

The simplest form of reproduction is cellular reproduction. Single celled organisms can use mitosis to reproduce the entire organism and increase the specie's numbers, but multicellular, organisms including man, use mitotic cell division to grow, repair, and replace **somatic** cells and tissues in the body. **Mitosis** is employed from the first division of the fertilized egg (zygote) to the development and maturation of all somatic cells and tissues. The cells it produces are all genetically identical, but they differentiate to become varied in structure and function and employ only the genes necessary for those specific structures and functions. If organisms only reproduced by mitosis, i.e. asexually, they would all be genetically identical, and vulnerable to any disease that came along to which the population was not resistant.

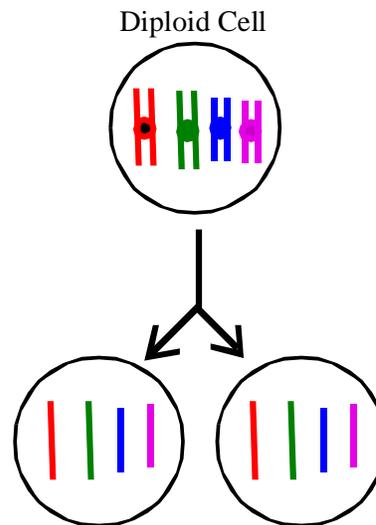
Sexual reproduction has evolved to provide genetic variability within the population. Even single celled organisms employ sex to maintain their genetic variability. And for complex organisms such as humans, sexual reproduction is the only form, future cloning notwithstanding! Sexual reproduction employs not a splitting of cells as in mitosis, but a union of cells from two different organisms (usually) in a process called **fertilization**. In order for this to occur **gametes** (sex cells, i.e. sperm and eggs) must be produced which have half the chromosome number as the somatic cells, so that when fertilization brings two such cells together the normal chromosome number is produced in the **zygote** (fertilized egg). We call this number **haploid** and the number of chromosomes in the somatic cells **diploid**.



## Cellular Reproduction

Mitosis – exact duplication of genetic material to produce daughter cells which are genetically identical to parent cell.

Produces all somatic cells of the body; all cells except gametes (sperm and eggs).



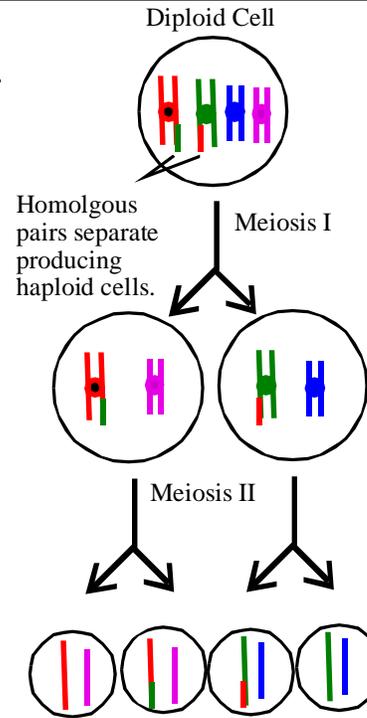
**Mitosis** produces all the **somatic cells** of the body (non-gametes), and they are all genetically identical.



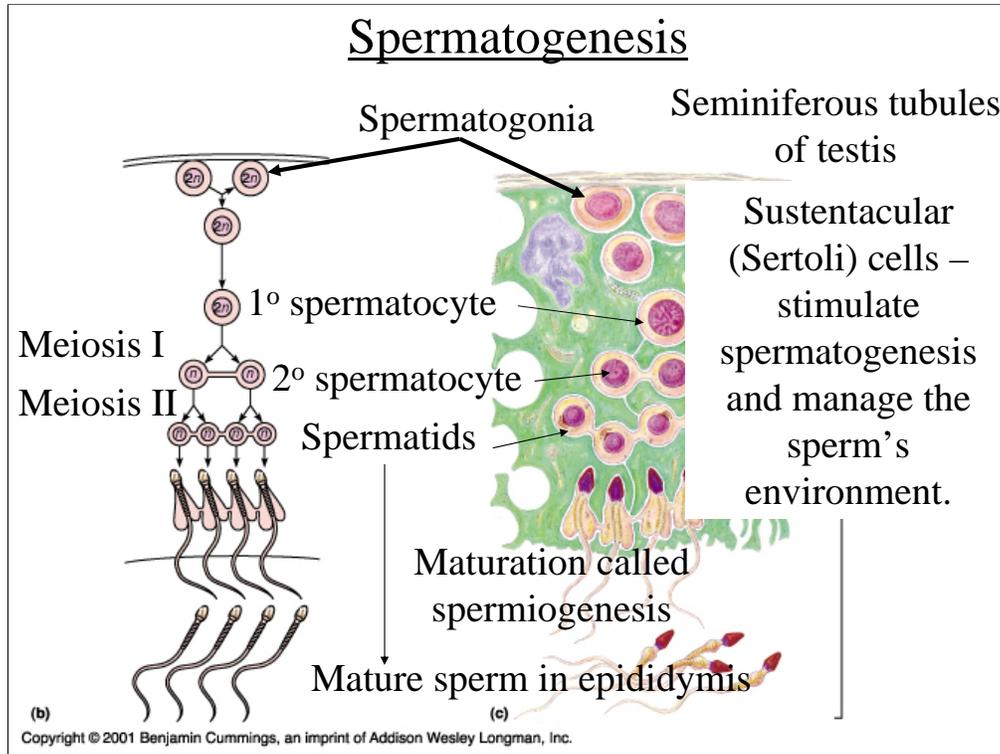
## Meiosis

Meiosis – division which reduces the number of chromosomes to produce haploid gametes.

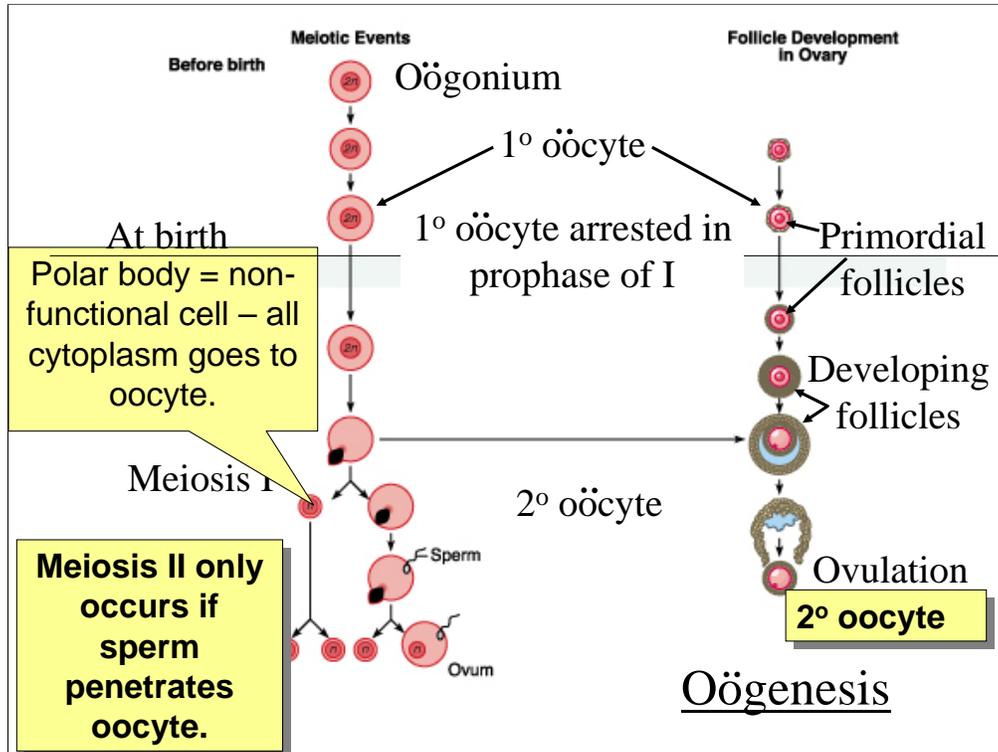
- Two division phases.
- Homologous pairs separate.
- Crossover magnifies the genetic variability.



The division process which produces haploid cells is called **meiosis**. In fact, not only must the number be half in the gametes, it must be a specific half, namely one of each **homologous pair** of chromosomes. Each pair consists of chromosomes having the same genetic loci or genetic characteristics represented. If proper separation of these homologs fails to occur (called non-disjunction), the resulting zygote can have too many or too few chromosomes. For example, Down's Syndrome results from three of chromosome number 21. Meiosis occurs in two division phases. In the first division the homologs separate producing two haploid cells. Since there are 23 homologs with a choice of 2 for each, the number of different possible combinations of these in the haploid cells is  $2^{23}$  or 8 million. In practice there are many times this because the homologs cross over and exchange parts (synapsis) in prophase of meiosis I, changing the assortment of the genes. In meiosis II, the chromatids of each chromosome separate in a process reminiscent of mitosis. The potential number of gametes is four for each meiosis, but that varies in practice as seen below.



The process of sperm formation occurs in the **seminiferous tubules** (See **Figure 28.3**). A man is born with stem cells or **spermatogonia** which have the potential to produce sperm. These cells divide continuously throughout the man's life producing more stem cells and, simultaneously, cells which undergo spermatogenesis. Spermatogenesis consists of two parts: meiosis which produces haploid pre-spermatozoa called **spermatids**, and **spermiogenesis** which is the maturation of these spermatids to produce mature sperm. **Sustentacular cells** manage the process in the seminiferous tubules, maintaining the environment of the spermatocytes and secreting ABP (Androgen Binding Protein) that, in combination with testosterone, stimulates the completion of spermatogenesis. Spermiogenesis begins in the seminiferous tubules, but is usually completed in the **epididymis** .

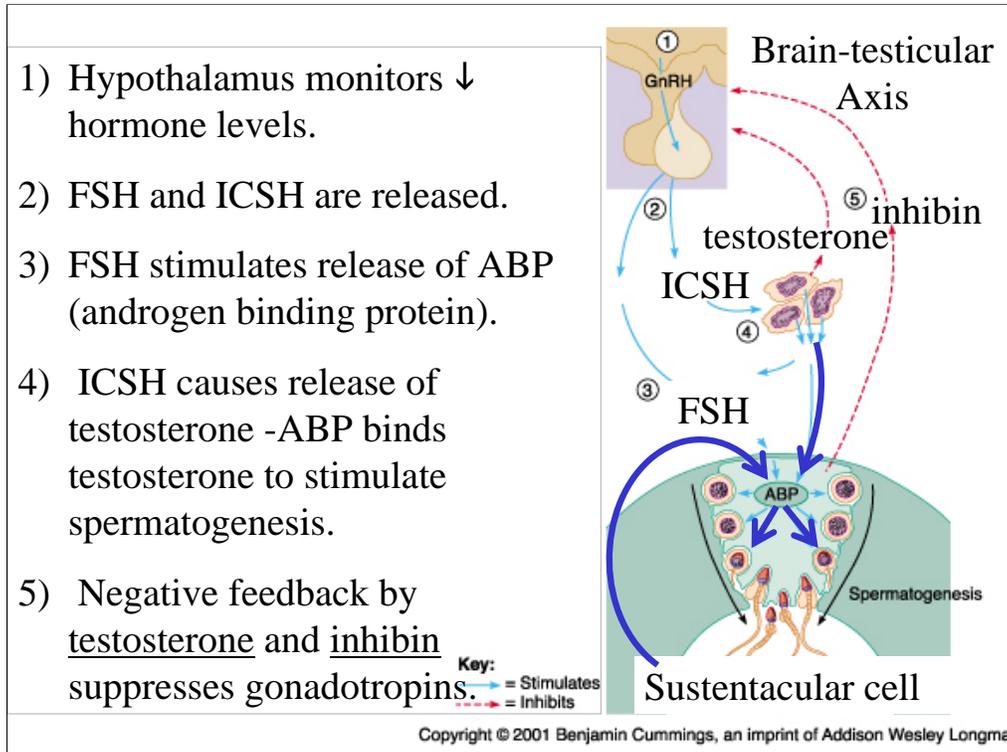


The **oogonia** have already matured before birth and women are born with a limited number of **primary oocytes** which have already begun, and are suspended in, prophase of the first meiotic division. Each month a small number of these primary oocytes continue meiosis I, usually from alternating ovaries, and usually only one becomes a **secondary oocyte**. (Fertility drugs are FSH derivatives and stimulate many follicles, which increases the probability that some will develop into secondary oocytes to be fertilized) It is the secondary oocyte which is ovulated. Surrounding each early primary oocyte is a **primordial follicle**. These follicles develop along with the oocytes, first becoming **primary follicles** and continuing as growing or **secondary follicles**, and ultimately becoming a **mature (a.k.a. Graafian or vesicular) follicle** which contains the secondary oocyte which is ovulated.



## Spermatogenesis vs. Oögenesis

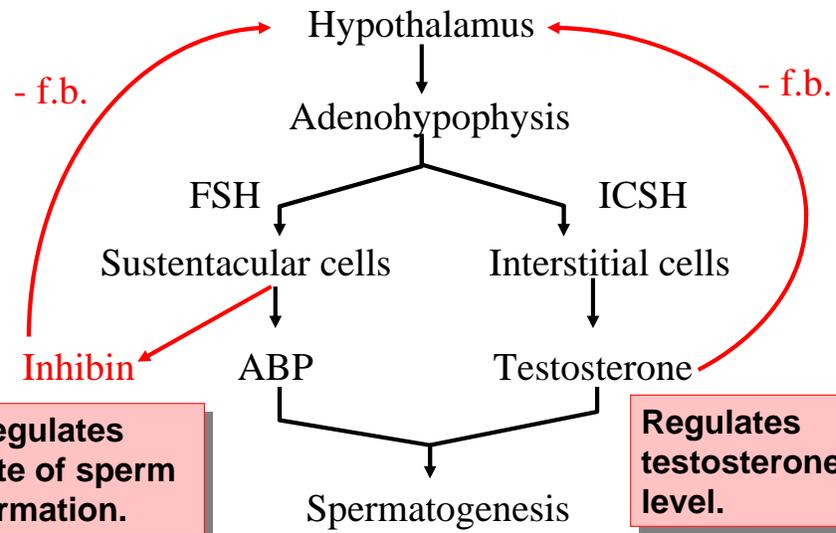
- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>• Four gametes formed per meiotic division<ul style="list-style-type: none"><li>• Unlimited number of gametes may be formed throughout the man's life</li></ul></li></ul> | <ul style="list-style-type: none"><li>• Only one functional gamete per meiotic division<ul style="list-style-type: none"><li>• Limited to those primary oocytes present at birth</li></ul></li><li>• Second division only occurs if fertilization occurs.</li></ul> |
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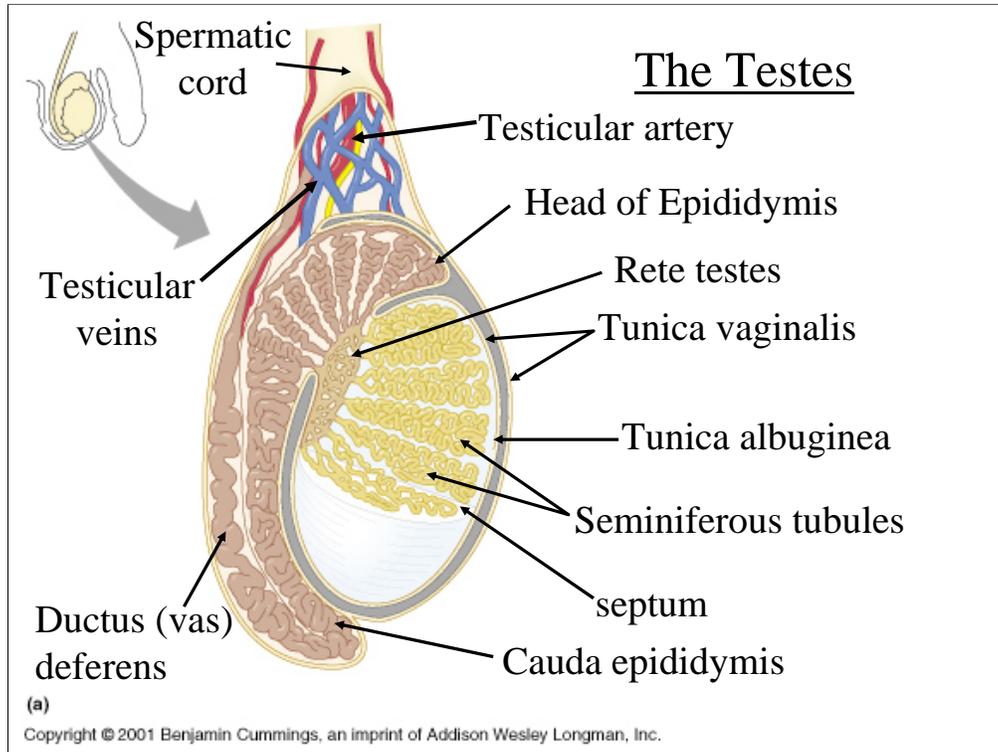


Spermatogenesis is controlled by the gonadotropins of the anterior pituitary, which in turn are controlled by the hypothalamus. **ICSH** (Interstitial Cell Stimulating Hormone, a.k.a. LH) stimulates the interstitial cells to produce testosterone and other androgens. **FSH** stimulates the Sertoli (Sustentacular) Cells to produce a substance called **Androgen Binding Protein (ABP)** which, as its name suggests, binds to the androgen testosterone. The testosterone-ABP combination stimulates spermatogenesis. Feedback to the hypothalamus-pituitary controls the process. Testosterone in the blood feeds back to suppress ICSH release. This modulates testosterone levels, keeping them within the normal range. Testosterone is important for other processes such as the normal function of the seminal vesicles and prostate, as well as other masculinizing effects. A hormone product of the Sertoli cells called **inhibin** acts to suppress the secretion of FSH by the adenohypophysis. Testosterone and inhibin act independently in suppressing ICSH and FSH, but both suppress GnRH from the hypothalamus. In ways not completely understood FSH is also suppressed when sperm are not ejaculated and build up in the epididymis. Under these conditions spermatogenesis slows to a crawl. Conversely, if sperm are ejaculated often and therefore don't build up FSH is not suppressed and spermatogenesis is encouraged.



## Control of Spermatogenesis

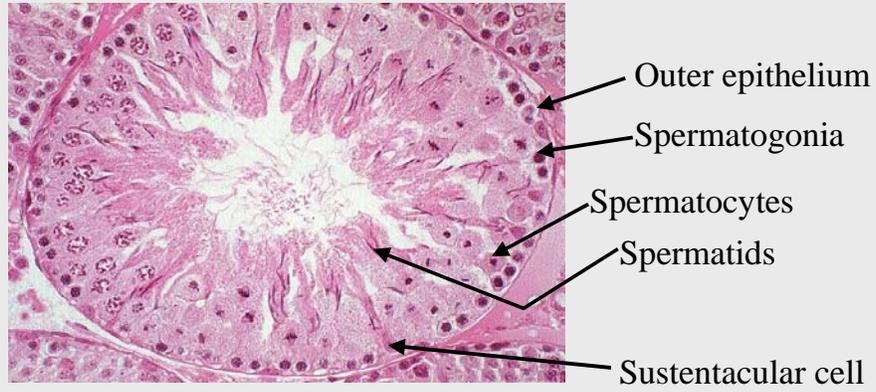




Testicles are suspended in a skin-and-muscular sac known as the **scrotum** into which the testes descend before birth. (See Figures 28.2 and 28.3) The scrotum is lined with a thick **tunica vaginalis** and each testis is covered by a whitish **tunica albuginea** which forms septa which divide the testis into lobes. The process of sperm formation occurs in the **seminiferous tubules**. From the seminiferous tubules the sperm migrate through the rete testes to the highly coiled epididymis (Figure 28.3). The epididymis actually stretches to 4 to 6 m. and consists of a head, a body, and a tail (the *cauda epididymis*), which wraps around the testis. The epididymis leads to the **vas (ductus) deferens** which carries sperm to the urethra. Sperm mature during their passage through the epididymis acquiring motility and the ability to fertilize an oocyte.

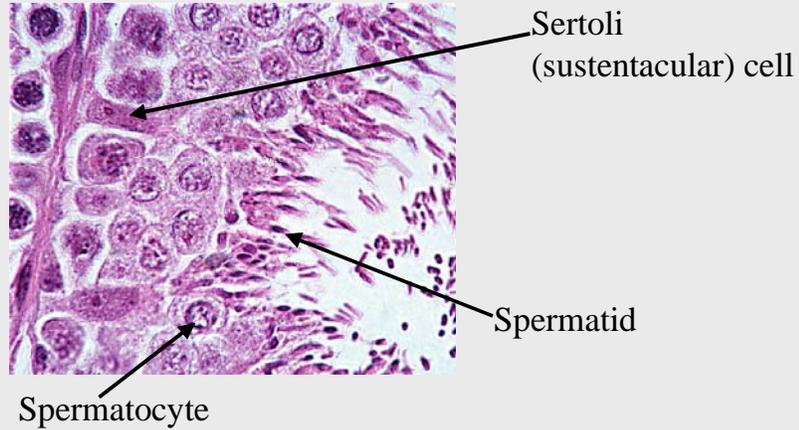


## Cells of the Seminiferous Tubule





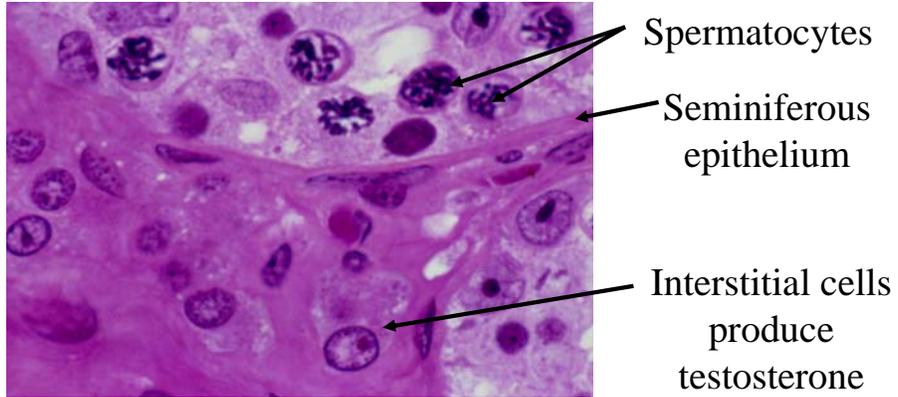
## Sustentacular (Sertoli) Cells



**Sustentacular (Sertoli) cells** surround the developing spermatocytes and manage their environment and protect them. Note the elongated spermatids entering the tubule's lumen.



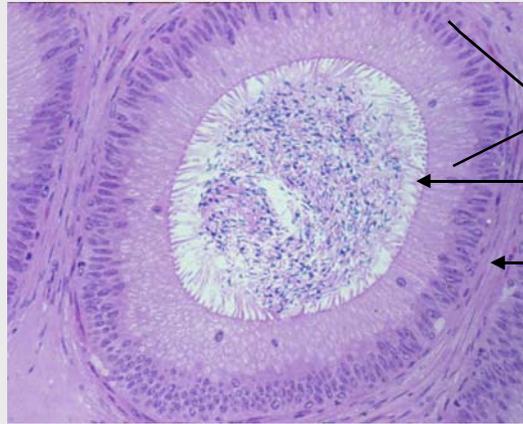
## Interstitial Cells



**Interstitial cells** are found in between the seminiferous tubules, and produce **testosterone**.



## Epididymis Tubule h.p.



Epididymis tubule (lined with pseudostratified columnar with stereocilia)

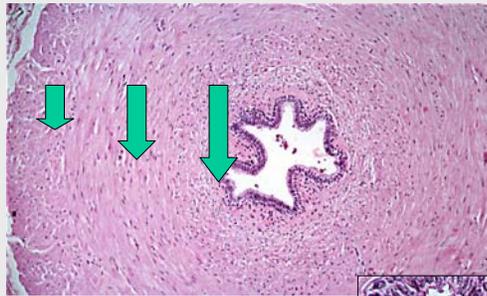
Smooth muscle

provides peristalsis for sperm movement toward the ductus deferens.

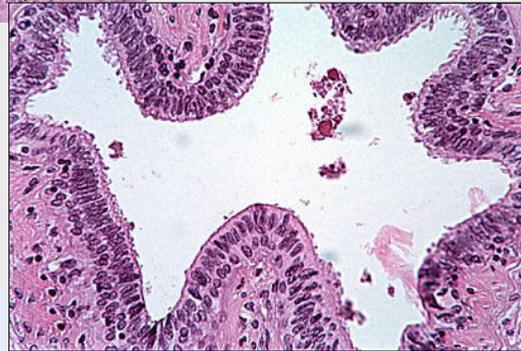
The lining of the epididymis is made of **pseudostratified columnar epithelial cells**, many of which possess **microvilli** (called **stereocilia**) which aid in secretion and absorption as the cells manage the sperm's environment. A thin layer (or two) of smooth muscle is also present.



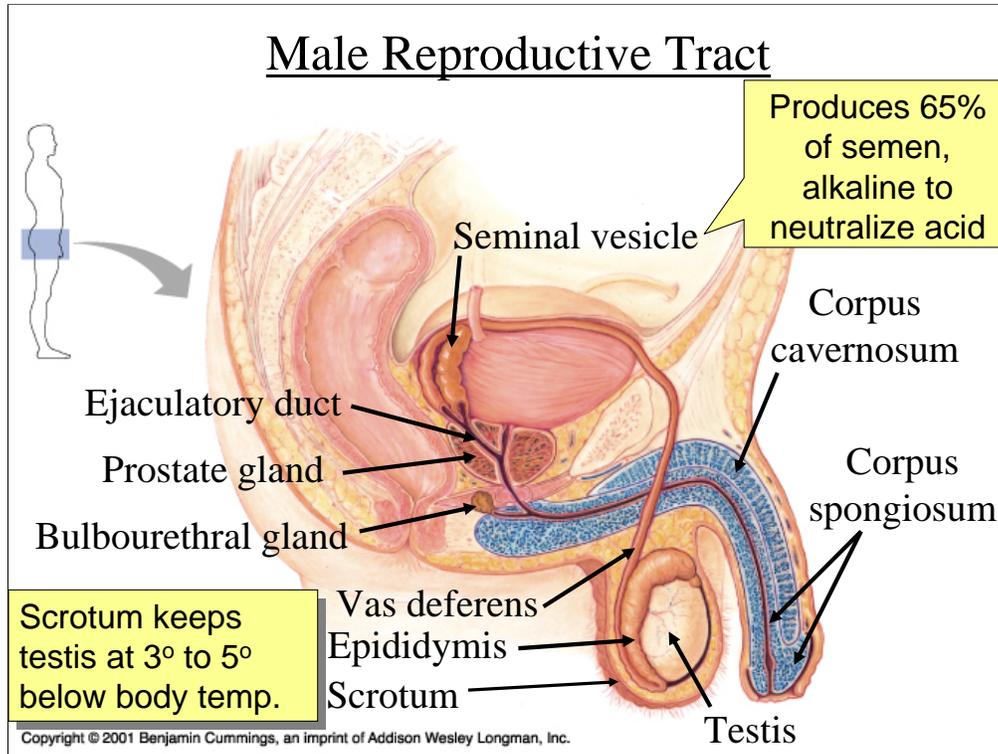
## Vas Deferens, Ip.



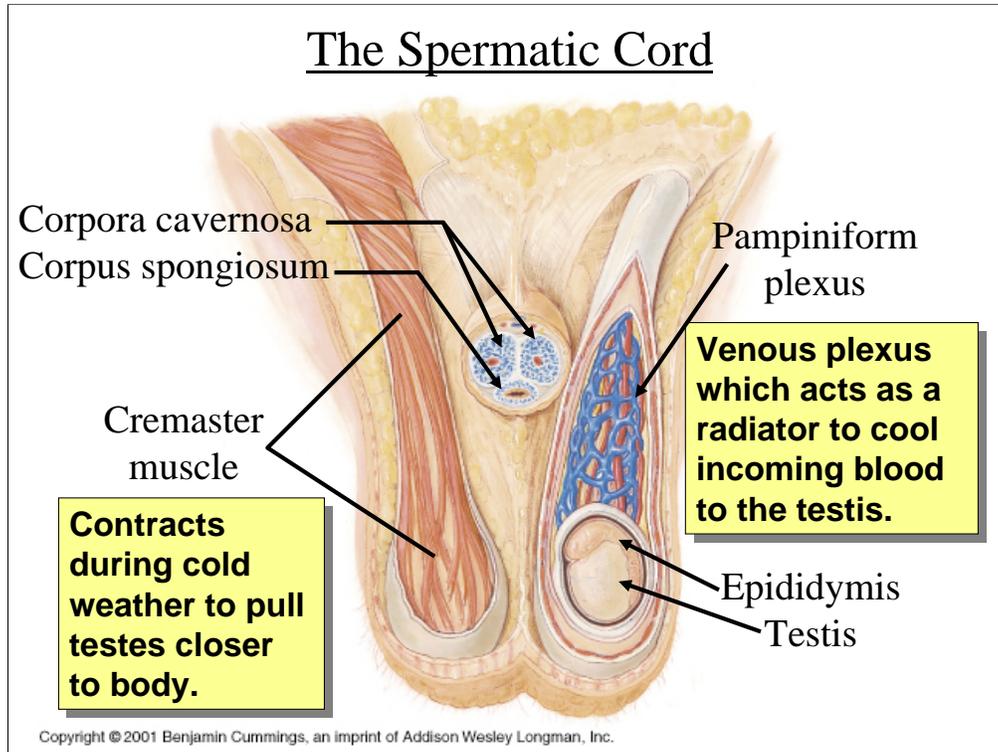
Three layers of smooth muscle:  
outer-longitudinal,  
middle-circular, and  
inner-longitudinal  
layers.



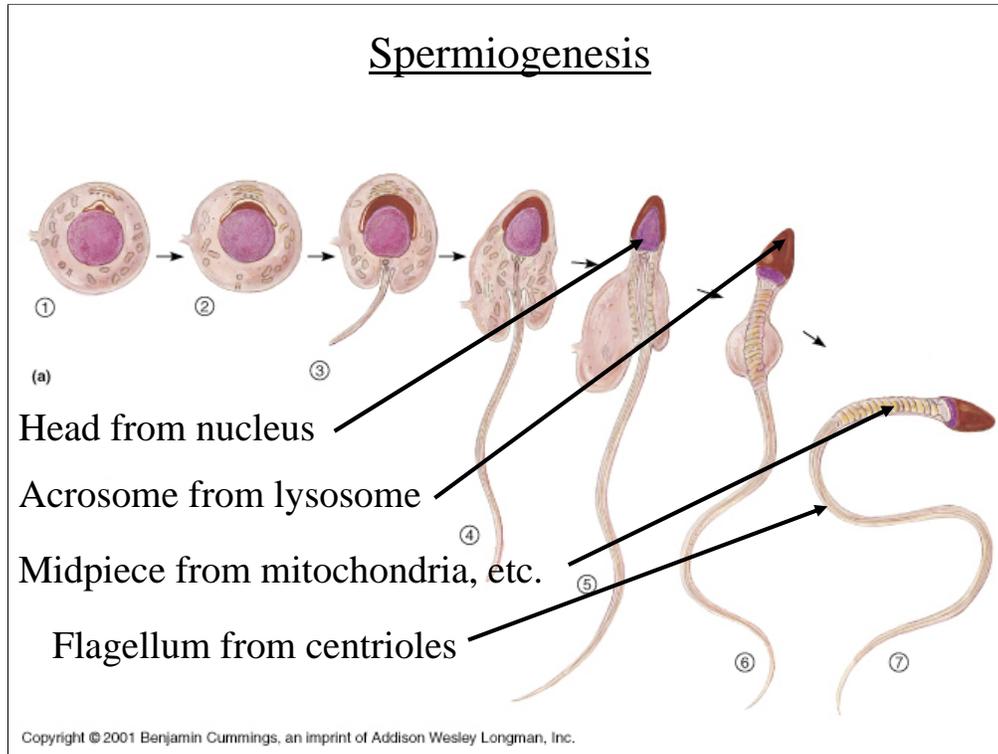
The **vas deferens** has three layers of smooth muscle which propels the sperm during emission and ejaculation. Pseudostratified columnar with **stereocilia (microvilli)** are present, similar to the lining of the epididymis.



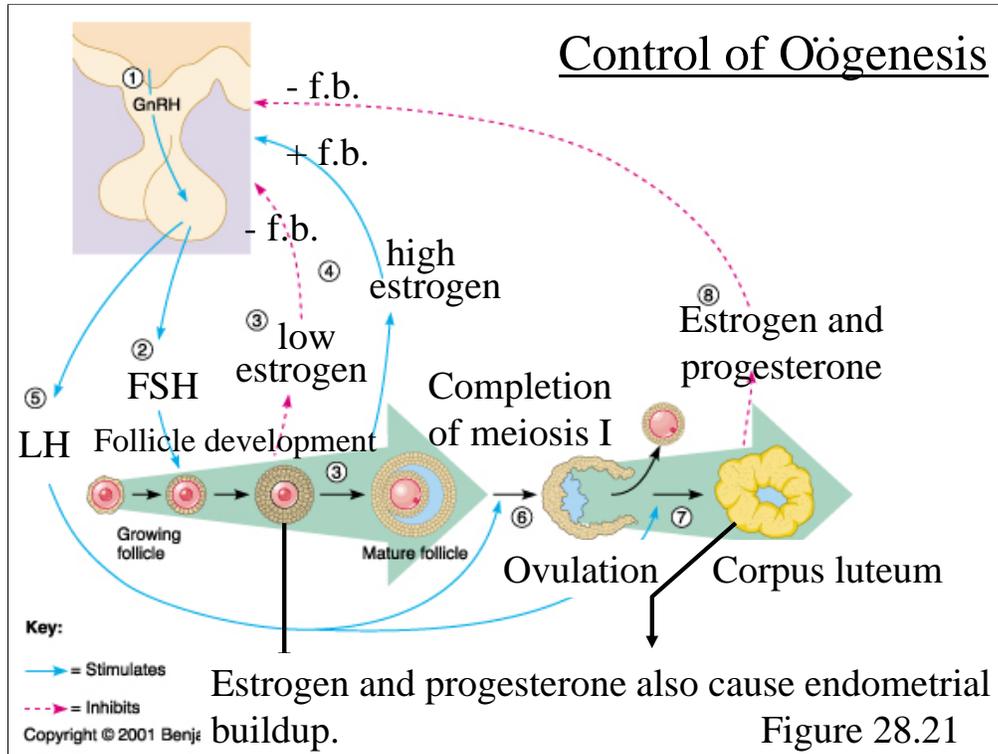
The vas deferens is a continuation of the cauda epididymis and is histologically very similar, including the pseudostratified columnar epithelium with microvilli and three layers of smooth muscle. The vas deferens continues into the body cavity through the **spermatic cord** until it joins with the duct of the **seminal vesicle** to form the **ejaculatory duct** which runs through the **prostate**. [prostate in situ] (See Figure 28.1) The prostate is composed of secretory epithelial glands which secrete a sperm-activating semen during ejaculation. Acid phosphatase is among the substances secreted. In patients with prostatic cancer, blood levels of acid phosphatase are used to check for metastasis. Fibromuscular tissue of the prostate propels the semen into the urethra and wraps around the ejaculatory duct to function in ejaculation. The **seminal vesicles** secrete an alkaline fluid containing sugars and other substances which makes up 65% of the semen. The bulbourethral (Cowper's) glands secrete mucus into the urethra prior to ejaculation.



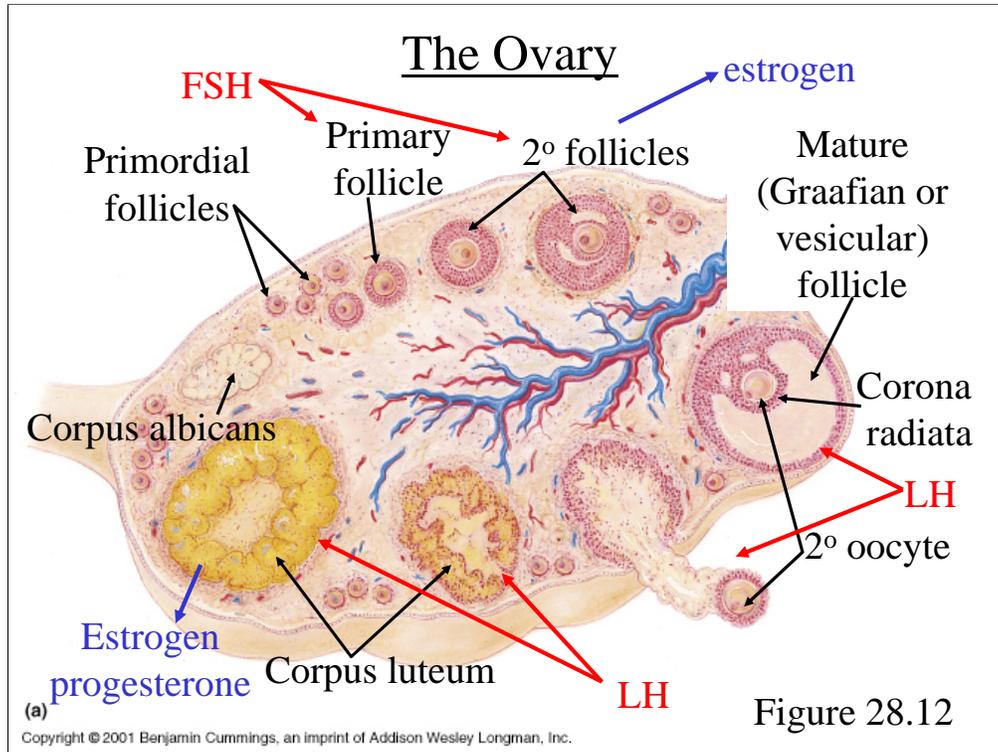
The spermatic cord has a heat control system resulting from a network of veins called the **pampiniform plexus**. (See Figure 28.2) These veins absorb heat from the incoming testicular artery and radiate it away from the testicle, helping to maintain the optimum temperature for spermatogenesis of 5 to 7 degrees below body temperature. The **dartos** muscle of the scrotum along with the **cremaster** muscle of the spermatic cord help to pull the testes closer to the body during cold weather.



Spermiogenesis begins in the seminiferous tubules, but is usually completed in the **epididymis**. In spermiogenesis all non-essential components of the spermatids are lost in order that the sperm have only the chromosomes and the machinery required to propel them to the female **oocyte**. The nucleus of the cell becomes the head of the sperm, and the lysosomes become the acrosome. (See Figure 28.9) The acrosome contains digestive enzymes in order to digest the cumulus mass (derived from the corona radiata) around the oocyte. The midpiece of the sperm is derived from the mitochondria and other metabolic organelles of the cell, and the flagellum is derived from the centrioles. The flagellum returns to its role as centrioles after fertilization has occurred.



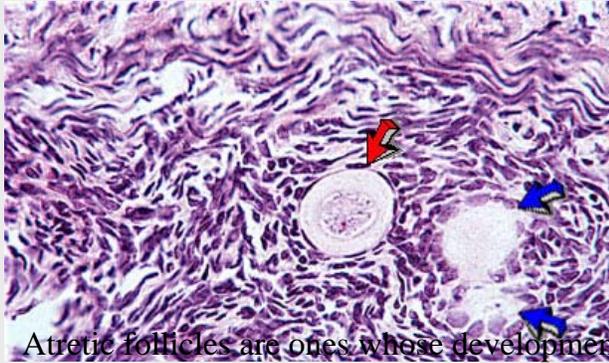
- 1) Hypothalamus sends GnRH to ant. Pituitary causing the release of FSH.
- 2) FSH causes follicle development and secretion of estrogen.
- 3) Low levels of estrogen suppress FSH release thru – f.b.
- 4) High levels of estrogen stimulate release of LH in a positive feedback mechanism.
- 5) LH causes completion of Meiosis I, (6) ovulation, and (7) development of the corpus luteum.
- 8) The corpus luteum produces both estrogen and progesterone which exert – f.b. on GnRH secretion.



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## The Primordial Follicle



The primordial follicle (red arrow).

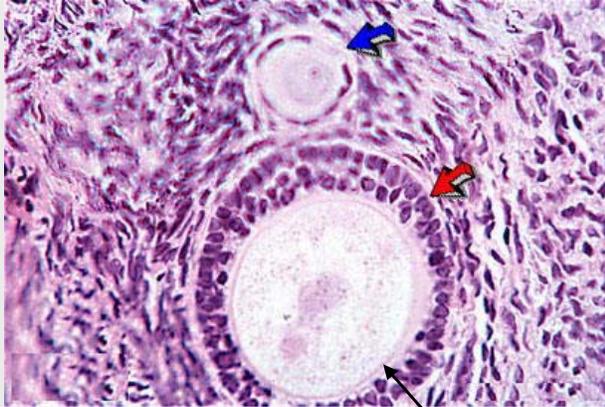
Atretic follicles (blue arrows).

Atretic follicles are ones whose development has been curtailed. Usually only one follicle will complete the entire process to maturity and ovulation.

A limited number of **primordial follicles** are present at birth. Each contains a **primary oocyte** arrested in prophase of Meiosis I.



## Primary Follicle



At least two layers of follicular cells identify the primary follicle (red arrow).

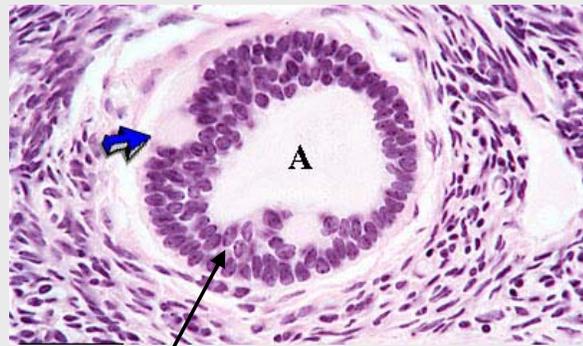
A primordial follicle (blue arrow).

Zona pellucida – a polysaccharide membrane surrounding the oocyte.

Under the stimulation of **FSH** a few primordial follicles develop each month, first forming a primary follicle.



## Secondary Follicle



Antrum (A) – a fluid-filled space characterizes secondary follicles and beyond.

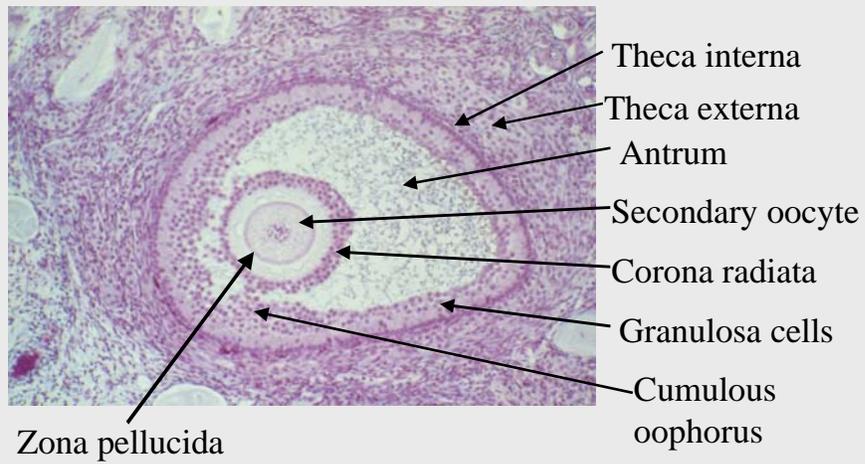
Oocyte (arrow)

Granulosa cells

A secondary or growing follicle contains the beginnings of a fluid-filled antrum (space).



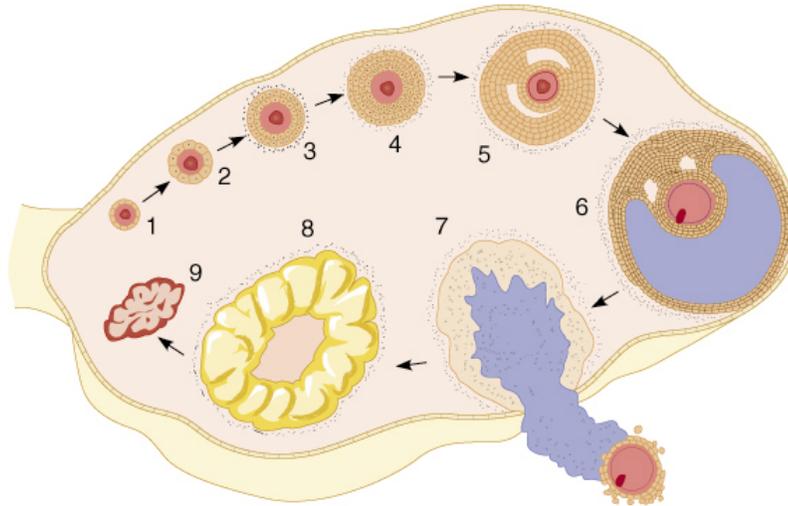
## Mature (Graafian) Follicle



A **mature (Graafian or vesicular) follicle** contains a secondary oocyte which has resulted from Meiosis I. This occurs under stimulus of **LH**.



## Test Diagram of Ovarian Structures



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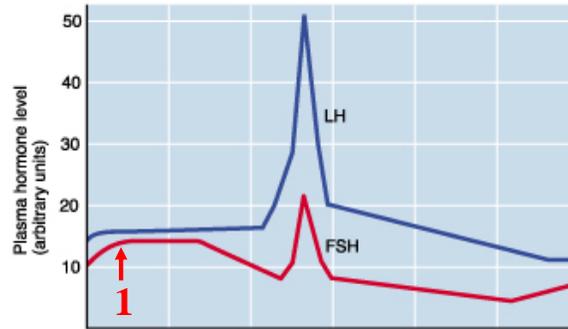
Figure 28.20

Use this diagram to test yourself on the stages seen previously.

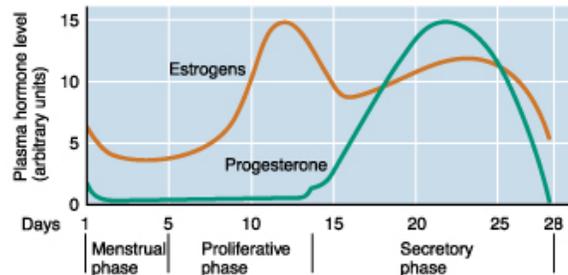
1. Primordial follicle
2. Primary follicle
3. through 5. Growing follicles
6. A mature or graafian follicle
7. A follicle at ovulation of the secondary oocyte
8. A corpus luteum
9. A corpus albicans



(1) Gonadotropin rise  
(FSH) starts cycle



(a) Fluctuation of gonadotropin levels



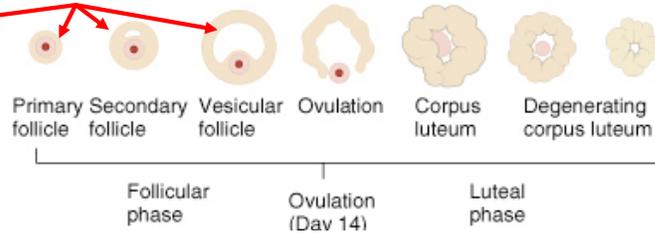
(b) Fluctuation of ovarian hormone levels

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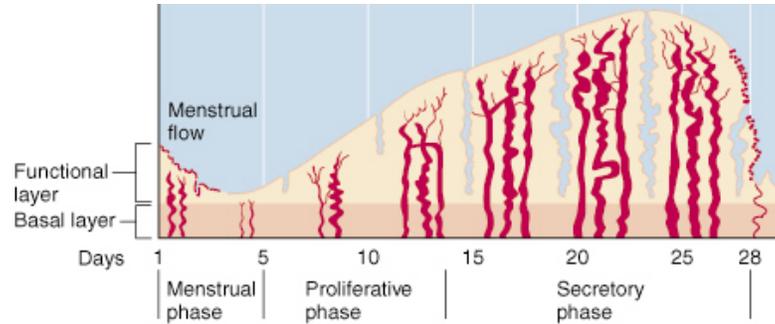
Gonadotropins control oogenesis under the regulation of the hypothalamus. (See Figures 28. 21 and 28.22 modified) The cycle begins about day 4 with **Follicle Stimulating Hormone (FSH)** stimulating the development of some of the primordial follicles to become primary follicles with accompanying development of the oocyte.



(2) FSH causes development of follicles, which produce estrogen.



Estrogen (and later, progesterone) causes endometrial buildup



(d) Uterine cycle

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FSH continues to exert influence over these follicles causing them to secrete **estrogen**. Estrogen has two effects at this point. The low levels of estrogen which occur at first exert negative feedback through the hypothalamus to suppress FSH secretion. Estrogen also causes the **proliferative phase** of endometrial development.



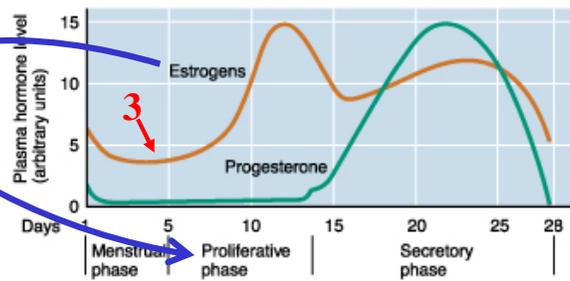
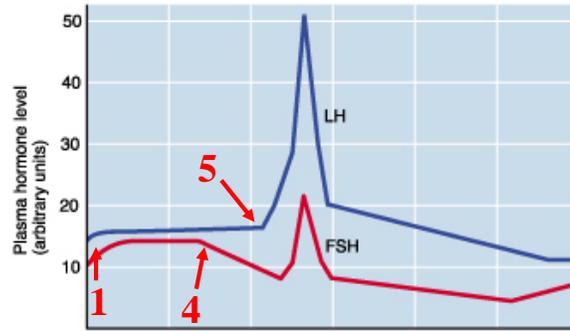
## Estrogen levels:

(3) Estrogen rises from secretion by follicles.

(4) Low estrogen exerts neg. feedback suppressing FSH

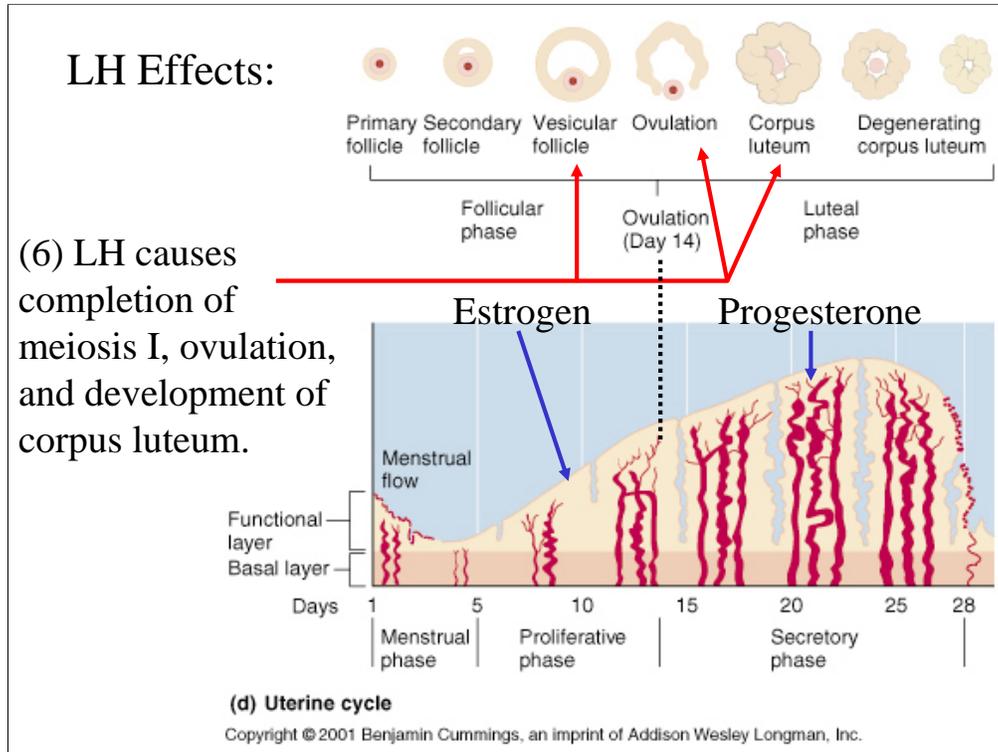
(5) High estrogen causes LH spike

Estrogen stimulates uterine proliferative phase.



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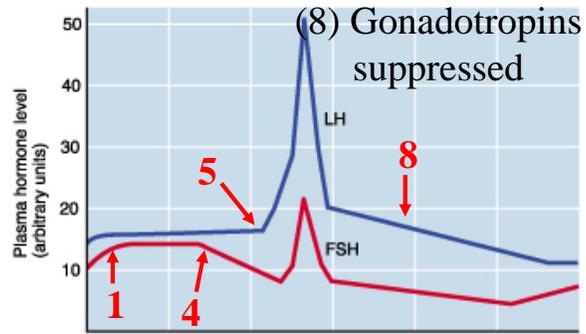
The low levels of estrogen which occur at first exert negative feedback through the hypothalamus to suppress FSH secretion. This prevents development of additional follicles. (Multiple births from fertility drugs usually result when they are not cut off as they should be when developing oocytes are discovered) The second effect of estrogen is to stimulate the buildup of the **functional endometrium**, the lining of the uterus which will accept a zygote. This first phase of endometrial buildup is called the **proliferative phase of the uterus** because it is characterized by the growth of large numbers of capillaries and secretory cells. Late in the **follicular phase of the ovary** estrogen levels peak. This estrogen surge actually exerts a positive feedback effect on the pituitary, causing the release of luteinizing hormone (LH).



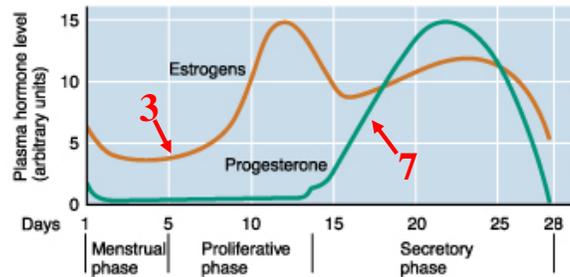
LH causes completion of Meiosis I and ovulation of the secondary oocyte produced. This occurs about day 14 of the cycle. LH also causes the follicle remaining in the ovary to become a glandular corpus luteum. The **corpus luteum** produces and secretes progesterone and estrogens. These hormones continue the buildup of the endometrium, now in its **secretory phase**. They also exert a feedback effect on the pituitary suppressing LH secretion.



The corpus luteum:



(a) Fluctuation of gonadotropin levels

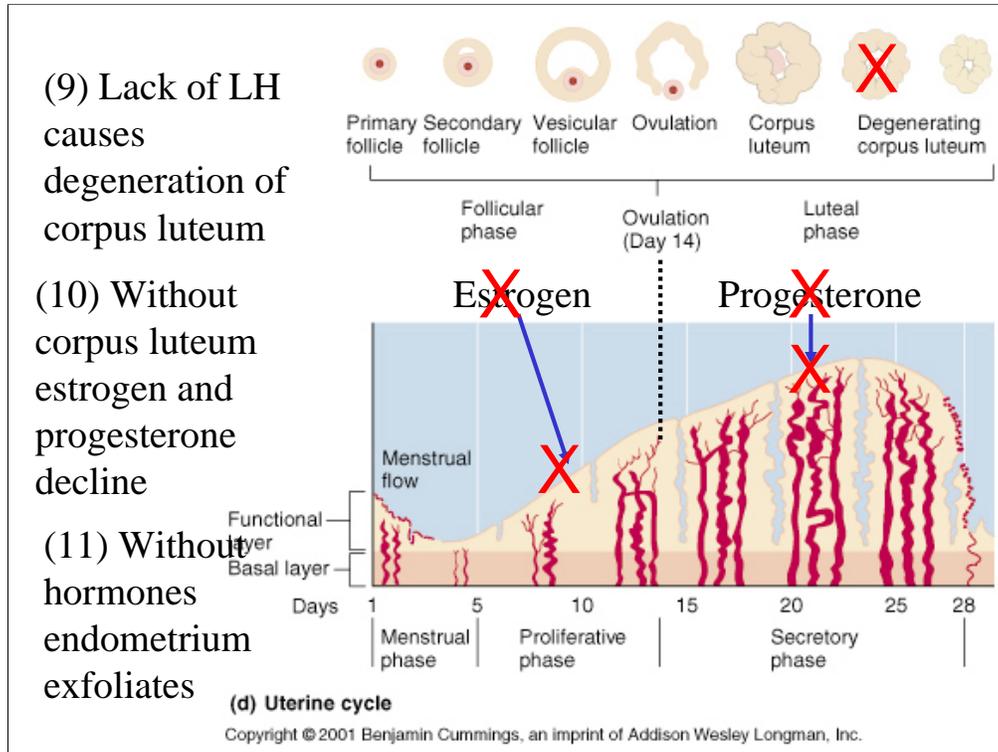


(b) Fluctuation of ovarian hormone levels

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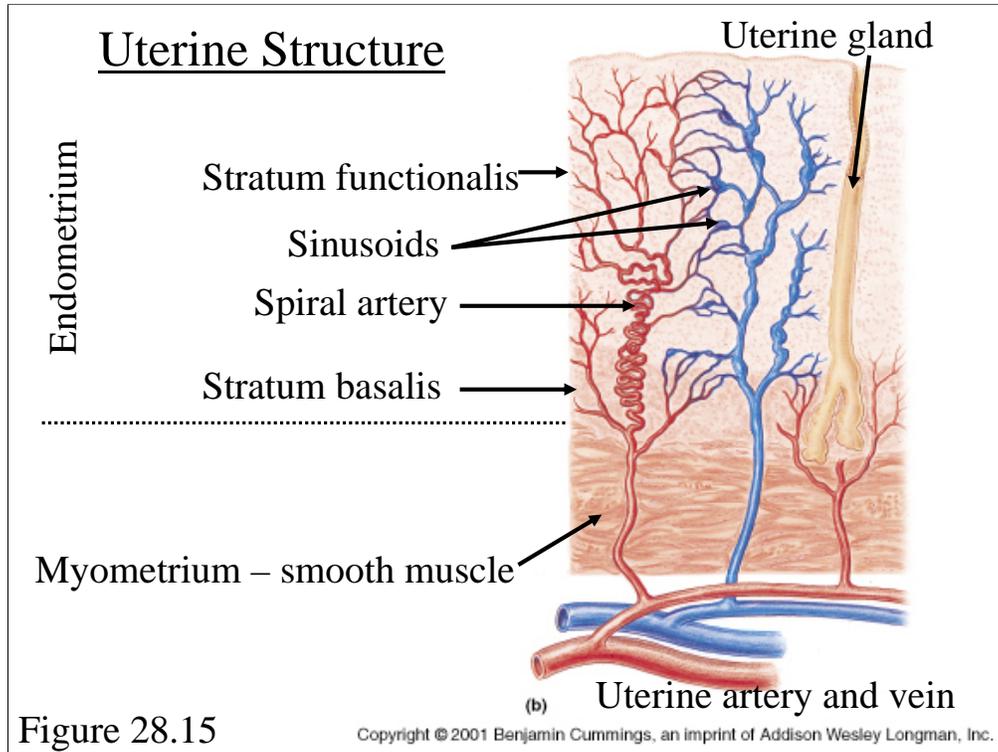
(7) Corpus luteum produces estrogen and progesterone.

Estrogen and progesterone secreted by the corpus luteum exerts negative feedback through the hypothalamus to suppress gonadotropin release.



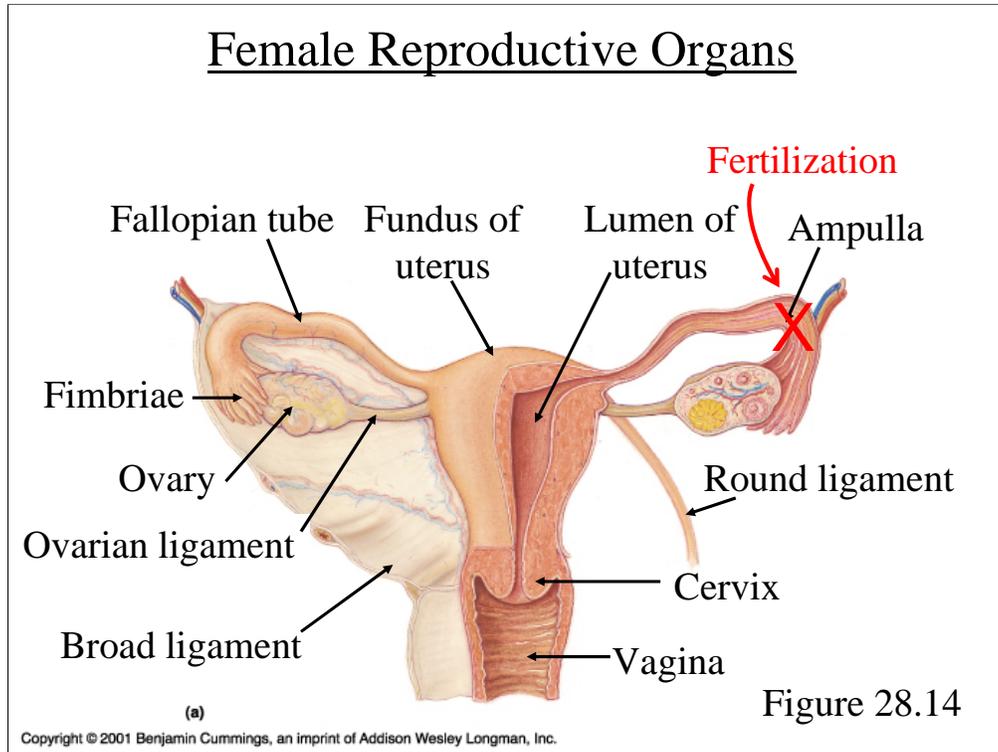
This becomes self-defeating if no egg is fertilized because without LH secretion the corpus luteum will break down, at about day 25 of the cycle. And without the corpus luteum progesterone and estrogen secretion will cease and the endometrium will break down, an event called menstruation, which occurs by day 28. (The corpus luteum shrinks and shrivels into the white **corpus albicans** which remains in the ovary. Old ovaries show the presence of many corpi albicans.

If an egg is fertilized resulting tissues (more below) will produce HCG, Human Chorionic Gonadotropin, which replaces LH to keep the corpus luteum intact and hormone levels high, continuing the maintenance of the endometrium. HCG together with other luteotropins, keeps the corpus luteum going for about 8 weeks into the pregnancy. It grows to 2 to 3 cm filling most of the ovary. After about 6 weeks of pregnancy the placenta will produce estrogen and progesterone to take over the function of the corpus luteum. HCG can be detected in the serum as early as 6 days after conception and in the urine as early as 10 to 14 days. An immunoglobulin response to HCG in urine is the basis for the modern pregnancy test.



**Blood Supply** - The uterine artery gives off 6 to 10 arcuate arteries which anastomose with one another in the myometrium. Branches from these called radial arteries enter the basal layer of the endometrium, giving off straight arteries which supply this region, and continuing upward into the functional layer as the highly-coiled **spiral arteries**. These spiral arteries lead to numerous arterioles which anastomose to supply a rich capillary bed that includes thin-walled dilated segments called **lacunae**. (See Figures 28.15 and 29.7) These lacunae play an important role in providing blood supply for the placenta.

The uterus is composed of three layers: the **endometrium** or cervical mucosa made of columnar epithelium, the **myometrium**, a thick smooth-muscular layer, and the **perimetrium**, an external serosa or visceral peritoneum. Both the endometrium and myometrium exhibit substantial change during pregnancy. As the uterus enlarges, the myometrial cells may grow to 10X their original size and new muscle cells are produced as well. The endometrium has two layers: (See Figure 28.15) the **stratum basale**, a supporting layer, and the **stratum functionalis** which proliferates then degenerates during the menstrual cycle, varying from 1 to 6 mm in thickness.



The vagina is a highly folded fibromuscular tube lined by non-keratinized stratified squamous epithelium. Vaginal mucosa contains no glands and is lubricated by mucus produced by the cervical glands. Vaginal mucosa undergoes changes during the menstrual cycle which somewhat mimics those of the endometrium.

Uterus - Once the **morula** is received from the oviduct all embryonic and fetal development occurs in the uterus. It is a melon shaped organ which has a **body**, a **fundus**, and a **cervix**.

The **cervix** is a barrel-shaped portion separated from the body by the isthmus. The lumen or **cervical canal** has a constricted opening or **os** at each end. The cervical mucosa is from 2-3 mm thick and undergoes little change in thickness, nor is it sloughed off during menstruation. At mid-cycle there is a ten-fold increase in the amount of mucus produced by the cervical glands, and this mucus is less viscous and provides a more favorable environment for sperm migration than at other times when it inhibits the passage of sperm into the uterus. The external os is the site of transition from vaginal stratified squamous to cervical simple columnar epithelium. Cervical epithelial cells are constantly exfoliated into the vagina, and stained preparations (called Papanicolaou cervical smears after the scientists who developed the technique) are used to screen for pre-cancerous and cancerous lesions of the cervix.



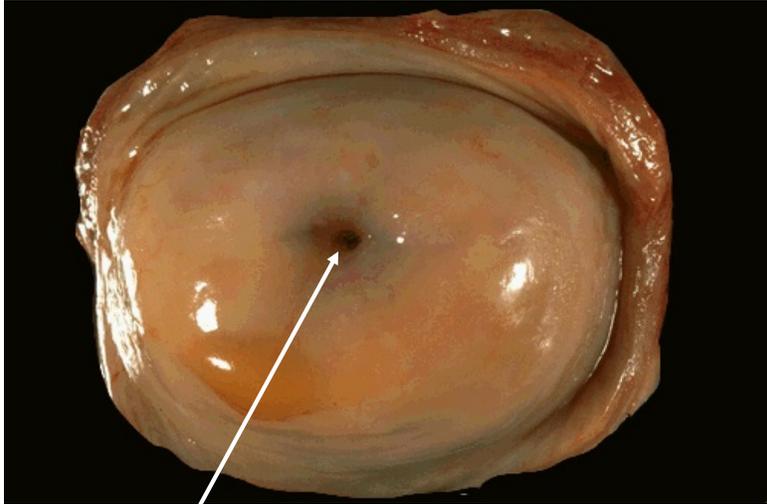
## Normal Uterus



Normal uterus with fundus (1), lower uterine segment (2), cervix, vaginal cuff (3), right fallopian tube (4), right ovary (5), fimbriae (6), ovarian ligament (7), broad ligament (8).



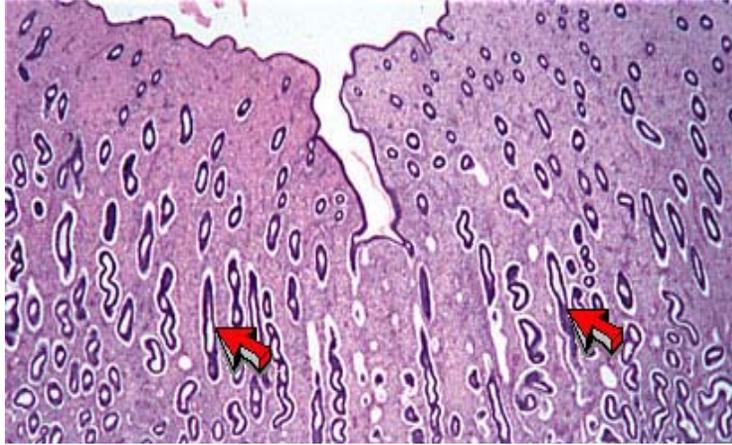
## The Cervix



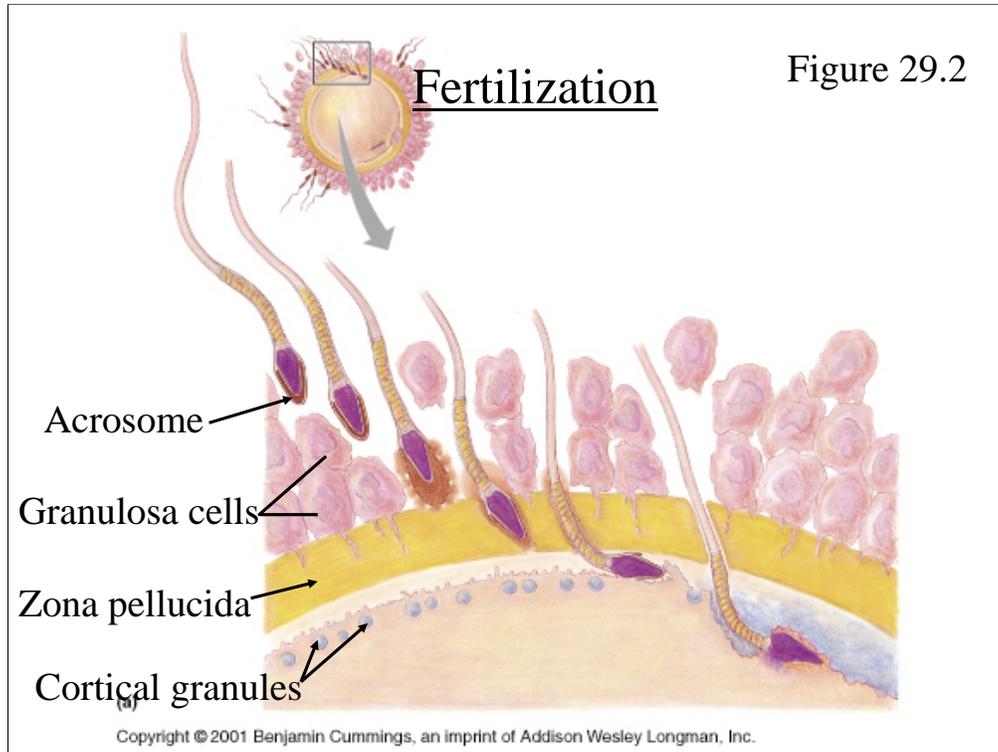
Cervical os



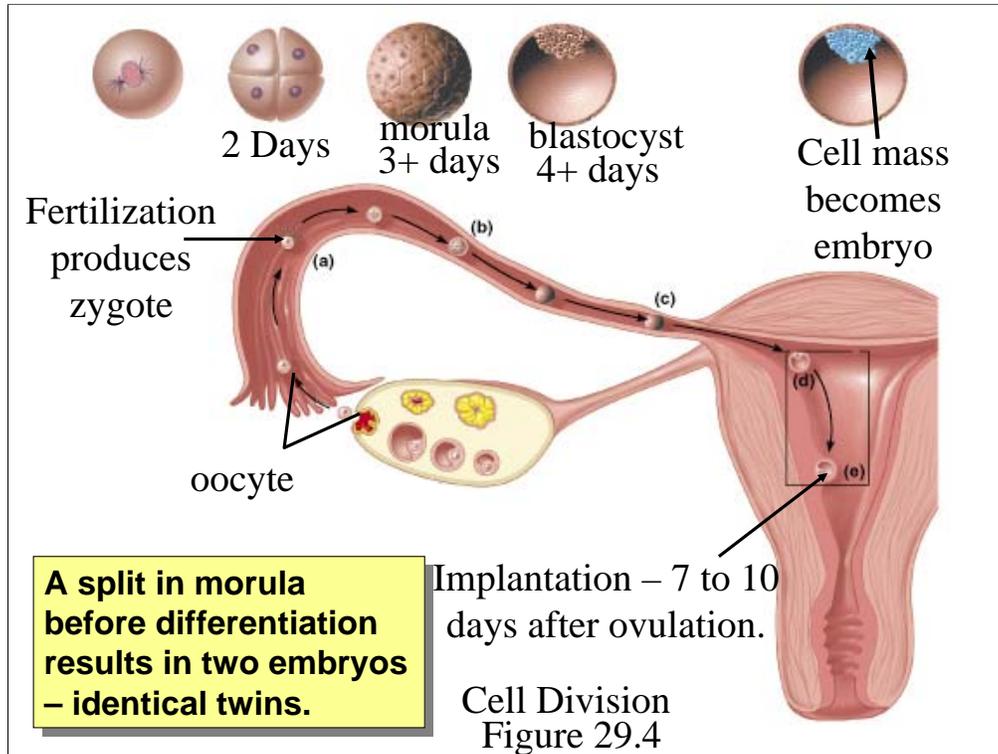
## Endometrial Proliferative Phase



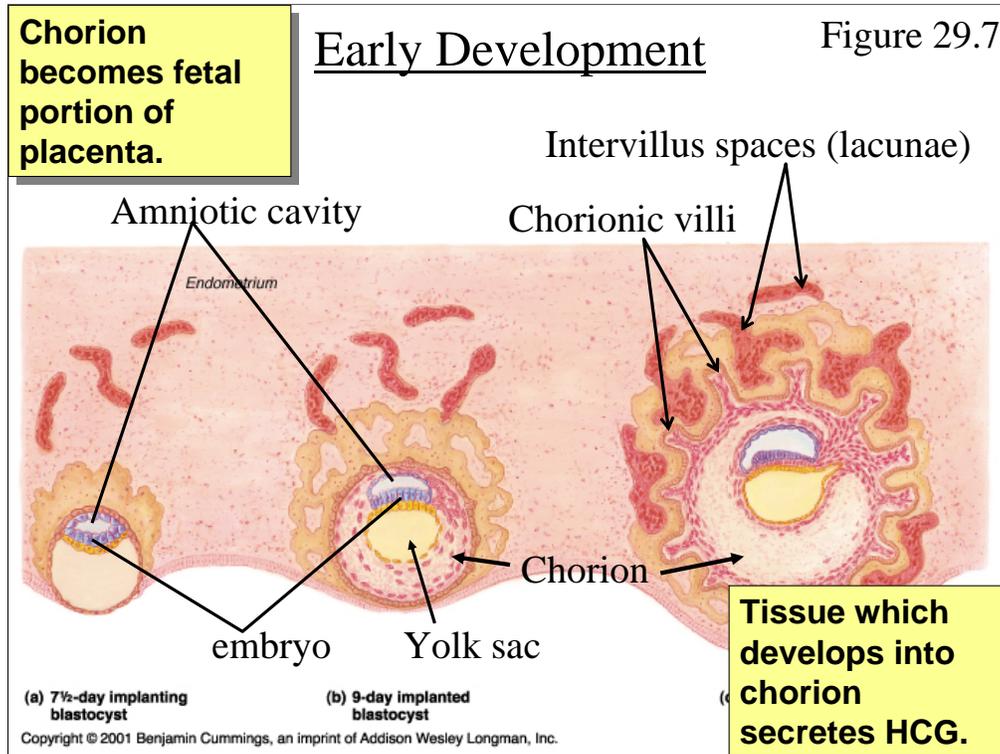
**Red arrows** = uterine glands, relatively straight during the proliferative phase, are cooidal epithelial tubules which become more and more convoluted in the later secretory phase.



Enzymes from many sperm are necessary to digest **cumulous mass** surrounding oocyte, but only one can penetrate. The **cortical reaction**: enzymes released from cortical granules cause rearrangement of fibers in **zona pellucida** and prevent further sperm penetration. Sperm is engulfed in cytoplasm – nucleus becomes pronucleus for first division, midpiece breaks apart, flagellum returns to role as centrioles.



The first **mitotic division** occurs within 24 hours after fertilization. Cell division continues producing a **morula** and about 3 days, and beginning differentiation as the **blastocyst** is produced at about 4 days. **HCG** must be produced by 6 or 7 days to prevent menstruation and permit implantation of the blastocyst at 7 to 10 days.



**The Placenta** - (See Figure 29.7) The developing fetus is maintained by a placenta which develops from fetal and maternal tissues. The fetal portion, formed by the **chorion**, and the maternal portion, formed by the **decidua basalis**, are together involved in physiologic exchange of substances between fetal and maternal circulation. Blood begins to circulate through the primitive cardiovascular system and into **chorionic villi** at about 21 days. The fetal heart rate initially is about 65 bpm but increases to around 140 bpm before birth. Intervillous spaces or **lacunae** provide the site for exchange of nutrients, wastes, hormones, and respiratory gases between the fetal and maternal circulatory systems.  $pO_2$  is comparatively low in fetal blood, but fetal hemoglobin is more highly saturated than adult hemoglobin and its concentration is higher.  $CO_2$  diffusion from fetus to mother causes a double Bohr effect which works in both the maternal and fetal blood to enhance the release of oxygen from maternal hemoglobin and the increase in saturation of fetal hemoglobin.





## Hormones Secreted During Pregnancy

Placental Hormones:

HCG – keeps corpus luteum intact through 6th week

Estrogens and progesterone – stimulate breast and other tissue development

Somatomammotropin – stimulates breast development

Adenohypophysis – ↑ 50%

↑ corticosteroids, ↑ T4 and T3

Ovaries – relaxin softens uterine ligaments for birth

Estrogen and progesterone are important in the growth and development of the breasts, but their presence actually inhibits the secretion of much milk before birth of the infant. Prolactin is produced both by the adenohypophysis of the mother and by the placenta, along with **somatomammotropin** which stimulates the development of secretory cells in the breast. These cells secrete a small amount of fluid, called **colostrum**, before birth, but actual milk secretion cannot occur until the inhibition of estrogen and progesterone are eliminated after delivery. Growth hormone, glucocorticoids, and insulin are also increased during pregnancy, as are the thyroid hormones T4 and T3, and parathyroid hormone.



## Changes During Pregnancy

Cardiac output ↑ 30%

Respiration ↑ 20%

↑ Na<sup>+</sup> and H<sub>2</sub>O reabsorption

Fetal hemoglobin - carries 20% to 50% more oxygen

Breast development – stimulated by estrogen and progesterone, prolactin, somatomammotropin, GH and others



## Parturition

### Hormonal stimuli

↑ estrogen/progesterone ratio

oxytocin – from mother and fetus

prostaglandins

### Mechanical stimuli

Stretch of uterine muscle and irritation to the cervix → positive feedback

Parturition, or delivery, occurs as a result of a combination of increased uterine muscle excitability and a positive feedback mechanism. Both hormonal and mechanical factors are involved. The hormone **oxytocin** is produced by both the placenta and the mother's neurohypophysis as a result of increasing estrogen:progesterone ratio. This hormone stimulates increasing contractions of the uterine fundus. These contractions cause more pressure to be exerted on the cervix by the head of the fetus. The cervix responds to this pressure through a neural and hormonal reflex to stimulate more forceful contractions of the uterine muscle. This positive feedback mechanism continues to result in ever more forceful contractions until birth occurs. Labor can often be induced by physically stretching the cervix. A hormone called **relaxin** causes the pelvic ligaments and cervix to "relax" and become more pliable for delivery and dilates the cervix to about 10 cm.



## Disorders Related to Pregnancy

Preeclampsia – high arterial pressure, protein deposited in glomerular basement membrane reduces GFR, produces edema.

Gestational diabetes – hormones produced during pregnancy increase resistance of insulin receptors, especially in susceptible individuals.