A decorative wreath of various botanical specimens, including ferns, leaves, and flowers in shades of green, red, orange, and purple, framing a central white circle.

Development of Genital System

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12/23/2024

Introduction to Embryology of Genital System

Embryology of Genital System

- Although the sex of an embryo is determined chromosomally at fertilisation, an undifferentiated stage of development initially occurs in which the primordia of both male and female genital organs are present.
- Depending on the genetically-determined sex of the individual, the genital organs appropriate for that sex develop while the genital organs for the other sex regress. Sexual identity is not confined solely to the reproductive organs but is evident also in other anatomical features and in physiological and behavioural characteristics.

Primordial Germ Cells

- At an early stage in embryological development, primordial germ cells, which eventually populate the undifferentiated gonad, can be detected in the epiblast by specific staining methods. These cells, which migrate through the primitive streak and then to the yolk sac and allantois, move along the wall of the hindgut to the genital ridge, a structure destined to become the undifferentiated gonad (Fig.1).

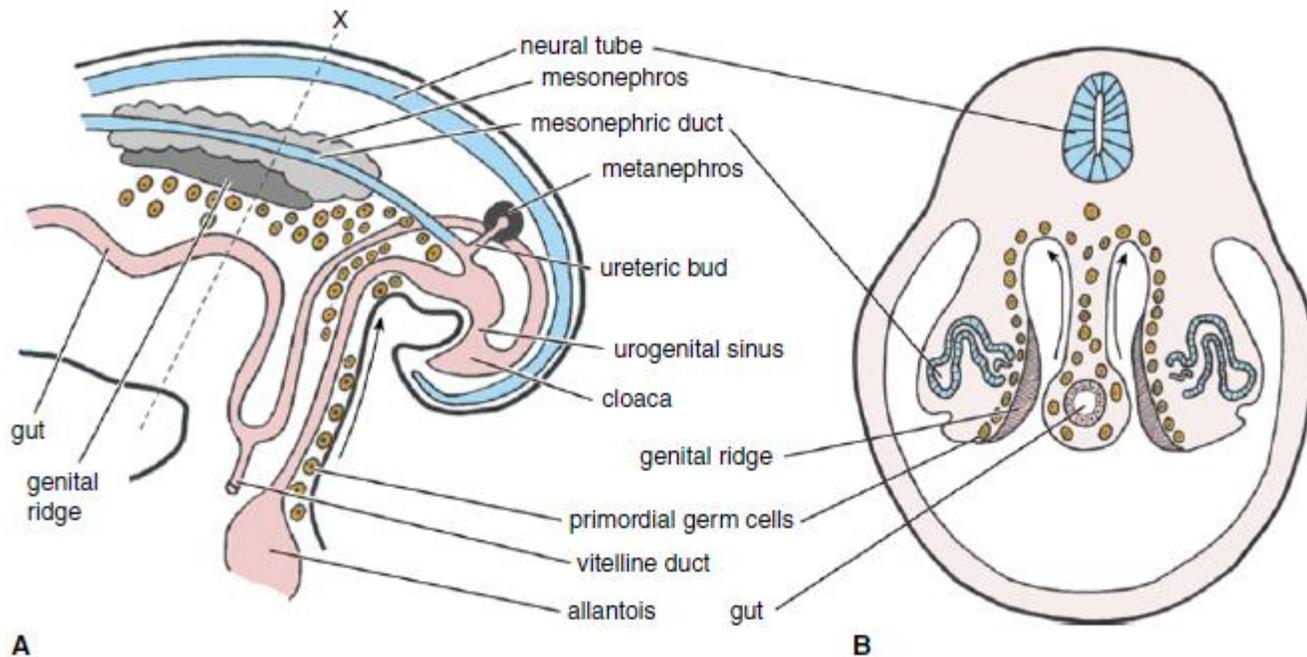


Figure 1 A. Route of migration of primordial germ cells from the allantois to the genital ridge, their site of differentiation. B. Transverse section through an embryo at the level indicated showing the migratory pathway of primordial germ cells along the dorsal mesentery to the genital ridge (arrows).

- In mammals, primordial germ cells arrive at their site of differentiation by active migration, whereas in avian species they reach the genital ridge via the blood stream. It has been suggested that germ cells may be attracted to the genital ridge by chemotaxis. Primordial germ cells can be detected in the genital ridge by day 18 in pigs, by day 21 in dogs, by day 22 in sheep and by day 28 in cattle and humans.

Primordial Germ Cells

Primordial germ cells divide mitotically during migration to the developing gonads. Soon after entering the primordial gonad, the germ cells become enclosed in specific germ cell compartments, seminiferous cords in the male embryo and primordial follicles in the female embryo. Both the proliferation and differentiation of primordial germ cells in these particular locations are strongly influenced by locally-secreted soluble factors.

Only germ cells which reach the undifferentiated gonad differentiate and survive. Most germ cells outside the gonadal region undergo apoptosis but some which survive outside this region may form germ cell tumours referred to as teratomata. Because these abnormal structures are composed of elements of the three embryonic germ layers, they may contain highly differentiated tissues such as skin, hair, cartilage and teeth.

Undifferentiated Stage of Gonad Formation

- Although the origin of the somatic gonadal cells is unresolved, three cellular sources have been proposed:
 - 1) Local mesenchymal cells
 - 2) Coelomic epithelium
 - 3) Cells derived from the mesonephric tubules
- It is proposed that the principal cells contributing to the gonadal primordia migrate from the degenerating mesonephric tubules to the presumptive gonadal tissue. Some cells contributing to the gonadal primordia may be derived from the coelomic epithelium and also from the underlying mesenchyme. Following proliferation of the coelomic epithelium and underlying mesenchyme, gonadal primordia develop as bilateral ridges. These ridges, which develop medial to the mesonephros and project into the coelomic cavity where they become covered by coelomic epithelium, extend from the thoracic to the lumbar region. The outline appearance of the gonadal ridges precedes the arrival of the primordial germ cells in the area.
- The undifferentiated gonads consist of primordial germ cells and mesodermal cells.
- The invading mesonephric cells and the mesonephric tubules form a tubular network called the rete system which consists of extra-gonadal cords, connecting cords and intra-gonadal cords (Fig 2).

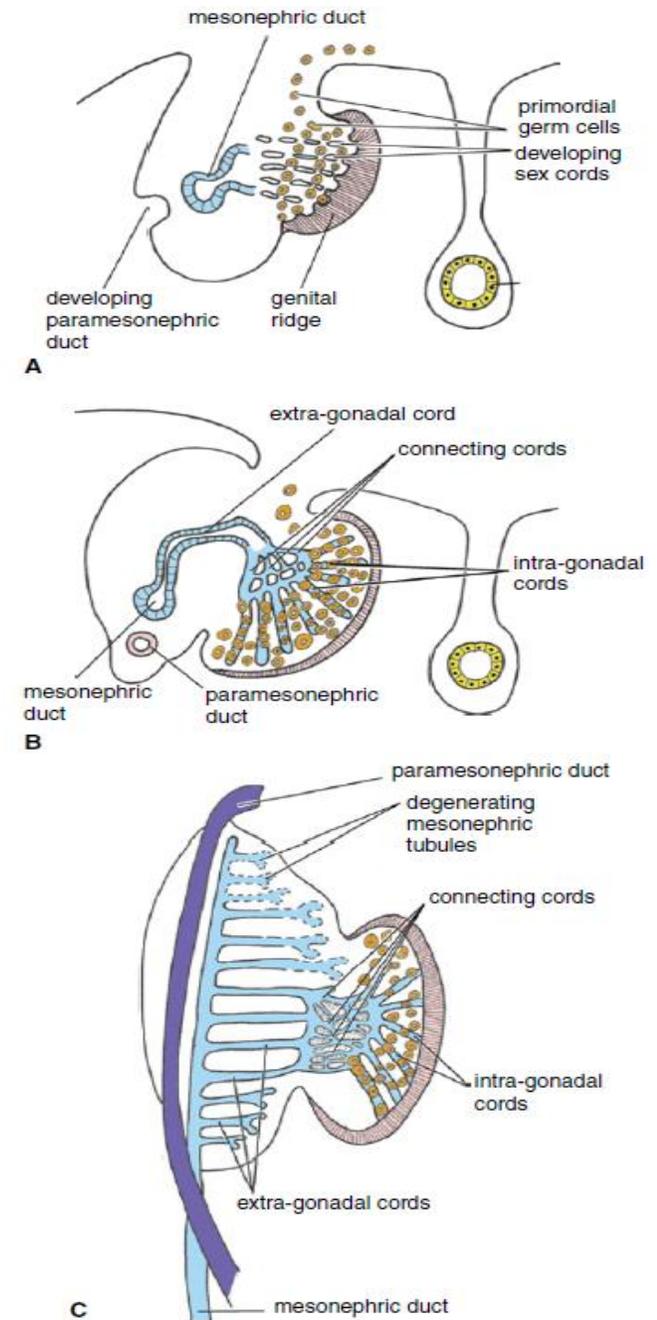


Figure 2 Sequential stages in the development of the undifferentiated gonad. A. Formation of sex cords in the genital ridge. B. Relationship between the mesonephric duct and the developing sex cords. C. Ventral view of the developing gonad shown in B.

Differentiation and Maturation of Testes

- In genotypic males, the mesonephric cells at the periphery of the intra-gonadal rete system develop into cords into which primordial germ cells become incorporated. These cords, known as seminiferous cords, become horseshoe-shaped and their extremities join with mesonephric cells at the centre of the developing gonad (Fig 3).
- The seminiferous cords become convoluted and form the tubuli contorti. During this period of development, the seminiferous cords are solid structures. On cross-section they are composed of a peripheral layer of 15 to 20 mesonephric cells which are destined to become Sertoli cells. These mesonephric cells surround a central core of up to four germ cells, the prespermatogonia.
- Later, a layer of mesonephric-derived myoid cells surrounds the cords.

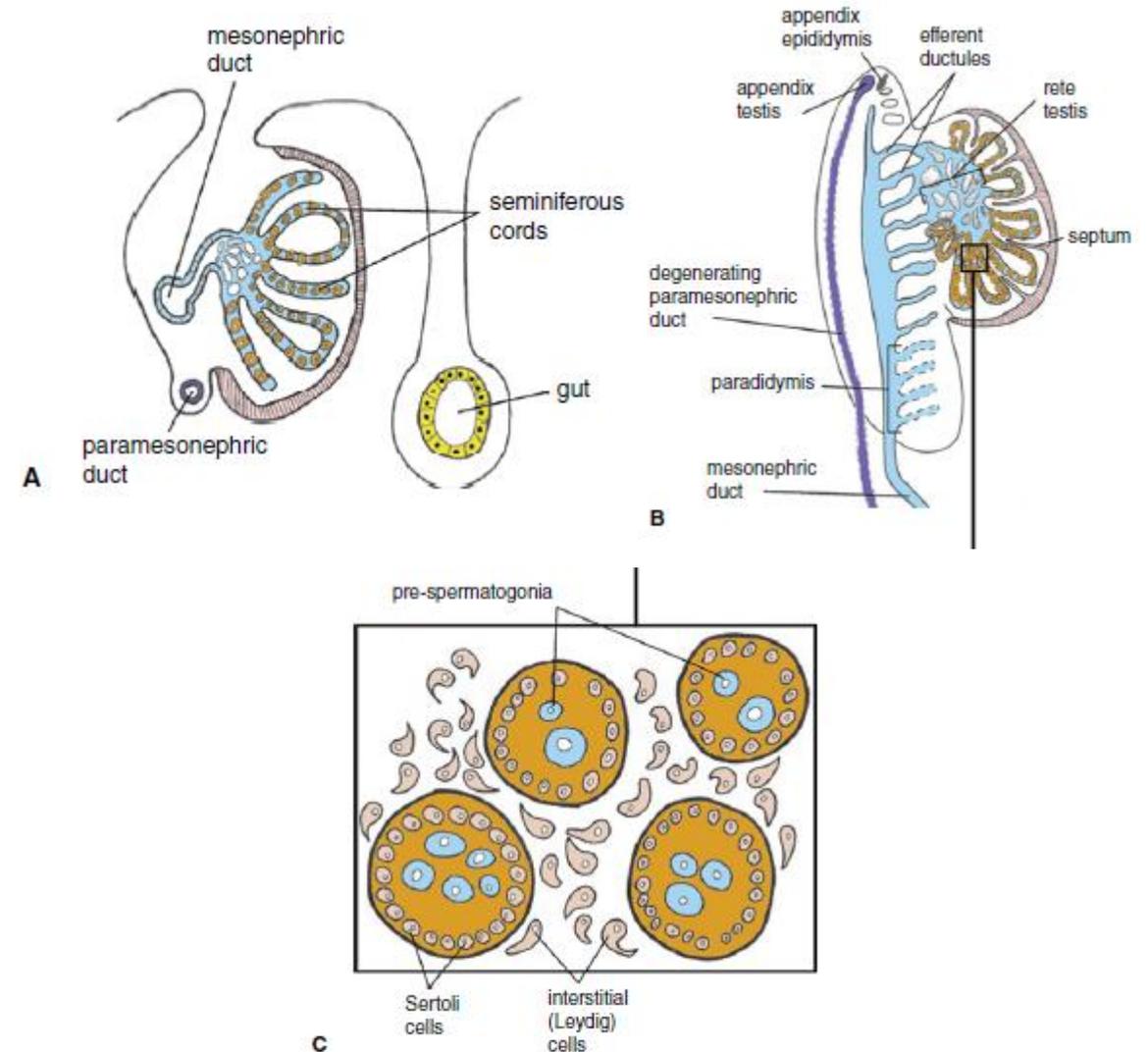


Figure 3 Cross-section A, and ventral view B, of the differentiation of the testis from the undifferentiated gonad, showing the formation of horseshoe-shaped seminiferous cords. C. Cross-section through seminiferous cords showing Sertoli cells, pre-spermatogonia and interstitial cells.

Differentiation and Maturation of Testes

- Under the influence of the seminiferous cords, mesodermal cells, located between the cords, differentiate into the interstitial cells (Leydig cells) of the testis, which produce testosterone.
- Subsequently, the mesonephric cells at the centre of the developing gonad give rise to the tubules of the rete testis.
- In cattle and dogs, interstitial cells increase in number until birth and then decrease.
- In horses, they undergo marked hypertrophy between days 110 and 220 of gestation and then decrease in number.
- The highest rate of secretion of testosterone is reached when the interstitial cells are most numerous.

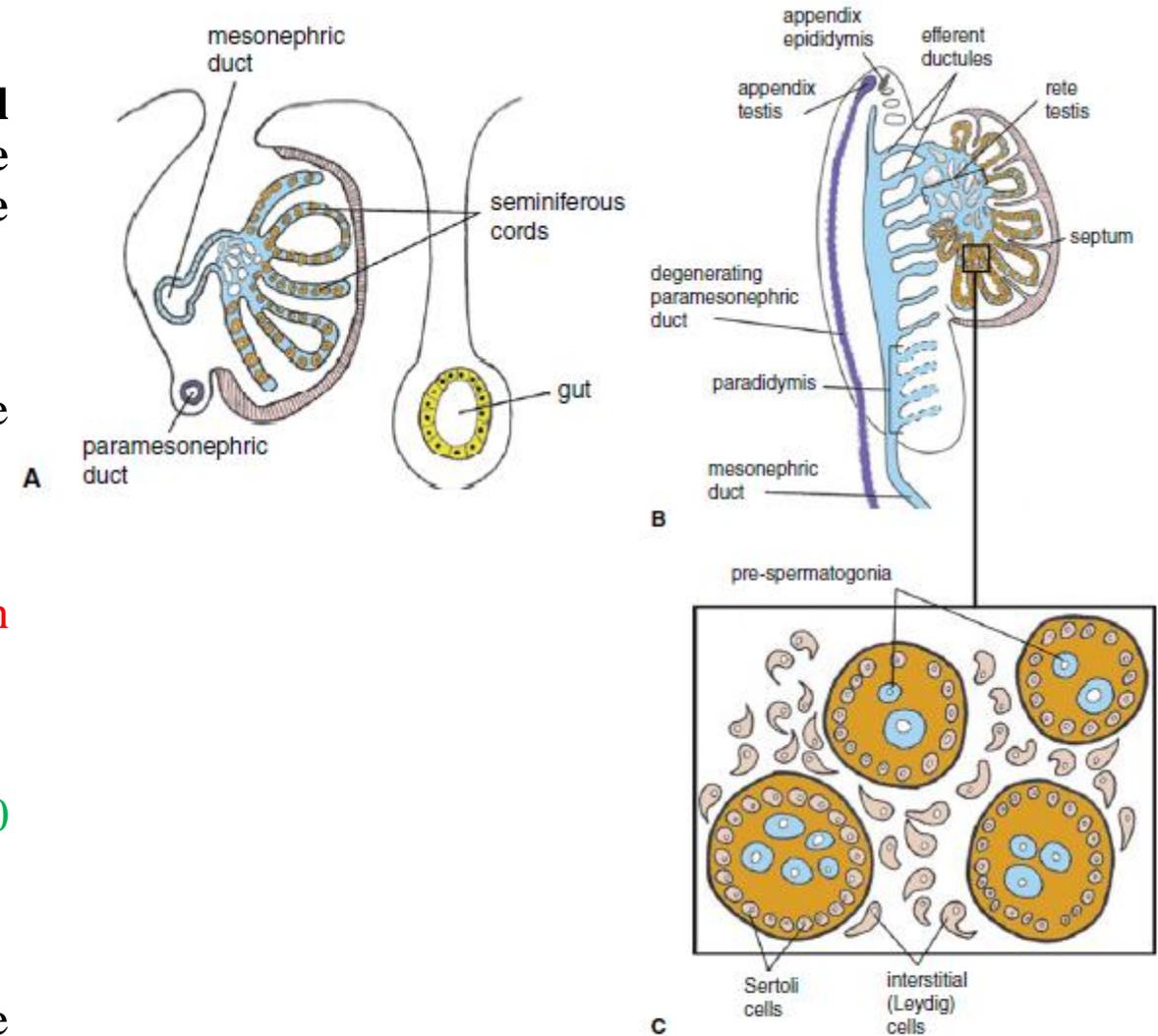
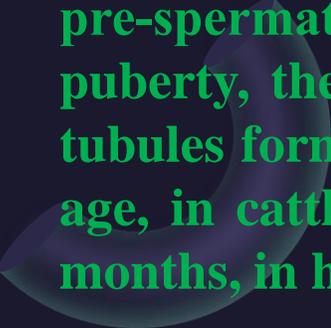


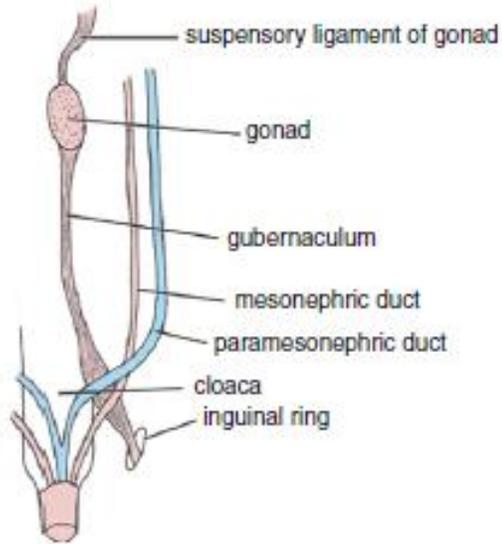
Figure 3 Cross-section A, and ventral view B, of the differentiation of the testis from the undifferentiated gonad, showing the formation of horseshoe-shaped seminiferous cords. C. Cross-section through seminiferous cords showing Sertoli cells, pre-spermatogonia and interstitial cells.



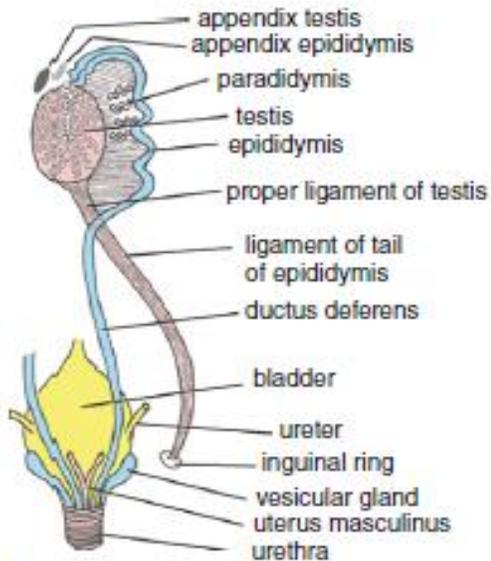
Differentiation and Maturation of Testes

- Mesenchymal cells under the coelomic epithelium of the developing testis develop into a fibrous layer known as the tunica albuginea. The mesenchymal cells between adjacent tubuli contorti form connective tissue septa which divide the testis into a number of lobules, while mesenchymal cells surrounding the tubules of the rete testis form a fibrous network called the mediastinum testis. The extent to which the testicular septa and the mediastinum testis become organised varies in individual species. In pigs, dogs and cats, they are well developed but in ruminants they are less well developed.
 - **Through the secretion of an inhibitory factor, the Sertoli cells, which surround the pre-spermatogonia, prevent further differentiation of the germ cells until, at puberty, the seminiferous cords become canalised and form tubules. Seminiferous tubules form and spermatogenesis begins in sheep at approximately five months of age, in cattle at around six to eight months, in dogs at approximately nine to ten months, in horses at about two years and in humans at 12 to 14 years.**
- 

Genital Ducts



A



B

- Irrespective of the genotype of the developing embryo, both male and female genital ducts form during the undifferentiated stages of gonadal formation. Differentiation of the male from the undifferentiated duct system is outlined in Figure 4. In the male embryo, elements of the mesonephric (Wolffian) duct system which persist are incorporated into the male genital system, while, apart from vestiges, the paramesonephric (Mullerian) ducts largely disappear.

Figure 4. Development of the undifferentiated genital duct systems, A, into the male duct system, B.

Differentiation of the male duct system in mammals

- The mesonephric tubules and mesonephric duct cranial to the developing testes atrophy, except for a small vestige of the mesonephric duct which is called the appendix epididymis. Depending on the species, from 9 to 12 mesonephric tubules, located in the region of the developing testes, lose their glomeruli and become the connecting portion of the rete system which forms the efferent ductules of the testes. Some of the mesonephric tubules at the caudal pole of the developing testes do not join the tubules of the rete testis and gradually lose contact with the mesonephric duct. These vestiges are collectively referred to as the paradidymis. Mesonephric tubules caudal to the developing testes atrophy.

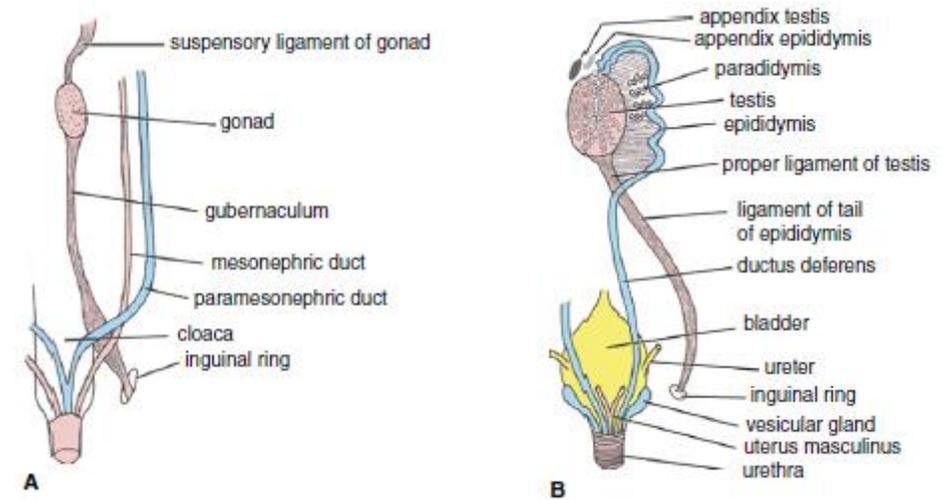


Figure 4. Development of the undifferentiated genital duct systems, A, into the male duct system, B.

- The mesonephric ducts, from the cranial poles of the testes to the urogenital sinus, persist as the male genital ducts. A segment of the mesonephric duct caudal to the point of entry of the efferent ductules elongates and becomes convoluted, forming the epididymis. The remaining caudal segment of the mesonephric duct, which develops a thick wall of smooth muscle, becomes the ductus deferens (Fig 4).

Differentiation of the male duct system in mammals

- With the exception of carnivores, the mesonephric ducts form evaginations near their junctions with the urogenital sinus. These mesodermal evaginations form the vesicular glands, the primordia of which are first observed in the bovine foetus around the 55th day of gestation.
- The definitive urogenital sinus forms the pelvic and penile urethra. The endodermal epithelium of the pelvic urethra forms outbuddings at its cranial and caudal ends. The cranial outgrowths give rise to the prostate gland in mammals and the caudal outgrowths form the bulbourethral glands in all domestic mammals, with the exception of dogs. The cranial vestiges of the paramesonephric ducts give rise to the appendix testis while the caudal vestiges fuse and form the uterus masculinus (prostatic utricle).

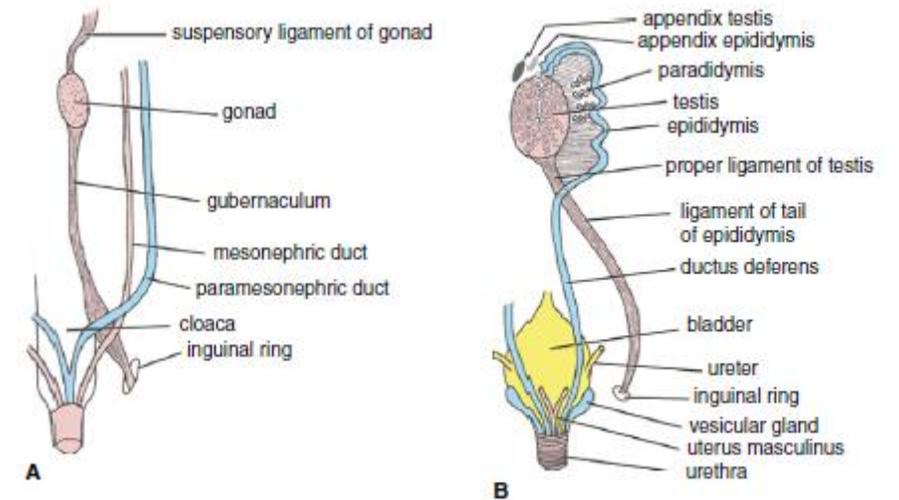
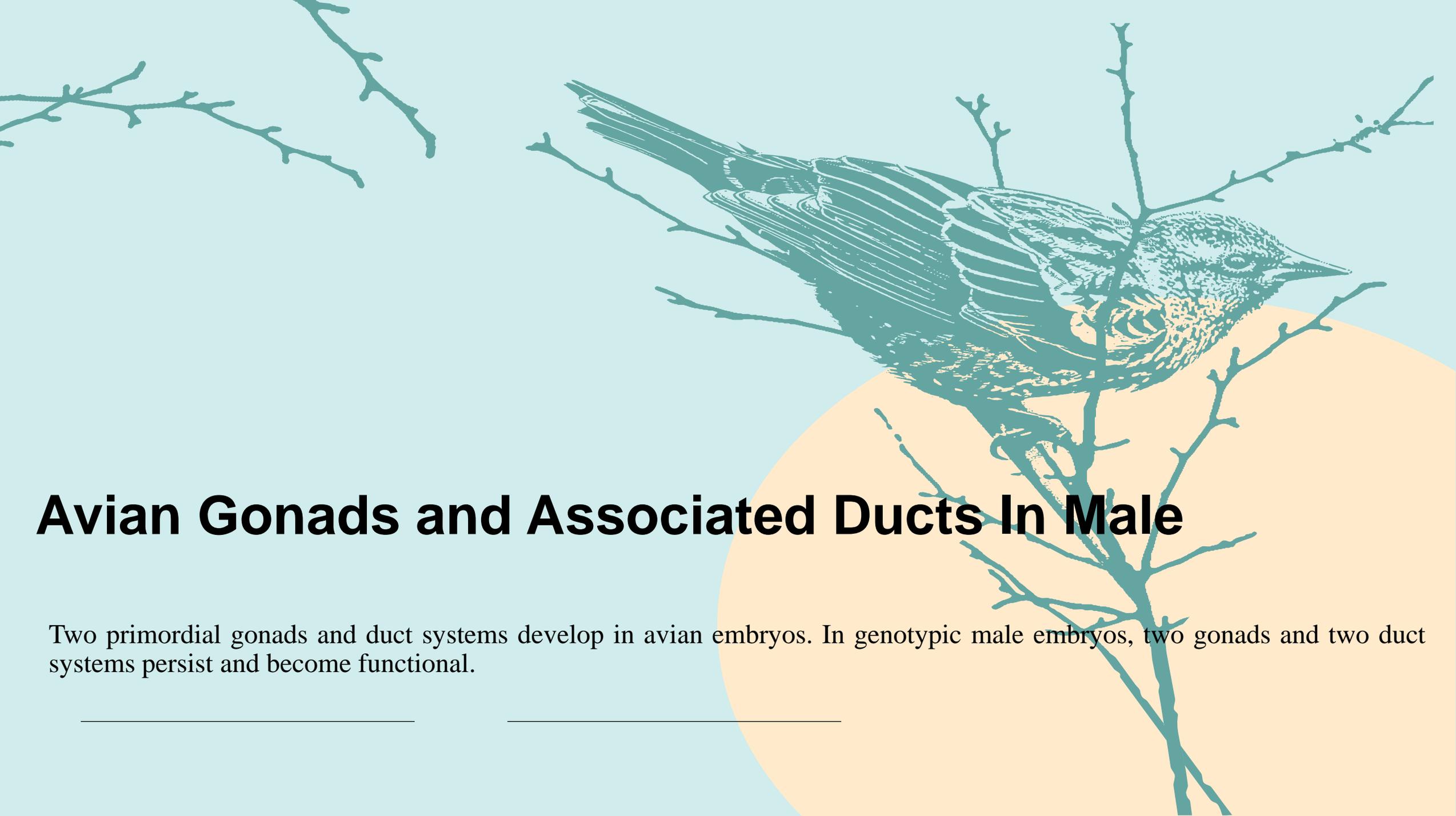


Figure 4. Development of the undifferentiated genital duct systems, A, into the male duct system, B.



Avian Gonads and Associated Ducts In Male

Two primordial gonads and duct systems develop in avian embryos. In genotypic male embryos, two gonads and two duct systems persist and become functional.

Formation of the genital fold

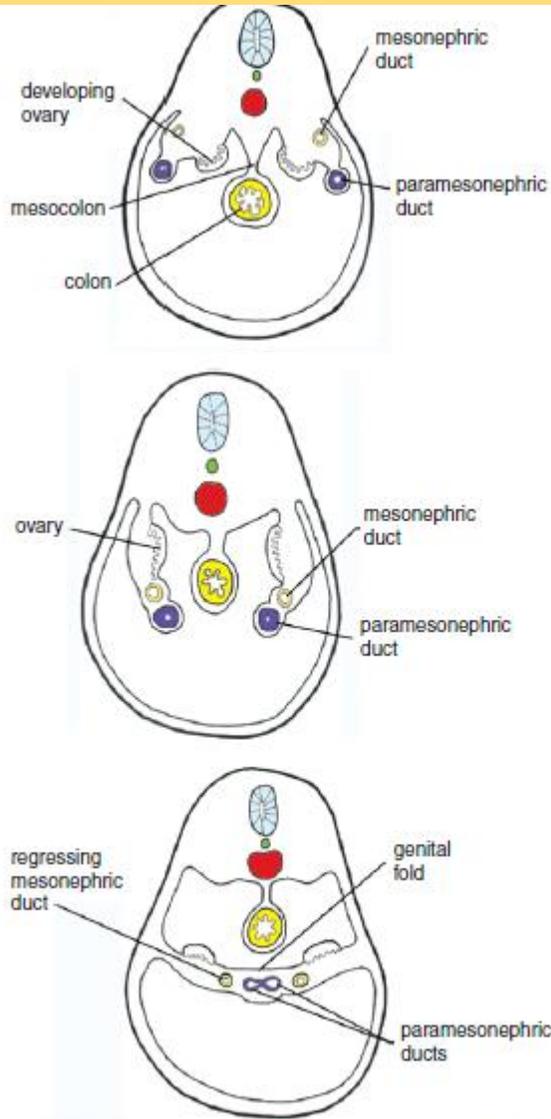


Figure 5. Cross-sections through a mammalian female embryo showing sequential stages in the formation of the genital fold.

- The urogenital system, which develops retroperitoneally, bulges into the peritoneal cavity.
- With the degeneration of the mesonephros, the gonads and genital ducts become suspended by thin folds of peritoneum.
- The caudal portions of the genital ducts meet and fuse in the midline. Fusion of their associated peritoneal folds forms the genital fold (Fig 5).
- In the male embryo, that part of the genital fold which suspends the testes is termed the mesorchium and the portion which suspends the ductus deferens, the mesoductus deferens.

External genitalia

- During the undifferentiated phase of sexual development in the embryo, mesenchymal cells from the primitive streak migrate to the region around the cloacal membrane and form two elevated folds, the cloacal folds. These folds fuse ventrally and form the genital tubercle. Later in development, as a consequence of the formation of the urorectal septum, the cloacal membrane is subdivided into an anal and a urogenital membrane.
- The anal and urogenital membranes subsequently break down allowing communication between the rectum and urogenital sinus and the exterior. Endodermal cells from the urogenital sinus proliferate and grow into the mesoderm of the genital tubercle, forming the urethral plate. The cloacal folds are also divided into the anal folds dorsally and the urogenital folds ventrally. Proliferation of mesoderm lateral to each urogenital fold forms elevations which are termed the genital (labio-scrotal) swellings (Fig 6).

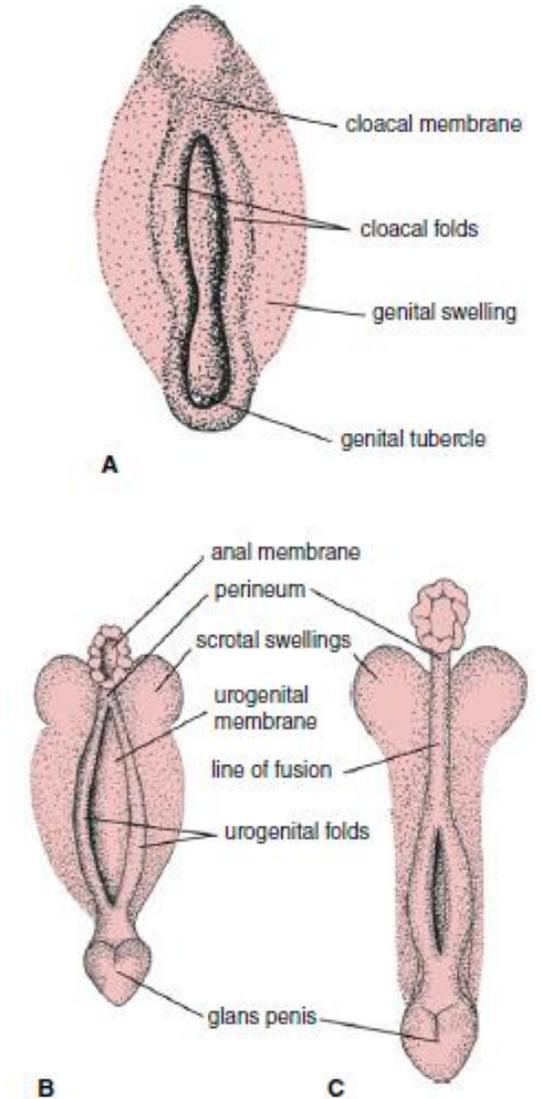


Figure 6. Development of the male external genitalia. Undifferentiated stage of the external genitalia, A, and sequential stages in the development of the male external genitalia, B and C.

Differentiation of the external genitalia

- In the male embryo, the genital tubercle elongates rapidly in a cranio-ventral direction and draws the urogenital folds forwards forming the lateral edges of the urethral plate, the floor of which gives rise to the urethral groove. The urogenital folds fuse, converting the urethral groove into a tube, the penile urethra (Fig 7).

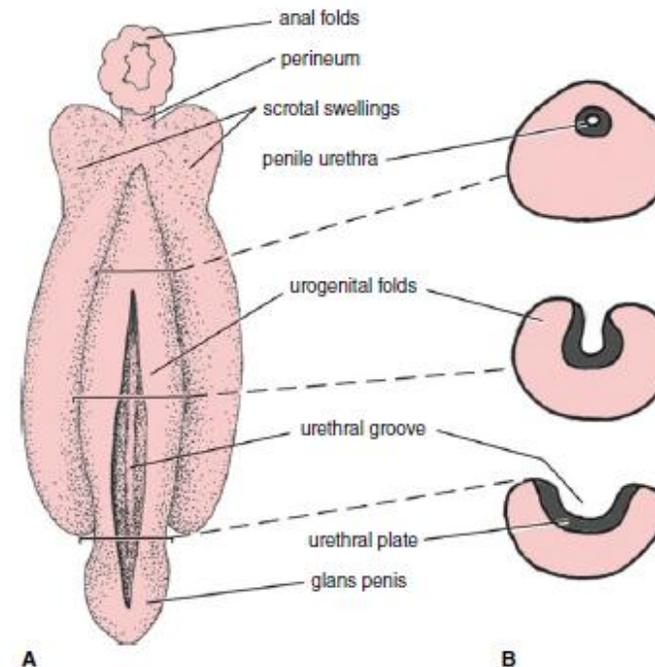


Figure 7. Closure of the urethral groove, A, and cross-sections at different levels, B, showing progressive stages in the conversion of the urethral groove into a tube, the penile urethra.

Differentiation of the external genitalia

- With closure of the urogenital folds, the penile urethra becomes incorporated into the body of the penis. The urethral plate, however, does not extend to the tip of the penis. An ectodermal bud which invaginates into the tip of the penis fuses with endodermal cells lining the penile urethra. Later, this cord of ectodermal cells becomes canalised and, as a consequence, the penile urethra opens at the tip of the penis (Fig 8).
- In the feline embryo, the genital tubercle does not extend cranio-ventrally and consequently the penis of the cat retains its embryonic orientation with its apex pointing caudally. In rams and male goats, the urethra forms an elongation, the urethral process, which extends beyond the tip of the penis. The corpus cavernosum penis, tunica albuginea and corpus spongiosum penis derive from genital tubercle mesenchyme. In carnivores, the mesenchymal tissue at the cranial end of the corpus cavernosum penis becomes ossified, forming the os penis. The prepuce forms from mesenchyme and ectoderm surrounding the genital tubercle.
- The genital swellings give rise to the scrotal pouches, which fuse at their medial aspects, ventral to the anus, forming the scrotum. The line of fusion of the scrotal pouches persists as the scrotal raphe. The final position of the scrotum differs among domestic species. In horses and ruminants, the genital swellings migrate cranially and the scrotum is located in the inguinal region unlike in cats and pigs where it is positioned ventral to the anus. In dogs, the scrotum is located in an intermediate position between the inguinal region and the anus.

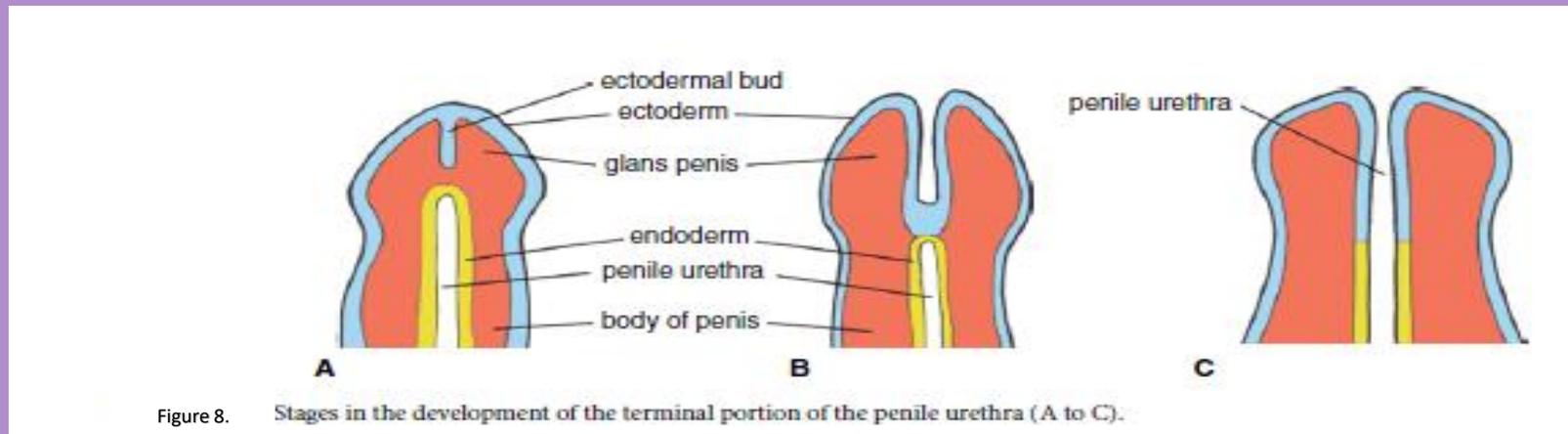


Figure 8. Stages in the development of the terminal portion of the penile urethra (A to C).

Influence of hormones on development of genital ducts and external genitalia

Table 1. Embryonic primordia from which structures in the male system arise.

Embryonic structure	Derivative in the male reproductive system
Primordial germ cells	Spermatozoa
Gonad	Testis
Sex cords	Seminiferous tubules, Sertoli cells, Leydig cells
Mesonephric tubules	Efferent ductules, epididymis, appendix testis
Mesonephric duct	Epididymis, ductus deferens, vesicular glands
Paramesonephric duct	Appendix testis, uterus masculinus
Definitive urogenital sinus	Pelvic urethra, prostate gland, bulbourethral gland and penile urethra
Genital tubercle	Body of penis
Urogenital folds	Tissue surrounding the ventral aspect of the penile urethra
Genital swellings	Scrotum

- Development of the male genital duct system and external genitalia is under the influence of the hormones produced by the developing testes. With the formation of the testes, the male duct system and external genitalia develop and the female duct system regresses. The foetal testes secrete two hormones, **testosterone and paramesonephric inhibitory hormone (anti-Mullerian hormone)**.
- **Testosterone**, produced by the **Leydig cells**, induces the differentiation of the paired male duct system, epididymis, ductus deferens and vesicular gland.
- **Paramesonephric inhibitory hormone**, secreted by the **Sertoli cells**, inhibits development of the paramesonephric ducts and induces regression of these structures.
- Embryonic primordia from which structures in the male reproductive systems arise are presented in Table 1.

SUMMARY

Chromosomal sex is determined at fertilisation.

Primordial germ cells migrate to the genital ridge, which subsequently develops into the appropriate gonad and duct system for that sex.

An indifferent stage of genital development occurs where primordia of the organs of both sexes co-exist.

Two defined antagonistic pathways exist for sexual differentiation. The presence of the SRY gene on the Y chromosome promotes the development of male genital organs.

Depending on the genetically determined sex of the individual, the organs appropriate for that sex develop, while the genital organs of the other sex regress, leaving only vestiges.

The sex cords of the gonads develop from intermediate mesoderm.

The mesonephric duct persists in the male embryo and gives rise to the ductus deferens and vesicular glands. The prostate and bulbourethral glands develop from endoderm.

External genitalia develop from the genital tubercle and the caudal portion of the urogenital sinus. Tissue differentiation is influenced by sex-specific hormones.

Descent of the testes

- Migration of the male gonads from their intra-abdominal site of development to an extra-abdominal subcutaneous location, usually in the inguinal region, is referred to as descent of the testes (Fig 10).
- In the majority of mammals, the testes migrate to an extra-abdominal location but, even in some of these mammals, such as rats, mice and guinea pigs, the testes may be temporarily withdrawn into the abdominal cavity as a consequence of sensing danger. In those animals in which the testes descend to an extra-abdominal location, a temperature of 2–4 °C below core body temperature is required for normal spermatogenesis.

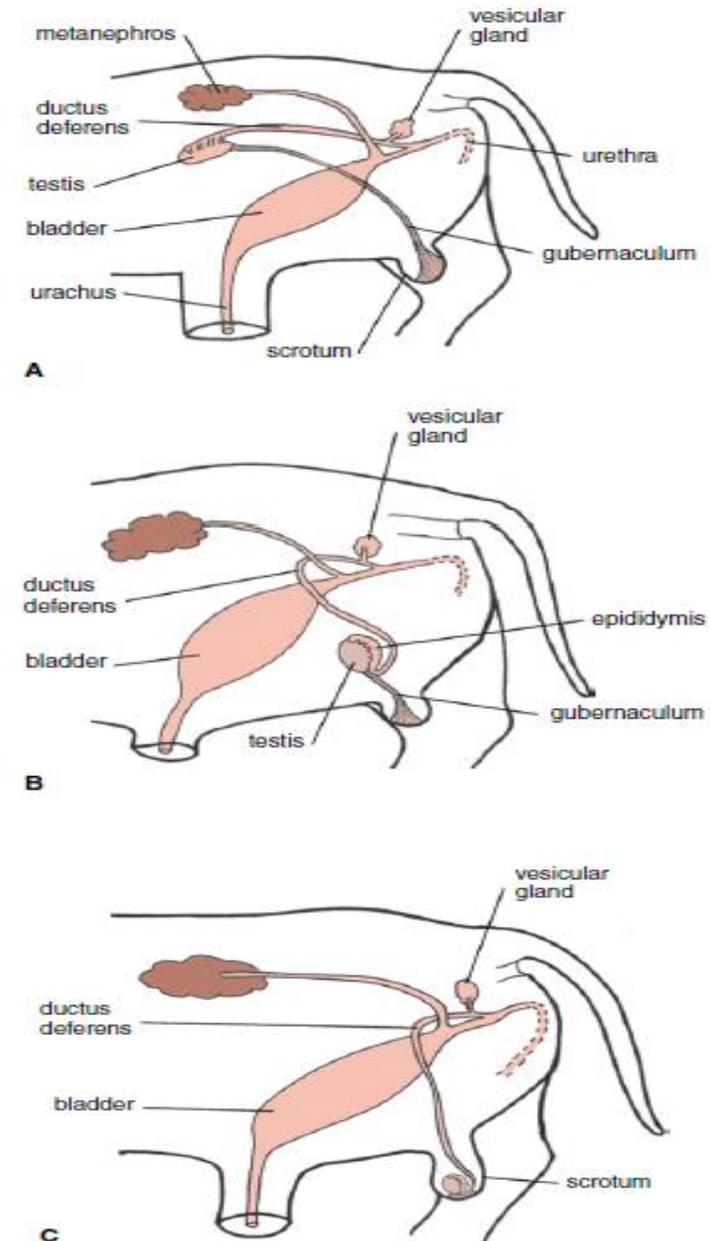


Figure 10. Stages in the descent of the bovine testis from a dorsal position in the peritoneal cavity, A, to a ventral location, B, and in its final position in the scrotum, C.

Descent of the testes

- During testicular development, a mesenchymal column, the gubernaculum, develops and extends from the caudal pole of the mesonephros and testis to the inguinal region. This structure (gubernaculum) is present in both male and female embryos. The extra-abdominal part of the gubernaculum, which is located in the embryonic abdominal wall, exists prior to the formation of abdominal musculature. This portion gradually extends caudally to the genital swellings and its caudal end acquires a bulbar shape.
- As the musculature of the abdominal wall develops around the gubernaculum, openings in the abdominal wall link the abdominal cavity to the developing scrotal sac. The passageway between these openings, occupied by the gubernaculum, is referred to as the inguinal canal.
- Invasion by the vaginal process divides the gubernaculum into three parts.
 - a) **The proximal part**, the gubernaculum proper, is enclosed by the vaginal process.
 - b) The outer layer of the gubernaculum lies on the external surface of the vaginal process and is termed **the vaginal part**.
 - c) **The distal portion**, known as the infra-vaginal part, lies ventral to the vaginal process.

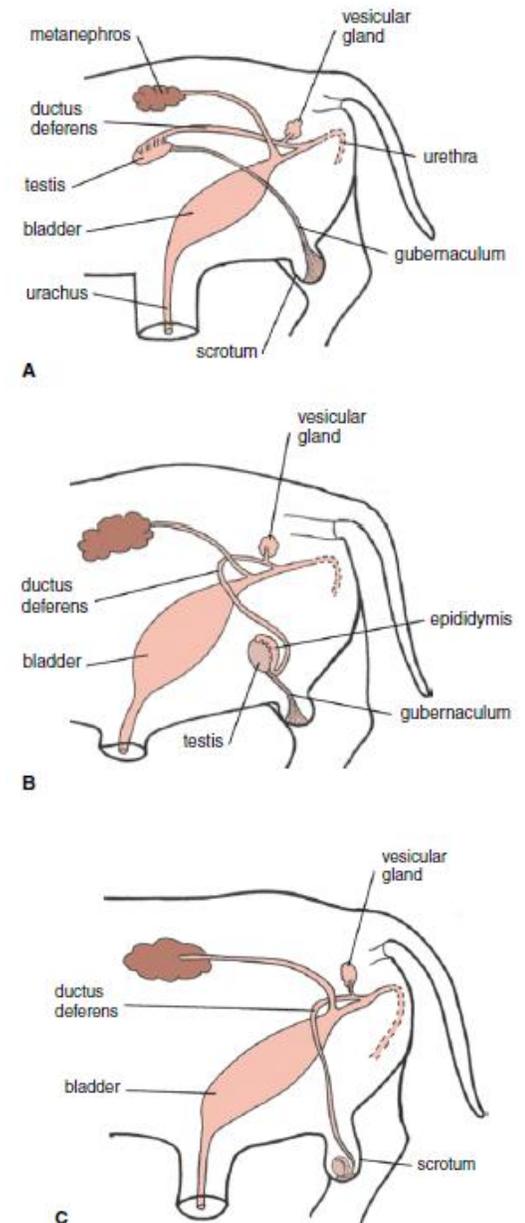


Figure 10. Stages in the descent of the bovine testis from a dorsal position in the peritoneal cavity, A, to a ventral location, B, and in its final position in the scrotum, C.

- The intra-abdominal part of the gubernaculum is attached to both the mesonephric and paramesonephric ducts at a point where the ducts change from a lateral to a medial position. In the male embryo, the part of the mesonephric duct cranial to this attachment becomes the epididymis and the part caudal to it becomes the ductus deferens. Descent of the testis occurs in two stages, **trans-abdominal descent** and **inguino-scrotal descent**.
- Trans-abdominal migration of the testes from the lumbar region to the inguinal ring is considered to be more apparent than real due to the rapid growth of the vertebral column and associated structures relative to the position of the gonads in the lumbar region. In both male and female embryos, the gonads are retained in a fixed position by the gubernaculum. The metanephros, which initially develops in a position caudal to the gonads, is drawn cranially by this developmental process and occupies a position cranial to the gonads. Testicular migration is influenced by paramesonephric inhibitory hormone, which induces enlargement of the gubernaculum.
- As the testis approaches the inguinal ring, the tail of the epididymis enters the inguinal canal. The enlarged gubernaculum dilates the deep inguinal ring, thereby facilitating entry of the testis into the inguinal canal. The testes are located at the deep inguinal rings in dogs at 50 days, in cattle at 90 days, in pigs at 70 days, in humans at 150 days and in horses at 240 days of gestation. Passage of the testis through the inguinal canal is rapid in cattle and pigs but slow in horses.

- Inguino-scrotal descent is androgen-dependent. Androgens act on the gubernaculum through the genitofemoral nerve, a lumbar spinal nerve, which passes through the inguinal canal. The genitofemoral nerve releases calcitonin gene-related peptide (CGRP) as a neurotransmitter and CGRP is postulated to act as a chemotactic agent, providing a directional signal for the gubernaculum, in addition to its role in promoting mitosis in the distal portion of the gubernaculum. Data showing the species variation in testicular development and descent are presented in Table 2.

Table 2. Times at which the major events in testicular descent occur in humans and in domestic animals. Numbers indicate days of gestation or days postpartum (dpp).

Species	Formation of genital ridge	Testis formation	Start of trans-abdominal phase	Start of inguino-scrotal phase	Completion of descent of testis
Human	49	56	70	182	245
Pig	21 to 22	27	55	90	Close to birth
Horse	30	34	45	310	Close to birth
Cattle	30 to 32	41	80 to 90	112	Close to birth
Sheep	22	31	60 to 65	75	Close to birth
Dog	23 to 24	29	42	4 to 5 dpp	35 to 45 dpp

Anomalies of sexual development

- During the complex series of events involved in the development of the reproductive system, there are numerous opportunities for developmental defects to occur. These anomalies can occur at the chromosomal level, during gonadal differentiation, or at the stage of differentiation of the duct system or of the external genitalia.
- Manifestations of sexuality can be evaluated at a number of levels: genotypic, gonadal, phenotypic and behavioural. Based on collective conformity to these criteria an animal is considered to be male or female.
- Intersex animals have some of the characteristics of each sex, including physical attributes and reproductive tissue, which may contribute to atypical sexual behaviour. In addition, an intersex animal may be one sex genotypically and the other sex phenotypically.

Anomalies of sexual development

- An individual with gonads of both sexes, either as separate ovaries and testes, or as combined ovo-testes, is termed **a hermaphrodite**.
- A *pseudohermaphrodite* has the gonads of one sex only, with duct systems, external genitalia and some of the sexual characteristics of the opposite sex. Thus, a male pseudohermaphrodite has male gonads but female external genitalia.
- What is referred to as *true hermaphroditism* results from gonadal defects at an early stage of development, so that both testicular and ovarian tissues develop either as separate gonads or as combined ovo-testes. **True hermaphroditism has been reported in all species of domestic mammals, especially pigs.**

Anomalies of sexual development

- Hypoplasia of both testes and ovaries, which is usually associated with genetic or chromosomal abnormalities, also occurs in domestic animals.
- Penile hypoplasia (incomplete growth) is a rare condition which has been observed in dogs and cats.
- Hypospadias is a congenital defect in males due to partial failure of the urogenital folds to close which results in the external urethral orifice being misplaced.
- **Klinefelter syndrome (XXY) results from non-disjunction of sex chromosomes during meiosis.** The presence of the Y chromosome results in male-determining genes inducing the formation of male gonads with production of male hormones and the development of a phenotypic male. The presence of the female chromosomes, however, prevents the occurrence of normal spermatogenesis, resulting in hypoplastic testes. **This syndrome is recognised in humans, dogs and cats.**

Cryptorchidism

- Failure of normal testicular descent, cryptorchidism, is a condition which occurs in all mammalian species. **It is most frequently encountered in horses and pigs, and in miniature dog breeds.** A bilaterally cryptorchid animal is sterile but as the interstitial (Leydig) cells are unaffected by core body temperature, the animal usually has the phenotypic and behavioural characteristics of an entire male.
- Cryptorchidism has been attributed to abnormal testicular development, failure or abnormal development of the vaginal process, abnormal development of the gubernaculum and hormonal imbalance or deficiency. Whether unilateral or bilateral, cryptorchidism is considered to be an inherited condition.
- In horses, the mode of inheritance is attributed to a dominant gene, whereas in other species it is probably an autosomal recessive pattern of inheritance. In humans and dogs, there is an increased frequency of neoplastic change in undescended testes, relative to descended testes.

REFERENCES

Ernst, L. M., Ruchelli, E. D., Carreon, C. K., & Huff, D. S. (Eds.). (2019). *Color Atlas of Human Fetal and Neonatal Histology*. Springer Nature.

Sadler, T. W. (2018). *Langman's medical embryology*. Lippincott Williams & Wilkins.

McGeady, T. A., Quinn, P. J., Fitzpatrick, E. S., Ryan, M. T., Kilroy, D., & Lonergan, P. (2017). *Veterinary embryology*. John Wiley & Sons.



Thank you for your attention.

