



# HRT: Looking at it with fresh eyes

Presented by:  
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  - ▶ Board Certified in Family Medicine
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# Disclaimers

- I'm married to a goddess.
- we both use HRT daily.
- I have no financial interest in any pharmacies or specific products.



# HRT = Hormone Replacement Therapy

- Replacing that which is lost
- Helps our body to function properly

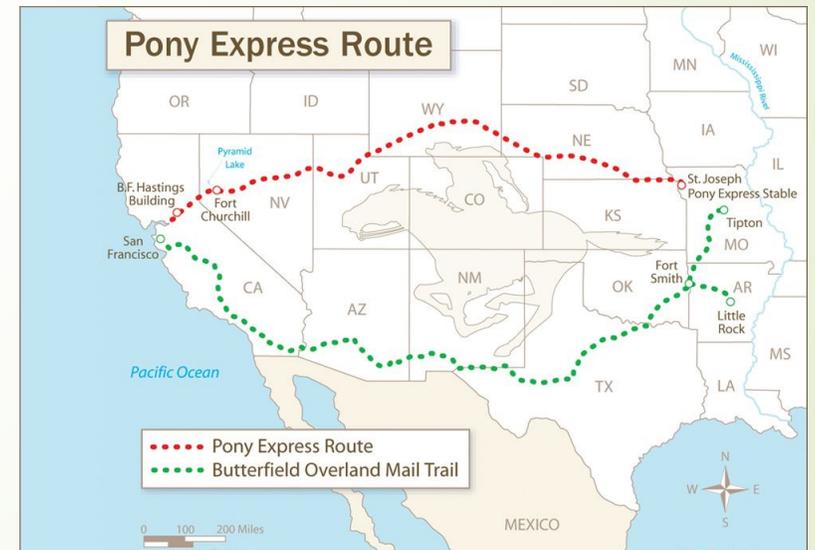
Best analogy that I can think of is oil in our cars. They run on gasoline fuel, but require oil in the engine so that they don't seize up. Hormones do the same thing in our bodies. They slow the breakdown processes throughout, helping our bodies to last longer.

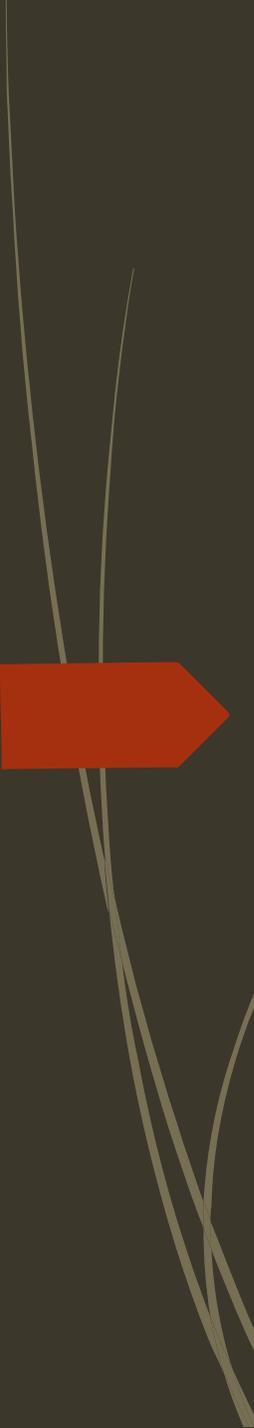
And, just as it's true that oil doesn't suddenly turn bad and stop working when the car hits 100,000 miles, similarly, our hormones don't suddenly "turn bad" at a certain age, either.



# Hormones

- ▶ chemical substances that act like messenger molecules in the body. After being made in one part of the body, they travel to other parts of the body where they help control how cells and organs do their work.
- ▶ Examples:
  - ▶ Insulin - affects sugars and fat.
  - ▶ Adrenaline (epinephrine) assists with fight or flight responses
  - ▶ TSH - stimulates the thyroid to regulate metabolism
  - ▶ Sex hormones (estrogen, progesterone, testosterone) responsible for reproduction
  - ▶ Melatonin – prepares the body for sleep





Hormones  
are created  
by glands  
that are part  
of the  
endocrine  
system

- ▶ **glands** are organized collections of cells designed to make hormones
  - ▶ **endocrine** system means that they're secreted directly into the blood i.e. no ducts.
  - ▶ **exocrine** glands have ducts e.g. sweat, salivary glands

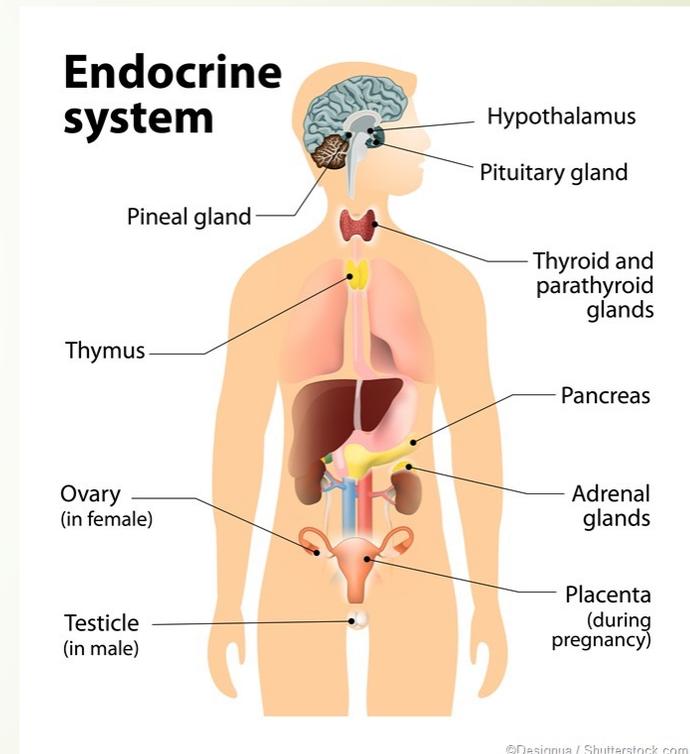
# Viaduct? Why not a chicken?

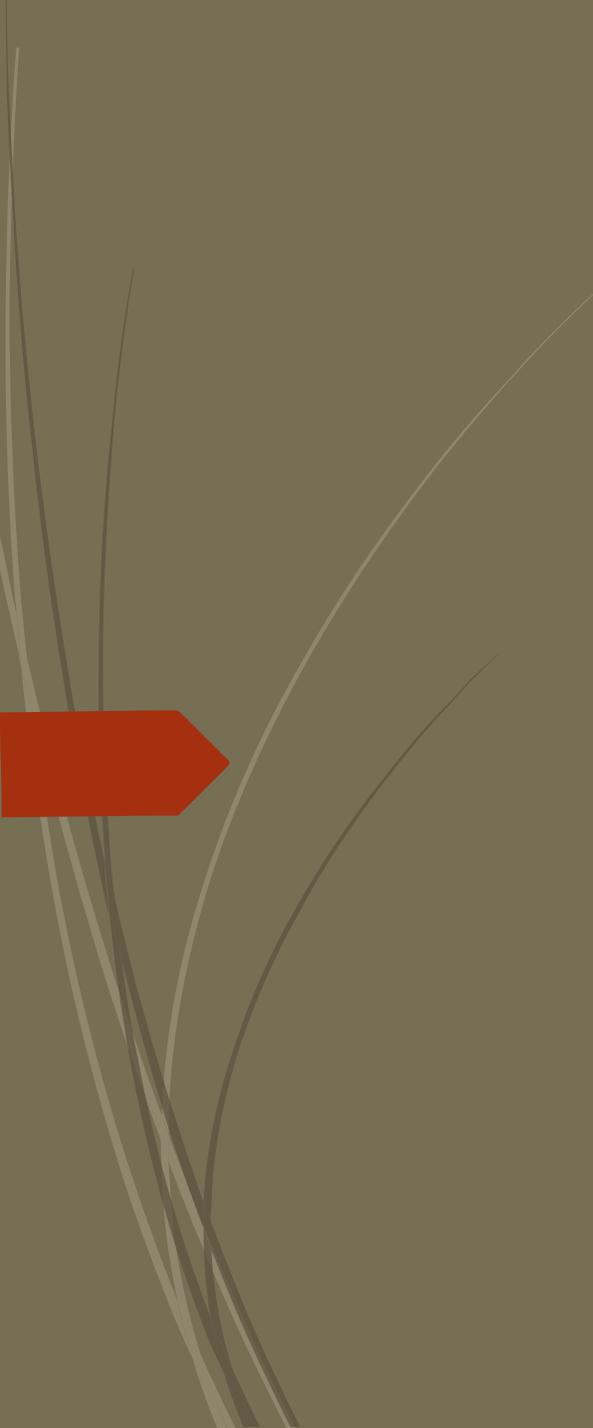
- ▶ **4 types of hormones**  
(based upon their chemical structure):
  - ▶ Steroid hormones – made from cholesterol (e.g. estrogen, testosterone)
  - ▶ Amino acid derived (e.g. norepinephrine)
  - ▶ Peptides, polypeptides (e.g. oxytocin)
  - ▶ proteins (e.g. human growth hormone)



# Endocrine Glands in the Body

- **Hypothalamus:** The hypothalamus is responsible for body temperature, hunger, moods and the release of hormones from other glands; and also controls thirst, sleep and sex drive.
- **Parathyroid:** This gland controls the amount of calcium in the body.
- **Thymus:** This gland plays a role in the function of the adaptive immune system and the maturity of the thymus, and produces T-cells.
- **Pancreas:** This gland produces the insulin that helps control blood sugar levels.
- **Thyroid:** The thyroid produces hormones associated with calorie burning and heart rate.
- **Adrenal:** Adrenal glands produce the hormones that control sex drive and cortisol, the stress hormone.
- **Pituitary:** Considered the "master control gland," the pituitary gland controls other glands and makes the hormones that trigger growth.
- **Pineal:** Also called the thalamus, this gland produces serotonin derivatives of melatonin, which affects sleep.
- **Ovaries:** Only in women, the ovaries secrete estrogen, testosterone and progesterone, the female sex hormones.
- **Testes:** Only in men, the testes produce the male sex hormone, testosterone, and produce sperm.





Our bodies eventually stop making some of the hormones.

Why?

“Because,  
obviously they  
turn evil.”



Before menopause:





“The change...”



After menopause:





Wrong! NOT EVIL!

Our bodies stopped  
making hormones  
because...

Wait for it.....

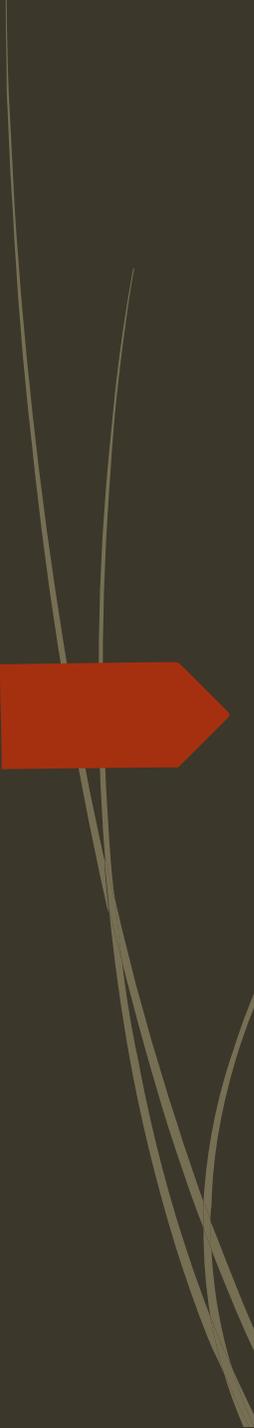


Wait for it...



100 years ago,  
we were dead.





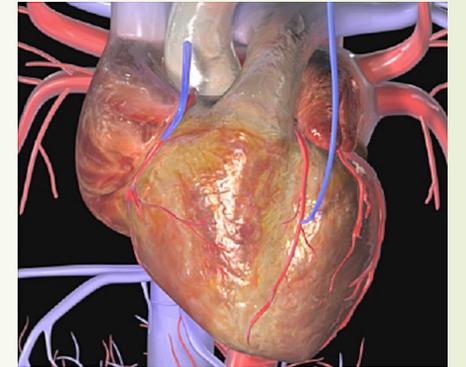
# Life expectancy for an individual born in 1910

- ▶ White women: 52 years old
- ▶ White men: 49 years old
- ▶ Black women: 38 years old
- ▶ Black men: 34 years old

# Things we didn't see back then

- ▶ Cataract surgeries
- ▶ Coronary artery bypass procedures
- ▶ Joint replacements

We didn't live long enough to wear out our parts!



1910: people died early and often.

- ▶ No good antibiotics: Penicillin discovered in 1928
- ▶ No good reliable antihypertensives until 1950's (diuretics)
- ▶ Poor cancer treatments: chemotherapy began in 1940's. Mainly surgery before that.



# Science to the rescue

- ▶ Thanks to the discovery of antibiotics and other pharmaceuticals to control high blood pressure and treat cancer, we now have patients living into their 60's, 70's, 80's, 90's, and 100's.
- ▶ Current life expectancies
  - ▶ American women: 81.6 years old
  - ▶ American men: 76.9 years old
  - ▶ Combined average: 78.7 years old
- ▶ An improvement of about 30 years in life expectancy over the last 100 years.



**News Flash!**

# EVOLUTION DOES NOT OCCUR THAT FAST!

- it takes about 1 million years for a major change to persist and for changes to accumulate.



We're keeping people alive longer, but without the benefit of their hormones.

- ▶ These hormones are necessary for continual repair and upkeep of our bodies. Without them, we gradually fall apart.
  - ▶ Soft, squishy parts dry out
  - ▶ Bones get weak and break
  - ▶ It takes longer to heal



You all get the  
point, right?



Hmmm... but...  
won't they  
cause cancer if  
taken too long?





...at least probably not.





We ALL die.

The longer we remain on this planet, our cells eventually do degrade and mutations occur in some of them, often leading to cancer and death. That risk rises with every decade that we live, again, regardless of hormone status.

Again...we ALL  
die.



# Quality vs Quantity?



# Not really a trade-off

- Quality of life improved.
- Quantity of life unaffected.

Ann Intern Med. 1999 Sep 21;131(6):463-6.

**The HERS trial results: paradigms lost? Heart and Estrogen/progestin Replacement Study.**

Herrington DM<sup>1</sup>.

Ⓜ Author information

**Abstract**

The Heart and Estrogen/progestin Replacement Study (HERS) found no overall effect of 4.1 years of therapy with estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. However, within the overall null effect, a 50% increase in cardiovascular events was seen in the first year, followed by fewer events after 2 years of treatment in the hormone therapy group than in the placebo group. Understanding the cause

6,518 views | Oct 10, 2012, 02:09pm

**Danish Study Gives A Boost To Hormone Replacement Therapy Timing Hypothesis**

 **Larry Husten** Contributor  
Pharma & Healthcare  
*I'm a medical journalist covering cardiology news.*

Hormone replacement therapy (HRT) suffered a sharp blow a decade ago when the Women's Health Initiative failed to show any cardiovascular benefit in women taking HRT. Despite the setback, many researchers theorized that HRT might still be beneficial in women who start HRT close to menopause. Now [a new study from Denmark published in BMJ](#) lends strong support to the "timing hypothesis."

The New York Times

# Taking Hormones for Menopause Doesn't Raise Early Death Risk

By Nicholas Bakalar

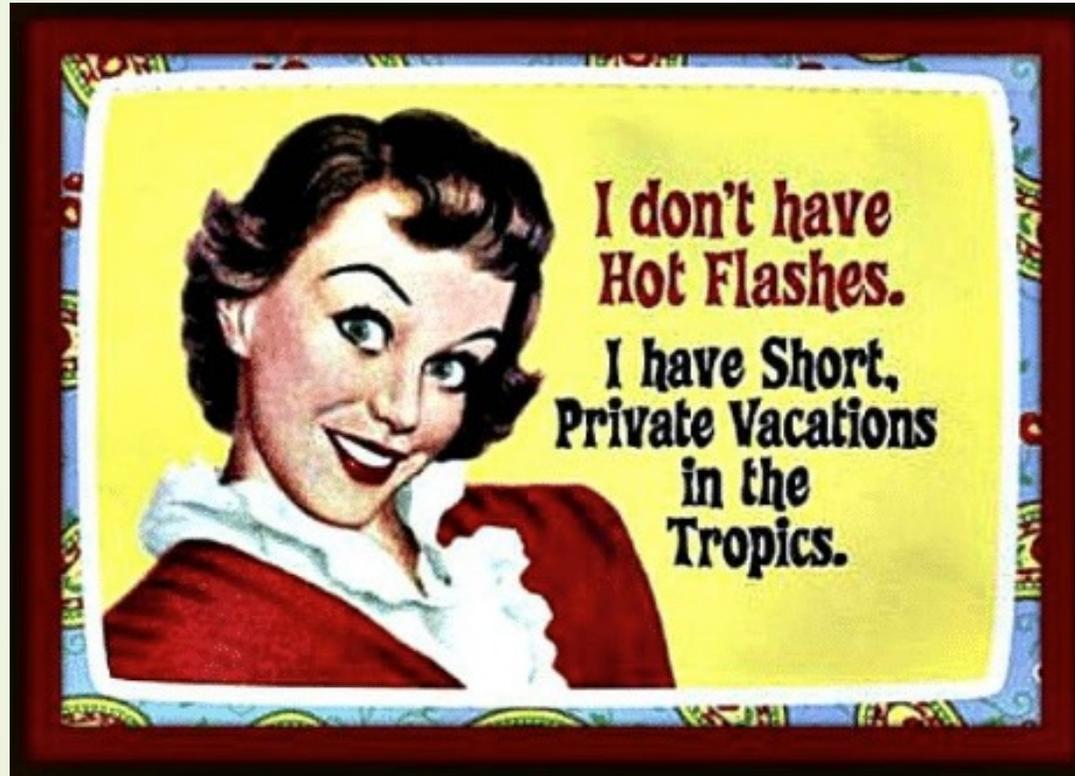
Sept. 12, 2017

 52



The largest and longest clinical trials to date of menopausal hormone therapy have found that the drugs do not increase the risk of premature death.

# Benefits of female hormones



# Benefits of female hormones (estradiol and progesterone)

- Keeps the soft squishy parts soft and squishy
- Keeps the bones strong
- Promotes restful sleep, less anxiety and depression
- Prevents against heart disease and breast cancer
- May prevent Alzheimer's dementia
- Also plays role in sexual function
- May keep women from killing their husbands prematurely?





# Benefits of testosterone

- For men: improves energy and endurance
- Regulates the following for everyone
  - sex drive and libido
  - **brain** function
  - bone mass
  - muscle mass
  - **strength**, and **fat** distribution

# Testosterone in post-menopausal women

- ▶ Production persists after body has stopped making estrogen.
  - ▶ Testosterone is produced by both the ovaries and the adrenal glands.
- ▶ Without the benefit of estrogen to balance the androgen, testosterone plays a role in hair loss in these women.





The Goal of HRT:  
Lead a normal life.



Yeah, but you still  
didn't talk about  
the bad stuff...

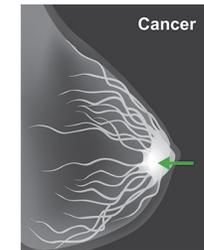
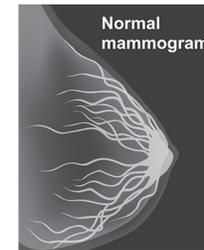




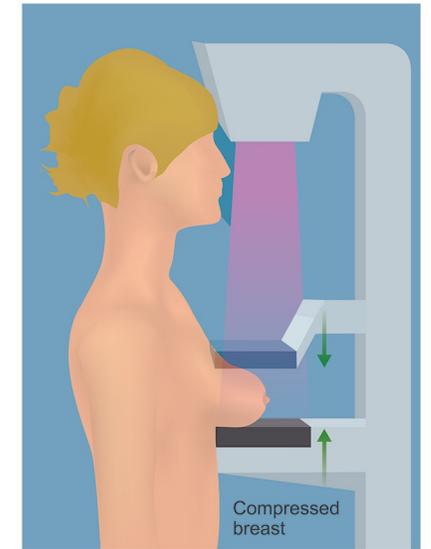
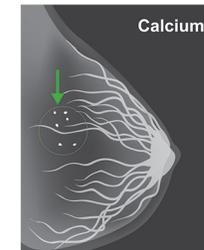
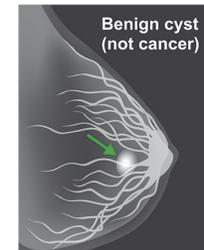
# Fear of breast cancer

- ▶ **1 out of 8** women will get breast cancer.
  - ▶ *7 out of 8 women will NOT!!!*
- ▶ About 85% of breast cancers occur in women *without* a family history of breast cancer. These occur due to genetic mutations that happen as a result of the aging process and life in general, rather than inherited mutations.
  - ▶ Historically, The most significant risk factors for breast cancer have been gender (being a woman) and age (growing older).
  - ▶ However, looking at pre-menopausal women: *it seems that women who develop breast cancer are either progesterone deficient or anovulatory (their cycles are off).*
  - ▶ Postmenopausal women who take estrogen only (without progesterone) are also at risk (they're progesterone deficient).
- ▶ *Bio-identical HRT (BHRT) has never been shown to increase risk of breast cancer. In fact, it seems to bestow a protective effect as those women have less breast cancer than women who take absolutely nothing.*

# Breast Cancer detection



X-ray illustrate

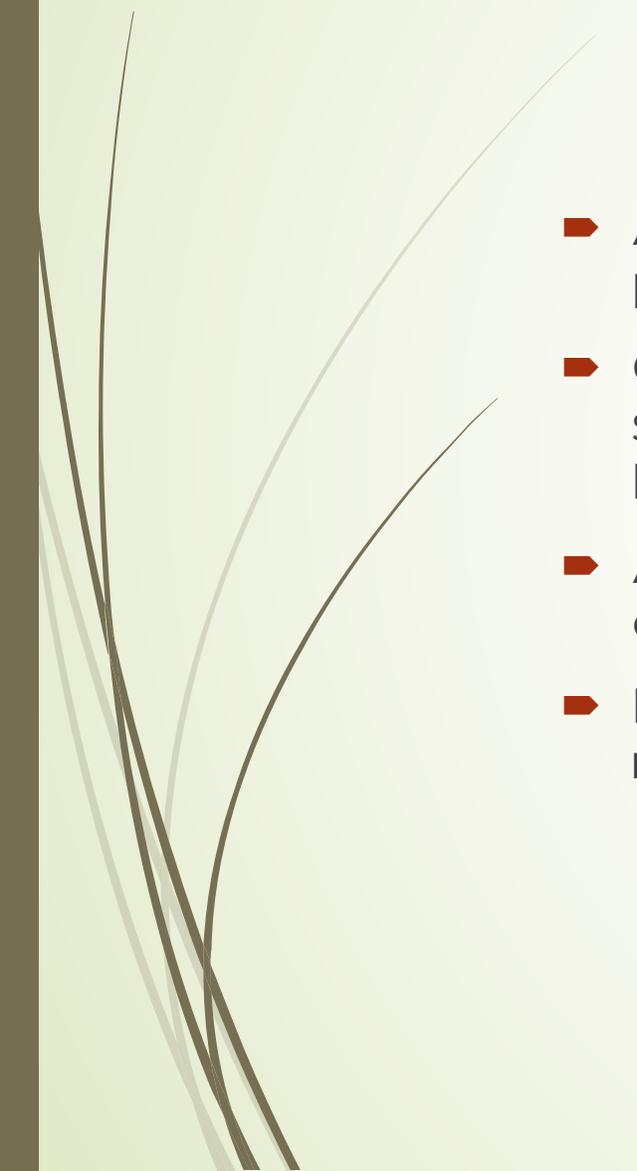


# Blood clots: heart attacks and strokes





# Blood clots: heart attacks and strokes

- ▶ After a few years in development, the FDA approved the first birth control pills in 1960.
  - ▶ One pesky problem arose i.e. some women sustained heart attacks and strokes, thought to be due to estrogen's effect on the liver, making the blood hypercoaguable (i.e. wanting to clot).
  - ▶ All providers of my generation were taught that estrogen was potentially dangerous for this reason.
  - ▶ However, researchers re-examined the data and it turned out that the likely reason for these events was not estrogen, but...
- 

# Smoking.

- In fact, recent studies involving ingestion of bioidentical estradiol failed to demonstrate any clotting activity hence the FDA approved the use of Bijuva in 2018.
- Still, transdermal application of bioidentical hormone therapy seems safer than oral use b/c the first pass effect on the liver is gone.



# Estrogen and heart attacks.

- ▶ Chest pain < 50 years of age.
  - ▶ Men much more likely to have a heart attack than women.
    - ▶ Women protected by estrogen, presumably by increasing HDL ('good' cholesterol), reducing LDL ('bad' cholesterol), relaxing/dilating muscles around blood vessels, soaking up free radicals, and probably other mechanisms.
- ▶ Chest pain > 50 years of age.
  - ▶ Odds are equal between men and women.





# H.E.R.S. (Heart and Estrogen/Progesterone Replacement Study) 1998

- ▶ found that the use of estrogen plus progestin in postmenopausal women with heart disease did not prevent further heart attacks or death from coronary heart disease (CHD).
- ▶ Average age of menopause in American women = 52 years old.
- ▶ Average age of women in the H.E.R.S. = 67 years old.
  - ▶ **Major Fail:** many of these women already had blockages before they entered the trial!

# WHI (Women's Health Initiative)

- National Institutes of Health (NIH) 1991 over 15+ years
- more than 160,000 postmenopausal women aged 50–79 years (at time of study enrollment)

**cmaj**News

## Landmark trial overstated HRT risk for younger women

Results of a major trial of hormone therapy may have been misleading

Lauren Vogel | CMAJ | April 12, 2017

**A** principal investigator of a landmark women's health study says initial results that linked hormone replacement therapy (HRT) to breast cancer and heart attacks were misleading and distorted for publicity. Others involved in the study claim the findings were merely misunderstood. Fifteen years on, a new consensus about risks and benefits is emerging, but too late for a generation of women who abandoned or avoided HRT due to reported risks.



*the*  
PHARMACEUTICAL JOURNAL

*A Royal Pharmaceutical Society publication*

# Establishing the risk related to hormone replacement therapy and cardiovascular disease in women

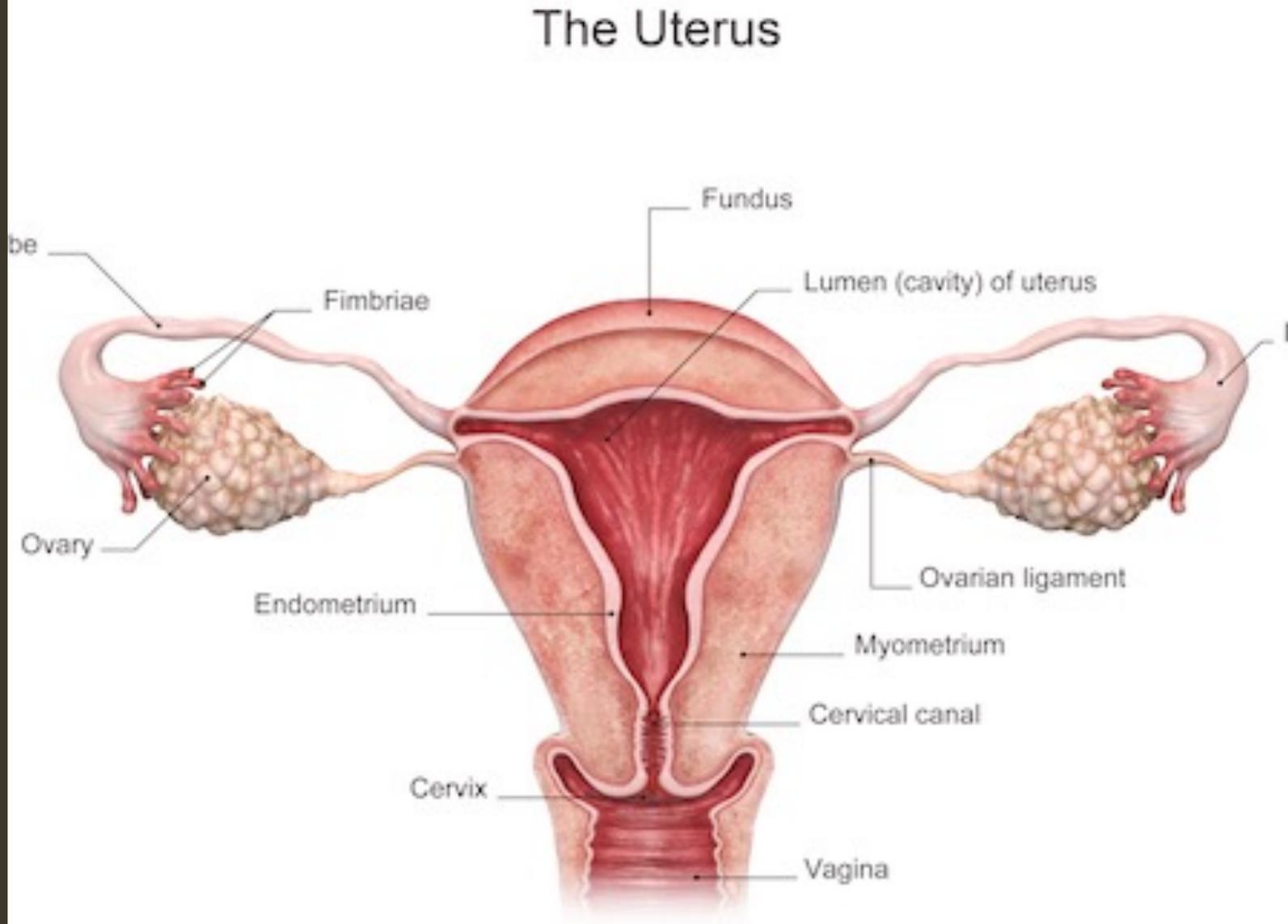
*Clinical Pharmacist* | 10 JAN 2017 | By Marie-Odile Gerval , John C Stevenson

## Abstract

Hormone replacement therapy (HRT) has a profound impact on the cardiovascular system in postmenopausal women, achieved through its effects on metabolic risk factors for coronary heart disease (CHD) and on arterial function. Observational studies have consistently shown an association between postmenopausal HRT use and a reduced incidence of CHD. However, the largest randomised trial initially reported no overall benefit on CHD risk. Subsequent analyses and follow-up of the study have demonstrated a significant benefit for CHD risk in healthy women initiating oestrogen therapy soon after the onset of menopause. This benefit of early initiation of HRT has been confirmed in more recent trials and in meta-analyses. The dose and type of hormones at initiation of therapy appears crucial to obtaining CHD benefit.

# Endometrial cancer

- ▶ Result of unopposed estrogen replacement
- ▶ Women who use balanced HRT have even less risk of this than women who do not take anything. i.e. a protective effect.





# Importance of progesterone

- ▶ Doctors have been taught that progesterone is only necessary for women with an intact uterus, to prevent endometrial cancer.
  - ▶ However, progesterone remains important for mood, controlling stress, better sleep, prevention of breast cancer, etc.
  - ▶ Hence ALL women need to be on a balanced HRT program with both estrogens and progesterone, even if they've had a hysterectomy.
- 



# But, I'll get fat!!!

- ▶ **The impact of estrogen.** In animal studies, estrogen appears to help control body weight.
  - ▶ With **lower estrogen levels**, lab animals tend to **eat more** and be **less physically active**.
  - ▶ Reduced estrogen may **also lower metabolic rate**, the rate at which the body converts stored energy into working energy. It's possible the same thing happens with women when estrogen levels drop after menopause.
  - ▶ Some evidence suggests that **estrogen replacement therapy increases a woman's resting metabolic rate**. This might help slow weight gain.
  - ▶ **Lack of estrogen may also cause the body to use starches and blood sugar less effectively**, which would increase fat storage and make it harder to lose weight.  
[Web MD; Reviewed by [Traci C. Johnson, MD](#) on February 15, 2019]



How to tell  
if a woman  
is low on  
estrogen?



Hot flashes



Mood changes: anxiety and depression



Sleep problems



No longer having menstrual periods



Laboratory testing not usually required.

# How to tell if a man has low testosterone?

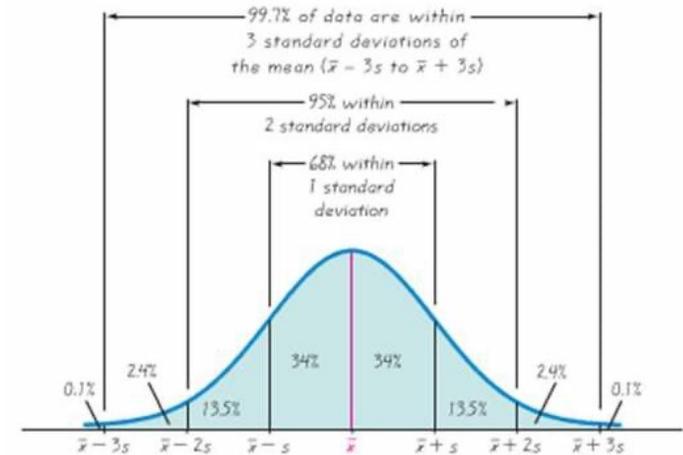
- ▶ Can be more difficult to diagnose.

Laboratory testing is helpful.



# How laboratory "normal" values are determined

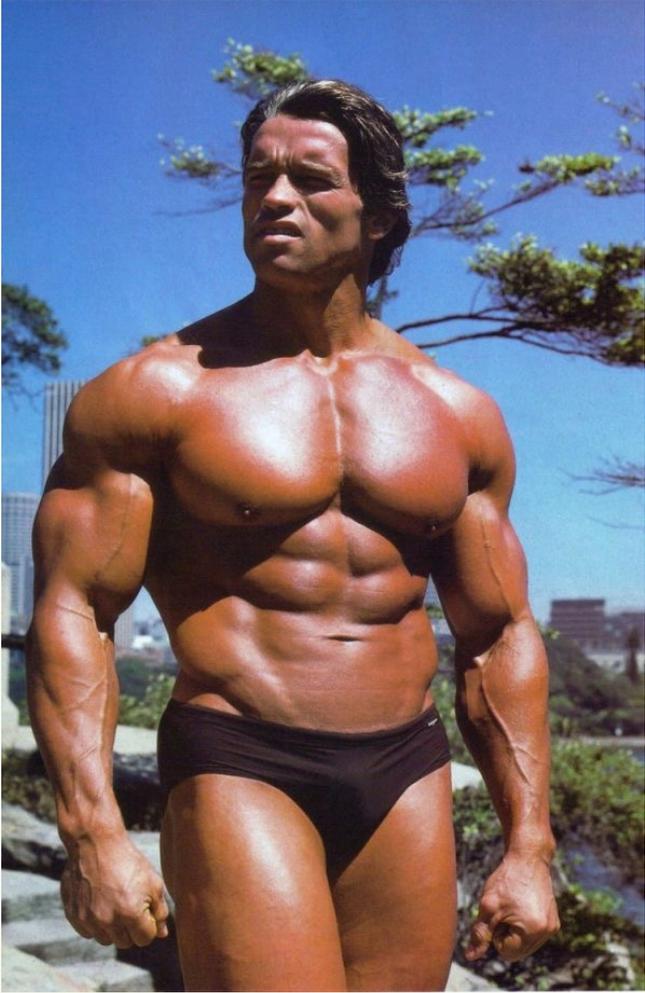
- ▶ They calculate the mean result of all patients, then cover 2 standard deviations on either side of the mean.
  - ▶ Labcorp: 264-916 ng/dl
  - ▶ Quest Labs: 250-1100 ng/dl
  - ▶ The Journal of Sexual Medicine (2006) surveyed many labs in a study of testosterone laboratory testing. Their conclusion: **Laboratory reference values for testosterone vary widely, and are established without clinical considerations.** [[J Sex Med.](#) 2006 Nov;3(6):1085-1089. doi: 10.1111/j.1743-6109.2006.00334.x.]
  - ▶ **A male's morning testosterone level should be >600 ng/dl, hence anything below this should be considered low, despite the so-called "laboratory normals."**



## Calculating Standard Deviation

$$S_x = \sqrt{\frac{\sum_{i=1}^n (x_i - \bar{x})^2}{n - 1}}$$

# Bodybuilders





# Problems associated with very high testosterone levels

- ▶ Prostate effects
  - ▶ Can cause enlargement; we monitor PSA.
  - ▶ It does NOT cause prostate cancer.
    - ▶ Males with the highest testosterone levels never get prostate cancer – teenage boys.
    - ▶ Males with low testosterone seem to be at risk for prostate cancer.
- ▶ Polycythemia
  - ▶ Blood can get thicker; we monitor CBC (complete blood count)
- ▶ Hyperlipidemia
  - ▶ Cholesterol levels can be raised
  - ▶ BUT, no increase in heart disease
- ▶ Aggression
  - ▶ WWE (wrestling)
- ▶ Gynecomastia
  - ▶ Excess testosterone gets converted to estrogen



# How is HRT administered?

- ▶ Women: can be taken as pills, topical creams, vaginal creams/suppositories, injections
- ▶ Men: topical creams, deep IM injections
  - ▶ There are NO testosterone pills
    - ▶ breakdown product dangerous for liver.

# How is HRT administered?

- Topical applications are probably the best and safest options.
  - Provide consistent levels from day to day
  - Avoid first-pass effect thru the liver





# Cost of HRT

- ▶ Brand name vs generic compounded products (cash prices)
  - ▶ Females: **Premarin** (\$200/mo), **Prometrium** (\$333/mo), **Vivelle Dot** (\$150/mo)
  - ▶ Males: **Androgel** (<\$400/mo), **Fortesta** (<\$400/mo) , Androderm, Testim, others

*Compounded HRT for women (bi-est, progesterone, testosterone): \$60-70/mo*

*Compounded testosterone for men: \$60-80/mo*



# FINNISH



Wow! THAT'S a  
BIG finish...