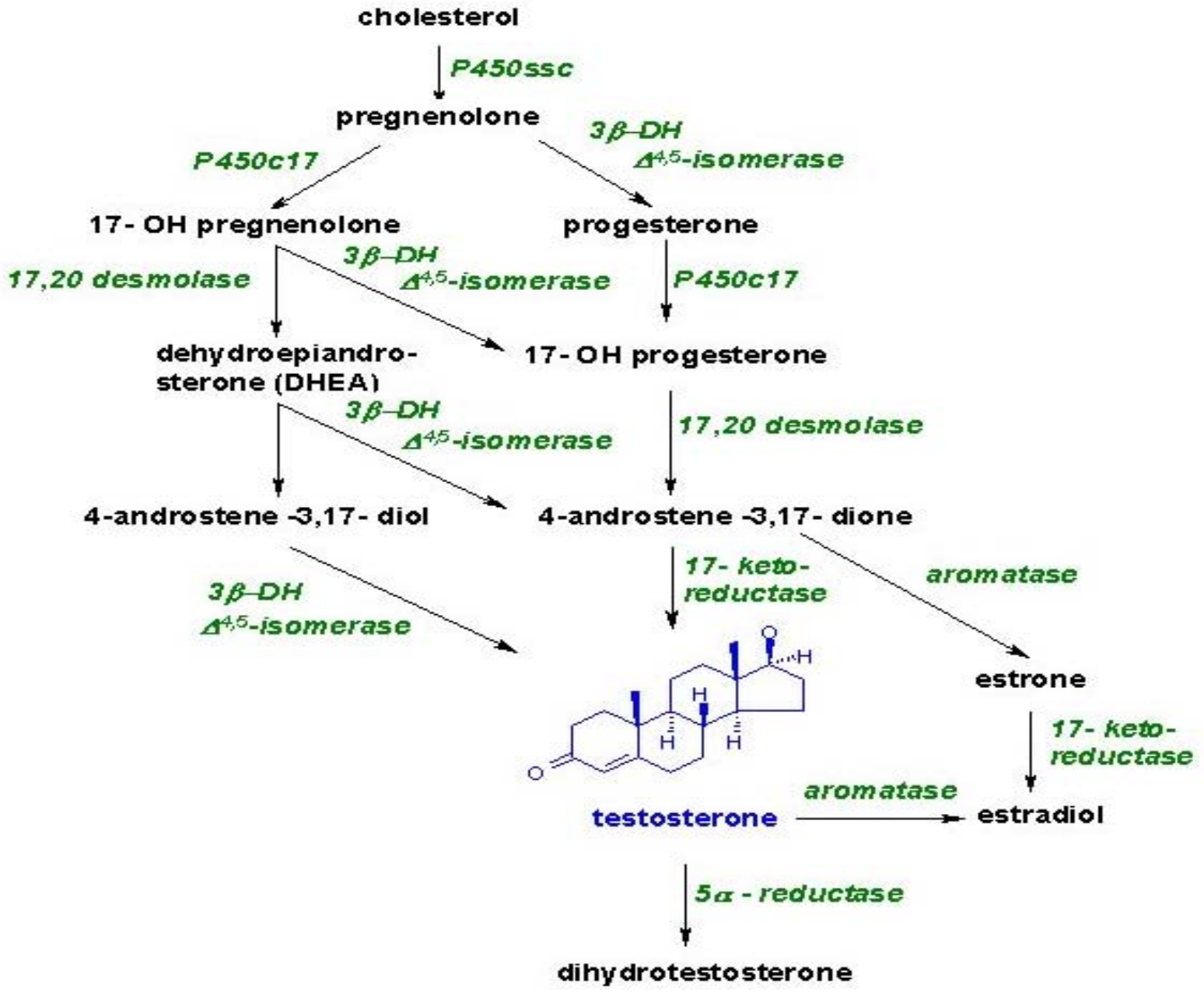


Bioidentical Hormones

- USP-certified bioidentical hormones mixed into creams, sublingual tablets, capsules, etc.
- convenient, low cost, locally-made
- individual preparations not studied, but… the hormones themselves are extremely well studied
- dose adjusted by symptoms and blood levels
- only a pharmaceutical corporations hate compounded bioidentical hormone

Steroidogenesis




cholesterol
P450ssc
pregnenolone
3β-DH
Δ4,5-isomerase
P450c17
17- OH pregnenolone
progesterone
3β-DH
Δ4,5-isomerase
17,20 desmolase
P450c17
dehydroepiandro-
sterone (DHEA)
17- OH progesterone
3β-DH
Δ4,5-isomerase
17,20 desmolase
4-androstene -3,17- diol
4-androstene -3,17- dione
17- keto-
reductase
aromatase
3β-DH
Δ4,5-isomerase
estrone
17- keto-
reductase
aromatase
testosterone
estradiol
5α - reductase
dihydrotestosterone

What Causes the hormone decline/imbalance?

- **we are genetically programmed to die**
- **cancer is a perfect example of programmed death**

Oral - Transdermal

Table 7 Effects of oral and transdermal estrogen replacement therapy on the cardiovascular system and various surrogate parameters. The effects may vary according to the type and dose of the estrogens, and may be modulated by the addition of progestogens

Parameter	*Oral estrogens*	*Transdermal estrogens*
Risk of thrombosis	increase	possibly smaller increase
Hemostasis	procoagulatory effect	minor effect
APC resistance	increase	minor increase
Atherosclerosis	prevention	prevention
Triglycerides	increase	minor decrease
HDL cholesterol, triglycerides, Apo A	increase	minor increase
LDL cholesterol, remnants, Apo B	reduction	minor reduction
Size of LDL particles	decrease	increase
Activity of metalloproteinases	increase	no effect
Vasodilation	increase	increase
Release of NO, prostacyclin	increase	increase
Release of endothelin-1	reduction	reduction
Angiotensinogen	increase	no effect
C-reactive protein	increase	no effect
Adhesion molecules	decrease	decrease
Cytokines (IL-1, IL-6, TNF-α)	no effect	no effect
PAI-1	decrease	no effect
IGF-1, IGFBP-3	decrease	no effect
IGFBP-1, GH, GHBP	increase	no effect

APC, activated protein C; HDL, high density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein; NO, nitric oxide; IL, interleukin; TNF, tumor necrosis factor; PAI-1, plasminogen activator inhibitor-1; IGF, insulin-like growth factor; IGFBP; insulin-like growth factor-binding protein; GH, growth hormone; GHBP, growth hormone-binding protein

Kuhl H. Pharmacology of estrogens and progestogens:influence of different routes of administration. Climacteric. 2005 Aug;8 Suppl 1:3-63.

Delivery system: oral vs transdermal estrogens

- **effect on the liver – CRP elevates, clotting factors elevate – increase risk of blood clots, strokes, heart attacks in the first year**
- **transdermal estradiol mimics normal production and does not increase blood clotting!**
- **oral but not transdermal estrogen is associated with an increased venous thromboembolism (VTE) risk**

Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007 Feb 20;115(7):840-5.

oral

- **first-pass effect on the liver: IGF-1 - decreases, SHBG – elevates, CRP - elevates, clotting factors increases**
- **risk of blood clots, strokes, heart attacks increases in the first year**

Transdermal

- transdermal E2 has none of these effects!
- oral but not transdermal estrogen is associated with an increased venous thromboembolism risk
- micronized progesterone appears safe with respect to thrombotic risk

Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007 Feb 20;115(7):840-5.

- transdermal estradiol improves insulin sensitivity more than oral estrogens
- transdermal estradiol provides normal estrone/estradiol ratio, while oral estradiol is heavily metabolized to estrone by first-pass effect.

Progesterone – route of administration

- **hormones are usually delivered orally, transdermally, or sublingually**
- **transdermal or sublingual routes are thought to be more advantageous because they bypass first-pass hepatic metabolism**
- **however, it is important to note that the oral bioavailability of progesterone is very low. More than 90% of orally administered progesterone is metabolized during first pass metabolism through the liver, which causes an abrupt increase in progesterone metabolites to an unphysiologically high level.**

Warren MP, Shantha S. Uses of progesterone in clinical practice. Int J Fertil Womens Med. 1999 Mar-Apr;44(2):96-103.

Progesterone – route of administration (cont.)

- the metabolites that are reduced at the 5-α position can cause sedation, which can be clinically useful for menopausal women with insomnia. For those women, oral dosing at night may be preferred.

Warren MP, Shantha S. Uses of progesterone in clinical practice. Int J Fertil Womens Med. 1999 Mar-Apr;44(2):96-103.

Implanted estrogen pellets

- serum levels from hormone pellets are unpredictable and can remain elevated for years
- lack of standardized dosing parameters for this nonregulated product likely contributes to the chance of hyperestrogenemia
- despite bypassing first-pass metabolism, supraphysiologic levels of these hormones can cause significant metabolic and gastrointestinal impairments

Forman EJ, Guyton JR, Filip SJ, Price TM. Implanted estrogen pellets associated with hypertriglyceridemia, biliary dyskinesia and focal nodular hyperplasia of the liver: a case report. J Reprod Med. 2010 Jan-Feb;55(1-2):87-90.

The practical aspects of Hormonorestorative therapy

W.W.W.

When?

When to apply?

- in the morning
- in the morning and in the evening - if patient has specific problems (insomnia, elevated BP, migraine, fibromyalgia, arrhythmia, etc

Progesterone secretion rates

	mg/day
Males	5
Females	
Follicular phase	4.7
Midluteal phase	31.8
Third trimester of pregnancy	335

Data from Dominguez & others: Progesterone Secretion in Man. Abstracts, 44th Meeting of the Endocrine Society, 1962.

Circadian Rhythm of Progesterone

- many studies were done on rats, hamsters, guinea-pigs, rabbits, skunks, canaries, ring doves, hens, ducks cows, mares, deers, sows, during normal and abnormal pregnancies…..

- it leads to confusion as to when progesterone should be used

Circadian Rhythm of Progesterone

Basic statistics for salivary progesterone in healthy children and adolescents in the morning, at noon, and in the evening.

			Age group			
			<4 weeks (n 13)	1–12 months (n 17)	1–2 years (n 10)	2–15 years (n 212)
Progesterone, pmol/L	Morning	Mean (SD)	677 (305)	235 (138)	115 (41)	137 (81)
		Range	350–1320	89–525	60–169	29–601
	Noon	Mean (SD)	423 (240)	102 (38)	63 (21)	101 (53)
		Range	153–875	51–162	25–99	16–282
	Evening	Mean (SD)	381 (191)	122 (67)	52 (24)	77 (46)
		Range	80–716	35–239	25–86	11–267

Groschl M, Rauh M, Dorr H-G. Circadian Rhythm of Salivary Cortisol, 17-Hydroxyprogesterone, and Progesterone In Healthy Children. Clinical Chemistry 2003 49;10:1688-91

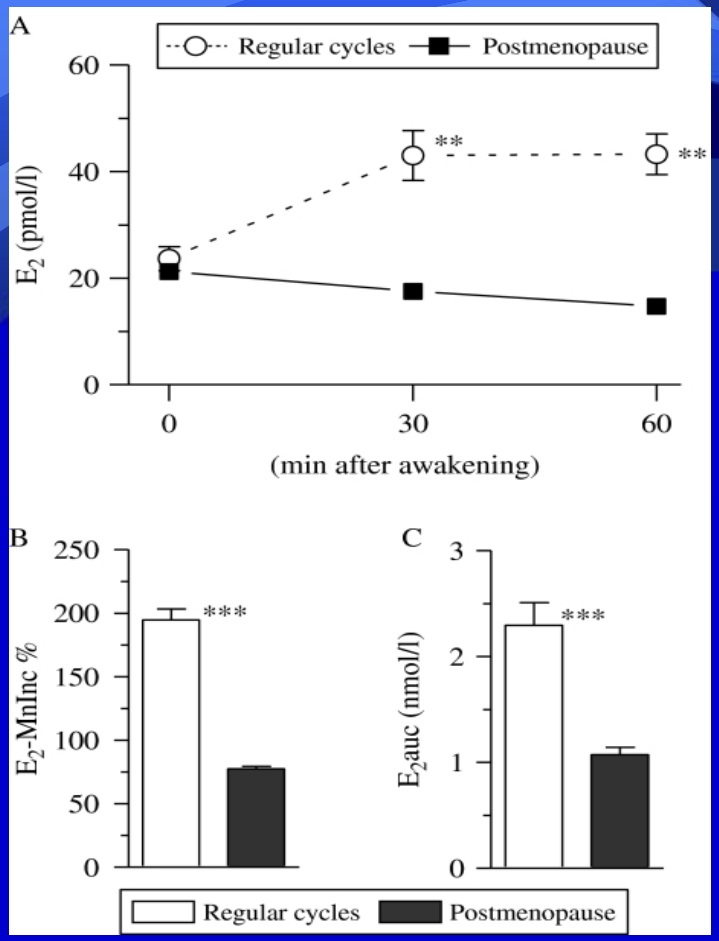
Circadian Rhythm of Steroid Hormones

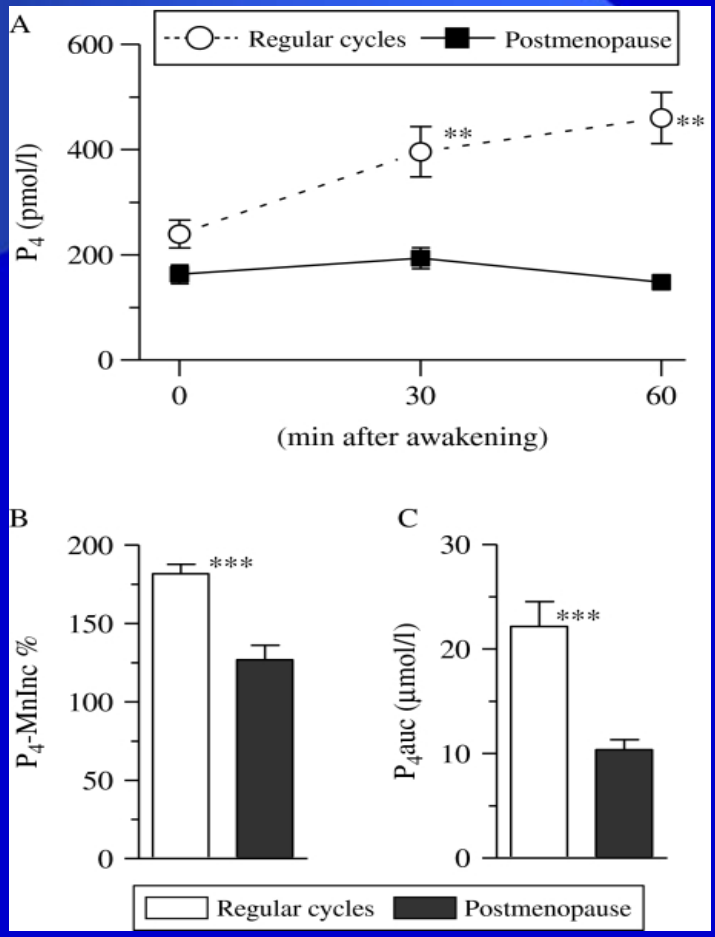
- **Cortisol concentration in both serum and saliva sharply increases and reaches a peak within the first hour after waking in the morning. Cortisol secretory activity during the post-awakening period was not influenced by menstrual status or the phase of menstrual cycle.**

- **Ovarian steroidogenic activity increased after awakening. E(2) and P(4) concentrations increased during the post-awakening period in women with regular menstrual cycles, but these phenomena were not seen in any postmenopausal women.**

Ahn RS, Choi JH, Choi BC, Kim JH, Lee SH, Sung SS. Cortisol, estradiol-17β, and progesterone secretion within the first hour after awakening in women with regular menstrual cycles. J Endocrinol. 2011 Dec;211(3):285-95. Epub 2011 Sep 29.

Circadian Rhythm of Steroid Hormones





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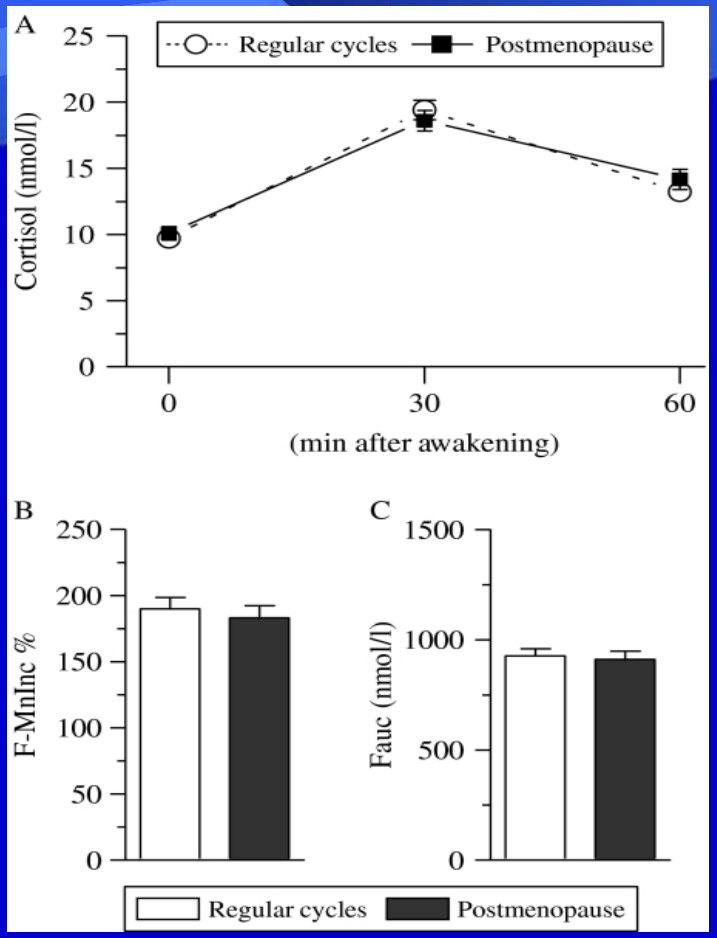
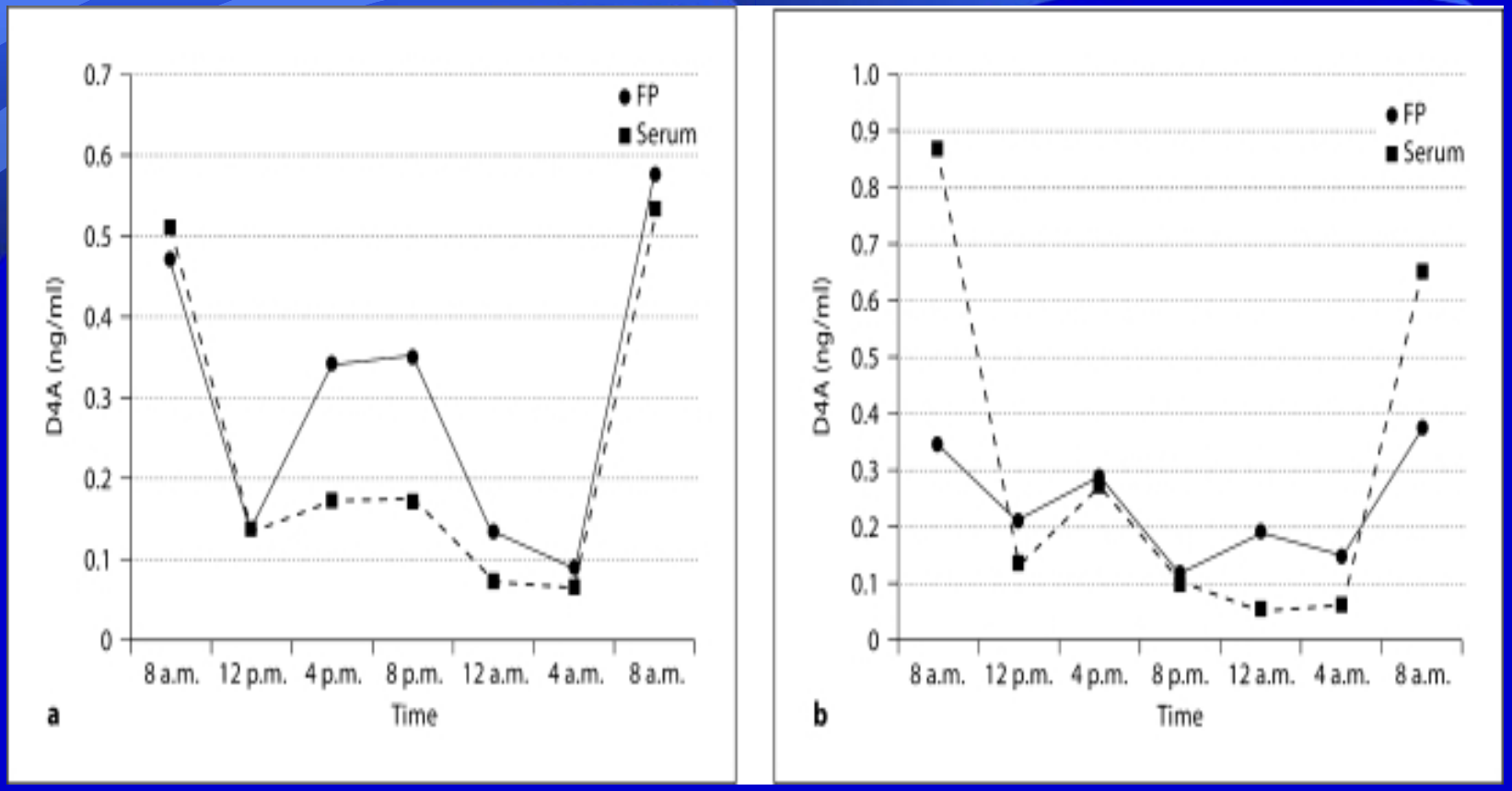
Circadian Rhythm of Steroid Hormones



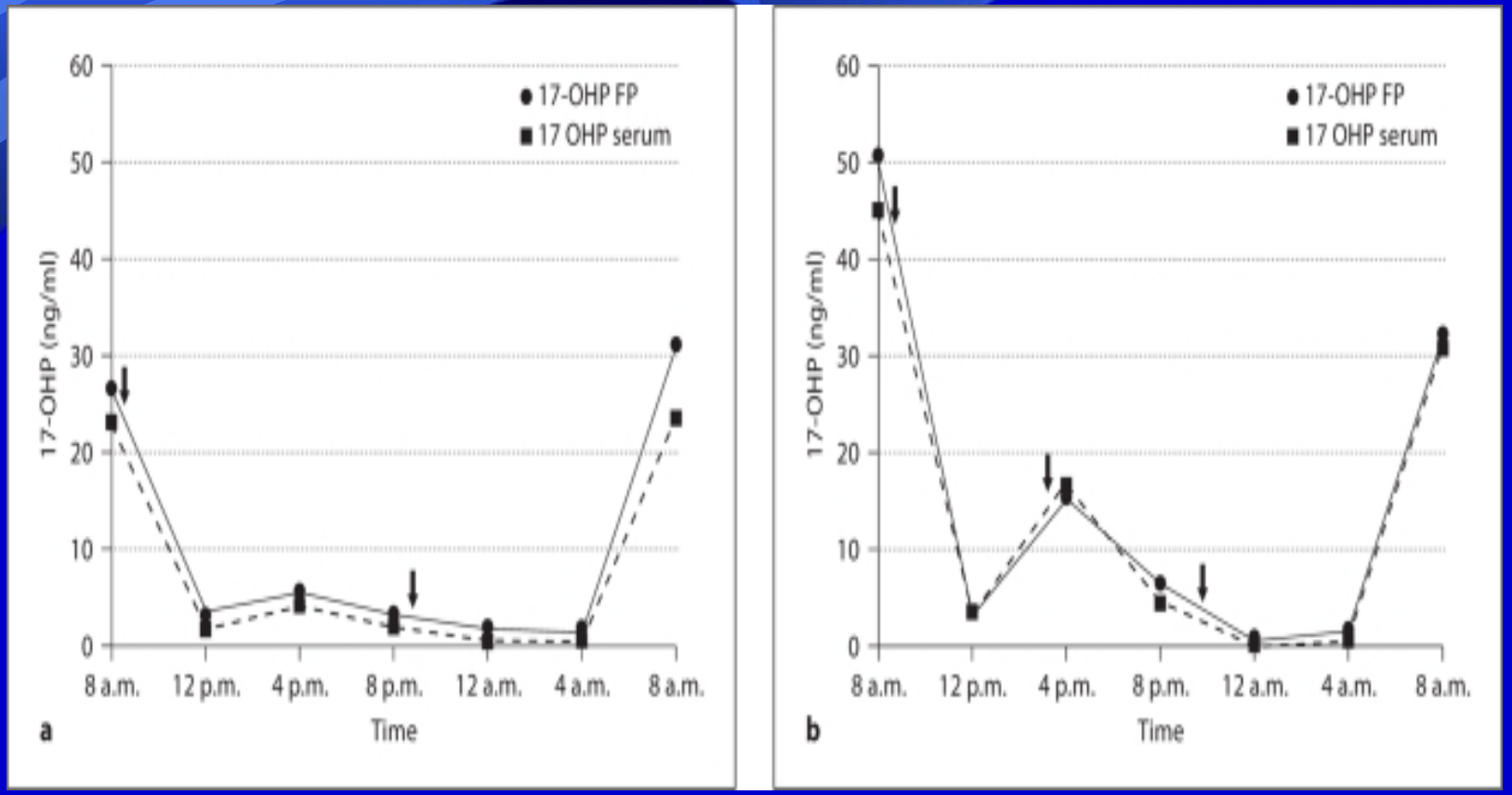
Ahn RS, Choi JH, Choi BC, Kim JH, Lee SH, Sung SS. Cortisol, estradiol-17β, and progesterone secretion within the first hour after awakening in women with regular menstrual cycles. J Endocrinol. 2011 Dec;211(3):285-95. Epub 2011 Sep 29.

Serum and DBS measurements of D4A over a 24-hour period



Sarafoglou K, Himes JH, Lacey JM, Netzel BC, Singh RJ, Matern D. Comparison of multiple steroid concentrations in serum and dried blood spots throughout the day of patients with congenital adrenal hyperplasia. Horm Res Paediatr. 2011;75(1):19-25. Epub 2010 Aug 25.

Serum and DBS measurements of 17-OHP over a 24-hour period



Sarafoglou K, Himes JH, Lacey JM, Netzel BC, Singh RJ, Matern D. Comparison of multiple steroid concentrations in serum and dried blood spots throughout the day of patients with congenital adrenal hyperplasia. Horm Res Paediatr. 2011;75(1):19-25. Epub 2010 Aug 25.

Plasma measurements of 17-OHP over a 24-hour period

- studies showed that 90% of the 17-hydroxyprogesterone (17-OHP) originated from the Leydig cell
- plasma 17-OHP production rate in normal men has a marked circadian variation, the 8 p.m. values being only 40% of the 8 a.m. values

Strott CA, Yoshimi T, Lipsett MB. Plasma progesterone and 17-hydroxyprogesterone in normal men and children with congenital adrenal hyperplasia. J Clin Invest. 1969 May;48(5):930-9.

Plasma measurements of 17-OHP over a 24-hour period

- plasma 17-OHP levels fell progressively during the early afternoon and evening

Atherden SM, Barnes ND, Grant DB. Circadian variation in plasma 17-hydroxyprogesterone in patients with congenital adrenal hyperplasia. Arch Dis Child. 1972 Aug;47(254):602-4.

Obesity

Obesity is a physiological state associated with alterations in hormone production and metabolism.

Obesity

- obesity is associated with increased estrone production in young and older women as well as in men.
- the source of this increased estrogen appears to be extragonadal metabolism of the androstenedione, which increases 3- to 4-fold in proportion to the obesity
- testosterone production is unchanged in obesity

Kirschner MA, Ertel N, Schneider G. Obesity, hormones, and cancer. Cancer Res. 1981 Sep;41(9 Pt 2):3711-7.

Obesity - SHBG

SHBG levels are reduced in obesity

Kirschner MA, Ertel N, Schneider G. Obesity, hormones, and cancer. Cancer Res. 1981 Sep;41(9 Pt 2):3711-7.

Morley JE, Melmed S. **Gonadal dysfunction in systemic disorders.** Metabolism. 1979 Oct;28(10):1051-73.

Rittmaster RS 1993

In obese women, androgen production rates are elevated and SHBG levels are depressed, in many cases to the same magnitude as that observed in hirsute women. *(Kirschner MA et al 1983)*

Rittmaster RS 1993

Obese women have higher androgen (DHT, testosterone and androstanediol) production rates and metabolic clearance rates than lean women, presumably due to decreased levels of sex hormone-binding globulin levels in obese women. (Samojlik E et al 1984)

Obesity

Other changes noted in obesity include:

(a) increased excretion of corticoid metabolites

(b) increased secretion of insulin but decreased insulin effectiveness

(c) blunted growth hormone responses to various challenges

(d) possibly blunted prolactin responsiveness

Kirschner MA, Ertel N, Schneider G. Obesity, hormones, and cancer. Cancer Res. 1981 Sep;41(9 Pt 2):3711-7.

Starvation

- studies in patients with protein and calorie malnutrition indicate changes similar to those occuring in chronic illnesses
- there is a marked loss of libido and also of secondary hair growth
- spermatogenesis may be better maintained than androgen secretion

Handelsman DJ. Hypothalamic-pituitary gonadal dysfunction in renal failure, dialysis and renal transplantation. Endocr Rev. 1985 Spring;6(2):151-82.

Starvation

- plasma T is low with poor response to hCG
- hypogonadism of protein-calorie malnutrition is primarily on the basis of diminished Leydig cell function

Smith SR, Chhetri MK, Johanson J, Radfar N, Migeon CJ. The pituitary-gonadal axis in men with protein-calorie malnutrition. J Clin Endocrinol Metab. 1975 Jul;41(1):60-9.

Diet – weight loss

Remember:

- **because weight loss and dieting per se are associated with many physiological changes, hormonal measurements during these times are difficult to interpret.**

Handelsman DJ. Hypothalamic-pituitary gonadal dysfunction in renal failure, dialysis and renal transplantation. Endocr Rev. 1985 Spring;6(2):151-82.

T and glycemic control

function of the hypothalamic pituitary testicular axis is impaired in diabetic men, that this impairment is at least partly related to the degree of preceding glycemic control and that multiple levels of the axis may be dysfunctional

Handelsman DJ, Conway AJ, Boylan LM, Yue DK, Turtle JR. Testicular function and glycemic control in diabetic men. A controlled study. Andrologia. 1985 Sep-Oct;17(5):488-96.

The practical aspects of Hormonorestorative therapy

W.W.W.

Where?

Anatomic site of gels application:[211,212]

- scrotum or vulva (excellent absorption)
- forearm, medial
- neck (areas of blushing)
- sides of chest and abdomen

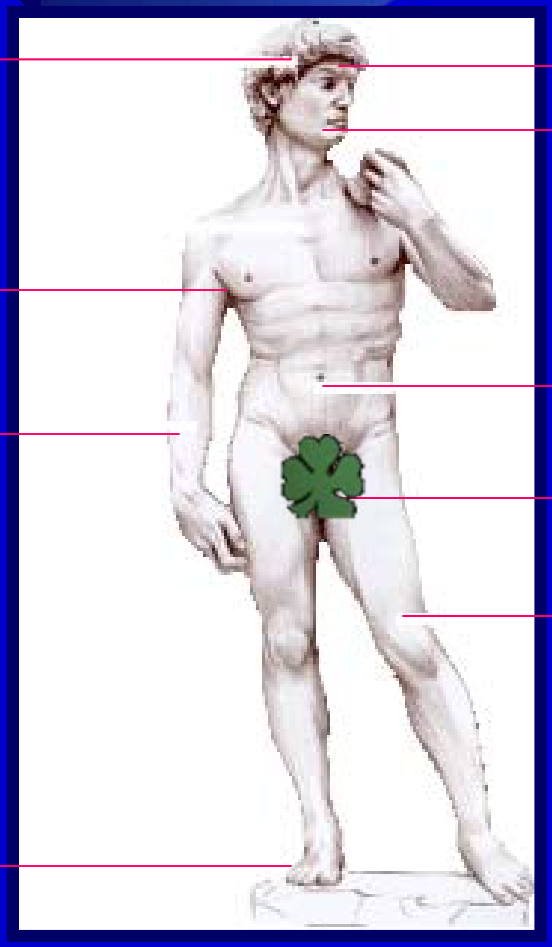
Wester RC, Noonan PK, Maibach HI. Variations in percutaneous absorption of testosterone in the rhesus monkey due to anatomic site of application and frequency of application. Arch Dermatol Res.1980;267(3):229-35.

Oriba HA, Bucks DA, Maibach HI. Percutaneous absorption of hydrocortisone and testosterone on the vulva and forearm: effect of the menopause and site. Br J Dermatol.1996 Feb;134(2):229-33.

Relative transcutaneous absorption (%) of testosterone at various anatomic sites

Wester RC, Noonan PK, Maibach HI. Variations in percutaneous absorption of testosterone in the rhesus monkey due to anatomic site of application and frequency of application. Arch Dermatol Res.1980;267(3):229-35.

Relative transcutaneous absorption (%) of hydrocortisone at various anatomic sites



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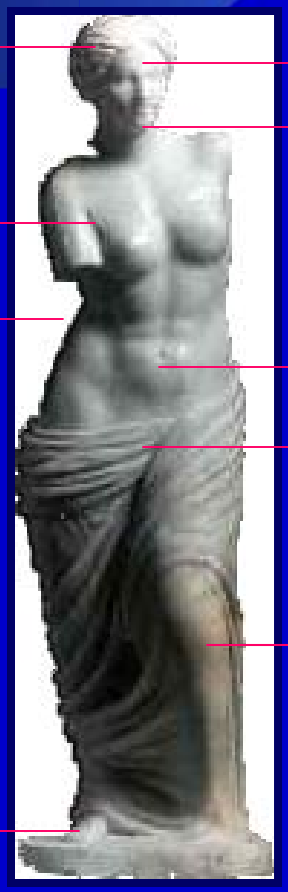

Scalp (4)

Forehead (6)

Jaw (13)

Axilla (4)

Forearm (1)

Abdomen (2)

Clitoris (42)

Leg (0.4)

Sole (0.1)

Physiologic route of administration

- transdermal route has a good absorption rate
- but…transmucosal route is preferable

WHI Study

DO NOT APPLY negative results of WHI to transdermal bioidentical hormones until proven Otherwise

Hormone-substitution therapy has been proven to be dangerous:
SO
Bioidentical hormone restoration is dangerous too!

Summary

- hormones are not dangerous
- the loss of any hormones is dangerous
- restoration of hormones is beneficial until proven otherwise
- Hormonorestoration has many well-known benefits; there is no proof of harm!
- hormone deficiencies are known to be harmful
- those who deny hormone restoration ignore the burden of proof that there are more benefits than possible harm
- doctors must study hormone restoration instead of hormone substitution!

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