Part

I

Male Reproductive Physiology

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Chapter
1

Development of Male Genitalia and Gonads

Digest: The sex can be reversed after birth in chickens, some ducks, and doves. The removal of the functional left ovary results in the development of the non-functional right ovary into a testis or ovotestis. A gonad containing both follicles and seminiferous tubules is called an ovotestis. The younger the bird when the left ovary is removed, the greater the chance that the right gonad will develop into a testis. The older the bird, the greater the probability that an ovotestis will develop.

Most of the reproductive system develops from the mesoderm. During organ formation, the reproductive system also develops. In mammals, males differentiate early at the genetic level, while females differentiate later. Sex determination is governed by the animal's genetic sex, which is established at fertilization. During sex differentiation, the genetic sex guides the development of either ovaries or testes, which then determine the phenotypic sex as the animal matures. In the undifferentiated stage of gonadal development, both Wolffian and Müllerian ducts are present, and later these develop into male or female secondary sex organs. The Müllerian ducts differentiate into the fallopian tubes, uterus, and vagina, while the Wolffian ducts form the epididymis, ductus deferens, and seminal vesicles.

DEVELOPMENT OF TESTES

The development of the testes occurs in the following ways:

- The **primordial germ cells** originate from the inner lining (endoderm) of the yolk sac of the early embryo. Thus, the **origins of primordial germ cells are extragonadal.**
- After origin, the primordial germ cells migrate by **ameboid movement** from the yolk sac to the **genital ridges** (or gonadal ridges). A pair of genital ridges (undifferentiated gonads) is located on either side of the dorsal wall of the abdomen of the embryo near the embryonic kidney.
- The primordial germ cells undergo mitotic division, and their numbers increase significantly.
- **Primordial germ cells** form **gonocytes**, which further differentiate into **spermatogonia** just before puberty.
- The primordial germ cells also stimulate the local connective tissue of the genital ridge to proliferate.
- Now, the undifferentiated gonad (genital ridge) differentiates into **medulla (inner)** and **cortex (outer)**.
- The proliferative genital ridge forms primary sex cords.

- **In the genetically male, primary sex cords** are found in the **medulla**, which develops into the testes, and the **cortex regresses**.
- **In the genetically female, secondary sex cords** develop in the cortex, which develops into the ovaries. The primary sex cords and medulla regress.

INTERESTING FACTS

In avian species, the H-Y antigen is present in females because females are heterogametic (ZW) and males are homogametic (ZZ).

- Now, primary sex cords (medullary cords) are differentiated into seminiferous tubules and rete testis.
- The Leydig cells arise from the intertubular element of the developing gonad.
- The connective tissue of the developing gonad forms the **tunica albuginea**.

The genes for testis-determining factor (TDF), located on the short arm of the Y chromosome, induce the embryonic gonad to become a testis. Two antigens are assumed to be responsible for male gonadogenesis: The **minor histocompatibility (H-Y) antigen** (recently no longer believed to be solely responsible) and the s**ex determining region Y (SRY) antigen**.

SEX-DETERMINING GENES

The key sex-determining genes are SRY (sex determining gene on Y) and SOX9 (SRY box) in mammals. These genes are involved in testis formation and in the development of the male phenotype. In the absence of the SRY gene, ovaries develop. SRY is located on the short arm of the Y chromosome **(Fig. 1.1)** and codes for a protein called the testis-determining factor (TDF). SRY is involved in the differentiation of Sertoli cells, the migration of primordial germ cells from the mesonephros to the genital ridges, and the proliferation of cells within the genital ridges. The exact role of SRY in testis differentiation is not known, but SRY is thought to trigger each of these events, possibly by activating a secondary gene, such as SOX9. SOX9 is up-regulated in the genital ridges of male embryos and down-regulated in females. The WNT genes appear to play a role in ovarian and oocyte development. WNT-4 may act as a suppressor of Leydig cell function in females and is necessary for the formation of Mullerian ducts. WNT-7α is involved in further development of the Mullerian ducts to form the oviduct and uterus.

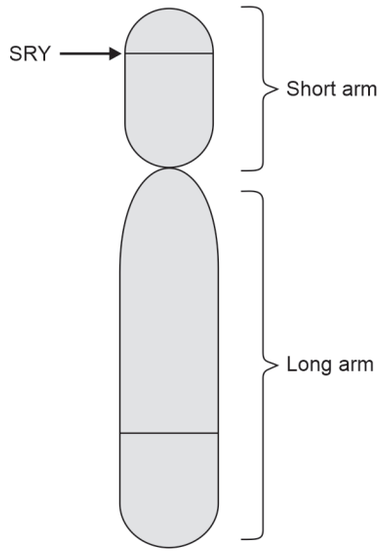


Fig. 1.1: Y-chromosome showing short and long arm

DO YOU KNOW?

The gene for the H-Y antigen is on the short arm of the Y-chromosome, whereas the H-Y antigen is found on the long arm of the Y chromosome.

DEVELOPMENT OF THE ACCESSORY GENITAL TRACT AND GLANDS

After the fetal testis has been formed in response to the testis-determining gene or genes, male testicular hormone causes the development of the male phenotype. Immature Sertoli cells produce the **first testicular hormone,** Müllerian inhibiting substance (MIS), which is responsible for the regression of the paramesonephric (Müllerian) ducts in the male fetus. Leydig cells secrete testosterone, the **second testicular hormone** that stimulates the development of the mesonephric (Wolffian) duct and tubules. Differentiation of the external genitalia in the male occurs under the influence of dihydrotestosterone (DHT). The accessory genital ducts and glands in the male arise from the mesonephric (Wolffian) ducts and tubules.

DO YOU KNOW?

MIS is also produced by the granulosa cells of the postnatal ovary in the female, but the physiologic role of MIS in the postnatal female has not been determined.

The reproductive system develops at the same time as the renal system. During development, the embryo utilizes three distinct renal systems. The development of the renal system and the accessory genital tract has been described below:

- The pronephros (pronephric kidney) regresses and is replaced by **mesonephros** (mesonephric kidney).
- The mesonephric kidney is closely associated with the undifferentiated gonad.
- The mesonephric kidney produces urine that is drained by a series of **mesonephric tubules** that merge into a larger **mesonephric duct**.
- The mesonephric duct extends caudally and empties urine into the **urogenital sinus**.
- When the mesonephric kidney is developing at the same time, a new pair of ducts begins to develop beside the mesonephric duct. Because these ducts are formed on either side of the mesonephric duct, they are called **paramesonephric ducts (Müllerian ducts)**.
- During the first 10–15% of the gestation period, the final form of the kidney begins to appear.
- The final form of the kidney is called the **metanephros (metanephric kidney)**.
- The **metanephric kidney initially** develops as a small bud.
- The **mesonephric kidney** begins to lose its function and decreases in size as the metanephric kidney increases in size.
- The gonad also continues its enlargement, as does the metanephric kidney.
- The metanephric kidney becomes fully functional, and the gonad becomes larger, while the **mesonephric kidney** is almost completely regressed.
- Now, some of the mesonephric tubules (5–15) penetrate into the **gonad** and make connections with the **primitive sex cords** via the rete testis.
- The **mesonephric tubules** are gradually transformed into the **efferent ducts**.
- The **mesonephric duct** will give rise to the **epididymis** and **ductus deferens** (vas deferens).
- Paramesonephric ducts degenerate in males.
- Shortly after the virilization of the mesonephric ducts, external genitalia develop from the urogenital sinus (inner genital folds).

- The **genital tubercle** becomes the **glans penis.**
- Fusion and caudal migration of the **labioscrotal swelling** form the scrotum.

Summary of the Development of the Male Reproductive System

Embryological structure	*Mature structure*
Yolk sac	Primordial germ cells
Primary sex cords	Testes
Secondary sex cords	Ovaries
Mesonephric tubules	Efferent ducts
Mesonephric ducts	Epididymis, vas deferens and seminal vesicles
Urogenital sinus	Penile urethra, bulbourethral glands
Urethral folds	Prepuce
Genital tubercle	Glans penis
Genital swelling	Scrotum

MULTIPLE CHOICE QUESTIONS

1. **The primordial germ cells originate from which part of the early embryo?**
   A. Mesoderm B. Endoderm of yolk sac
   C. Ectoderm D. Genital ridge
   Ans: B. Endoderm of yolk sac
2. **Which movement helps primordial germ cells migrate from yolk sac to genital ridges?**
   A. Diffusion B. Ameboid movement
   C. Active transport D. Ciliary movement
   Ans: B. Ameboid movement
3. **In genetically male embryos, which structure develops into the testes?**
   A. Cortex B. Secondary sex cords
   C. Medulla (primary sex cords) D. Mesonephric tubules
   Ans: C. Medulla (primary sex cords)
4. **In genetically female embryos, which structure develops into the ovaries?**
   A. Medulla B. Primary sex cords
   C. Cortex (secondary sex cords) D. Wolffian ducts
   Ans: C. Cortex (secondary sex cords)
5. **Which cells arise from the intertubular element of the developing gonad?**
   A. Sertoli cells B. Spermatogonia
   C. Leydig cells D. Granulosa cells
   Ans: C. Leydig cells
6. **The connective tissue of the developing gonad forms:**
   A. Rete testis B. Tunica albuginea
   C. Seminiferous tubules D. Epididymis
   Ans: B. Tunica albuginea

7. The SRY gene is located on:

A. Long arm of Y chromosome
B. Short arm of Y chromosome
C. X chromosome
D. Autosomes

Ans: B. Short arm of Y chromosome

8. The protein encoded by the SRY gene is:

A. H-Y antigen
B. DHT
C. Testis-determining factor (TDF)
D. MIS

Ans: C. Testis-determining factor (TDF)

9. Which gene is up-regulated in male embryos during testis development?

A. WNT-4
B. SOX9
C. WNT-7
D. FSH

Ans: B. SOX9

10. WNT-4 plays a role in:

A. Leydig cell activation
B. Suppression of Leydig cell function in females
C. Formation of efferent ducts
D. Formation of rete testis

Ans: B. Suppression of Leydig cell function in females

11. Which hormone is produced by immature sertoli cells?

A. Testosterone
B. Dihydrotestosterone (DHT)
C. Mullerian inhibiting substance (MIS)
D. Oestrogen

Ans: C. Mullerian inhibiting substance (MIS)

12. Leydig cells secrete:

A. Oestrogen
B. MIS
C. Testosterone
D. SOX9

Ans: C. Testosterone

13. Differentiation of male external genitalia occurs under the influence of:

A. MIS
B. DHT (Dihydrotestosterone)
C. SOX9
D. WNT-7

Ans: B. DHT (Dihydrotestosterone)

14. Which duct develops into the epididymis, vas deferens, and seminal vesicles?

A. Paramesonephric duct
B. Wolffian (mesonephric) duct
C. Ureteric duct
D. Allantoic duct

Ans: B. Wolffian (mesonephric) duct

15. Which duct forms the Fallopian tubes, uterus, and vagina?

A. Wolffian duct
B. Paramesonephric (Müllerian) duct
C. Urogenital sinus
D. Metanephric duct

Answer: B. Paramesonephric (Müllerian) duct

16. The genital tubercle develops into:

A. Scrotum
B. Glans penis
C. Prepuce
D. Bulbourethral glands

Ans: B. Glans penis

17. Fusion and caudal migration of the labioscrotal swelling form:

A. Prepuce
B. Penis
C. Scrotum
D. Testes

Ans: C. Scrotum

18. Which kidney structure regresses first during development?

A. Metanephros
B. Mesonephros
C. Pronephros
D. Wolffian duct

Ans: C. Pronephros

19. The final functional kidney in mammals is:

A. Pronephros
B. Mesonephros
C. Metanephros
D. Urogenital sinus

Ans: C. Metanephros

20. Which embryonic structure gives rise to efferent ducts?

A. Genital ridge
B. Mesonephric tubules
C. Paramesonephric ducts
D. Urogenital sinus

Ans: B. Mesonephric tubules

FILL IN THE BLANKS

1. The primordial germ cells originate from the _____ of the yolk sac of the early embryo.

Ans: Endoderm

2. The migration of primordial germ cells from yolk sac to genital ridges occurs by _____ movement.

Ans: Ameboid

3. In genetically male embryos, the _____ develops into testes, while in females the _____ develops into ovaries.

Ans: Medulla; Cortex

4. The connective tissue of the developing gonad forms the _____.

Ans: Tunica albuginea

5. The _____ gene located on the short arm of the Y chromosome codes for the testis-determining factor (TDF).

Ans: SRY

6. The first testicular hormone produced by immature Sertoli cells is _____.

Ans: Mullerian inhibiting substance/MIS

7. Differentiation of the male external genitalia occurs under the influence of _____.

Ans: Dihydrotestosterone/DHT

8. **The _____ ducts differentiate into epididymis, ductus deferens, and seminal vesicles.**
   Ans: Wolffian/Mesonephric
9. **The genital tubercle develops into the _____.**
   Ans: Glans penis
10. **The final functional kidney in mammals is called the _____.**
    Ans: Metanephros

TRUE/FALSE STATEMENTS

1. **The primordial germ cells originate from the mesoderm of the yolk sac.**
   Ans: False
   Explanation: Primordial germ cells arise from the endodermal lining of the yolk sac and later migrate to the genital ridges.
2. **In the genetically male embryo, the cortex of the genital ridge develops into the testes.**
   Ans: False
   Explanation: In male embryos, the medullary region forms the primary sex cords that develop into testes.
3. **Leydig cells of the developing gonad secrete testosterone.**
   Answer: True
   Explanation: Leydig cells located in the interstitial tissue of the testes produce testosterone which supports male reproductive development.
4. **The SRY gene is located on the short arm of the Y chromosome.**
   Answer:
   Explanation: The SRY gene initiates the process of testis formation by producing the testis-determining factor.
5. **In the absence of the SRY gene, ovaries develop instead of testes.**
   Answer: True
   Explanation: Without SRY gene activity, the undifferentiated gonad follows the female developmental pathway and forms ovaries.
6. **MIS (Müllerian inhibiting substance) produced by Sertoli cells causes regression of Müllerian ducts in males.**
   Answer: True
   Explanation: MIS secreted by sertoli cells prevents the development of female internal reproductive structures in male embryos.
7. **Differentiation of male external genitalia occurs under the influence of estrogen.**
   Ans: False
   Explanation: DHT, derived from testosterone, stimulates the formation of male external genital organs.
8. **The Wolffian (mesonephric) ducts develop into Fallopian tubes and uterus.**
   Ans: False
   Explanation: The Fallopian tubes and uterus develop from the Müllerian (paramesonephric) ducts.

9. **The genital swelling (labioscrotal swelling) develops into the scrotum in males.**
   Ans: True
   Explanation: During male development, the labioscrotal swellings move downward and fuse in the midline to form the scrotum.
10. **The final functional kidney in mammals is the metanephros.**
    Ans: True
    Explanation: The metanephros develops into the permanent kidney, while pronephros and mesonephros are temporary embryonic structures.

MATCH THE CORRECT PAIRS

	Column A (Structure)		*Column B (Develops into)*
1.	Yolk sac	A.	Epididymis, vas deferens, seminal vesicles
2.	Primary sex cords	B.	Efferent ducts
3.	Secondary sex cords	C.	Ovaries
4.	Mesonephric tubules	D.	Tunica albuginea
5.	Mesonephric ducts (Wolffian)	E.	Glans penis
6.	Paramesonephric ducts (Müllerian)	F.	Fallopian tubes, uterus, vagina
7.	Genital tubercle	G.	Primordial germ cells
8.	Urogenital sinus	H.	Penile urethra, bulbourethral glands
9.	Urethral folds	I.	Prepuce
10.	Genital swelling (labioscrotal swelling)	J.	Scrotum

ANSWERS

1. G 2. D 3. C 4. B 5. A 6. F 7. E 8. H 9. I 10. J

> Give me six hours to chop down a tree, and I will spend the first four sharpening the axe.
>
> **—Abraham Lincoln**