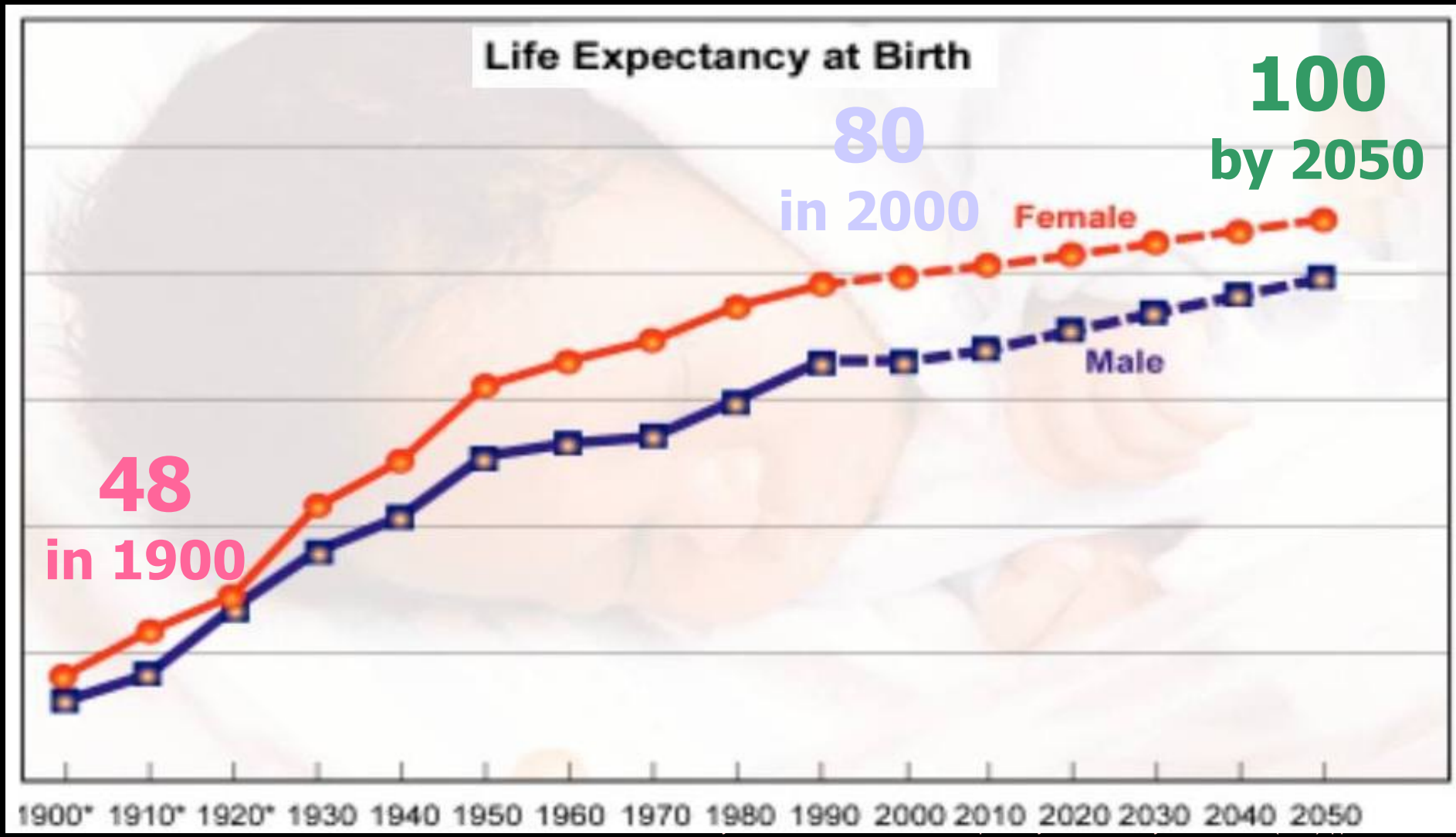
Prof. Vittorio Calabrese

MD PhD

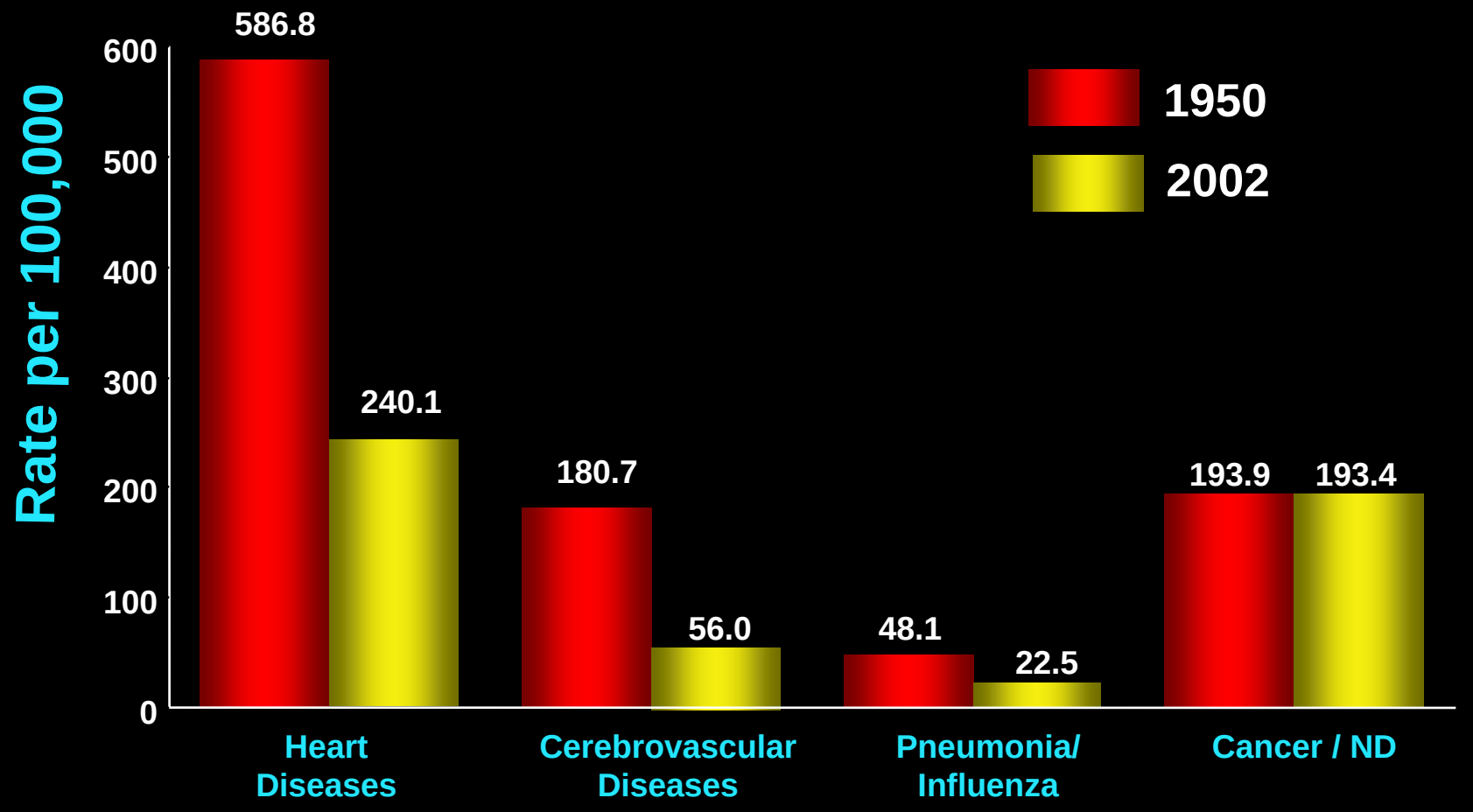
Bioidentical Hormones and Antiaging Medicine: The Good, The Bad and The enigmatic

Vittorio Calabrese MD, PhD

The Climbing Maximum Human Lifespan



Change in the US Death Rates* by Cause, 1950 & 2002



* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2002 Mortality Data: US Mortality Public Use Data Tape, 2002, NCHS, Centers for Disease Control and Prevention, 2004

ANTIOXIDANTS & REDOX SIGNALING
Volume 8, Numbers 3 & 4, 2006

Forum Editorial

Antiaging Medicine: Antioxidants and Aging

VITTORIO CALABRESE[1] and MAHIN D. MAINES[2]

THE AGING PROCESS is a continuous set of events that causes gradual decrements in cellular functions (28). Individual actions of various factors as well as interplay among them are responsible for the cumulative untoward effects of aging. These factors can originate from within the cell or imposed upon it extracellularly. Accordingly, although the process of aging cannot be halted, offsetting the deleterious effects of these factors can significantly decelerate it. A common denominator of aging factors is their association with free radicals and modulation of redox potential of the cell (1, 2, 10, 11).

Oxygen radicals can originate within the cell organelles, as occurs in the course of normal functioning of the mitochondria respiratory chain complexes (11) or extra mitochondrially by redox-available iron generated in the course of heme (Fe-protoporphyrin IX) degradation. The synergistic action of active oxygen species and catalytically active iron on the tissue prominently figure in tissue damage (7, 22). The target organelles for iron-catalyzed oxygen radicals are the mito-

degradation products of the porphyrin ring—CO and biliverdin/bilirubin—in therapeutic settings is currently under consideration (17, 28). While bilirubin inactivation of free radicals of oxygen has been known for some time now (27), a newly discovered activity of the bile pigment, that is denoted by Mancuso *et al.* (19), is its interaction with nitric oxide. Nitrogen oxide radicals, particularly peroxyinitrite, are among the most potent oxidizing radicals (1).

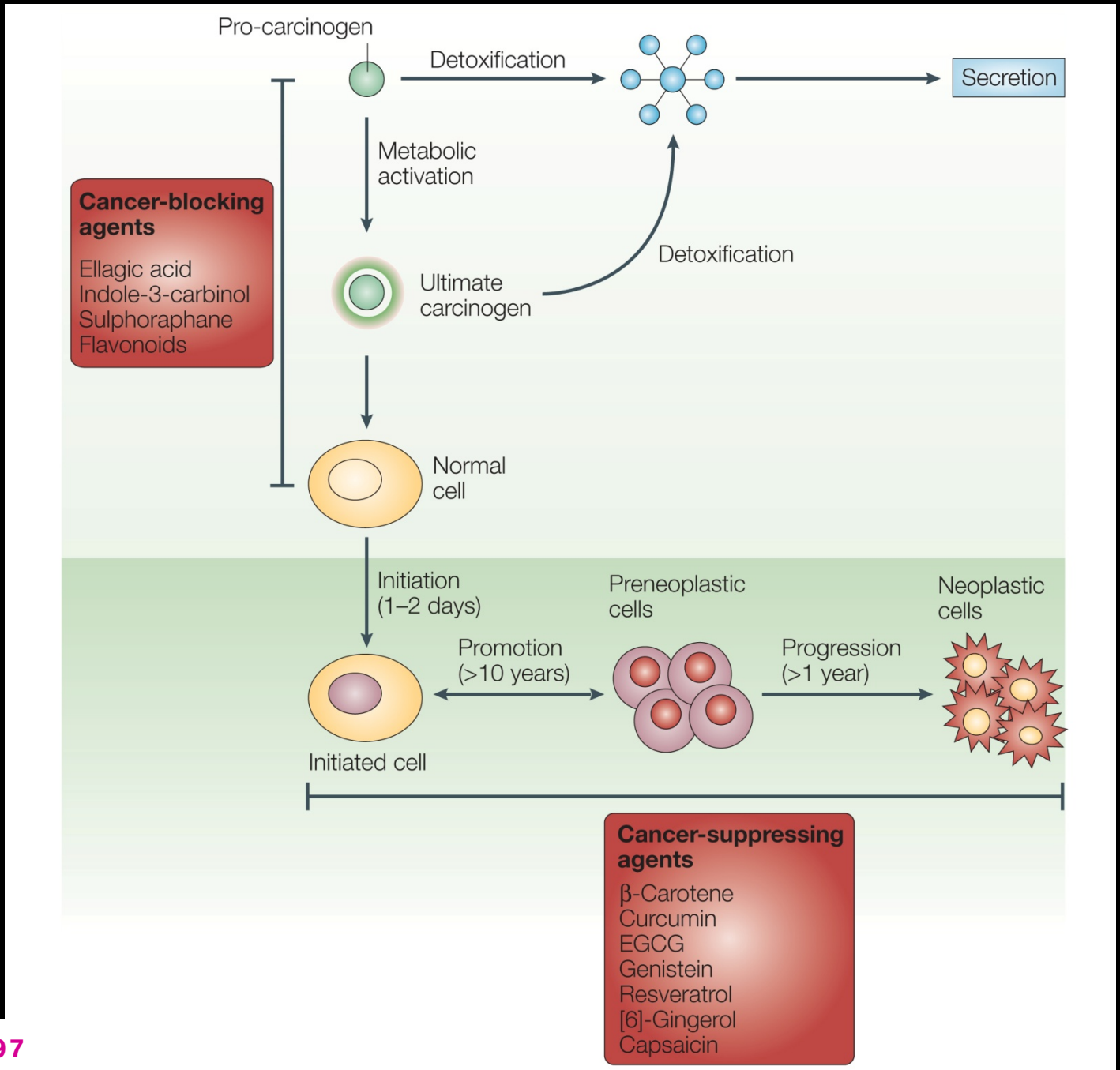
Although heme is degraded extramitochondrially, it is synthesized in the mitochondria. Heme synthesis, which is a complex and lengthy chain of reactions, is initiated in the mitochondria by condensation of succinyl-CoA and glycine, undergoes a series of oxidation and condensation steps in the cytosol, and is terminated by chelation of iron into the protoporphyrin IX tetrapyrrole ring. Uroporphyrin and coproporphyrin isomers constitute intermediary compounds in the pathway of protoporphyrin IX synthesis. The porphyrin intermediates as well as protoporphyrin itself in the presence of molecular oxygen produce free radicals that target cellular

Neurodegenerative disorders related to overproduction of free radical

- Alzheimer disease
- Parkinson disease
- Multiple sclerosis
- Amyotrophic lateral sclerosis
- Huntington disease
- AIDS Dementia
- Aging

Calabrese V. Nature Neurosci 2007
Calabrese V. Antioxidant Redox Signal 2009
Calabrese V. Antioxidant Redox Signal. 2010
Calabrese V. Molecular Aspects Med 2011
Calabrese V. Biogerontology 2012
Calabrese V. Antioxidant Redox Signal 2013

Multistage Carcinogenesis



M. Sporn, Science 278, 1997

Recent Advances in Chemoprevention of Cancer

Waun Ki Hong* and Michael B. Sporn

Chemoprevention is the use of pharmacologic or natural agents that inhibit the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred. Recent advances in our understanding of the mechanisms of carcinogenesis have led to the synthesis of new drugs that can inhibit tumor development in experimental animals by selective action on specific molecular targets, such as the estrogen, androgen, and retinoid receptors or inducible cyclooxygenase. Several of these agents (including tamoxifen, 13-*cis*-retinoic acid, retinyl palmitate, and an acyclic retinoid) are clinically effective in preventing the development of cancer, particularly in patients who are at high risk for developing second primary tumors after surgical removal of the initial tumor.

In spite of immense efforts to improve treatment and find cures for advanced disease, overall mortality rates for most forms of epithelial cancer have not declined in the past 25 years. The prognosis for a patient with metastatic carcinoma of the lung, colon, breast, or prostate (four of the most common and lethal forms of cancer, which together account for more than half of all deaths from cancer in the United States) remains dismal (*1*). A current scientific view indicates that damage to numerous regulatory genes ultimately results in the development of invasive and metastatic cancer, which is the culmination of the chronic disease process, carcinogenesis. The natural history of carcinogenesis and cancer provides a strong rationale for a preventive

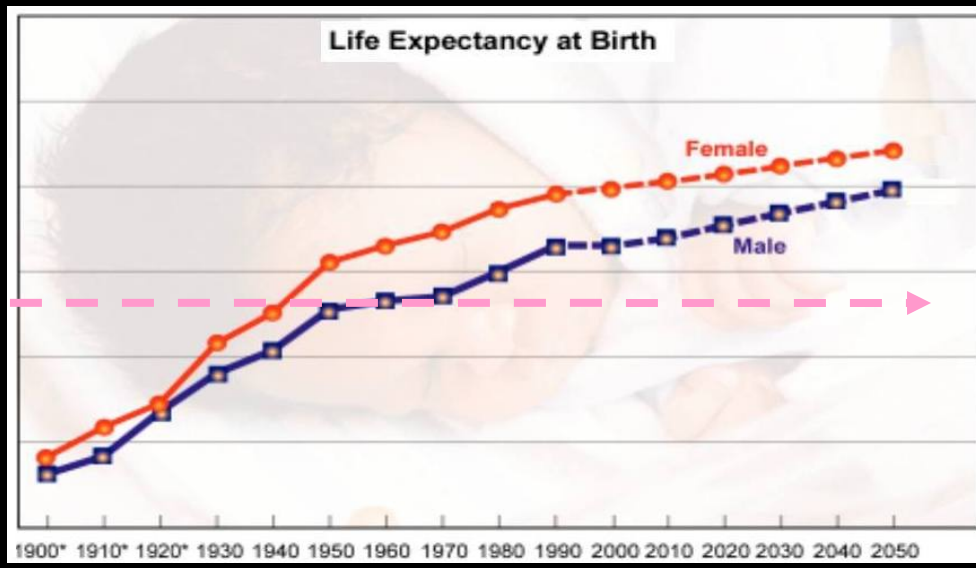
Perspectives:

Targeting cell signaling pathways for drug discovery:

an old lock needs a new key

Cellular Stress Response Pathway

(Vitagene system)



Calabrese V., Calabrese EJ., and Mattson MP. *Antioxidant Redox Signaling* 2010.

Glutathione Transferases
γ-Glutamatecysteine Ligase
Glutathione Reductase
Glutathione Peroxidase
Thioredoxin Reductase
Glutathione Conjugate Exporters

GSH Related

Inducible Cytoprotective Proteins: Vitagenes

Epoxide hydrolase
Ferritin
Dihydrodiol dehydrogenase
Leukotriene B4 dehydrogenase

NQO1
Heme oxygenase 1/CO
Hsp72 / Hsp90
γ-GCL
TRXred/Trx
Sirt1, Sirt2

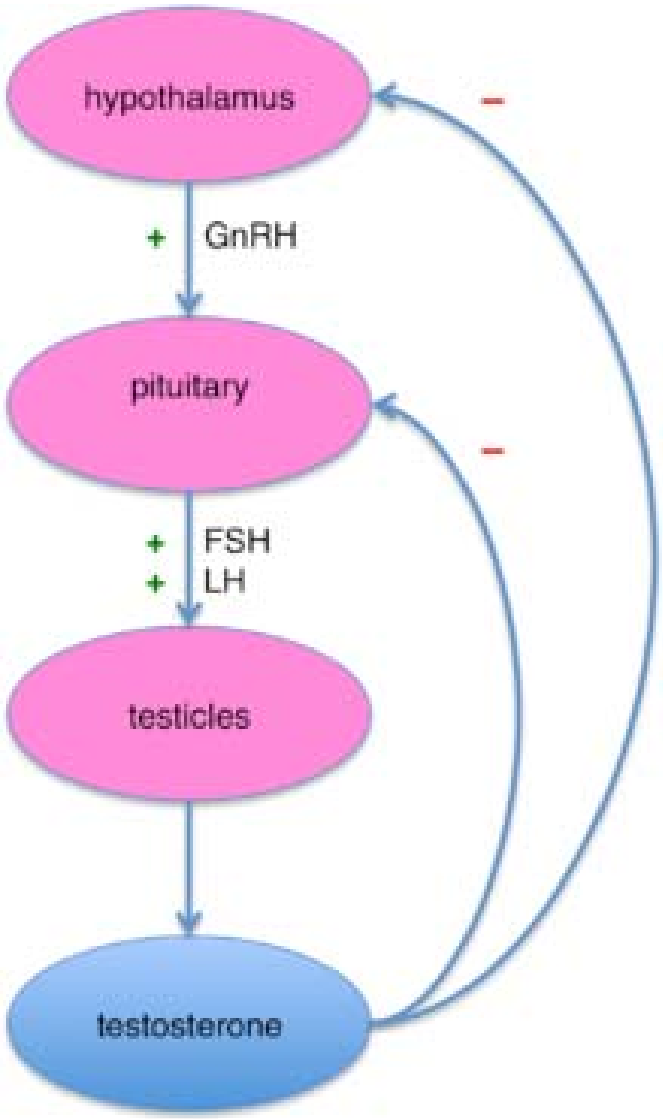
Calabrese V., *et al Antiox Red Signal* . 13: 1763-1811, 2013

Misconception and Concerns about

Bioidentical Hormones

Used for Custom-Compounded

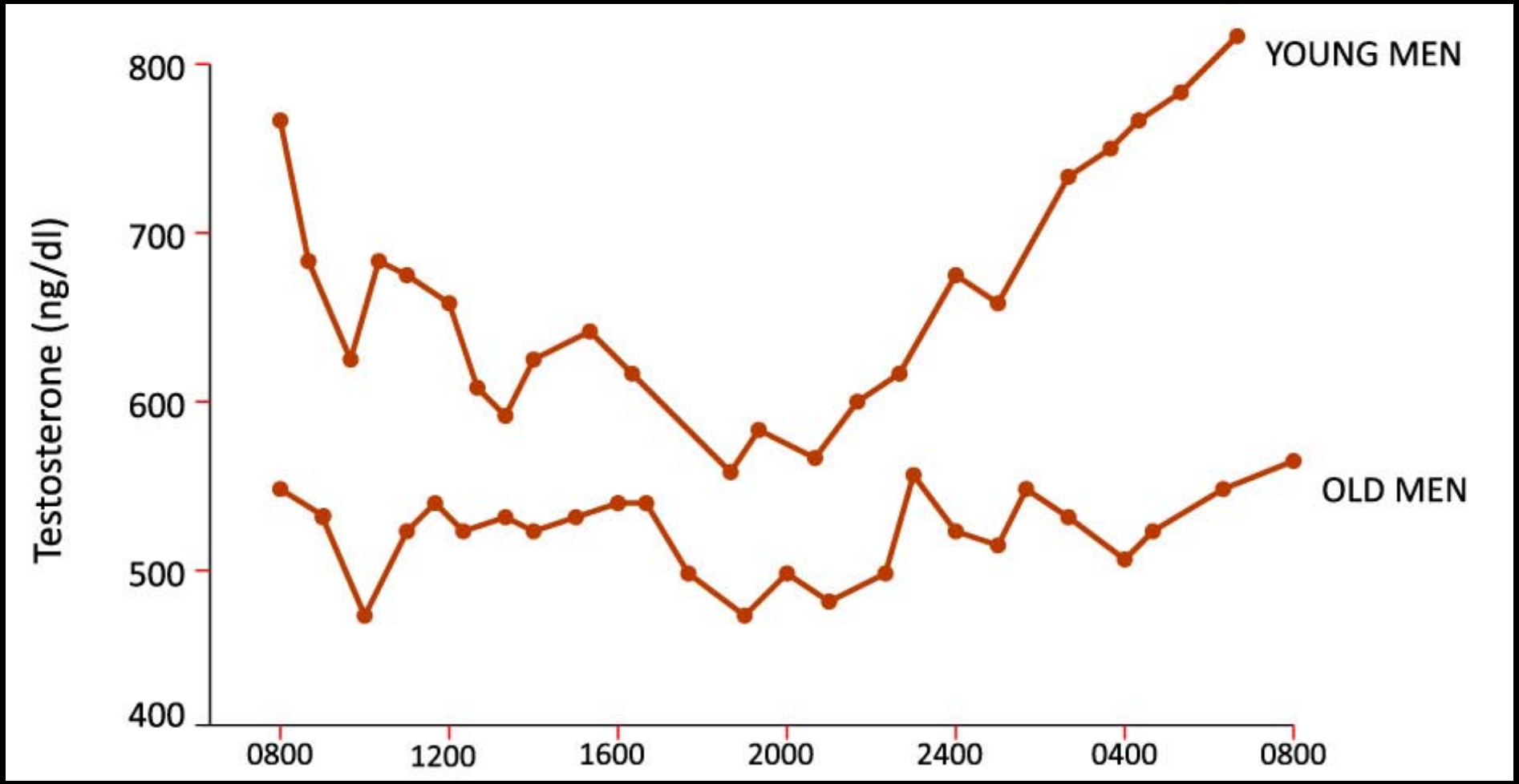
Hormone Therapy



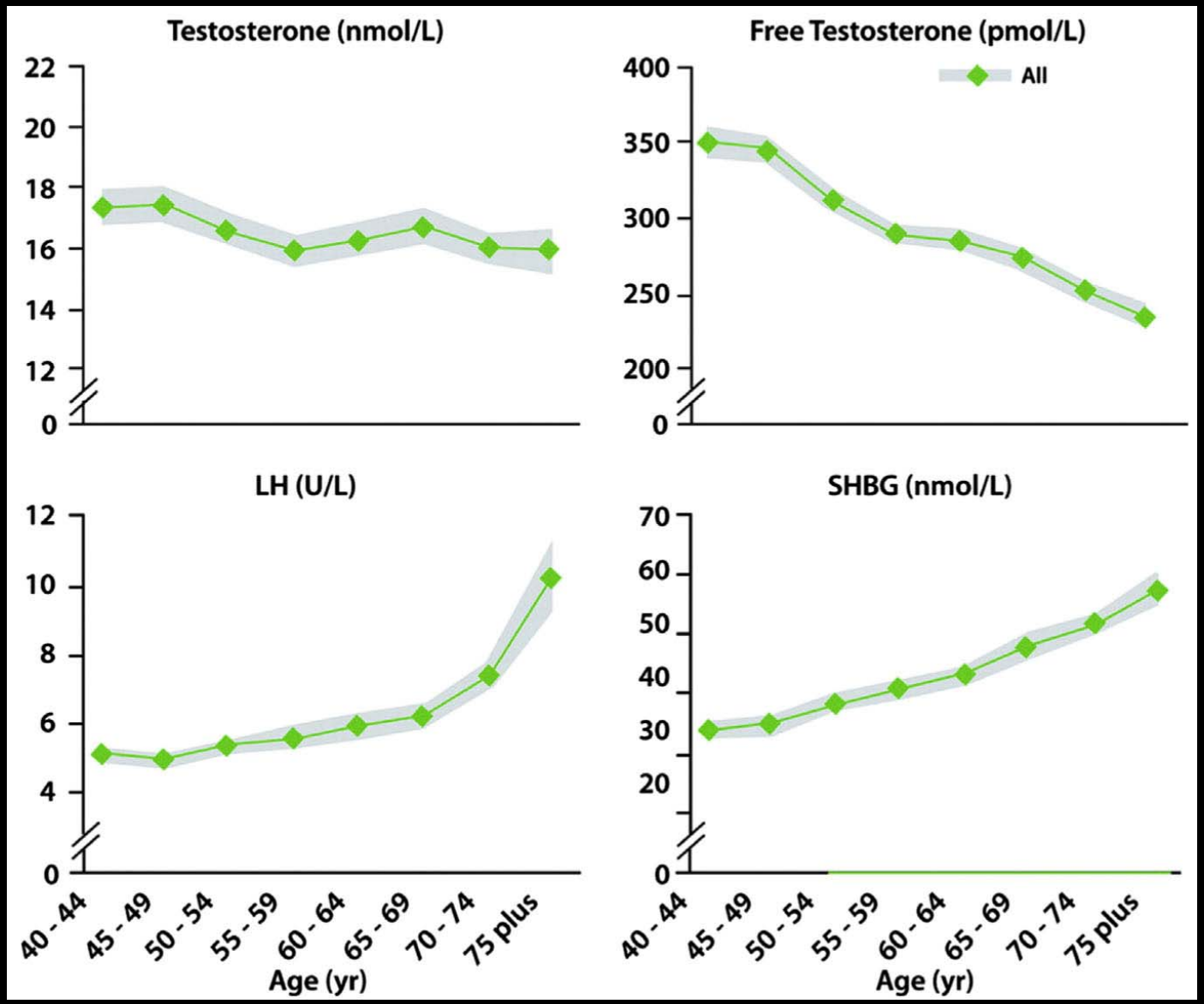
Gonadotropin releasing hormone

Luteinizing hormone

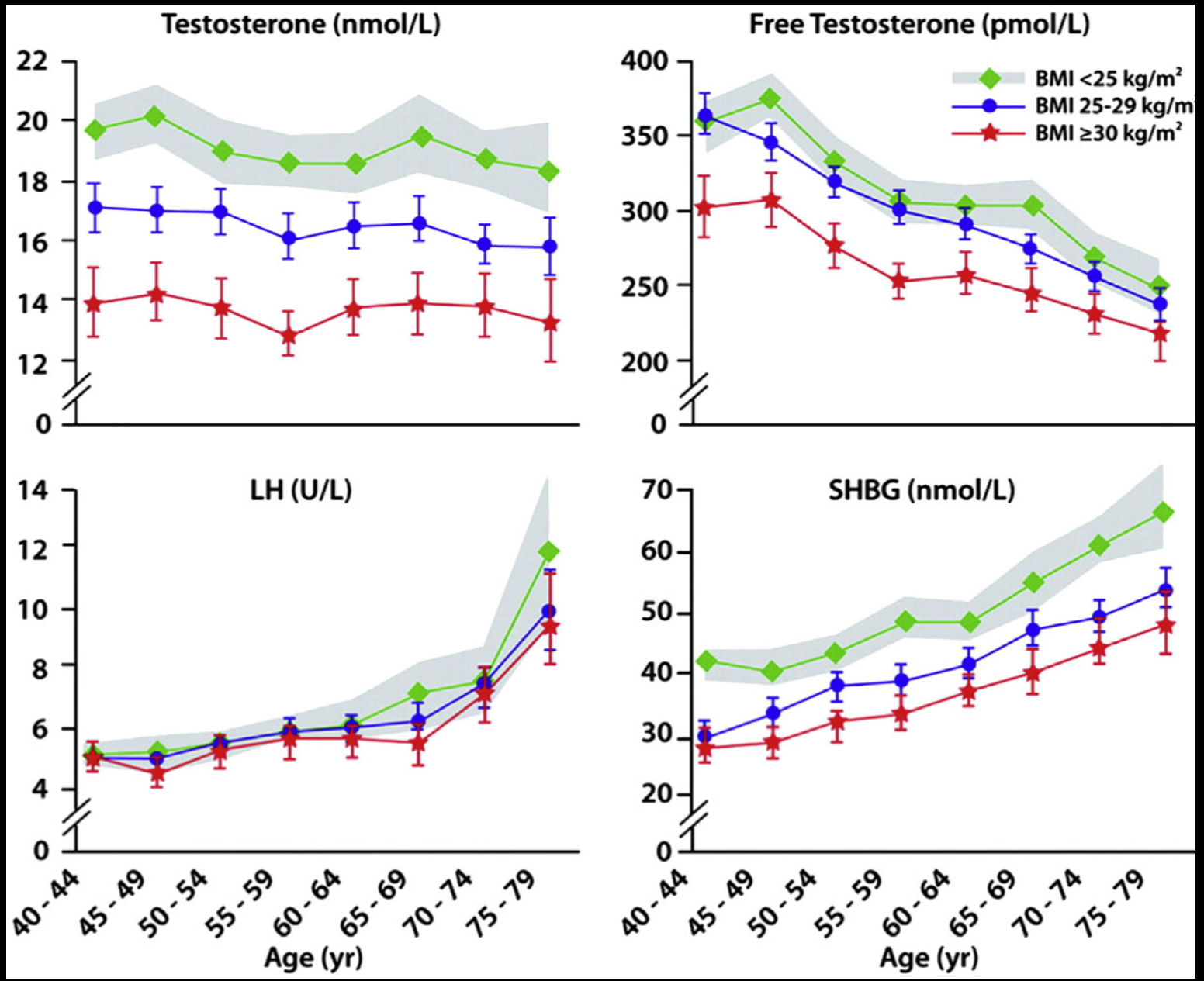
axis


Testosterone (ng/dl)
800
700
600
500
400
0800
1200
1600
2000
2400
0400
0800
YOUNG MEN
OLD MEN

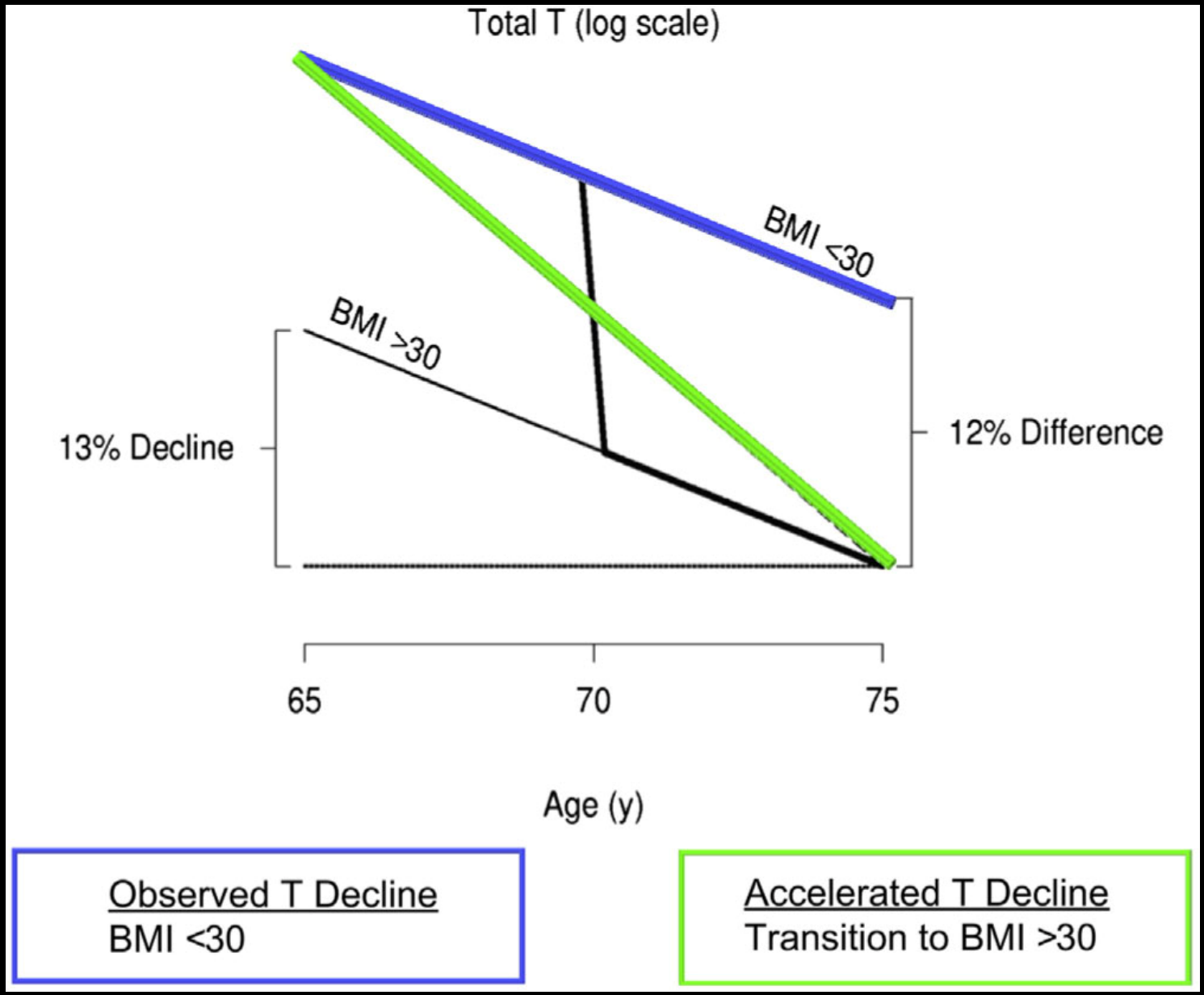
INFLUENCE OF AGING ON THE CHANGES IN TOTAL Testosterone (T), Free-T , LH, AND SHBG LEVELS.



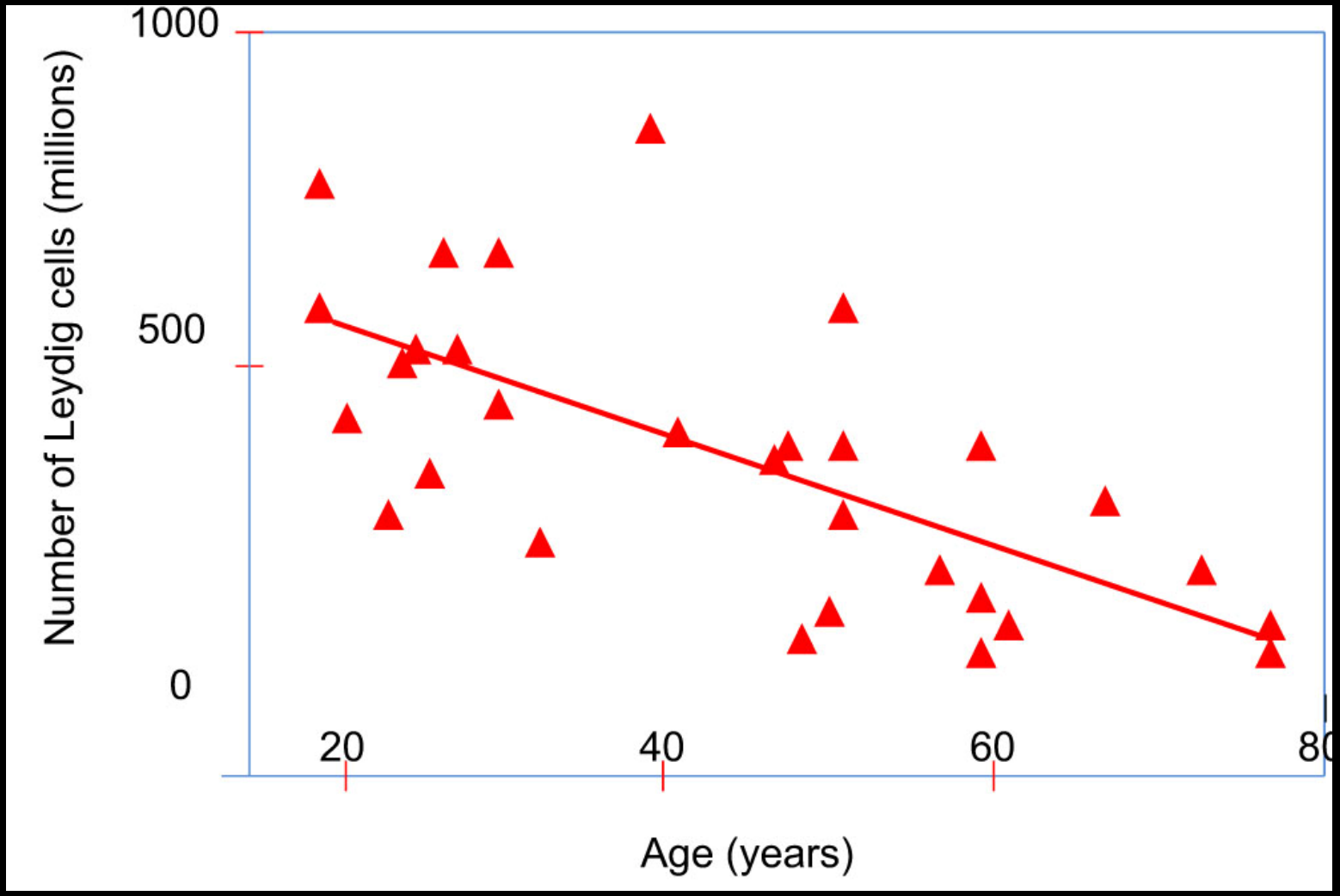
INFLUENCE OF BODY MASS INDEX ON AGE-RELATED DECLINE IN GONADAL HORMONES



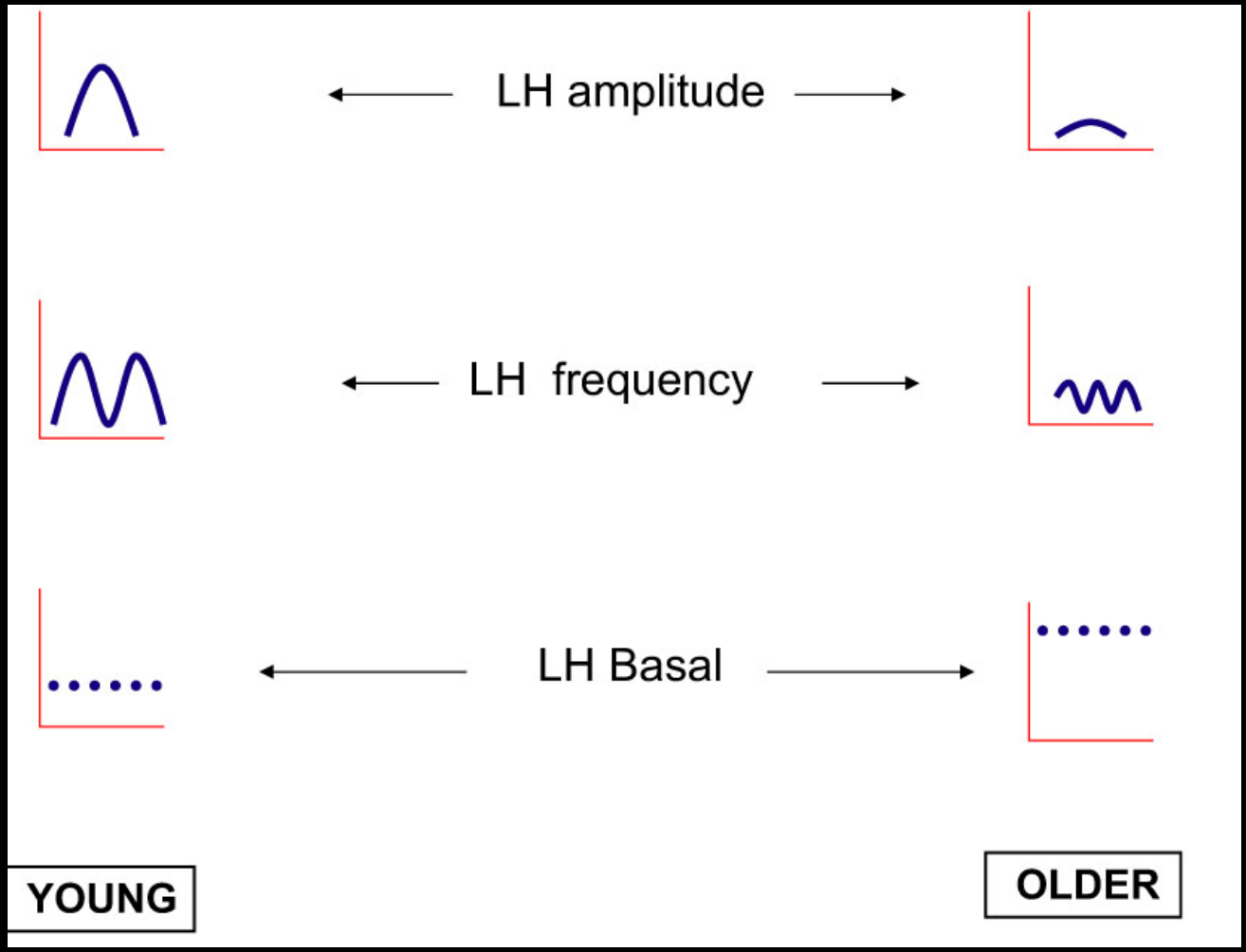
EFFECT OF OBESITY ON THE TRAJECTORY OF AGE-RELATED DECREASE IN TOTAL TESTOSTERONE



AGE-RELATED ATTRITION OF HUMAN LEYDIG CELLS



Characteristics of LH secretion in older and younger men decreased pulse amplitude, increased pulse frequency, and elevated basal LH levels.



Late-Onset Hypogonadism (LOH)

Definition:

The definition of late onset hypogonadism in the aging male is controversially debated, and according to the latest literature consists of at least three especially sexual symptoms:

- **Loss of morning erection,**
- **Low sexual desire and erectile dysfunction**
- **Total testosterone <8-11 nmol/l.**

Biochemical T CUT-OFFS

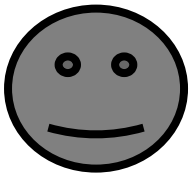
Mean normal levels

young :

5 - 7 ng/ml

(17,3 - 24,3 nmol/L)

>3,45 ng/ml
>12 nmol/l



2,3-3,45 ng/ml
8-12 nmol/l

< 2,3 ng/ml
< 8 nmol/l

In case of low levels of T it is recommended a second evaluation with
LH and PRL

Other causes of post-pubertal hypogonadism

- Pituitary adenomas
- Uremia
- Systemic illness
- Hyperprolactinemia
- Hemochromatosis
- Cushing’s Syndrome
- Cirrhosis
- Morbid obesity
- Cranial irradiation

One alternative HT involves

Custom-compounded hormone preparations

The hormones in these preparations include estrogen estradiol, estrone, progesterone, testosterone, androstenedione, and dehydroepiandrosterone.

These products can be prepared in individualized dosages and forms such as creams, gels, lotions, sublingual tablets, troches for buccal administration, and suppositories by compounding pharmacies from a clinician's prescription.

Proponents also claim that custom-compounded HT is associated with fewer side effects and may provide better symptom relief than conventional HT because the hormones used in the preparations are "bioidentical," *i.e.* identical to those made in the body.

The majority of these claims are unsubstantiated, and no rigorous randomized control trials have been carried out to support any of the claims. Because the custom-compounding of HT products is not regulated, a particular concern is that patients may be overdosed, or treated with ineffective products, or subject to unidentified risk.

The objectives of the present commentary are:

1) To show that the so-called “bioidentical” hormones in custom-compounded HT preparations may not be identical to those made in the body;

2) to point out how the lack of regulation of these hormone products can cause adverse effects in individuals undergoing treatment using them.

Hormones used for HT can be divided into four groups:

1. **Class A** (natural)
2. **Class B** (native to the body and synthesized from natural precursors**)**
3. **Class C** (native to the body and synthesized from nonsteroidal precursors)
4. **Class D** (synthetic and not native to the body)

Class A steroids

The steroids in class A are found in nature and are formulated into drugs without undergoing any chemical modifications.

Class B steroids

The class B steroids are semisynthetic.

They are steroids that exist in nature and are biosynthesized by the human body, but for these to be formulated as therapeutic agents, they need to be chemically synthesized from a natural starting material, most commonly from a plant sources containing sterols such as diosgenin and stigmasterol, which are used as precursors for the synthesis of a variety of steroids.

Essentially, steroid hormones such as estradiol, progesterone, dehydroepiandrosterone, androstenedione, testosterone, cortisol, aldosterone, synthetic conjugated estrogens, *etc.*, have been chemically synthesized from these sources for decades.

Contrary to many claims, it is important to note that ingestion of the Mexican yam or soybean does not result in the formation of any of the above steroids because the human body lacks the enzymes needed to convert diosgenin or stigmasterol to those steroids.

The chemical synthesis of a steroid hormone such as estradiol from diosgenin requires at least 15 reactions.

Another misconception pertains to the occurrence of mammalian steroid hormones in plants. It is only recently that some steroid hormones such as progesterone and androstenedione have been positively identified in plants, using rigorous assay methodology.

However, their concentrations are very low.

There are no hormonal preparations on the market that are derived by extraction of a steroid hormone from a plant !

On a biomolecular level steroids synthesized from plant precursors such as diosgenin by the semisynthetic process are not actually identical to the corresponding endogenous steroids in the human body.

There are two naturally occurring isotopes of carbon, 12C and 13C, in the carbons that comprise the chemical structure of steroids in plants and humans.

Studies show that semisynthetic steroids consist of a different 13C/12C ratio, when compared with the corresponding human endogenous compounds.

This observation is based on the fact that endogenous steroid hormones reflect an average of the 12C and 13C isotopes of carbon from vegetal and animal food eaten by humans, whereas plant sterols such as those found in soy exhibit a fixed 13C/12C ratio.

Class C steroids

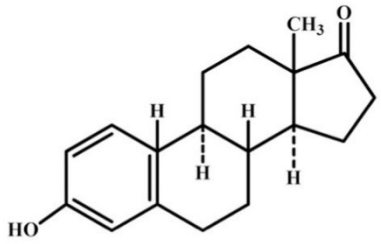
The steroids in the class C group are “synthetic” compounds that exist in nature but are synthesized from simple nonsteroidal starting materials by a process generally called “total synthesis.” This is one of the oldest means by which steroid hormones were first synthesized.

In total synthesis, there is one fundamental requirement and, that is, the steroid synthesized has to have the same precise stereochemistry as that of the naturally occurring hormone. It is only then that the synthesized hormone will have the same biological activity.

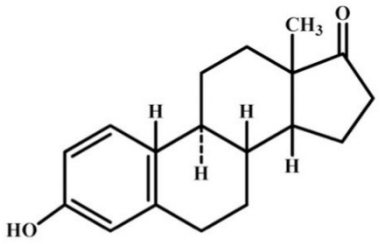
It is obligatory that the very specific three-dimensional structure be the same for a compound to behave as an agonist because the activity of the compound is expressed by its interaction with its specific endogenous receptor.

Unfortunately, total synthesis can give rise to a number of isomers; for example, in the total synthesis of estrone, there are eight possible racemates (16 isomers), only one of these beeing the natural hormone; others have different physical properties, and some of them are totally inactive.

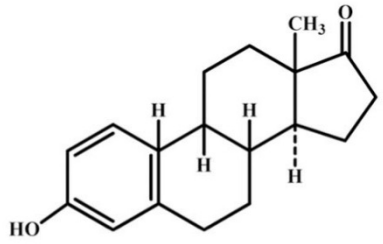
Eight isomeric racemates of estrone



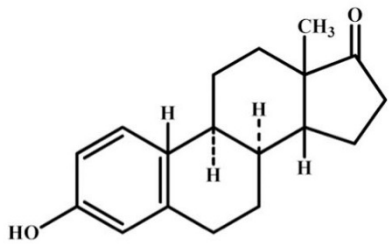
Estrone
mp 253-255*
(Natural)



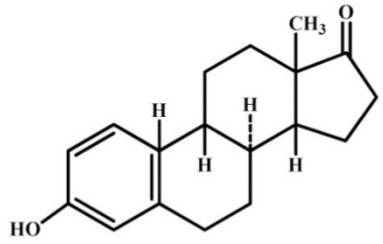
mp 216-217



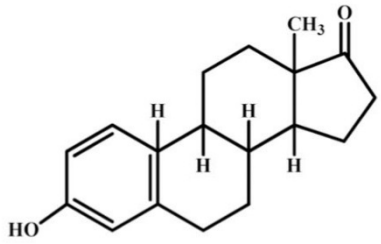
mp 197-198



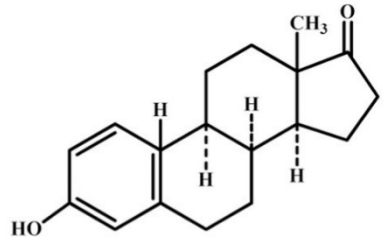
mp 180.5-181.5



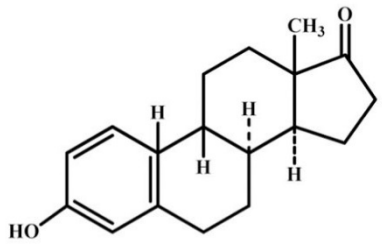
mp 238.5-260



mp 214-215



mp 254-255



mp 230-232

***mp = melting point**

Class D steroids

The group of class D steroids includes steroids not found in humans, animals, or plants, and includes drugs such as medroxyprogesterone acetate, ethinyl estradiol, norethindrone, norgestrel, *etc.*

.

Because estrogen preparations compounded by pharmacists do not undergo any rigorous testing or approval by regulatory bodies, it is very possible that some mixtures, depending on the route of synthesis, may not be as potent or can be totally inactive therapeutically.

In other words, the so-called bioidentical hormones may not be identical to the natural hormones produced *in vivo* by the human body.

The U.S. Food and Drug Administration (FDA) regards the use of the terminology "bioidentical hormone" as a marketing ploy, implying a benefit for a drug for which there is no medical or scientific basis.

A major concern about the custom-compounded products is that the practice of drug compounding is not subject to the same degree of regulations and oversight by the FDA and by regulatory authorities in other countries, which is required for the commercial production and marketing of prescription medicines.

Unlike commercially available drugs, compounded medicines are not tested routinely by any regulatory agency for quality, purity and potency. In addition, there are no product labeling requirements for the custom formulations.

This differs from commercially available drugs, which are required to be sold with a package insert that details the product's indications for use, contraindications, pharmacokinetics, and adverse events, using language approved by regulatory authorities.

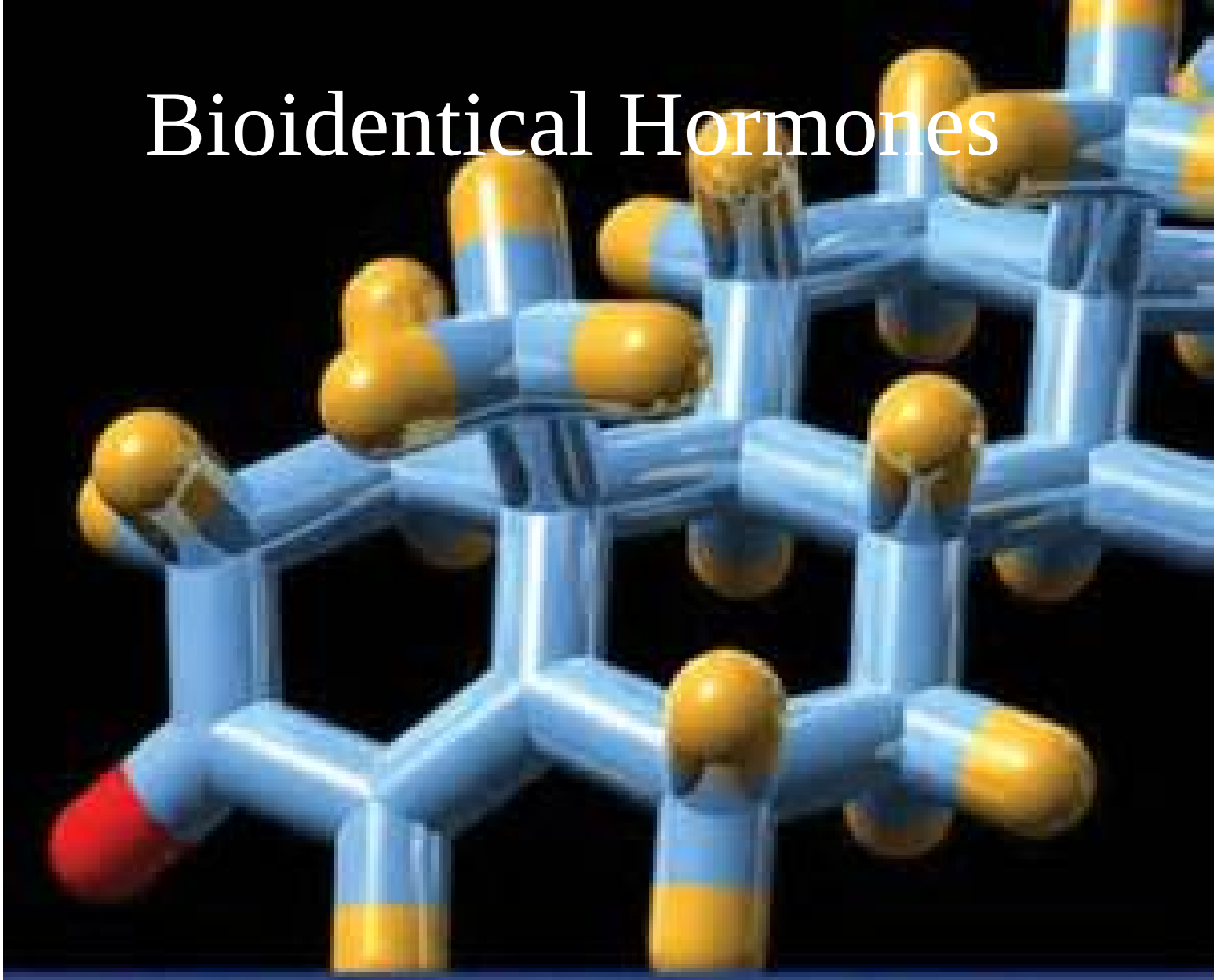
Because there is no strict regulation and oversight of compounded medicines, patients using custom-prepared hormonal preparations may be subject to underdosing or overdosing of the products.

Steroid doses of products prepared by custom-compounding pharmacies are not regulated, and most often little is known about the pharmacokinetics of the products.

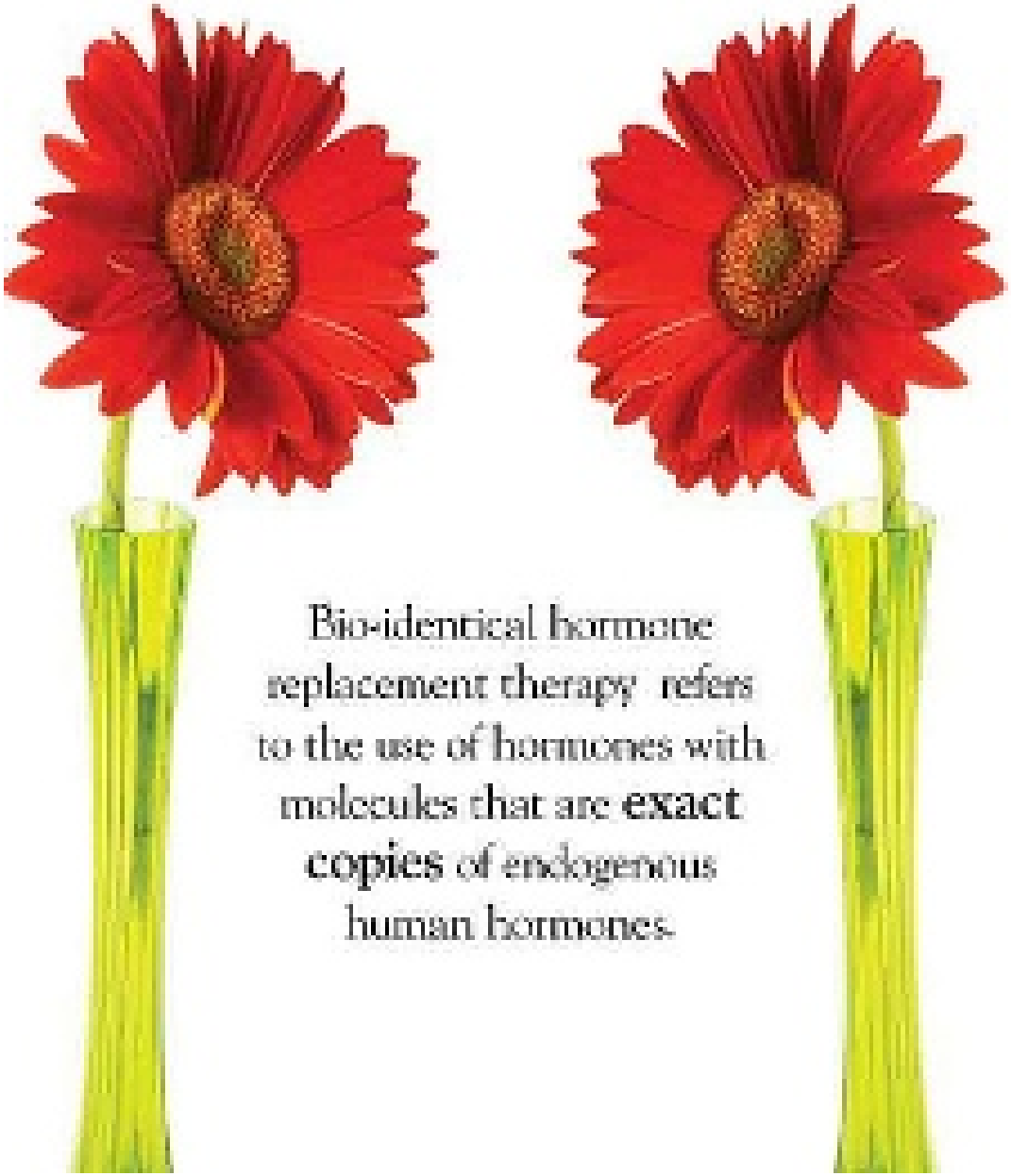
In most instances, serum levels achieved by a particular custom prepared hormonal preparation are not determined by the physician.

Custom-compounded hormonal preparations can be purchased and used with no oversight by physicians as to the medical history of the patient, potential presence of risk factors, or **the serum levels of active hormones attained with these products.**

Bioidentical Hormones

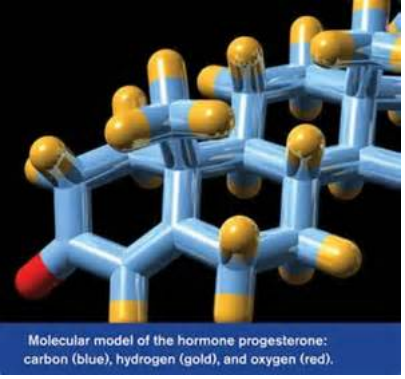


Molecular model of the hormone progesterone: carbon (blue), hydrogen (gold), and oxygen (red).



Is this true?

Absolutely not !


Molecular model of the hormone progesterone: carbon (blue), hydrogen (gold), and oxygen (red).

Bioidentical

- Those hormones which are structurally and chemically the same as the substances present in our body are known as bioidentical hormones.

- These hormones, despite their advantages, can be dangerous. The damage depends upon the duration for which the product has been used for and the prescribed dosage.
- Another danger of bioidentical hormones is that their prolonged use can slow down the natural production of hormones in the body. In such a case, all those hoping to prevent the process of aging are just ..

..kept "hoping.“ !!

In conclusion, we need to consider the scientific evidence to determine the safety and efficacy of all hormonal preparations used for HT.

Use of the misleading term

“bioidentical hormone”

is inappropriate, and its use should be discouraged

Reproductive aging in men.

Aging in men is associated with a decrease in serum testosterone levels due to attrition in testicular Leydig cells and slowing of the hypothalamic GnRH pulse generator.

The practicing endocrinologist is frequently consulted for consideration of testosterone therapy in older men with late-onset hypogonadism (LOH), a condition that many clinicians fail to distinguish from organic hypogonadism.

Recent data using syndromic definition show that only 2% of 40-80-year-old men have LOH. Co-morbidities and obesity strongly contribute to LOH, suggesting that testosterone is a biomarker of health.

Hence, prevention and treatment of these co-morbidities might attenuate age-related decline in androgen levels.

Testosterone replacement therapy in the aging male has been shown to have a beneficial effect on muscle and fat mass as well as on bone mineral density, with more conflicting effects observed on muscle strength, sexual function, mood and quality of life.

Importantly, so far the long-term safety and efficacy of testosterone replacement therapy has not been established.

Although until now no clear evidence has been found that testosterone replacement therapy has a causative role in prostate cancer or indeed in changes of the biology of the prostate, in a recent meta-analysis a 4-fold increased risk of prostate-associated event rates in testosterone treated elderly men sounds a note of caution.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10
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