




# The Role of Hormones: Menopause and the Brain



To include..

- The evolution of menopause
  - Hormones and our brains
  - WHICH hormones matter and what to do?
- 



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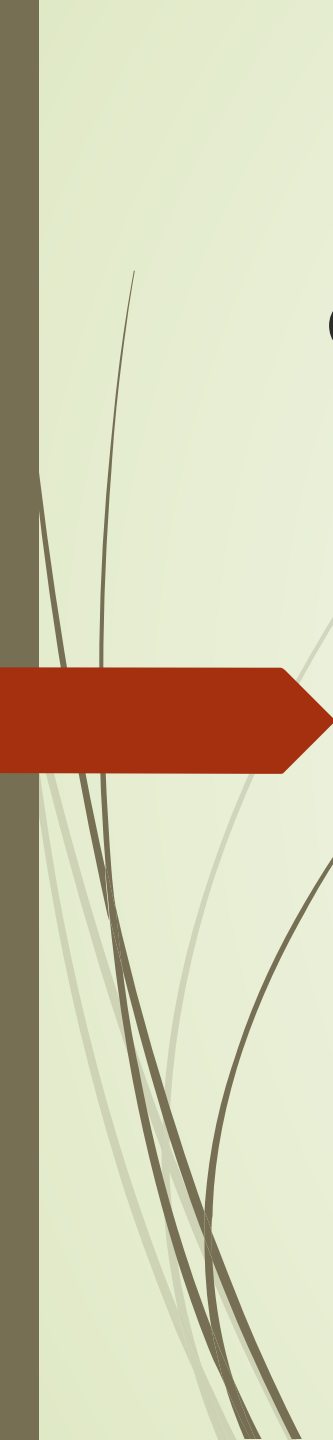
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*DocsTalkShop.com*

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*NorthwestWellness.net*



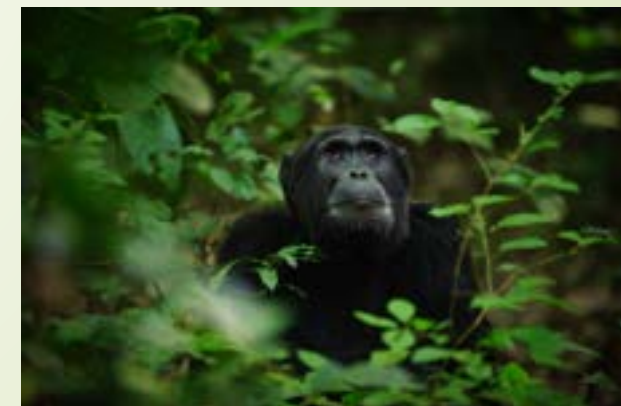
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No conflicts of interest.

# Menopause...

Little known  
fact...



# *Menopause in that 5<sup>th</sup> species...*



- 300 BC, first noted, at about 40
- 1500 – 1900 @ 45
- 1900 – 2026... menopause 48-52


Our life expectancy now @ **80**

***Women survive 30+ years  
after menopause***



# Why survive *AFTER FERTILITY*?

- ▶ Extended roles...
- ▶ Extended family units
  - ▶ Males keep on hunting
  - ▶ A woman *no longer reproducing*...
  - ▶ ..is perfectly happy to be a grandmother!



Did  
someone say happy as  
a grandmother?



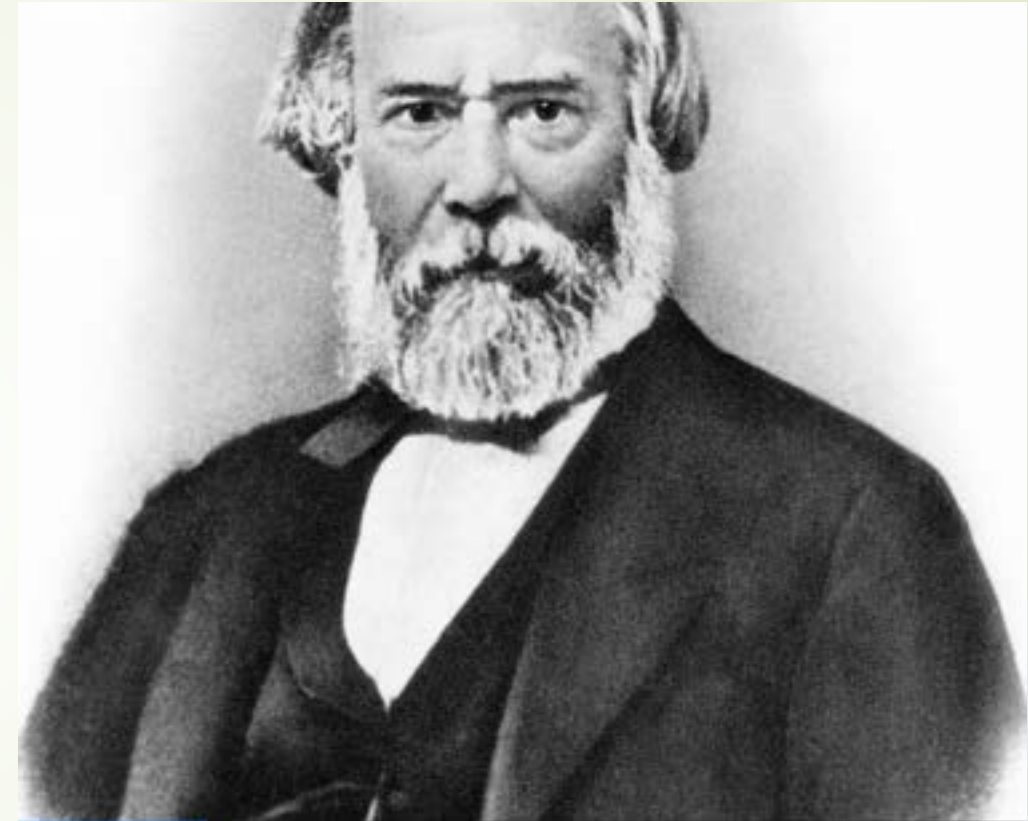
Menopause medicated  
Mid – 1800's

Testicle juice & Cannabis?

Ovarian tissue ?

Oral preparations ~ 1900 ..?

- **1941 Premarin and in  
1959 Provera**



**CHARLES BROWN-SEQUARD,**

by

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px



## By 1985 30-40% on HRT...

Primarily *Premarin* and *Provera*  
(Minority of women on compounded hormones)

*Growing scientific interest led to WHI beginning 1993*

### **UNTIL: July 2002 Headlines**

“Study Is Halted Over Rise Seen In Cancer Risk”



ALMOST all women stopped their hormones



Sadly, a mass traumatic brain injury blocking learning



## ... the later news, **NOT** in headlines:

- Premarin only group had less breast cancer  
(it was the Provera!)
- But oral estrogen is hazardous (...the Premarin)
- OH... LOTS of women had real benefits
  - Reduced hip & other fractures
  - Reduced colon cancer
  - Improved cardiovascular health
  - Better gum & dental health



# Hormone Use Trends

- Prior to WHI: 30-40% of women on HRT, declined to < 5% by 2002-2010
- 2022 < 5% ...*far fewer doctors trained in HRT and even fewer savvy about its use*
- *SINCE 2022 a definite renaissance*



# Something else happened after 2002

In the 1990's beginning to notice...

by the early 2000's, significant attention:  
women have more Alzheimer's than men and..

By 2010 Alzheimer's Association officially stated that  
2/3 of all Alzheimer's cases occur in women.



# Likely Risk Factors

- Advancing Age ?
- Metabolic health, sarcopenia
- Factors affecting women
  - Socio-economic
  - But one needn't go far to wonder:
  - Could it be ... something else?



# Risk Factors: Genetics

- ApoE4 markedly increases risk for women
- ApoE4 interacts with 1700+ other genes!
- Examples include
  - Higher cholesterol and BP
  - Persistent beta-amyloid pTau

# Should hormones be replaced?

## BASED ON STUDIES

- ▶ using hormones of all types,
- ▶ including the worst, and
- ▶ using them improperly.

**“Sure!.... *Uh, but just AT menopause!*”**

- ▶ *Not for too long and don't start too late  
(Critical Window Hypothesis)*

# Association between menopausal hormone therapy and risk of neurodegenerative diseases

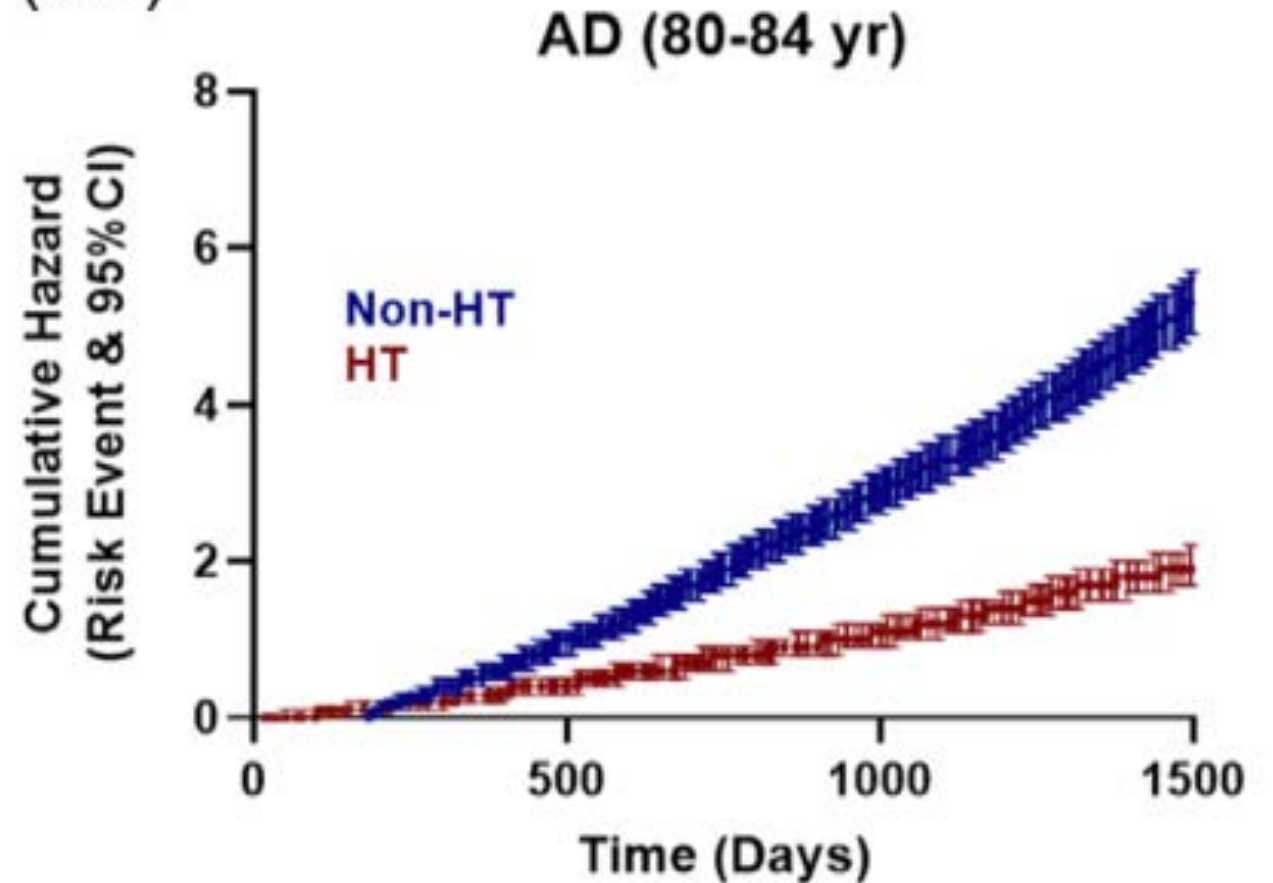
- ▶ Women, 45-89 yrs, w/ or w/o hormone therapy
  - ▶ Neurodegenerative diseases identified for RR
  - ▶ In ~380,000 women: use of HT a/w significantly lower risk of all NDD's, *especially estradiol/progesterone.*
- ▶ RR for all combined NDD's 0.73, especially
  - ▶ in women 65 years & older
  - ▶ , longer duration of treatment

Kim YJ, Soto M, Branigan GL, et al.

Association between menopausal hormone therapy and risk of neurodegenerative diseases: Implications for precision hormone therapy.

Alzheimers Dement (N Y). 2021 May 13;7(1):e12174. doi: 10.1002/trc2.12174. PMID: 34027024; PMCID: PMC8118114.

(b-5)



# Perfect Storm

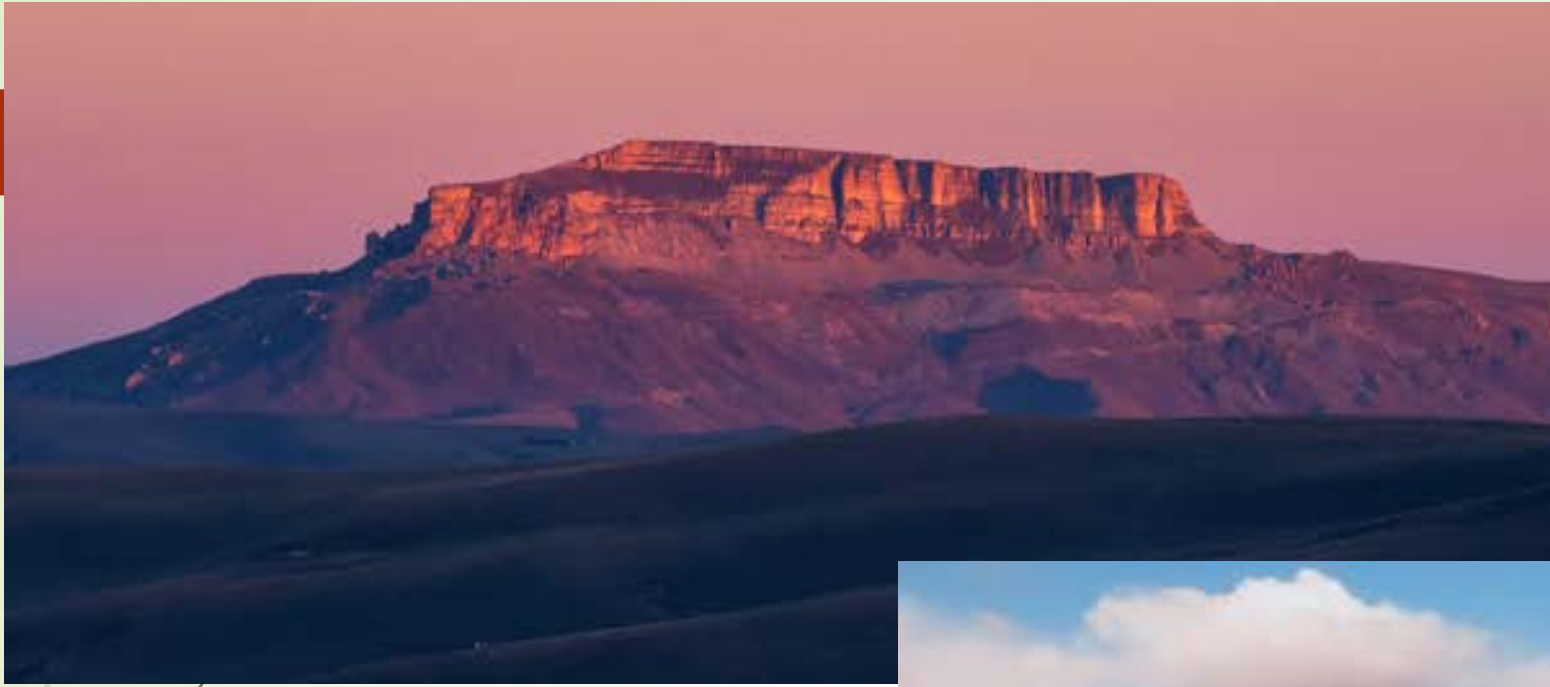
- Female
- ApoE4 gene
- Long survival...
- Long time in Menopause
- .... Aftermath of the WHI study





# MENOPAUSE: FIVE hormones of interest...

- Estrogen
  - Progesterone
  - Testosterone
  - DHEA
  - Pregnenolone . . .
- 



# ESTROGEN

## E2 Estradiol

**ESTRADIOL** *Youth and fertile years*  
**BRAIN** **Neuron growth and repair**  
**Increases/cleans beta amyloid & pTau**  
**BONES** Bone growth and repair and health  
**BREASTS** Health and, at worst, cancers  
**UTERUS** Fertility, pregnancy

## E1 Estrone

**ESTRONE** *Hormone after fertile years*  
**BRAIN** Weaker brain benefit  
**BONES** Weaker bone benefit  
**BREASTS** Higher risk of breast & uterine cancer

## E3 Estriol

**ESTRIOL** *Pregnancy*  
Weaker in the brain, helpful for breast & bone

# Ahh... estrogen and the brain

## **ENERGY & CONNECTION**

- ▶ Neuronal cell maintenance
- ▶ High density estrogen receptors in areas crucially affected in AD
- ▶ Neuroplasticity enhanced by neurogenesis, synapse vitality and transmission
- ▶ Increased ATP (energy) production by increasing glucose transport

## **NEUROMODULATION/PROTECTION**

- ▶ Neuroprotective in ischemia
- ▶ Enhances neuronal repair

## **ENHANCED MITOCHONDRIAL FUNCTION**

Brain mitochondria rich in estrogen receptors

- ▶ DNA protective against oxidation
- ▶ Reduces free radical generation

## **AMYLOID BETA**

- ▶ While increases  $A\beta$  and pTau, also
- ▶ Reduces toxicity & levels of  $A\beta$
- ▶ Increases clearance of  $A\beta$
- ▶ Reduces inflammatory response  $A\beta$



# PROGESTERONE

NOT Provera (MPA) as used in WHI

- ▶ **SIMILAR:** BOTH modulate endometrial response estrogen, reduced risk of uterine cancer
- ▶ **OPPOSITE:**
  - ▶ Progesterone alone increases BDNF & neuroprotective after TBI
  - ▶ MPA blocks estrogen benefits with mitochondria
  - ▶ MPA alone documented increased breast cancer risk
  - ▶ Very different effects on mood



# And for the brain...?

**Progesterone** Brain protective, especially AGING, as *allopregnanolone and other neuro-steroids*:

*\*New neurons & synapses, myelin sheath and more*

**Testosterone** Supports brain and bone health

*...**AND** supports muscle growth & strength → brain health  
(losing muscle associated with 2-5 x risk cognitive impairment)*

**DHEA** Neuron growth & repair, improves memory and mood



# One more, the mother hormone.. *pregnenolone*

- FIRST hormone made from cholesterol, men make more!
- YIELDS: Estrogen, Progesterone, DHEA, allopregnanolone, other neurosteroids
- Cognitive health, anti-inflammatory, cortisol modulation, sleep quality (deep sleep)... women need it more than men do

# ***“ So...what happens at menopause?”***




*Yes it's the hormones,*

*.... What can women do about it?*



# *Sounds simple...*

- *Start as early as possible*
  - *Continue as long as it remains helpful*
  - *Precision hormone prescribing*
- 



# PRECISION HORMONE THERAPY

Choose your hormone(s) & methods

**MEASURE THE EFFECT.**

Adjust and manage



# ESTROGEN as ESTRADIOL

Prescription only, always bio-identical.. *Need a savvy prescriber.*

## Topical

Compounded creams

Pharmaceutical patches or gels

***Pellets not recommended at this time***

**Oral definitely not recommended (2 reasons)**

## GOALS

Estradiol levels 50-150 pg/mL, *depending on goal*

***“Adjust and manage” ... that savvy prescriber!***



# PROGESTERONE

**Prescription only, always bio-identical..**

Pharmaceutical capsules (oral, rectal or vaginal use)

And compounded creams, capsules, various uses.

**Goal** 5-10% of the blood level estradiol. (different units)

***“Adjust and manage” ... that savvy prescriber!***



# TESTOSTERONE

Prescription only, always ... *Need a savvy prescriber.*

**Topical**

Compounded creams

Pharmaceutical gels

***Pellets not recommended at this time***

***“Adjust and manage” ... that savvy prescriber!***

# PRECISION not requiring a prescription...

1. These also require a TEST! *You might already be fine !*
2. Available as supplements, typical starting doses
  - a. Pregnenolone 25-50 mg, MOST often PM dose (80-120)
  - b. DHEA 25-50-mg, MOST often AM dose (DHEA-S labs & symptoms)
  - c. A phytoestrogen Genistein 125-250 mg (brain & bones)
  - d. OTC progesterone creams, estriol creams: fine but low doses immeasurable
3. AND Test again so you can *“Adjust and manage”*



# RESOURCES

- The Menopause Society Directory
- Unusual resource list: recommendations by patients on the website The Pause Life (.com)
- Provider and patient pertinent videos available from Dr. Felice Gersh on her various social media platforms



**EVERYTHING** else ....  
*...Yes, it all matters!*

- Eat
  - Sleep
  - Think! .... And rest your brain
  - Workout! Play! ...rest your body
  - Stay engaged
  - Choose organic
- Etc. etc.!

*Family history?*

*Consider genetics testing...*