

# The menstrual cycle (From the Latin *menses* - month)

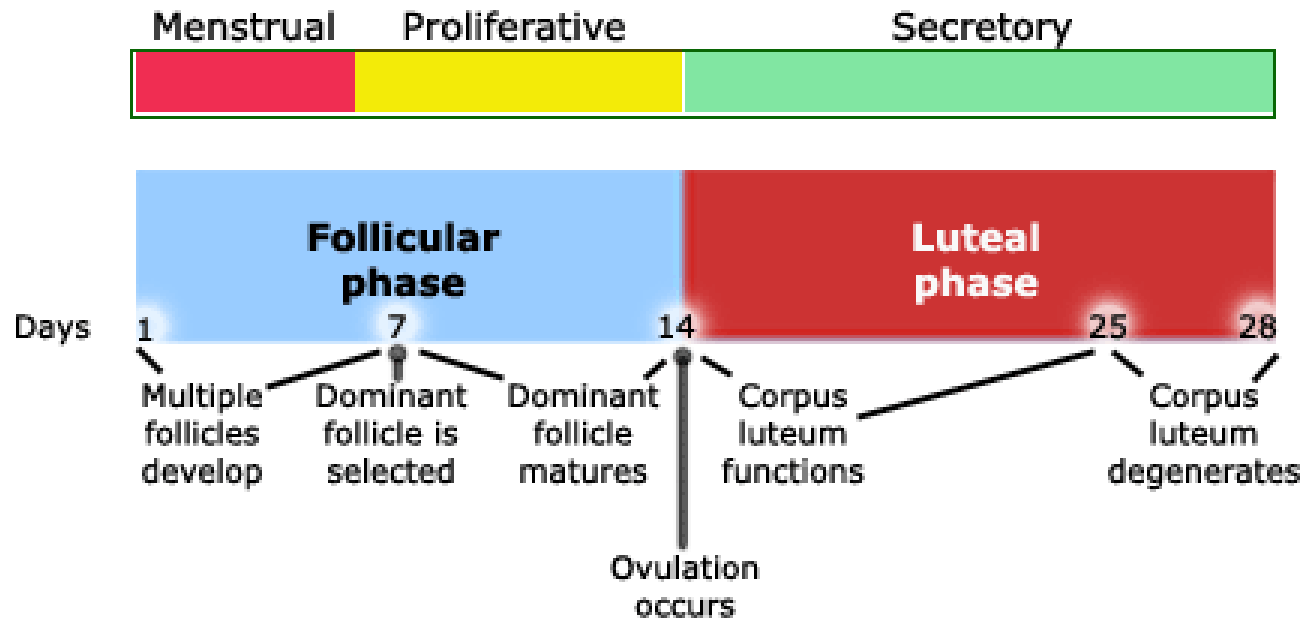


Figure 5.1

- Prior to day one, endometrium thickens under influence of **estradiol**.
- Progesterone** induces the appearance of specialized glycogen-secreting glands.
- Day 1** - first day of detectable vaginal bleeding - deterioration of uterine endometrium.
- Menses (bleeding)** begins when estradiol and progesterone very low in circulation, when the blood vessels supplying endometrium constrict reducing the blood supply.
- endometrium deteriorates, flows through the cervix into the vagina.
- Bleeding occurs for ~5 days during which, ovaries are endocrinologically rather inactive.

-Low estradiol and progesterone lead to increased pituitary FSH secretion (lack of –ve feedback loop).

-Also, decrease in non-steroidal ovarian *inhibin*, which selectively inhibits secretion of FSH, may contribute to elevation in FSH release.

-Under influence of FSH, cohort of ovarian follicles develop. FSH stimulates granulosa cells of follicles to proliferate -> production of estrogen, which further stimulates granulosa cell proliferation.

-Day 8, one follicle becomes dominant and committed to further development. Remaining follicles begin to degenerate by atresia. ***In humans, how one follicle becomes dominant still unknown.***

-Dominant follicle produces increasingly more estradiol, which becomes important in late stages of cycle.

- increasing estradiol stimulates uterine endometrium proliferation.

-By day 13, the endometrium very thick. Estradiol induces production of endometrial ***progesterone receptors***.

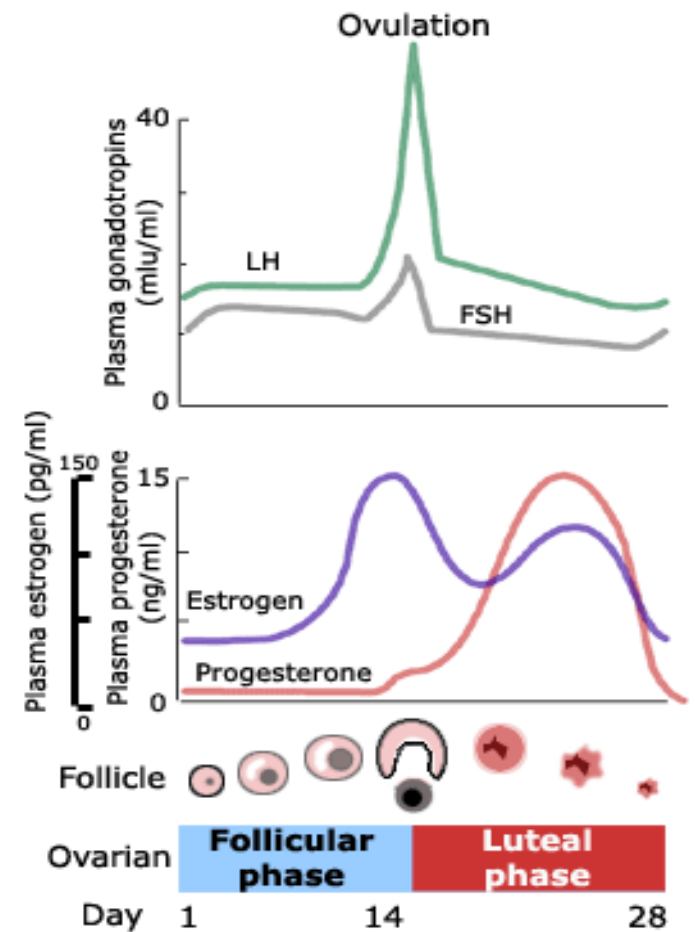


Fig. 5.2

# Estradiol effects on brain and pituitary

## ***Moderate estradiol concentrations:***

- negative feedback on FSH release
- stimulate** synthesis of LH by pituitary and increase sensitivity of pituitary to GnRH -> stimulates LH synthesis.

***Note, although moderate estradiol concs. stimulate LH synthesis, they inhibit LH release. Therefore, LH accumulates to high levels within pituitary.***

## ***High estradiol concentrations.***

- Under influence of developing follicle*** estrogen concs. continue to build.

## ***Elevated estrogen concs. stimulate LH release - LH surge***

- ~day 14 (small increase in FSH release also occurs).
- Stimulation of LH synthesis by estradiol and increased sensitivity of the anterior pituitary to GnRH leading to increased LH synthesis by anterior pituitary *known as estrogen +ve feedback control mechanism.*

***-Thus, estrogens exert -ve feedback - decreased GnRH and LH release and +ve feedback - increased sensitivity of anterior pituitary cells to GnRH and increased LH synthesis.***

-Meanwhile, at the ovary the follicle has become huge. *The sudden surge of LH causes the follicle to rupture (mechanism unclear) and the ovum is ejected.*

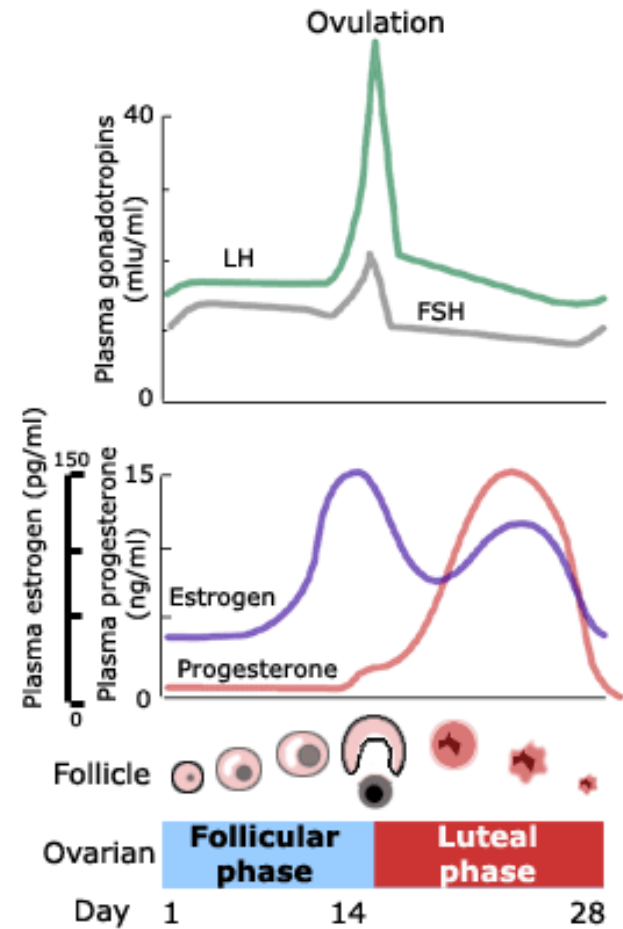


Figure. 5.3

# Feedback mechanisms of steroid hormones on gonadotropin action

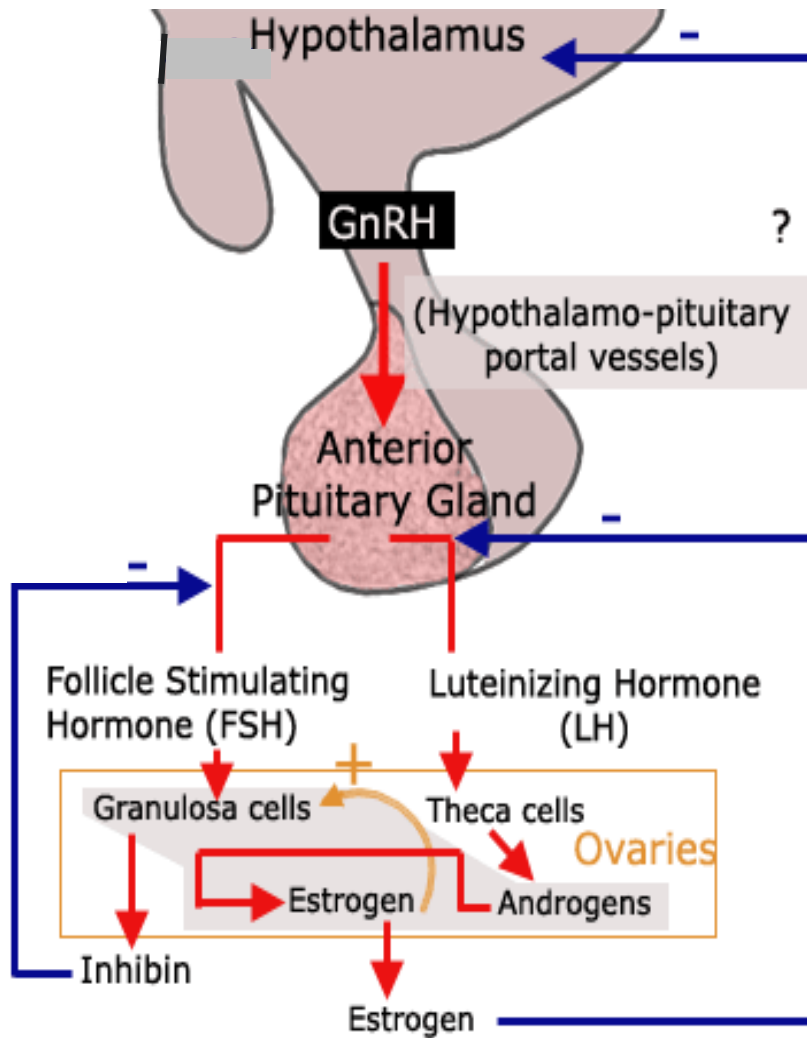


Figure 5.4

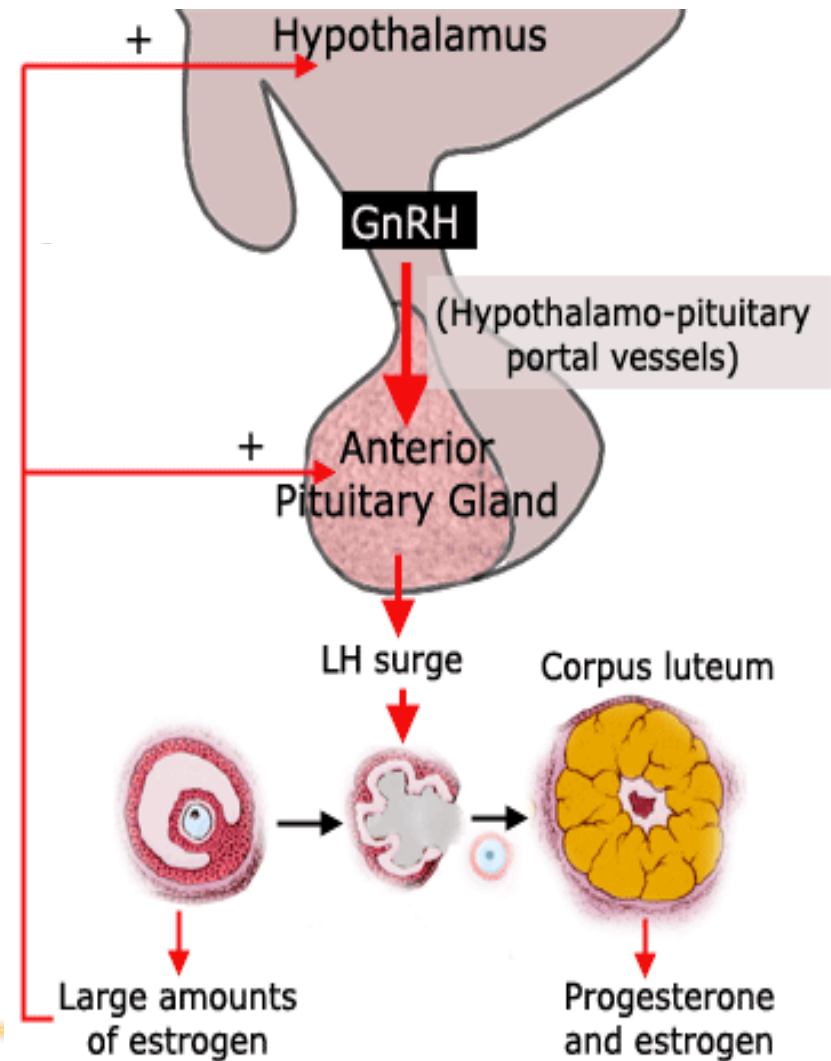


Figure 5.5

## Oral contraceptives.

Pills contain estrogen and progesterone - maintain moderate circulating levels of estrogen and progesterone suppress the *release* of LH and FSH from the pituitary and prevent ovarian follicles from maturing and being ovulated.


➤ 99 % success, provided that the pill is taken daily for 21 consecutive days with seven days of no medication that would induce menstruation.

## Corpus Luteum.

Under the influence of LH the follicle becomes *corpus luteum* -produces large amounts of estradiol and progesterone induce endometrial growth of the uterus. In addition, under the influence of progesterone the endometrium becomes glandular. *The endometrium is now fully prepared to receive and support the development of a growing embryo.*

## Luteal Phase

No fertilization - egg degenerates, corpus luteum degenerates (*luteolysis*). Lasts a constant 14 days, known as the *luteal phase* of cycle since steroids produced by corpus luteum dominate. After 14 days in absence of implantation corpus luteum degenerates, steroid levels drop, uterine endometrium degenerates, menstruation begins and pituitary starts to increase its secretion of FSH, and we are back to the beginning of the cycle.



# Fertilization and implantation

-At ovulation, unfertilized egg is taken by the *fimbria* of the oviduct (or *fallopian tube*) and is being propelled towards the lumen of the uterus.

-If sexual intercourse takes place around this time, some spermatozoa deposited in the vagina will travel as far as the oviduct and one of these will fertilize the egg.

-Egg starts dividing to the stage of *blastocyst* during its transport down the oviduct into the uterine lumen.

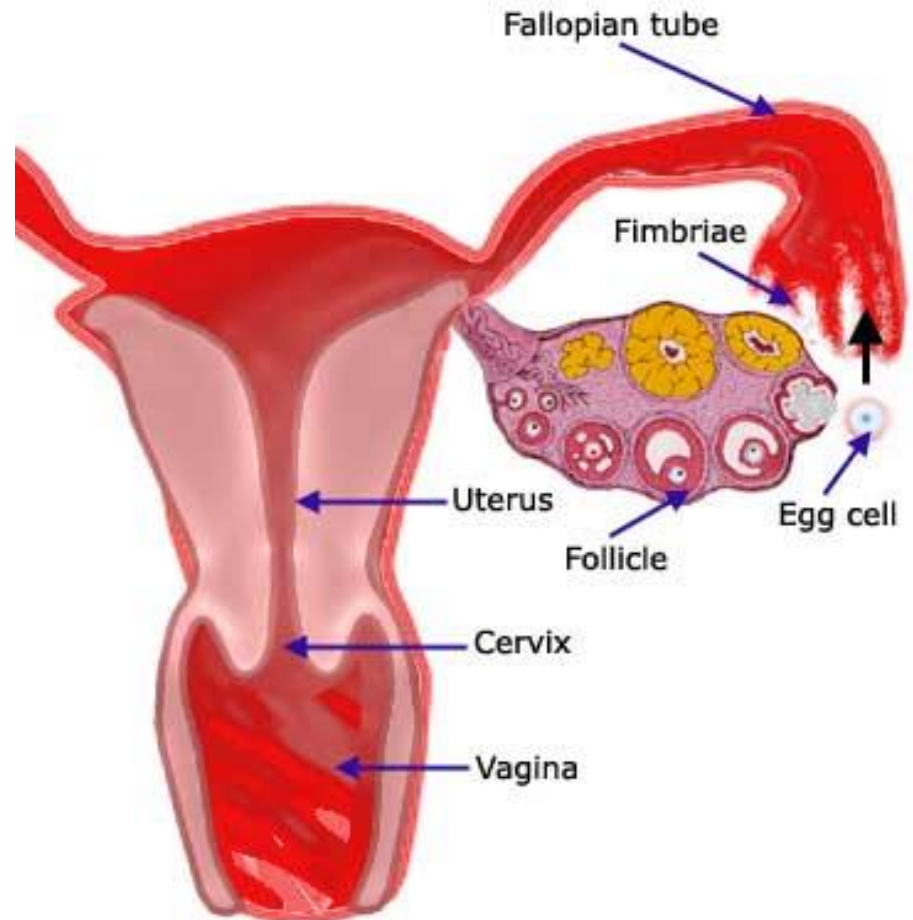


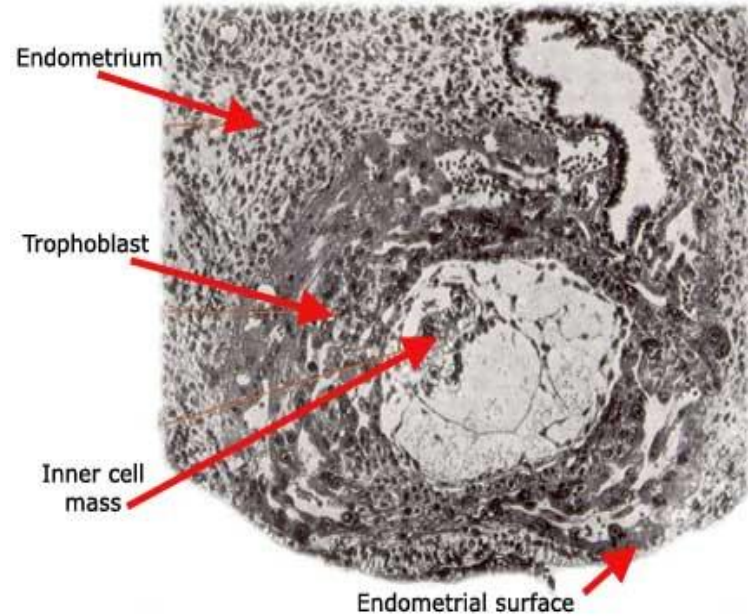
Figure 5.6

# AFTER IMPLANTATION

Figure 5.7

Blastocyst differentiates into **trophoblast** (becomes the **placenta**) and the **inner cell mass** (which will form the **embryo**). Trophoblast invades uterine mucosa -> embedding of developing embryo in endometrium.

Around time of implantation, trophoblast starts to synthesize *human chorionic gonadotropin (HCG)* which has LH-like properties and stimulates the corpus luteum to continue secreting gonadal steroids.



After about *12th week* of pregnancy endocrine function of corpus luteum taken over entirely by placenta, which together with developing fetus forms the **fetoplacental unit**.

Close functional interdependence between the fetal and maternal compartments, and **fetal liver** acquires an important function in the synthesis of estriol (an estrogen).

-Placenta also produces **human chorionic somatotropin**, **progesterone**, and **relaxin**.

HCG quickly appears in blood and urine where it forms the basis for the biological or immunological pregnancy test.

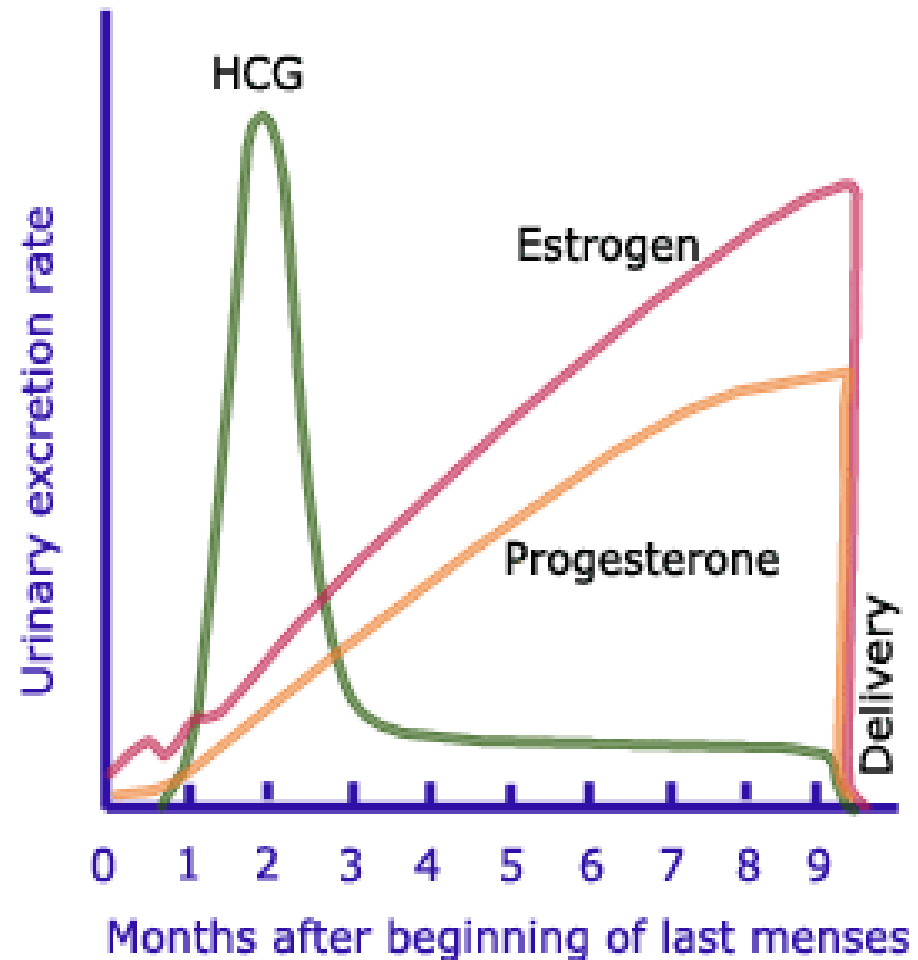


Figure 5.8

# Lactation

The secretion of milk by the breast (mammary glands) is termed ***lactation***. Normal mammary development required for lactation - under endocrine control.

## Mature non-pregnant mammary glands (Ductal)

- With onset of puberty under the action of increasing levels of estrogens, marked enhancement of duct growth and duct branching but relatively little development of the **alveoli**.
- Progesterone stimulates growth of alveoli.
- However, most breast enlargement due to *fat deposition* under the glandular tissue.

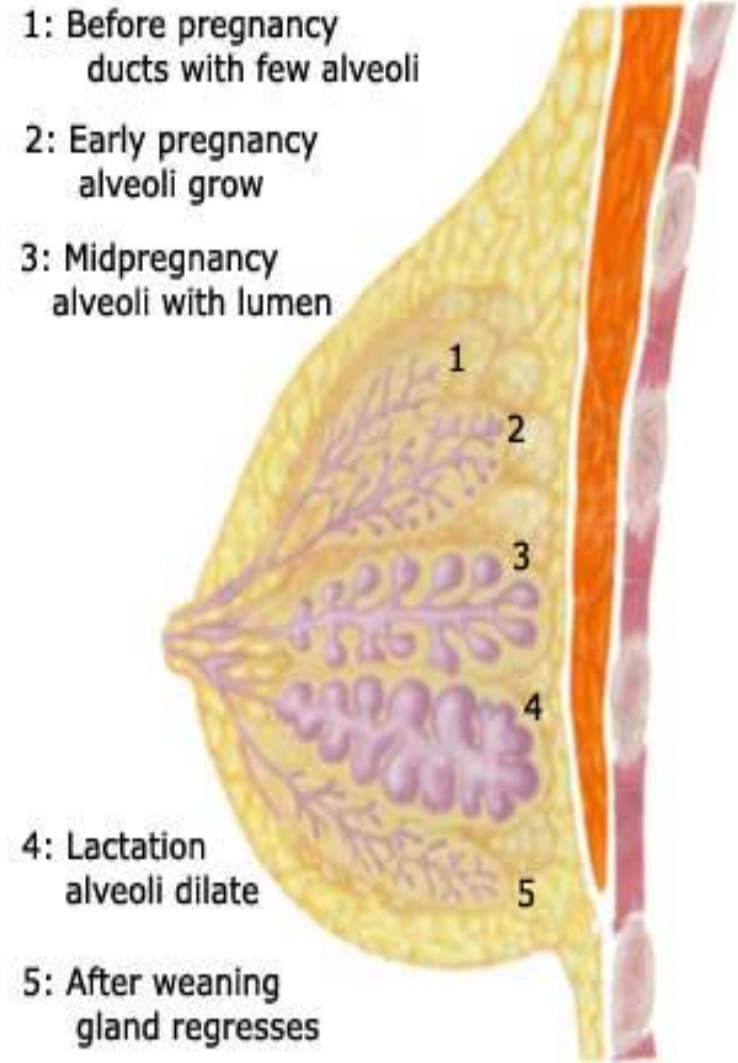


Figure 5.9

## Pregnant mammary gland (Lobulo-alveolar)

Under influence of several hormones, including estrogen, progesterone, **prolactin**, **human placental lactogen**, both ductal and alveoli structures fully develop.

Milk production during pregnancy controlled by **prolactin**, however high estrogen levels inhibit secretion.

## Lactating mammary gland

After parturition, levels of estrogen decrease, while levels of **prolactin** remain high.

**Prolactin** induces milk synthesis and the alveoli secrete milk, filling the ducts.

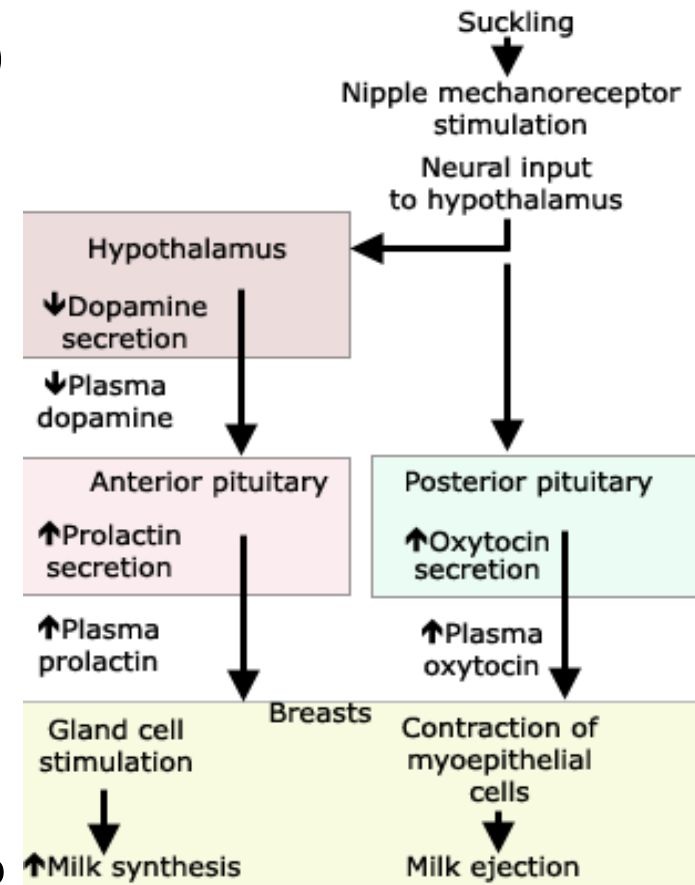


Fig. 5.10

**Nursing:** under action of **oxytocin**, ducts contract to cause **milk ejection**.

**Prolactin** from anterior pituitary and **oxytocin** from posterior pituitary stimulated by afferent fibers (nerves) from nipple. Prolactin sustains milk production, oxytocin causes milk letdown or ejection.

**Milk:** water, protein, fat and carbohydrate lactose and antibodies. *However, infectious agents such as viruses and drugs may be transmitted from the mother to infant through breast milk.*

## **Lactational amenorrhea:**

*Maintained nursing stimulates prolactin production, which inhibits the secretion of FSH and LH.* This blocks the resumption of the reproductive cycle. Actually, nursing used to be a natural method of contraception. However, the intensity and frequency of suckling appears to be an important parameter for the maintenance of the blockade on the reproductive cycle and ovulation. Thus, if suckling is not frequent then ovulation, and pregnancy, may occur.

## **Menopause - loss of ovarian steroid production:**

-At the end of reproductive period, most ovarian follicles have disappeared by atresia and a few hundred have been ovulated during successive menstrual periods.

*-Depletion of follicles results in loss of capacity for steroid (estrogen and progesterone) hormone production by the ovary.*

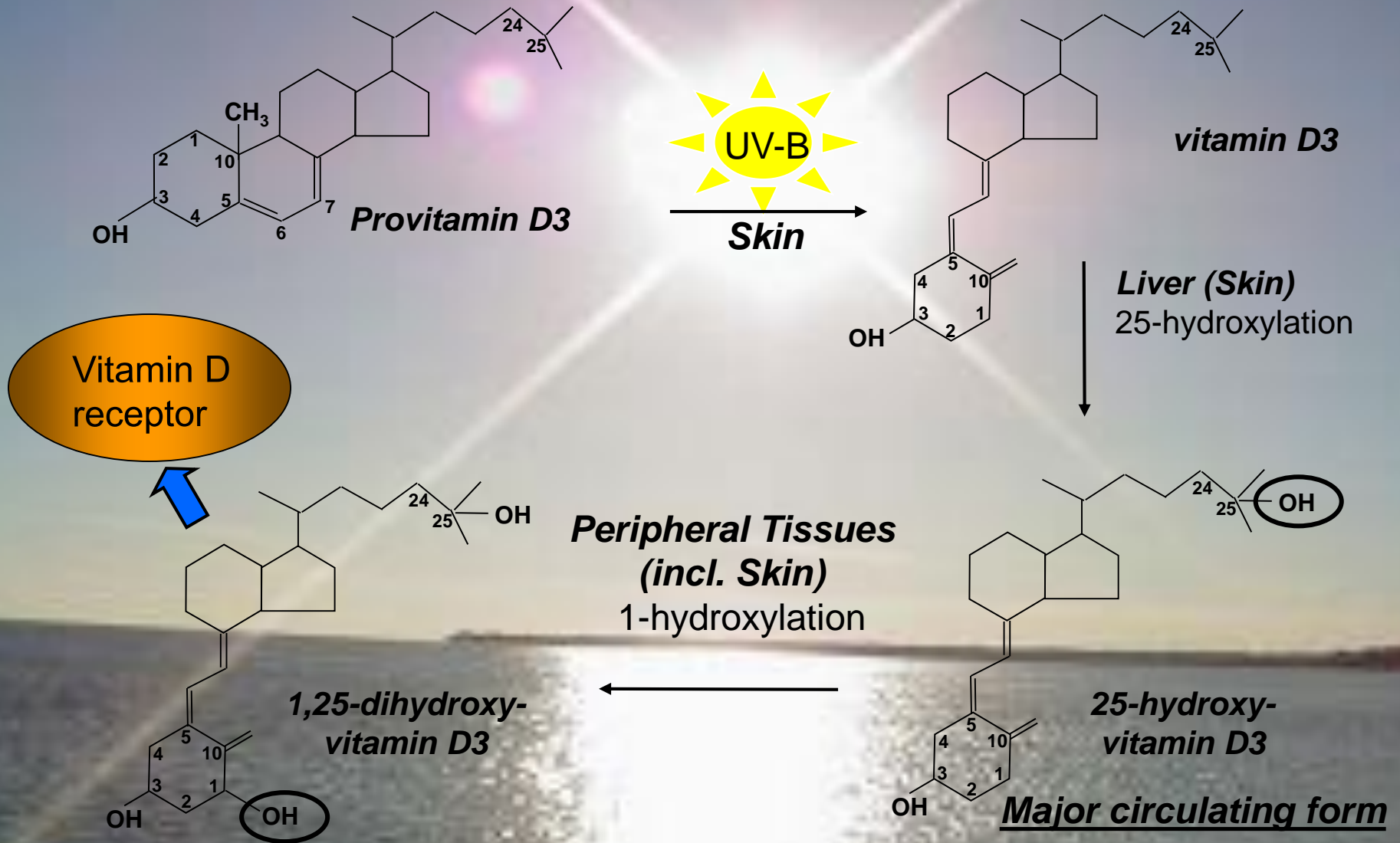
-Lack of estrogens often induces number of symptoms: hot flashes, dry vagina, restlessness, bone loss (osteoporosis - long term), etc.

-Cessation of ovarian steroid hormone production eliminates –ve feedback loop and rise in levels of plasma gonadotropins FSH and LH. *The constantly high levels of plasma FSH is most reliable indicator for onset of menopause.*

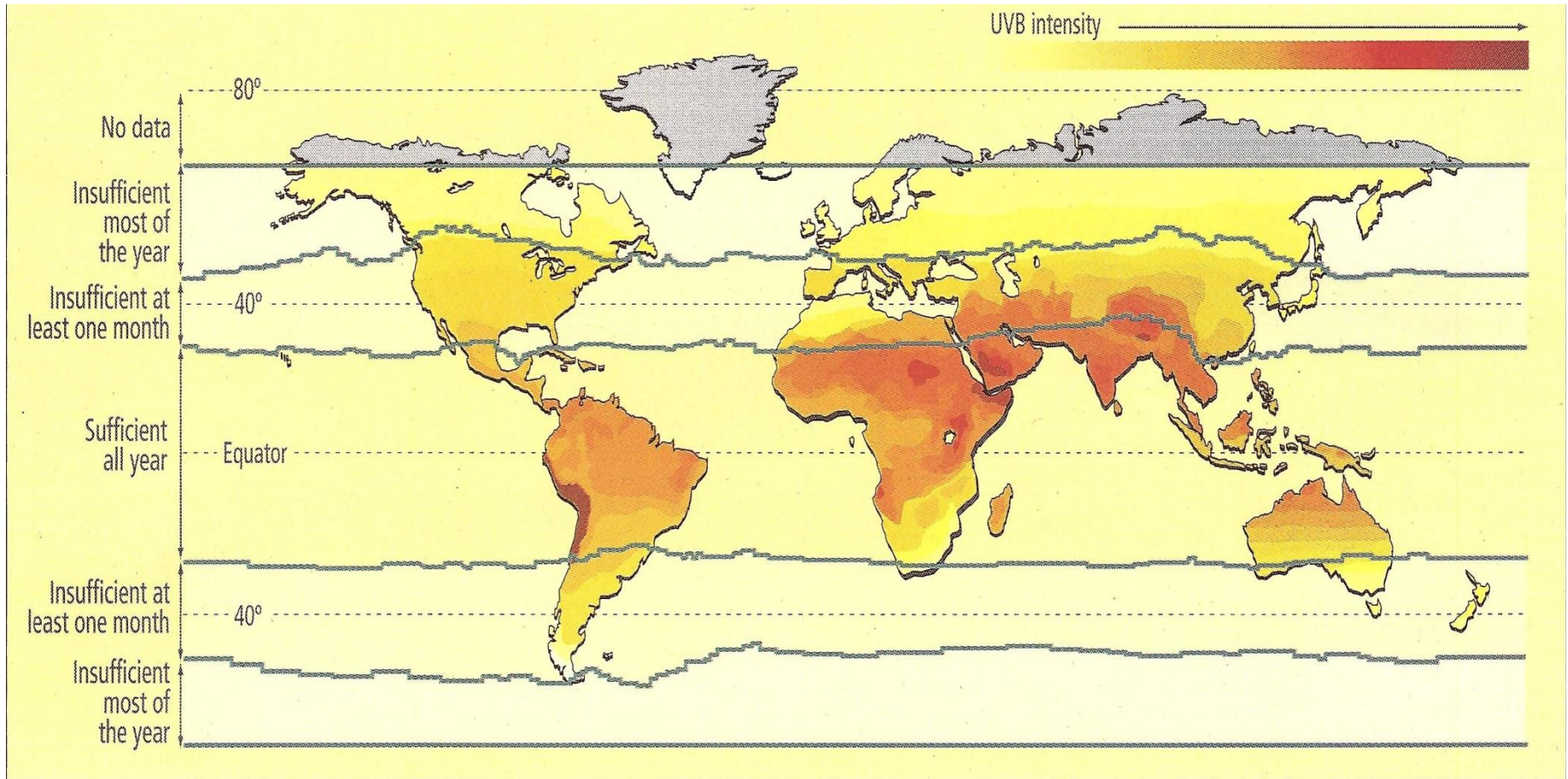
-Symptoms caused by estrogen lack respond readily to estrogen replacement therapy. However, because follicular depletion is primary cause of menopause, fertility cannot be restored by steroid replacement therapy.

# **New insights into vitamin D physiology**

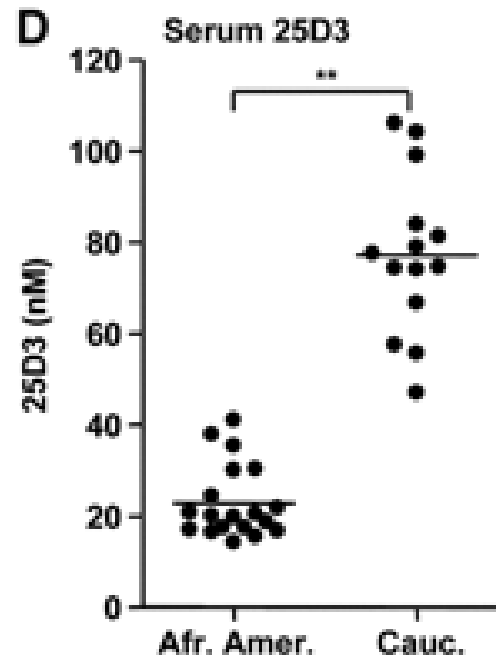
# 1,25-dihydroxyvitamin D3 Biosynthesis



# Vitamin D Winter

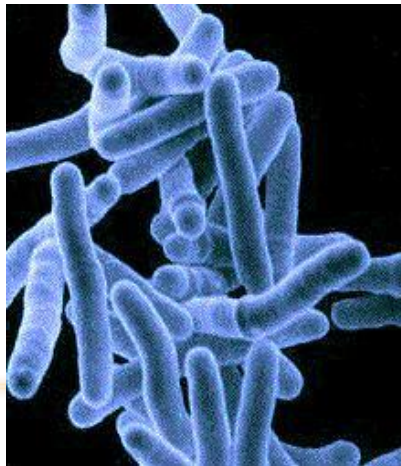


## Levels of major circulating vitamin D metabolite, 25-hydroxyvitamin D<sub>3</sub>, in African and Caucasian Americans.



# Three types of diseases have demonstrated north-south gradients

1. Certain types of cancers (in particular digestive cancers and leukemias).
2. Autoimmune diseases: e.g. multiple sclerosis.
3. Infectious diseases.

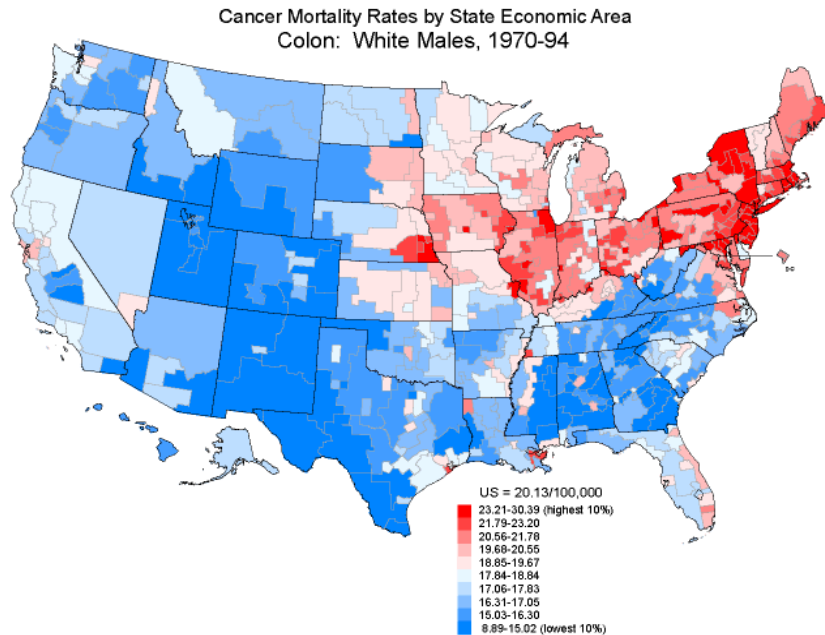


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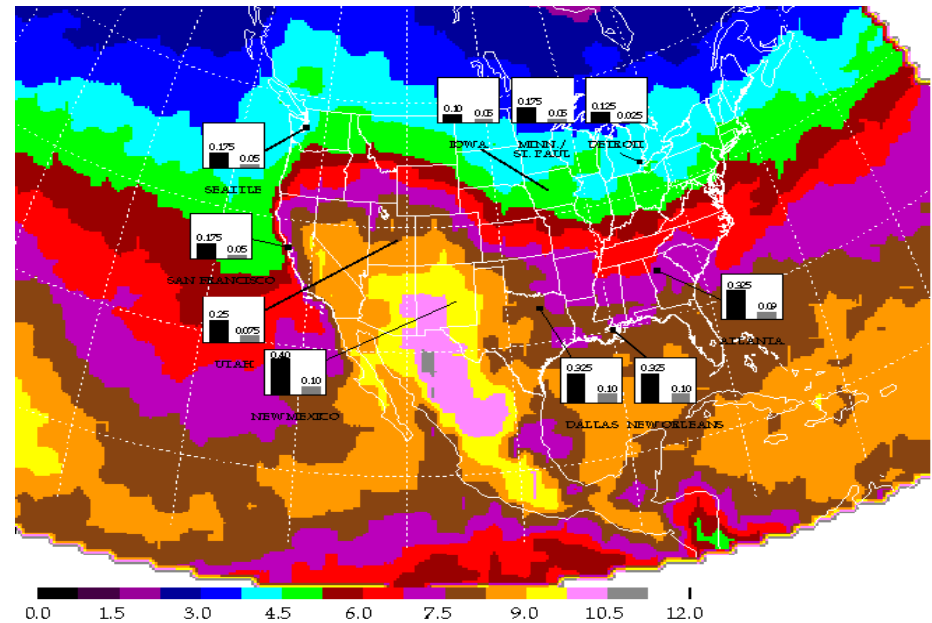


Sanitorium ~1920

## Colon cancer rates and summer surface UVB levels.



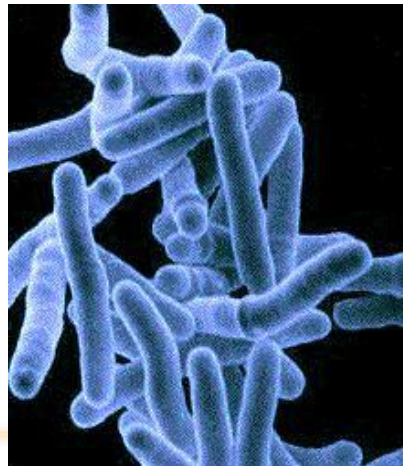
*Colon Cancer rates 1970-94, White males*



*Spectral UVB exposure kJ/m July, 1992*

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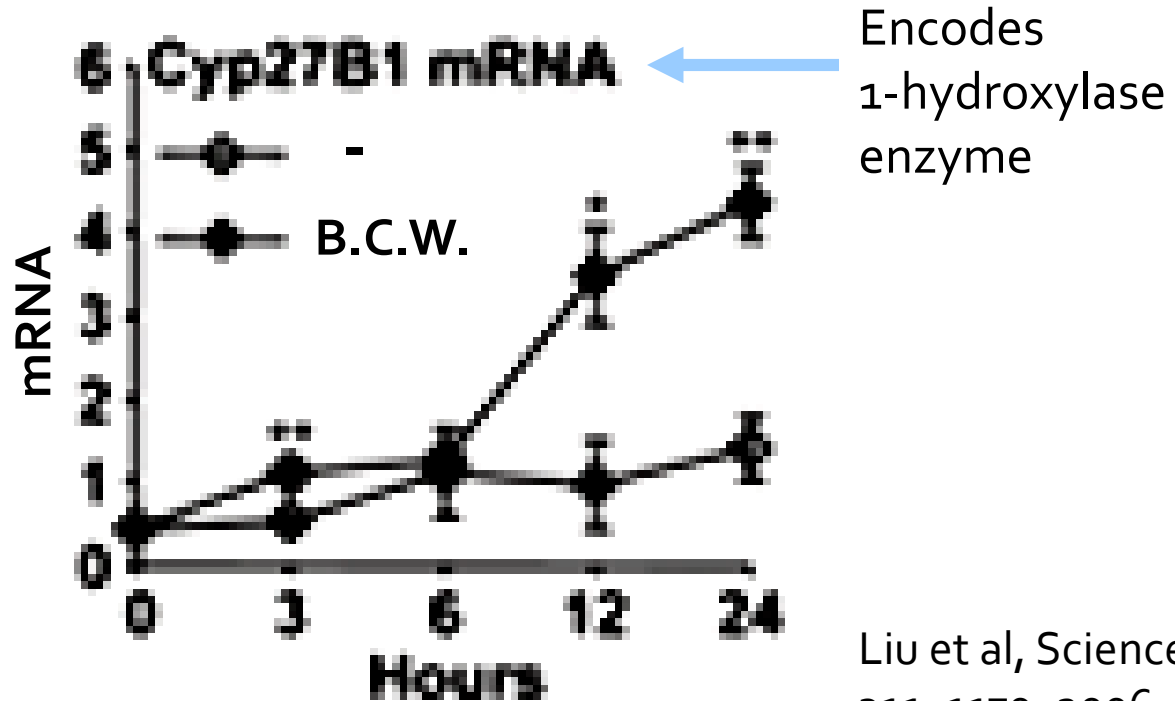
TB bacilli



Sanatorium ~1920

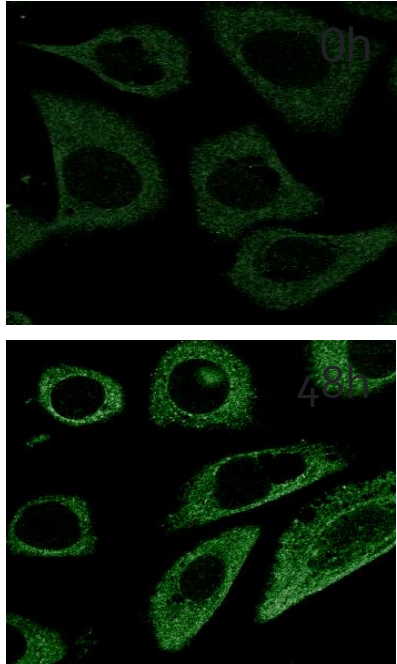
Cells of the immune system become responsive to  $25D_3^*$  after sensing the presence of bacterial cell wall (B.C.W.) components.

\*An example of the circulating precursor determining hormonal status and not the hormone itself

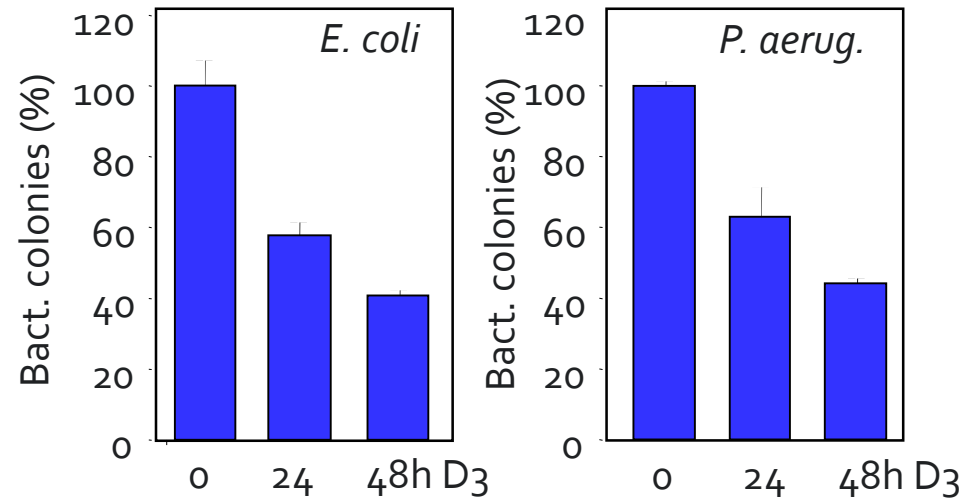


Liu et al, Science,  
311, 1170, 2006

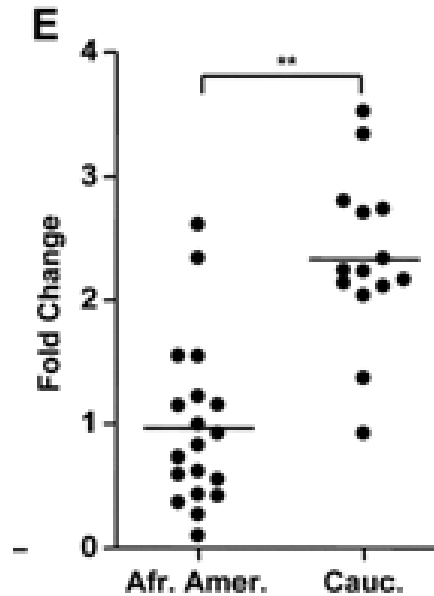
Treatment of cells with 1,25-dihydroxyvitamin D<sub>3</sub> induces secretion of antibacterial activity in the form of antimicrobial proteins.



48 hour 1,25-dihydroxyvitamin D<sub>3</sub> treatment of cells in culture increases levels of antimicrobial proteins inside cells



# Stimulation of antimicrobial peptide gene transcription by serum from African and Caucasian Americans.



Liu et al, Science 311, 1770, 2006