OVERVIEW OF THE HUMAN REPRODUCTIVE SYSTEM

The physiologic systems that we have studied in the previous sections function to ensure the proper maintenance of the individual and are fairly similar in males and females. In this last section, we will focus on the *reproductive system*, whose function is aimed at ensuring the continuation and survival of the species and whose parts and organs are *sexually dimorphic* – i.e., they are structurally and functionally different in males and females.

Reproductive system performs diverse sexual & reproductive functions – Reproductive organs are a mixtures of ducts, organs, and glands. Some of the glands are endocrine, secreting sex hormones; others are exocrine, secreting mucus or various fluids for maintenance of the germ cells, or *gametes*. Some reproductive organs function in development of the gamete and the embryo, while others are important in copulation and in transmission and transport of the gametes.

Sex hormones stimulate growth and function of reproductive organs – The organs of the reproductive system grow and function in response to the stimulation provided by the male and female *sex steroid hormones*, secreted by the *gonads*. The gonads are in turn stimulated by the *gonadotropin hormones* released by the *anterior pituitary* gland. In the absence of these hormonal stimuli, the target glands and organs will cease to function and will atrophy.

Reproductive functions begin at puberty and show aging – Though the various organs of the reproductive system are formed during the embryonic period, the normal functions of this system begin during puberty and last for about forty years in women, terminating in "menopause," cessation of ovarian function, which typically occurs in the early fifties. In men, reproductive functions decline slowly with advancing age.

OVERVIEW OF THE MALE REPRODUCTIVE SYSTEM

The reproductive system of the human male consists of the *penis* and *scrotum*, the *testes*, *prostate*, and *seminal vesicles*, the *epididymis* and *vas deferens*, and the *bulbourethral glands*. The penis and scrotum, which contains the testes, are externally visible; the remaining organs are internal. The two testes (testicles) are the only organs with *endocrine* functions. They secrete the hormone *testosterone*, the most potent of the androgenic (= male-producing) sex steroids. The testes also produce the male gametes, *spermatozoa* (sperm), through a process called *spermatogenesis*. Testicular functions are controlled by gonadotropin hormones from the anterior pituitary gland. The epididymis consists of convoluted tubules that help store and mature the sperm. The vas deferens is a conduit for sperm delivery during *emission* and *ejaculation*, events occurring in the male during sexual excitation and intercourse.

The prostate and seminal vesicles are *exocrine glands* producing the plasma of the *semen*, a fluid essential for activity and survival of the sperm within the female reproductive system. The penis, with its inflatable tissue, acts as the organ of *intromission*, delivering sperm through its *urethral canal* and depositing them in the *vagina* of the female, near the *uterine cervix*. The scrotum is a sac containing the testicles, and, through extension and retraction, it maintains the temperature of the testes a few degrees *below* body temperature, to ensure proper spermatogenesis.

Secondary sex characteristics in the human male – The secondary sexual characteristics of the human male are large body size, enhanced muscular and skeletal growth, wide shoulders and narrow pelvis, enlarged larynx and vocal cords (producing a low-pitched voice), facial and body hair, pubic and axillary (armpit) hair, and receding scalp hairlines and baldness (if genetically susceptible). These characteristics appear after puberty in response to increasing levels of the testosterone hormone and may include psychological changes such as active and aggressive attitudes and independence, although these latter may occur in females as well.

OVERVIEW OF THE FEMALE REPRODUCTIVE SYSTEM

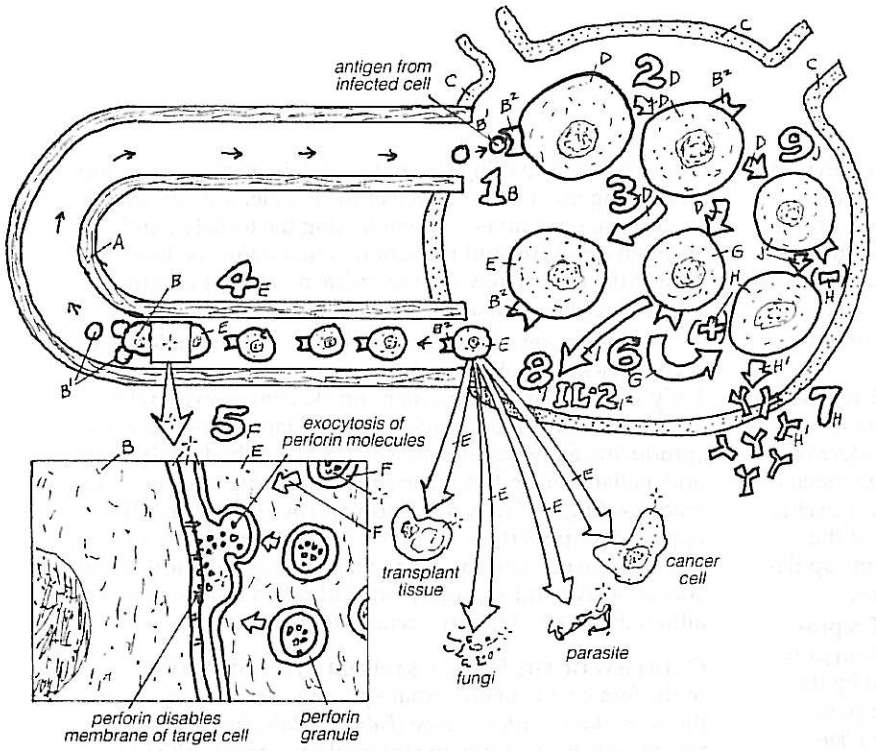
In the female, the main sexual and reproductive organs are the *ovary*, *uterus*, *uterine tube* (*Fallopian tube*, *oviduct*), and *vagina*, which constitute the internal sex organs. The *labia majora*, *labia minora*, and *clitoris* constitute the external *genitalia* (the *vulva*). The two ovaries act as the main endocrine glands of the female system, secreting the female sex steroid hormones, *estrogen* and *progesterone*. In addition, the ovaries are the site of formation and release of the female gametes – the *ova*, or *eggs* – by a process called *oogenesis*. The ovarian functions are controlled by gonadotropin hormones from the anterior pituitary gland.

The uterine tubes are the site of *fertilization* and transport of the egg as well as the young *embryo*. The uterus is the organ of *pregnancy*, providing a nest for *implantation* and growth of the young embryo. The uterine muscles generate the contractions necessary for birth (*parturition*). The clitoris is densely innervated by tactile receptors and functions in female sexual excitation. The vagina is adapted to receive the penis and sperm during intromission and ejaculation. As the *birth canal*, the vagina also participates in delivery and birth of the newborn. The female *breasts* contain fatty tissue and *mammary glands*, which secrete milk for nourishment of the newborn.

Secondary sex characteristics in the human female – The human female secondary sexual characteristics include a wide pelvis, narrow shoulders, high-pitched voice, non-receding scalp hairlines, and soft skin. Females are shorter than males on the average and have less muscle and bone mass. Females have larger subcutaneous and deep fat deposits, which underlie the shape of breasts, buttocks, and thighs in women. Mature human females, like males, possess axillary and pubic hair; pubic hair has the form of an inverted triangle, the opposite of its form in the male. Facial and body hair are absent or very soft and sparse in women. All these characteristics are promoted by the female sex hormone estrogen.

CN: Use dark colors for C and H. Begin with the male system, coloring the same structure in both the side view and the smaller frontal view above, before going on to the next structure.

ACQUIRED IMMUNITY: CELL-MEDIATED RESPONSE D



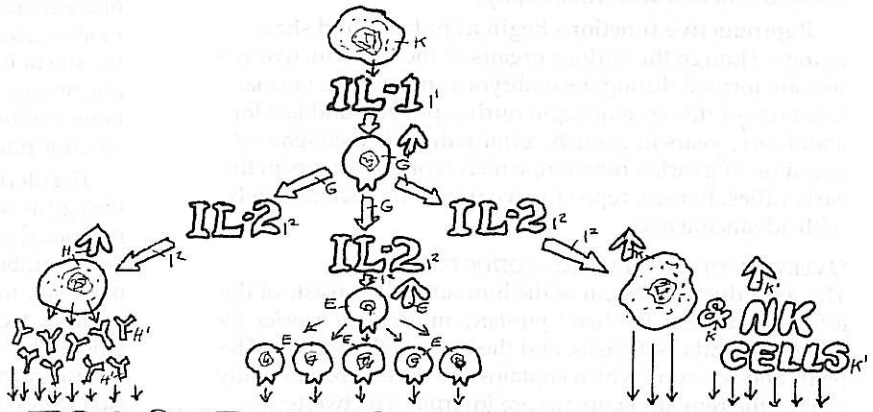
BLOOD CIRCULATION A
INFECTED (TARGET) CELL B
VIRAL ANTIGEN B'
LYMPH NODE C
T-LYMPHOCYTE D
CYTOTOXIC T-CELL E
(KILLER T-CELL)
AG RECEPTOR B²
PERFORIN GRANULE F
HELPER T-CELL G
B-LYMPHOCYTE H
ANTIBODIES H'
CYTOKINES I
SUPPRESSOR T-CELL J

The AG on slow-acting bacteria (tuberculosis), fungi, cancer cells, and cells of transplanted tissue (1) sensitize another type of lymphocyte—i.e., T-cells (TC) (2). Sensitized TCs proliferate (3), forming several subtypes. Cytotoxic (killer) TCs (4) contain AB-like receptor molecules, enabling them to bind with AG on infected or foreign cells. After attachment, TCs release granules containing perforins, which form large pores on membrane of the antigenic cell (5), causing swelling and death. Another TC type, the helper TC (6), enhances AB production by BCs (7) and activated cytotoxic T-cells. Helper TCs produce cytokines (lymphokines), hormone-like substances (8) that regulate functions of other TCs and BCs. The suppressor TC (9) opposes the action of the helper TC, homeostatically regulating immune responses.

HELPER T-CELLS G & CYTOKINE FUNCTIONS I

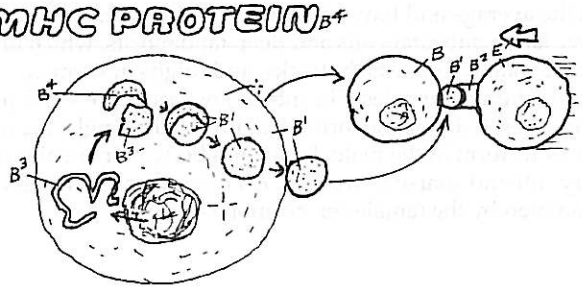
IL-2 I²
MACROPHAGE K
IL-1 I'

Helper T-cells release hormone-like cytokines (interleukins, e.g. IL2) to regulate many functions including activation and proliferation of cytotoxic cells and promote their attack on infected cells; cytokines from helper also stimulate B-cells to secrete antibodies against bacteria and certain viruses and stimulate macrophages and NK (natural killer) cells to perform their phagocytosis of microbes. Cytokines secreted from certain macrophages (IL-1) stimulates helper cells to begin their function.



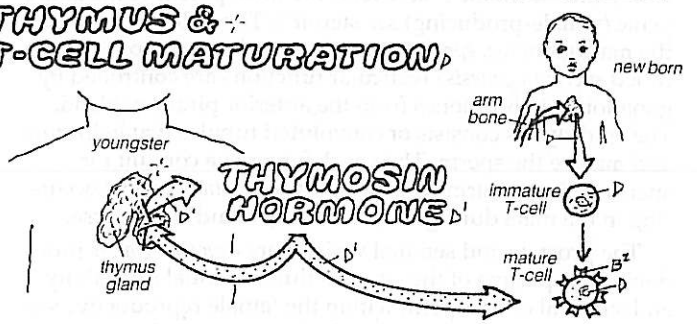
ANTIGEN PRESENTATION B'

VIRAL PROTEIN B³
MHC PROTEIN B⁴



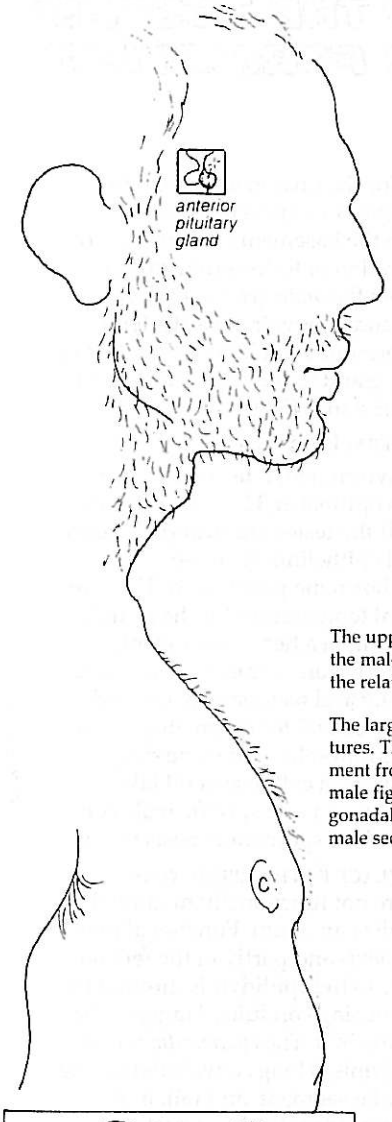
All infected, abnormal, foreign cells must "present" their antigens on their surface in order for cytotoxic T-cell to recognize, attack and kill them. Virus infected cells synthesize viral proteins. These are combined with cells own MHC proteins and inserted in the cell membrane for recognition by cytotoxic T-cells which bind to these antigen complexes and launch their attack by their perforin molecules which cause target cell death.

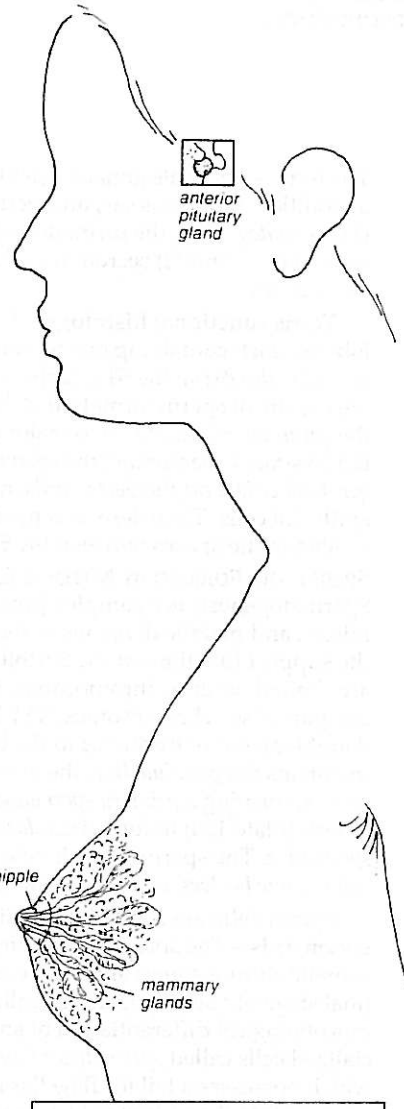
THYMUS & T-CELL MATURATION D



Thymus is a primary lymphatic organ in the chest cavity. It helps mature T-cells and secretes thymosin hormone. Thymosin promotes maturation of T-cells in the thymus and periphery. Thymosin secretion declines after middle age and may cause reduced cell-mediated immunity in the aged. Removal of thymus in neonates (but not adults) results in marked immune deficiency against viruses, tumors, cancer and foreign cells.

T-cell ancestors migrate from bone marrow to thymus in the fetus and neonate. Here they differentiate and mature, i.e., develop specific receptors to detect antigens. Once mature, they leave the thymus to circulate in blood or lymph or lymph organs where they attack antigen bearing (abnormal, infected, foreign) cells.





MALE*

TESTIS A
EPIDIDYMIS B
VAS DEFERENS C
SEMINAL VESICLE D
EJACULATORY DUCT E
PROSTATE GLAND F
BULBOURETHRAL GLAND G
URETHRA H
PENIS I

The upper diagram shows a frontal view of the organs of the male reproductive system, depicting diagramatically the relationship of the various parts.

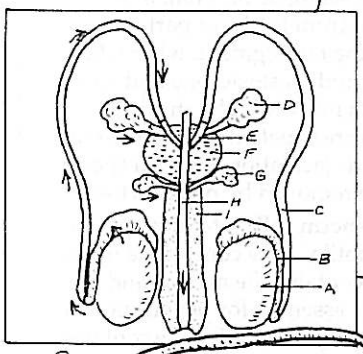
The larger, lower illustration is a side view of these structures. The arrows point to the direction of sperm movement from their sites of origin. In the head portion of the male figure, the anterior pituitary gland, which regulates gonadal activity, is shown. Also depicted are some of the male secondary sexual characteristics.

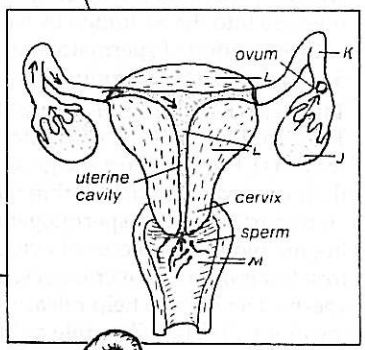
FEMALE*

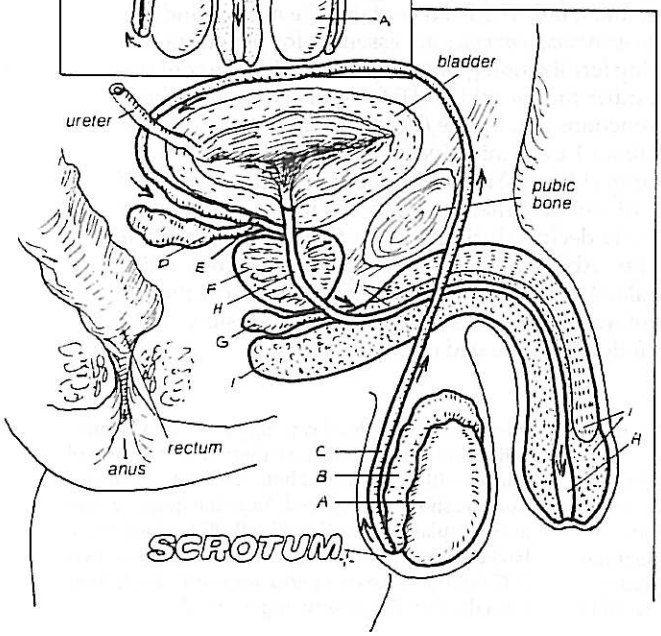
OVARY J
UTERINE TUBE K
UTERUS L
VAGINA M

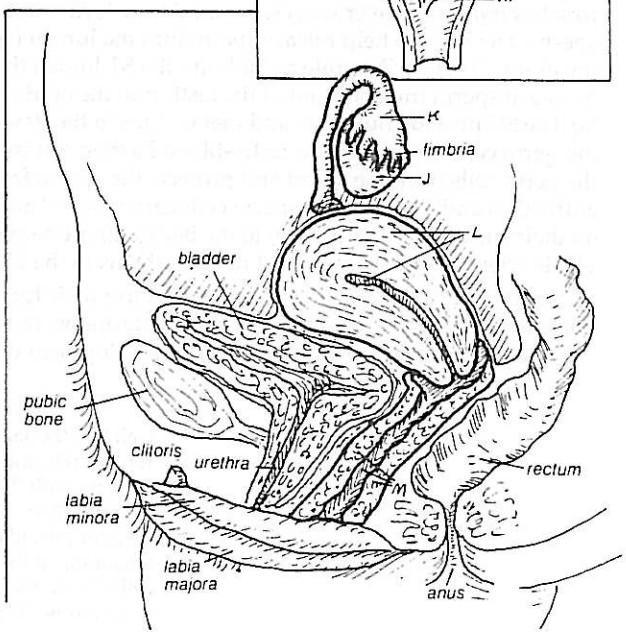
The upper diagram shows an outline of the organs of the reproductive system in the female, from an anterior view. The arrows depict the direction of movement of the ovum (and later the embryo) from the ovary to the uterine cavity. Note the fimbria of the uterine tube. Sperm enter the uterus through its cervix.

The lower diagram is a side view of the female internal and external genitalia. Note the interposition of the vagina between the rectal and urinary structure (bladder and urethra) and the pear-shaped form and muscular nature of the uterus.









FUNCTIONS OF THE TESTES: SPERM FORMATION

The testes—the male gonads—are located within the scrotum, a modified cutaneous sac, and perform two major functions: (1) *spermatogenesis*, the formation of the male *gametes* (*sperm, spermatozoa*), and (2) secretion of the male sex hormone, *testosterone*.

Testis functional histology—Each testis is divided into lobules, each containing one to four long, convoluted *seminiferous tubules* (STs); the STs, each 0.2 mm wide and 70 cm long, are the site of sperm formation. A *basement membrane* supports the *germinal epithelium*. Two major cell types are attached to the basement membrane: the *spermatogonia*, or the *primordial germinal cells*, and the *Sertoli cells*, non-germinal, supportive epithelial cells. Testosterone is produced by the *Leydig cells*, located in the spaces between the STs (plate 151).

SPERM ARE FORMED BY MITOSIS & MEIOSIS OF GERM CELLS

Spermatogenesis is a complex process involving repeated mitotic and meiotic divisions of the germ cells and requires the support functions of the Sertoli cells. The spermatogonia are diploid, with 46 chromosomes (22 pairs of somatic and one pair of sex chromosomes, XY). They divide by *mitosis* into daughter cells; one adheres to the basement membrane and maintains the *germinal line*, the other moves into the epithelial matrix, forming a *primary spermatocyte*, which divides by *meiosis* (plate 150) to form *secondary spermatocytes* and finally *spermatids*. The spermatogenic cells are interconnected by *cytoplasmic bridges*, enabling them to divide in synchrony.

Sperm cells are formed from differentiation of haploid spermatids—The spermatids are *haploid* cells, having 22 somatic chromosomes and one sex chromosome, X or Y. The final stage of spermatogenesis, called *spermiogenesis*, involves morphological differentiation of spermatids into unique, specialized cells called *spermatozoa (sperm, sperm cells)*, each of which possesses a tail for flagellar motility. Sperm cells are released into the ST lumen by a process called *spermeation*. The entire duration of spermatogenesis takes about 10 weeks; over 500 sperm cells are produced from each spermatogonium.

THE SERTOLI CELLS SUPPORT SPERM FORMATION

The Sertoli cells (SC) participate in spermatogenesis in several ways. (1) They support the germ cells, moving them along their inward migration within the epithelium. (2) The SC play an important role in spermiogenesis by engulfing and digesting the remaining pieces of cytoplasm and cellular debris *(residual bodies)* left over from spermatid transformation into sperm. The SC also help release sperm into the lumen (spermeation). (3) The SC secrete a fluid into the ST lumen that assists in sperm transport out of the testis into the epididymis. (4) The SC provide nutrients and metabolites to the developing germ cells and provide a testis–blood barrier that isolates the germ cells from the blood and protects the sperm from antibodies and T-cell attack; sperm cells carry several antigens on their surface that are foreign to the body's immune system. The barrier also stops leakage of these antigens to the blood.

Secretions of the Sertoli cells—To perform their functions, the SCs require the male sex steroid hormone, *testosterone*. Testosterone is also required for the development of germinal cells in the STs and for the final maturation of the sperm in the *epididymis*. Testosterone is provided to the SCs from the Leydig cells, through the basement membrane. To maintain a high local concentration of testosterone, the SCs form and secrete into the lumen the *androgen-binding protein (ABP)*, which acts as a carrier and reservoir for testosterone. Adult SCs also produce the hormone inhibin for regulation of testis function by the pituitary gland (plate 152); fetal SCs produce a Mullerian Inhibiting Substance (MIP) (plate 160).

FACTORS THAT INFLUENCE SPERM FORMATION

Temperature is a critical environmental factor in sperm formation. Spermatogenesis is optimal at 32 °C, five degrees below the body temperature. If the testes are strapped tightly against the body, the germinal epithelium regresses, with no effects to the Leydig cells and hormone production. The scrotum helps maintain the optimal temperature for the testis by retracting in the cold and relaxing in a hot environment. Blood entering the testes is cooler than normal due to special vascular mechanisms. Other physical factors: as X-ray and ionizing radiation, are also detrimental for spermatogenesis. Malnutrition, alcoholism, cadmium salts, and some drugs reduce spermatogenesis. Gossypol, a cottonseed oil taken orally, attacks spermatids and can act as a specific male contraceptive. Vitamin E is essential for spermatogenesis in rats.

SPERM MATURATION TAKES PLACE IN THE EPIDIDYMIS

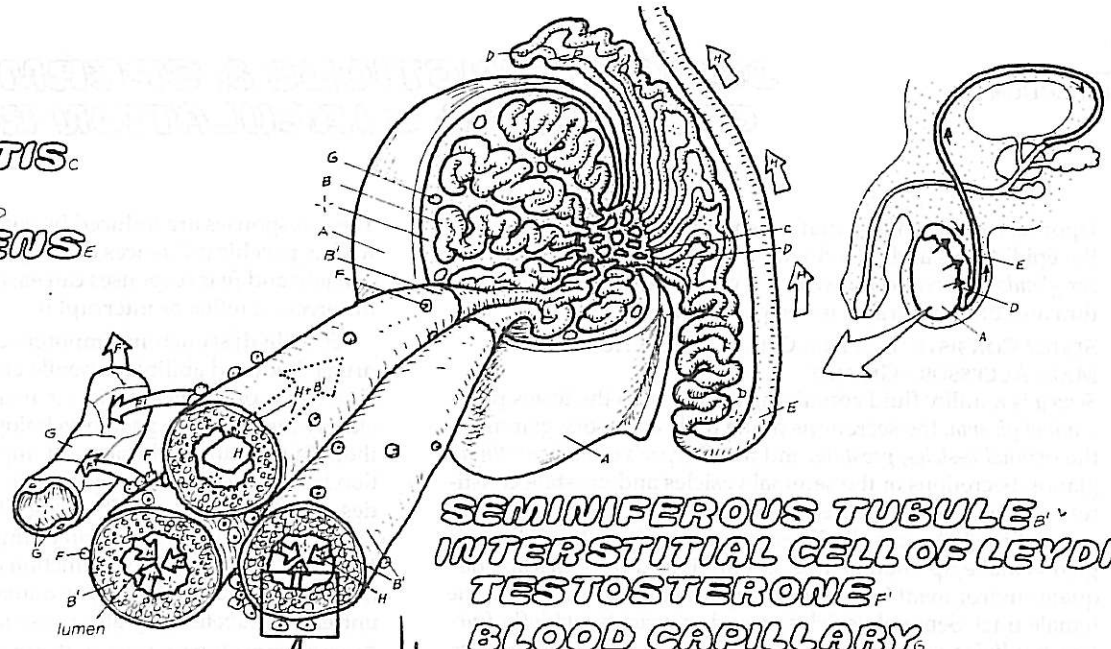
The sperm released into STs are not functionally mature; they are not motile and cannot fertilize an ovum. Functional maturity occurs mainly in the *epididymis* and partly in the female tract (*capacitation*). Sperm move to the epididymis through the *rete testis*, a network of anastomosing conduits. Transport is aided by a fluid produced by the SCs. The *efferent ducts* connect the rete testis to the epididymis, a long convoluted tubule that has three parts: head, middle segment, and tail. In the course of two weeks, sperm move from the head part to the middle segment and finally into the tail segment, where the functionally mature sperm are stored. Testosterone and special proteins secreted from epididymis wall cells stimulate sperm maturation. Mature sperm are expelled through the *vas deferens* upon sexual excitation and ejaculation. Unused sperm undergo aging and death and are removed by phagocytosis.

Number & characteristics of sperm cells—Mature sperm cells are 50 μm long and highly motile. They comprise a head, a mid-piece, and a tail. The head contains the *nucleus* and the *acrosome*; the *acrosomal enzymes* are essential for penetration of the egg during fertilization (plate 156). The mid-piece contains the mitochondria that provide ATP for sperm motility. The sperm tail functions as a motile *flagellum* enabling it to swim at a rate of about 1 mm/min. Sperm production begins in boys at puberty (14 years) and continues to old age, at a rate of about 200×10^6 per day; there is a seasonal increase in the winter and a steady decline during old age. Sperm number is critical for fertility. About 100×10^6 sperm per ml of semen (300×10^6 per ejaculate) is normal for proper fertility. Sperm counts below 20% of normal are infertile. The count reversibly diminishes following repeated ejaculations.

CN: Use the same colors as on the previous page for (A), (D), and (E). Use red for G.
1. Begin with the diagram in the upper right corner, and then color the large illustration to its left.
2. Color the enlargement of a tubule section, beginning at the bottom of the square. Interstitial cells (F) are shown outside the tubule, secreting testosterone (F^1) into the Sertoli cells (O) as well as into an adjacent blood capillary (G). The various cells within the tubule have their identifying labels placed within them, and both their cytoplasm and nucleus should be colored. Note the huge nucleus and cytoplasm of the Sertoli cells (O), which form a backdrop to the much smaller cells adjoining them.
3. Color the stages of spermatogenesis, beginning with the dividing spermatogonium (K).

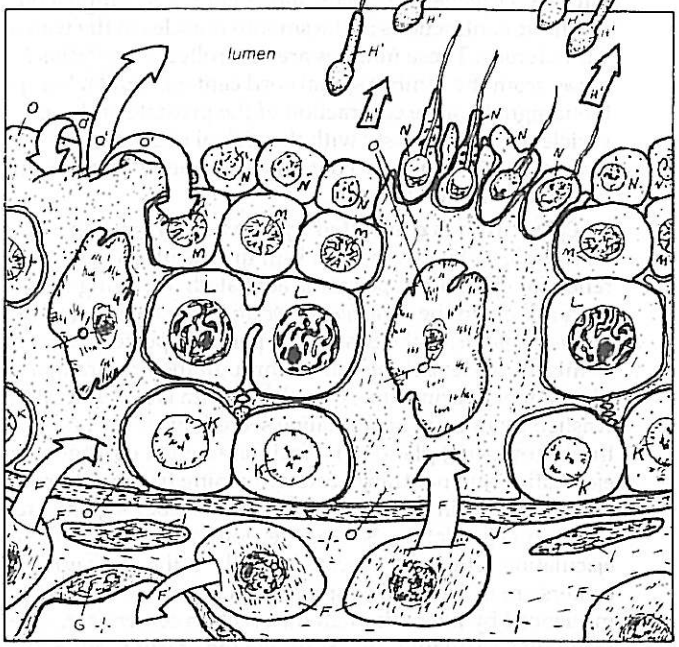
TESTIS A
LOBULE B
RETE TESTIS C
EPIDIDYMIS D
VAS DEFERENS E

Both testes have many lobules, each containing long, very convoluted seminiferous tubules (STs). These STs form the spermatozoa – the male gametes – which are released into the ST lumen and are transported to the epididymis through the rete testis (see H arrows). Upon final maturation in the epididymis, sperm are expelled via the vas deferens (H arrows) during sexual ejaculation.



SEMINIFEROUS TUBULE B'
INTERSTITIAL CELL OF LEYDIG F
TESTOSTERONE F'
BLOOD CAPILLARY G

The interstitial cells of Leydig, located between the STs, secrete testosterone, the male sex hormone, into the blood capillaries (F arrows). Testosterone is also necessary for spermatogenesis.



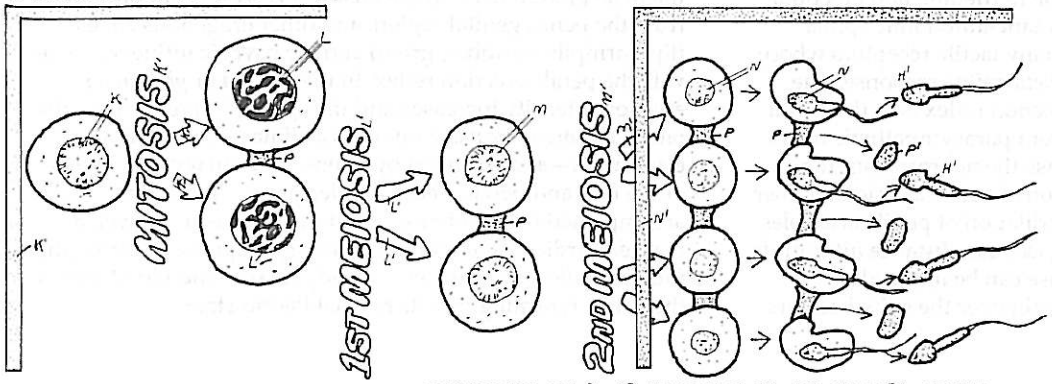
SPERM FORMATION H-
MYOID CELL I
BASEMENT MEMBRANE J
SPERMATOGONIUM K
PRIMARY SPERMATOCYTE L
SECONDARY SPERMATO. M
SPERMATID N
SPERMATOZOON H'
SERTOLI CELL. ABP O'

Spermatogenesis occurs in the STs. Spermatogonia, attached to the basement membrane, undergo successive stages of mitotic and meiotic divisions, forming first the primary and then the secondary spermatocytes, followed by the spermatids. The spermatids undergo morphologic changes, forming the spermatozoa (sperm), which are highly differentiated, specialized cells that possess a flagellum (tail) for motility. The Sertoli cells form androgen-binding protein and play crucial roles in support of spermatogenesis.

STAGES OF SPERMATOGENESIS H-

46 K' CHROMOSOMES K'

23 N' CHROMOSOMES N'



CYTOPLASMIC BRIDGE P
RESIDUAL BODY P'

Spermatozoa contain only one half the number of chromosomes found in spermatogonia. This reduction is accomplished through division by meiosis; spermatogonia (diploid) divide first by mitosis to produce primary spermatocytes and preserve their own line. Each diploid (2n) spermatocyte divides by meiosis, forming tetraploid spermatocytes (4n chromosomes), which then go through two meiotic divisions to form four haploid (n chromosomes) spermatids/spermatozoa. Cytoplasmic bridges between several germ cells (a clone) allow their synchronous divisions. Spermatozoa are released into the lumen by the shedding their extra cytoplasmic remnants (residual bodies).

SEMEN FUNCTIONS & SPERM DELIVERY; ERECTION & EJACULATION RESPONSES

Upon sexual excitation, mature sperm are mobilized out of the epididymis and mixed with the secretions of the *accessory sex glands* to form *semen*, which is expelled through the urethra and urethral orifice in the penis head.

SEMEN CONSISTS OF SPERM CELLS & SECRETIONS OF MALE ACCESSORY GLANDS

Semen is a milky fluid containing sperm from the testes plus *seminal plasma*, the secretions of the male accessory glands—the *seminal vesicles, prostate,* and the *Cowper's* or *bulbourethral* glands. Secretions of the seminal vesicles and prostate constitute 60% and 20% of semen volume, respectively; the sperm account for 10%, and alkalines and mucus from the Cowper's glands make up another 10%. Seminal fluid provides an adequate environment for sperm nourishment and survival in the female tract. Seminal vesicles provide nutrients—chiefly *fructose*, but *lipids*, some *amino acids*, and *vitamins B* and *C* are also found. All are needed for sperm activity and survival. Prostaglandins, also from the seminal vesicles, may aid in sperm transport by stimulating smooth muscles in the female tract.

Like blood, semen clots when outside the body; this clot will then liquefy. The proteins and enzymes (fibrinogen, phosphatase, fibrinolysin) needed for clotting and lysing are secreted by the prostate. Semen contains zinc and electrolytes (K^+, Na^+, Ca^{++}, Mg^{++}, HCO_3^-, and Cl^-) and shows a somewhat alkaline pH of about 7.4, due to bicarbonate buffers from the Cowper's glands. Bicarbonate neutralizes acidity related to vaginal secretions and urine passage in the urethra; acidity is detrimental to the sperm.

PENILE ERECTION INVOLVES NEURAL & VASCULAR RESPONSE

The main function of the penis is to ensure deposit of sperm deep in the vagina, near the uterine cervix. Penile insertion and penetration of the vagina is called *intromission*. The penis is normally short and flaccid. To enable intromission, the penis develops a state of *erection*, which transforms it into a hardened, lengthened organ capable of penetrating the vagina. Erection occurs following sexual excitation and involves dilation of penile arterioles, allowing substantial inflow of blood to penile *erectile tissue*. Two *cavernous bodies* run along the dorsal and lateral aspects of the penis and one *spongy body* lies along its ventral aspect; the spongy body surrounds the urethra and fills the penis head (*glans*). The erectile tissue consists of numerous small elastic chambers of modified vascular and connective tissue that can fill with blood.

Erection is controlled by spinal reflexes and psychogenic stimuli from the brain. During sexual excitation, penile arterioles dilate and blood fills the chambers of the erectile bodies, leading to their turgidity and inflation. The resultant pressure closes the elastic venous outlets, trapping the blood within the erectile tissue, leading to penile hardening and erection. Erection is brought about by a somatic-autonomic spinal reflex. The glans penis contains many tactile receptors whose stimulation initiates a *parasympathetic* reflex response. The neural center for control of the erection reflex is in the sacral segments of the spinal cord. Efferent parasympathetic fibers in the *pelvic splanchnic nerves* release the neurotransmitter acetylcholine to induce vasodilation of penile arterioles. Other neurotransmitters that cause vasodilation of penile arterioles are the polypeptide *VIP* and the gaseous substance *nitric oxide* (NO). In humans, erection response can be induced by descending influences from the brain over the spinal centers. These responses are induced by sight, sound, and smell as well as psychic influences of imagination and dreaming. Anxiety and fear responses can easily inhibit the activation of the erection reflex or interrupt it.

Erectile dysfunction (impotence) may be treated with drugs. Reduced ability for penile erection is called *erectile dysfunction* or *impotence* and occurs in some adults and many elderly males. In the past, psychological influences were thought to be the main cause of impotence, but recently attention has focused on the physiological and vascular abnormalities of the penile tissue. The drug Viagra, now used widely to correct erectile dysfunction or improve performance, enhances the vasodilatory function of the neurotransmitter nitric oxide. Autonomic nerve damage due to advanced untreated diabetes may also cause impotence.

EJACULATION IS THE REFLEX EXPULSION OF SEMEN

The expulsion of semen from the penis occurs in two stages, *emission* and *ejaculation proper*. Emission refers to the movement of sperm from the epididymis up along the *vas deferens* into the *ejaculatory duct*. This movement is accomplished by rhythmic contractions of the smooth muscles in the wall of the vas deferens. These muscles are controlled by *sympathetic nerves* from the lumbar spinal cord centers. Similar sympathetic signals cause contraction of the prostate and seminal vesicles simultaneously with the arrival of sperm into the ejaculatory duct, so that the contents of the prostate and seminal vesicles are added to them.

Ejaculation is controlled by nerves and smooth & skeletal muscles. Once the semen is in the ejaculatory duct, a new reflex for ejaculation proper is activated, involving somatic motor fibers in the *pudendal nerve* and the skeletal muscle *bulbospongiosus*, at the base of the penis. Repeated contractions of this muscle expel the semen through the urethra in a pulsatile manner. During emission, the urethra is prelubricated and washed by mucoid and alkaline secretions of the bulbourethral (Cowper's) glands that facilitate semen passage during ejaculation and neutralize acid remaining from past urination. Abnormalities in the functions of the Cowper's glands result in painful ejaculation. Sensory receptors for emission and ejaculation reflexes are located mainly at the *glans penis*; their centers are in the lumbar spinal cord. These centers are less influenced by the brain than the erection centers are. As a result, the ejaculation reflex, unlike the erection reflex, cannot be interrupted by inhibitory stimuli from the brain.

HUMAN SEXUAL RESPONSE HAS FOUR PHASES

The bodies of human males and females show a general pattern of stereotypic responses during sexual activity. Four phases are recognized that occur consecutively. We review the male pattern here. In the *excitement phase*, erotic stimuli from the penis, genital region, and other erogenous zones (lips, armpits, earlobes, groin) and/or psychic influences activate the penile erection reflex. In the second or *plateau phase*, erection intensity increases and the ejaculation reflex is facilitated. The *orgasmic phase* involves a climax—completion of ejaculation—accompanied by intense muscular contractions of the face and pelvic, chest, and leg areas. This phase is accompanied by an intense sensation of pleasure as well as marked cardiovascular and respiratory responses. During the final *resolution phase*, the entire body relaxes and blood leaves the penis, returning it to its normal flaccid state .

CN: Use dark colors for A, C, and light blue for L.
1. Color the titles in order as you follow the numbered sequence, beginning with a rise in external temperature (A') lowering the scrotum (A) and testes (B).
2. Color the neural regulation diagrams with the title "inputs."
3. Color the actions of Viagra in the lower left corner.

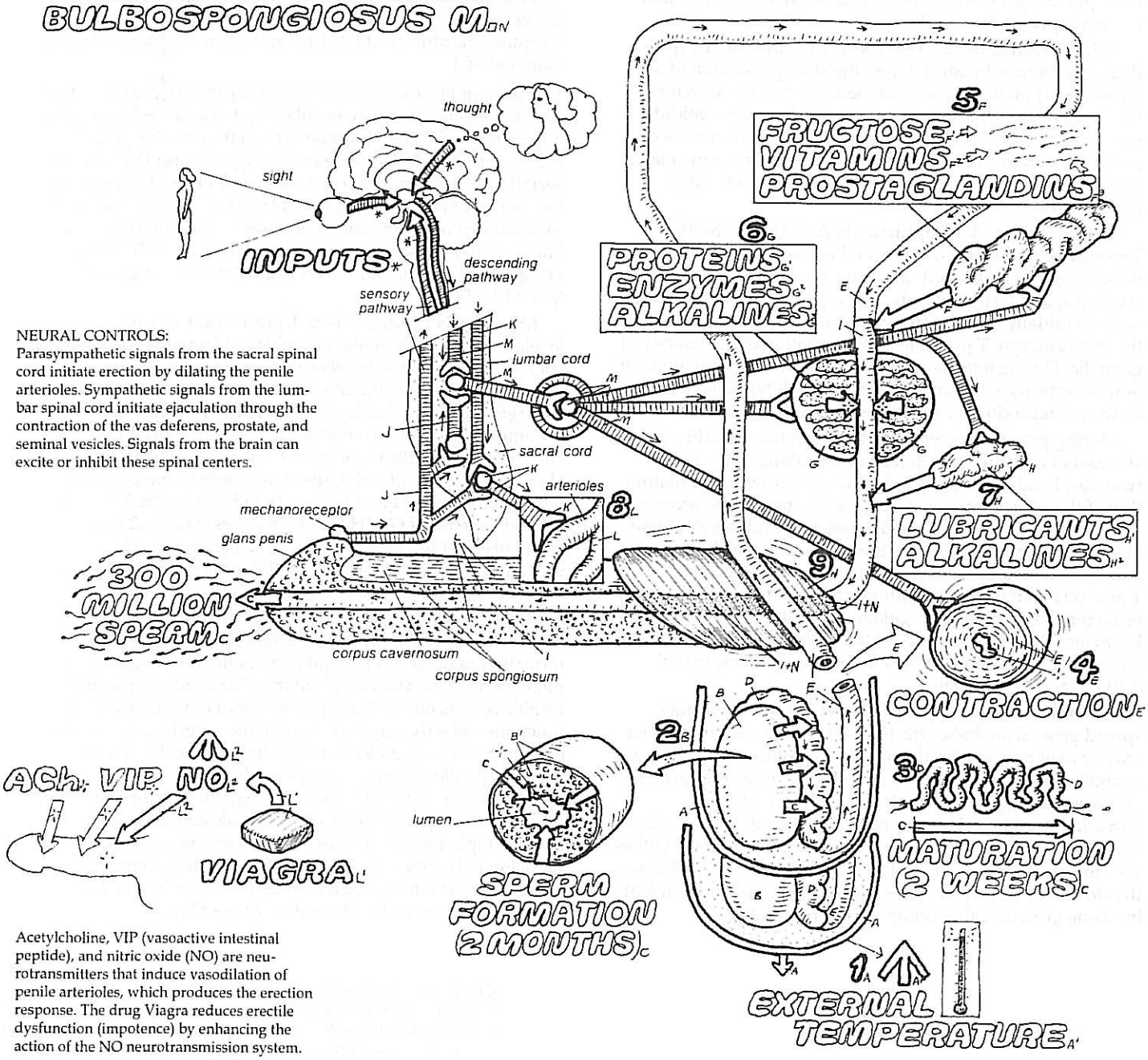
SCROTUM A
TESTIS B
SEMINIFEROUS TUBULE B'
SPERM C
EPIDIDYMIS D
VAS DEFERENS E
SEMINAL VESICLE F
PROSTATE GLAND G
BULBOURETHRAL GLAND H
URETHRA I

ERECTION OF PENIS J
SENSORY NERVE J
PARASYMPATHETIC NERVE K
ERECTILE VASCULAR TISSUE L

EJACULATION OF SEMEN J'
SYMPATHETIC NERVE M
BULBOSPONGIOSUS M AND N

(1) The optimal temperature for sperm formation is 32°C, five degrees below body temperature. The scrotum maintains the testes at an appropriate distance from the body. (2) Sperm formation occurs in the testes and takes two and a half months. (3) Newly formed sperm are continuously released into the lumen of the seminiferous tubules and transported to the epididymis, where they stay for two weeks to mature. (4) Contractions of the vas deferens transport sperm into the ejaculatory ducts, where they are joined by the secretions of the prostate and seminal vesicles and are expelled out through the urethra. (5) The seminal vesicles secrete nutrients. (6) The prostate secretes proteins and enzymes for sperm survival. (7) The bulbourethral glands secrete alkalines and lubricants to facilitate sperm transport. (8) Erection of the penis is a vasocongestive response of the penile erectile tissues—the corpus cavernosum and the corpus spongiosum. (9) The bulbospongiosus muscle expels semen through the urethra.

NEURAL CONTROLS:
Parasympathetic signals from the sacral spinal cord initiate erection by dilating the penile arterioles. Sympathetic signals from the lumbar spinal cord initiate ejaculation through the contraction of the vas deferens, prostate, and seminal vesicles. Signals from the brain can excite or inhibit these spinal centers.



Acetylcholine, VIP (vasoactive intestinal peptide), and nitric oxide (NO) are neurotransmitters that induce vasodilation of penile arterioles, which produces the erection response. The drug Viagra reduces erectile dysfunction (impotence) by enhancing the action of the NO neurotransmission system.

ACTIONS OF TESTOSTERONE & HORMONAL REGULATION OF TESTES

Testosterone (T) is the principal testicular hormone, secreted from the *interstitial cells of Leydig* at a rate of 10 mg per day. T is a steroid made from cholesterol and is the principal circulating androgen ("male maker" hormone). Other androgenic steroids are *di-hydroxy-testosterone* (DHT) and *de-hydro-epi-androsterone* (DHEA). DHEA is a precursor of T synthesis and is the main adrenal gland androgen. DHT is formed by conversion of T by the enzyme *α-reductase* and is present in plasma and in some body cells. Androgenic potency of T is less than DHT but much higher than DHEA.

TESTOSTERONE EXERTS THREE MAJOR TYPES OF ACTIONS

T has widespread effects in the body, which may be divided into three groups: (1) effects in adult male sexuality and reproduction; (2) actions on the development of the reproductive system and brain of the fetal male, as well orchestrating male puberty and body growth and behavior changes; and (3) non-reproductive, anabolic effects in the adult.

Stimulation and maintenance of the adult male reproductive system—In adult males, the steady secretion of testosterone (1) maintains spermatogenesis and the secretory functions of the accessory sex organs and glands—epididymis, prostate, and seminal vesicles; (2) maintains male secondary sex characteristics, including muscle and bone mass; and (3) promotes sex drive (libido) and other brain and mental effects.

Actions on the developing male & during puberty—The testes of the embryo, fetus, and neonate secrete T during these stages. In childhood, the testes remain inactive, only to start up again during puberty. The reproductive organs of the embryo initially are sexually indifferent and bipotential. In the male embryo, T promotes differentiation of the male-type genitalia. During fetal development, T promotes development of male-type hypothalamic systems, which regulate neural control of reproductive hormones and male sexual behavior.

During puberty, secretion of T in boys rises steadily from 10 years of age through adolescence, peaking in the early twenties. In adolescent boys, T promotes growth and maturation of the *primary sex organs* (e.g., testes, penis) and *accessory sex glands* (e.g., prostate, seminal vesicles), and development of *secondary sex characteristics* (low-pitched voice, dense facial and body hair, enhanced muscular and skeletal growth). T also acts on the brain to promote final maturation of the brain centers involved in regulating sexual activity and sexual behavior. Thus, immature boys transform into young men with fertile sperm and interest in the opposite sex, sexual activity, and procreation.

Anabolic and non-reproductive effects—T has widespread general anabolic effects on body cells and tissues that may or may not be related to maleness. Androgens enhance anabolism in many tissues by increasing synthesis of proteins and stimulating tissue growth. Increasing levels of T in adolescent boys increase bone growth and calcium deposition and enhance muscle mass by increasing protein synthesis. However, peak levels of T in post-adolescent boys induce the closure of epiphyseal plates of the bone, thereby terminating bone growth. Other non-reproductive effects include increasing the size of the kidneys and formation of red blood cells in the bone marrow. Large doses of T are used to stimulate tissue growth in emaciated patients and to enhance muscle mass in athletes. However, negative side effects of increased libido and decreased fertility (sperm production) discourage such uses.

Cellular mechanisms of T actions in target tissues—The cellular mechanism of action of T in its targets follows the general pathway for steroid hormones (plate 114). In the adult male reproductive tissue, T diffuses into a target cell nucleus to bind with nuclear androgen receptors possessing binding sites for T and DNA, initiating gene action and synthesis of mRNA and proteins that mediate T actions. In the developing brain, T is first converted to estrogen by neuronal aromatase before receptor binding. In certain body tissues during sexual maturation and puberty, T is first converted to DHT by the target cell α-reductase; DHT then binds to the androgen receptor. The affinity of DHT for androgen receptors is higher than that of T.

TESTICULAR FUNCTIONS REGULATED BY PITUITARY LH & FSH

The testes' functions are controlled by LH and FSH, two gonadotropin glycoprotein hormones from the anterior pituitary gland. LH controls T release by Leydig cells and FSH acts on Sertoli cells to control spermatogenesis. LH and FSH actions follow these steps: binding with plasma membrane receptors → activation of membrane G-proteins → activation of membrane adenylate cyclase → formation of cyclic AMP, which brings about the cellular effects of LH/FSH on target cells (plate 12, 114).

LH controls Leydig cells & T production—Steady plasma levels of T in mature males are achieved by the negative feedback effect of T on the *hypothalamus* and *anterior pituitary*. A decrease in T level stimulates the hypothalamus to release more *gonadotropin-releasing hormone* (GnRH), which stimulates the anterior pituitary to release LH into the blood. LH stimulates the Leydig cells to increase T release. If T levels increase above the normal set point, the same feedback mechanism will diminish GnRH and LH levels and restore the T level to normal. Release of GnRH occurs in *pulses* every 1–2 hours, each pulse lasting a few minutes. Changes in T levels change the frequency and intensity of GnRH pulses. Pulsatile secretion of LH is critical, since continuous secretion of GnRH desensitizes the pituitary, reducing plasma LH levels.

FSH controls Sertoli cells & spermatogenesis—Sperm formation in the testes is regulated mainly by the gonadotropin FSH from the anterior pituitary. FSH exerts tropin and trophic actions on the Sertoli cells, stimulating their various functions—chiefly, support of spermatogenesis and secretion of *androgen binding protein* (ABP). The Sertoli cells in turn secrete a peptide hormone, *inhibin*, which acts on the anterior pituitary to regulate FSH release by negative feedback. In fact, inhibin has the potential for use as a male contraceptive, because high doses of it cause reduced sperm production by reducing FSH secretion. LH is also important for spermatogenesis, but its effect is mediated by release of T, which in turn stimulates Sertoli cell function (plate 151).

CN: Use red for B and a dark color for A.
1. Begin with testosterone (A) functions as shown by the three arrows from an interstitial cell (G) in the right central portion of the page.
2. Go to the titles at the top of the page.

HORMONAL REGULATION OF TESTIS FUNCTION

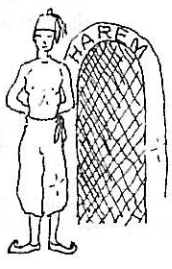
HYPOTHALAMUS$_C$
GONADOTROPIN RELEASING HORMONE,
ANTERIOR PITUITARY$_E$
LUTEINIZING HORMONE (LH)$_F$
INTERSTITIAL CELL (OF LEYDIG)$_G$
FOLLICLE-STIMULATING HORMONE (FSH)$_H$
SERTOLI CELL$_I$
ANDROGEN-BINDING PROTEIN (ABP),
INHIBIN$_K$

ACTIONS OF TESTOSTERONE$_A$

Testosterone (T), the testes' main androgen hormone, is a steroid derived from cholesterol and secreted by the Leydig cells to promote growth and maintenance of the male reproductive system and secondary sexual characteristics, including enhanced bone and muscular development as well as anabolic effects on body cells. Direct secretion of T into the seminiferous tubules stimulates Sertoli cell functions: promotion of spermatogenesis and maturation and survival of sperm cells. Cellular effects of T are exerted either directly or by conversion to estrogen or to dihyroxy-testosterone (DHT), a more potent androgen.

SPERMATOGENESIS*

Secretion of T by Leydig cells is regulated by pituitary LH via negative feedback. High T inhibits LH secretion and low T stimulates it. Sperm formation is regulated by pituitary FSH. FSH stimulates Sertoli cells which support formation of sperm and androgen-binding protein (ABP). This protein provides high T levels in the tubules for sperm formation and maturation. FSH levels are regulated by the hormone inhibin from Sertoli cells. Low FSH decreases inhibin, which then increases FSH release by negative feedback effects, and vice versa. The hypothalamic peptide hormone GnRH regulates FSH and LH by a pulsatile release pattern. GnRH mediates the T negative feedback and other psychic and brain influences over the gonads.



Abnormally low T levels are caused by *hypogonadism*, mainly due to pituitary disorder. In *eunuchs*, testes or Leydig cell are absent or deficient from childhood. Low T levels prevents development of male secondary sexual characteristics. Eunuchs are femalelike but tend to be tall with long limbs due to delayed closure of epiphyseal plates in the long bones.

In rare cases, young male children show *precocious puberty*, usually because of hypothalamus or pituitary tumors; T levels are increased, leading to early sexual development and appearance of male secondary sexual characteristics as well as excessive muscle growth ("boy Hercules"); stature is stunted, due to premature closure of epiphyseal plates.

FUNCTIONS OF THE OVARY: FORMATION OF THE EGG & OVULATION

The *ovary* performs two functions: (1) formation, development, and release of the egg (ovum); and (2) secretion of the female sex hormones, *estrogen* and *progesterone*.

THE OVARY HELPS FORM, MATURE, & RELEASE OVA

Oocytes form only prenatally & occur within follicles— In the ovaries of the developing female embryo, the *oogonia* proliferate by mitosis to form millions of *primary oocytes* but cease to divide thereafter. This is in contrast to males, where spermatogonia divide after puberty and through old age. The fetal primary oocytes begin meiosis but stop at the prophase stage and remain in this arrested state through birth and childhood until puberty, when division is resumed. Each primary oocyte is surrounded by a thin layer of *granulosa cells*, forming the *primary* or *primordial follicle*. The follicular cells are important in nourishment and development of the oocytes and their preparation for fertilization.

Most follicles and their oocytes are lost before puberty— The initial number of primary follicles, 3 million per fetal ovary, diminishes to about 1 million at birth and 100,000 by puberty, a loss of more than 95%. The loss is called *atresia* and may be a form of programmed cell death (*apoptosis*). Atresia continues throughout maturity so that by 40 years, less than 1000 and by 50 years no primary follicles and oocytes are found in the ovaries. The loss of primary follicles is the main cause of *menopause*, the cessation of menstrual cycles and fertility in women over fifty. Since less than 500 eggs in all will be released in a woman during her reproductive period (15 to 50 years), the atretic losses of eggs may not be so significant. But aging of ova and follicles may underlie developmental abnormalities such as Down's syndrome.

FOLLICULAR & LUTEAL PHASES OF OVARIAN CYCLE

Development and release of ova occur in cycles— In contrast to sperm production by the testes, which occurs continuously, maturation and release of ova in the ovaries of mature women occur cyclically at 28-day intervals. During each cycle, usually one oocyte undergoes development and the resulting ovum is released at midcycle (day 14). About 1% of ovarian cycles involve development of multiple oocytes and ovulation, resulting in the birth of fraternal twins, triplets, etc. The ovarian cycle is the basis of the menstrual cycle (plate 154).

In the follicular phase, a follicle matures, forming theca and granulosa cells and a fluid-filled antrum— At the beginning of each 28-day cycle a few primary follicles begin to grow. A week later, only one—the *dominant follicle*—continues development while the others regress. In the dominant follicle, follicular cells proliferate, forming several layers of the *granulosa cells* surrounding the oocyte. Later another layer, *theca interna cells*, forms around the granulosa cells, with a *basement membrane* in between. The granulosa cells form a cavity around the oocytes called the *antrum*, filled with *antral fluid;* this fluid is rich in some proteins, hormones, and *hyaluronic acid*, a sticky substance. Theca interna and granulosa cells also produce *estrogen*, the female sex hormone, for release into the blood and the antral cavity, respectively. A fully mature Graffian follicle reaches a size of about 2 cm. The development of a follicle during the follicular phase is regulated by the gonadotropins FSH and LH. FSH is required for proliferation of granulosa and theca cells; LH preferentially stimulates estrogen secretion. Theca interna cells have many receptors for LH. Estrogen also aids follicular development.

Zona pellucida & cumulus oophorus surround the oocyte— In the Graffian follicle, the oocyte is surrounded by a zone of transparent jellylike substance, the *zona pellucida*. This zone is in turn surrounded by a thin layer of granulosa cells, forming the *cumulus oophorus* ("egg cloud"), which is continuous with the main mass of granulosa cells. The oocyte and its membranes are exposed to the antral fluid, which helps nourish and mature the developing egg. By days 12–13 of the cycle, the oocyte along with its surrounding cell layers is often found floating in the antrum.

A burst in LH and internal follicular changes lead to ovulation— By day 14 (midcycle), the *Graffian follicle*, is seen protruding from the weak ovarian surface, ruptures, releasing the oocyte, with its appendages of follicular cells and antral fluid, into the peritoneal cavity near the *fimbria* of the *uterine tube*. An event called *ovulation*. Ovulation is caused by increased pressure of the antral fluid and lysis of the follicular wall and is associated with increased release of histamine, prostaglandins, and proteolytic enzymes as well as bleeding in the follicle. A burst of LH lasting for 2—3 days stimulates ovulation. This burst and the cyclical changes in LH and FSH during the cycle are controlled by the gonadotropin-releasing hormone GnRH from the hypothalamus along with the feedback effects of estrogen and progesterone (plate 155).

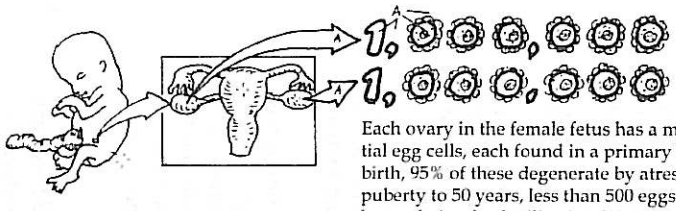
Formation & secretions of the corpus luteum constitute the luteal phase— After ovulation, the remaining follicular cells form the *corpus luteum* (yellow body), which secretes mainly progesterone and some estrogen and grows for at least a week (*mature corpus luteum*). Formation of the corpus luteum and its growth are stimulated chiefly by the pituitary hormone LH, but FSH is also needed. If the egg is fertilized and an embryo forms, an LH-like hormonal signal from the young embryo (hCG, human chorionic gonadotropin, plate 157) stimulates the corpus luteum to grow further and secrete larger amounts of progesterone and estrogen to maintain pregnancy. In the absence of fertilization and hCG, the corpus luteum degenerates into the *corpus albicans* (white body).

GROWTH, MATURATION, & FINAL DIVISIONS OF THE OVUM

Early in the follicular phase, the primary oocyte resumes its meiotic division and grows in size. High concentrations of hormones and growth factors in the antral fluid may aid the ovum's development. The first meiotic division is completed before ovulation, forming the secondary oocyte and one *polar body* (cell). The secondary oocyte receives half the chromosomes and all the cytoplasm, while the polar body receives little cytoplasm but an equal share of chromosomes. Before ovulation, the secondary oocyte begins its second meiotic division but stops at metaphase and the ovum undergoes ovulation. After fertilization, the ovum completes its second meiotic division, forming the mature and haploid *female pronucleus* and the second polar body. The first polar body may also divide, forming three polar bodies altogether.

CN: Use yellow for G. Use light colors throughout.
1. Begin with the diagram in the upper right corner, coloring the 2 million "eggs."
2. Color the follicle-stimulating hormone (B') chartline and then the development of a single follicle, starting with a primary follicle (B'). When you reach the 14th day of the sequence, color the luteinizing hormone (G^3) and the corpus luteum (G) development.
3. Color the stages of oogenesis along the bottom.

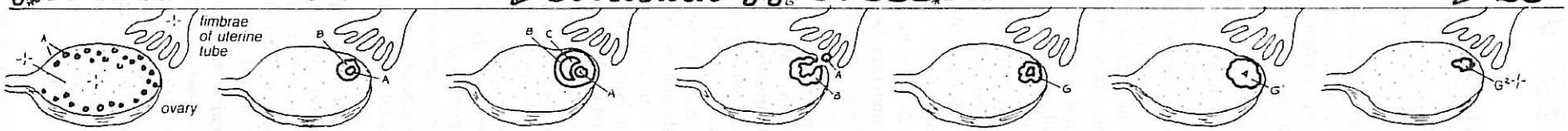
PRIMARY OOCYTE
GRANULOSA CELLS
ANTRUM, ANTRAL FLUID
THECA CELLS, ZONA PELLUCIDA
CUMULUS OOPHORUS
SECONDARY OOCYTE (OVUM)



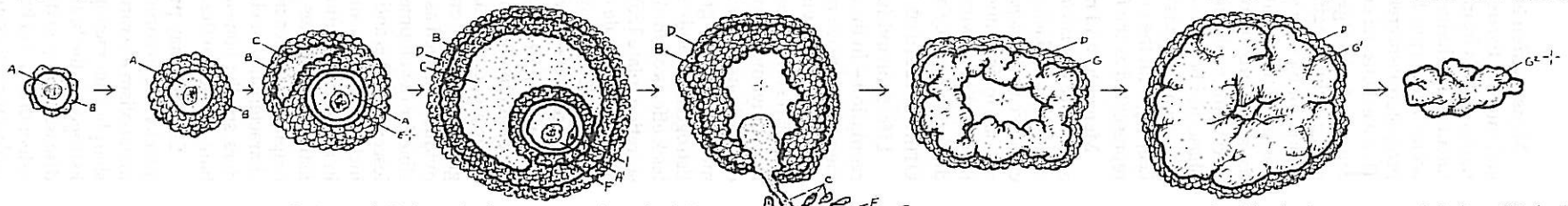
Each ovary in the female fetus has a million potential egg cells, each found in a primary follicle. After birth, 95% of these degenerate by atresia. From puberty to 50 years, less than 500 eggs are released by ovulation for fertilization (12 per year for 35 years); the rest degenerate by atresia.

DAYS

1 OVARIAN 14 CYCLE 28



PRIMARY FOLLICLE | MATURING FOLLICLE | MATURE FOLLICLE | RUPTURED FOLLICLE | CORPUS LUTEUM | MATURE CORP. LUT. | CORPUS ALBICANS



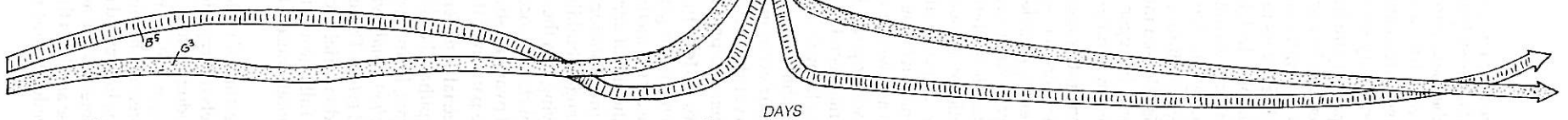
During each 28-day cycle, the ovary goes through a follicular phase (days 1–14) and a luteal phase (days 14–28). In the follicular phase, pituitary FSH (plus LH) stimulates the granulosa cells (GC) of the primary follicles to proliferate and grow. The maturing follicle develops a fluid-filled cavity (antrum) and a layer of theca cells around the GCs. The GCs form estrogen, which diffuses to theca cells for release into blood. The ovum also develops in this phase into a secondary oocyte with a zona pellucida and layers of follicular cells (cumulus oophorus) around it.

OVULATION

At midcycle, due to a surge of pituitary LH, the Graffian follicle ruptures, releasing the ovum (ovulation) along with surrounding follicular cells (cumulus oophorus) and antral fluid into the peritoneal cavity. This is followed by the luteal phase (days 14–28), when the remnants of the mature follicle form the corpus luteum, which grows for a week and secretes mainly progesterone and some estrogen, in response to LH. If no fertilization occurs, the corpus luteum degenerates, forming an inert white mass, the corpus albicans.

FOLLICLE-STIMULATING HORMONE

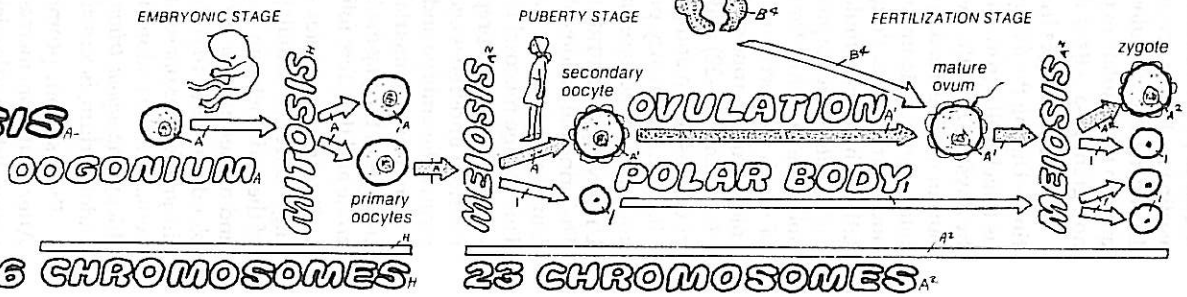
LUTEINIZING HORMONE



DAYS

1 FOLLICULAR PHASE 14 LUTEAL PHASE 28

STAGES OF OOGENESIS



In female embryos, oogonia divide and multiply by mitosis to form the diploid primary oocytes, which undergo meiosis to form the haploid ovum. But meiosis remains arrested at prophase and resumes only after puberty, when the ovary becomes active. A secondary oocyte forms shortly before ovulation. Of the two secondary oocytes, one forms the small and non-functional polar body; another becomes the large ovum, to be ovulated. The second meiotic division occurs after fertilization, forming a third polar body and the female pronucleus.

FUNCTIONS OF THE OVARY: SECRETION & ACTIONS OF FEMALE SEX HORMONES

Estrogen and *progesterone* are the hormones of the ovary. They are steroid compounds derived ultimately from cholesterol. *Estradiol*, the most potent and the main estrogen secreted, has two hydroxyl groups; progesterone has two ketone groups. As female sex hormones, they regulate many aspects of female reproduction, sexuality, and secondary sex characteristics.

Granulosa and theca cells participate in estrogen secretion—In primates, estrogen can be formed by both *granulosa* and *theca interna* cells of ovarian follicles. The theca cell layer is vascularized, allowing access to plasma cholesterol used for synthesis of estradiol, which is released into the plasma. The granulosa cell layer is avascular; these cells lack access to plasma cholesterol and synthesize estradiol by converting androgen precursors, which diffuse from theca cells. Estrogen from granulosa cells is released into the follicle antrum to stimulate ovum growth. Estrogen secretion by theca and granulosa cells is stimulated by pituitary LH and FSH.

Cyclical changes in estrogen and progesterone secretion—During the *follicular phase*, estrogen secretion increases as follicle cells grow and proliferate; peak levels are reached by days 12–13 of the ovarian cycle. After ovulation, estrogen output diminishes due to the transformation of the follicle into a corpus luteum, but secretion continues into the third and fourth weeks. Progesterone secretion increases after ovulation when LH stimulates formation of the corpus luteum. *Luteal cells* of the corpus luteum are the source of progesterone and have receptors for the gonadotropins LH and FSH, both of which are necessary for optimal secretion of female sex steroids. Progesterone secretion peaks by the middle of the luteal phase (days 20–22) and declines thereafter. The lowest levels of both estrogen and progesterone occur in the absence of fertilization. Pregnancy promotes survival of the corpus luteum and marked increases in estrogen and progesterone secretion.

UTERINE ENDOMETRIUM SHOWS A MONTHLY CYCLE

The principal actions of estrogen and progesterone in the female reproductive system are on the *uterine endometrium*. This uterine mucosal lining is the site of *implantation* of the young embryo. To prepare for implantation, the endometrium undergoes cyclical changes, building up its wall to receive the embryo and destroying it in the absence of fertilization. The endometrial cyclical changes occur as a result of changes in the plasma levels of ovarian estrogen and progesterone and therefore follows the pattern of the ovarian cycle.

Estrogen promotes endometrial proliferation & thickening—Estrogen stimulates the epithelial cells of the *basal layer* of the endometrium to proliferate, forming a thick mucosa and numerous *endometrial (uterine) glands* with extensive blood vessels (*spiral arteries* and *veins*). These events constitute the *proliferative* phase of the endometrial cycle (days 6–14). At ovulation, the endometrium is fully grown (about 5 mm thick). The *myometrium*, the smooth muscle layer under the endometrium, is less affected.

Progesterone promotes secretion of endometrial glands—After ovulation, increasing levels of progesterone from the corpus luteum stimulate the endometrial gland to secrete a juice rich in proteins and glycogen that is important for survival and maintenance of the preimplantation and implanting embryo and for adherence of the implanted embryo. This part of the endometrial cycle, promoted by the action of progesterone, is termed the *secretory phase* and lasts through days 14–28 of the cycle. Progesterone is needed to sustain pregnancies.

Menstruation is caused by shedding and bleeding of endometrial tissue—In the absence of fertilization, the hormonal signals from the embryo for survival of the corpus luteum—i.e., human chorionic gonadotropin (hCG)—will not occur. The corpus luteum regresses, decreasing estrogen and progesterone secretion in the later part of the secretory phase. This weakens the endometrium, reducing blood flow and causing local oxygen deficiency *(ischemic phase)*. By day 28, the endometrium begins to collapse and shed. Endometrial debris, along with some blood, constitutes the *menstrual flow* (menstruation, menses). This *menstrual phase* lasts about five days. The growth of follicles and increasing estrogen output during the next follicular phase terminate the menstrual phase and begin the next proliferative phase. Although the menstrual phase is the last phase of the endometrial cycle, in keeping with the events of the ovarian cycle it is customarily represented as the first phase (days 1–5).

Menarche and menopause—Menstrual cycles commence at puberty (*menarche*), usually at 12 to 13 years of age. Early cycles usually lack ovulation. In the early fifties, menstrual cycles cease (*menopause*). This event is a result of exhaustion of ovarian follicles and signals the end of reproductive functions, but not sexual activity. Menstrual cycles do not occur during pregnancy and in many lactating women.

OTHER EFFECTS OF ESTROGEN & PROGESTERONE

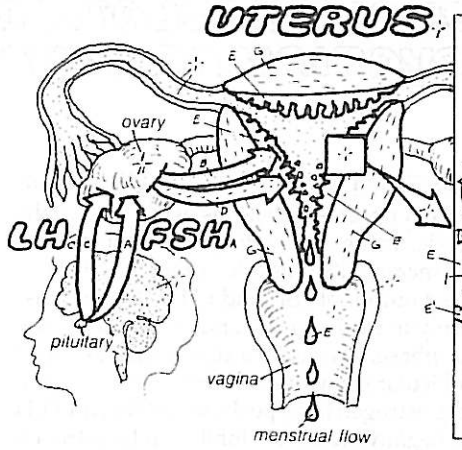
Effects on oviduct, myometrium, lactation, and feedback regulation—In the oviduct, estrogen stimulates the development of extensive mucosal folds and cilia, which function in transport of the ovum and young embryo. During pregnancy, estrogen stimulates the growth of uterine smooth muscle mass (myometrium), which functions in parturition and birth contractions (plate 158). Estrogen and progesterone stimulate mammary gland growth and support lactation (plate 159). Estrogen is mainly responsible for negative and positive feedback effects on the hypothalamus involved in regulation of its secretion (plate 155). In the brain and certain other tissues that are targets of male androgen hormones, estrogen is the true intracellular hormone mediating the androgenic effects, since androgens are converted to estrogens by aromatase.

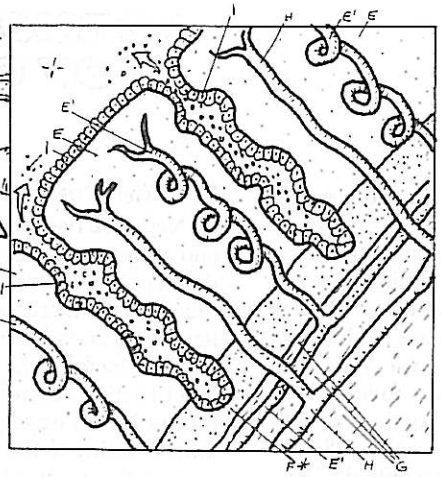
Estrogen promotes puberty and secondary sex characteristics in females—During puberty, estrogen (along with adrenal androgens) enhances bone calcium deposition and growth. It also promotes growth of the uterus, vagina, and oviducts, as well as the mammary glands. Estrogen is responsible for development of secondary sex characteristics in adolescent females and their maintenance during maturity. These include soft skin and increased subcutaneous fat, particularly in breasts and buttocks, leading to the mature female shape. Estrogen promotes the growth of a wide pelvis and closure of epiphyseal plates in long bones. Some female secondary sex characteristics, such as a high-pitched voice, narrow shoulders, smaller bone and body mass, and lack of facial and body hair, are due to the absence of male androgens.

Estrogen may protect against aging diseases—Heart attacks due to coronary occlusion and abnormal cholesterol metabolism are rare in premenopausal women but increase sharply after menopause when plasma estrogen is deficient. Estrogen in the brain may diminish the effects of Alzheimers disease. Estrogen deficiency underlies the marked increase in osteoporosis and bone fractures in elderly women. Estrogen replacement therapy can ameliorate these aging disorders.

CN: Use the same colors for FSH (A) and LH (C) as on the preceding page. Use red for E, blue for H.
1. Begin with the bottom panel, and follow the FSH contribution to the ovarian cycle and the growth of the follicular cells into the sex hormone cycle panel. Then do the LH and luteal phase portion of the ovarian cycle.
2. Go to the upper left corner and color the diagram of the uterus. Color the enlargement of the uterine wall section.

UTERUS

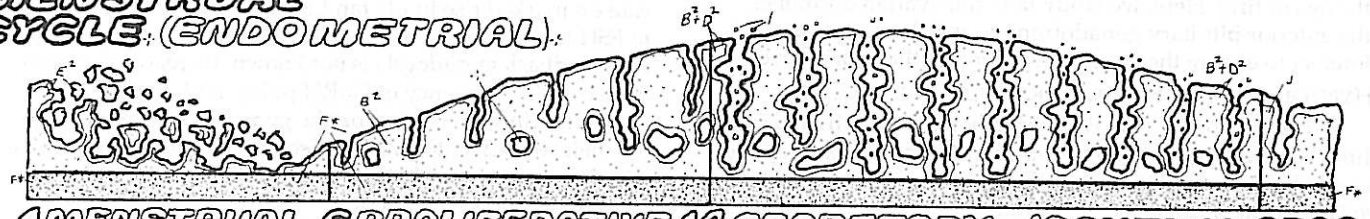




ENDOMETRIUM
BASAL LAYER
MYOMETRIUM
SPIRAL ARTERY
VEIN
UTERINE GLAND

The pear-shaped uterus is connected to the uterine tubes dorsally and to the vagina ventrally, through the uterine cervix. The uterine wall consists of two layers, the muscular myometrium and mucosal endometrium. The endometrium is an epithelium consisting of a permanent basal layer and a functional layer that is continually rebuilt and destroyed. Within the endometrium are the uterine glands, spiral arteries, veins, and the surface epithelium.

MENSTRUAL CYCLE (ENDOMETRIAL)



1 MENSTRUAL PHASE

In the first five days of the ovarian cycle, the endometrium is shed, and the debris mixed with blood constitutes the menstrual flow.

6 PROLIFERATIVE PHASE

Between days 6 to 14 (proliferative phase), stimulated by estrogen, the endometrium is rebuilt, glands are formed, and the vascular supply is reestablished.

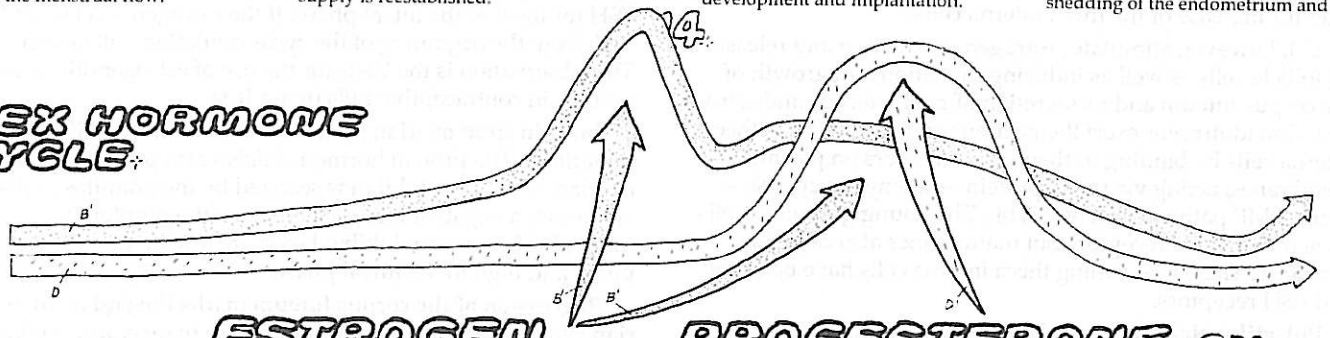
14 SECRETORY PHASE

After ovulation, in response to progesterone, endometrial glands secrete uterine fluid necessary for embryonic development and implantation.

27,28 ISCHEMIC PHASE

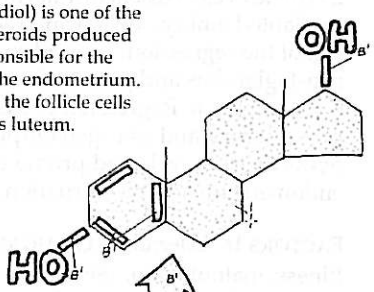
Without fertilization, estrogen and progesterone decline and endometrial blood flow diminishes (ischemic phase), causing the shedding of the endometrium and its blood.

SEX HORMONE CYCLE



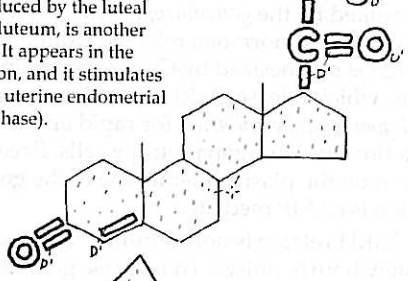
ESTROGEN

Estrogen (mainly estradiol) is one of the principal female sex steroids produced by the ovary. It is responsible for the proliferative phase of the endometrium. Estrogen is secreted by the follicle cells as well as by the corpus luteum.

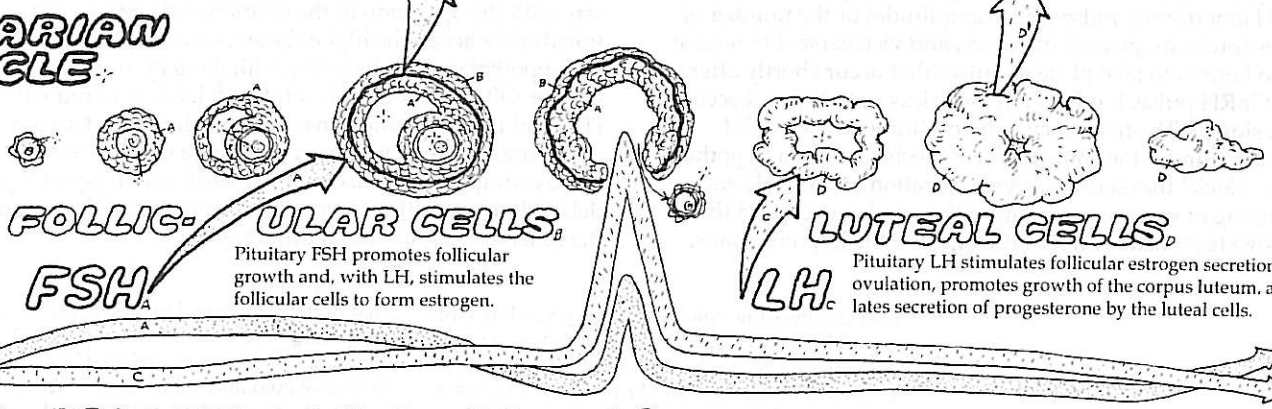


PROGESTERONE

Progesterone, produced by the luteal cells of the corpus luteum, is another female sex steroid. It appears in the blood after ovulation, and it stimulates the secretion of the uterine endometrial glands (secretory phase).



OVARIAN CYCLE



FOLLICULAR CELLS

Pituitary FSH promotes follicular growth and, with LH, stimulates the follicular cells to form estrogen.

FSH

LUTEAL CELLS

Pituitary LH stimulates follicular estrogen secretion, triggers ovulation, promotes growth of the corpus luteum, and stimulates secretion of progesterone by the luteal cells.

LH

1 FOLLICULAR PHASE — 14 DAYS — LUTEAL PHASE 28

HORMONAL REGULATION OF OVARIAN ACTIVITY

In the testes spermatogenesis and testosterone secretion occur continuously at a steady rate. The *ovary*, however, shows a cyclical pattern of activity. Thus, follicle formation (including ovum growth) and ovulation, as well as the formation and regression of the corpus luteum, all occur in sequence within a single cycle that is then repeated. Similarly, the secretion of ovarian hormones *estrogen* and *progesterone* follow a cyclical pattern, estrogen appearing in the follicular phase followed by progesterone in the luteal phase (plate 154). Average duration of the ovarian cycle in the mature human female is 28 days. Cycles begin at puberty and are interrupted only during pregnancy and lactation and by illness, and they cease after the age of fifty. Here, we study how the ovarian hormones, the anterior pituitary gonadotropins, and the hypothalamus interact to ensure the orderly operation of the ovarian cycle.

HYPOTHALAMUS & PITUITARY REGULATE THE OVARIES

Gonadotropins LH & FSH directly regulate follicular and luteal functions—The anterior pituitary secretes two gonadotropin hormones that regulate the activity of the ovary—the *follicle-stimulating hormone* (FSH) and the *luteinizing hormone* (LH). Gonadotropins are glycoprotein hormones secreted from the basophilic gonadotrope. Both LH and FSH are necessary for ovarian activity, although each may act in different phases of the cycle. FSH is essential in proliferation and growth of granulosa cells early in the follicular phase and later for increase of the theca interna cells.

LH, however, stimulates estrogen production and release by follicle cells as well as inducing ovulation and growth of the corpus luteum and its secretion of progesterone and estrogen. Gonadotropins exert their actions on granulosa and theca interna cells by binding to their own receptors on plasma membranes, acting via the G-protein → adenylate cyclase → cyclic AMP pathway (plate 12,114). The young granulosa cells have mainly FSH receptors but mature ones also carry LH receptors. The later-forming theca interna cells have both LH and FSH receptors.

Pulsatile release of GnRH from the hypothalamus controls pituitary LH & FSH—Secretion of LH and FSH are controlled by the *gonadotropin-releasing hormone* (GnRH), a peptide neurohormone released from the hypothalamus. GnRH is synthesized by GnRH-containing hypothalamic neurons, which release GnRH by their axon terminals into the *portal hypophyseal capillaries*, for rapid and direct delivery to the anterior pituitary gonadotrope cells. Receptors for GnRH are found on the plasma membrane of the gonadotropes. GnRH action is cAMP mediated.

GnRH release is not continuous but occurs in approximately hourly pulses. To increase gonadotropin secretion, GnRH amount per pulse (pulse amplitude) or the number of pulses (pulse frequency) increases, and vice versa. LH release is also known to take place in pulses that occur shortly after each GnRH pulse, but FSH release is less pulsatile and occurs more slowly. The frequency and amplitude of the GnRH pulses are under the control of two mechanisms—a hypothalamic "clock" that sets the overall duration of the cycle and the timing of major events within the ovarian cycle and the negative feedback control of estrogen on the hypothalamus.

ESTROGEN CONTROLS GNRH RELEASE THROUGH FEEDBACK

Negative feedback at onset—Low levels of estrogen at the end of the ovarian cycle, acting via *negative feedback*, stimulates the hypothalamus to increase its pulsatile output of GnRH. This leads to increased output of FSH and LH from the pituitary. FSH rises sharply in the first days and remains high for most of the follicular phase; LH shows a steady increase. FSH and LH stimulate follicular growth and secretion of estrogen. By day 13 of the cycle, estrogen level peaks while FSH and LH diminish, due to the negative feedback inhibition by estrogen.

Positive feedback at midcycle—At this point a new *positive feedback* mechanism comes into play: high estrogen levels cause a marked rise in LH (an LH burst) and a moderate one in FSH levels. Exactly how negative feedback switches to positive feedback in midcycle is not known. Increased estrogen increases the frequency of GnRH pulses and possibly augments the GnRH receptors on the gonadotrope cells, enhancing their sensitivity to GnRH pulses. These events produce the preovulatory burst of LH secretion that triggers the process of ovulation within several hours.

Return of negative feedback in the luteal phase—The postovulatory high levels of LH (and also of FSH) promote corpus luteum growth and progesterone (with some estrogen) release. By midluteal days the negative feedback effect returns; high estrogen and progesterone act to lower LH and FSH for most of the luteal phase. If the estrogen level is kept high from the beginning of the cycle, ovulation will not occur. This observation is the basis for the use of estrogen-like compounds in contraceptive pills (plate 161).

Inhibin from ovarian granulosa cells inhibits FSH secretion—The protein hormone *inhibin* also plays a role in ovarian regulation. Inhibin is secreted by the granulosa cells and exerts a negative feedback effect on the pituitary to inhibit FSH secretion. Inhibin levels are low in the follicular phase and high in the luteal phase.

Regression of the corpus luteum marks the end of an ovarian cycle—The corpus luteum begins to regress around day 25 of the cycle. Absence of hormonal signals from the implanted embryo (hCG) and the reduced LH and FSH levels signal the regression. A number of local hormones, such as prostaglandins and proteolytic enzymes, promote lysis of the corpus luteum. Regression of the corpus luteum reduces progesterone and estrogen output. This event marks the end of the ovarian cycle and promotes the shedding of the endometrium and menstruation.

FACTORS INFLUENCING OVARIAN FUNCTION

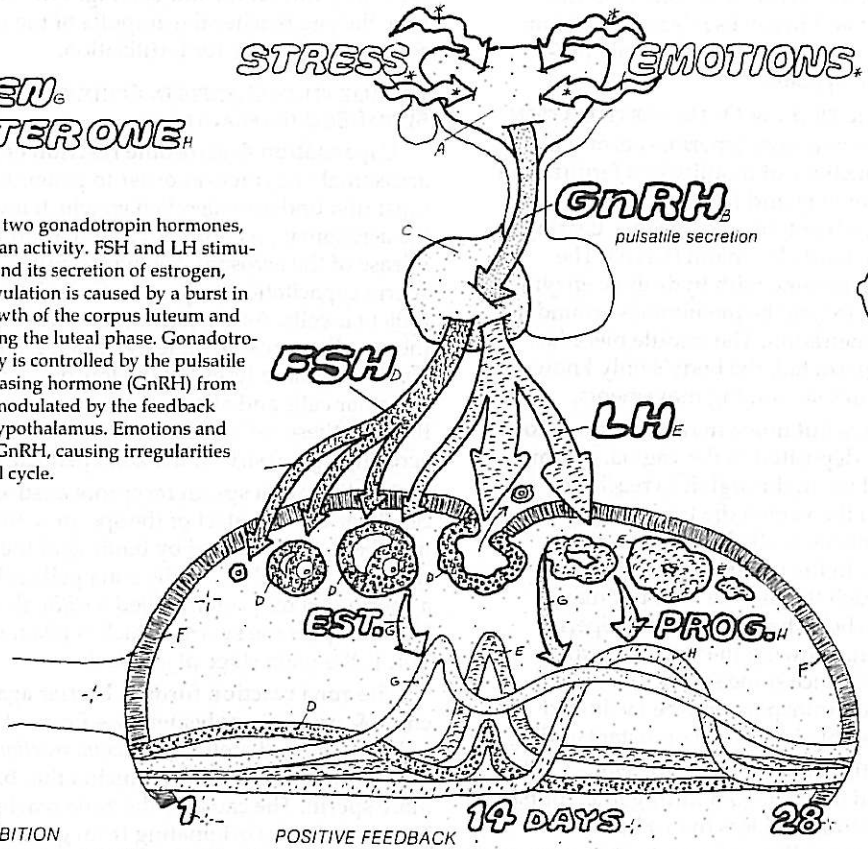
Illness, malnutrition, severe stress, and emotional crises interfere with the operation of the ovarian cycle. Stress and emotional crises act on the higher brain centers and, from there, on the hypothalamus, interfering with the pattern of GnRH release. Often the release is inhibited, leading to reduction in FSH and LH levels and consequently diminished secretion of sex hormones. Depending on the timing of the stress, diminished estrogen may cause undue menstruation (spotting) or delayed menstruation (secondary amenorrhea) that occurs in the absence of endometrial proliferation.

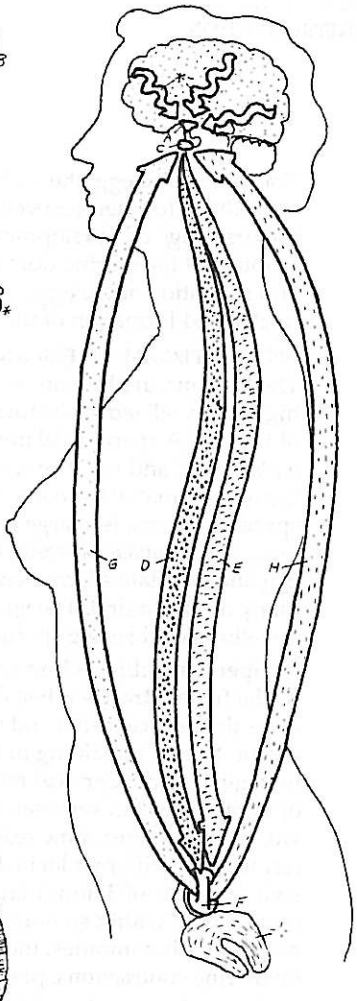
CN: Use the same colors as on the preceding page for FSH (D), LH (E), estrogen (G), and progesterone (H). Use light colors for A and C.
1. Color the large control illustration in the center.
2. Color the three bottom panels. Color only the bold portions of the hormone levels. Color gray that portion of the endometrium involved during the period described. The dotted ascending line in the left panel represents reduced levels of estrogen. Note that bold dotted lines in the right panel represent a cessation of FSH and LH secretion.
3. Color the diagram in the upper right.

HYPOTHALAMUS A
GONADOTROPIN-RELEASING HORMONE (GnRH) B
ANTERIOR PITUITARY GLAND C
FOLLICLE-STIMULATING HORMONE (FSH) D
LUTEINIZING HORMONE (LH) E

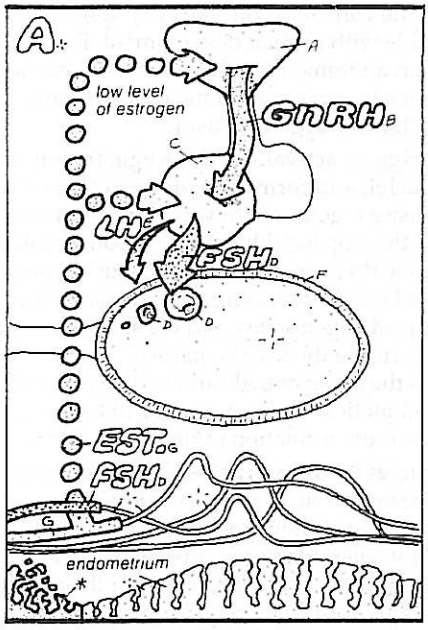
OVARY F
ESTROGEN G
PROGESTERONE H
INHIBIN I

The anterior pituitary releases two gonadotropin hormones, FSH and LH, to regulate ovarian activity. FSH and LH stimulate the growth of the follicle and its secretion of estrogen, during the follicular phase. Ovulation is caused by a burst in LH, which also stimulates growth of the corpus luteum and secretion of progesterone during the luteal phase. Gonadotropin secretion from the pituitary is controlled by the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus but is also modulated by the feedback effects of sex steroids on the hypothalamus. Emotions and stress disturb the secretion of GnRH, causing irregularities in ovulation and the menstrual cycle.





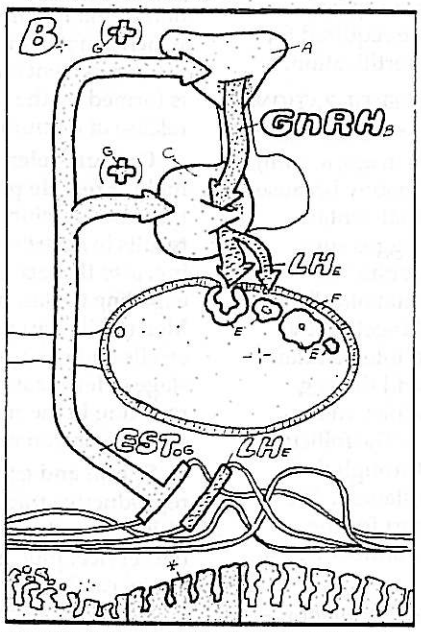
RELEASE FROM FEEDBACK INHIBITION



LOW ESTROGEN G

Low estrogen levels in the menstrual phase, acting via a negative feedback mechanism, increase release of GnRH, which in turn increases FSH and LH release (see also panel C). These stimulate follicular growth and elevate estrogen levels to their peak by day 13 of the ovarian cycle.

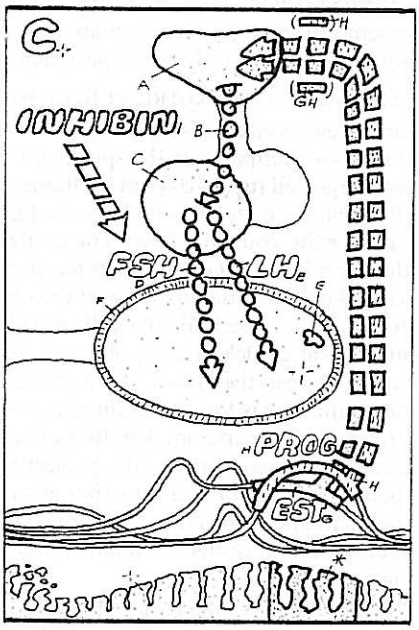
POSITIVE FEEDBACK



HIGH ESTROGEN G

High preovulatory levels of estrogen act via positive feedback to increase GnRH pulse frequency which triggers a burst of LH release by day 14. High LH leads to ovulation, growth of the corpus luteum, and its secretion of progesterone, which peaks at day 22; estrogen secretion continues at lower levels. Inhibin from granulosa cells inhibits FSH secretion in the luteal phase.

NEGATIVE FEEDBACK



HIGH ESTROGEN G **& HIGH PROGESTERONE** H

In the absence of fertilization and an implanted embryo, high estrogen and progesterone levels reduce secretion of LH and FSH by negative feedback. Reduced gonadotropin levels lead to regression of the corpus luteum and decreased output of sex steroids, then menstruation. The cycle continues with panel A.

PHYSIOLOGY OF SPERM, EGG & FERTILIZATION

The sperm and egg, the male and female gametes, are highly specialized for their respective functions in fertilization and the first stage of development. Fertilization occurs in the ampulla of the uterine duct and involves release of calcium and activation of the egg, fusion of male and female pronuclei, and formation of the zygote.

SPERM: SPECIALIZED FOR MOTILITY & OVUM FERTILIZATION

The fully mature human *spermatozoon* (sperm, sperm cell) is highly specialized for its functions of motility and fertilization of the egg. A sperm is 60 μm long and has three parts—*head*, *middle piece*, and *tail*. The *head* contains the nucleus, bearing the genetic material—condensed chromatin (DNA). The sperm acrosome is a large lysosome with hydrolytic enzymes (e.g., *hyalouronidase, acrosin*) to lyse the membranes around the egg and facilitate sperm penetration. The middle piece has many mitochondria. The sperm tail, the body's only known flagellum, enables the sperm's swimming movements.

Sperm are able swimmers but move in random directions in the female tract—When deposited in the vagina, sperm enter the cervical canal and swim through it to reach the uterus. Sperm remaining in the vagina die from to exposure to vaginal acids. Cervical mucus is alkaline and therefore optimal for sperm survival. In the uterus, sperm swim in various directions; some reach the uterine tube but many terminate in different loci where they age and die. Sperm swim at a rate of 3 mm/min, allowing them to reach the uterine tube within an hour. Since some sperm reach the oviduct within minutes, their transport may be facilitated by uterine contractions, possibly induced by prostaglandins.

Fewer than one in a million sperm reach the egg—Of the 300 million sperm deposited in the vagina during intercourse, only 0.1% reach the uterine tube and less than a hundred reach the egg (*ovum*). High mortality and random sperm movement are some reasons so many sperm are required for fertility, even though only one is sufficient for fertilization.

EGG: SPECIALIZED FOR NUTRIENT STORAGE & FERTILIZATION

Human egg contains large nutrient reserves and several membranes—Compared to the sperm, the human egg (ovum) is a very large cell (up to 200 μm in diameter), mainly because of its large stores of *cytoplasmic granules* (*yolk*) that contain nutrients for the young embryo. The ovulated egg is surrounded by a layer of *follicular cells* (cumulus oophorus, corona radiata), which help support the egg metabolically and nutritionally. The follicular cells are glued together by *hyalouronic acid*, a sticky mucopolysaccharide ("intercellular cement"). Between the layer of follicular cells and the egg plasma membrane is the *zona pellucida*, a 5-μm-thick membrane made of a transparent, jellylike substance. The follicular cells and the egg send microvillar projections through the zona pellucida, possibly for interchange of substances. The zona pellucida helps provide mechanical support for the young embryo and protects it against maternal antibodies and macrophages.

Cilia and uterine tube contractions aid in egg transport—After ovulation, the sweeping movements of the uterine tube and its *fimbriae* create suction, drawing the immobile egg (and cumulus oophorus) into the uterine tube. Uterine tube contractions and the constant oarlike beating of the cilia on the epithelial cells of the *mucosal folds* propel the egg toward the uterus. Estrogen is necessary for uterine tube contraction and for ciliary formation and beating. Within hours after ovulation, the egg reaches the ampulla of the uterine tube. At this time, it is fully ripe for fertilization.

FERTILIZATION OCCURS IN OVIDUCT & INVOLVES MULTIPLE SPERM-EGG INTERACTIONS

Capacitation & acrosome reaction ensure release of acrosomal enzyme—In order to penetrate the egg, the sperm must first undergo *capacitation*, which involves the removal of the acrosomal glycoprotein coat that prevents premature release of the acrosomal enzymes. Substances that induce sperm capacitation may come from the oviduct or from follicular cells. As a capacitated sperm prepares to penetrate the egg, the acrosome releases its enzymes (*acrosome reaction*). Hyalouronidase lyses the hyalouronic acid, dispersing the follicular cells and allowing the sperm to make its way through these cells. Other lysosomal enzymes, such as acrosin, digest parts of the zona pellucida.

Binding with sperm receptors ensures sperm entry and fertilization—Contact of the sperm with the egg plasma membrane is enhanced by binding of the sperm to a specific *sperm receptor* (ZP-3) on the zona pellucida. Next, aided by a sperm surface protein called *fertilin*, the egg plasma membrane engulfs the sperm, which is taken in, head and tail. This is the main stage of *fertilization*.

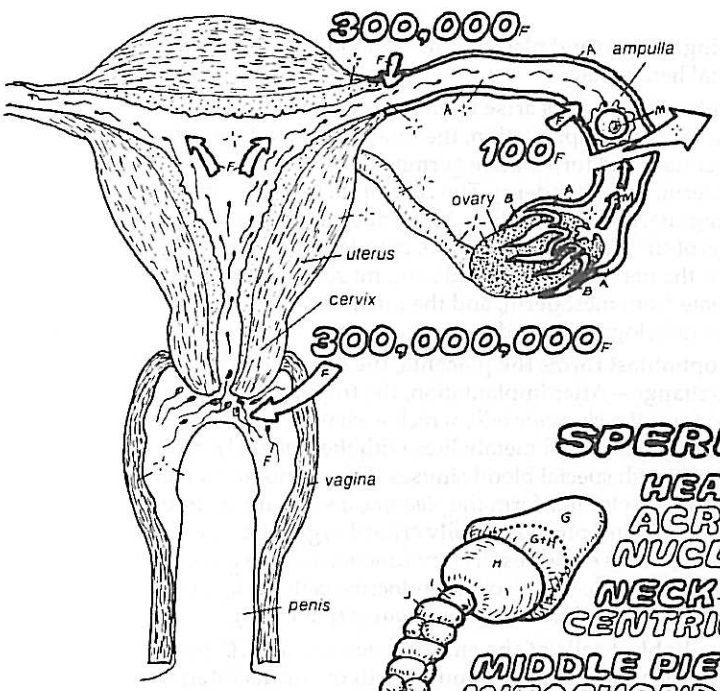
The zona reaction forms a barrier against more sperm entry & prevents polyspermy—Entry of the first sperm is followed immediately by the *zona reaction*, a rapid chemical modification of the zona pellucida that blocks penetration by more sperm. The cause of the zona reaction is the outflow of some substances originating from granules in the *cytoplasm* of the egg. Failure of the zona reaction leads to *polyspermy*, which is not compatible with normal development. Before this permanent barrier, an immediate and temporary barrier is formed by the change in egg's membrane potential and release of calcium within the egg cytoplasm.

Calcium release triggers activation of the egg, fusion of male & female pronuclei, and formation of the zygote—The increased calcium release together with sperm penetration results in *activation* of the egg, including its metabolic awakening; also the last meiotic division of the egg nucleus occurs, expelling the last polar body and forming the *female pro-nucleus*. Meanwhile the sperm tail degenerates, and the sperm nucleus swells and enlarges, forming the *male pronucleus*. The last stage of fertilization is the *fusion* of male and female pronuclei, resulting in the recombination of chromosomes of the male and female gametes and the formation of the *zygote nucleus*.

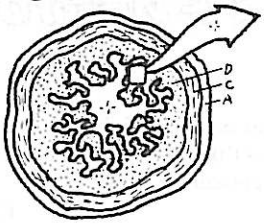
Sperm and egg longevity & survival—Within the female reproductive tract, sperm can survive up to four days, especially those stored in the cervical mucosa and nourished by the cervical mucus. However, when appropriately frozen, sperm can be kept several years and still maintain the ability to fertilize an ovum. Long-term storage of human eggs has recently become possible. The egg has a shorter life span after ovulation (about one day), and if not fertilized, it will age and degenerate. The optimum time for fertilization is within the first twelve hours after ovulation.

CN: Use light colors for D, G, H, and M–R.
1. Begin with the uterine tube.
2. Color the material on the spermatozoon (F)
3. Color the ovum and the five stages of fertilization. Note that the dotted line in the last one represents the degenerating tail of the spermatozoon.

Sperm deposited in the vagina swim through the cervix into the uterus and up into the uterine tube. Since sperm move in all directions, fertilization requires a very large number of sperm. Of the 300 million deposited, 0.1% reach the oviduct and about 100 reach the uterine tube ampulla to meet the ovum. Uterine contractions triggered by prostaglandins may also facilitate sperm transport.



UTERINE TUBE

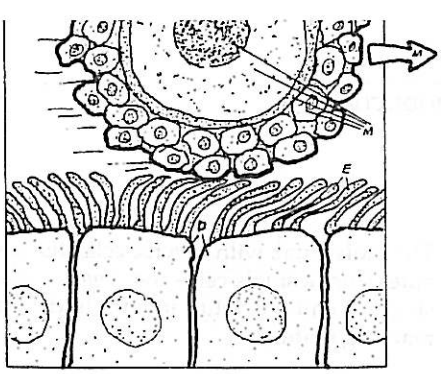


FIMBRIAE

SMOOTH MUSCLE

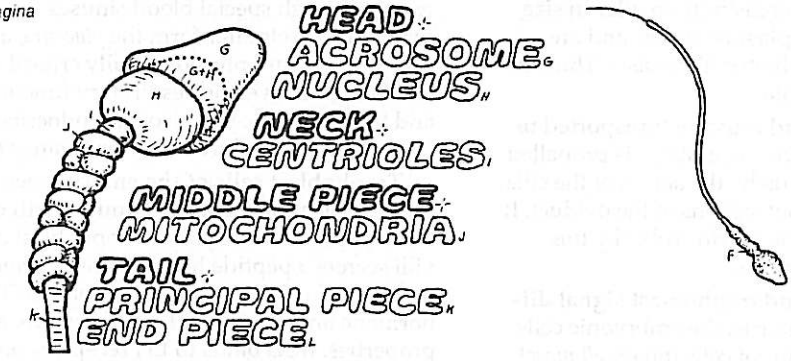
MUCOSAL FOLDS

CILIA



The ovum has no self-motility. Contractions of the smooth muscles in the uterine tube cause sweeping movements of the fimbriae, sucking the ovulated egg from the peritoneal cavity into the uterine tube. These contractions (strongest at ovulation), and the beating of cilia (on the oviduct mucosal epithelium), propel the egg mass toward the uterus.

SPERMATOZOON



HEAD

ACROSOME

NUCLEUS

NECK

CENTRIOLES

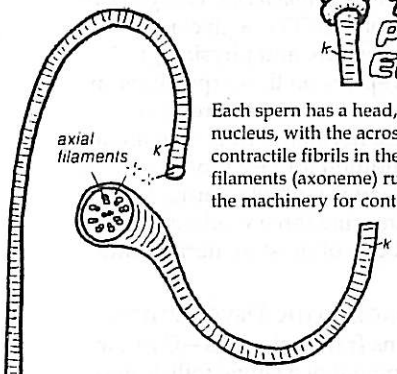
MIDDLE PIECE

MITOCHONDRIA

TAIL

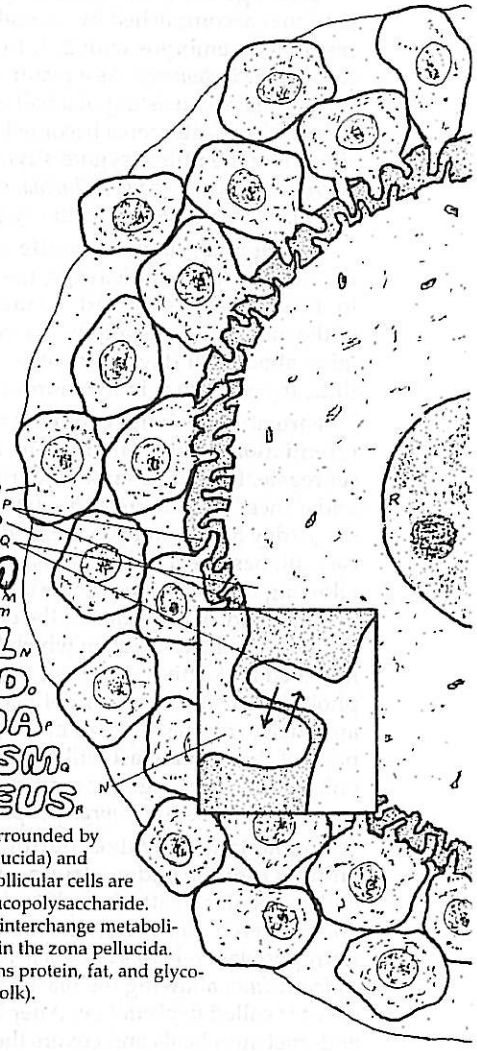
PRINCIPAL PIECE

END PIECE



Each sperm has a head, a neck, a middle piece, and a tail. Inside the neck is the nucleus, with the acrosome over it. The neck contains the centrioles that anchor contractile fibrils in the tail. The middle piece contains the mitochondria. Axial filaments (axoneme) run from the neck to the endpiece of the tail and provide the machinery for contractions of the tail, producing sperm motility.

OVUM (EGG)



FOLLICULAR CELL

HYALURONIC ACID

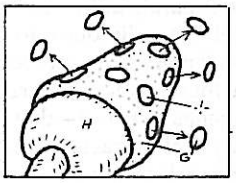
ZONA PELLUCIDA

CYTOPLASM

NUCLEUS

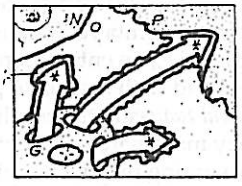
The human ovum is a large cell (200 μm) surrounded by a transparent gelatinous membrane (zone pellucida) and aggregates of follicular cells (corona radiata). Follicular cells are glued together by hyalouronic acid, a mucopolysaccharide. Follicular cells and egg cytoplasm interchange metabolically through the microvilli in the zona pellucida. The cytoplasm contains protein, fat, and glycogen granules (yolk).

CAPACITATION



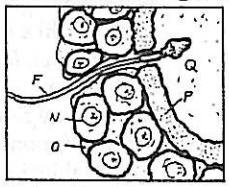
Capacitation, a reaction necessary for fertilization, refers to removal of the glycoprotein coat covering the acrosome. It occurs in the uterine tube by the action of substances and enzymes released from follicular cells or the cumulus oophorus.

ACROSOME REACTION



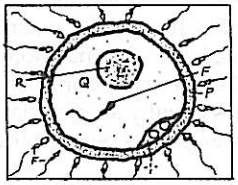
Acrosome reaction refers to the release of acrosomal hydrolytic enzymes that lyse the membranes around the egg, facilitating sperm entry. Hyalouronidase lyses hyaluronic acid, separating follicular cells. Acrosin digests the zona pellucida.

FERTILIZATION



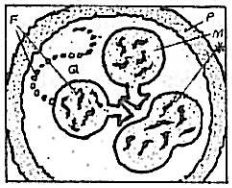
Fusion of sperm, plasma membrane, and egg results in the egg engulfing the entire sperm. Sperm entry releases calcium, activating the egg and triggering the main events of fertilization.

ZONA REACTION



After sperm entry, the zona pellucida undergoes electrical and chemical changes, becoming impermeable to other sperm (zona reaction).

PRO-NUCLEI FUSION



After sperm entry, the egg completes its second meiotic division, expelling the last polar body, forming the female pronucleus. The sperm tail degenerates, and its nucleus enlarges, forming the male pronucleus. The two pronuclei fuse to form the zygote nucleus.

EARLY DEVELOPMENT, IMPLANTATION & EMBRYO-MOTHER INTERACTIONS

The individual, with diverse cells, tissues, and organs, originates from a single cell—the *zygote*—and goes through the stages of embryo, fetus, infant, child, and adolescent before reaching maturity.

DEVELOPMENT OF THE YOUNG EMBRYO

Following fertilization, the zygote undergoes cell *proliferation* to increase the number of its cells and form the rudiments of the young embryo. In later stages, embryonic cells undergo *differentiation* to form the body's diverse cell types and tissues.

Cleavage divisions form the young embryo—Cell proliferation is accomplished by several *mitotic* divisions (cleavage), resulting in embryos with 2, 4, 16, and 32 daughter cells, called the *blastomeres*. As a result, the zygote transforms into a *young embryo* consisting of a ball of uniform cells (*morula*, mulberry). The blastomeres become increasingly smaller in size, since they the utilize zygote's cytoplasmic stores, and are surrounded by its *zona pellucida*, which still persists. Thus the morula is the same size as the zygote.

Young embryo is not motile and must be transported to the uterus—During cleavage, the young embryo is propelled in the uterine tube toward the uterus by the action of the cilia of the mucosal lining and by the contractions of the oviduct. It takes about four days to traverse the uterine tube; by this time, the embryo is in the morula stage.

Formation of inner cell mass and trophoblast signal differentiation—Upon entering the uterus, the embryonic cells segregate, forming an internal group of cells *(inner cell mass)* and a sheet of cells *(trophoblast)* that surround a *cavity*. At this stage (day 5), the embryo is called a *blastocyst*. The early *blastocyst* still has the zone pellucida, which soon degenerates allowing it to obtain nutrients and oxygen directly from the uterine fluid. This results in the embryo's growth and formation of the *late blastocyst*, in which the trophoblast cells become flattened and active. A diffuse external layer of syncytiotrophoblast cells with poorly defined cellular forms surrounds an orderly internal layer of cytotrophoblast cells. The various parts of the trophoblast will later form the *placenta* and embryonic membranes (e.g., the amniotic sac), while the inner cell mass cells forms the *embryo* proper.

Implantation involves burrowing of the blastocyst embryo into the endometrium—By days 6–7, the growing embryo begins to attach itself to the uterus to obtain nutrients and oxygen directly from the maternal blood. The syncytiotrophoblast releases *lysosomal enzymes*, which lyse the *endometrium*, allowing the blastocyst to burrow into it. This event is called *implantation*. After implantation, the endometrium heals and covers the embryo. As a result the human embryo grows within the uterine endometrium and not in the uterine cavity.

Ectopic pregnancies are not viable—Implantation usually occurs in the dorsal wall of the uterus, but it also may occur in various *ectopic sites* in the uterine tube, the cervix, or even the peritoneal cavity. Ectopic pregnancies usually are not viable. Tubal pregnancies create medical emergencies because the growing embryo and placenta cause blood vessel rupture and internal hemorrhage.

Embryonic tissues arise from three germinal layers—One week after implantation, the inner cell mass begins to differentiate and forms three germinal layers—ectoderm, mesoderm, and endoderm. The cells of these layers proliferate, migrate, and differentiate to produce the tissues and organs of the developing embryo. Ectoderm produces the cells of the nervous system and skin, muscle and bone tissue originate from mesoderm, and the inner lining of visceral organs develops from endoderm.

Trophoblast forms the placenta, the organ for nutrient & gas exchange—After implantation, the trophoblast proliferates to form the *chorionic villi*, which exchange nutrients, respiratory gases, and metabolites with the *maternal blood vessels* through special blood sinuses. The chorionic villi and maternal vessels later form the *placenta*, a separate, anatomically distinct and physiologically critical organ that serves in essential nutritive and respiratory functions of the embryo and fetus; the placenta also has endocrine cells that secrete hormones for the duration of pregnancy (plate 158).

Trophoblast cells of the embryo secrete the hCG hormone to stimulate survival and growth of corpus luteum—After implantation, syncytiotrophoblast cells in the chorionic villi secrete a peptide hormone called *human chorionic gonadotropin* (hCG) into the maternal blood. hCG is a glycoprotein hormone and resembles LH in structure and physiological properties. hCG binds to LH receptors on the corpus luteum and promotes its survival and growth and its secretion of progesterone and estrogen. These hormones in turn maintain the endometrium in optimal condition for gestation. The detection of hCG in maternal blood is possible during the second week of implantation and in urine three weeks after implantation; this ability is the basis of most modern immunochemical pregnancy tests.

TWINNING: DIZYGOTIC VS. MONOZYGOTIC DEVELOPMENT

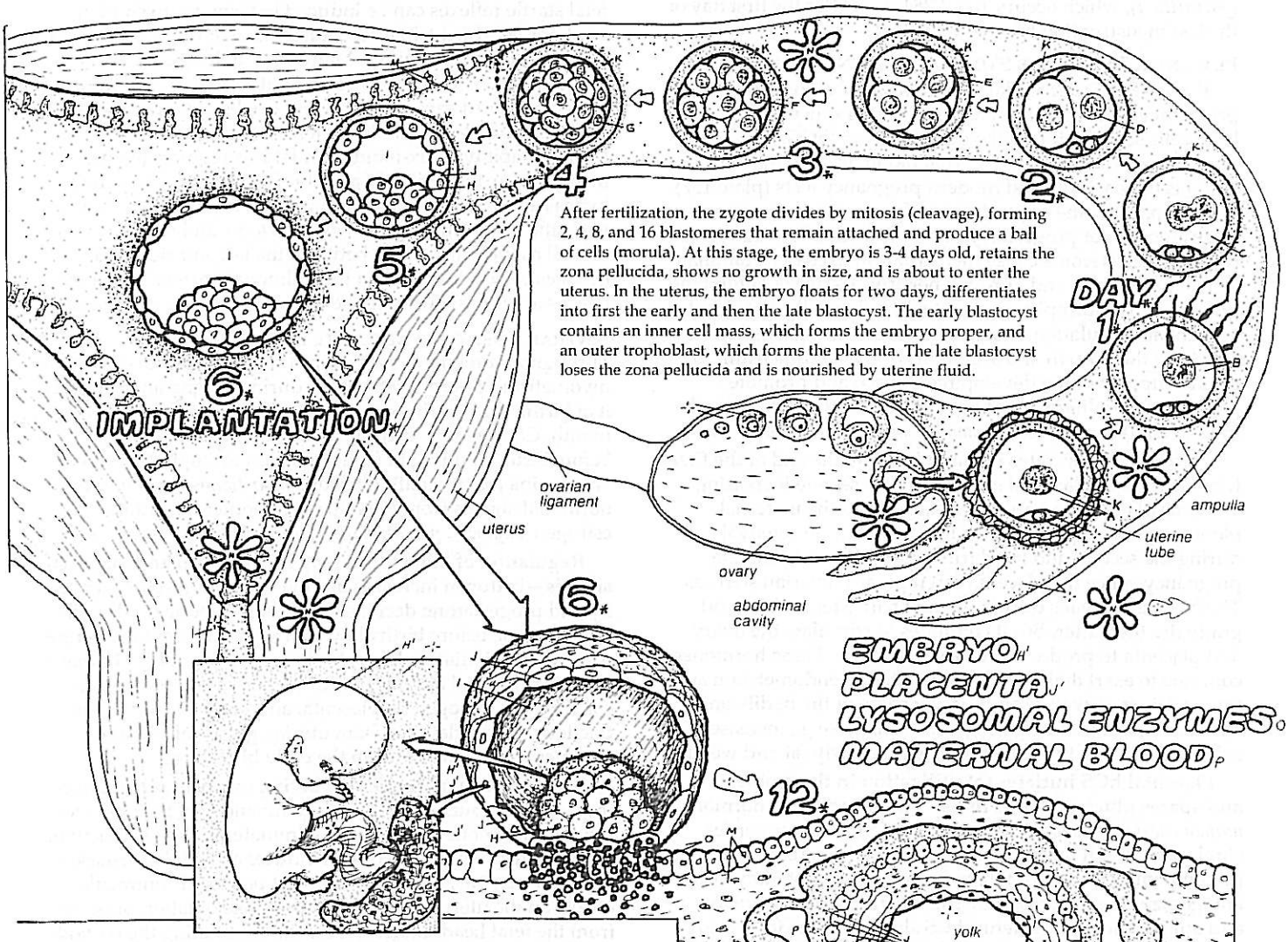
Dizygotic development forms fraternal twins—Ovarian cycles normally involve development of a single follicle and release of one egg at ovulation. Growth of more than one follicle results in multiple ovulation and formation of two or more zygotes. Each of these implants separately, forming *fraternal twins or triplets*, or more, not necessarily of the same sex.

Monozygotic development forms identical twins—If the two blastomeres from a single zygote separate at the first cleavage division, or if the single inner cell mass divides into two separate masses, each blastomere or cell mass will proceed to form an independent embryo. Because these embryos share a common *genotype*—i.e., an entire set of genes (*genome*)—they will be alike in sex and with respect to physical characteristics (*phenotype*). *Identical twins* are the result of such common development; they may share a placenta or may have their own. Dizygotic twinning may be hereditary but the occurrence of monozygotic twinning appears to be accidental. Normal incidence of twinning is 1% for fraternal twins and 0.3% (one in about 300 pregnancies) for identical twins.

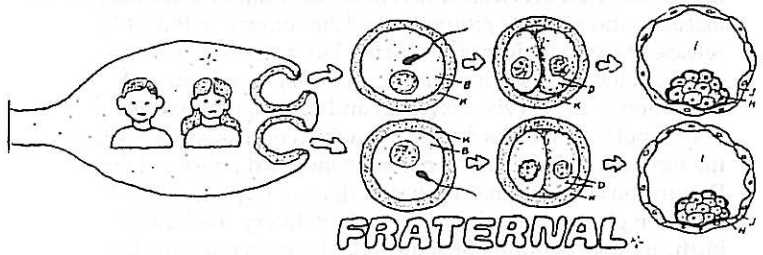
CN: Use red for P. Use light colors throughout, except for structures L, N, and O, which receive dark colors. Use your lightest colors for H and M.
1. Begin with the entrance of the ovum into the uterine tube. Note that the zona pellucida (K) and polar body (L) titles are in the upper right corner. Color the day numbers gray. Color the ectopic implantation (N) sites (marked by large asterisks).
2. Continue with the three-dimensional drawing of the later blastocyst at day 6 and the large drawing of day 12. Color in the uterine endometrium (M) in the large drawings before dotting in the lysosomal enzymes (O) in day 6.
3. Color the three hormonal influences in the lower right corner.
4. Color the diagrams illustrating twin formation.

EARLY STAGES OF DEVELOPMENT

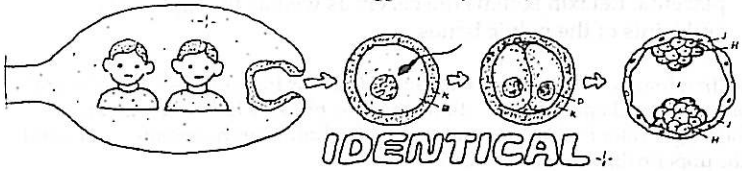
OVUM A
FERTILIZATION B
ZYGOTE C
2-CELL STAGE D
4-CELL STAGE E
8-CELL STAGE F
MORULA G
EARLY BLASTOCYST (5)
INNER CELL MASS H
BLASTOCYST CAVITY I
TROPHOBLAST J
LATE BLASTOCYST (6)
ZONA PELLUCIDA K
POLAR BODIES L
UTERINE ENDOMETRIUM M
ECTOPIC IMPLANTATION SITES N



FORMATION OF TWINS



Fraternal (dizygotic) twins form from fertilization of more than one egg and may or may not be the same sex.



Identical twins form either when the first two blastomeres separate or when the inner cell mass splits into two masses. Identical twins have the same sex and genotype and very similar phenotypes.

REGULATION OF PREGNANCY AND PARTURITION

Duration of human *pregnancy* or *gestation* is about 270 days (~38 weeks) from conception. Pregnancy is divided into three trimesters (3-month-long periods). The first covers the development of the *embryo*, the second and third entail the growth and development of the *fetus*. Pregnancy involves major hormonal and metabolic changes in the mother. Maternal and fetal hormonal mechanisms end pregnancy by inducing birth (*parturition*), which occurs about 284 days after the first day of the last menstruation before pregnancy.

PLACENTAL HORMONES STIMULATE PREGNANCY CHANGES

Placental hCG stimulates formation of corpus luteum of pregnancy—After implantation, placental syncytiotrophoblast cells secrete an LH-like gonadotropin (hCG, *human chorionic gonadotropin)* in maternal blood. hCG in maternal blood is the basis of most modern pregnancy tests (plate 157). hCG helps form the *corpus luteum of pregnancy* that secretes large amounts of progesterone and estrogen in the maternal blood. These steroids cause menstruation to cease, a familiar sign of pregnancy, and, through negative feedback, inhibit the pituitary gonadotropins, preventing further follicular development and ovulation. Maternal estrogen and progesterone stimulate the growth and secretions of the endometrium to ensure support of the developing embryo and promote growth and proliferation of the *myometrium* (uterine smooth muscle wall) as well as the *mammary glands* and breast tissue.

Placenta also secretes sex steroids—By the end of the first trimester, other placental endocrine cells secrete increasing amounts of estrogen and progesterone into the maternal blood, augmenting the corpus luteum. Ovarian removal during the second and third trimesters will not terminate pregnancy, since the placenta can replenish ovarian steroids. The hCG level peaks during the first trimester and falls off gradually thereafter. But it continues to stimulate the ovary and placenta to produce female sex steroids. These hormones continue to exert their effects on the uterine endometrium and myometrium as well as stimulating some of the bodily and metabolic changes in the pregnant woman—e.g., increased subcutaneous fat, fluid retention, gain in body fat and weight.

Placental hCS initiates fat utilization in the mother and spares glucose for the fetus—Another protein hormone, *human chorionic somatomammotropin* (hCS), with properties similar to growth hormone and prolactin, is secreted from the placenta into the maternal blood throughout gestation. hCS antagonizes the action of maternal insulin, sparing glucose and amino acids for the fetus; hCS also mobilizes fatty acids for maternal tissues. Fetal growth is reduced in cases of hCS deficiency because of the decreased nutrient supply to the fetus. hCS also stimulates growth of maternal mammary glands (plate 159).

Major events of embryonic and fetal development & control of fetal growth—During the embryonic period (weeks 1–8), development consists largely of proliferation and differentiation of cells and tissues and *organogenesis*, the formation of the organs and systems. Major organs form during weeks 4–8, making this period a significant and critical one in terms of the effects of drugs and other teratological agents on embryonic development. By the third month, the embryo is called a *fetus*. The fetal period (3–9 months) is characterized chiefly by growth of the tissues, organs, and body of the fetus, but differentiation in several tissues and systems, such as the nervous system, continues to occur. Fetal growth is regulated by fetal *insulin* and *insulin-like growth factors* (IGF 1, IGF 2) but not by fetal growth hormone. Anencephalic fetuses, which have no pituitary, are of normal body size.

Functional development of fetus & newborn—Fetal movements can be felt during the second trimester. Later on fetal startle reflexes can be induced in response to sudden loud noises. Third-trimester fetuses have open eyes and occasionally suck their thumbs. Maturation of lungs, blood, and immune system and subcutaneous fat formation continue during the third trimester. Fetuses born before term are called *premature*. Eight-month-old preterm fetuses are often viable but the viability of six-month-old fetuses requires intensive medical care. Immediately after birth, reduced oxygen and increased CO_2 in the plasma stimulates breathing and activates the newborn lungs. *Umbilical arteries* and veins close, as well as the connections between the left and right atria (*foramen ovale*) and between the pulmonary artery and aorta (*ductus arteriosus*), forming the mature pattern of circulation.

SEVERAL HORMONES REGULATE PARTURITION

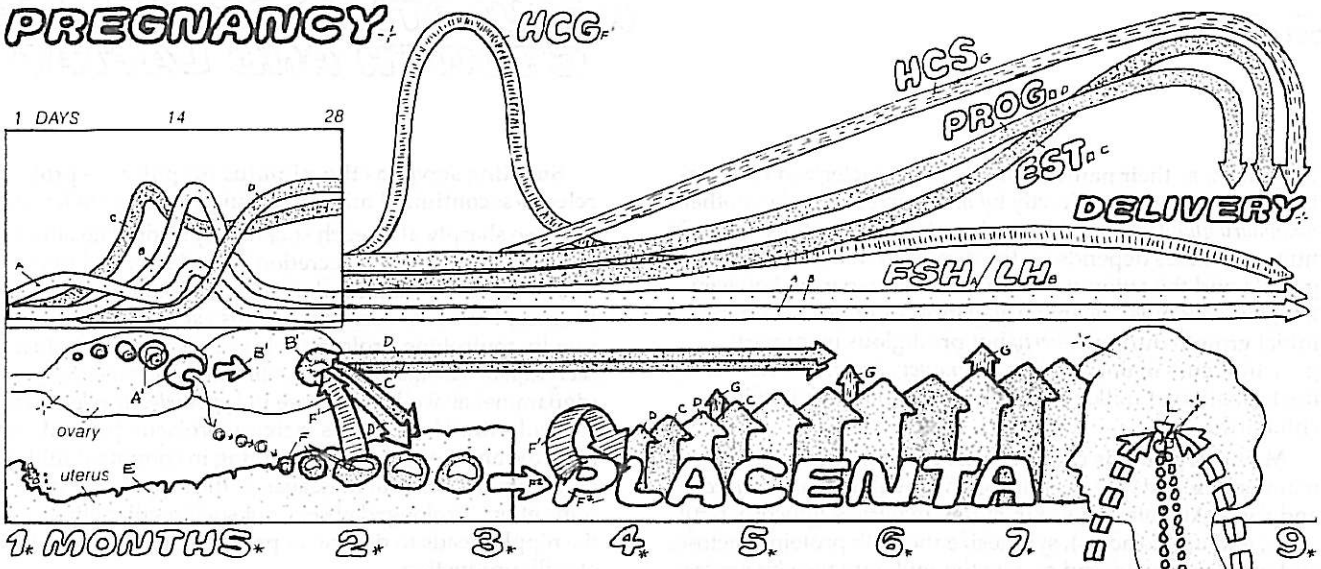
Throughout pregnancy, estrogen stimulates growth of uterine myometrium to support the fetus during pregnancy and expel it at birth. Mild uterine contractions begin with the fourth month. Contractions become strong and rhythmic hours before birth, resulting in fetal expulsion through the cervix and vagina (birth canal). Birth or *parturition* is regulated by hormonal signals from the fetus and mother, including estrogen, *oxytocin*, *prostaglandins*, and *relaxin*.

Regulation of labor onset may involve fetal and maternal signals—Estrogen increases uterine smooth muscle excitability and progesterone decreases it. In some species, a drop in progesterone before birth allows estrogen to stimulate uterine contractions, initiating labor. In sheep and possibly in humans cortisol from fetal adrenal glands increases before labor, is converted to estrogen by placenta, and induces uterine contractions. Prostaglandins from uterine glands also induce myometrium contractions in the early birth stage.

A neurohormonal reflex involving oxytocin release promotes fetal expulsion—One of the functions of the posterior pituitary hormone *oxytocin* is to stimulate uterine contraction. During late pregnancy estrogen induces a 100-fold increase in oxytocin *receptors*, enabling it to exert powerful contractile effects on the uterus. During the first stage of labor, pressure from the fetal head dilates the cervix, stimulating the *cervical/stretch receptors* and activating a *neurohormonal reflex*. Sensory nerves from the cervical stretch receptors stimulate the *hypothalamus* and *posterior pituitary* to release oxytocin. Pulsatile release of oxytocin increases during labor due to a positive feedback loop and is terminated after fetal expulsion and relaxation of the cervix. Oxytocin and prostaglandins also help expel the placenta (*afterbirth*), which occurs shortly after the birth of the baby and constitutes the third phase of labor. Parturition can be induced by injections of oxytocin, which are often given during labor to aid in delivery. To facilitate birth, another peptide hormone, relaxin, is secreted during gestation by the corpus luteum of pregnancy and by the placenta. Relaxin softens the cervix as well as the ligaments and joints of the pelvic bones.

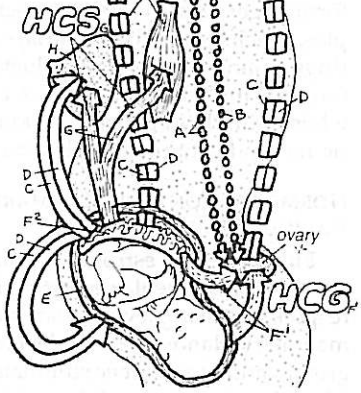
CN: Use same colors for the first four hormones (A–D) used in the earlier plates of this chapter. Use a dark color for F and N and a light color for O.
1. Begin with the titles of the upper half, and color all the material in the large rectangle. Color the pregnant woman, beginning with the secretion of hCG (or HCG). Note the large word PLACENTA with an HCG arrow indicating secretion by and stimulating the placenta to produce greater amounts of the hormones represented by a solid line of arrows.
2. Color the parturition panel. Complete the left illustration before going on to the next. Note that the wall of the cervix is uncolored.

PREGNANCY



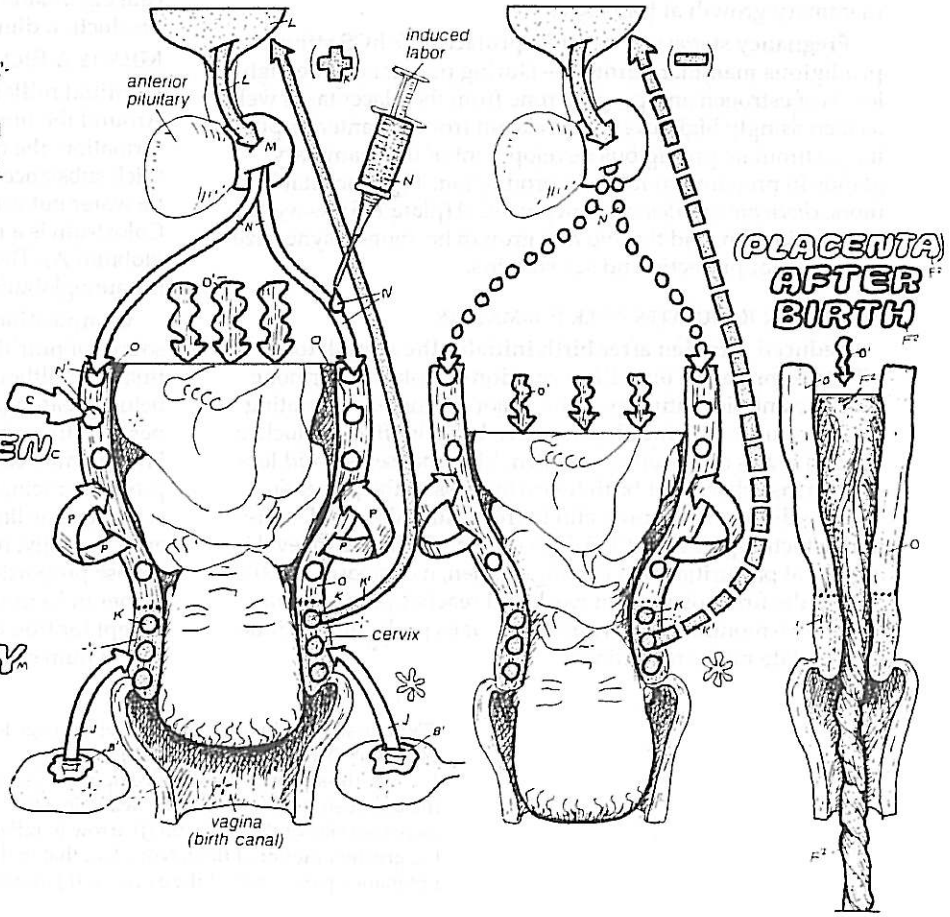
FSH / FOLLICLE A'
LH / CORPUS LUTEUM B'
ESTROGEN C
PROGESTERONE D
UTERINE ENDOMETRIUM E
TROPHOBLASTIC CELLS F
HUMAN CHORIONIC GONADOTROPIN (HCG) F'
PLACENTA F²
HUMAN CHORIONIC SOMATOMAMMOTROPIN (HCS) G
MAMMARY GLAND H
MATERNAL TISSUE I

During pregnancy, in response to placental hCG, first the corpus luteum of pregnancy and then the placenta secrete increasing amounts of estrogen and progesterone. These promote the growth of uterine endometrium and myometrium and mammary glands. In the mother, placental hCS mobilizes fats and antagonizes insulin to ensure high glucose supply to the fetus. High estrogen and progesterone inhibit FSH and LH by negative feedback, preventing follicular growth and ovulation and arresting menstrual cycles.



PARTURITION

Placental estrogen induces uterine contractions in early labor and prostaglandins from uterine glands during labor. Cortisol from fetal adrenals may also signal labor onset by conversion to estrogen. The role of oxytocin in labor involves a neurohormonal reflex. Pressure from the fetal head dilates the cervix and stimulates its stretch receptors, signaling the hypothalamus to release oxytocin pulses from the posterior pituitary. Oxytocin binds to its receptors (which have increased due to estrogen action) and induces strong uterine contractions, which force the fetus out. After passage of the head, stretch receptors relax, and oxytocin release diminishes. Oxytocin also helps expel the placenta ("afterbirth") and its injection can enhance weak labor contractions.



ESTROGEN C
RELAXIN
CERVICAL STRETCH RECEPTORS K
SENSORY NERVE K'
HYPOTHALAMUS L
POSTERIOR PITUITARY M
OXYTOCIN N
RECEPTORS N'
MYOMETRIUM O
CONTRACTION O'
PROSTAGLANDIN P

REGULATION OF MAMMARY GROWTH AND LACTATION

Mammals, as their name implies, are characterized by nourishing their newborn directly by *milk*, secreted by the mother's *mammary glands*, located in the *breast*. The size of the breast in human females depends on the degree of mammary gland growth and the amount of *fatty tissue* interspersed between the gland's lobules. Mammary glands and breasts undergo initial growth during *puberty* but prodigious mammary growth occurs mainly during *pregnancy*. *Lactation* refers to the formation of milk by the mammary glands following childbirth.

Mammary glands consist of alveoli and ducts—The mammary glands are exocrine glands with extensive *alveoli* and *ducts*. Alveolar cells extract raw materials (glucose, fatty acids, and amino acids), synthesize the milk proteins, lactose, and other nutrients, and secrete the milk into the *alveolar sacs*. The milk flows initially through small ducts that converge to form larger ducts, which connect with their outlets in the nipples. Specific smooth muscle *myoepithelial cells* form contractile rings around the mammary ducts. Contractions of these ducts force the milk out. Nipples also contain tactile receptors whose stimulation during suckling are important for *milk ejection* and continued milk formation.

HORMONES CONTROL MAMMARY GROWTH DURING VARIOUS STAGES

Puberty stage: estrogen stimulates duct growth, progesterone alveolar growth—During adolescence, in response to rising levels of sex steroids from the ovaries, the mammary glands begin to develop. *Estrogen* enhances duct growth and *progesterone* stimulates alveolar development. Alveoli are sparse in adolescents. Several other hormones (*insulin, growth hormone, prolactin* and *adrenal glucocorticoids*) also are necessary for the successful actions of sex steroids on mammary growth at this stage.

Pregnancy stage: sex steroids, prolactin, & hCS stimulate prodigious mammary growth—During pregnancy, the high levels of estrogen and progesterone from the placenta, as well as increasingly high levels of prolactin from the anterior pituitary, stimulate prodigious development of the mammary glands in preparation for milk production. The placental hormone *chorionic somatomammotropin (hCS)* (plate 158), as well as cortisol, insulin, and thyroid and growth hormones, synergize the effects of prolactin and sex steroids.

PROLACTIN REGULATES MILK FORMATION

Reduced estrogen after birth initiates the stimulatory effects of prolactin on milk formation—Prolactin hormone from the anterior pituitary is the major hormone stimulating milk production by the alveolar cells, but this effect is blocked by high levels of placental estrogen. Maternal sex steroid levels decrease sharply at birth following loss of the placenta. This condition allows prolactin to freely stimulate milk secretion, which begins about 1–3 days after birth. Prolactin level is highest at parturition; in lactating women, it decreases by 50% during the first postpartum week and reaches pregestation levels by 6 months postpartum. How does prolactin continue to stimulate milk production?

Suckling serves as the stimulus for pulsatile prolactin release & continued milk production—Prolactin levels increase sharply after each suckling episode. The effective stimulus for continued secretion of prolactin and milk production is the suckling-induced stimulation of the nipple tactile receptors. These sensory signals excite the hypothalamic centers controlling prolactin release, resulting in reduced secretion of *hypothalamic release-inhibiting hormone* for prolactin (dopamine) as well as increase in *hypothalamic release hormone* for prolactin. These effects increase prolactin pulsatile release from the anterior pituitary, resulting in continued milk formation. Regular artificial massages of the nipples will have the same effect. Prolonged absence of such regular stimulation of the nipples leads to decline in prolactin release and cessation of milk production.

MILK EJECTION INVOLVES A NEUROHORMONAL REFLEX

Nipple stimulation & afferents to hypothalamus form the neural part of the reflex—Mechanical stimulation of the nipple also enhances milk ejection from the mammary ducts. Secreted milk accumulates in the alveoli and ducts but will not flow out unless the myoepithelial smooth muscle cells around the mammary ducts contract. This is brought about by the action of the hormone *oxytocin* from the posterior pituitary gland. A neuroendocrine reflex controls this process. Sensory impulses generated by sucking stimuli travel up the afferent nerves from the breast to reach the brain.

Oxytocin from the posterior pituitary contracts mammary ducts and stimulates milk outflow—This activates the hypothalamus–posterior pituitary system and promotes oxytocin release in the blood, which stimulates the ducts cells to cause milk ejection. In the absence of such regular sensory stimuli from the nipples, the secreted milk accumulates in the glands, causing inflation of the ducts and pain, in the long run, milk production diminishes, leading to drying up of the breast.

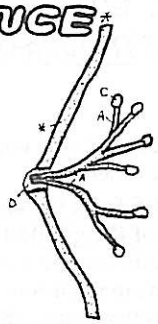
MILK IS A RICH SOURCE OF INFANT NUTRITION

Initial milk (colostrum) is rich in antibody proteins—Around the time of childbirth, and before the onset of milk formation, the mammary glands secrete small amounts of a thick substance called *colostrum*, which contains no fat and little water but is rich in proteins and other milk constituents. Colostrum is a rich source of maternal antibodies (immunoglobulin A). The infant's intestine is capable of absorbing immunoglobulins, which provide passive immunity.

Composition of normal human milk—Milk is a complete source of nutrition for the newborn, particularly during the first year, although human infants often suckle for two years before weaning. Milk is produced initially at a rate of 500 mL per day; this rate doubles by the sixth month of lactation. Human milk contains 88% water, carbohydrates (lactose), protein (casein, lactalbumins), and fat (cholesterol and fatty acids such as linoleic acid) as well as many vitamins and minerals. Initially, milk is richer in protein but later the fat and lactose proportions increase. Compared to cow's milk, it is higher in lactose, lower in protein, and similar in fat content. Except for iron and vitamin D, the mineral and vitamin content of human milk make it a complete food for the infant.

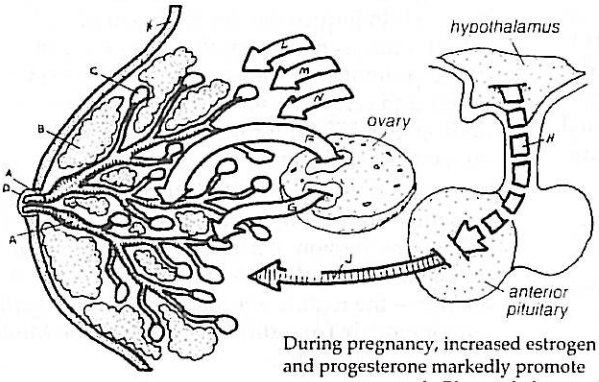
CN: Use same colors as on the previous page for estrogen (F) and progesterone (G).
1. Color the stages of breast development, completing each before going on to the next. Note the increased size of the prolactin (J) arrow to reflect the greater amount of flow. Note, too, that in the pregnancy panel, part of the estrogen (F) output has the effect of blocking the prolactin (J) effect on the breast. In the lactation panel, the blowup of a portion of breast development shows the secretion of milk globules from the alveoli. These are left uncolored.
2. Color the chart illustrating the comparison between mother's and cow's milk.

ADOLESCENCE



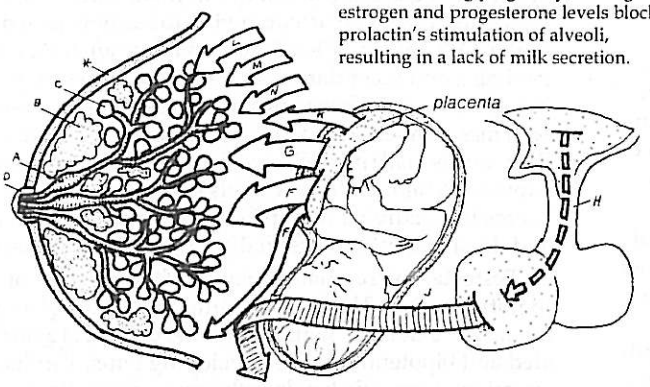
Early in puberty, the mammary glands are poorly developed and breasts contain little subcutaneous fat. During adolescence, estrogen promotes the development of the mammary ducts and the deposition of fatty tissue, while progesterone induces alveolar development. Growth hormones, glucocorticoids, and insulin are also necessary. Prolactin secretion from the anterior pituitary is low due to the strong inhibitory effect of hypothalamic-inhibiting hormone.

YOUNG ADULT

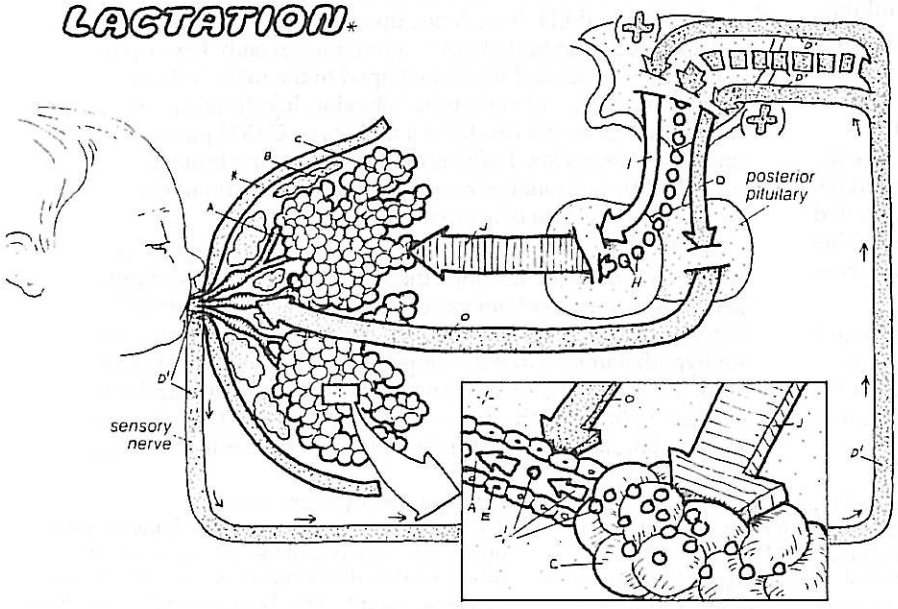


During pregnancy, increased estrogen and progesterone markedly promote mammary growth. Placental glucocorticoids and somatomammotropin and insulin are also needed for mammary and breast growth. Prolactin, the hormone that stimulates milk production, increases during pregnancy, but high estrogen and progesterone levels block prolactin's stimulation of alveoli, resulting in a lack of milk secretion.

PREGNANCY



LACTATION



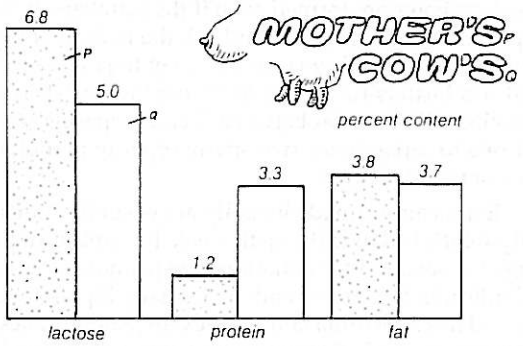
BREAST

- DUCT A
- FATTY TISSUE B
- ALVEOLI C
- NIPPLE D
- TOUCH RECEPTOR D'
- MYOEPITHELIAL CELL E

HORMONES

- ESTROGEN F
- PROGESTERONE G
- PROLACTIN-INHIBITING HORMONE H
- PROLACTIN-RELEASING HORMONE I
- PROLACTIN J
- HUMAN CHORIONIC SOMATOMAMMOTROPIN K
- GLUCOCORTICOID L
- INSULIN M
- GROWTH HORMONE N

COMPARISON OF MILK



Milk contains all the nutrients needed for infant growth. Human milk contains carbohydrates (lactose), protein (casein, lactalbumins), fat, minerals, and vitamins. Cow's milk contains the same nutrients, but in different proportions.

MILK FORMATION
PROLACTIN J

MILK EJECTION
OXYTOCIN O

After childbirth, estrogen and progesterone levels decline sharply because of loss of the placenta. Prolactin, no longer inhibited by sex steroids, stimulates the alveoli and milk is produced. The infant's sucking activity stimulates nipple tactile receptors. Sensory impulses activate the hypothalamus and cause increased secretion of prolactin-releasing hormone. This stimulates surges of prolactin release, ensuring continued milk formation. Infant sucking stimuli also cause release of oxytocin from the posterior pituitary. Oxytocin then stimulates the contractions of myoepithelial cells of the mammary ducts, forcing milk out of the nipple.

REGULATION OF SEX DETERMINATION & SEXUAL DEVELOPMENT

SEX DETERMINATION & SEXUAL DEVELOPMENT

The true gender of an individual is based primarily on the type of sex chromosomes (X and Y) the zygote has at conception. Somatic cells of normal males have 22 pairs of somatic chromosomes plus one X and one Y chromosome (XY). Normal females have 22 + XX combination. The expression of the specific sex-related genes during the various phases of development produces the biological and behavioral phenotype of sexuality. Thus, as explained below, human genetic sex is determined at fertilization, the phenotypes of gonads and genitalia at embryonic weeks 8 and 12 respectively, the brain hypothalamus sexual phenotype in the late fetal period, and final maturation of the reproductive system and the secondary sex characteristics during puberty and adolescence. The male hormone testosterone (T) plays critical roles in of sexual development. The actions of sex hormones on sexual maturation during puberty are discussed in plates 128 and 152.

X & Y chromosomes determine the genetic sex at fertilization—In males, meiosis of spermatocytes results in two types of sperms, one bearing the X chromosome and another with the Y chromosome. Meiosis of primary oocytes in the female produces only X-bearing eggs. Fertilization of the egg by a sperm carrying an X chromosome produces a XX zygote—i.e., female—while a Y-bearing sperm produces an XY zygote (male). The genetic sex is determined by the father.

X & Y sperms show functional differences—The X- and Y-bearing sperms show functional differences as well; Y sperms are lighter and may swim faster, explaining why more male zygotes are formed even if the numbers of X and Y sperm number are equal. Indeed, the majority of spontaneously aborted embryos are male, yet the male-to-female sex ratio at birth is 107 to 100, implying higher rates of male conceptions. Differences between X and Y sperms are the basis of efforts to separate the two sperm types to predetermine the sex of the conceptus.

Embryonic gonads initially are sexually indifferent and bipotential—Up to the sixth week, the embryo does not show signs of sexual differentiation. The primordial gonads appear identical in both sexes and are sexually bipotential. Each gonad has a medulla and a cortex. In genetic males, by the 8th embryonic week, the cortex regresses and the medulla forms the fetal testis. The Leydig and Sertoli cells differentiate in the fetal testis and secrete testosterone (T) and Mullerian Inhibitory Substance (MIS), respectively. In the female embryo, the medullary part regresses and cortex develops into an ovary. The fetal ovary does not secrete any hormones.

Y-chromosome genes induce testis formation—The regression of the cortex and formation of the fetal testis are the result of the action of a single *testis-determining gene*, called the *SRY gene* (Sex-determining Region of Y chromosome), located on the short arm of the Y chromosome. The expression of this gene in the male embryo produces SRY protein, which acts as a transcription factor and promotes testis formation.

Ovary development occurs autonomously in the absence of SRY gene—Female embryos are missing the Y chromosome and hence the SRY gene, so the SRY protein will not be expressed. In the absence of these influences, the medulla part of the indifferent gonad degenerates and the cortex part autonomously develops into the female ovary around the eighth week of development.

Testosterone & MIS from the embryonic testis determine sexual development of the genitalia—Sex organs of the 7-week embryo are undifferentiated and the potential exists for development in the male or female direction. By the 12th week—i.e., the early fetus stage—the appropriate sex organs have differentiated in each sex from their bipotential primordia. This development depends on testis secretions. T from Leydig cells is secreted in the fetal blood and acts on the *Wolffian ducts* to induce the development of male *internal genitalia* (epididymis, seminal vesicles, vas deferens) on both sides. T also promotes the development of male *external genitalia* (penis and scrotum); for this action T is converted to another androgen, DHT (dihyrotestosterone), by the target tissue enzyme 5-α-reductase.

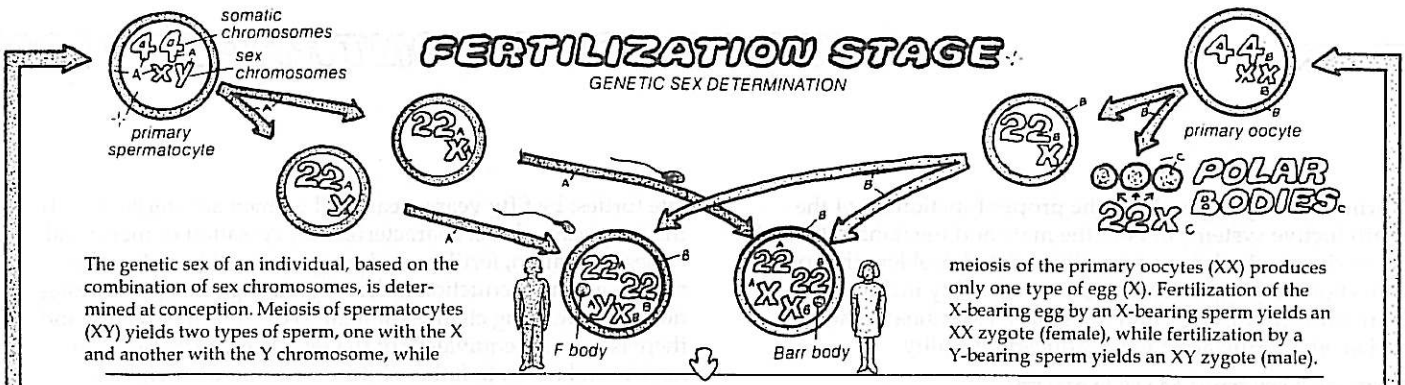
Sertoli cells release *MIS* (*Mullerian Inhibiting Substance*) into their immediate tissue environment. MIS from each testis induces regression of *Mullerian ducts* (primordia of female genitalia). In the absence of T and MIS—i.e., in a female embryo—the female internal and external genitalia develop autonomously from differentiation of the Mullerian ducts and other primordia.

Chromosomal, enzymic, and hormonal anomalies lead to abnormal genitalia—Embryos with no X chromosomes do not survive, but X-chromosome trisomy ("superfemale") is not abnormal. In the absence of a Y chromosome (XO; Turner syndrome), gonads will not differentiate but female genitalia will; puberty will not occur, owing to sex hormone deficiency. In the XXY pattern (Kleinfelter's syndrome), testes, male genitalia, and secondary sexual characteristics may develop, but not the seminiferous tubules. Absence of 5-α-reductase enzymes, converting T to DHT, creates female external genitalia in males *(male pseudohermaphrodites)*. Female embryos exposed to high androgen levels from a fetal or maternal source (e.g., adrenal tumors) develop male external genitalia and deranged internal genitalia *(female pseudohermaphrodites)*

Testosterone regulates sexual differentiation of the hypothalamus—The hypothalamic mechanisms underlying sexual behavior and neuroendocrine control are undifferentiated and bipotential in the developing fetus. T induces differentiation of the *male-type hypothalamus*, promoting a *continuous* (non-cyclical) secretory pattern of GnRH pulses and gonadotropins FSH and LH. In rodents, this effect occurs in the neonate. A specific hypothalamic region, the Sexually Dimorphic Nucleus, is larger and well-developed in the male. T determines this effect and male-type behavior. Injections of T in newborn female rats results in a male-type GnRH pattern and sexual behavior. T effects on the developing brain are mediated by neuronal estrogen produced in the brain tissue from T by the action of aromatase enzyme.

In the absence of T (as in normal females), the hypothalamus spontaneously develops the *female-type* cyclical and pulsatile regulatory mechanisms of GnRH and of FSH and LH secretions as well as female sexual behavior. Similar T effects on hypothalamic sexual development occur in fetal monkeys; behavior is affected more than GnRH cyclicity. Structural differences in the hypothalamus of human males and females are known, but not the exact functional and behavioral correlates.

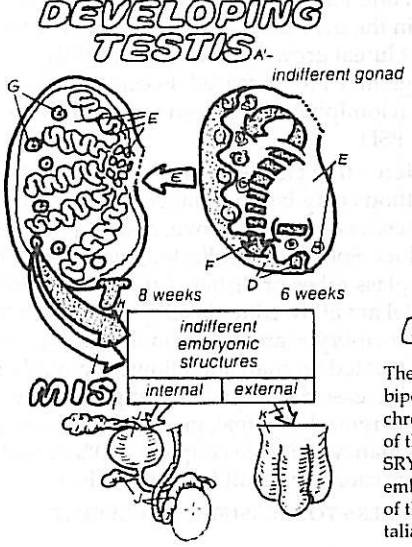
CN: Use very light colors for D, E, J, and K. Use colors previously used for estrogen (O), progesterone (G), FSH (N), and LH (O).
1. Begin at the bottom, coloring in the mature testis and ovary, and color the long arrows up the sides to the top panel, where those colors become primary spermatocytes and oocytes.
2. Color the embryonic stage, first doing the developing testis. Begin with the testis closest to the titles, and then do the outer one. Note that in the outer one, except for the Leydig cells (G), the entire structure receives the medulla color (E).



The genetic sex of an individual, based on the combination of sex chromosomes, is determined at conception. Meiosis of spermatocytes (XY) yields two types of sperm, one with the X and another with the Y chromosome, while meiosis of the primary oocytes (XX) produces only one type of egg (X). Fertilization of the X-bearing egg by an X-bearing sperm yields an XX zygote (female), while fertilization by a Y-bearing sperm yields an XY zygote (male).

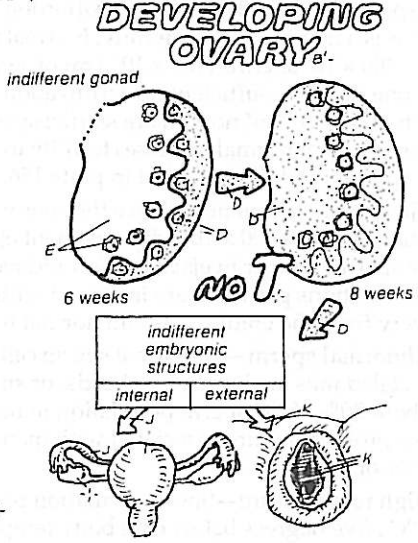
EMBRYONIC STAGE

DIFFERENTIATION OF GONADS AND ACCESSORY REPRODUCTIVE ORGANS



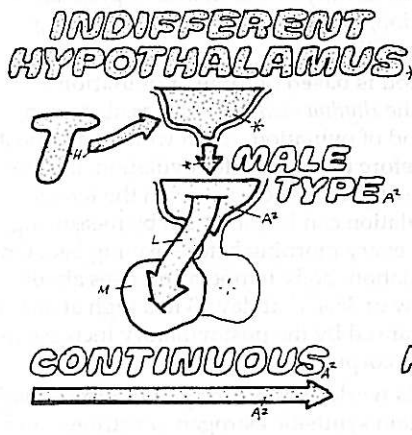
CORTEX
MEDULLA
SRY PROTEIN
LEYDIG CELL
TESTOSTERONE
MRF
INTERNAL GENITALIA
EXTERNAL GENITALIA

The early gonad has a cortex and a medulla and is sexually bipotential. The expression of the SRY gene in the male Y chromosome promotes formation of testes from the medulla of the early gonads, plus cortex regression. In females, the SRY gene is absent and the cortex forms the ovary. The embryonic testis secretes T and MIS, inducing development of the male genitalia from indifferent structures. Female genitalia develop spontaneously in the absence of T and MIS.



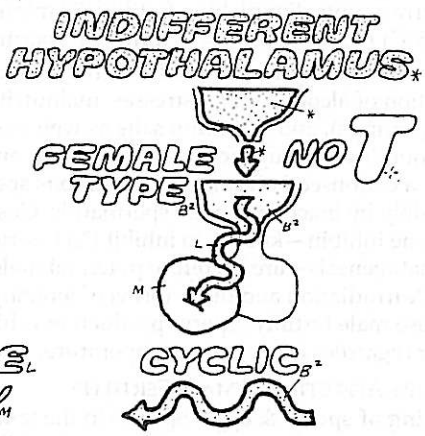
NEONATAL STAGE

BRAIN DEVELOPMENT



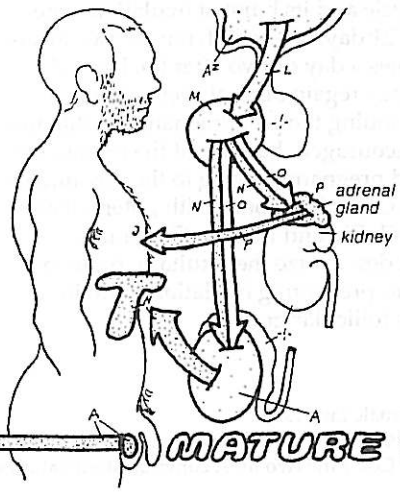
In animals, the hypothalamus is sexually bipotential at birth. T promotes the development of a male-type hypothalamus. Absence of T promotes the spontaneous development of a female-type hypothalamus (cyclical release of GnRH).

GONADOTROPIN-RELEASING HORMONE
ANTERIOR PITUITARY



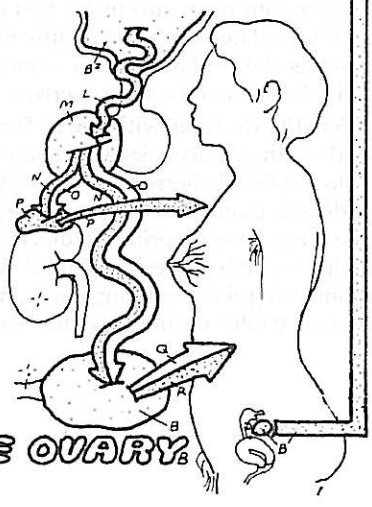
PUBERTY STAGE

SEXUAL MATURATION



FSH
LH
ADRENAL SECRETION
ESTROGEN
PROGESTERONE

At puberty, hypothalamic control mechanisms mature and GnRH pulses begin; in response to pituitary FSH and LH, gonads mature and secrete estrogen and progesterone in the female and T in the male. These promote growth and maturation of sex organs and development of secondary sexual characteristics. Adrenal androgens are involved in skeletal growth in girls and in pubic and axillary hair growth in both sexes.



FERTILITY & CONTRACEPTION

Normal fertility depends on the proper functioning of the reproductive systems in both the male and the female. One of every six couples has an infertility-related problem that prevents normal pregnancy. Causes of infertility include problems with sperm, eggs, and ovulation. Hormonal treatment and *in vitro* fertilization have reduced infertility.

FACTORS AFFECTING MALE FERTILITY

Sperm number is important for male fertility—In males, low sperm count and/or a high proportion of abnormal sperms is a major cause of sterility. Normal male ejaculate has about 300×10^6 sperms (100×10^6 /ml of semen), even though only one sperm is sufficient for fertilization. Men with sperm counts below 20% of normal are sterile; sperm count between 20% and 40% of normal increases fertility to 50%. The basis for high sperm number is detailed in plate 156.

Ejaculation frequency—Since the sperm production rate is constant at about 200×10^6/day, frequent ejaculation leads to a low sperm number in ejaculate and reduced fertility. About 3–4 ejaculations per week are in accord with adequate sperm delivery from the epididymis and normal fertility.

Abnormal sperm—Abnormal sperm cells with no tail, two tails, coiled tails, no heads, two heads, or small heads make up about 20% of the sperm population in normal fertile men; higher proportions are associated with increasingly higher degrees of infertility.

High temperature—Sperm formation proceeds optimally at 32°C , five degrees below core body temperature. If the testes are kept inside the body or too close to it, the seminiferous tubules reversibly degenerate and sperm formation ceases. Tight clothing worn by athletes may result in a decline in sperm counts diminishing fertility; 30 minutes in a hot bath (43–45°C) may lead to a 90% decline in sperm number.

Other factors affecting male fertility—Excessive consumption of alcohol, major stresses, malnutrition, some infections (mumps), and cadmium salts as well as some natural compounds and drugs reduce sperm count and fertility. Gossypol, a cottonseed oil compound, inhibits spermatogenesis reversibly by inactivating the spermatids. Gossypol and the hormone inhibin—known to inhibit FSH, Sertoli cells, and spermatogenesis—are therefore potential male contraceptives. X-irradiation and other forms of ionizing radiation decrease male fertility. Sperm production is higher in winter regardless of scrotum temperature.

FACTORS AFFECTING FEMALE FERTILITY

Aging of sperm & egg—Sperms in the female tract undergo aging but retain motility and the ability to fertilize for up to four days; survival is best in the cervical mucus. Freshly ovulated eggs are mature; the best time for fertilization is about 12 hours after ovulation. Thereafter, eggs gradually age and become overripe, unable to be fertilized.

Fertility declines with age in females—Since oogonia divide in the embryonic period only, the ovarian oocytes are as old the female herself. Most oocytes die by atresia during childhood. Decline continues throughout maturity; by age 50, the ovaries have no primary follicles and oocytes left. As a result of ovarian losses, menstrual cycles and ovulation become irregular, resulting in a gradual decline in fertility. Pregnancy rates decline from the early forties to the late forties; by fifty years, nearly all women are sterile. This is the *menopause* phase, characterized by cessation of menstrual cycles, ovulation, fertility, and pregnancy. Although males show a gradual reduction in fertility during old age, the testes do not show aging changes similar to those of the ovaries and there is no male equivalent of the female menopause. Men have been known to father children even in their eighties.

Hormonal treatments enhance female fertility—Injections of gonadotropins LH and FSH or hCG enhance the number of follicles developing in the ovaries as well the chances of their ovulation and corpus luteal growth; as a result, fertility and the likelihood of pregnancy are increased. Recently, purified GnRH or its analogs (clomiphene) has been used to increase endogenous LH and FSH.

***In vitro* fertilization**—If *in vivo* fertility treatments fail, *in vitro* fertilization methods may be undertaken. Women are primed with hormones, as described above, and eggs are harvested from the oviduct. Sperms are collected, washed, and added to the eggs in glass tubes or dishes. After fertilization, zygotes with pronuclei are allowed to develop to the 4- to 8-cell stage; several such embryos are placed in the uterine cavity of a progesterone-treated woman and allowed to implant. The *in vitro* methods increase the probability of pregnancy from 0 to about 20%—a remarkable feat, given that the normal rate of successful pregnancy in fertile couples is 40% at best. Fertility treatments occasionally result in multiple births.

"CONTRACEPTION" REFERS TO MEASURES TO PREVENT PREGNANCY

Contraception or "birth control" may be achieved by a variety of mechanical and physiological methods. Contraceptive methods aim to reduce fertility or the chance of pregnancy by preventing ovulation, the encounter of sperm and egg, fertilization, or implantation.

The rhythm method is based on time of ovulation & sperm survival—In the *rhythm method*, coitus is abstained from during the period of ovulation, when women are most fertile (from 4 days before to 3 days after ovulation, in consideration of the 4-day survival time of sperms in the female tract. The time of ovulation can be estimated by measuring *basal body temperature* every morning before leaving bed. One to two days after ovulation, body temperature rises about 0.4°C (1°F), from a low of 36.4°C at day 13 to a high at 36.8°C at day 22; the rise is caused by the postovulatory increase in progesterone from the corpus luteum.

Contraceptive pills work by inhibiting ovulation—*Oral contraceptive pills* contain synthetic estrogen or estrogen and progesterone; they prevent ovulation by feedback inhibition of the rise of LH in the cycle and its burst at ovulation. One pill is taken each day for 21 days, from fifth day of menstruation. Menstruation resumes a day or two after the last pill. Women desiring pregnancy regain normal cycles one to several months after discontinuing the pill. Pregnancy within the first 1–3 months is not encouraged, because of the possibility of multiple ovulation and pregnancy owing to the rebound of pituitary gonadotropins. Other hormones with potential as contraceptive agents are GnRH and inhibin. Continuous and high levels of GnRH desensitize the pituitary, reducing LH and FSH secretion and preventing ovulation. Inhibin reduces FSH and inhibits follicular growth.

CN: Use red for C and a dark color for E.
1. Begin with the four factors affecting male fertility.
2. Note the presence of sperm (A) among the female factors.
3. Color the methods of contraception.
4. Color the two most common sterilization sites.

FERTILITY

FACTORS AFFECTING MALES:

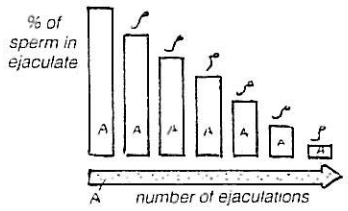
SPERM NUMBER

NORMAL:
100,000,000
per mL/semen

STERILE:
<20,000,000
per mL/semen

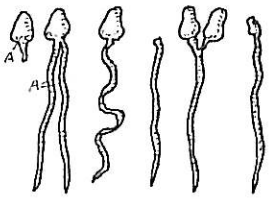
A normal sperm count (~100 million/ml of semen) is necessary for male fertility. Below 40% of normal, fertility is reduced by 50%. Below 20%, fertility ceases.

EJACULATIONS



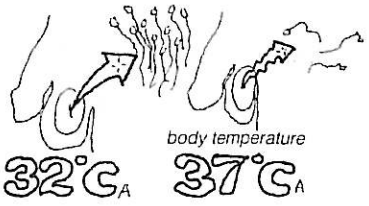
Since the sperm production rate is limited (~200 million/day), repeated ejaculation gradually decreases the number of sperm in the ejaculate.

BAD SPERM



About 20% of sperm are abnormal: they may have no tails, two tails, twisted tails, no heads, two heads, or shrunken heads. More abnormalities decreases fertility.

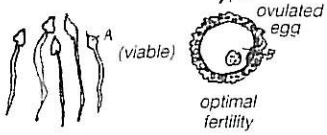
TEMPERATURE



Sperm form normally at 32°C (5°C below body temperature). If the testes are subject to heat, seminiferous tubules reversibly degenerate, interrupting sperm production and causing sterility.

FACTORS AFFECTING FEMALES:

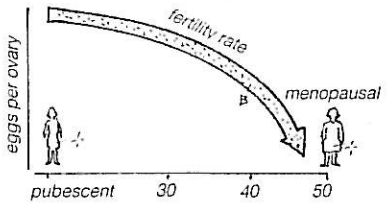
AGE OF SPERM, EGG



1-4 DAYS **1 DAY**

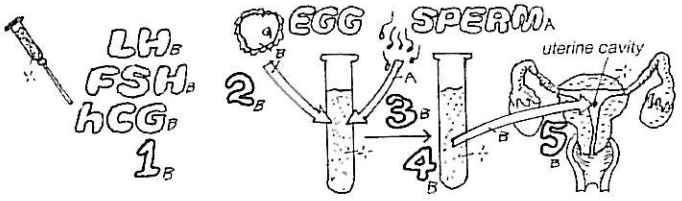
A woman's optimal fertility period in each monthly cycle is within 2 days of ovulation. Sperm usually survive ~1 day, but some up to 4 days. Most eggs live ~1 day, few up to 2 days.

FEMALE AGE



Fertility is high in females in their 20s and early 30s, declining beyond the late 30s to very low levels in the late 40s and ceasing around 50 (menopause).

HORMONES / IN VITRO FERTILIZATION

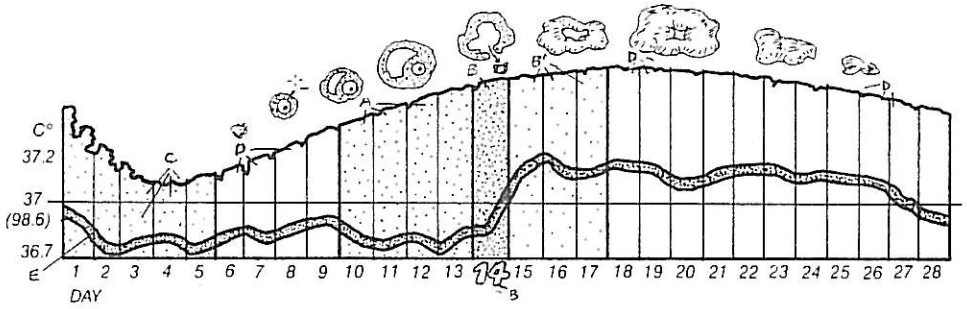


For *in vitro* fertilization, a woman is first treated with hormones (FSH, LH, hCG, GnRH) to increase follicular growth and ovulation rates (1). Eggs are collected (2) and mixed with male sperm (3) in a test tube (dish) for fertilization (4). Young embryos are then transferred to the uterus of the progesterone-treated mother and allowed to implant (5).

CONTRACEPTION

RHYTHM METHOD

MENSTRUATION
SPERM VIABILITY
OVULATION
EGG VIABILITY
SAFE DAYS



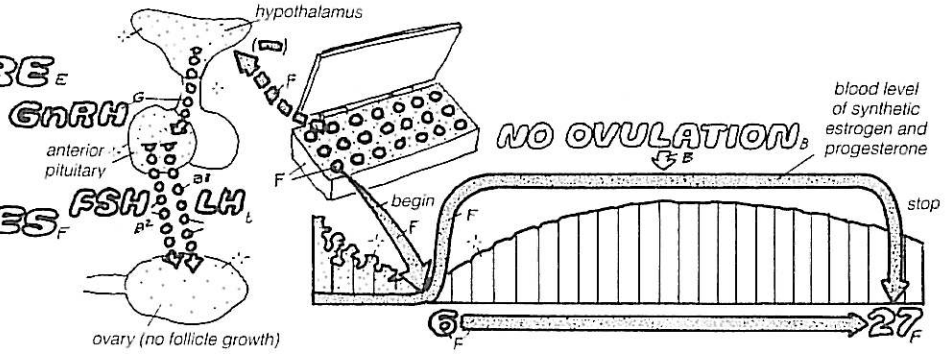
In the rhythm method, coitus is avoided during the week when the likihood of pregnancy is high. This period (4 days before ovulation to 3 days after) is based on the maximum survival time of sperm (4 days) and egg (2 days) in the female reproductive tract, allowing for ovulation variability.

BASAL TEMPERATURE

Basal body temperature, taken early in the morning, before leaving bed, shows a rise of ~0.4°C (~1°F) after ovulation. This rise indicates ovulation and is caused by progesterone secretion; it lasts until the next menstruation.

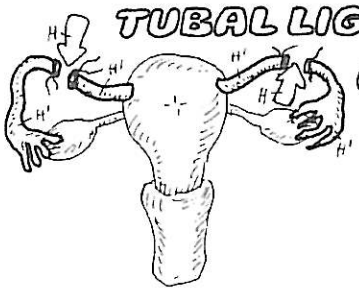
ORAL CONTRACEPTIVES

Oral contraceptives (pills containing synthetic estrogen and progesterone) are taken by women for 21 days following menstruation. The rapid increase of these estrogen-like substances in the blood inhibits the release of FSH and LH, preventing follicular growth and ovulation.



STERILIZATION

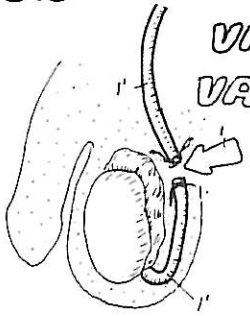
TUBAL LIGATION



UTERINE TUBE

Tubal ligation (cutting and tying or cauterization of the uterine tubes) results in permanent sterility, since sperm can no longer reach the ovulated egg. Tubal ligation and vasectomy (illustration to the right) have a 50% chance of reversibility.

VASECTOMY



VAS DEFERENS

Cutting and tying the two vas deferens ducts is a simple operation that permanently obstructs the delivery of sperm through the vas deferens during ejaculation, thereby causing male sterility.