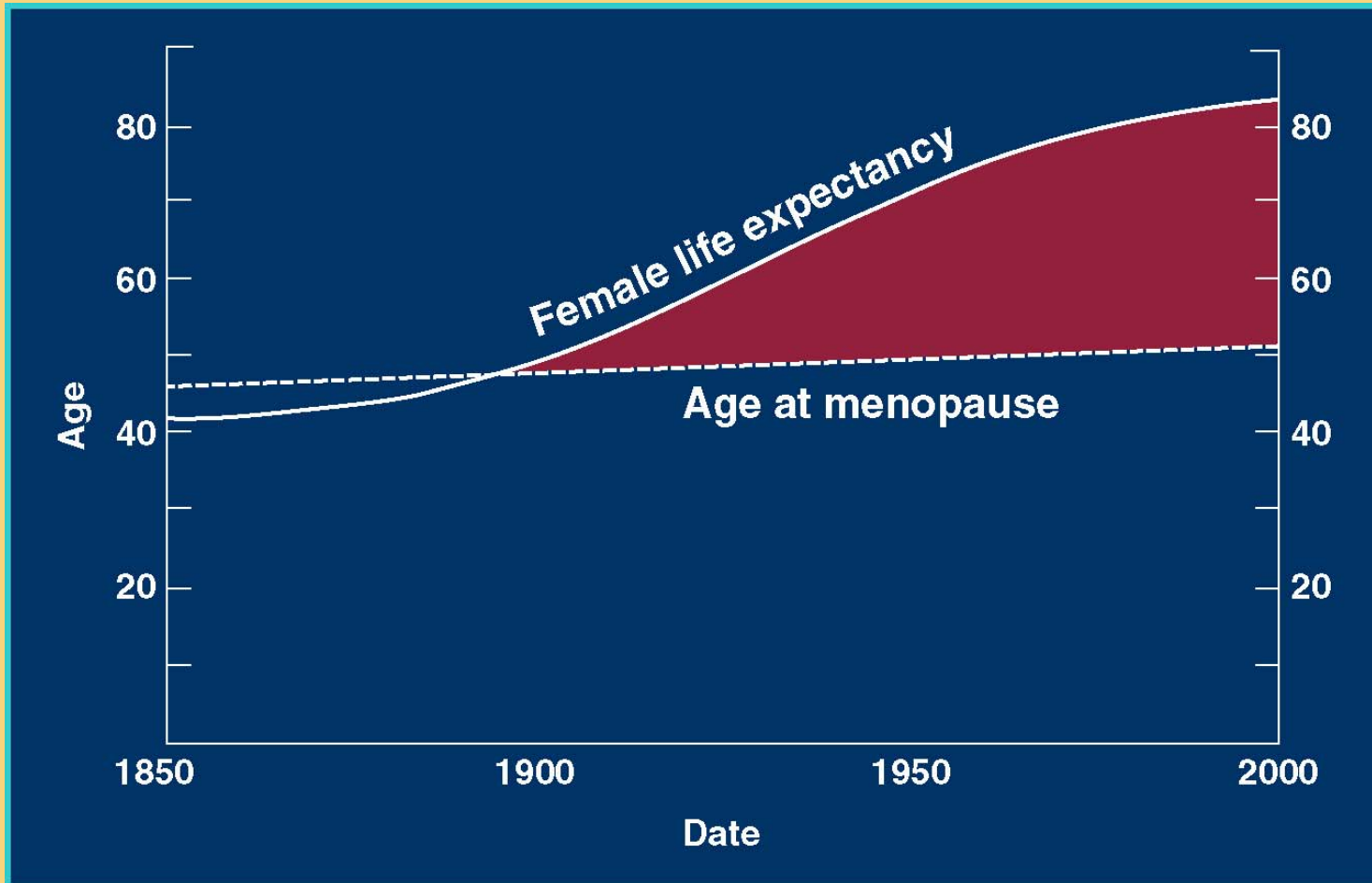


Premenopausal Protection Against Chronic Diseases of Aging: Rethinking the Paradigms

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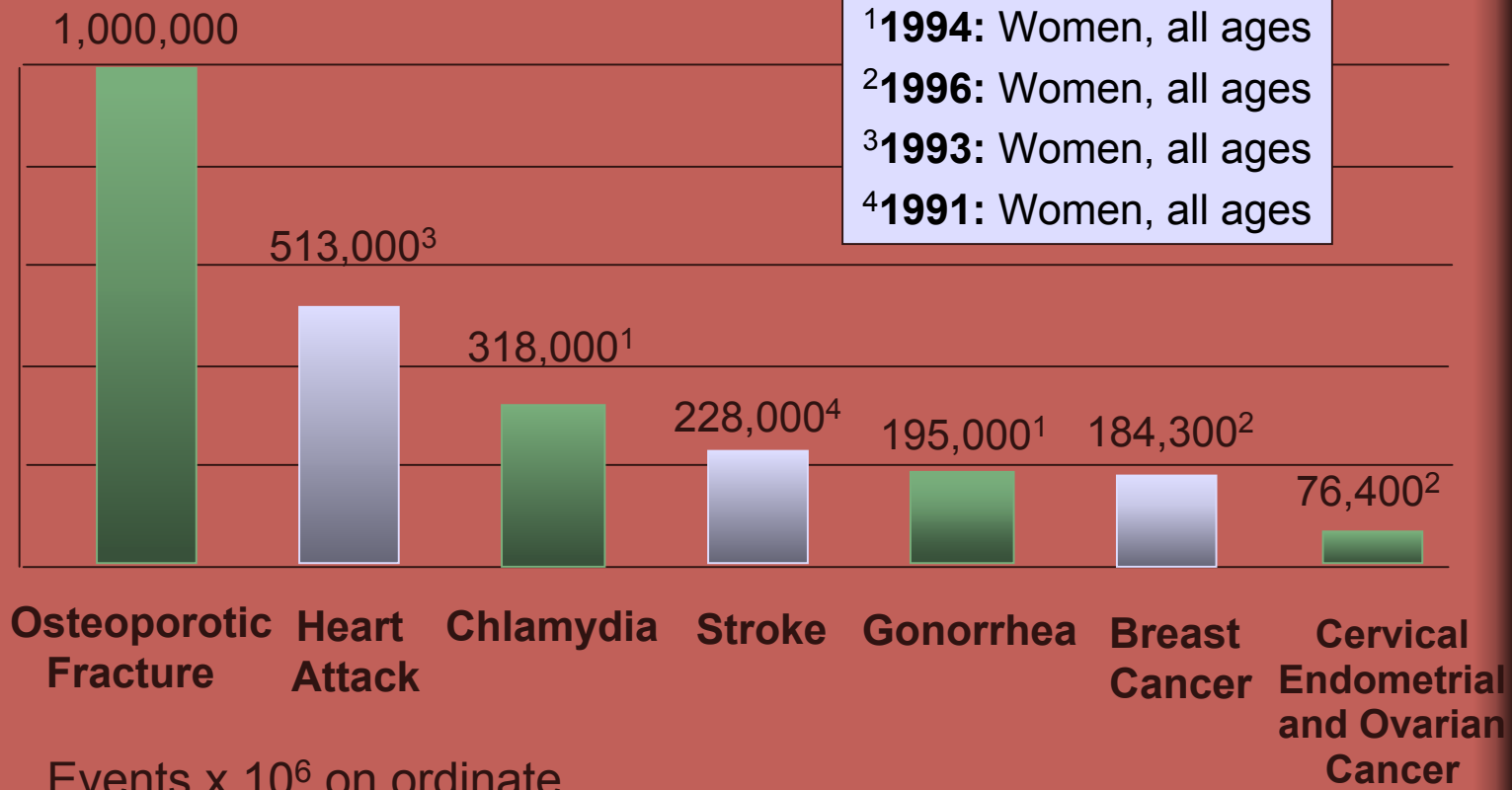


Menopause and Female Life Expectancy

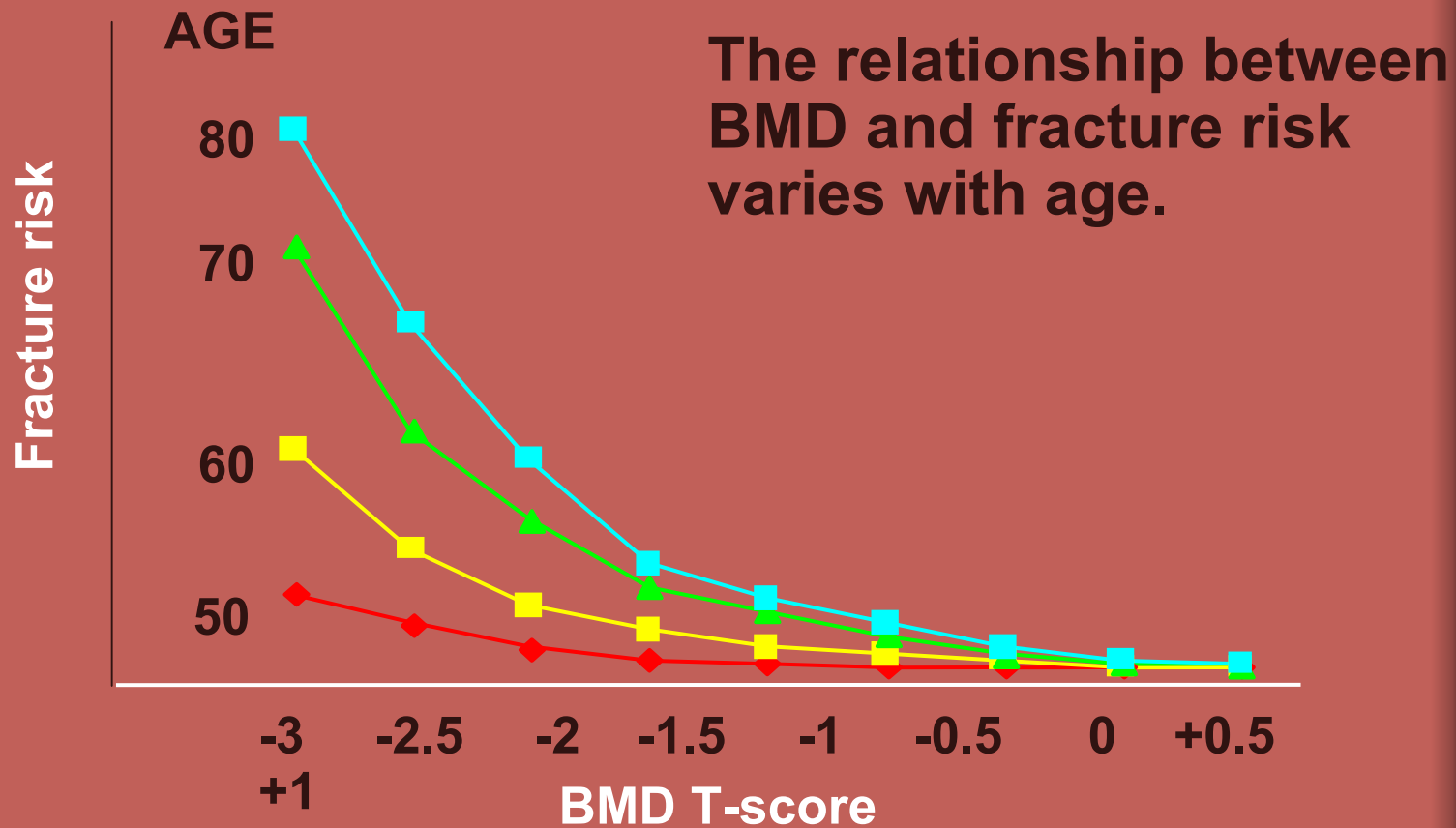


Annual Incidence of Common Disease in Women

¹1994: Women, all ages
²1996: Women, all ages
³1993: Women, all ages
⁴1991: Women, all ages



BMD, Age, and Fracture Risk



Source: Kanis et al. *Osteoporos Int.* 2002.

Courtesy of M. McClung, MD

Heart Disease by Gender

| | <u>Male</u> | | <u>Female</u> | |
|-------|------------------|--------------|------------------|--------------|
| | <u>thousands</u> | <u>rates</u> | <u>thousands</u> | <u>rates</u> |
| <15 | .9 | -- | .7 | -- |
| 15-24 | .7 | -- | .4 | -- |
| 25-34 | 2.5 | 11.3 | 1.1 | 5.1 |
| 35-44 | 9.1 | 52.2 | 3.0 | 16.8 |
| 45-54 | 23.5 | 199.8 | 8.3 | 66.7 |
| 55-64 | 60.2 | 584.7 | 27.3 | 237.0 |
| 65-74 | 107.9 | 1358.1 | 68.2 | 685.6 |
| 75-84 | 116.1 | 3239.1 | 126.0 | 2122.4 |
| 85+ | 64.6 | 7830.9 | 144.6 | 6810.1 |



Shifting the Paradigms...

- Concept: *Do protective factors drop out with aging and*
 - Are they actively preserved premenopausally?
- Focus: *Is endocrine deficiency the sole locus of loss of protection, or*
 - Are other organ systems also losing disease resistance due to unrelated aging effects?



Shifting the Paradigms...

- Approach: *Do reproductive and somatic aging go hand in hand, or*
 - Are there complex interactions?
- Therapy: *Do we continue to regard hormones as the 'WD-40' for aging in women or*
 - Do we develop an integrated physiological model for aging that incorporates menopause without excluding other key variables?

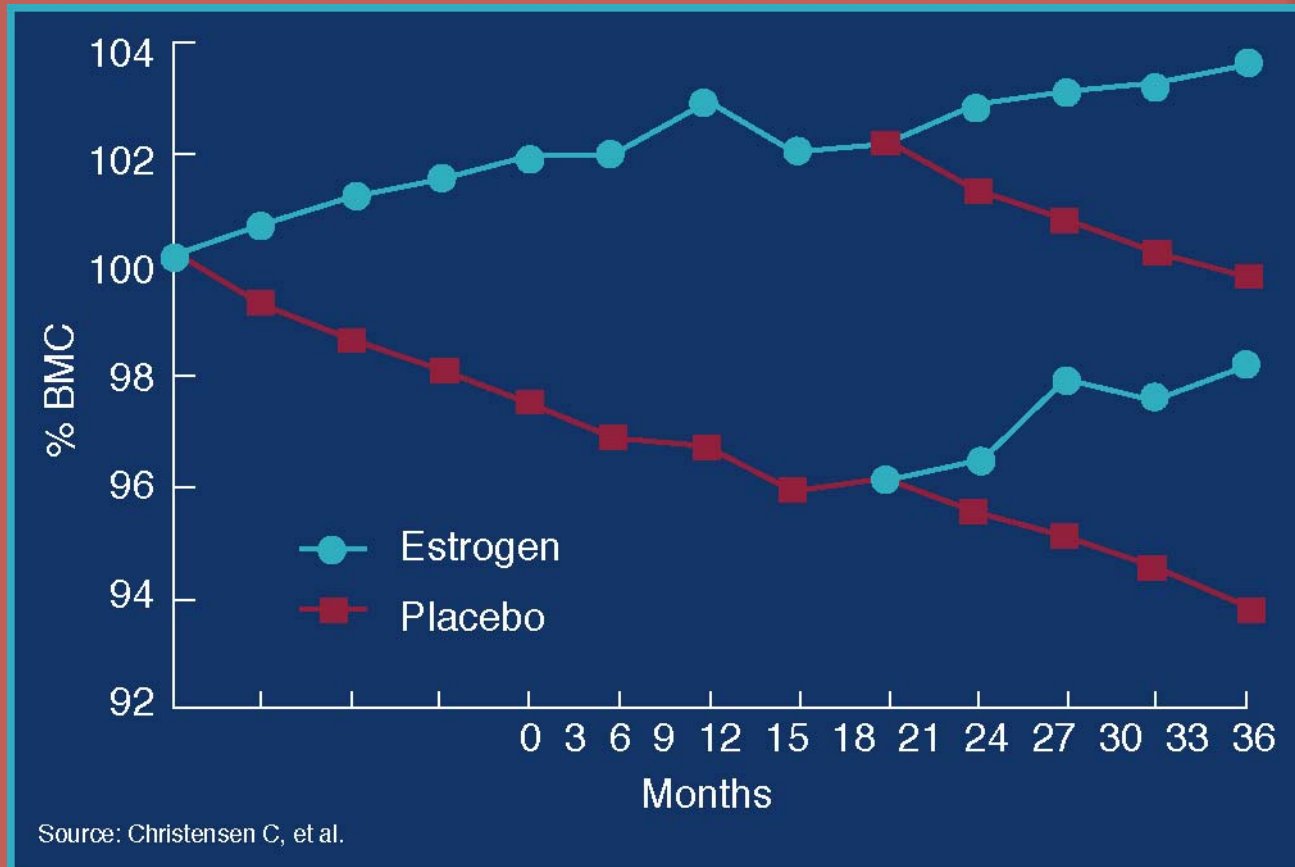


Different Diseases, Different Models

- Simple endocrine: Bone
 - Direct relationship between endogenous and exogenous E2 and osteoprotection
 - Classical receptor mediated actions
 - Essential action of E2 confirmed in multiple ablation/replacement models



Bone Mass: Estrogen vs Placebo



Source: Christiansen et al. *Lancet*. 1981;1(8218):459-461.

Type 2 Diabetes

| | Age | Rate |
|------------------------|------------|-------------|
| White Female | 0-44 | 1.17 |
| | 45-64 | 7.56 |
| | 65-74 | 13.63 |
| | 75+ | 11.66 |
| Black Female | 0-44 | 2.43 |
| | 45-64 | 15.65 |
| | 65-74 | 26.03 |
| | 75+ | 22.42 |
| Hispanic Female | 0-44 | 1.14 |
| | 45-64 | 12.31 |
| | 65-74 | 25.22 |
| | 75+ | 18.51 |



HERS and WHI: Incident Type II DM and Hormone Therapy

HERS:

The incidence of diabetes was 6.2% in the hormone therapy group and 9.5% in the placebo group (relative hazard, 0.65 [95% CI, 0.48 to 0.89]; $P = 0.006$).

NNT=30 (18-103)


WHI: Similar findings, data in press (Diabetologica)

CVD: Can Hormones Be Both Good and Bad for You?

- Do older women have hormone related liabilities that were previously unappreciated/ignored?
- Does the timing of the intervention make a critical difference in the outcome?
- Do the effect modifiers change dramatically with the menopause?



In Other Words...

 ***Have we failed to recognize the interactions between reproductive and somatic aging?***



How Might Aging Change the Backdrop?

- Progressive, age related change: vascular distensibility decreases, BP increases, lipids and lipoproteins worsen
- Loss of other, non-gonadal factors?
 - Adrenal axis?
- A reversal of R/B ratio due to sudden accelerated, reciprocal risk?
 - Increased vulnerability to thrombogenesis



Experiment of Nature: POF

- Hypergonadotropic amenorrhea prior to age 40
- No detectable 'progeria' of other endocrine axes if polyglandular failure is r/o (Santoro)
- POF predicts increased CV mortality (Cooper, Snowdon, Bairey Merz)
- CVD *precedes* the diagnosis of POF (Luborsky)



Does early loss of ovarian function lead to accelerated somatic aging or does accelerated somatic aging lead to early loss of ovarian function?



Another Experiment of Nature: The WISE Study

- Young women with FHA, not ovarian in nature:
- OR of angiographic CAD: 7.4 (1.7-33.3)
- 69% vs 29% prevalence of CAD in women with FHA vs. those without

Bairey Merz, CN, J Am Coll Cardiol 2003;41:413





OR



Different Disease, Different Models

- **Complex endocrine: Type 2 DM**
 - Consistent beneficial effect, not directly related to estradiol
 - Possibly mediated through inflammatory cytokine systems or via 'adipokines'
- **Complex, contradictory: CVD**
 - Animal and observational data currently at variance with clinical trial evidence



SWAN

- 7 multicenter sites, 5 ethnic groups
- Central Lab (U Mich)
- Data Coordinating Center (Pitt EDC)
- SC Chair: Susan Johnson, MD
- Major Committees: Bone, CV, Ovarian Markers, LSB
- Substudies: Psych, DHS, Cognition, CAM



SWAN Design

- 3150 women enrolled from community based sampling frames nationwide
- Entry criteria: 1 menses in past 3 mos, no bilateral oophorectomy, hysterectomy or hormone use, age 42-52 at baseline
- Annual visit with physical, biological and survey measurements
- Repository for serum, urine and DNA
- Now in 7th follow up year



How Do Unfavorable Metabolic Profiles Act as Disease Accelerants?

- SWAN: median BMI app 28 kg/m²
- IR associated with decreased SHBG, increased ovarian androgens, increased BMI
- High BMI associated with functional limitations, **decreased** FSH and E2 in early menopause transition
- IR increases CVD risks dramatically in younger women



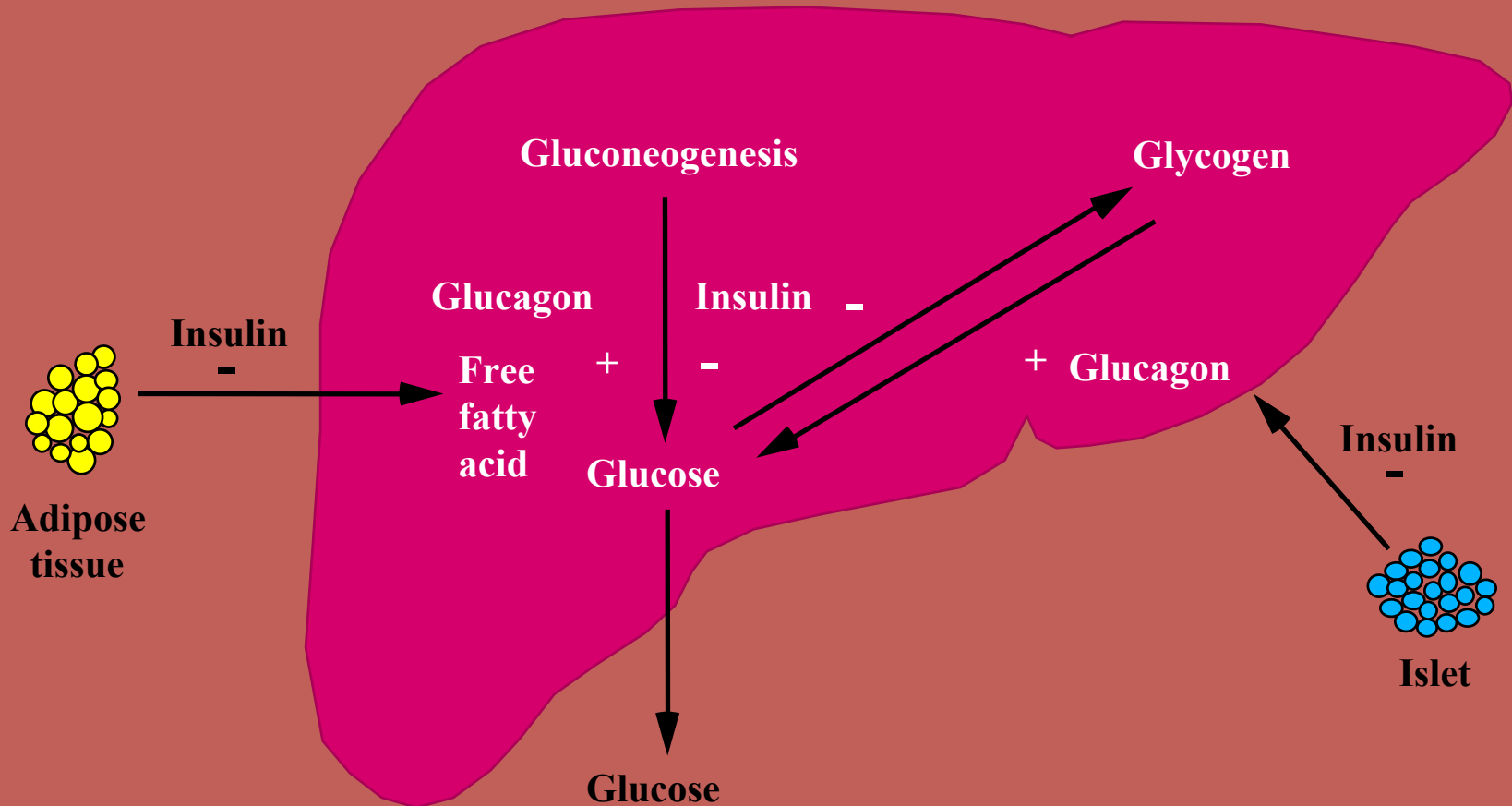
Insulin Effects

DIRECT EFFECTS OF INSULIN

Glycogenolysis
Gluconeogenesis

INDIRECT EFFECTS OF INSULIN

Decrease free fatty acid flux to liver
Glucagon secretion



Where Do We Go From Here?

Is there a 'recipe' of appropriate ovarian products that make a tonic for the menopausal women (give her back what she's lost when her ovaries stopped producing sex steroids)

'The WD-40 Model'



Evolution of Thinking...

...or do we need to begin thinking about a dynamic system of complex hormone effects that are modified by both healthy and unhealthy aging, incorporating the concepts that postmenopausal women may both lose protective factors and acquire risk factors as they age?

