

Women's Fracture Prevention: Co-therapy of an Anti-resorptive Osteoporosis Therapy with Progesterone

Jerilynn C. Prior

University of British Columbia

www.CeMCOR.ubc.ca



WOMEN'S HEALTH
RESEARCH INSTITUTE
AT BC WOMEN'S



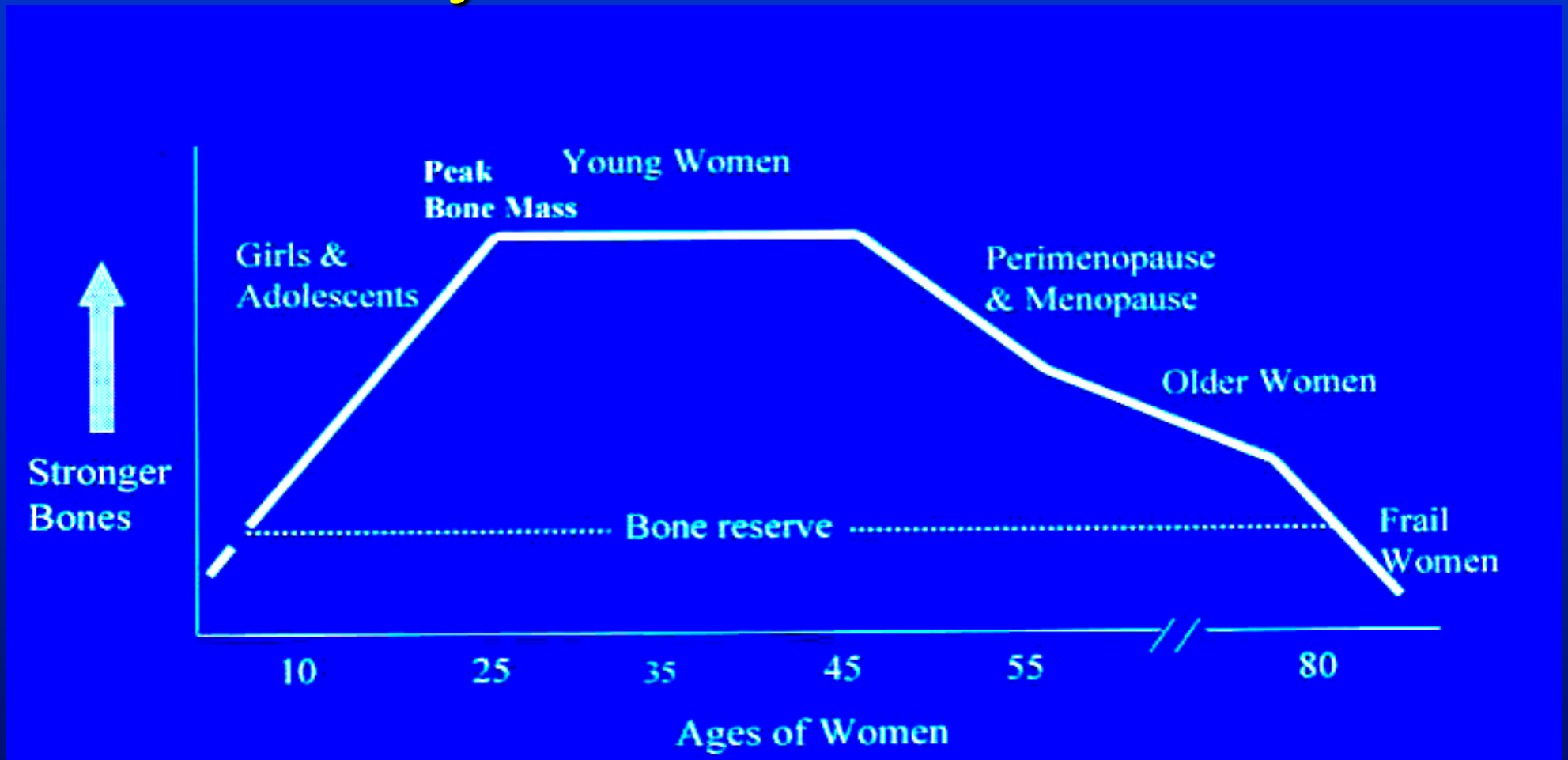


Progesterone with Antiresorptives

What we will learn:

- ◆ How does bone **renovation**/remodeling work?
 - ◆ Linkage between bone loss and formation
 - ◆ Different rates of work and jobs for different cells
- ◆ How are women's hormones (estrogen and progesterone) related to bone remodeling?
- ◆ Could progesterone added to anti-resorptive therapy help prevent fractures?

Life Cycle of Bone—Women



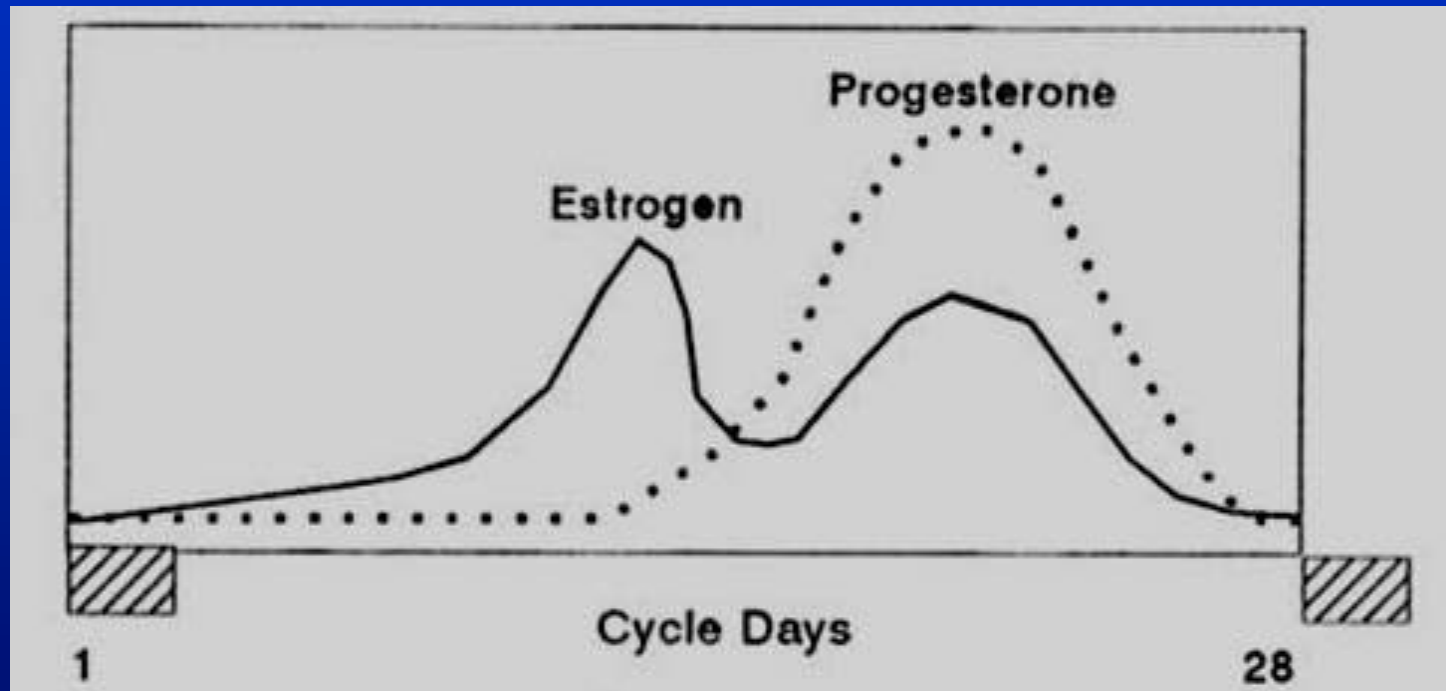
Note that, with normal peak bone mass and its maintenance to perimenopause, women don't have increased risks for fractures until their 80s

Progesterone with Antiresorptives

What we will learn:

- ◆ How does bone **renovation**/remodeling work?
 - ◆ Linkage between bone loss and formation
 - ◆ Different rates of work and jobs for different cells
- ◆ How are women's hormones (estrogen and progesterone) related to bone remodeling?
- ◆ Could progesterone added to anti-resorptive therapy help prevent fractures?

Overview of Progesterone and Estrogen

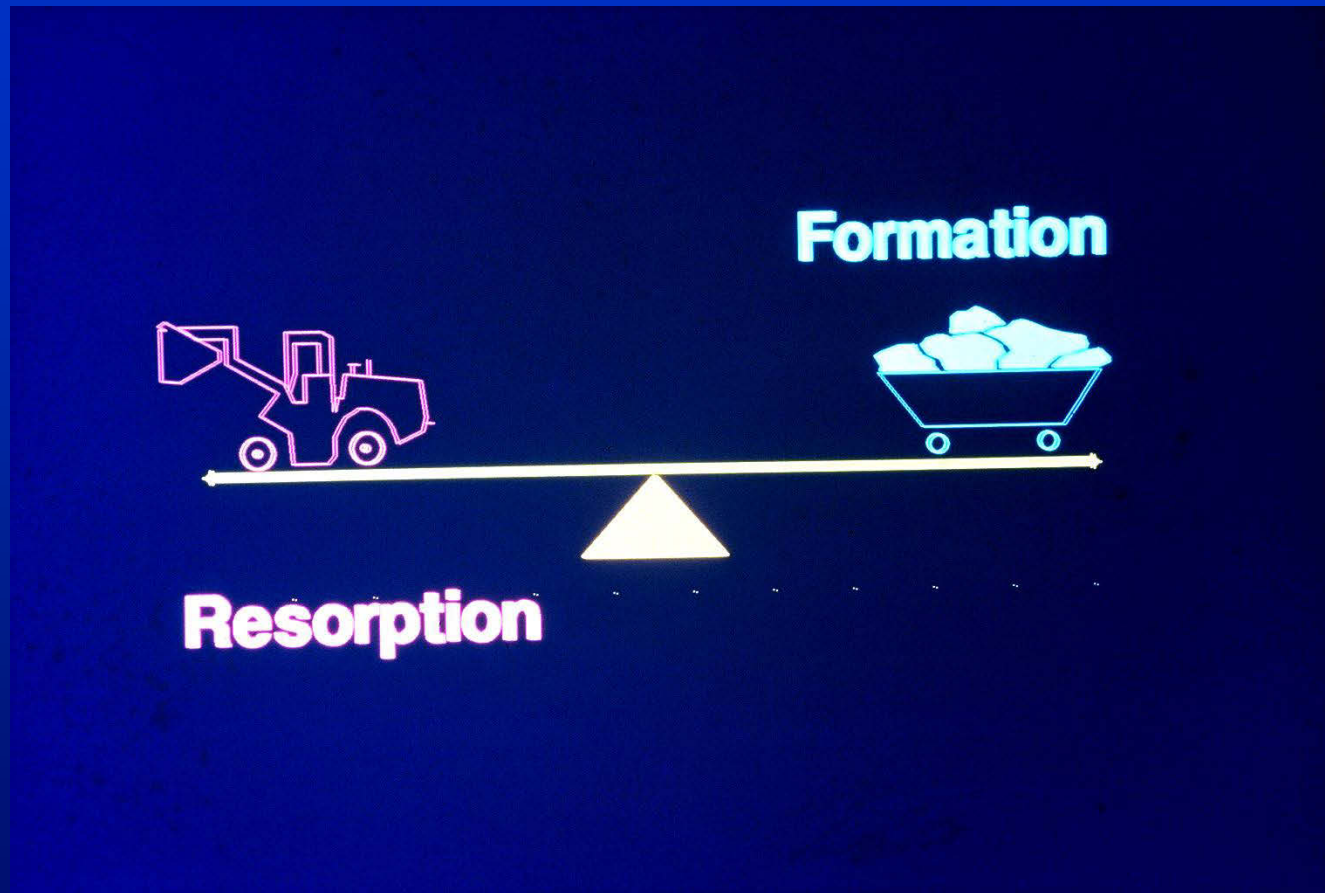


Flow

Flow

The “Estrogen Deficiency”
(menopause) idea
led to the importance of bone
loss-stopping therapies for
Osteoporosis

Bone Remodeling BALANCE



Bone Remodeling (renovation)

Bone resorption

haematopoietic stem cell

pre-osteoclast

osteoclast

Bone formation

mesenchymal stem cell

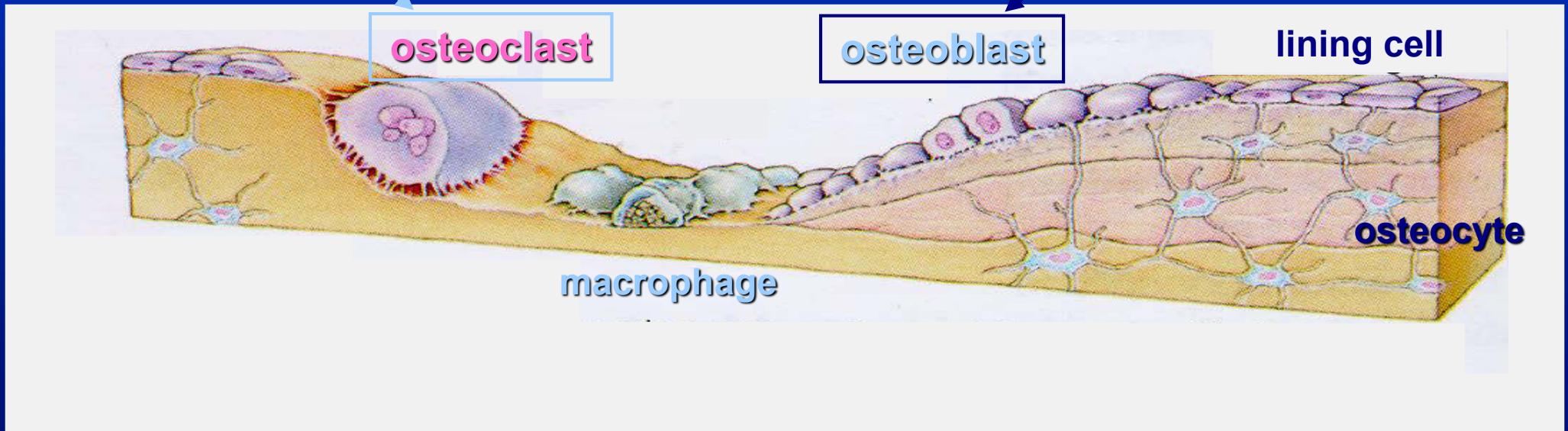
pre-osteoblast

osteoblast

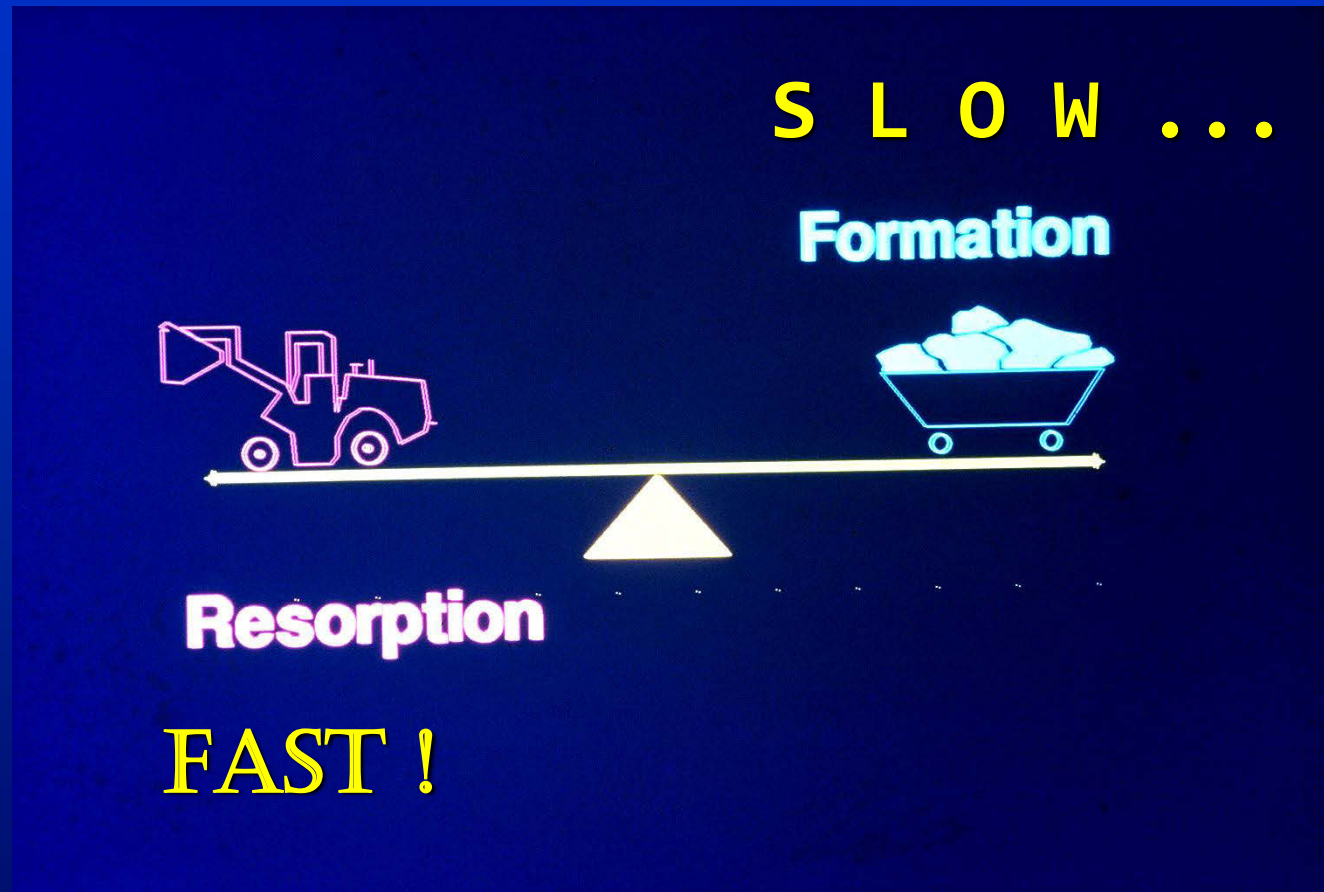
lining cell

osteocyte

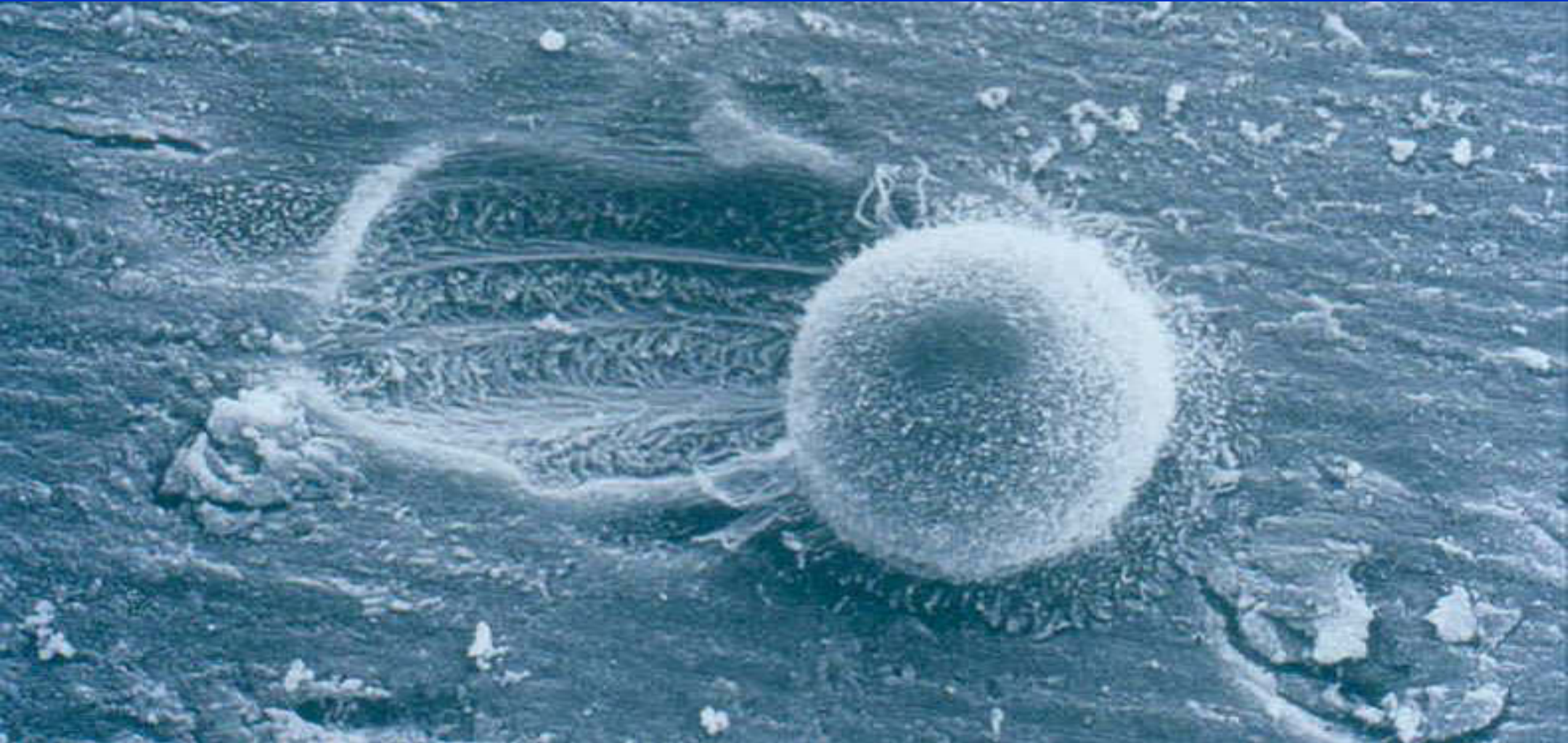
macrophage



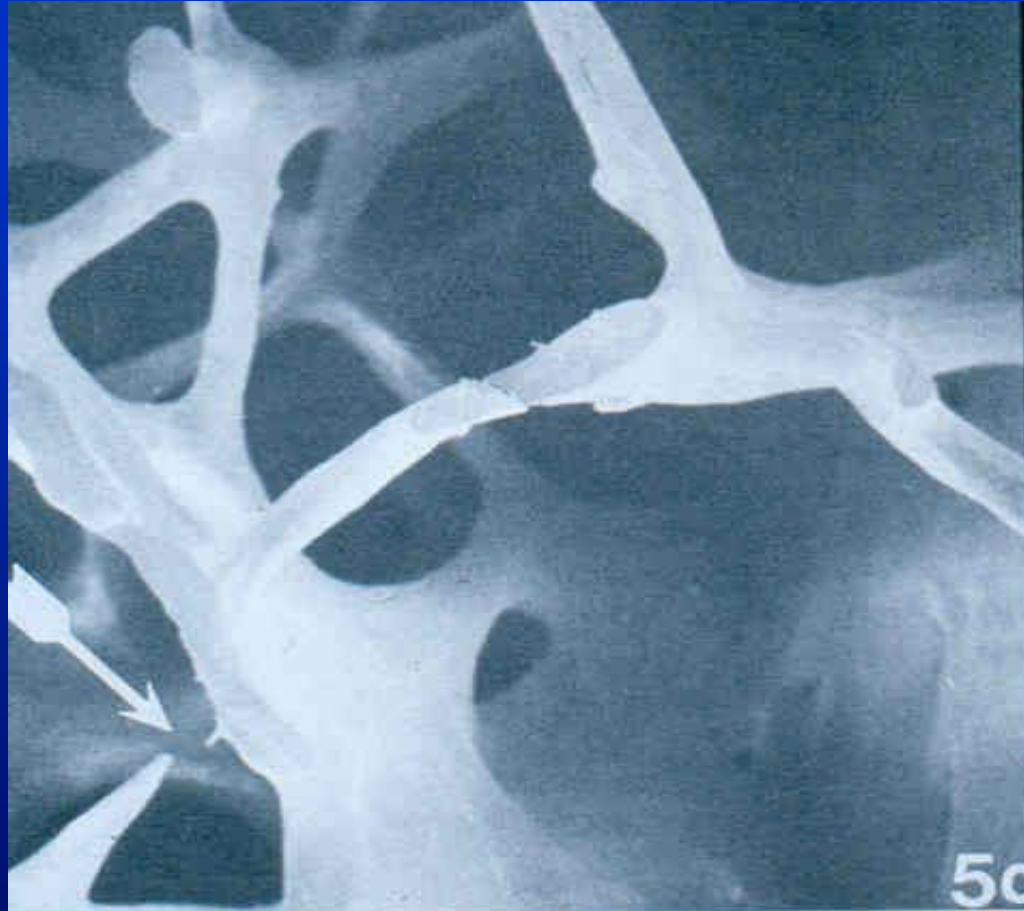
Bone Remodeling BALANCE



Osteoclast—Resorption



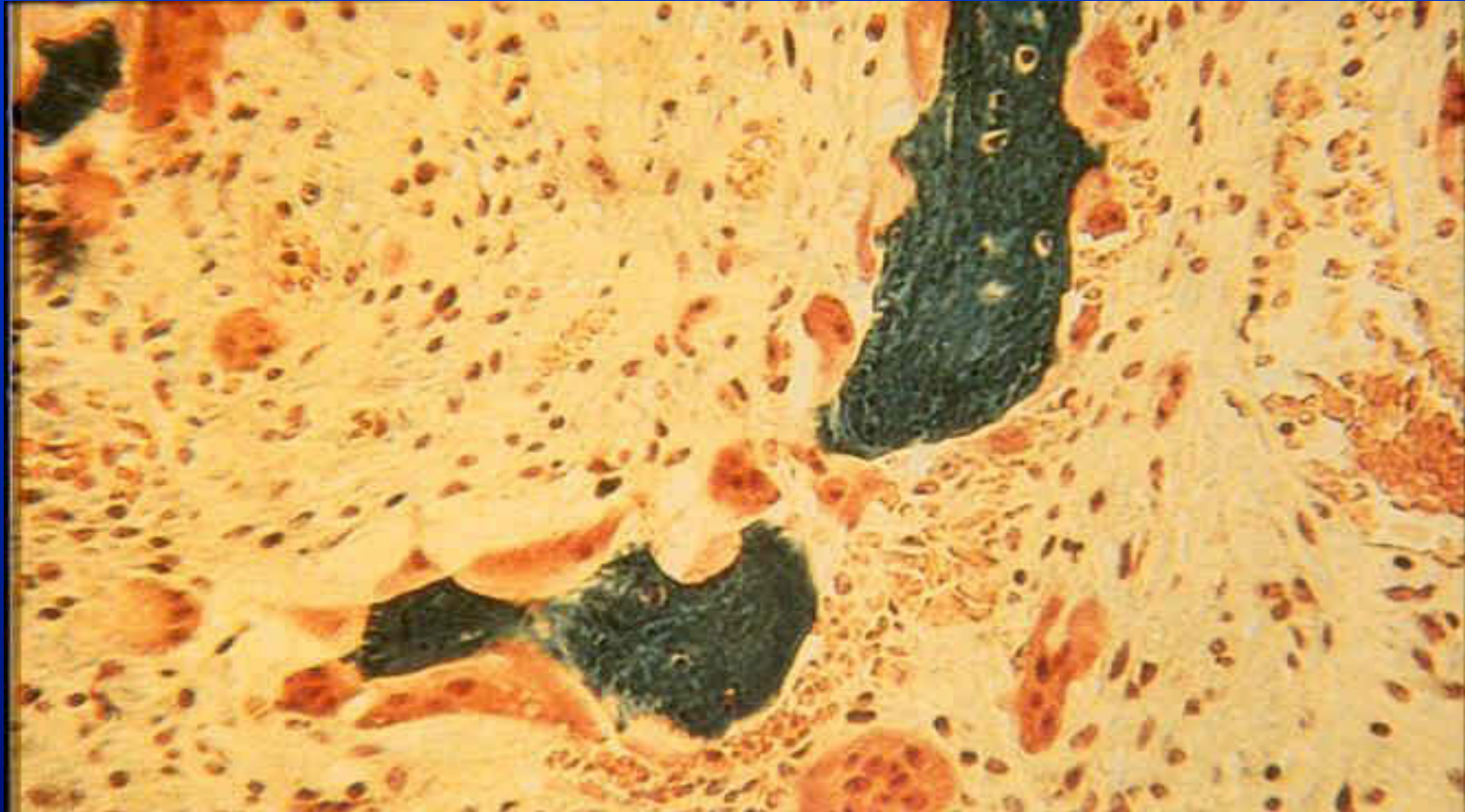
Trabecular perforation—photomicrograph



Dempster DW J. Bone Miner. Res. 1986; 1: 15

Trabecular perforation—microscopic

● is
bone



Eriksen EF Bone Histomorphometry ASBMR 1994, Raven Press

Bone Remodeling (renovation)

Bone resorption

haematopoietic stem cell

pre-osteoclast

osteoclast

Bone formation

mesenchymal stem cell

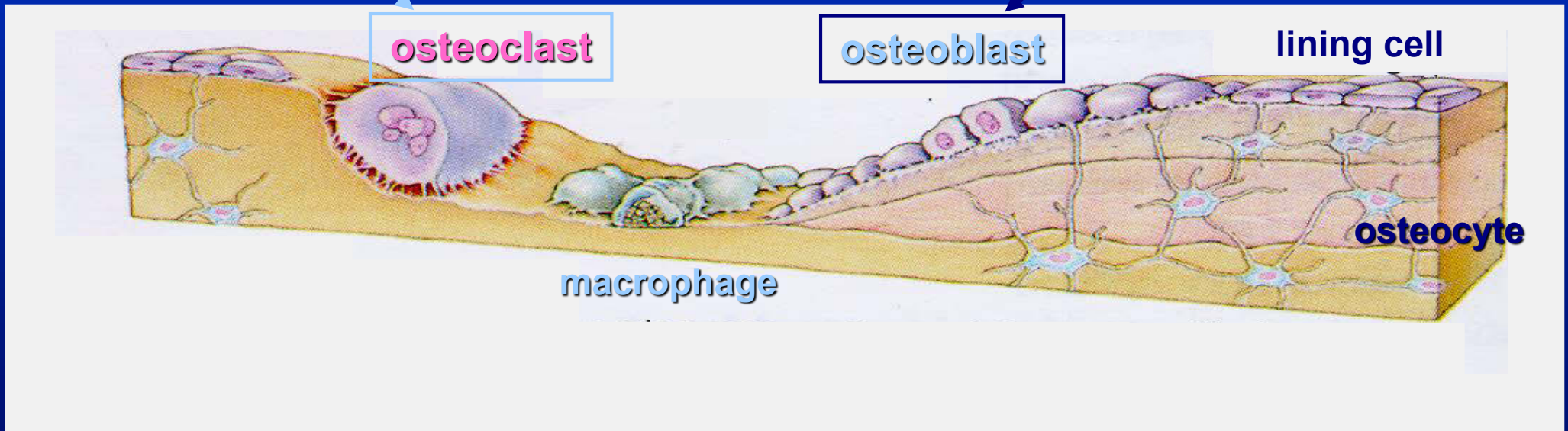
pre-osteoblast

osteoblast

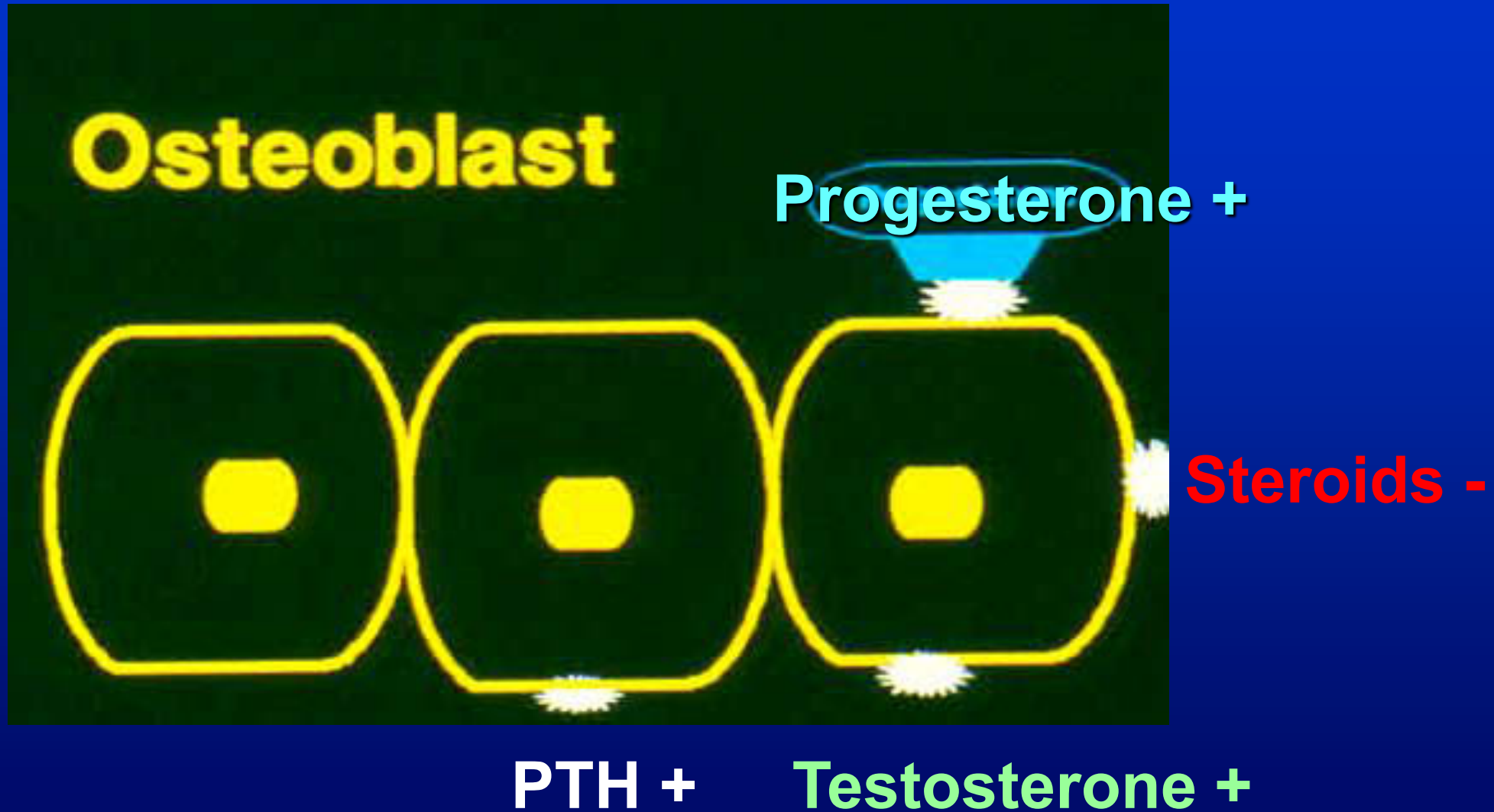
lining cell

osteocyte

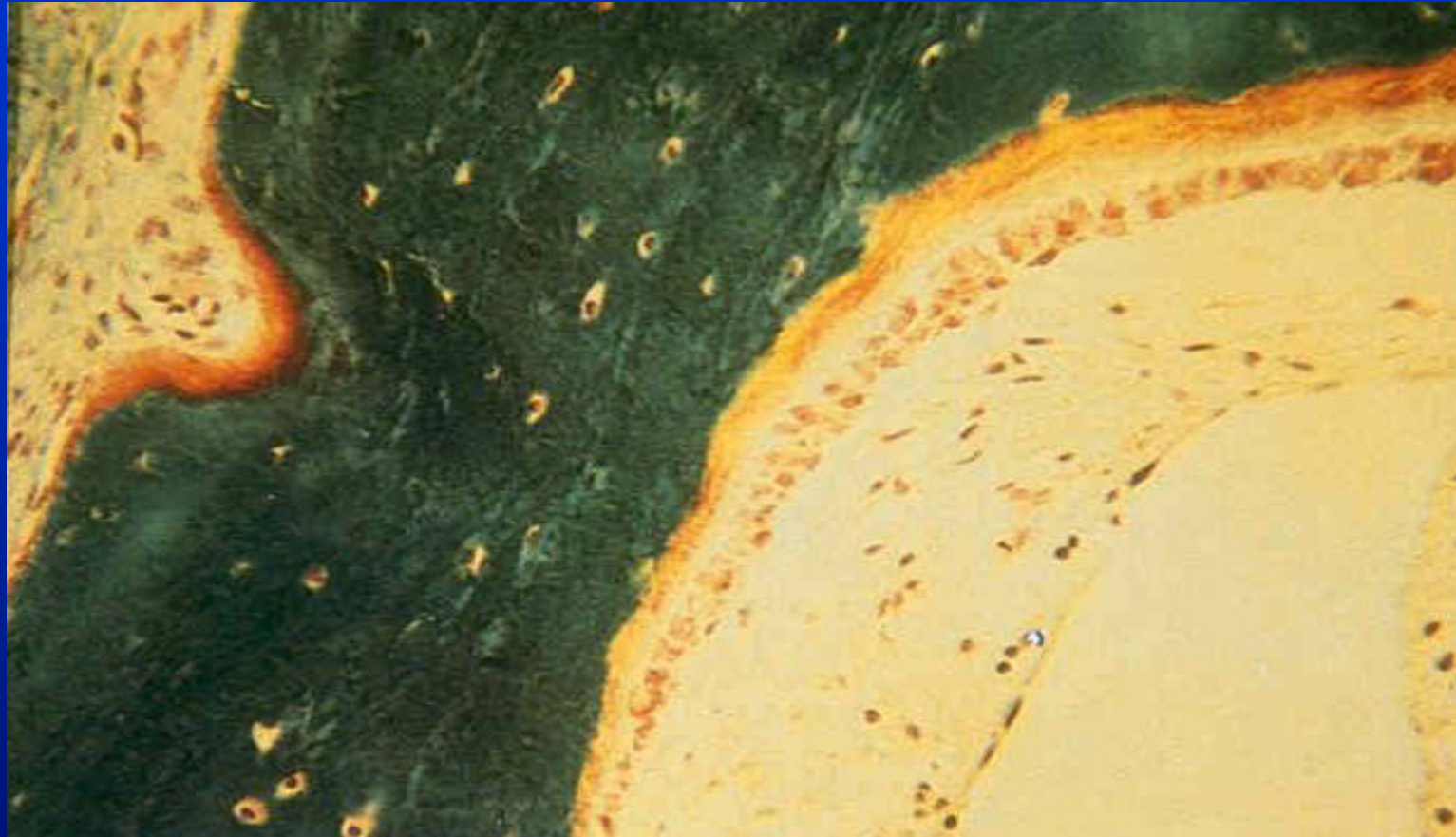
macrophage



Osteoblast—Bone Formation



Bone remodeling—formation



←osteoid

←osteoblasts

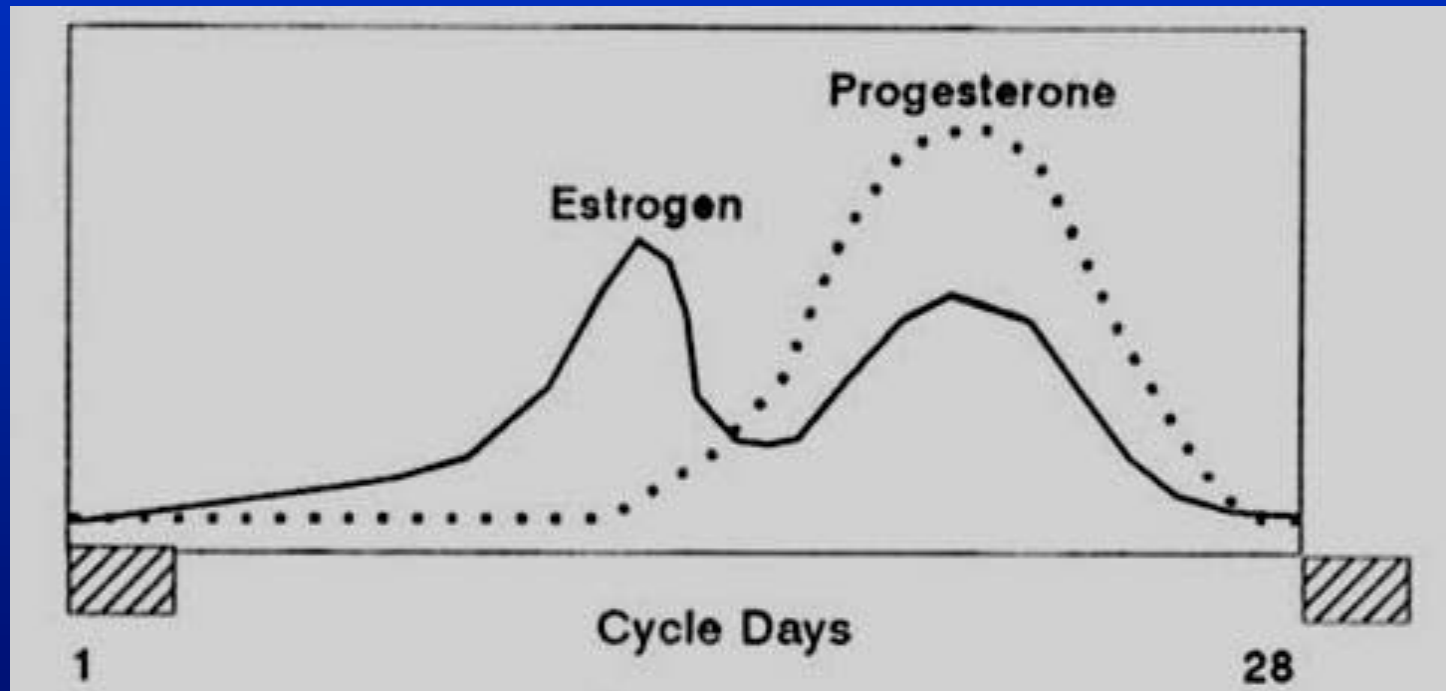
Eriksen EF *Bone Histomorphometry* ASBMR 1994, Raven Press

Progesterone with Antiresorptives

What we will learn:

- ◆ How does bone renovation/remodeling work?
 - ◆ Linkage between bone loss and formation
 - ◆ Different jobs for different cells
- ◆ How are women's hormones (estrogen and progesterone) related to bone remodeling?
- ◆ Could added progesterone therapy help prevent fractures? *Will progesterone plus anti-resorptive therapy stop its long-term use from being bad for bones?*

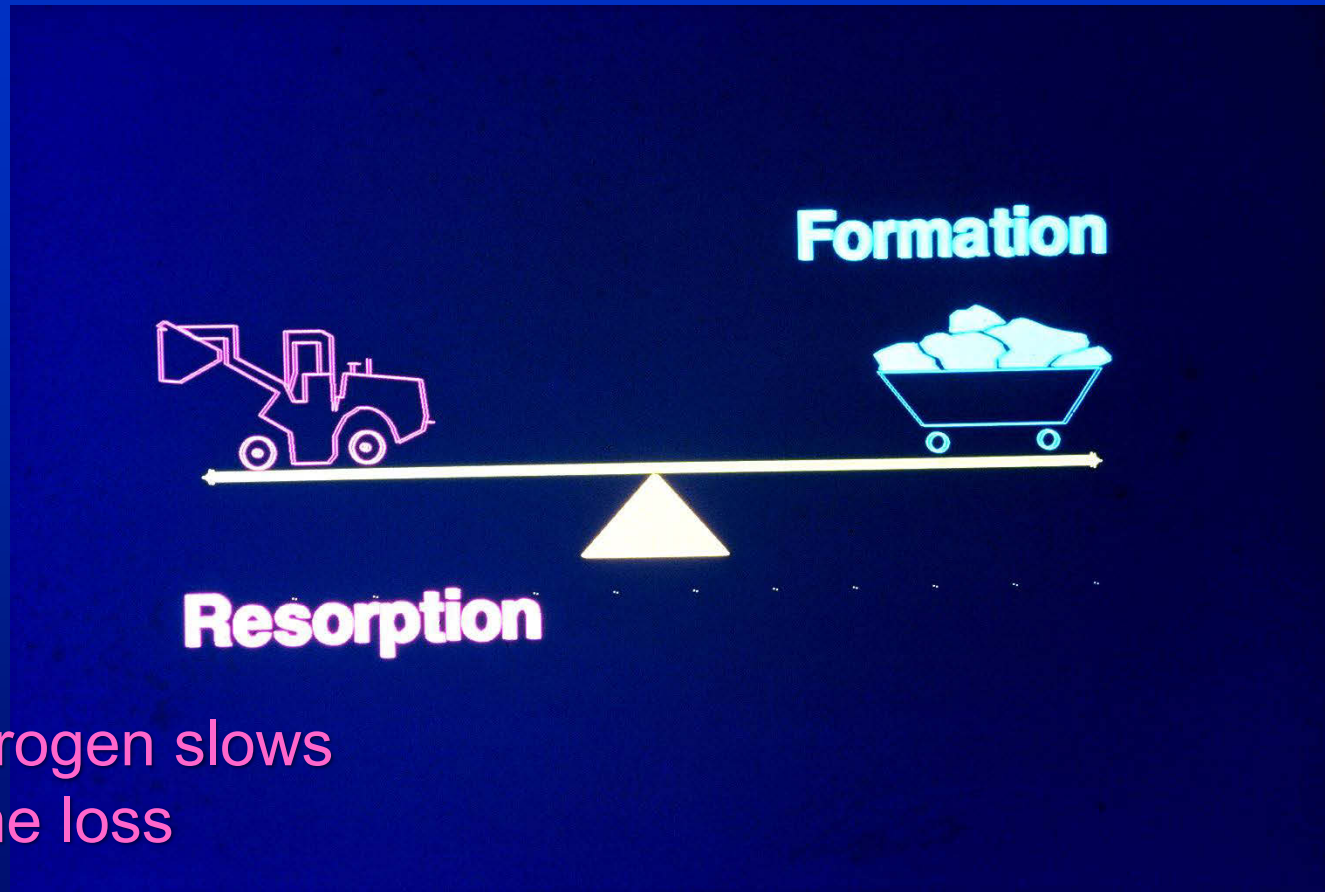
Overview of Progesterone and Estrogen



Flow

Flow

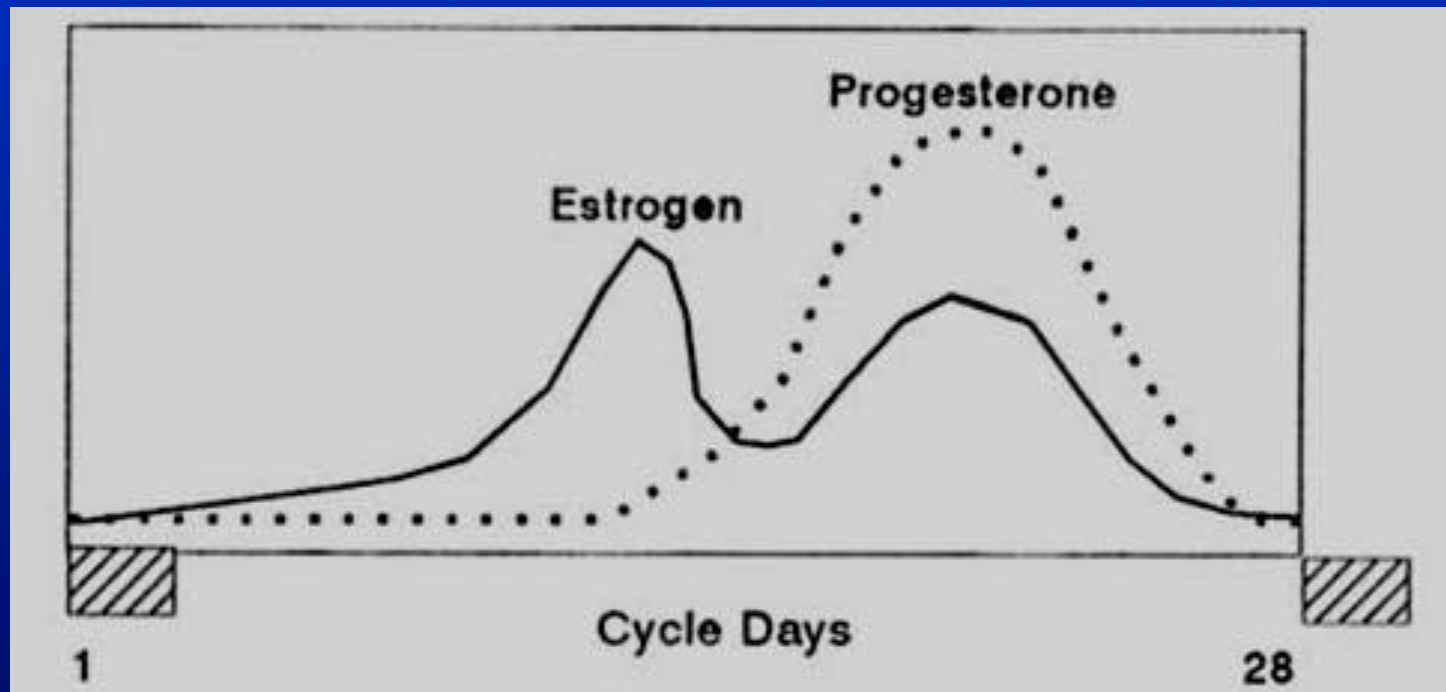
Bone Remodeling BALANCE



Estrogen slows
bone loss

Premenopausal Bone Remodelling

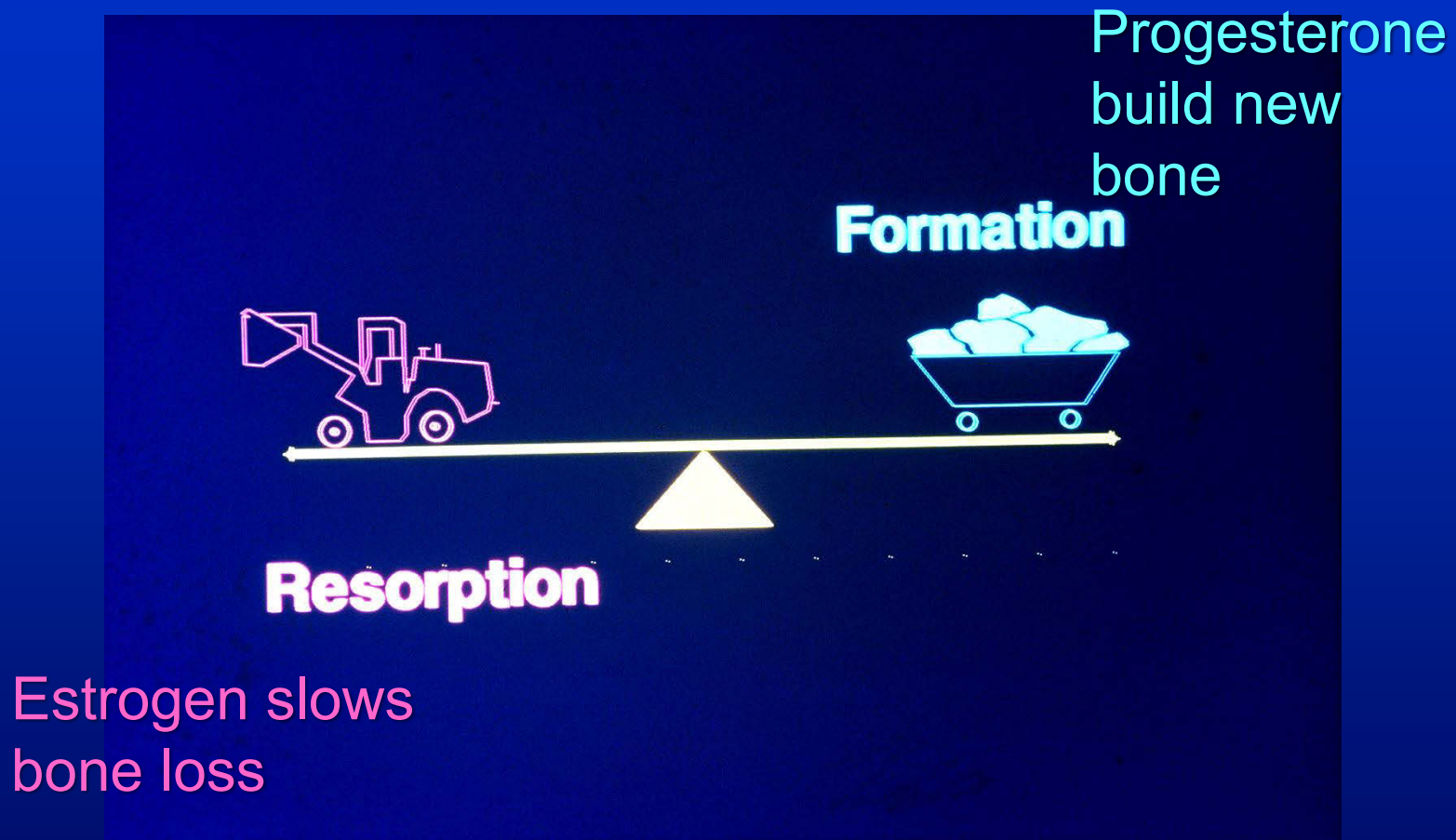
↓ Estrogen peak



Flow

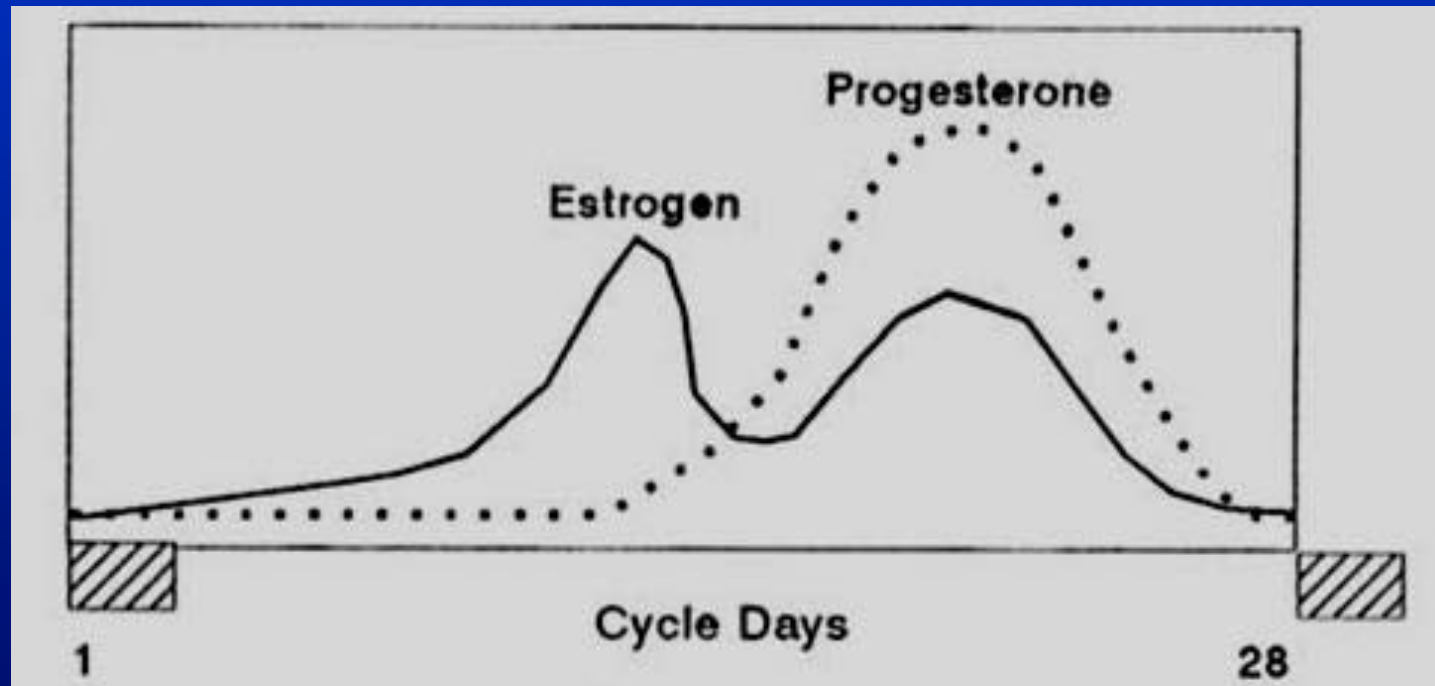
Flow

Bone Remodeling BALANCE



Premenopausal Bone Remodelling

↓ Luteal Phase ↓

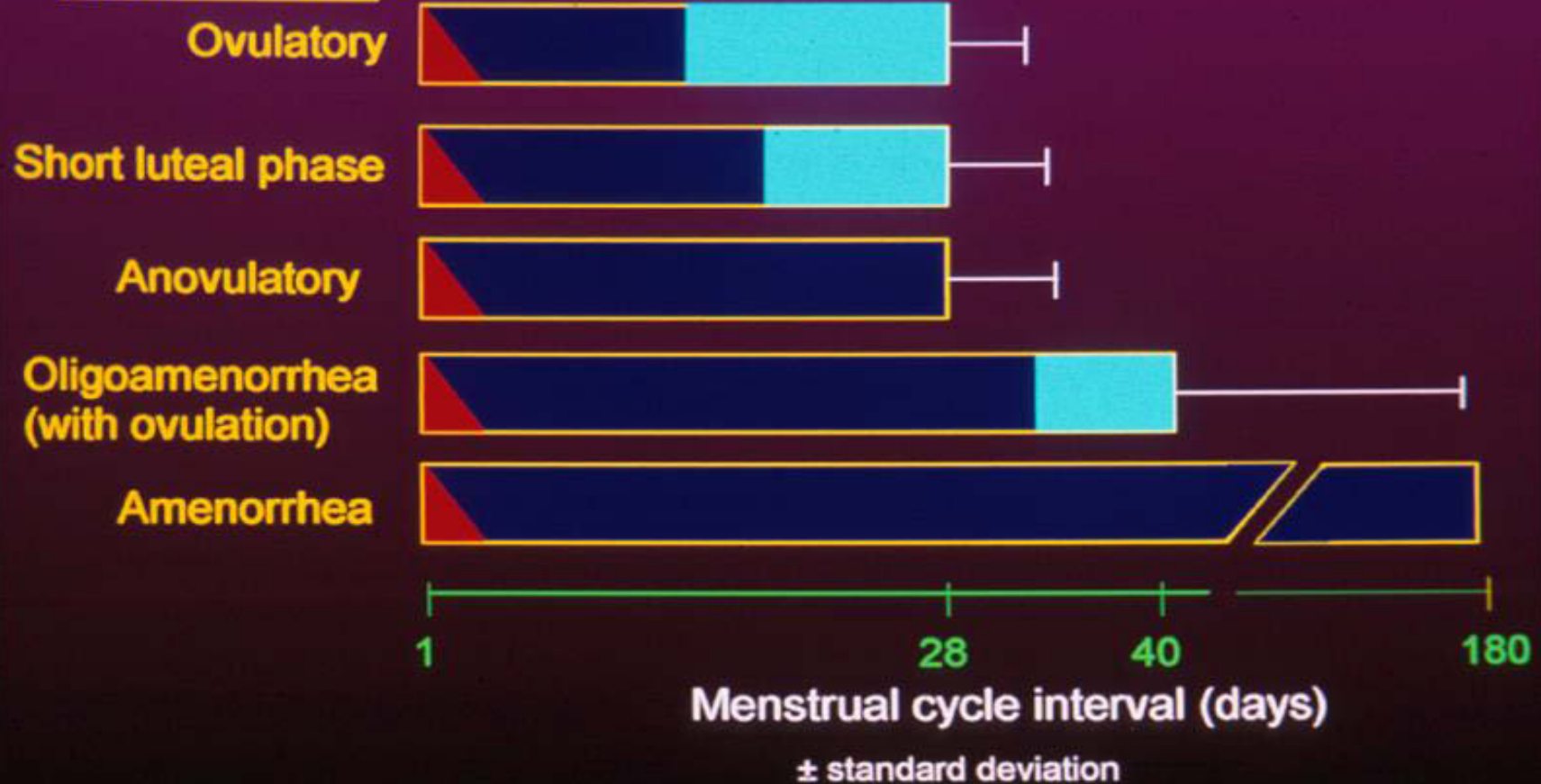


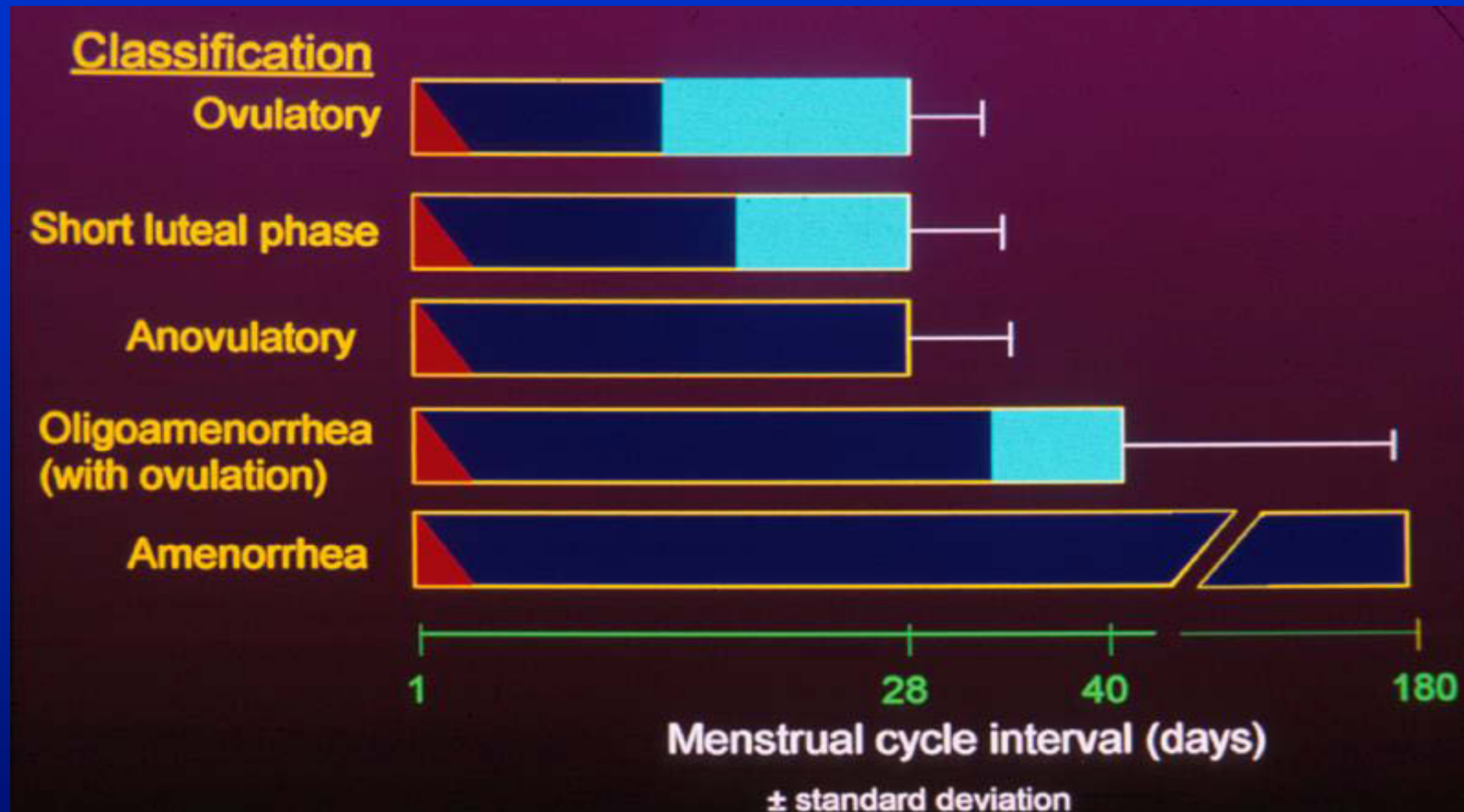
Luteal phase
length
= 10-16 days

Flow

Flow

Classification





Menstrual cycle disturbances in young adulthood associated with increased later fractures

Prospective Ovulation Cohort

Prospective observational study in 66 women

All premenopausal, ages 20-42, 18.5-25 BMI

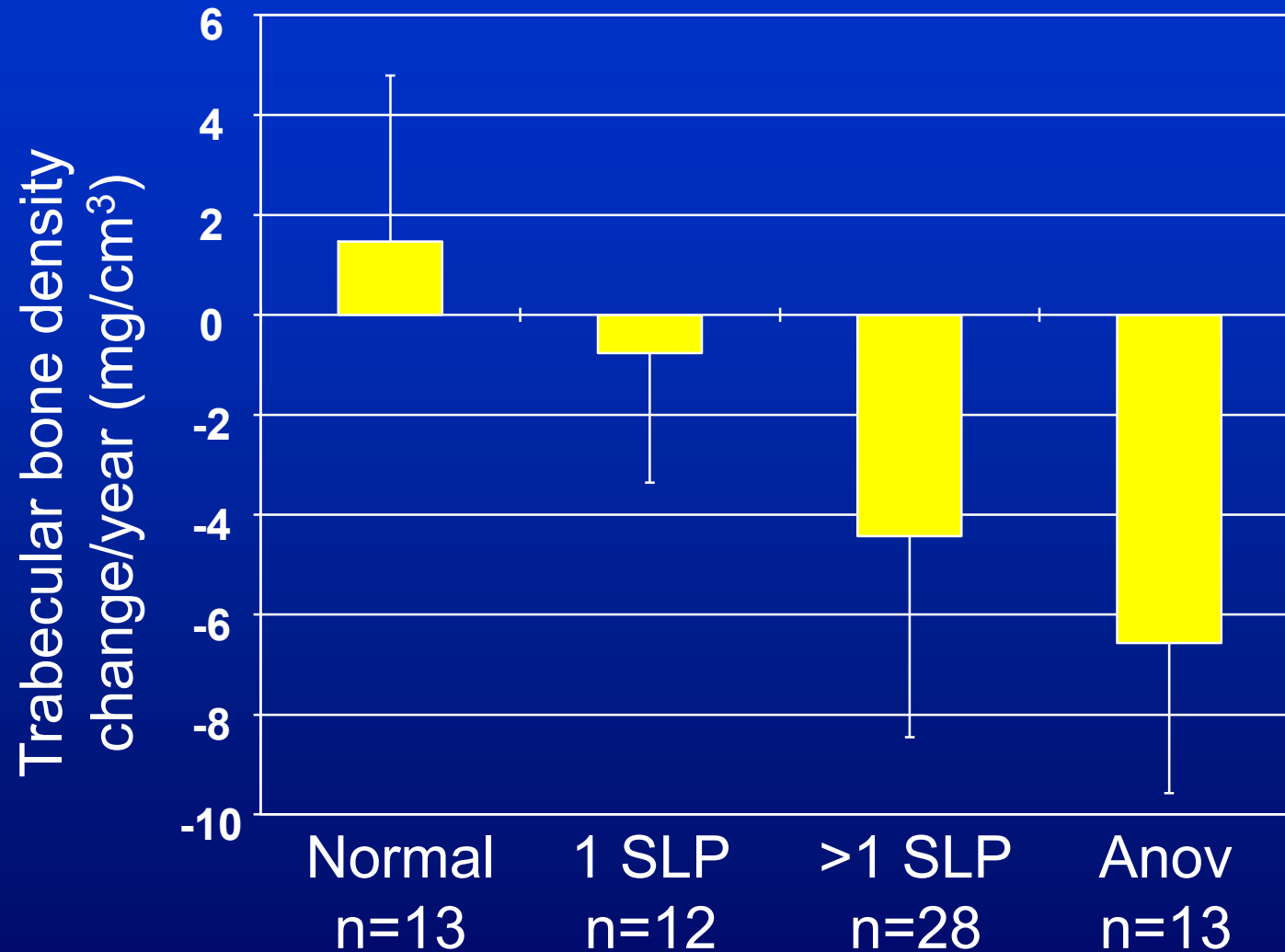
Varying exercise habits —normal activity to training for and running a marathon

Required to have regular cycles AND normal length luteal phases on 2 consecutive cycles

QCT bone change—by ovulatory experience

Prior JC *New England J. Med.* 1990; 323:1221

Prospective Ovulation Cohort



SLP =
Short luteal
phase

ANOV =
anovulation

Hormones in Bone Renovation

positives

↓ Bone Loss

Estrogen—women
& also in men

Testosterone—men

↑ New Bone

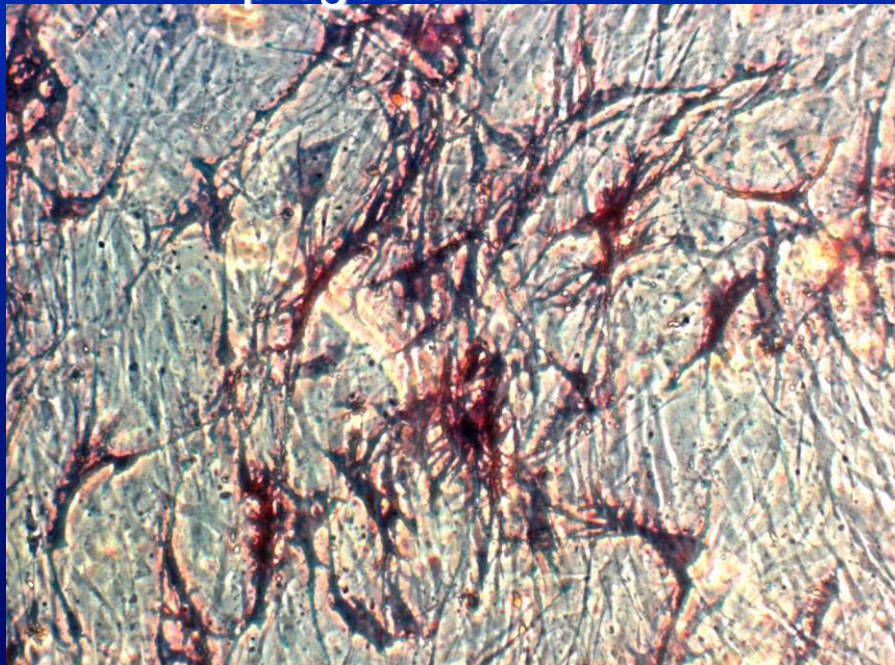
Progesterone—
women

Testosterone—men

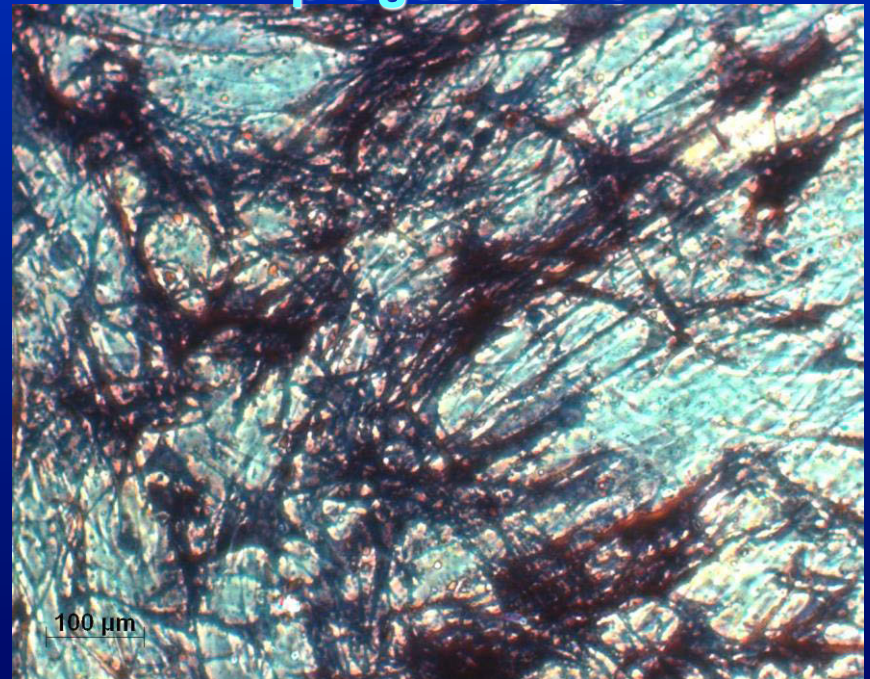
Osteoblast cells in culture—bone formation assessed with Alkaline Phosphatase (ALP)

in situ staining ALP = dark blue/black

28 days of incubation with
estradiol, no incubation with
progesterone ◀



28 days of incubation with **estradiol**,
21 days of incubation with $10^{-7}M$
progesterone



Premenopausal Bone Remodelling

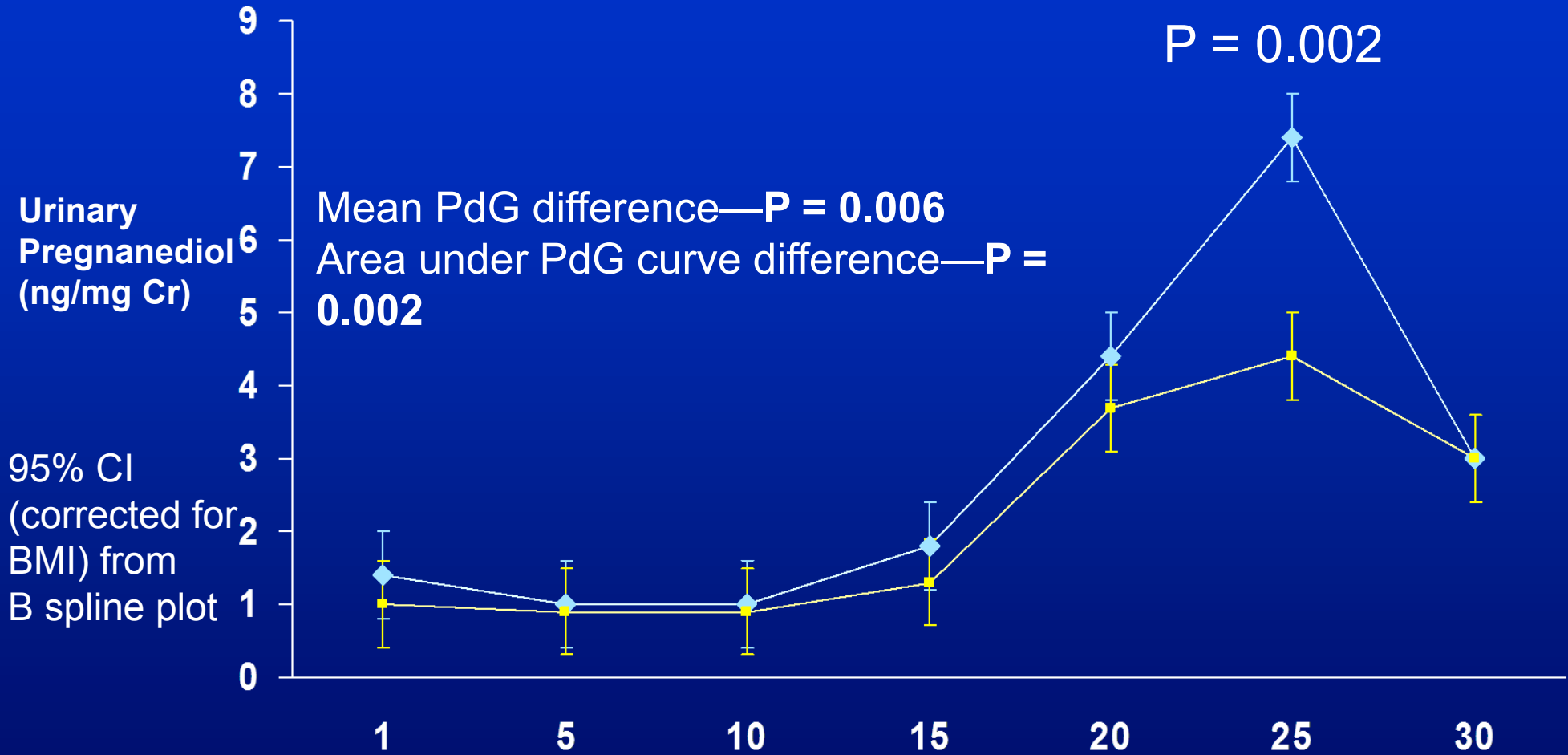
Epidemiology links low BMD with Ovulatory Disturbances

- ◆ Population-based longitudinal study, women 25-45
- ◆ Nested case-control within the Michigan Bone Health Study, USA
- ◆ **N = 582**; bone mineral density (BMD) in the lowest 10% = **cases** vs. 3rd quartile = **controls**
- ◆ Daily urines **E** and **P** X 2 cycles
- ◆ Participation rate = 86%

Sower M-F *J. Bone Min. Res.* 1998;13:1191-1202

Progesterone Levels in Urine in one cycle

- ◆— Normal BMD n = 34
- Lowest 10th percentile BMD n = 31

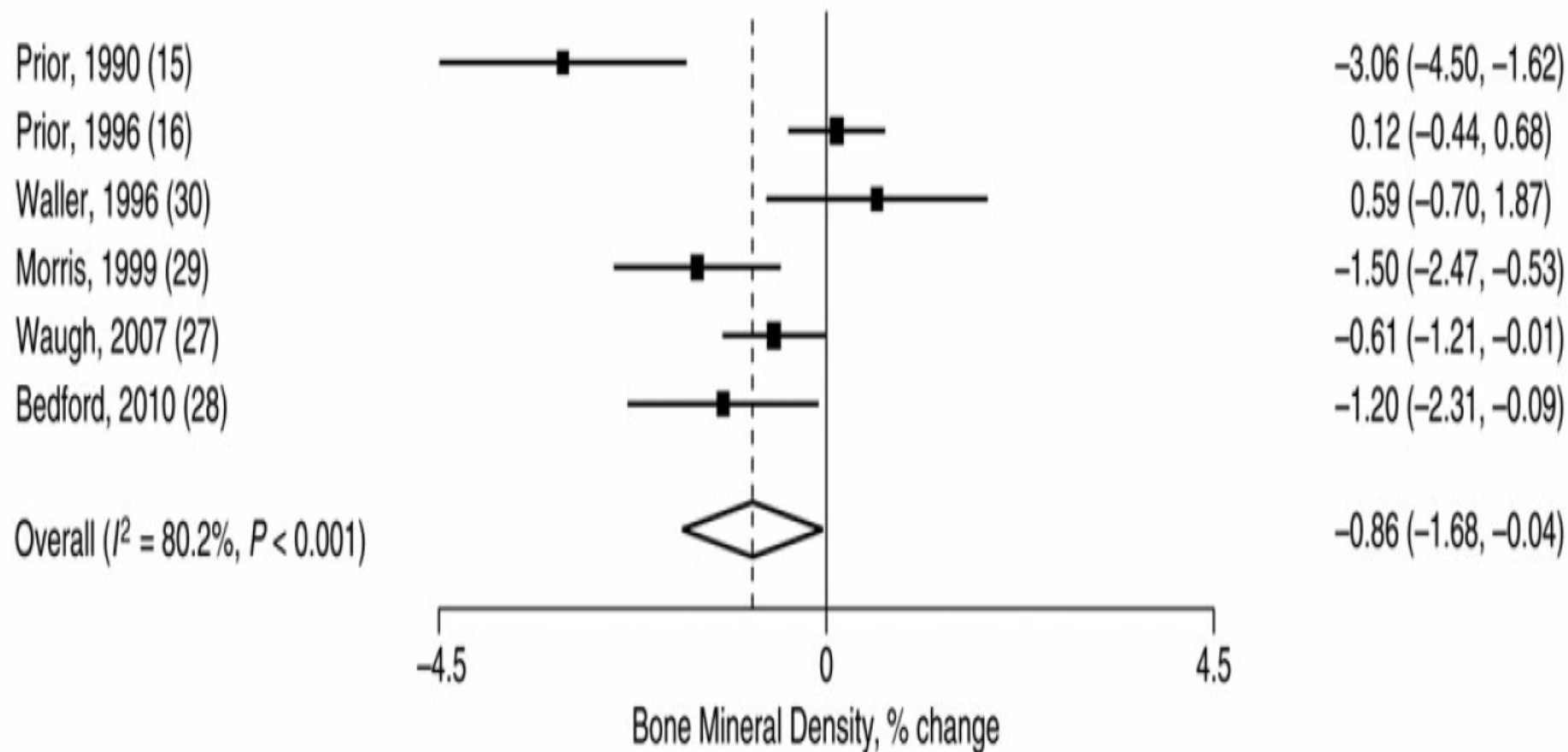


Re-drawn from **MF Sowers** *J Bone Min Res* 1998;13:1191

First Author, Year (Reference No.)

Weighted Mean Difference (95% CI)

Ovulation Disturbances Worse Ovulation Disturbances Better



Controlled Trial of Cyclic Progestin for Abnormal Cycles/Ovulation

Purpose—to prove that **progestin causes increased bone formation**

Normal weight, physically active, ages 20-40

Amenorrhea, oligomenorrhea, regular cycles with short luteal phases, or with anovulation

61 women completed a 1-yr randomized double-blind study of **cyclic progestin**/placebo with or without an additional 1000 mg calcium

Cyclic Progesterone Therapy

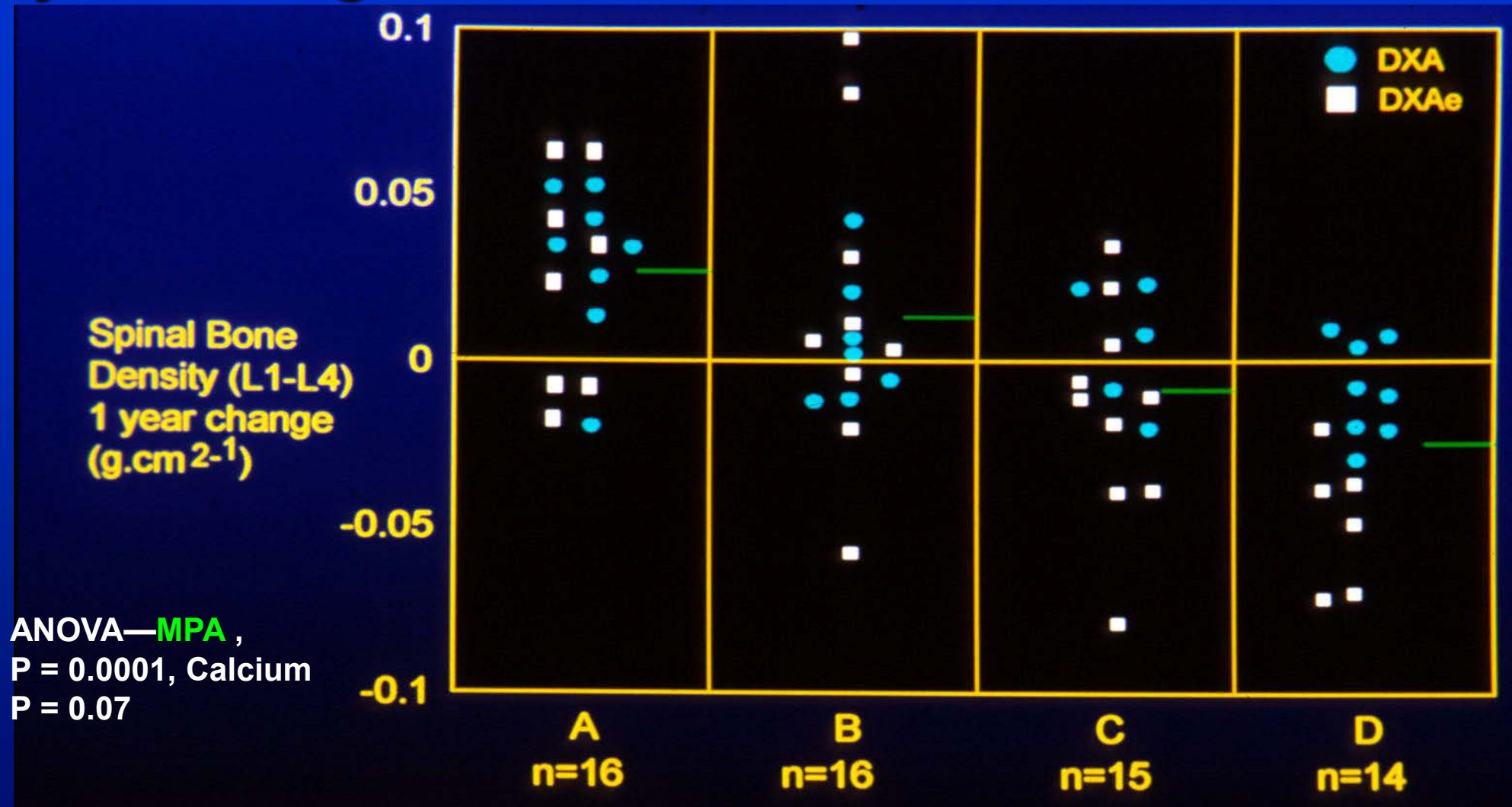


Cyclic Progesterone Therapy-

www.cemcor.ca

JcPrior 2019

Cyclic Progestin Therapy for Abnormal Cycles



A = Cyclic MPA with 1000 mg calcium; B = MPA/calcium placebo; C = calcium; D = double placebo *J Prior Am J. Med* 1994;96:524

Progesterone with Antiresorptives

What we will learn:

- ◆ How does bone renovation/remodeling work?
 - ◆ Linkage between bone loss and formation
 - ◆ Different jobs for different cells
- ◆ How are women's hormones (estrogen and progesterone) related to bone remodeling?
- ◆ Could anti-resorptives plus added progesterone therapy help prevent fractures?

Absolute Fracture Risk Reduction

Current Therapies

Drug	Non-Vertebral	Vertebral
Alendronate	3%	7%
Risedronate	3-5%	5-11%
OHT (E +/- p)	2.2-3.5%*	0.2-0.5%**
Raloxifene	0.2%	0.6-6.5%
Teriparatide	3%	9%
Denosumab	1.5%	5%

*In women without fracture risks or osteoporosis—from WHI trial

**Clinical rather than X-ray diagnosed vertebral fracture

Bone Loss Preventing (anti-resorptive) agents

Absolute Fracture Risk Reduction

Current Therapies—anti-resorptive

Drug	Non-Vertebral	Vertebral
Alendronate	3%	7%
Risedronate	3-5%	5-11%
OHT (E +/- p)	2.2-3.5%*	0.2-0.5%**
Raloxifene	0.2%	0.6-6.5%
Teriparatide	3%	9%
Denosumab	1.5%	5%

*In women without fracture risks or osteoporosis—from WHI trial

**Clinical rather than X-ray diagnosed vertebral fracture

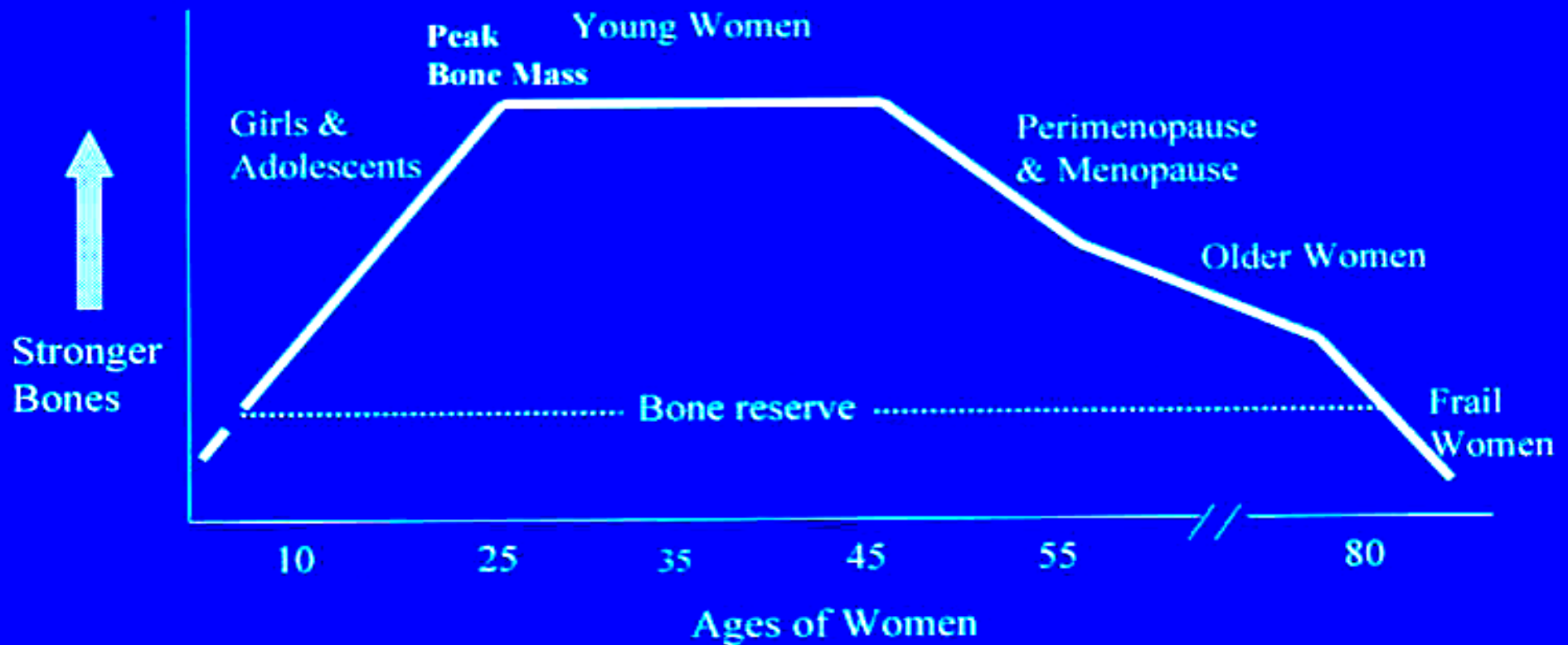
Anti-resorption Therapies

potentially carry long-term (> 5 yr) risks

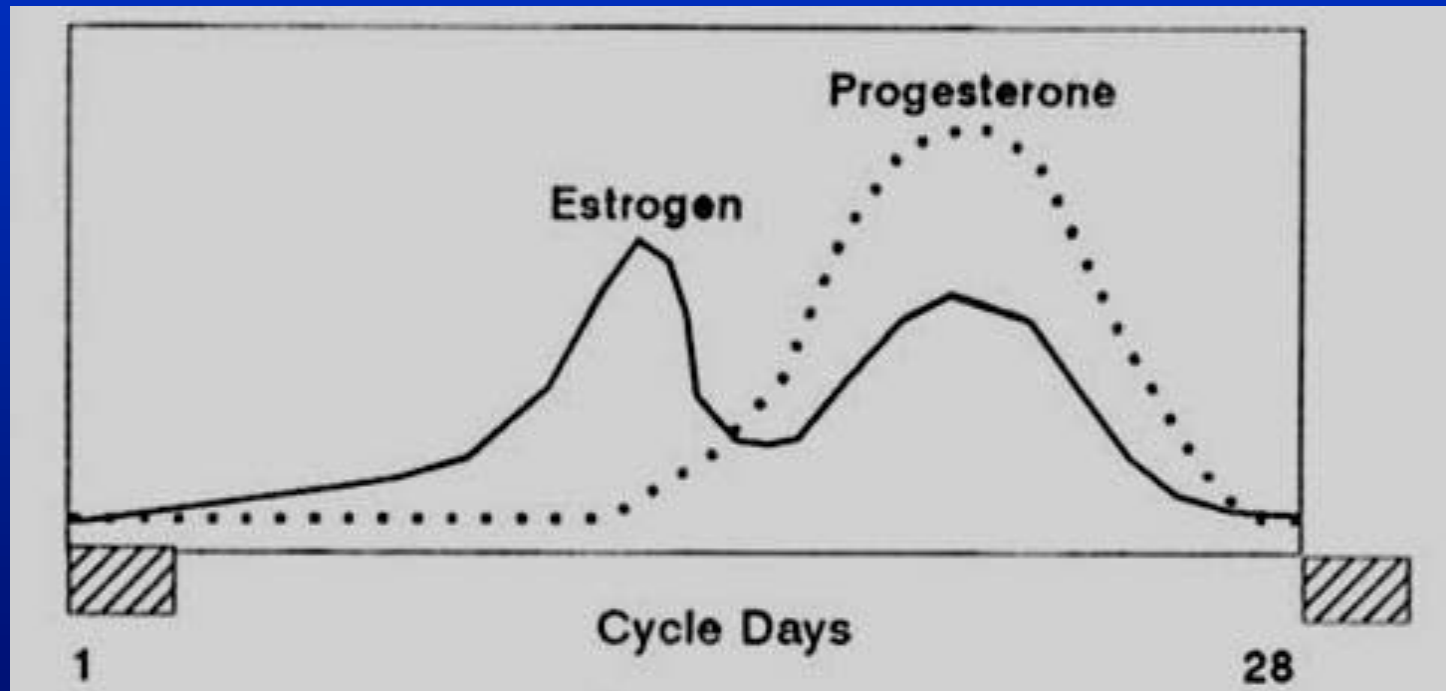
- All therapies that slow bone loss (**Anti-resorptive**) also decrease bone formation.
- With powerful osteoporosis medicines (like **aminobisphosphonates**) there are now new bone problems—*atypical femur fractures*
- With these powerful medicines—also some immune changes like *aseptic jaw necrosis*

Bone Loss Preventing
(anti-resorptive) agents
also
Decrease
Bone Formation!

Life Cycle of Bone—Young Women



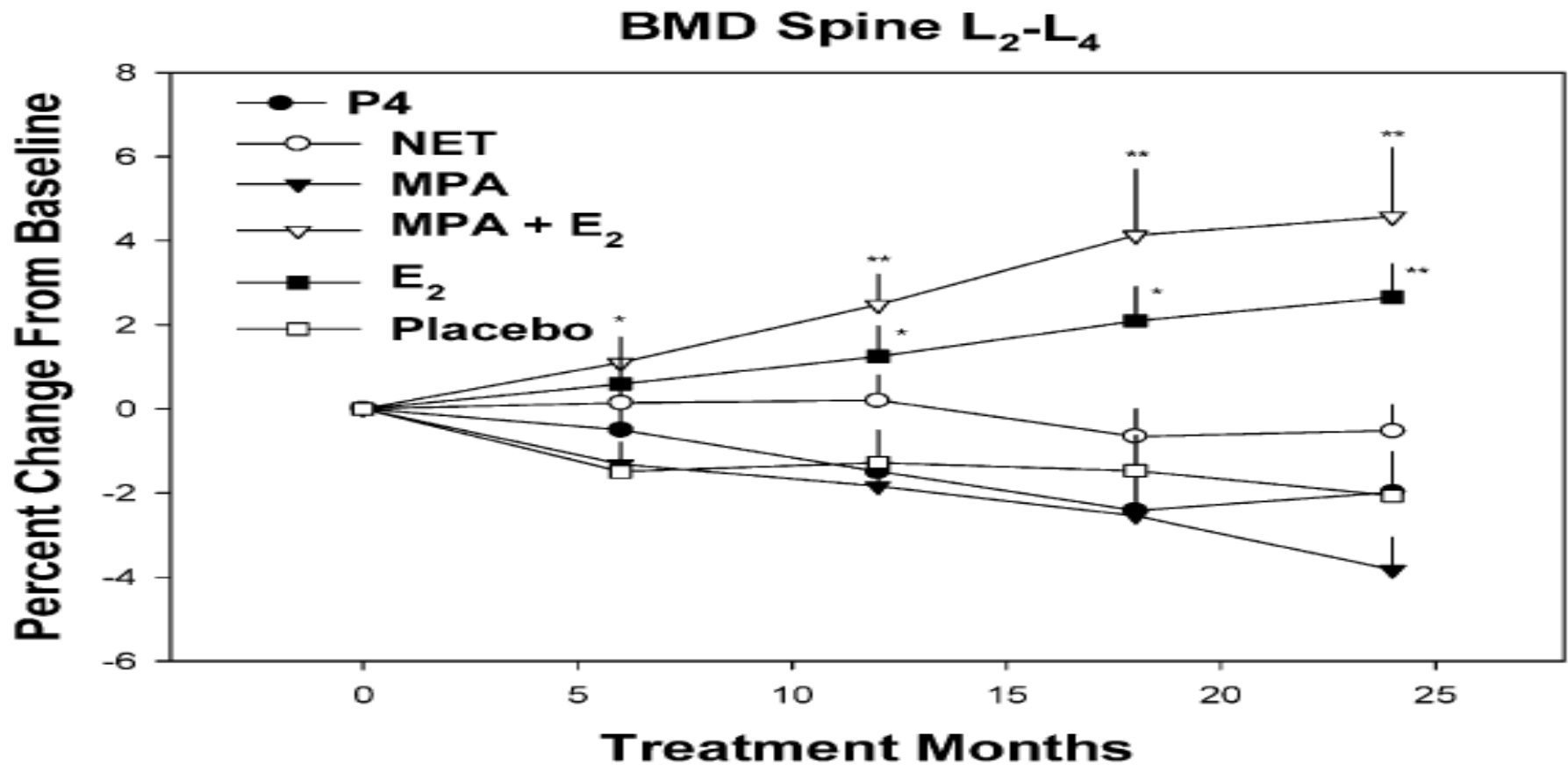
The Normal Menstrual Cycle—rising and falling Estrogen and Progesterone



Flow

Flow

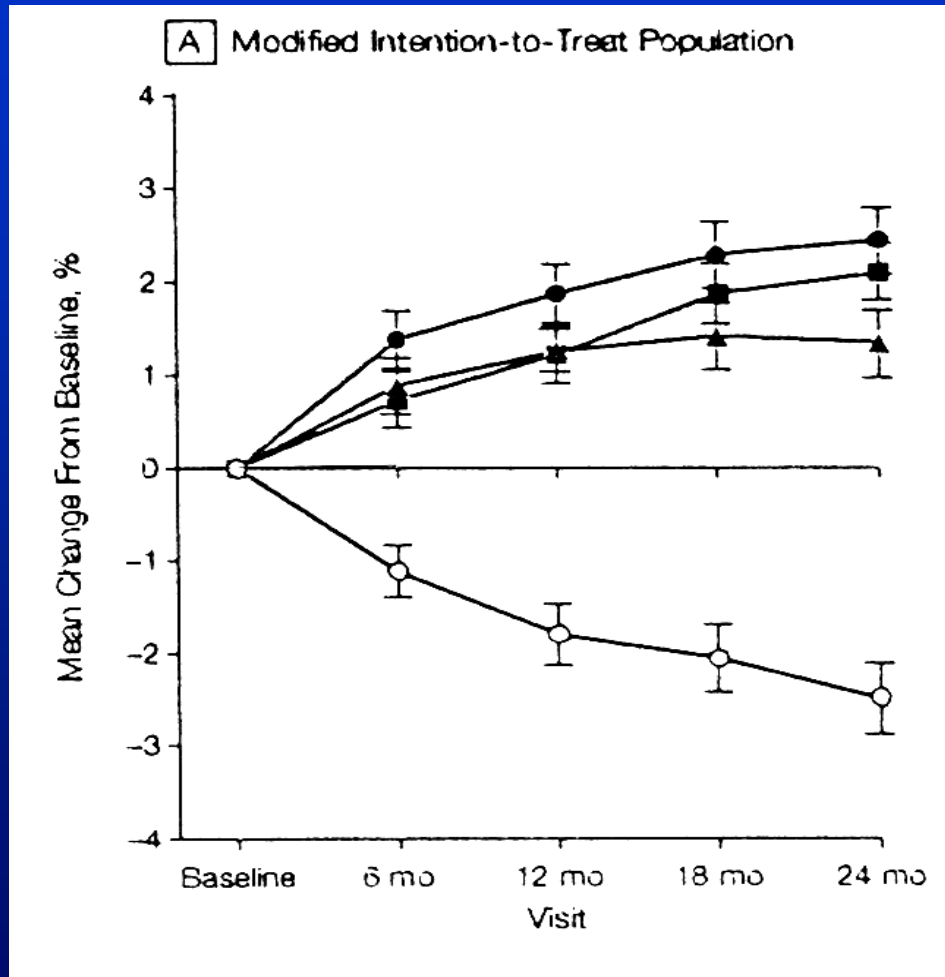
RCT of Hormones including Progesterone (P4 •) in women early in menopause



Progesterone alone does not
prevent bone loss if bone
resorption is ↑

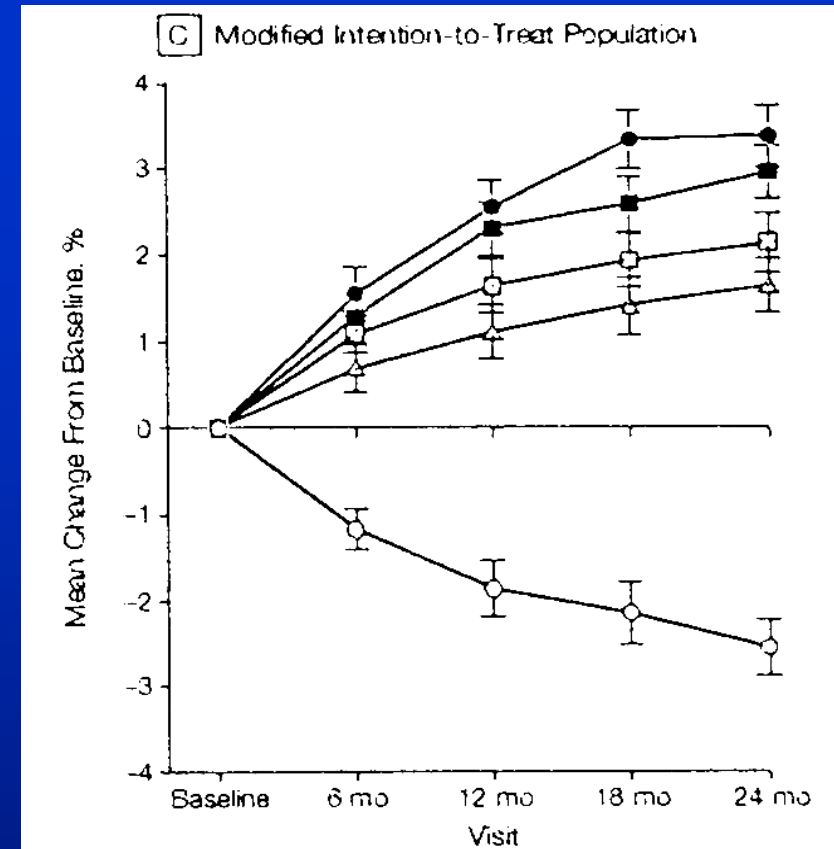
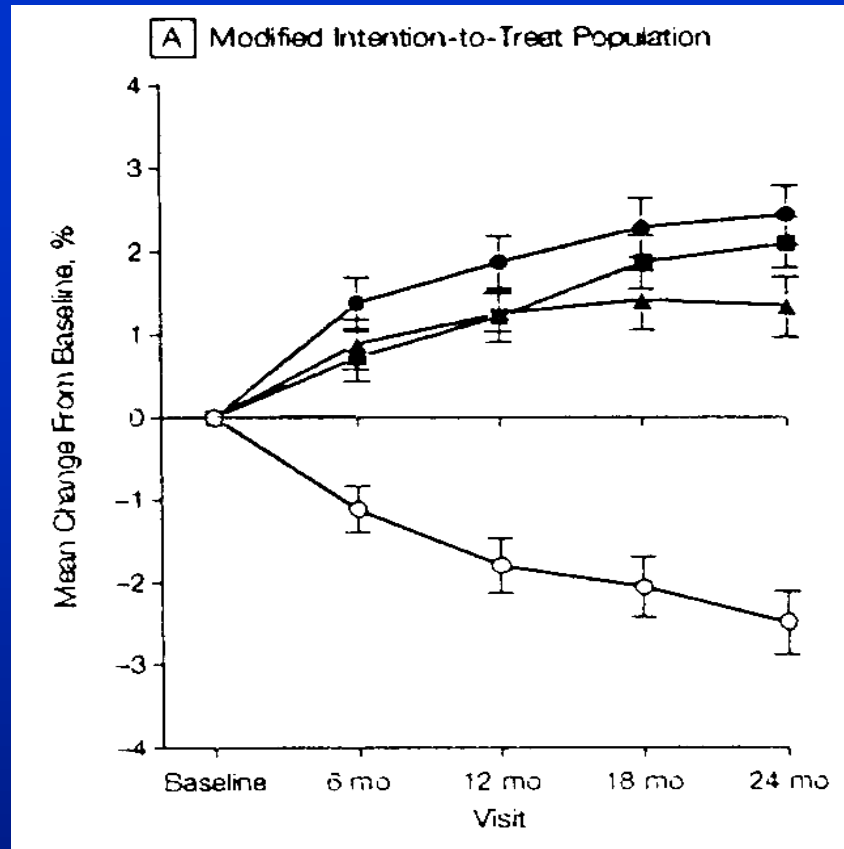
Women's HOPE trial Estrogen Therapy

Change in Spine DXA on estrogen alone = 2.3%



Estrogen stops
bone loss and
allows resorption
pits to fill

- CEE 0.625 mg/d
- CEE 0.45 mg/d
- ▲ CEE 0.3 mg/d
- Placebo



- CEE 0.625 MPA 2.5 mg/d
- CEE 0.45 MPA 2.5 mg/d
- CEE, 0.45 MPA 1.5 mg/d
- △ CEE 0.3 MPA 1.5 mg/d

Estrogen-alone

Lindsay R, *JAMA* 2002; 287:2673

Estrogen & Progestin

Comparison: Estrogen vs. E + P

Estrogen alone = $\uparrow 2.3\%$ over two years

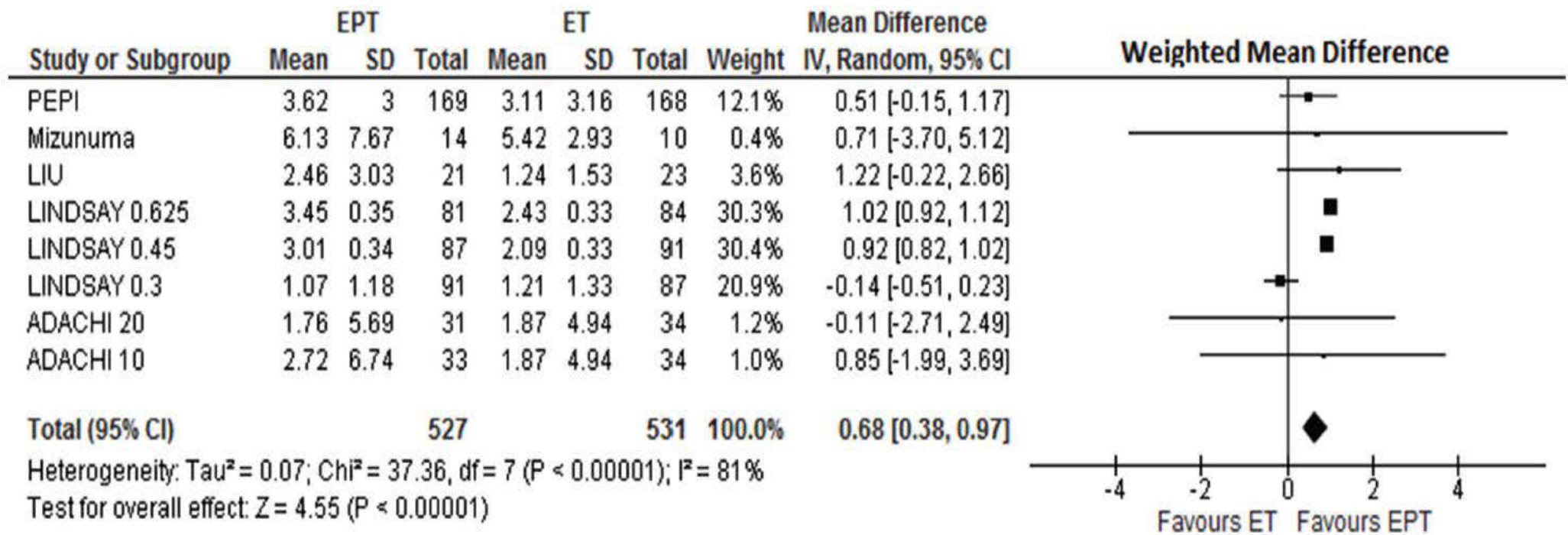
Significantly greater bone gain:

Co-therapy of Estrogen plus low dose daily

Progestin = $\uparrow 3.3\%$ over two years

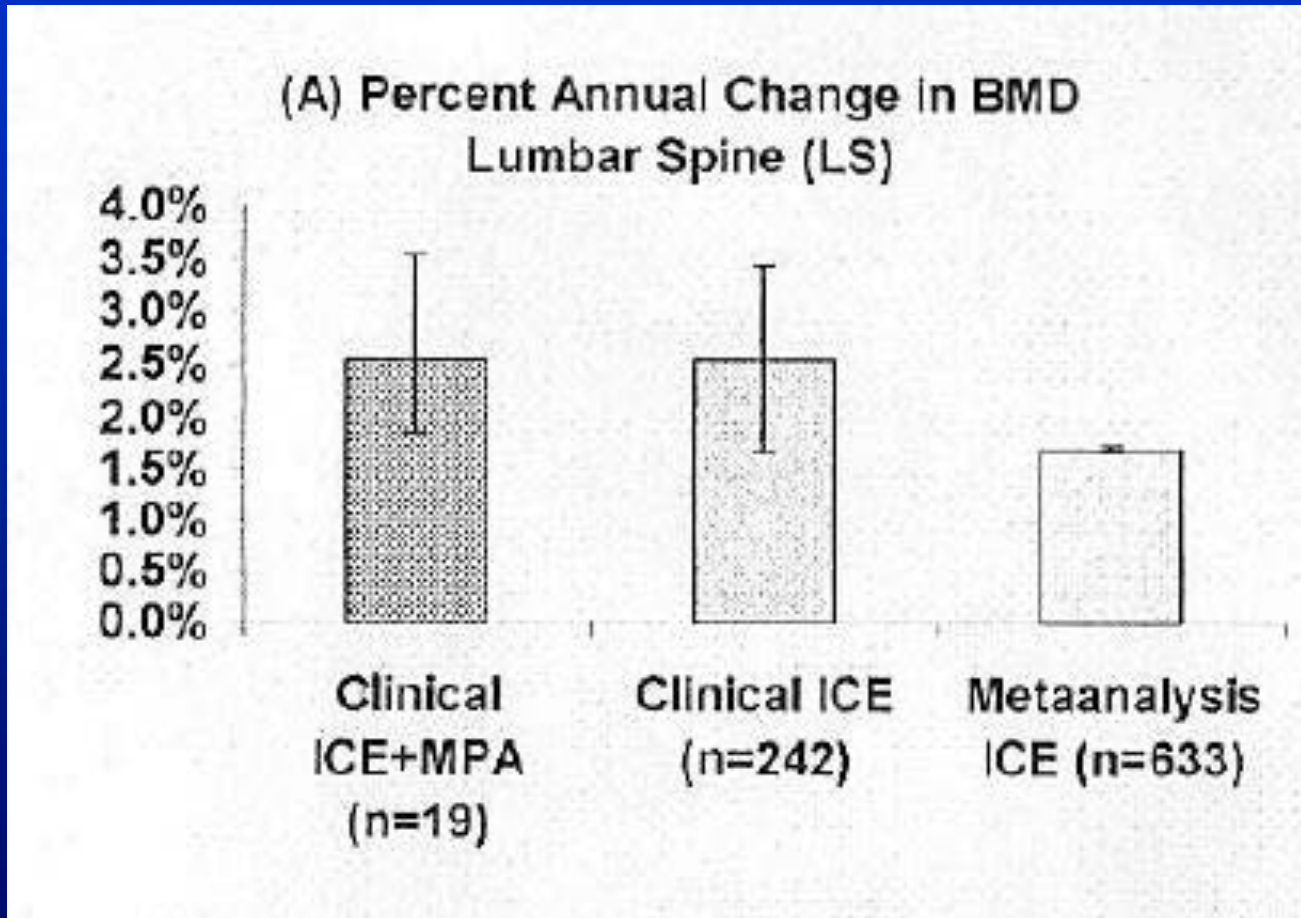
$P < 0.03$

Meta-analysis—Progestin /P4 adds to E2 bone benefit in menopause



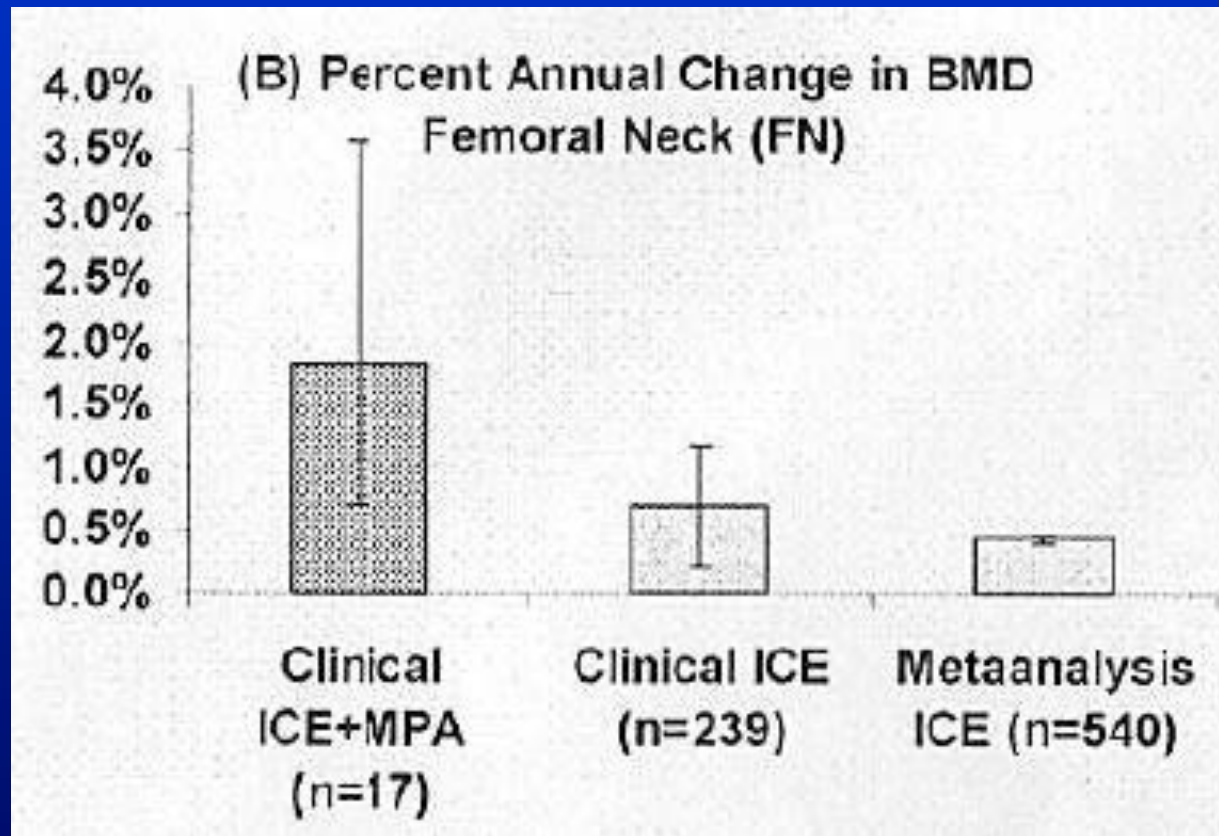
Prior *J Musculoskeletal Neuronal Interact* 2017;17(3):146-154

Does Co-Therapy of Progesterone with Bisphosphonates Work?



These are a co-therapy data are from a random sample of Prior's clinical charts of menopausal women treated with both progesterone/MPA and **etidronate** = ICE

Does Co-Therapy of Progesterone with Bisphosphonates Work?



These are a co-therapy data are from a random sample of Prior's clinical charts of menopausal women treated with both progesterone/MPA and **etidronate** = **ICE**

Bone Changes in Older Adulthood



ABCs of Osteoporosis Prevention



Activity



Easy-going



Brawny



Formation



Calcium



Good Habits



Vitamin D

Atypical Femoral Shaft Fractures— ? due to >5 y a-bisphosphonates ?





Questions?



Progesterone with Antiresorptives

What we have learned:

- ◆ Bone resorption-formation imbalance causes fractures—antiresorptives ↓ bone formation
- ◆ We know little about formation therapies & fracture prevention—except for PTH
- ◆ Progesterone ↑ formation but, when bone loss ↑, it works without (*visible*) benefit
- ◆ Progesterone added to estrogen-benefitted BMD gains—will likely add to fracture prevention. This needs testing. . .

CeMCOR

*The Centre for Menstrual Cycle
and Ovulation Research*

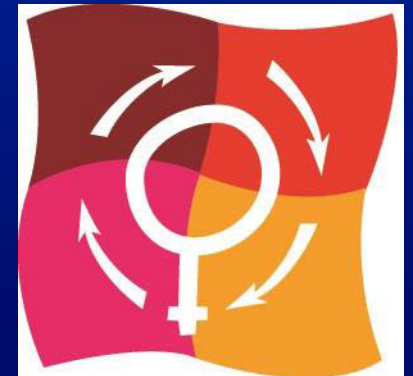
Centre for Menstrual Cycle & Ovulation Research



**WOMEN'S HEALTH
RESEARCH INSTITUTE
AT BC WOMEN'S**



www.CeMCOR.ca



JcPrior 2019