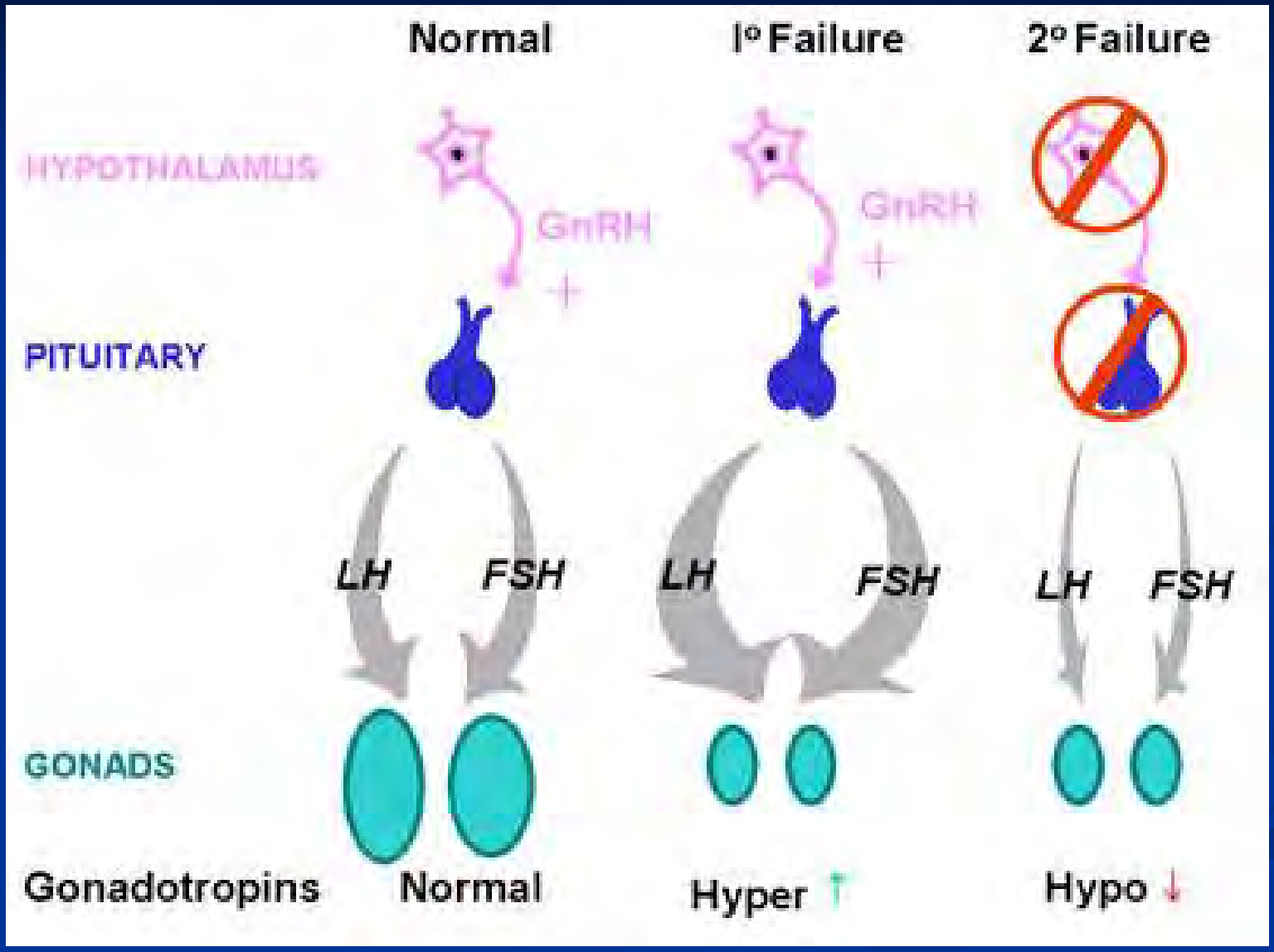
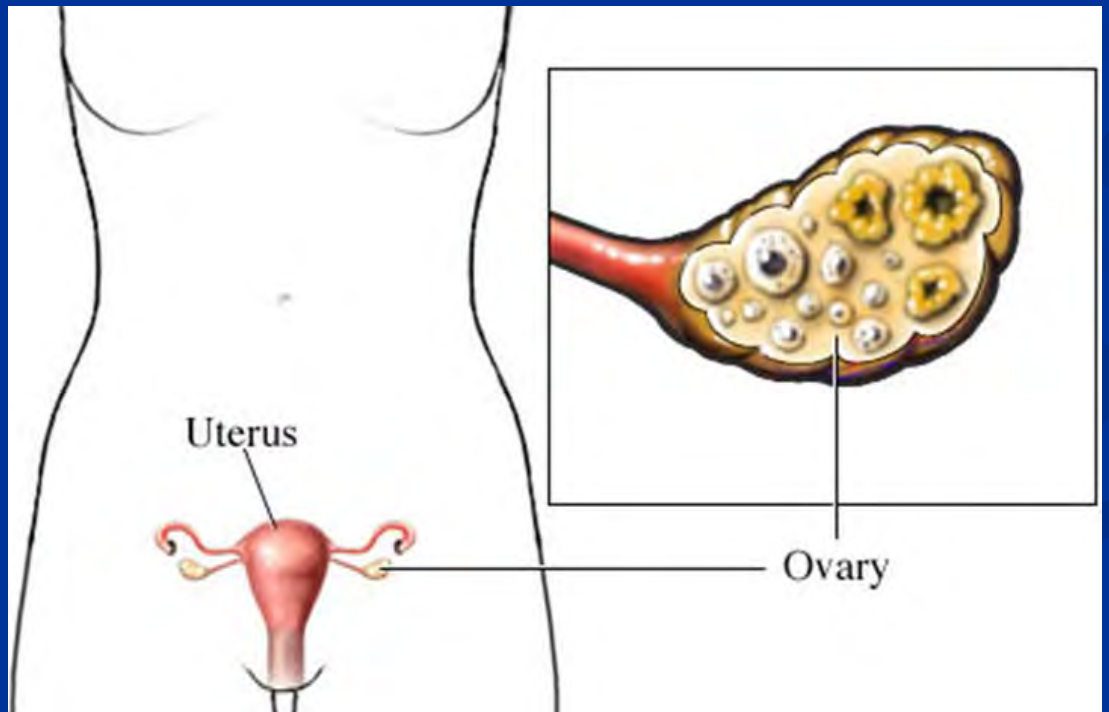

Normal
Iº Failure
2º Failure
HYPOTHALAMUS
GnRH
+
PITUITARY
LH
FSH
GONADS
Gonadotropins
Normal
Hyper ↑
Hypo ↓

Female hypogonadism:

"menopause"

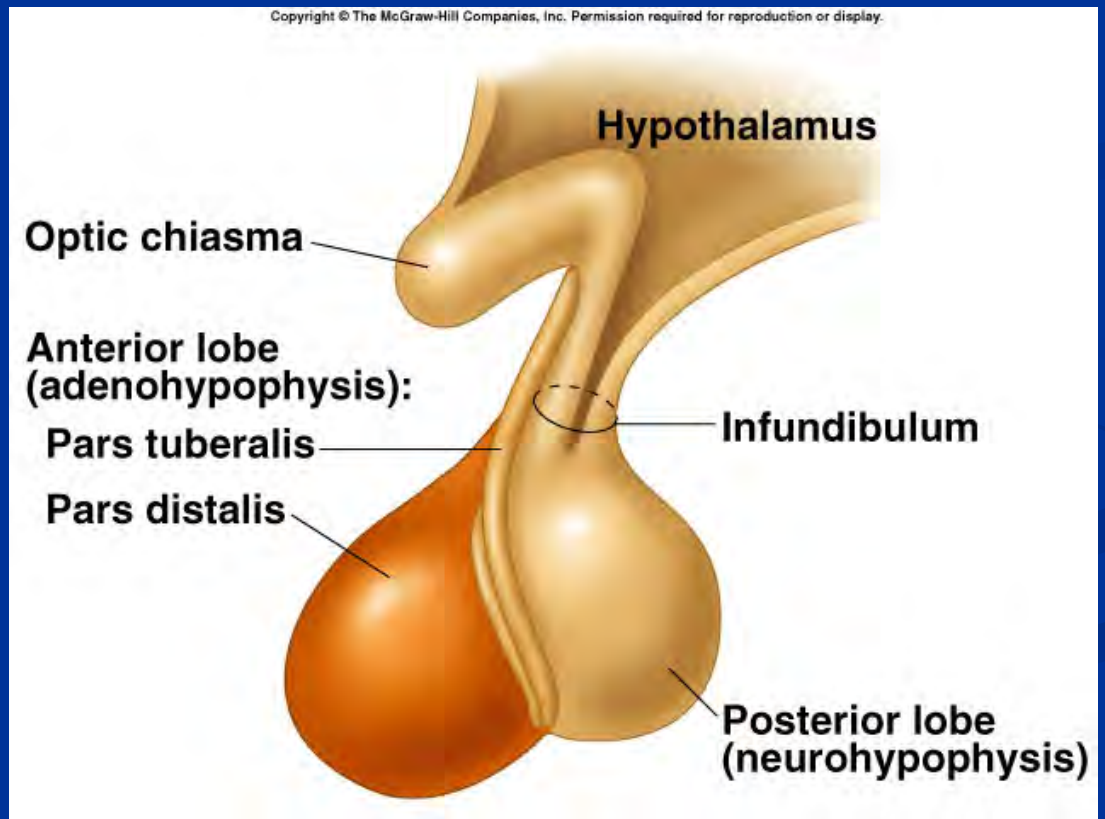
1^0 hypogonadism

- Low oestradiol } **menopause**
- Elevated LH and/or FSH }



2^0 hypogonadism

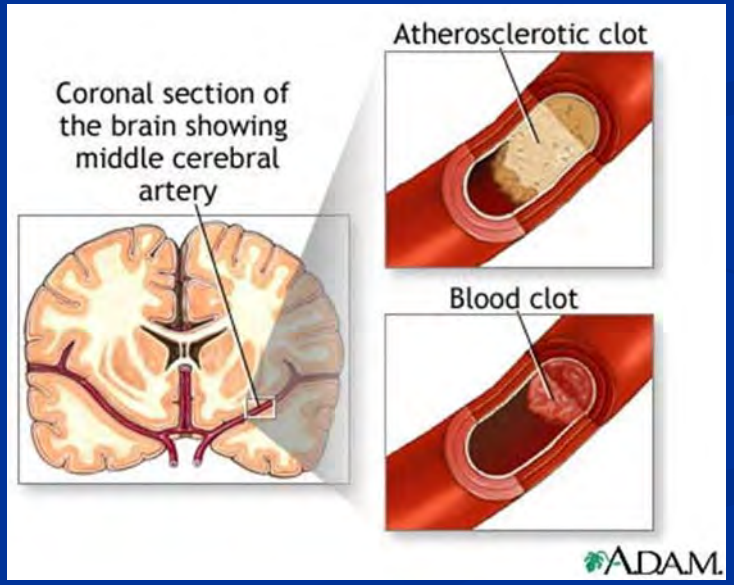
- Low oestradiol
- Normal or reduced LH and/or FSH



Post-menopausal hormone replacement therapy (HRT): Women's Health Initiative (WHI)

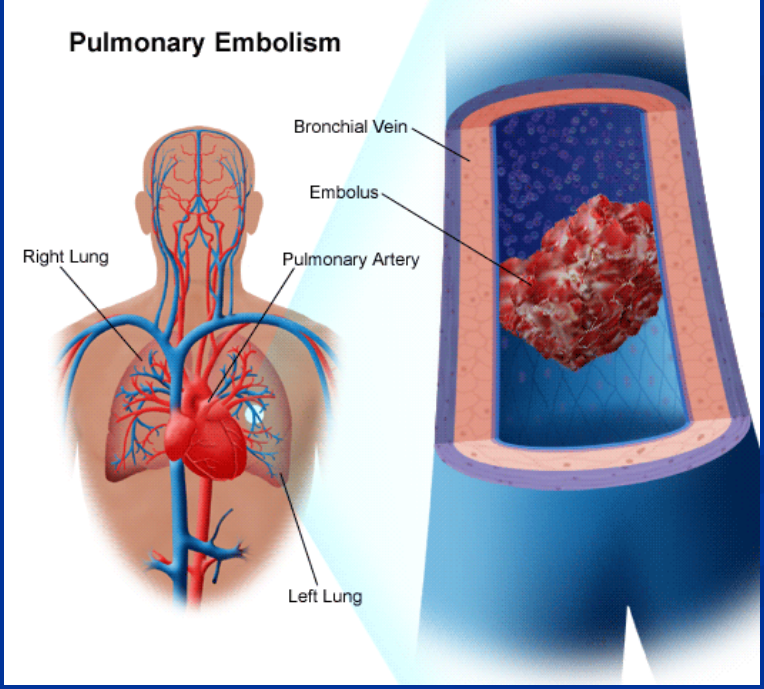
- **EPT** (**E**strogen **P**rogesterone) arm: an increase in non-fatal **CHD** (coronary heart disease) in patients started on HT > 10 years after beginning of menopause
- Excess of 7/10 000 women per year

- Increased risk of **stroke** (HR = 1.39)
- Risk not confined to the 1st year; may be dose-related



- Modest increase in risk of **invasive breast cancer** if used for > 5 years (RR = 1.35, but absolute risk is small: 8/10 000 per year), and risk increases with duration of therapy if initiated after the age of 50
- No /minimal increased risk of breast cancer if oestrogen alone is used

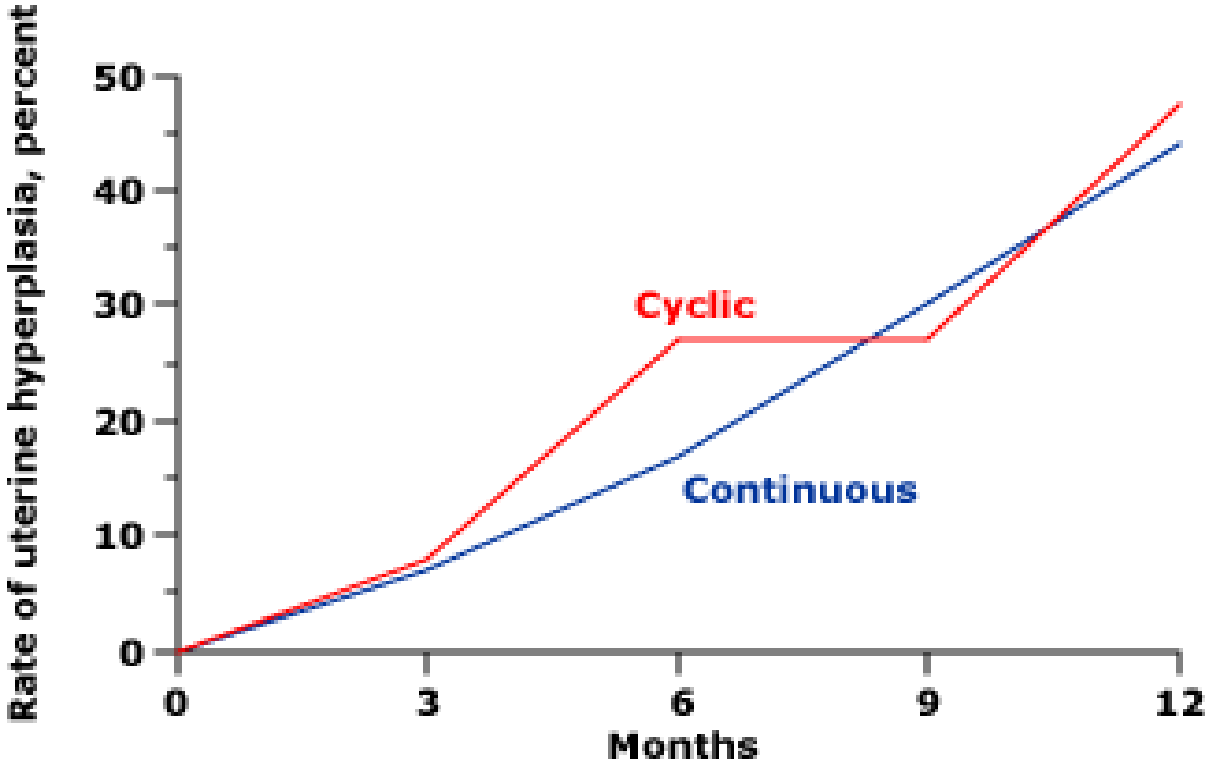
- Risk of **venous thromboembolism** is doubled; absolute risk of VTE is increased by 18 cases per 10 000 women per year
- Maximum in 1st year of therapy (small risk age group 50 – 60)



- **No beneficial effect** on **Alzheimer's disease** or **dementia**
- If started age > 65 years:

  - worsening of cognitive capacity

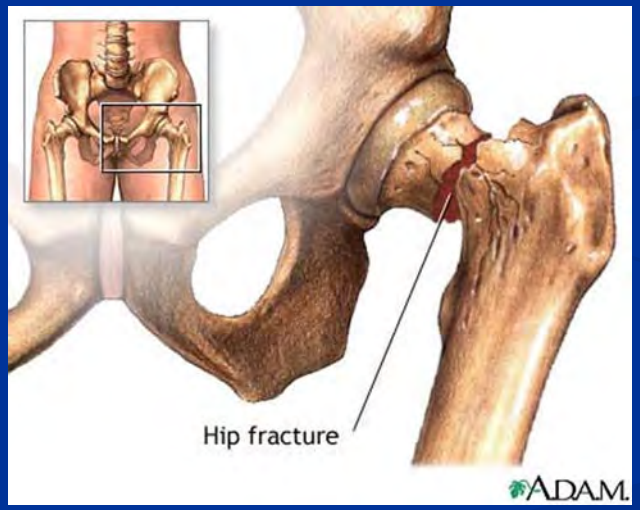
Estrogen replacement induces uterine hyperplasia



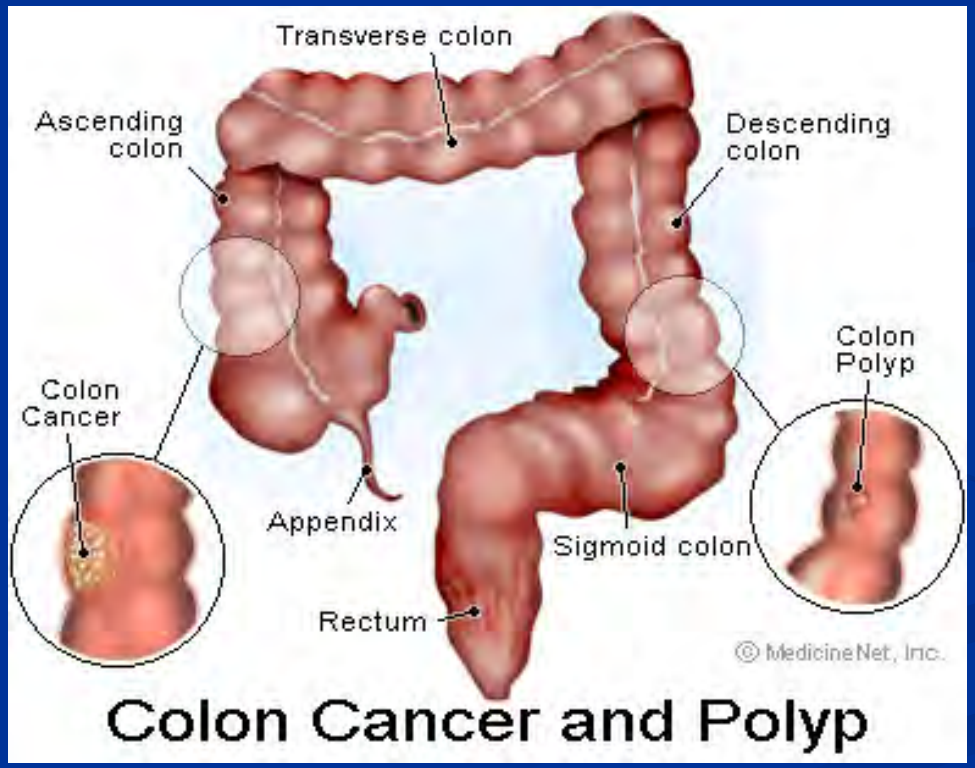
Cumulative rate of uterine hyperplasia in women receiving continuous or cyclic estrogen replacement therapy. There was no difference between the two groups, and uterine hyperplasia occurred in almost one-half of the women in each group at one year.

Data from Schiff, I, Sela, HK, Cramer, D, et al, Fertil Steril 1982; 37:79.

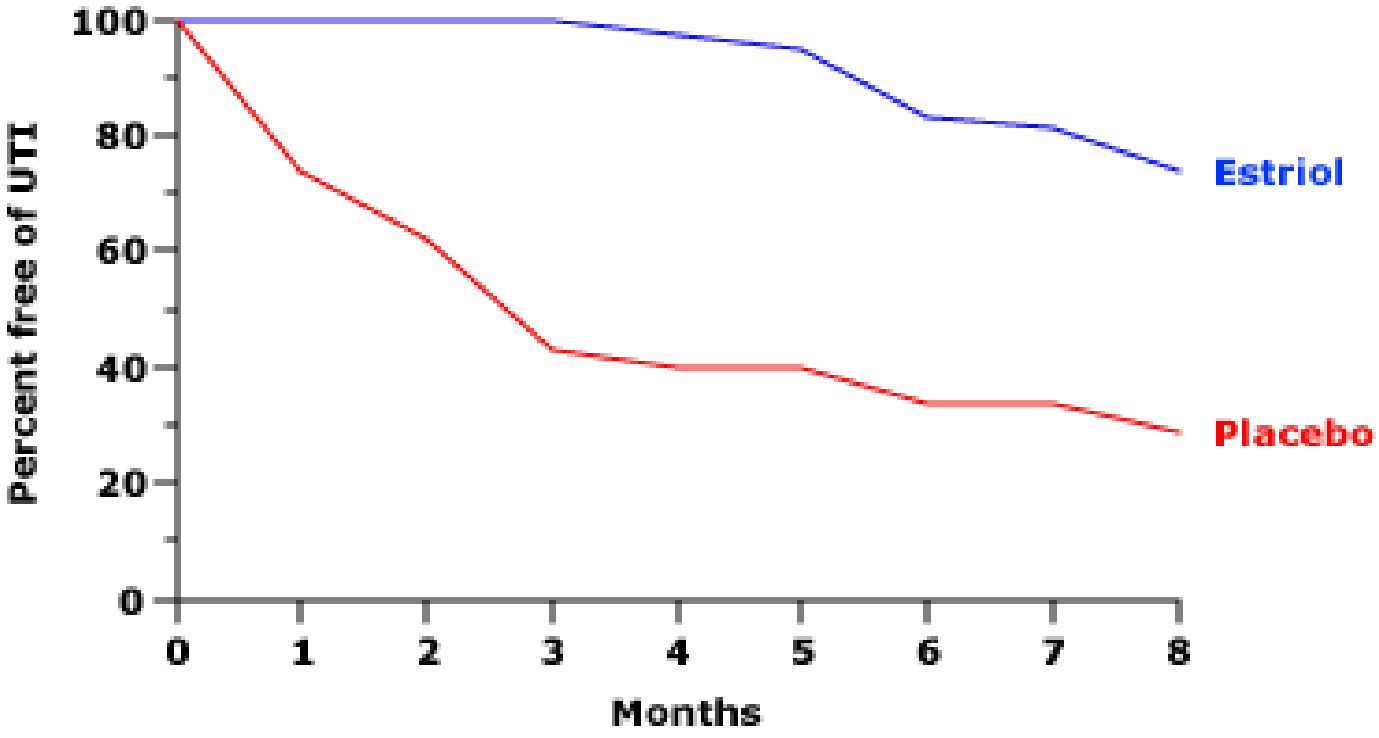
- HT **reduces** the risk of all **osteoporotic** fractures, including hip fractures



- EPT **reduces** the risk of **colorectal cancer**



Estrogen minimizes recurrent urinary tract infection



The effect of intravaginal estriol or placebo on the incidence of urinary tract infection in postmenopausal women with recurrent urinary tract infections. Estrogen therapy was associated with a much greater likelihood of remaining free of infection.

Data from Raz, R, Stamm, WE, N Engl J Med 1993; 329:753.

Timing hypothesis (therapeutic window)

- The timing of HT introduction plays a crucial role in CV outcome
- Hypothesis: when atherosclerosis is at **early stage** (fatty streaks) HT is **beneficial**
- In older **unstable plaque** it is **deleterious**
- In WHI the average age of starting HT was 63 years (about 12 years into menopause)
- In WHI: significant trend for CHD events on HT to be lower, the shorter the period since menopause

Hormone Therapy (HT) indicated

- Premature menopause
- Early post-menopause with above average risk of future fracture and menopausal symptoms (up to the age of 60)
- Significant vasomotor symptoms

HT NOT indicated

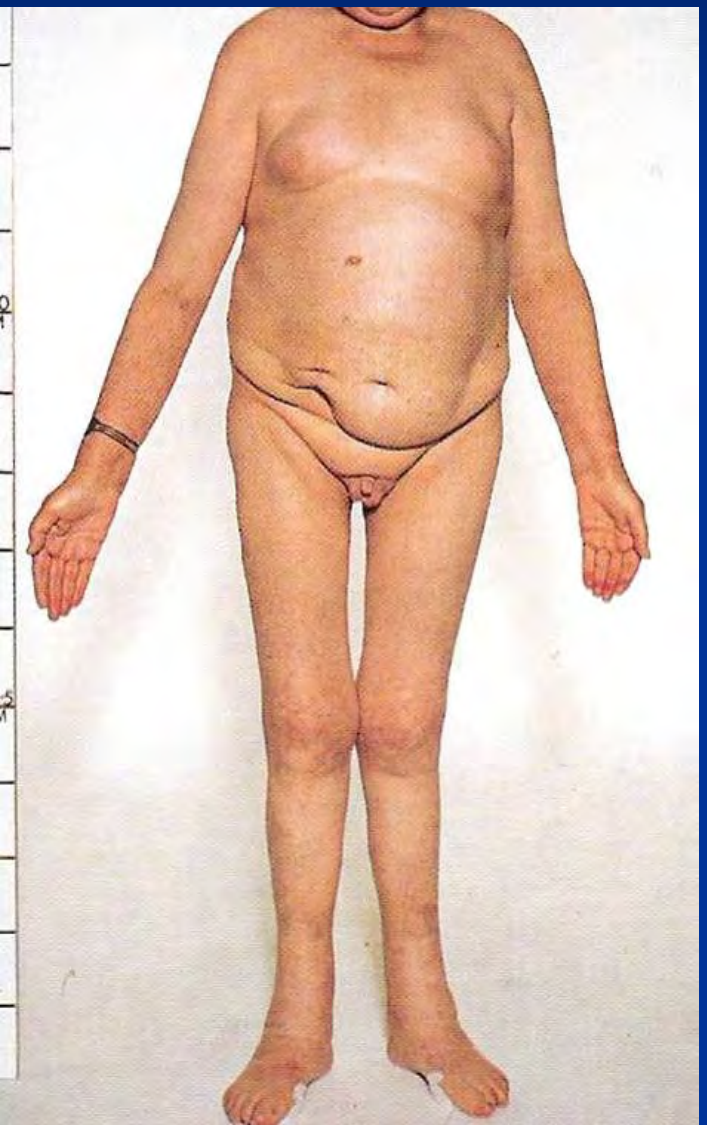
- Universal treatment at menopause
- Initiation of HT after the age of 60
- Purely as strategy to prevent CVD

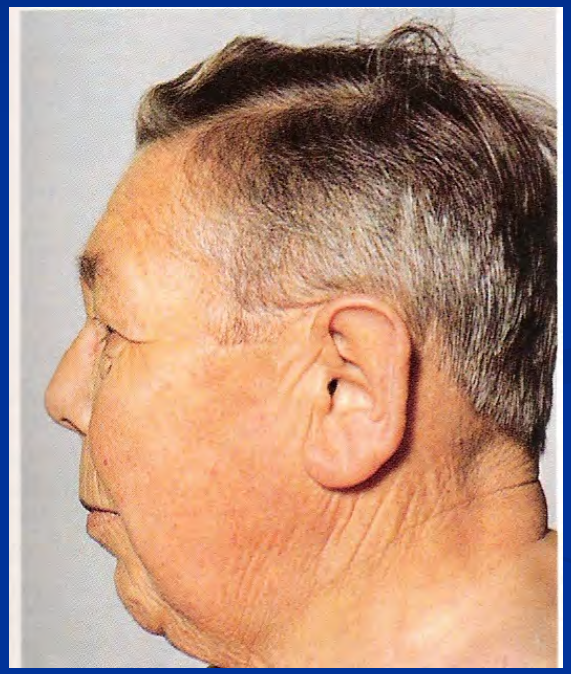
Therapy

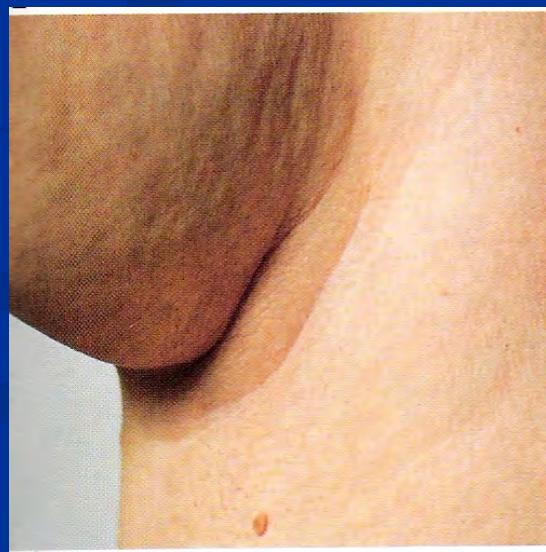
- **Intact uterus**: combine oestrogen with progesterone (cyclic or continuous)
- **No uterus**: unopposed oestrogen
- Transdermal and vaginal preparations available

Male hypogonadism

"andropause"

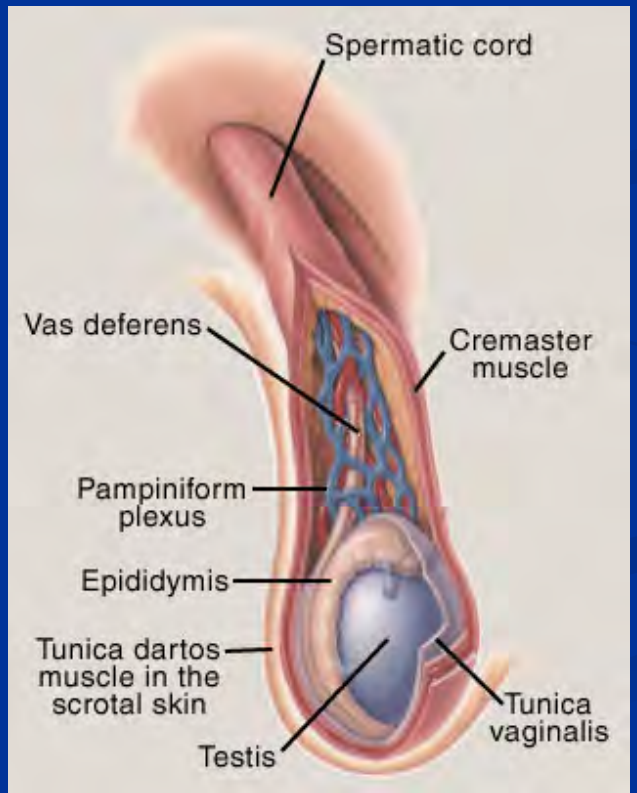






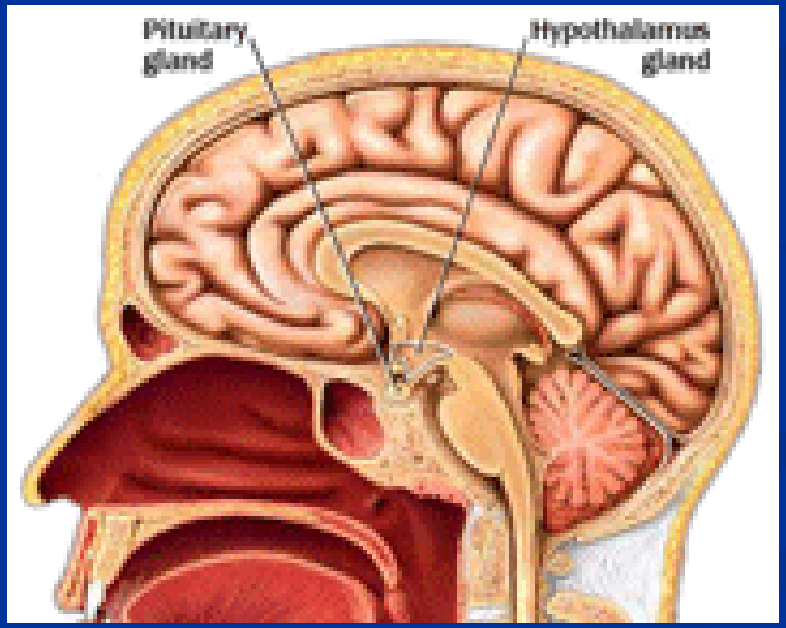
1^0 hypogonadism

- Low testosterone and/or sperm count
- Elevated LH and/or FSH



2^0 hypogonadism

- Low testosterone and/or sperm count
- Normal or reduced LH and/or FSH



Old age

- Serum **total testosterone falls** slightly with increasing age
- **SHBG increases** with increasing age
- Binding to SHBG increases slightly with increasing age

- Thus: **serum free testosterone** falls to a greater degree
- Men who are 80 years old have values that are 1/2 to 1/3rd of those in men who are 20 years old
- Hypogonadism in elderly men can be 2^0 or 1^0
- **Questions:**

1) Is this physiologic or pathologic?

2) Should this be treated with testosterone?

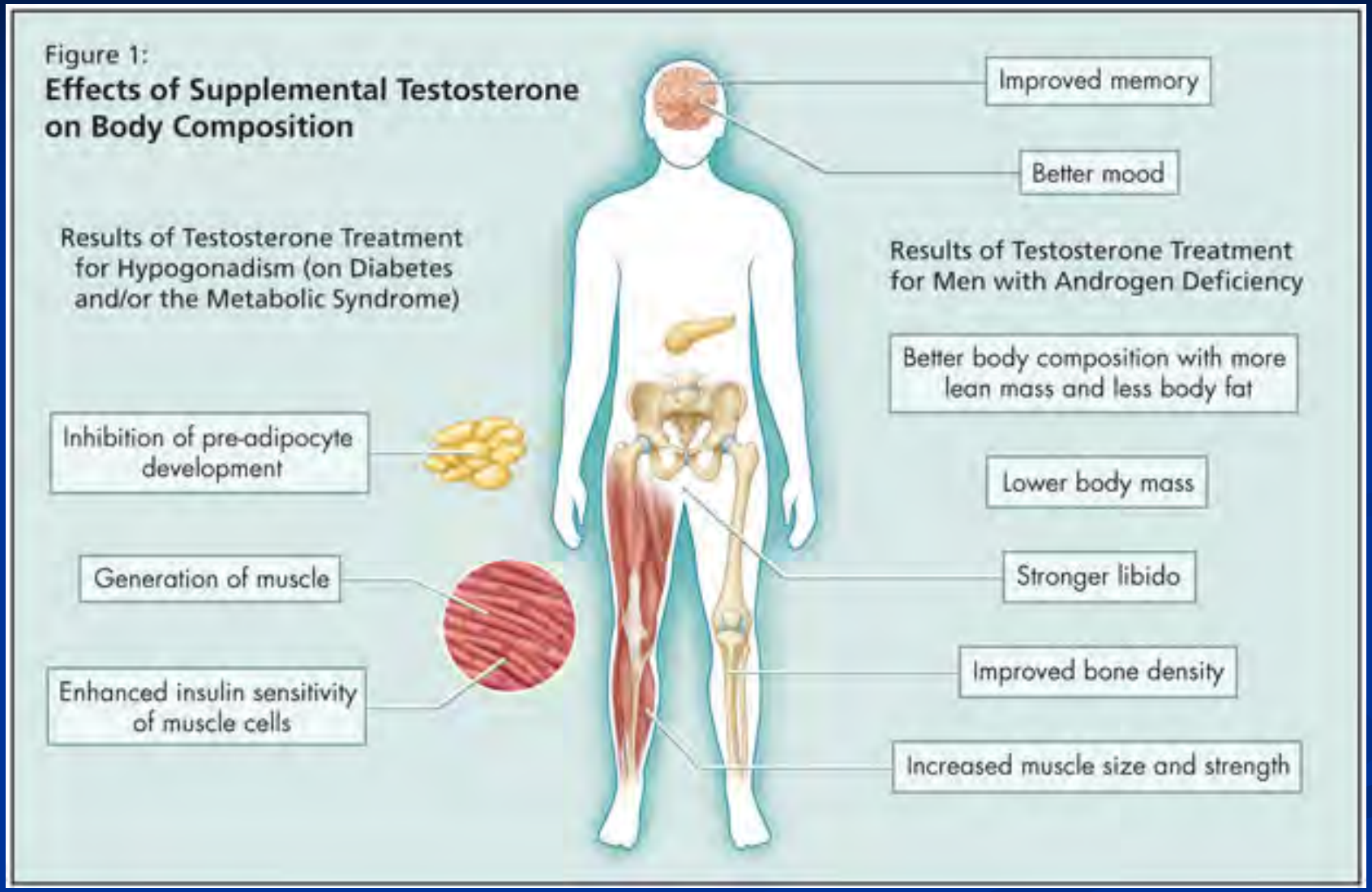
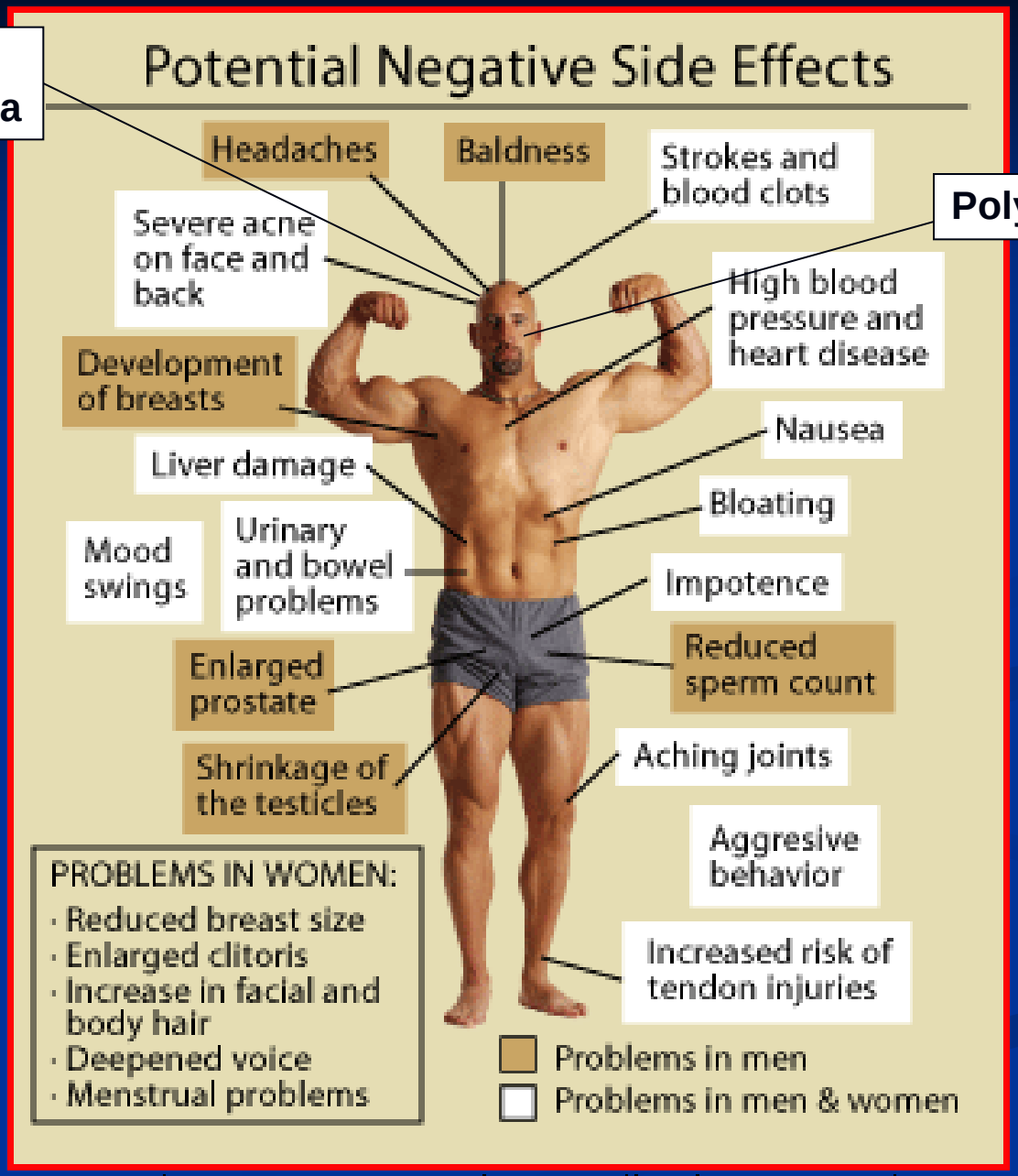


Figure 1:
Effects of Supplemental Testosterone on Body Composition
Improved memory
Better mood
Results of Testosterone Treatment for Hypogonadism (on Diabetes and/or the Metabolic Syndrome)
Results of Testosterone Treatment for Men with Androgen Deficiency
Better body composition with more lean mass and less body fat
Inhibition of pre-adipocyte development
Lower body mass
Generation of muscle
Stronger libido
Improved bone density
Enhanced insulin sensitivity of muscle cells
Increased muscle size and strength

Sleep disturbances
Obstructive sleep apnoea

Polycytaemia

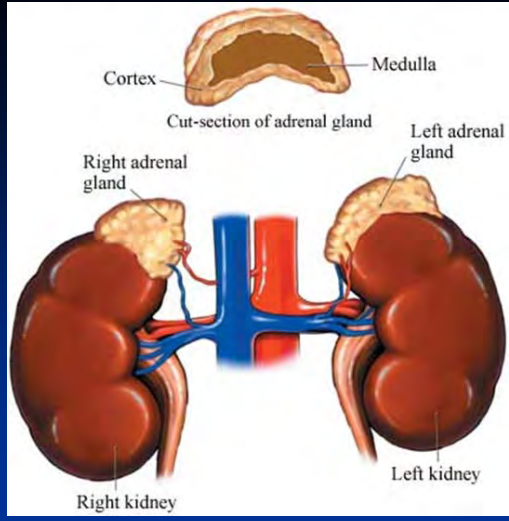


Testosterone abuse

Erectile dysfunction (ED)

- It becomes more prevalent with age, but an endocrine cause becomes less likely
- Prevalence in men > 75 years: 50%
- Often **multiple overlapping causes**: psychosocial, neurovascular, metabolic (DM), medications, vascular
- **NOT** routinely treated with testosterone; only if proven hypogonadism is present

DHEAS / DHEA



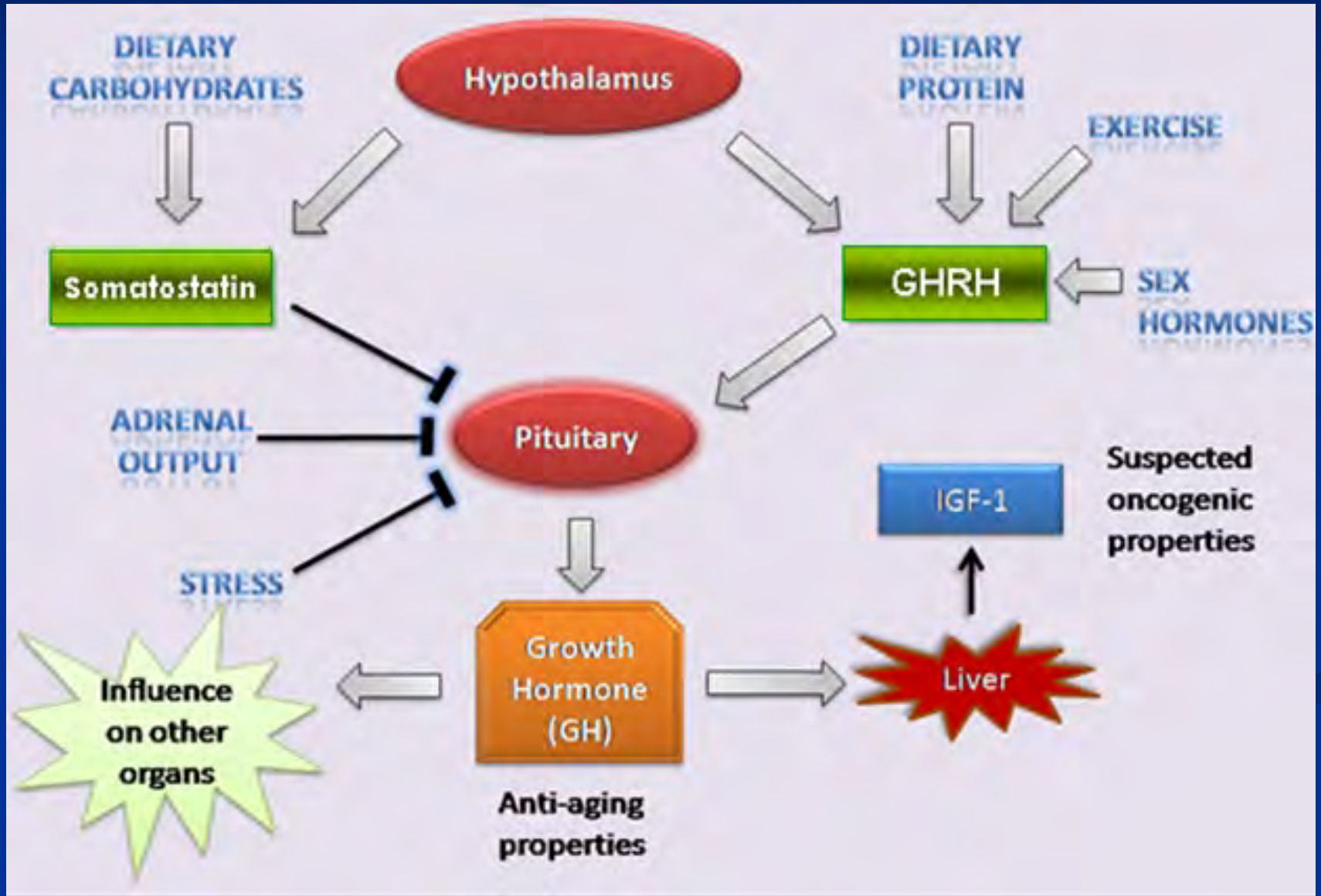
- **"Adrenopause":** gradual decline in circulating levels of dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) produced by the adrenal cortex
- These molecules have no certain function except as minor precursors of active androgens and oestrogens
- Speculations: can DHEAS administration reverse some of the changes in body composition and behaviour that occur in aging?

Placebo-controlled trials

- **Minimal benefit**: small increases in bone density at some sites, small increases in muscle mass, quality of life
- **Some harm**: androgen effects in women and oestrogen effects in men
- ? Effect on steroid-dependent cancer risk? (ovarian, prostate)
- Sold as a food supplement; widely used

Growth hormone (GH)

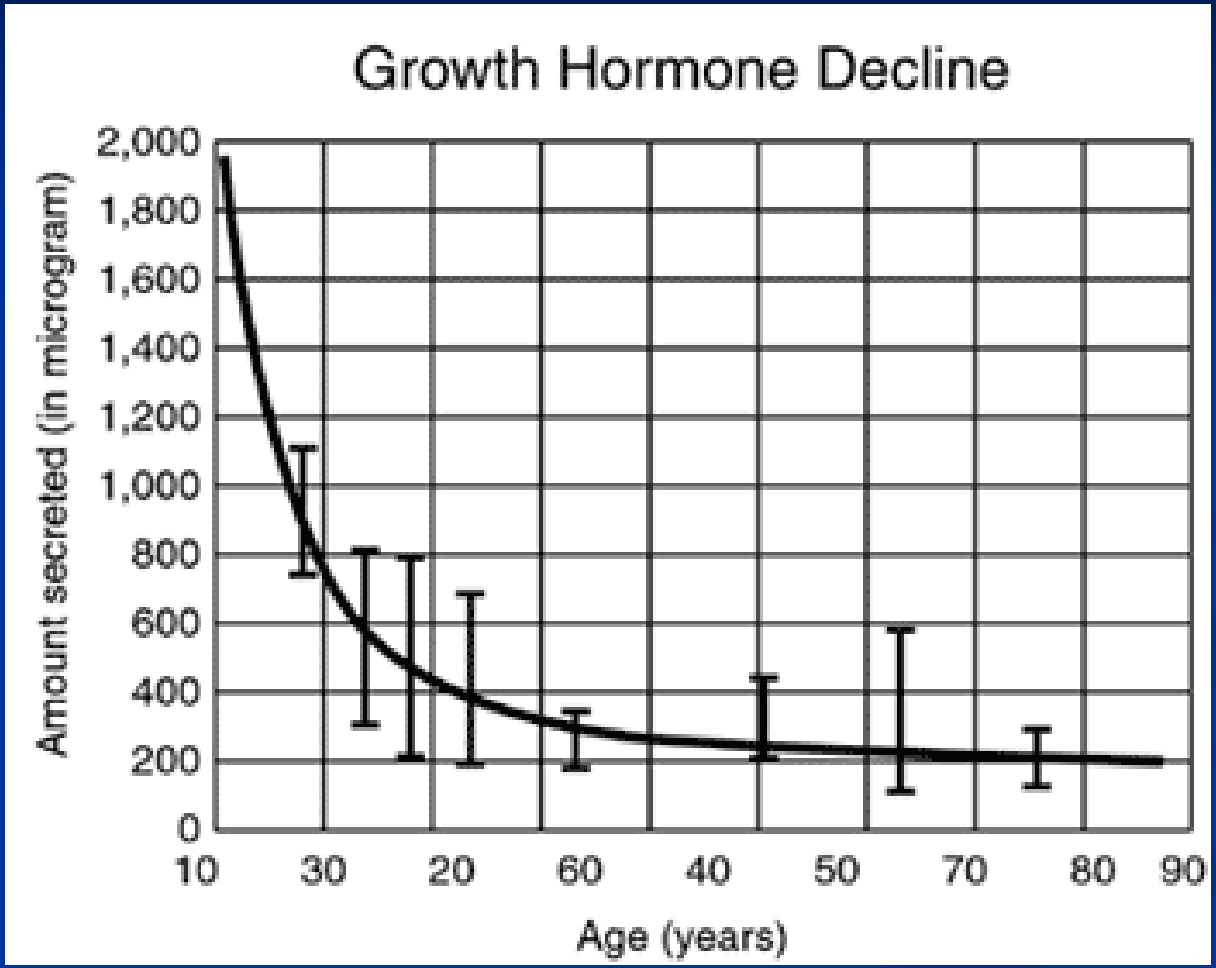
Growth Hormone axis



- **"Somatopause":** Gradual decrease in GH and IGF-1 in the elderly

In growth hormone deficient adults:

- GH therapy increase muscle mass, strength, bone mass, and quality of life
- Decreases lipids and fat mass
- **BUT**: will GH-replacement in the normal elderly reverses some of the normal processes of aging?


Growth Hormone Decline
Amount secreted (in microgram)
2,000
1,800
1,600
1,400
1,200
1,000
800
600
400
200
0
10
30
20
60
40
50
70
80
90
Age (years)

Claims

"HGH therapy and the benefits you discover are huge"
Would you like to:

- Lose fat, gain muscle
- Increase energy
- Improve immune function
- Enhance sexual performance
- Increase cardiac output
- Improve skin elasticity
- Remove wrinkles
- Eliminate cellulite
- Improve vision
- Increase memory retention
- Improve quality of sleep
- Lower blood pressure
- Improve cholesterol
- Increase bone mass
- Quicken wound healing
- Increase exercise performance and endurance

Can GH therapy prevent or perhaps even reverse aging?

- 1990 study reported:

6 months of treatment of men over 65 years of age who have low levels of plasma IGF-1 with rhGH:

- Reduced adiposity
- Increased muscle mass
- Increased bone mineral density in some of the examined sites of the skeleton
- Improved general well-being

Later studies

- Treatment of **endocrinologically normal** healthy elderly individuals with rhGH produces:
- Small improvements in body composition

Undesirable side effects:

- Arthralgias
- Oedema / fluid retention
- Carpal tunnel syndrome
- Insulin resistance (possibly also diabetes)
- Gynaecomastia

Other concerns:

- Cancer (especially breast, prostate, colon)
- Atherosclerosis