Block 11 - Theme: Congenital abnormalities & female sex hormones

By

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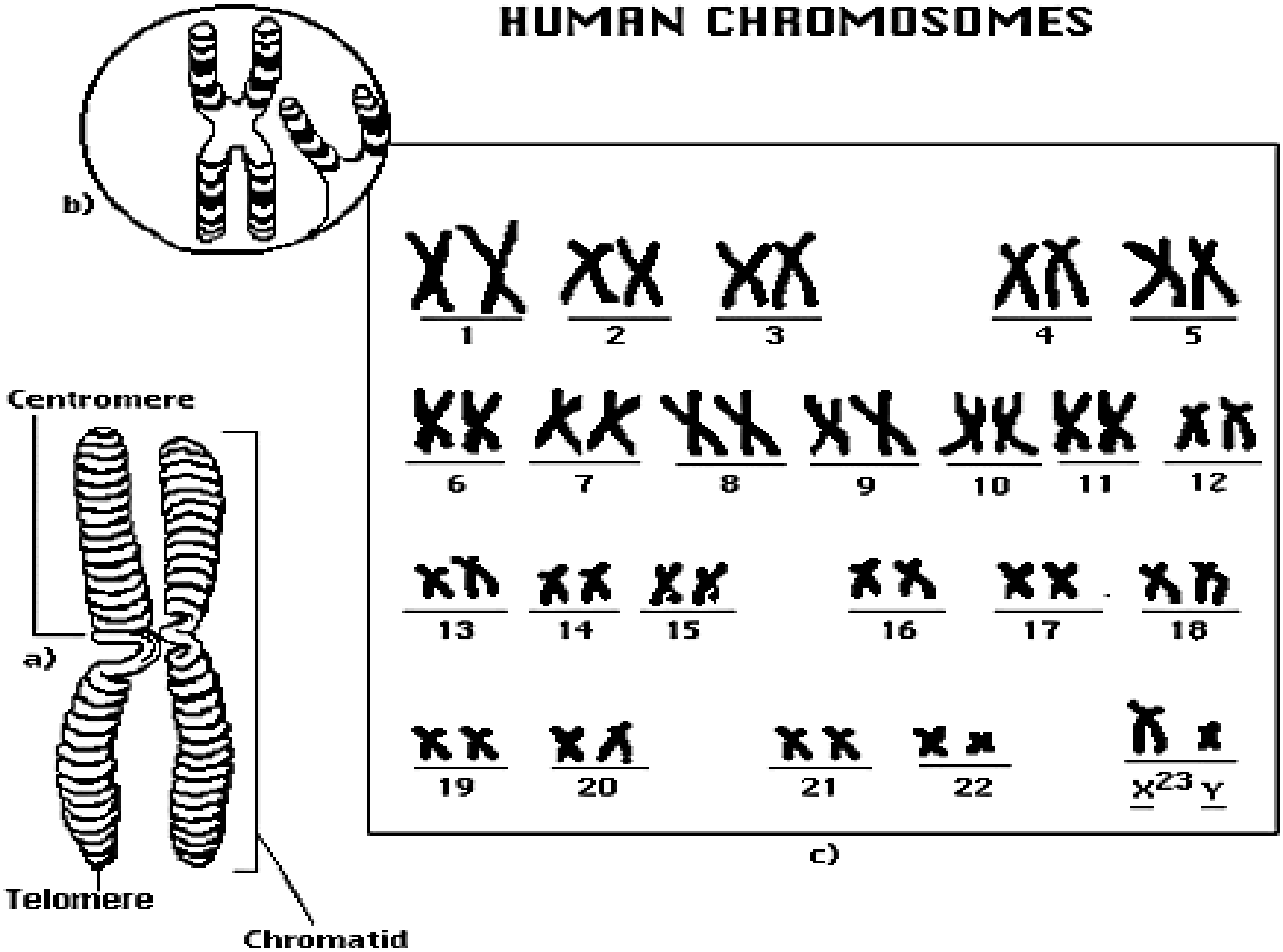
Sex determination

HUMAN CHROMOSOMES



Gametogenesis occurs by meiosis.

- Cell division involves the division of the nucleus and the division of the cytoplasm.
- Mitosis is cell division maintains the chromosome number, chromosome combination, and genetic identity of the chromosomes from the dividing parent cell to the two daughter cells produced. Mitosis produces somatic cells.
- Meiosis produces gametes. Only one chromosome from each chromosome pair is inherited in each of the four daughter cells produced from a parent cells. The gametes have one-half the chromosome number.

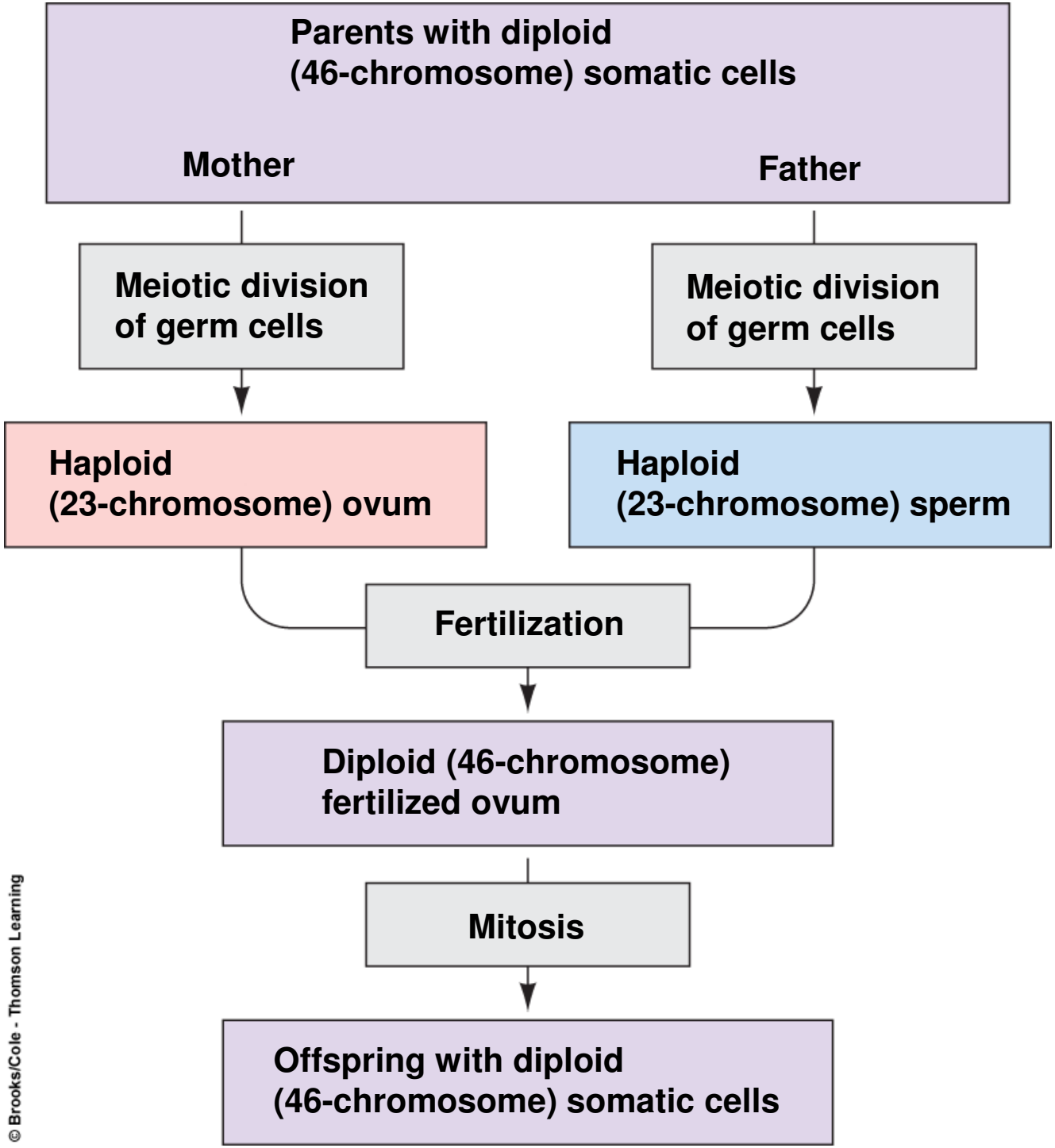


Figure 20.3
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A combination of sex chromosomes determines the sex of an individual.

- 23 pairs of homologous chromosomes are separated during meiosis.
- 22 pairs of the chromosome pairs are autosomes. The 23rd pair is either XX(female) or XY (male).
- Sex determination depends on the combination of chromosomes at fertilization.

Sexual differentiation in humans depends on the presence or absence of masculinizing determinants.

- The combination of sex chromosomes determines gonadal sex. A sex-determining region (SRY) of the Y chromosome influences gonadal specificity at the seventh week of intrauterine life. The region masculinizes the gonads.
- Females lack the SRY gene. Their gonadal cells do not receive a signal for testicular formation.
- Phenotypic sex is the apparent anatomic sex of an individual.

- Male and female external genitalia develop from the same embryonic tissue. The reproductive tracts also develop from a common source.
- Undifferentiated embryonic tissue develops into female structures unless actively signaled by masculinizing factors.
- Genetic and phenotypic sex are usually compatible. However several factors can produce errors in sexual differentiation.

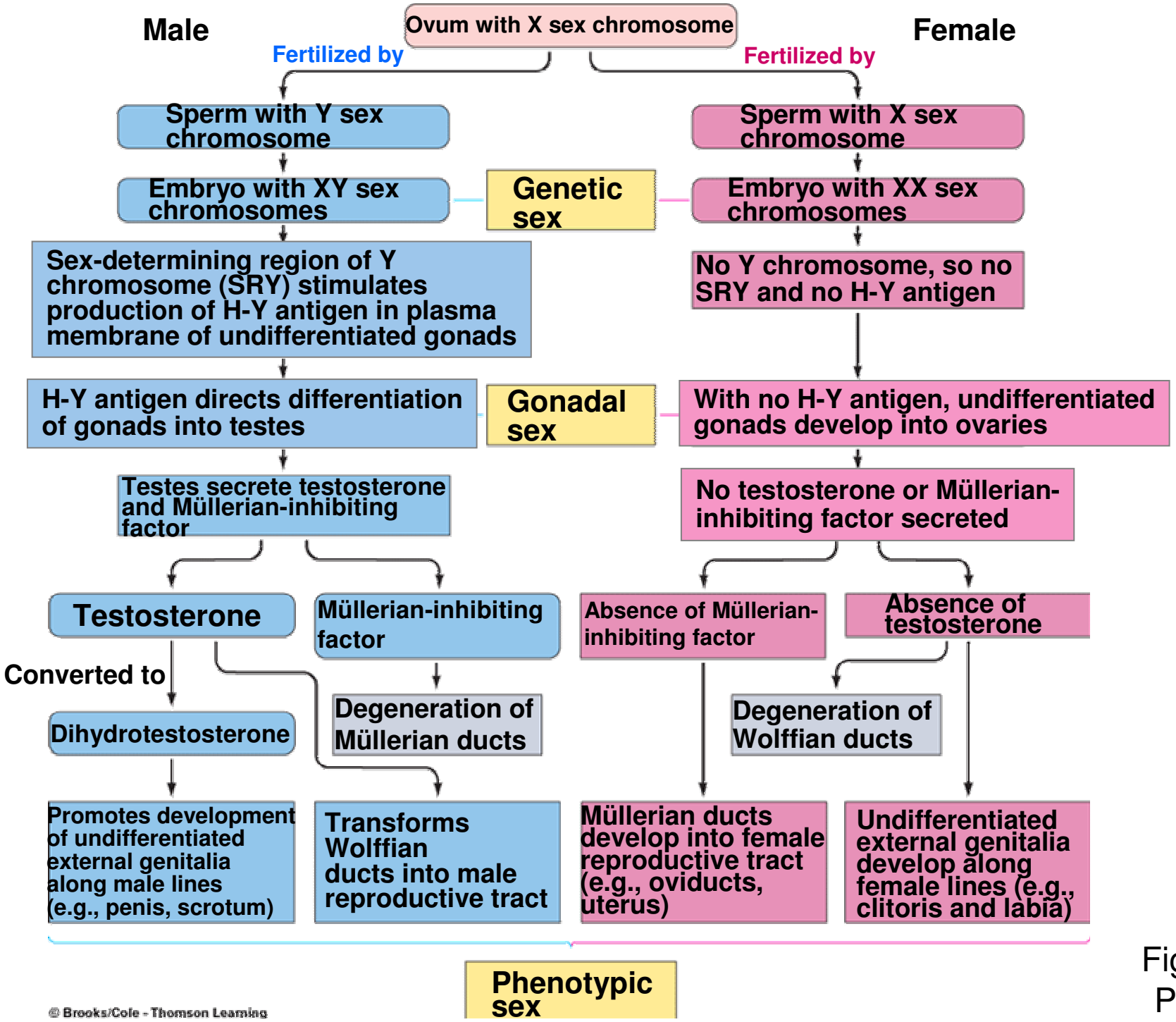

Figure 20.4
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Chromosomal abnormalities

Autosomal Abnormalities

- The majority of human chromosomal abnormalities occur in the autosomes.
- Most of these abnormalities are monosomies or trisomies.
- All fetuses with autosomal monosomies spontaneously abort early in pregnancy.
- Likewise, almost all fetuses with trisomies die before birth. Those that survive usually have multiple physical malformations, mental retardation, and relatively short lives.

Down's Syndrome

- The most well known and most common autosomal abnormality is **Down syndrome** .
- People with Down syndrome have an irregularity with autosome pair 21.
- In most cases, there is an extra chromosome (i.e., trisomy).
- The actual gene or genes on chromosome 21 that are responsible for Down syndrome are now being identified in a critical region of 20-40 genes. About 2-4% of Down syndrome people are genetically mosaic.

People with Down syndrome frequently have other medical problems

- These include epilepsy , hypothyroidism , crossed eyes, near-sightedness or far-sightedness, cataracts , hearing impairment, heart defects, intestinal malformations, hernias , and a marked susceptibility to respiratory infections, such as pneumonia.
- Childhood leukemia is as much as 20 times more common than average.

- The most prominent and debilitating trait of people with Down syndrome is mental retardation.
- They usually only reach a mental age level of a 3-7 year old normal child.
- They are slow learners and their abstract reasoning is particularly limited.
- However, some high achieving individuals with Down syndrome have mental levels of 12 year olds, which is sufficient to function in society with little assistance.

Sex Chromosome Abnormalities

- The majority of known types of chromosomal abnormalities involve sex chromosomes.
- Sex chromosome abnormalities are gender specific.
- A single Y chromosome is sufficient to produce maleness while its absence is necessary for femaleness. Female abnormalities are due to variations in the number of X chromosomes.
- Male abnormalities are the result of irregular numbers of either the X or the Y chromosome or both.

Sex Chromosome Abnormalities			
Female Genotype	**Syndrome**	**Male Genotype**	**Syndrome**
XX	normal	XY	normal
XO	Turner	XXY	Klinefelter
XXX	Triple-X	XYY	XYY

Turner syndrome

- Occurs when females inherit only one X chromosome--their genotype is X0.
- Incidence: Current estimates of its frequency range from 1 in 3,000 female infants to 1 in 5,000.
- Characteristics:
  - short in stature, averaging 4 foot 7 inches as adults
  - distinctive webbed necks (i.e., extra folds of skin),
  - small jaws, and
  - high arched palates.
  - They generally lack prominent female secondary sexual characteristics.

- They have exceptionally small, widely spaced breasts, broad shield-shaped chests, and turned-out elbows.
- Their ovaries do not develop normally and they do not ovulate.
- They also have a higher than average incidence of thyroid disease.
- In some individuals, there is slight mental retardation.

Common symptoms of Turner syndrome include:

- Short stature
- Lymphoedema (swelling) of the hands and feet
- Broad chest (*shield chest*) and widely-spaced nipples
- Low hairline
- Low-set ears
- Reproductive sterility
- Rudimentary ovaries Gonadal Streak (underdeveloped gonadal structures)
- Amenorrhea, or the absence of a menstrual period

Common symptoms cont.:

- Increased weight, obesity
- Shield shaped thorax of heart
- Shortened metacarpal IV (of hand)
- Small fingernails
- Characteristic facial features
- Webbing of the neck (webbed neck)
- Coarctation of the aorta
- Poor Breast Development
- Horseshoe kidney

Metafemales , or triple-X females

- inherit three X chromosomes--their genotype is XXX or more rarely XXXX or XXXXX.
- As adults, these "super-females" are usually an inch or so taller than average with unusually long legs and slender torsos, but otherwise appear normal.
- The frequency is approximately 1 in 1,000 female infants and it occurs more commonly when the mother is older.

- Characteristics:
  - They have normal development of sexual characteristics and are fertile.
  - They may have slight learning difficulties and are usually in the low range of normal intelligence (especially the XXXX and XXXXX individuals).
  - They tend to be emotionally immature for their size during childhood.

Klinefelter syndrome

- males inherit one or more extra X chromosomes--their genotype is XXY or more rarely XXXY, XXXXY, or XY/XXY mosaic.
- Characteristics:
  - have relatively high-pitched voices,
  - asexual to feminine body contours as well as breast enlargement, and comparatively little facial and body hair.
  - sterile or nearly so, and their testes and prostate gland are small. As a result, they produce relatively small amounts of testosterone.
  - likely to be overweight.
  - learning difficulties as children, especially with language and short-term memory.

- They are usually capable of normal sexual function
- Klinefelter syndrome males with more than two X chromosomes usually have extreme symptoms and are often mentally retarded.
- Men who are mosaic (XY/XXY) generally have the least problems.
- They have a higher than average risk of developing osteoporosis, diabetes and other autoimmune disorders.

- Incidence: The frequency of Klinefelter syndrome has been reported to be between 1 in 500 and 1 in 1000 male births.

XYY syndrome

- Males inherit an extra Y chromosome--their genotype is XYY.
- As adults, these "super-males" are usually tall (above 6 feet) and generally appear and act normal. However, they produce high levels of testosterone.
- During adolescence, they often are slender, have severe facial acne, and are poorly coordinated. They are usually fertile and lead ordinary lives as adults.
- The frequency of XYY syndrome is not certain due to statistical differences between different studies. It may be as common as 1 in 900 male births to as rare as 1 in 1500 or even 1 in 2,000.

- Early studies of XYY syndrome done in European prisons initially led to the erroneous conclusion that these men were genetically predisposed to antisocial, aggressive behavior, below average intelligence, and homosexuality.
- However, some researchers suggest that the high testosterone levels of XYY men can make them somewhat more prone to violence and that this may cause higher rates of wife beating.

Physiology of primary and secondary female sex organs

Sex Organ: primary

- The Latin term genitalia, is used to describe the externally visible sex organs, known as primary genitalia or external genitalia:
- in males the penis and scrotum,
- in females the clitoris and vulva.

Secondary genitalia or internal genitalia

- The other, hidden sex organs are referred to as the secondary genitalia or internal genitalia.
- The most important of these are the gonads, a pair of sex organs, specifically the testes in the male or the ovaries in the female.
- Gonads are the true sex organs, generating reproductive gametes containing inheritable DNA. They also produce most of the primary hormones that affect sexual development, and regulate other sexual organs and sexually differentiated behaviors.

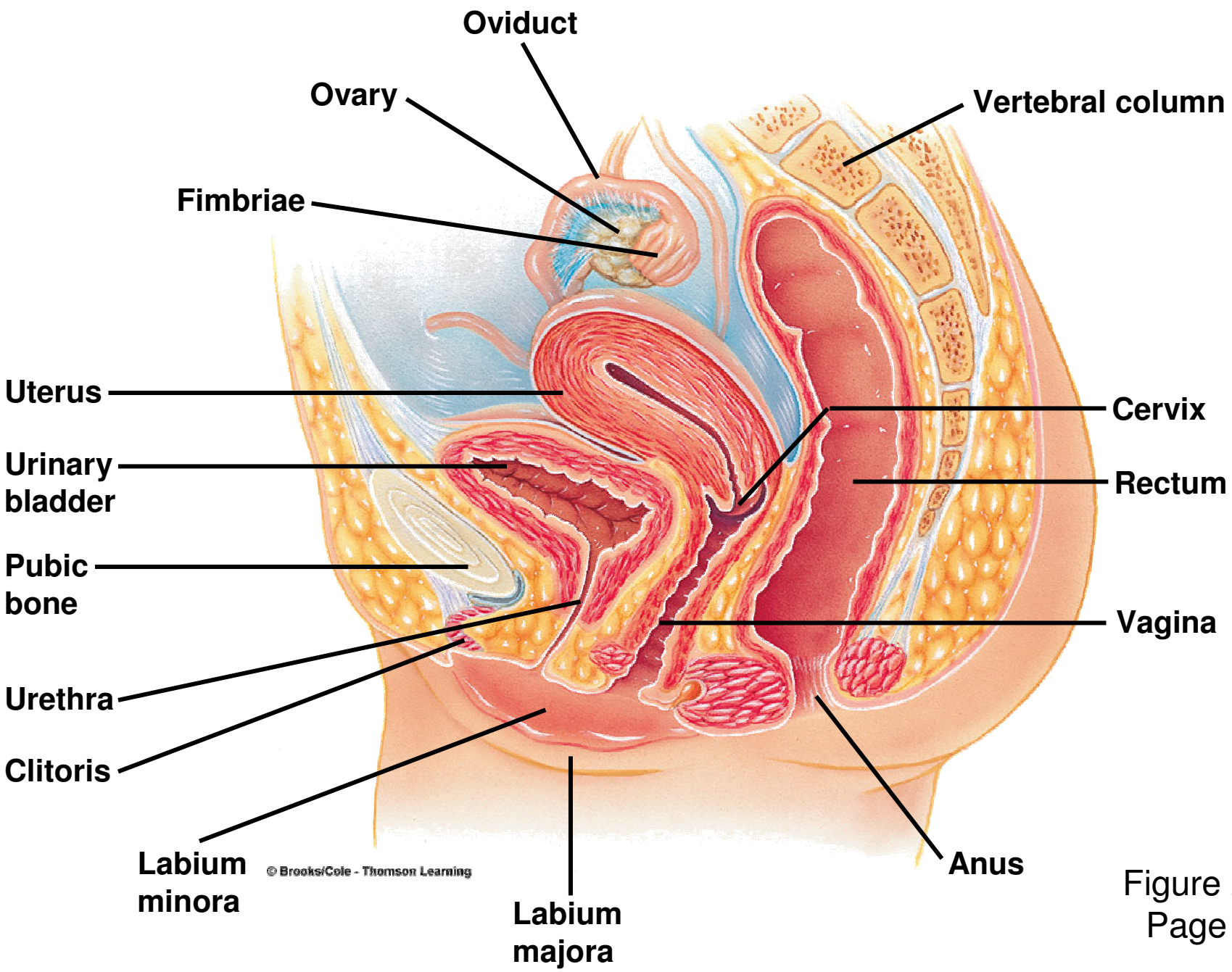

Figure 20.2a
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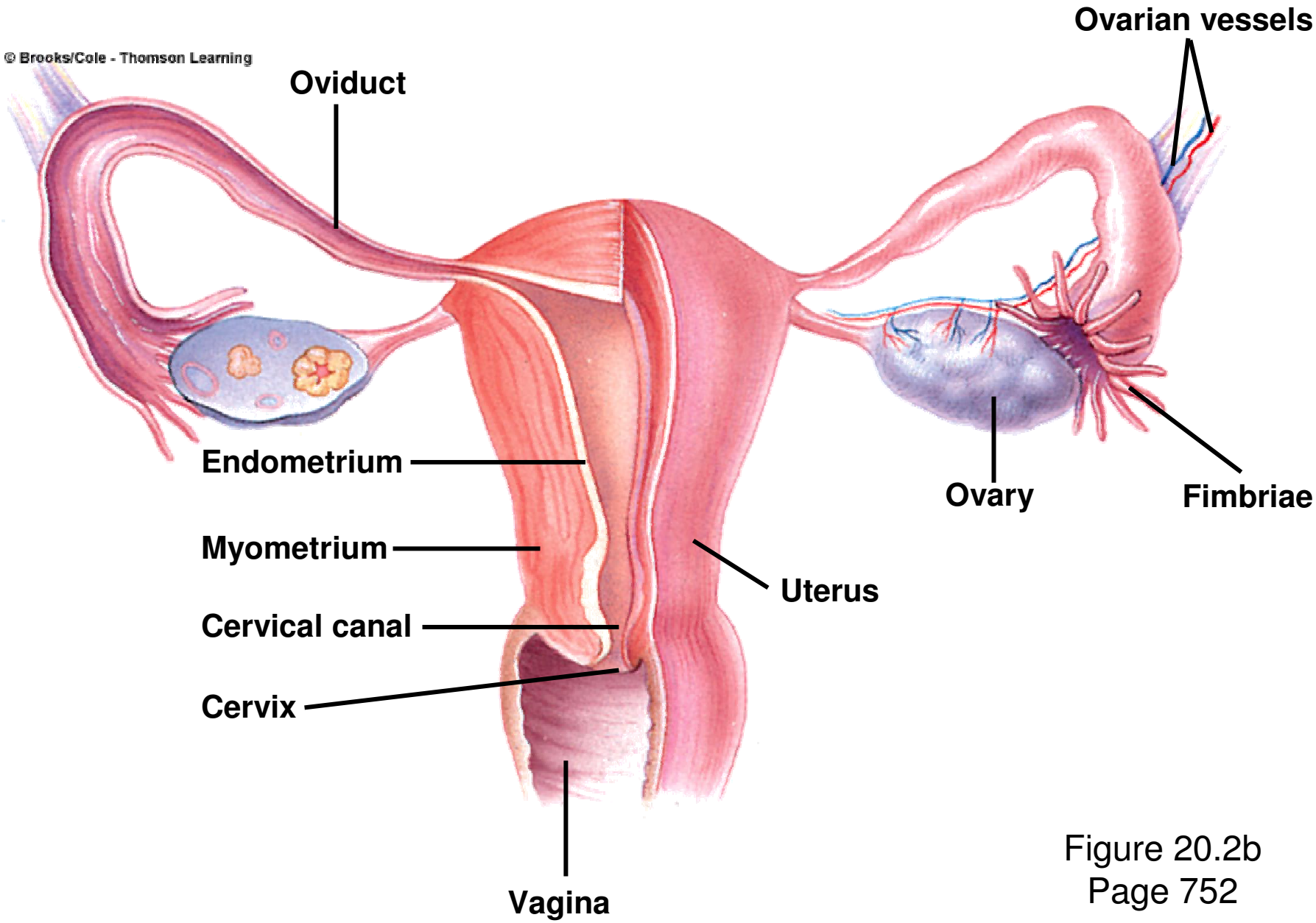

Figure 20.2b
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The reproductive system consists of the gonads, reproductive tract, and accessory sex glands.

- Reproduction depends on the union of male and female gametes.
- The primary reproductive organs are the pair of testis and pair of ovaries. Both systems produce gametes and secrete hormones
- A reproductive tract plus accessory organs are found in either sex.
- Unique secondary sexual characteristics are found in each sex.

The reproductive system in each sex carries out essential functions.

- In the male these functions are
  - production & delivery of sperm to the female.

- Functions in the female are
  - production of ova,
  - reception of sperm,
  - transport of sperm and ova to a common site for union, maintenance of the developing fetus,
  - partuition, and nourishing the infant.

Oogenesis

- Production of active ova, occurs monthly in ovarian cycle
- Primary oocyte is surrounded by a primordial follicle which grows & matures each month
- Cytokinesis is unequal, secondary oocytes are haploid (1N)

Oogenesis is gametogenesis in the female.

- Oogonia divide mitotically.
- The first meiotic division of an oogonium produces a primary oocyte (diploid). It is surrounded by a primary follicle.
- From puberty to menopause some primary follicles develop into secondary follicles on a cyclical basis.
- Just before ovulation the primary oocyte completes its first meiotic division. One product is a larger secondary oocyte. The other is the first polar body.
- The secondary oocyte is ovulated and possibly fertilized. Sperm entry into this oocyte triggers the second meiotic division.

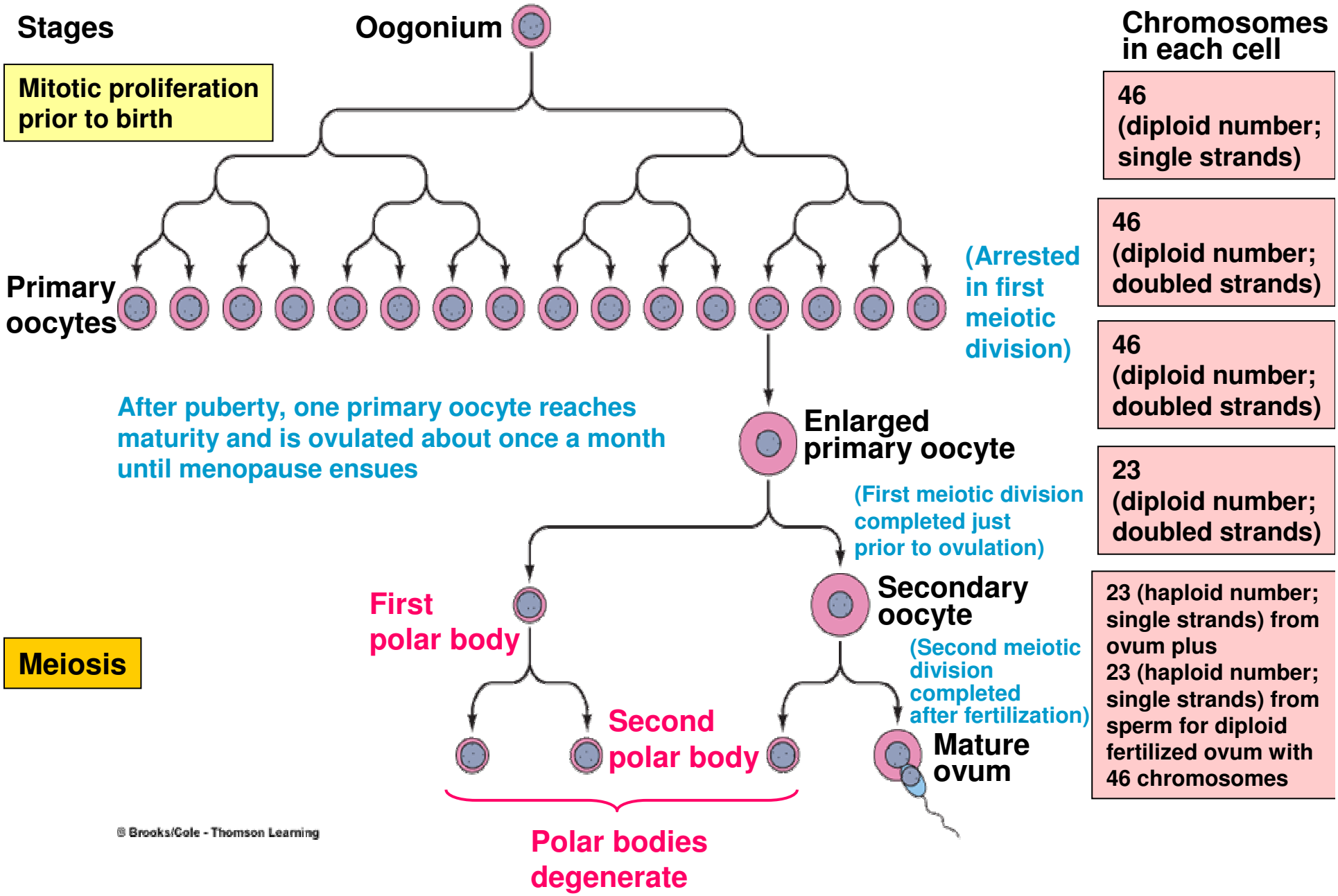

Figure 20.12
Page 771

Ovarian cycle

The ovarian cycle consists of alternating follicular and luteal phases.

- The follicular phase is dominated by maturing follicles.
- During the follicular phase the granulosa cells of some primary follicles proliferate.
- Rapid follicular growth continues during the follicular phase.
- One follicle usually grows more rapidly and matures about 14 days after the onset of follicular development. This follicle ruptures to release the oocyte from the ovary. This event is called ovulation.
- This released sex cell enters the oviduct where it may or may not be fertilized.
  - **See Figure 20-13**

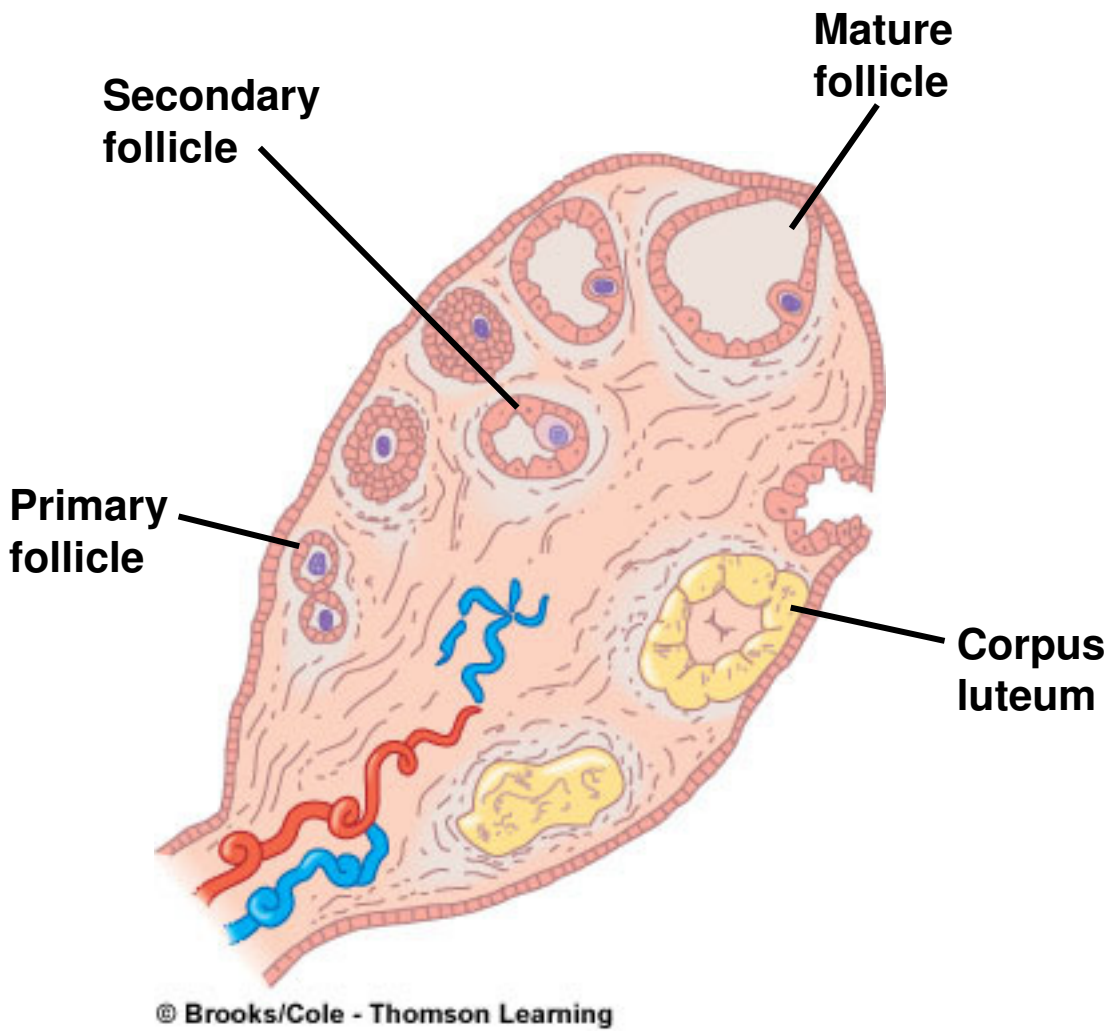

Figure 20.13e
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The corpus luteum operates the last 14 days of the cycle.

- It is a the converted follicle left behind in the ovary after it loses its sex cell by ovulation.
- The corpus luteum secretes an increased amount of progesterone compared to the follicular phase. It also secretes estrogen.
- The corpus luteum degenerates 14 days after its formation unless fertilization and implantation occurs. If this occurs the corpus luteum continues to secrete its hormones.
- It is now called the corpus luteum of pregnancy.

Oogonium

↓ Mitotic division

Primary oocyte

Prophase I

↓

Meiosis I

Secondary oocyte & First Polar Body

Metaphase II

Ovulation

↓

Meiosis II if sperm penetration

Mature ovum & Second Polar Body

Primordial follicle

↓ Squamous epithelium, Monthly FSH

Primary follicle

↓ Cuboidal epithelium

Growing follicle

↓ Antrum forms

Secondary follicle

↓

Mature\Graafian follicle

↓

Corpus luteum

↓ Degenerates

Corpus albicans

Hormonal regulation of monthly ovarian cycle

Day 1

- Rising levels of GnRH stimulate release of FSH & production of LH by anterior pituitary
- FSH stimulates proliferation of granulosa cells & the follicle grows
- Granulosa cells secrete follicular fluid producing small fluid-filled cavities which merge to form the fluid-filled antrum
- Increasing numbers of granulosa cells release estrogens & inhibin

Day 6-8

- Inhibin & estrogen decrease GnRH release & FSH release
  Higher levels of estrogen stimulate production & release of LH (positive feedback)
- LH accelerates growth & maturation of follicle (1 dominant ovum)

Day 12-14

- While follicle migrates to ovarian surface, estrogen level increases sharply causing a surge of LH & 1 follicle ruptures & releases ovum.
- Other follicles degenerate forming atretic follicles. Estrogen levels fall.

Day 15

- LH levels are elevated for 2 days, cause follicle cells to be filled with lipid & yellow pigment (luteinized) forming a corpus luteum.
- The corpus luteum secretes progesterones & estrogens which inhibit the hypothalamus production of GnRH & decrease FSH & LH levels

Day 26

- Corpus luteum degenerates & forms the corpus albicans if there is no pregnancy.
- Decreasing levels of progesterone & estrogen result in renewed production of GnRH

There are concurrent changes in the uterus with the cyclical changes in the hormones during the female cycle.

- During the uterine menstrual cycle (beginning of the cycle) there is a sloughing off of the endometrium of the uterus.
- An increased level of estrogen late in the follicular phase causes a thickening in the uterine lining (proliferative phase).
- After ovulation, progesterone produces further thickening of the uterine lining.
- The degeneration of the corpus luteum starts a new ovarian follicular phase. Menstruation begins.

Uterine Cycle

Day Menses: degeneration & loss of the functional layer.

- **Day 1** Decrease in progesterones & estrogens stimulates the release of prostaglandins which cause the spiral arterioles to constrict.
- O2 & nutrient deprivation causes endometrial necrosis, desquamation & bleeding. Only the stratum basalis remains.

Day 5-14 Proliferation:

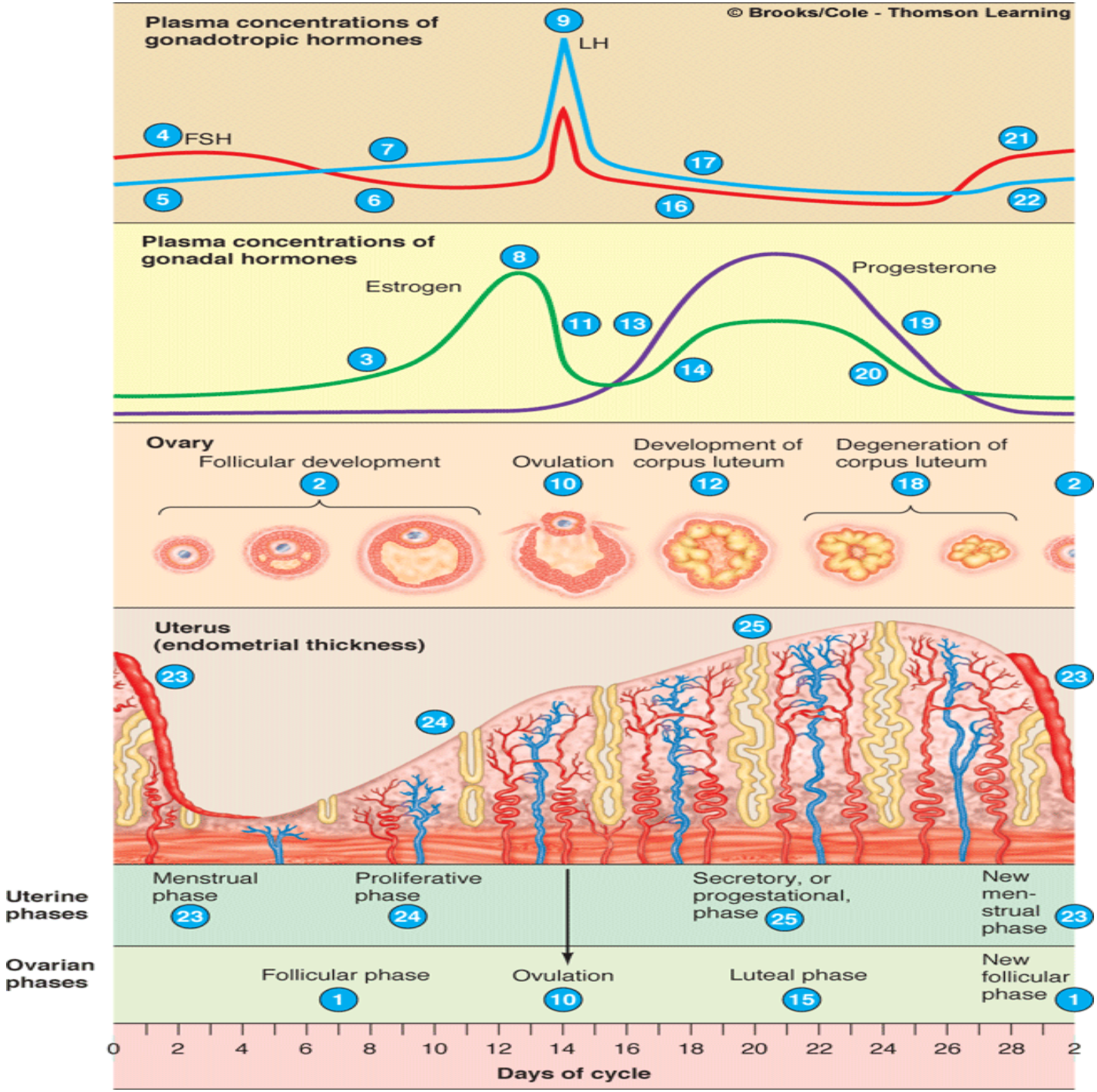
- restoration of the functional layer.
- Follicular cells secrete increasing amounts of estrogen.
- Stratum basalis cells proliferate producing the s. functionalis. Short straight endometrial glands form, spiral arterioles regrow.

Day 15-26 Secretion:

- increased growth & secretion prepares uterus for implantation.
- Levels of progesterones & estrogens produced by the corpus luteum increase.
- Glands enlarge, coil into corkscrew shapes & secrete glycogen. Vascularization of the s. functionalis increases.

Day 26-28

- If fertilization does not occur, the corpus luteum degenerates and progesterone & estrogen levels decline.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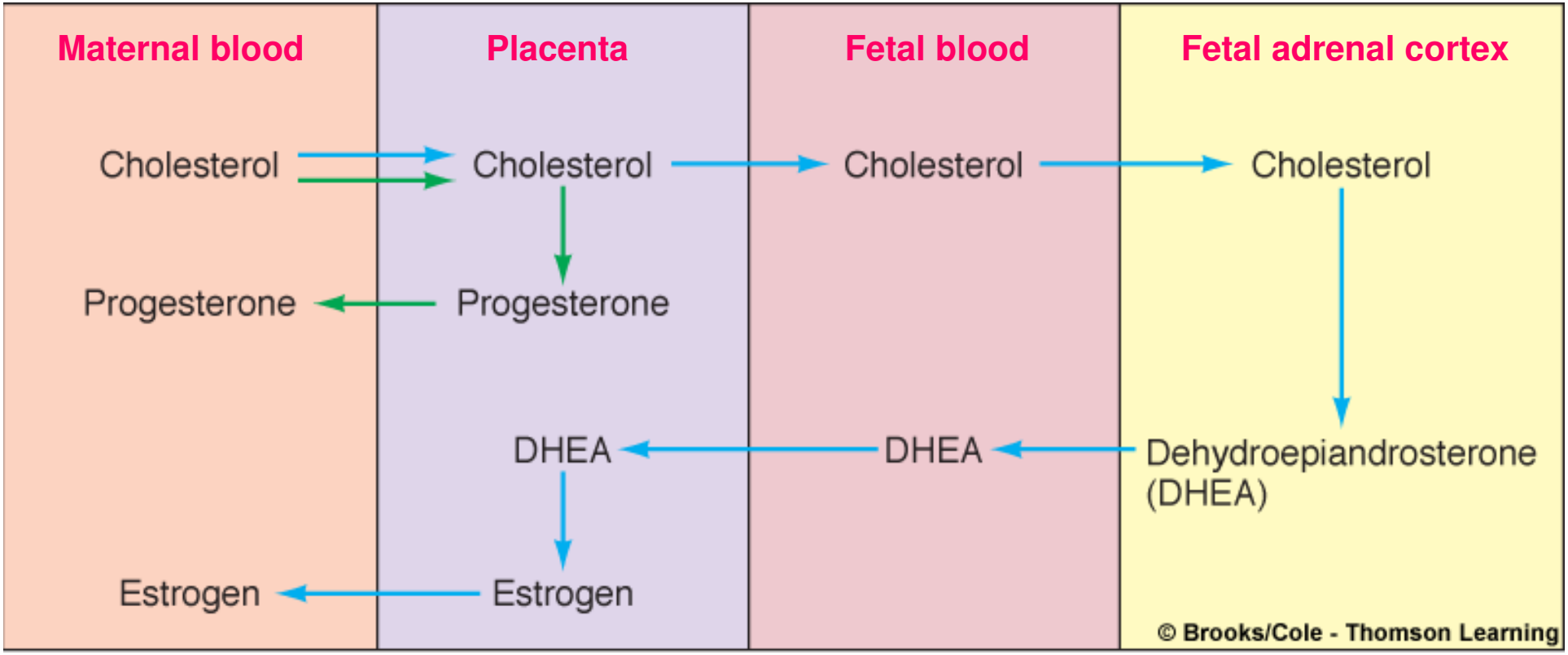
Plasma concentrations of gonadotropic hormones
LH
FSH
Plasma concentrations of gonadal hormones
Estrogen
Progesterone
Ovary
Follicular development
Ovulation
Development of corpus luteum
Degeneration of corpus luteum
Uterus (endometrial thickness)
Uterine phases
Menstrual phase
Proliferative phase
Secretory, or progestational, phase
New men-strual phase
Ovarian phases
Follicular phase
Ovulation
Luteal phase
New follicular phase
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 2
Days of cycle

Fig.20-15

Oestrogen & Progesterone

- Chemistry of sex hormones
  - The estrogens and Progestins
- Synthesis of estrogens and progestins
- Transport of estrogens and progesterone in the blood
- Fate of estrogens
  - Functions of the liver in estrogen degradation
- Fate of progesterone



Pathway for placental synthesis of progesterone

Pathway for placental synthesis of estrogen

Figure 20.28
Page 791

Oestrogens

- These are major female sex hormones
- Apart from the small amounts produced by the adrenals, most oestrogens are synthesised by the cells of the corona radiata, theca interna & corpus lutuem
- During pregnancy the placenta produces large amounts.
- Some oestrogen is formed - circulating testosterone.
- Ovary produces 2 oestrogens, viz. oestradiol & oestrone
- Large quantities of both oestradiol and oestrone are hydroxylated at C_{16} & thus converted to oestriol (liver).

- Another major pathway for catabolism of oestrogens is hydroxylation at C_2 & C_4
- Oestrogens contain 18 carbon atoms.
- In plasma 90% of circulating oestrogens are bound to albumin and sex hormone-binding globulin
- Oestrogens and their metabolites are conjugated to glucuronic acid or sulphate in liver.
- Most of these soluble conjugates are excreted by the kidneys, but some are secreted in bile and reabsorbed from the intestines

Functions of Estrogens – their effects on the primary and secondary female characteristics

- Principal function of the estrogens is to cause cellular proliferation and growth of the tissues of the sex organs and other tissues related to reproduction

- Effects include:

➢ On the uterus and external female sex organs

➢ On the fallopian tubes

Effects continued:

- On the breasts
- On the skeleton
- On the protein deposition
- On body metabolism an fat deposition
- On hair distribution
- On the skin
- On electrolyte balance

summary

- Promote follicle development & ovulation
- Stimulate proliferation of epithelial cells of uterine tubes, uterus & vagina
- Stimulate proteins synthesis
- Reduce membrane potential of myometrial muscle fibres
- Stimulate duct growth in mammary glands
- Are largely responsible for development of female characteristics
- Are invloved in skeletal growth & maintenance of structural integrity of bones

Progesterone

- Term designates any substance possessing progestational activity.
- Natural ones are progesterone and 17-hydroxyprogesterone
- Both are 21-carbon compounds-progesterone plays the major role
- Non-pregnant females - Predominantly produced by corpus luteum; small amounts are produced by developing follicle & adrenals
- Pregnancy - large amounts are produced by corpus luteum & placenta
- Binds mainly to albumin & transcortin; it is converted to pregnanediol and excreted.

Functions of progesterone

- Effect on uterus:
  - By far most NB fxn is to promote secretory changes in the uterine endometrium during the latter half of female sexual cycle
- On the fallopian tubes
  - Increased secretion by mucosal lining of tubes
- On the breasts
  - Promotes development of lobules and alveoli
  - Causes breast to swell

Summary

- Stimulates secretory activity of uterine tubes, uterus & vagina
- Is responsible for the progestational changes in the endometrium
- ↑ membrane potential of myometrial muscle fibres
- Prevents ovulation when present in high concentration
- ↓ no. of oestrogen receptors
- Promtes protein anabolism
- Responsible for rise in body temperature – ovulation
- Stimulates alveolar formation in breasts
- Stimulates respiration
- Antagonises action of aldosterone on kidney

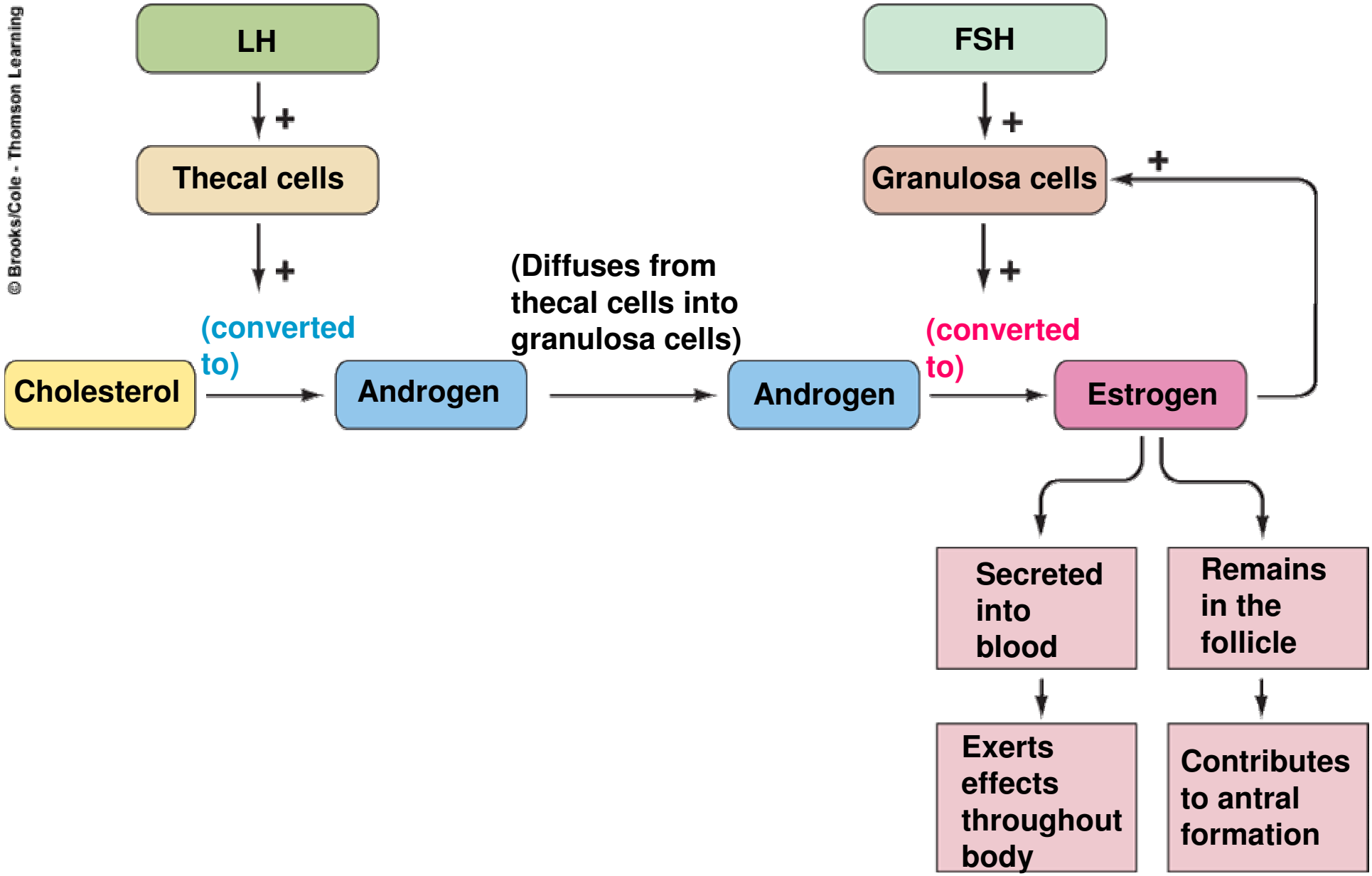


Figure 20.16
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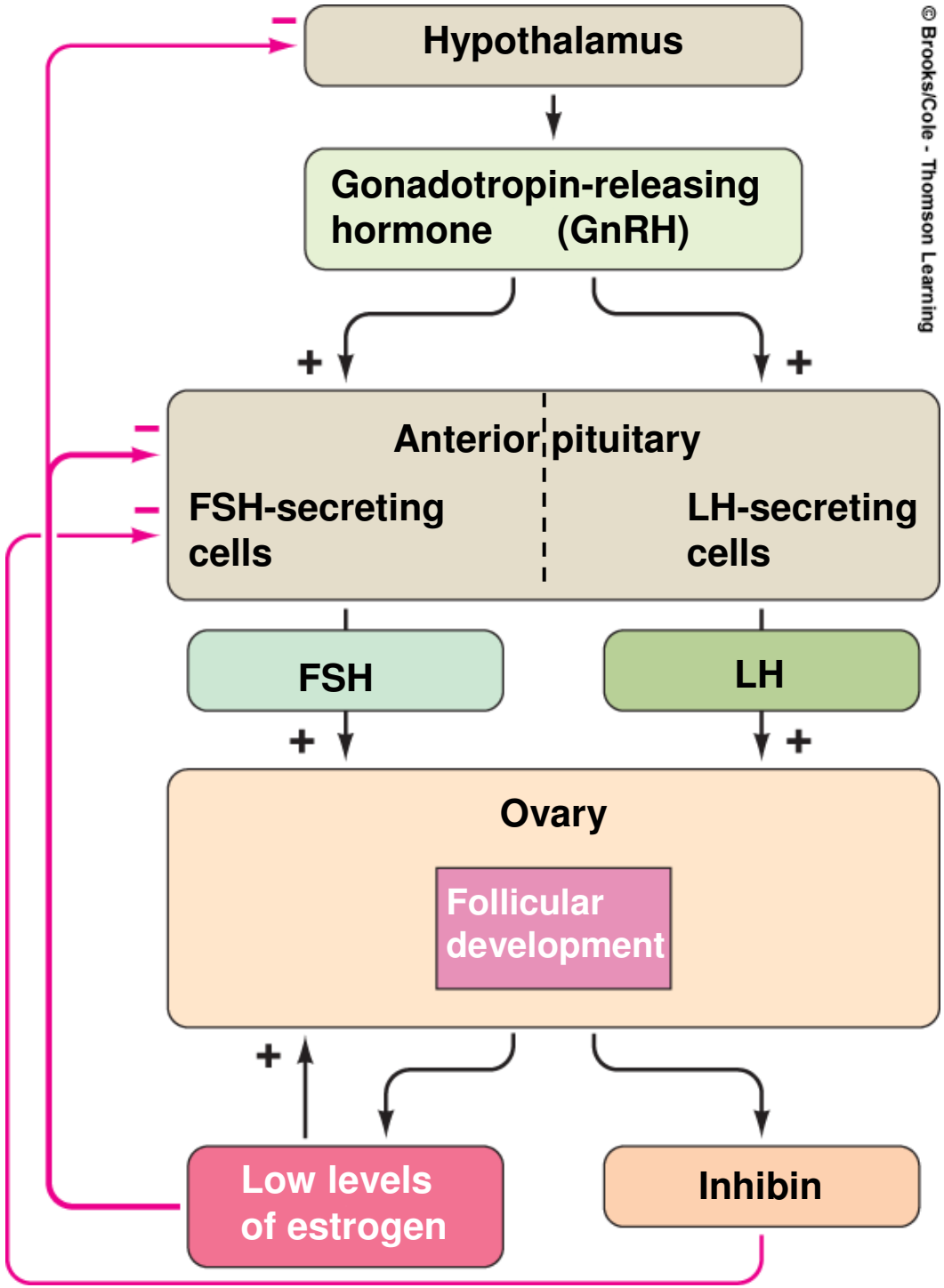

Figure 20.17
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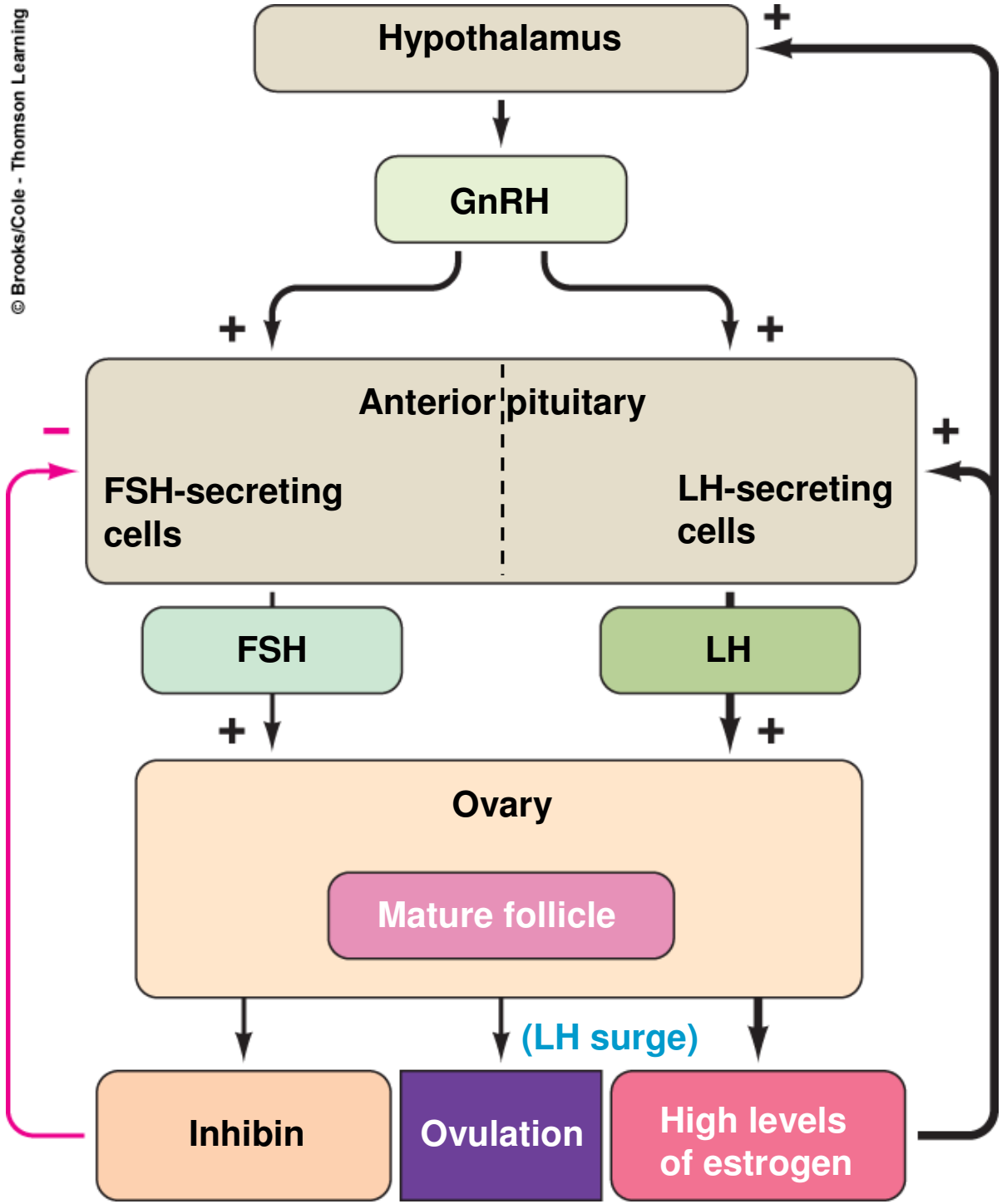

Figure 20.18
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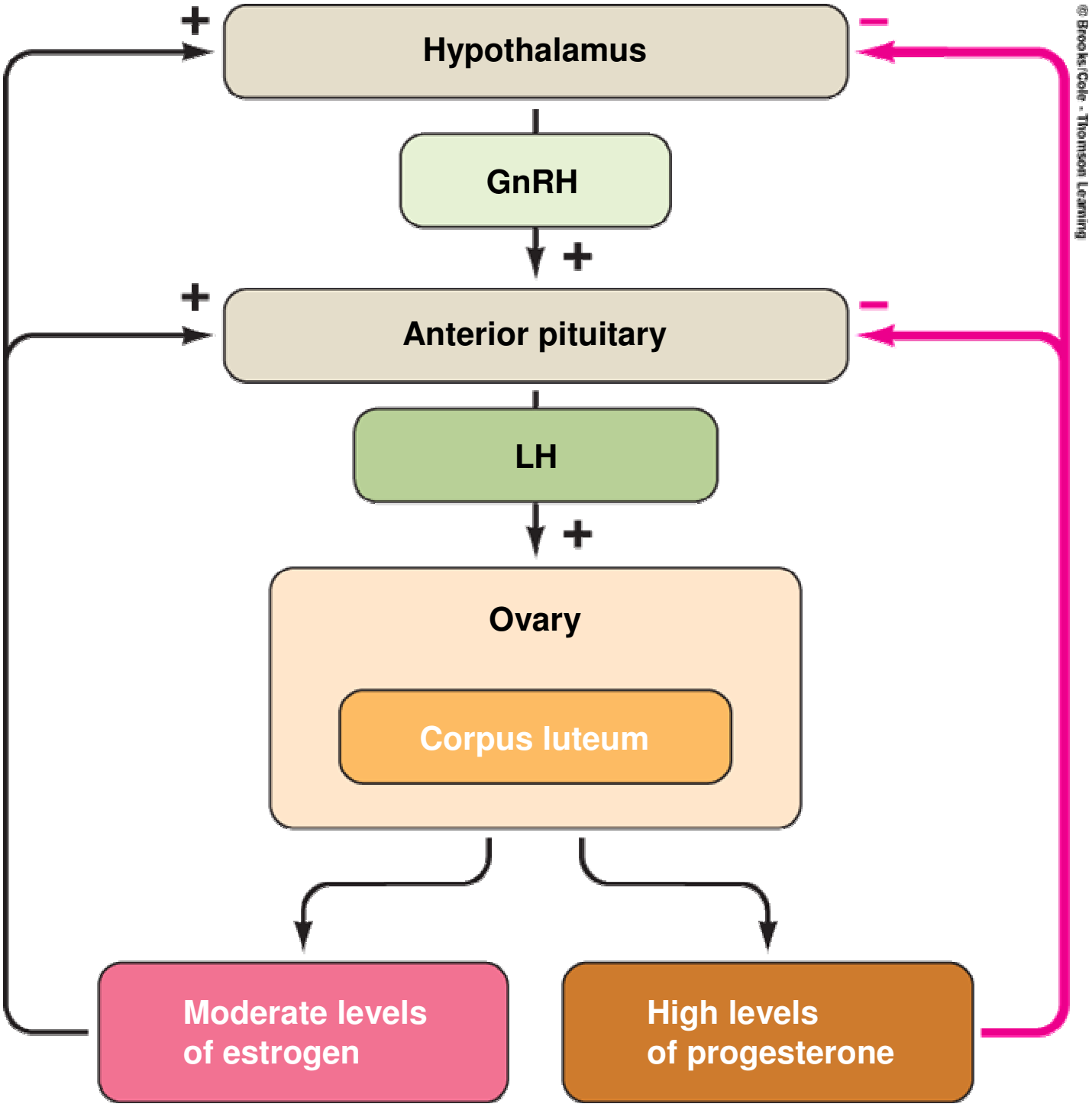

Figure 20.19
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Block 11 - Theme: Male sex hormones

Physiology of primary and secondary male sex organs

- Testes are suspended outside the abdominal cavity by the scrotum, a pouch of skin that keeps the testes close or far from the body at an optimal temperature for sperm development.
- Seminiferous tubules are inside each testis, and are where sperm are produced by meiosis. About 250 meters of tubules are packed into each testis.
- Spermatocytes inside the tubules divide by meiosis to produce spermatids that in turn develop into mature sperm.

Testes - paired oval bodies, about 1.5 in long

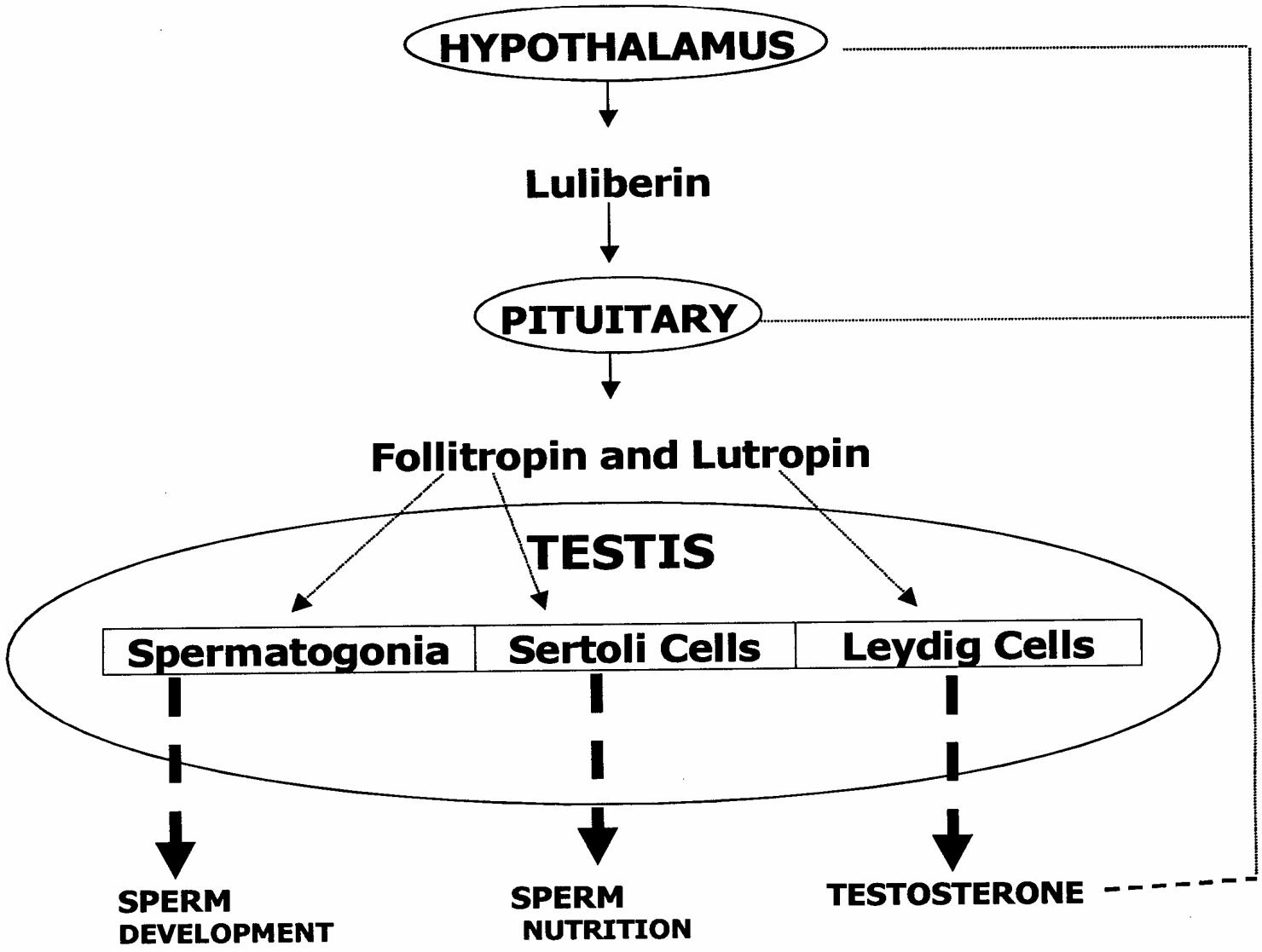
- Outer covering is white fibrous connective tissue called *tunica albuginea*. Inner covering is visceral peritoneum called *tunica vaginalis*
- Develop in the abdominal cavity & descend through the inguinal canal into the scrotum before birth.
- Divided into lobules containing coiled seminiferous tubules which empty into a central network of tubules called the rete testis

Cellular components of testis

- Interstitial cells (Leydig)
  - Secrete testosterone
- Sustentacular cells (Sertoli)
  - Form blood-testes barrier, cells joined by tight junctions
  - Supply nutrients to spermatids
  - Secrete inhibin which depresses FSH production
  - Secrete androgen-binding protein (ABP) which concentrates androgens in tubules
  - Secrete Müllerian-inhibiting factor (MIF), involved in testes descent

TESTIS FUNCTION

Control:



Sexual Structures

- Sperm pass through the vas deferens and connect to a short ejaculatory duct that connects to the urethra.
- The urethra passes through the penis and opens to the outside.
- Secretions from the seminal vesicles add fructose and prostaglandins to sperm as they pass.
- The prostate gland secretes a milky alkaline fluid.
- The bulbourethral gland secretes a mucus-like fluid that provides lubrication for intercourse. Sperm and secretions make up semen.

Male Sex Hormones

- The anterior pituitary produces follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
- Action of LH is controlled by the gonadotropin-releasing hormone (GnRH).
- LH stimulates cells in the seminiferous tubules to secrete testosterone.
- FSH acts on cells to help in sperm maturation. Negative feedback by testosterone controls the actions of GnRH

Testosterone

Secretion, metabolism and chemistry

- Testes secrete several male hormones which are collectively called androgens
- Androgens:
  - Testosterone
  - Dihydrotestosterone
  - Androstenedione
- Testosterone most abundant, most active hormone is dihyrotest

Secretion of androgen elsewhere in body

- Definition of androgen
- Source except testes
  - Adrenal glands – 5 androgens
- Chemistry
  - Steroid compounds
  - Synthesized from cholesterol or directly from acetyl coenzyme A

Metabolism of testosterone

- After secretion, 97% bound SHBG & circulates in blood for 30 min – hrs
- By that time transferred to:
  - Tissues
  - Degraded into inactive products and excreted
- Testosterone fixed to tissues or if not converted in liver
- Excretion: gut or urine

Functions

- Is responsible for distinguishing characteristic of masculine body
- Fetal life – testes stimulated by chorionic gonadotropin to produce testosterone throughout fetal life and 10 w after birth
- Testosterone produced is under stimulus of anterior pituitary gonadotropins at onset of puberty

During fetal development

- Is responsible for development of male body characteristics, including formation of a penis and scrotum
- Causes formation of prostate gland, seminal vesicles and male genital ducts, while at same time suppressing formation of female genital organs
- Also causes descent of testes

Effect on the development of adult primary and secondary sexual characteristics

- After puberty causes penis, scrotum and testes to enlarge x8 before age 20
- Causes secondary sexual characteristic of male to develop at puberty
- Other effects include:
  - Distribution of body hair
  - Baldness

effects include cont:

- Voice
- Skin and development of acne
- Protein formation and on muscle development
- Bone growth and calcium retention
- Basal metabolism
- RBC
- Electrolyte and water balance

Control of sexual functions

- Production of testosterone is controlled by the release of **luteinizing hormone** (**LH**) from the anterior lobe of the pituitary gland, which is in turn controlled by the release of GnRH from the hypothalamus.
- LH is also called interstitial cell stimulating hormone (ICSH).

Hypothalamus
↓
GnRH
↓
Pituitary
↓
LH
↓
Testes
↓
Testosterone

- The level of testosterone is under negative-feedback control: a rising level of testosterone suppresses the release of GnRH from the hypothalamus. This is exactly parallel to the control of estrogen secretion in females.

Spermatogenesis

Spermatogenesis

- Sperm production begins at puberty at continues throughout life, with several hundred million sperm being produced each day.
- Once sperm form they move into the epididymis, where they mature and are stored.
- Steps of spermatogenesis:

Spermatogenesis - production of sperm, requires 9 weeks

- Spermatogonia - 2N stem cells form basal layer of the seminiferous tubule
  - Separated by blood-testis barrier from spermatocytes which contain different membrane antigens
  - Mitotically divide to form primary spermatocytes

- Primary spermatocytes - 2N cells
  - Undergo meiosis I (reduction division) to form two haploid secondary spermatocytes
- Secondary spermatocytes - 1N cells
  - Complete meiosis II to form four haploid spermatids connected by cytoplasmic bridges

- Spermatids - 1N
  - Undergo structural change (spermiogenesis) to form spermatozoa
- Sperm - 1N
  - Head contains nucleus & acrosomal cap containing enzymes
  - Midpiece contains two centrioles + microtubules, mitochondrial spiral
  - Tail contains flagellum surrounded by fibrous sheath

Sperm

- Maturation of sperm in epididymis
  - Capability of motility
- Storage of sperm
  - Some stored in epididymis, most in vas deferens
- Physiology of mature sperm

Hormonal factors that stimulate spermatogenesis

- Testosterone
- LH
- FSH
- Estrogens
- GH