Lecture 6

General medicine_3rd semester

DEVELOPMENT OF URINARY SYSTEM AND OVERVIEW OF ITS CONGENITAL MALFORMATION

DEVELOPMENT OF REPRODUCTIVE SYSTEM: INDIFFERENT STAGE

DEVELOPMENT OF INTERNAL AND EXTERNAL SEXUAL ORGANS

OVERVIEW OF MOST IMPORTANT CONGENITAL MALFORMATIONS

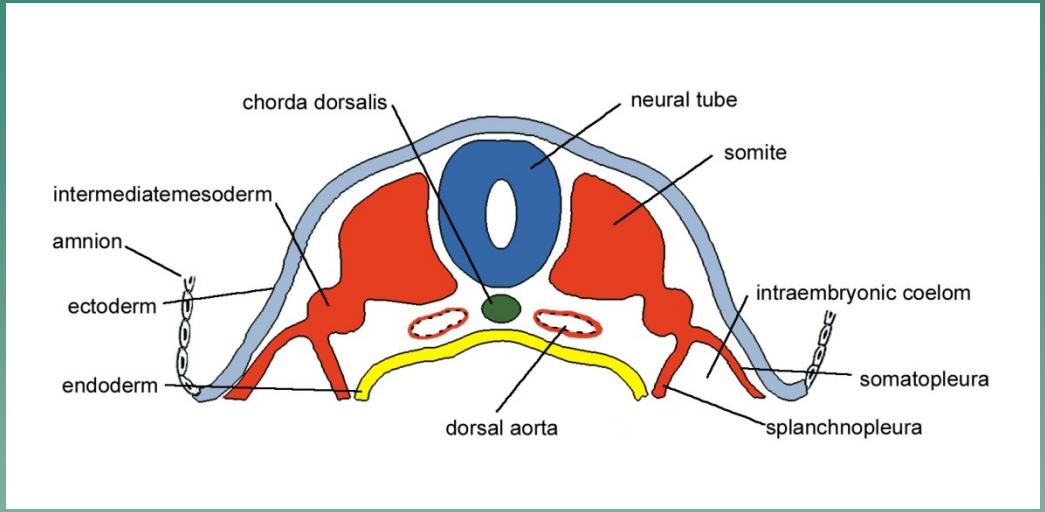
Introduction

the urinary system and internal sexual organs develop from **the intermediate mesoderm** or **nephrotomes**

a part of the third germ layer

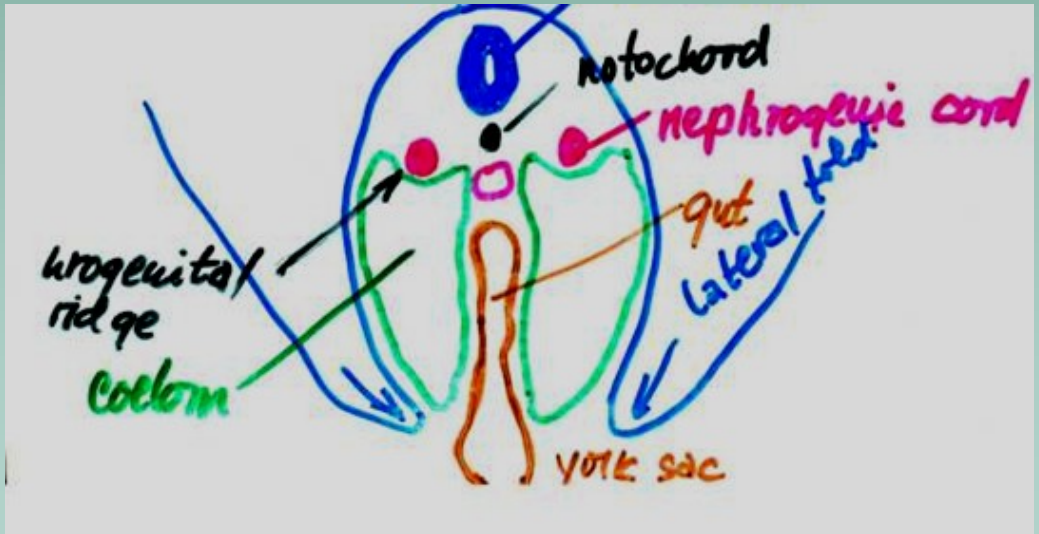
interposed between the axial mesoderm or somites and lateral mesoderm

the intermediate mesoderm extends along the entire length of the dorsal body wall of the embryo



it soon loses connection with somites and fuses to form the **nephrogenic cords** on each side of the primitive aorta

the cords rapidly grow, become larger and produce bilateral longitudinal bulges called the **urogenital ridges**



a medial side of each ridge is then separated from the surrounding and is called as the **gonadal ridge** (see the next chapter)

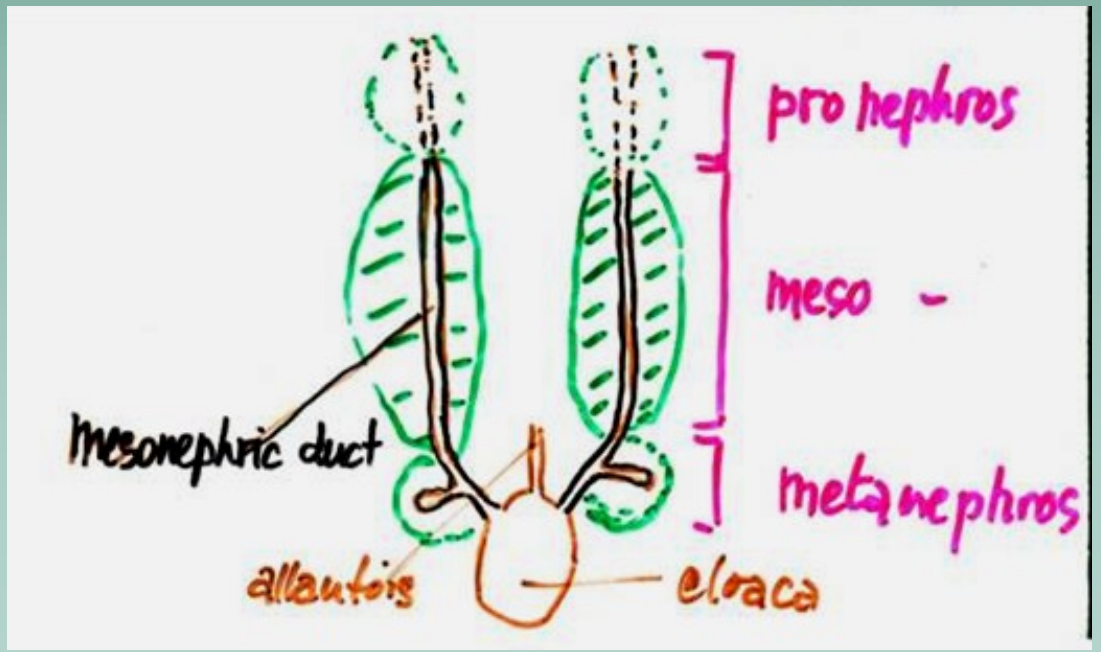
DEVELOPMENT OF KIDNEYS, URETERS, BLADDER, AND URETHRA

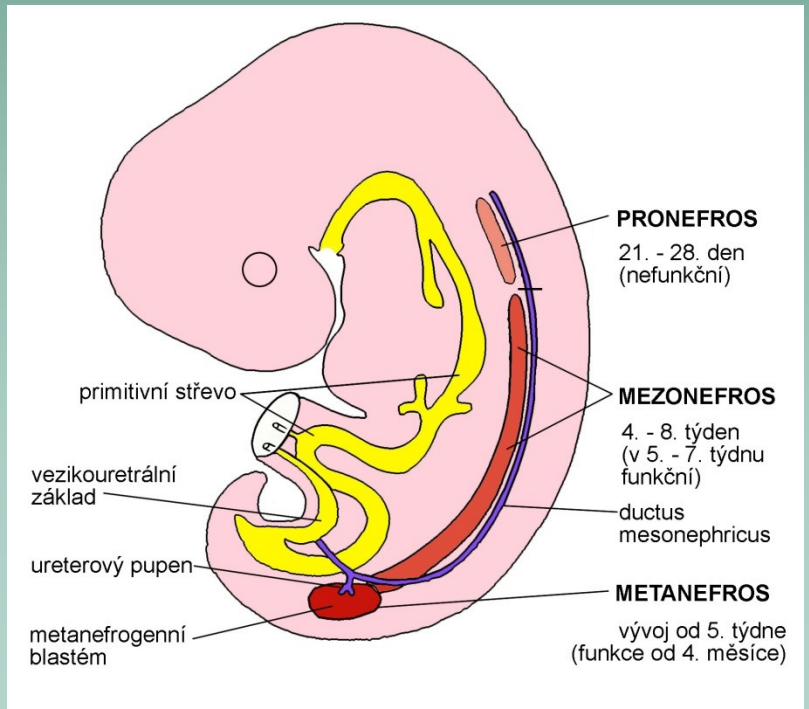
in the human, three sets of excretory organs develop:

the **pronephros** (-oi) - "forkidney" - is **rudimentary** and nonfunctional; forkidney is analogous to the kidney of some primitive fishes,

the **mesonephros** (-oi) -" midkidney" - is analogous to kidney of fishes and larval stages of amphibia amphibians; in human embryos, midkidney is in **function for a short time** and then undergoes involution

the **metanephros** (-oi) - "hindkidney" or **permanent kidney**, it begins to produce urine in fetuses aged 11 to 13 weeks



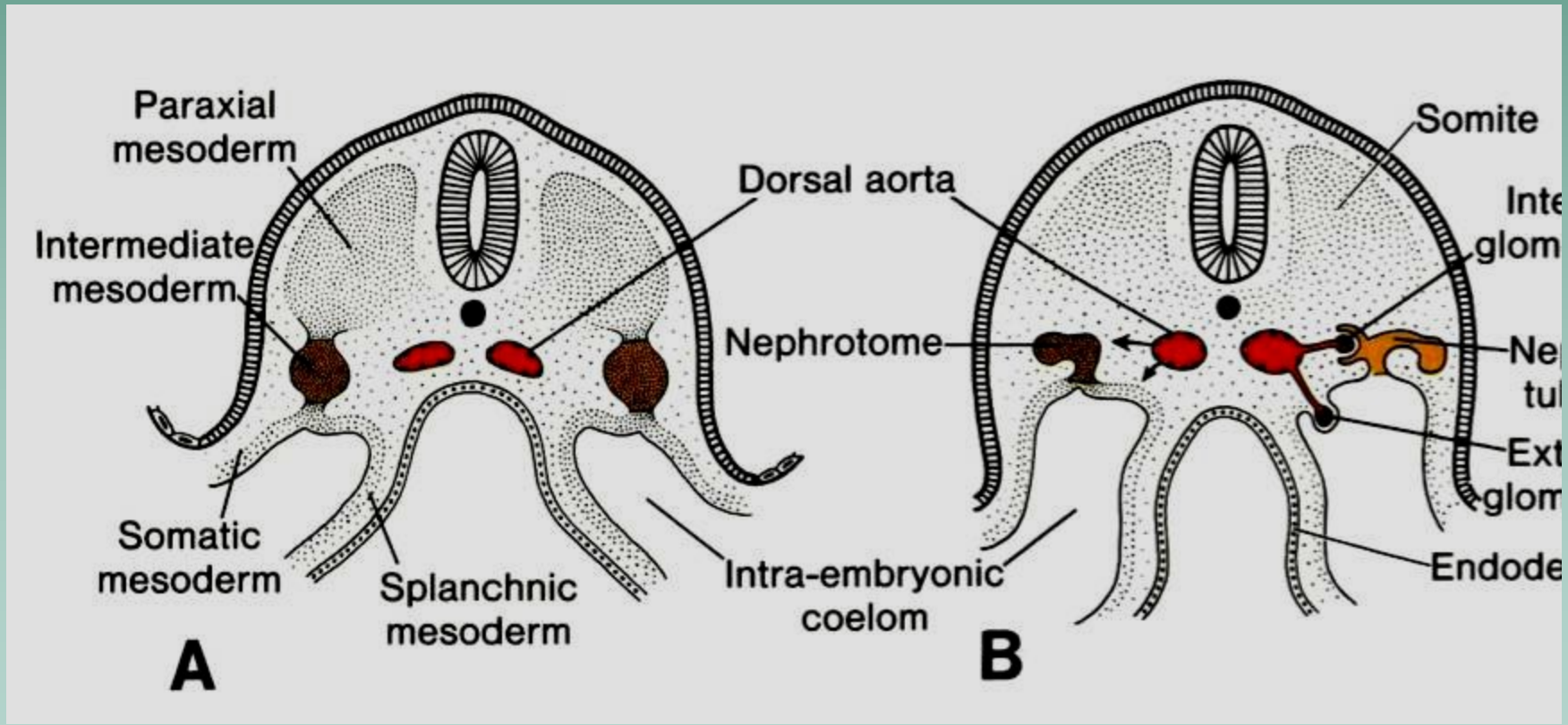


Pronephros (oi)

occurs early in the fourth week in the cervical region on each side

it consists of a few solid cell clusters, rarely short **pronephric tubules** and the **pronephric duct**, which runs caudally and opens into **the cloaca**

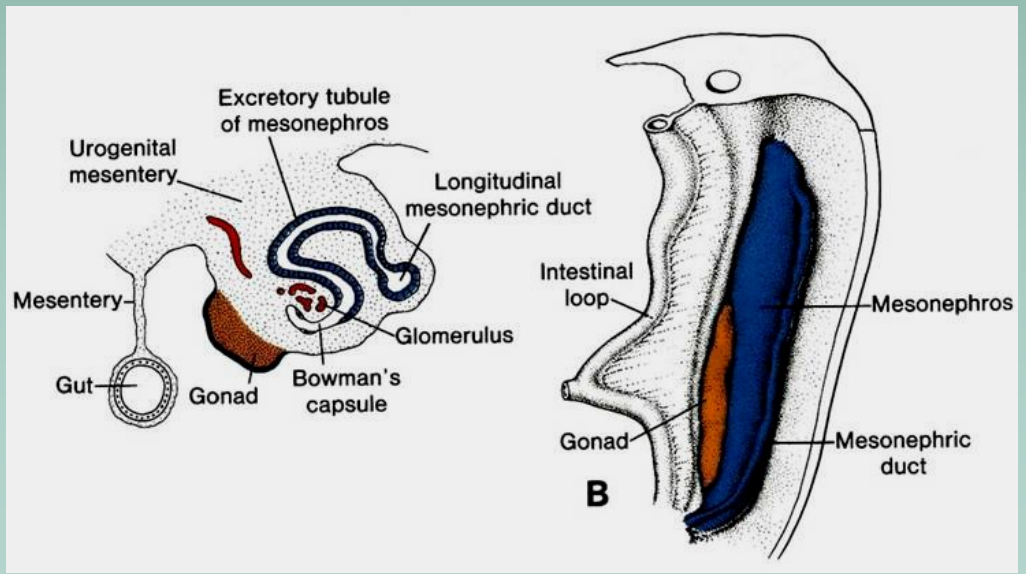
the pronephros soon degenerates, but most of both pronephric ducts are utilized by the midkidney as **mesonephric or Wolffian duct**

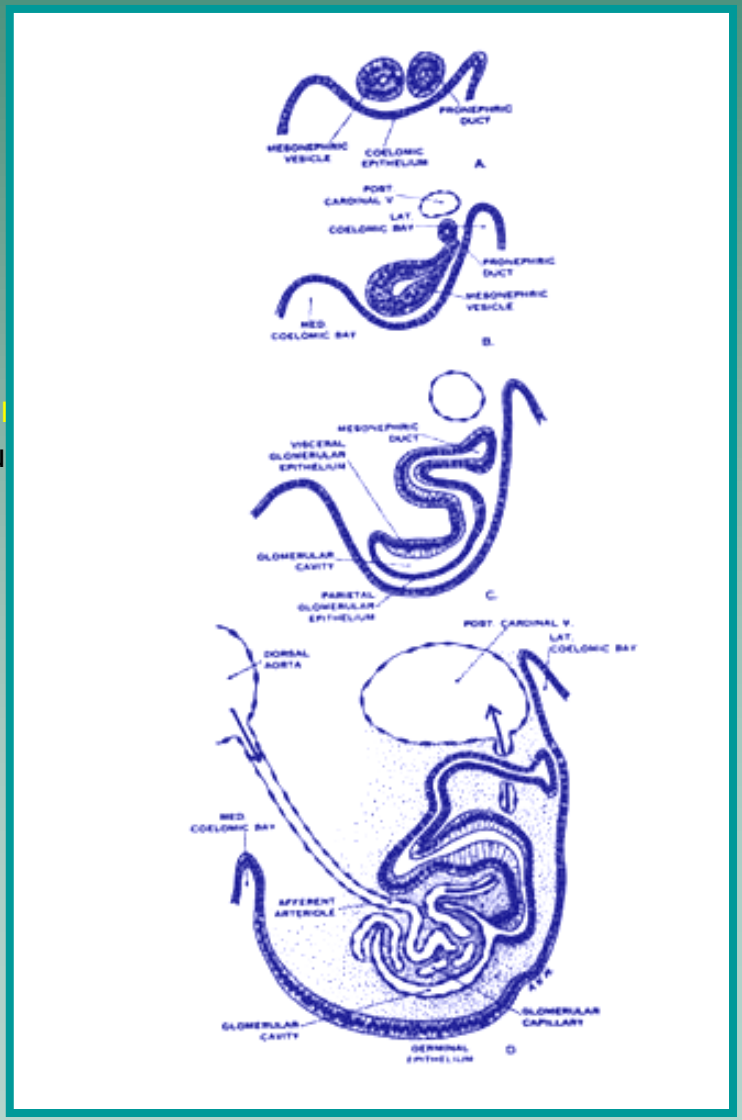


Mesonephros (oi)

develops later in the 4th week caudal to the pronephros in **C_6 to L_3 region**
initially, solid nephrogenic cord (blastema) divides into 40 - 50 mesodermal cell clusters within them lumina develop - **mesonephric vesicles** arise
mesonephric vesicles grow into S-shaped **mesonephric tubules** whose laterally ends become continuous with the **mesonephric duct** or **Wolffian duct**
the medial end of each tubule expands and transforms into the **Bowman´s capsule** (capilary loops of the glomerulus are deriving from the mesonephric artery)
the capsule with glomerulus form a **mesonephric corpuscle** together

cervical and thoracical parts of mesonephroi rapidly degenerate
the lumbar part consisting of a few mesonephric tubules and mesonephric duct persists and is involved in developme of genital ducts in males (ductuli efferentes, ductus deferens and ductu ejaculatorius) or vestigial remnants in females (epoophoron and paroophoron)



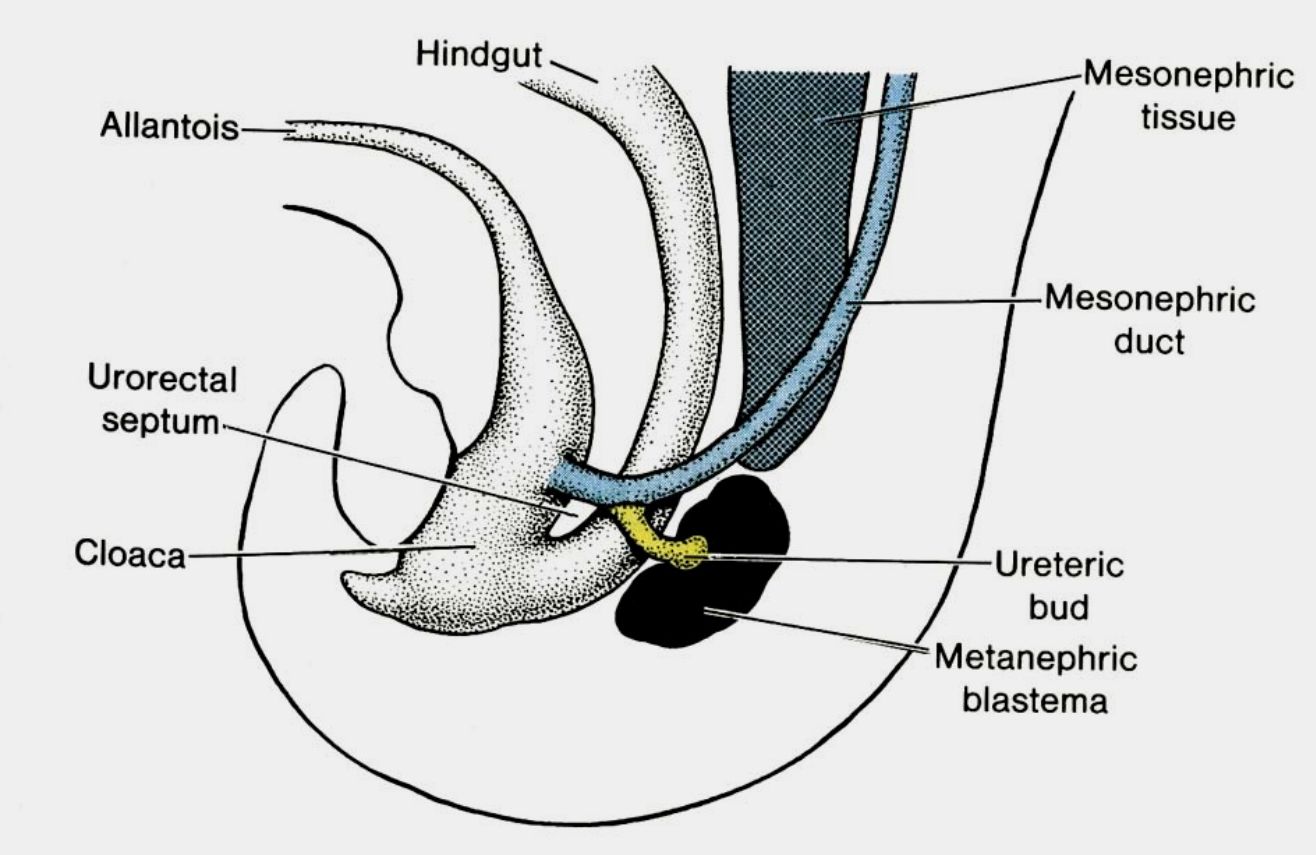


Metanephros (oi)

"hindkidney" or permanent kidney begins to develop early in the 5th week

two different sources:

- the **ureteric bud** or **metanephric diverticulum,** which gives rise to the ureter, pelvis, major and minor calyces and system of papillary ducts and collecting tubules
- the **metanephrogenic blastema** or **metanephric mesoderm** = a caudal part of the nephrogenic cord extending between **L_4 to S_1** - it gives rise to the nephrons



the ureteric bud is a **dorsal outgrowth of the mesonephric duct** near its entry into the cloaca

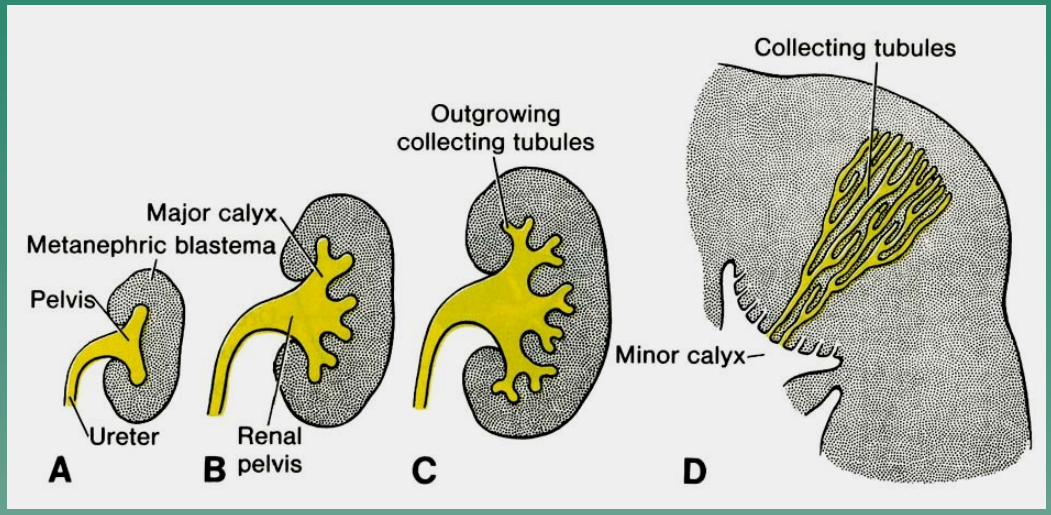
the bud then extends dorsocranially, penetrates the metanephric mesoderm and divides it into cell clusters, located near blind ends of the collecting tubules

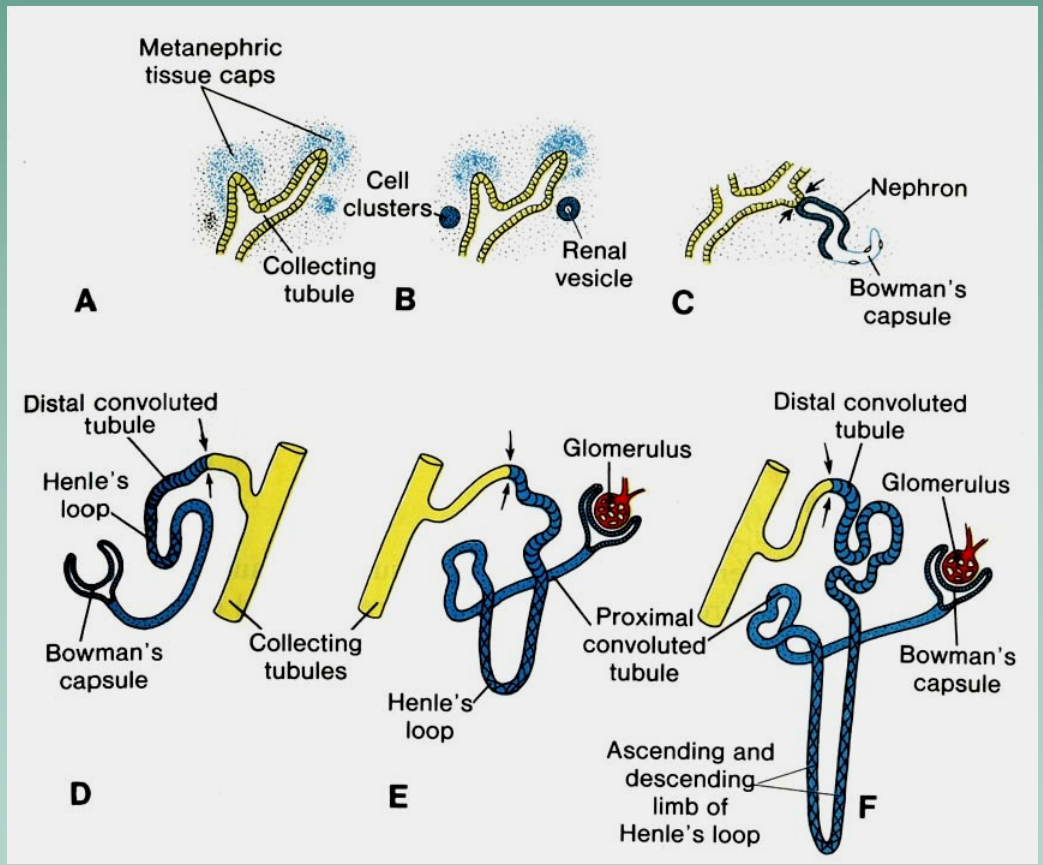
clusters of mesodermal cells become **metanephric vesicles** that are later transformed into **metanephric tubules**

the proximal part of each tubule becomes dilated
and forms the **Bowman s capsule** of a renal corpuscle, while
the distal end contacts the respective collecting tubule and both tubules become soon confluent

the remaining part of the metanephric tubule undergoes continual lengthening and gradually differentiates into definitive segments of the uriniferous tubule

the proximal tubule, the loop of Henle, and the distal tubule





Positional changes of the kidneys

kidneys develop low in the pelvis

from the 2nd trimester, they gradually come to lie in the abdomen

the migration of kidneys is mainly resulted from growth of the embryo´s body caudal to the kidneys
ascensus renis

Development of renal pelvis and ureter

both derive from the **distal part of the ureteric bud**

Development of bladder and urethra

both organs develop from the **ventral part of the cloaca**

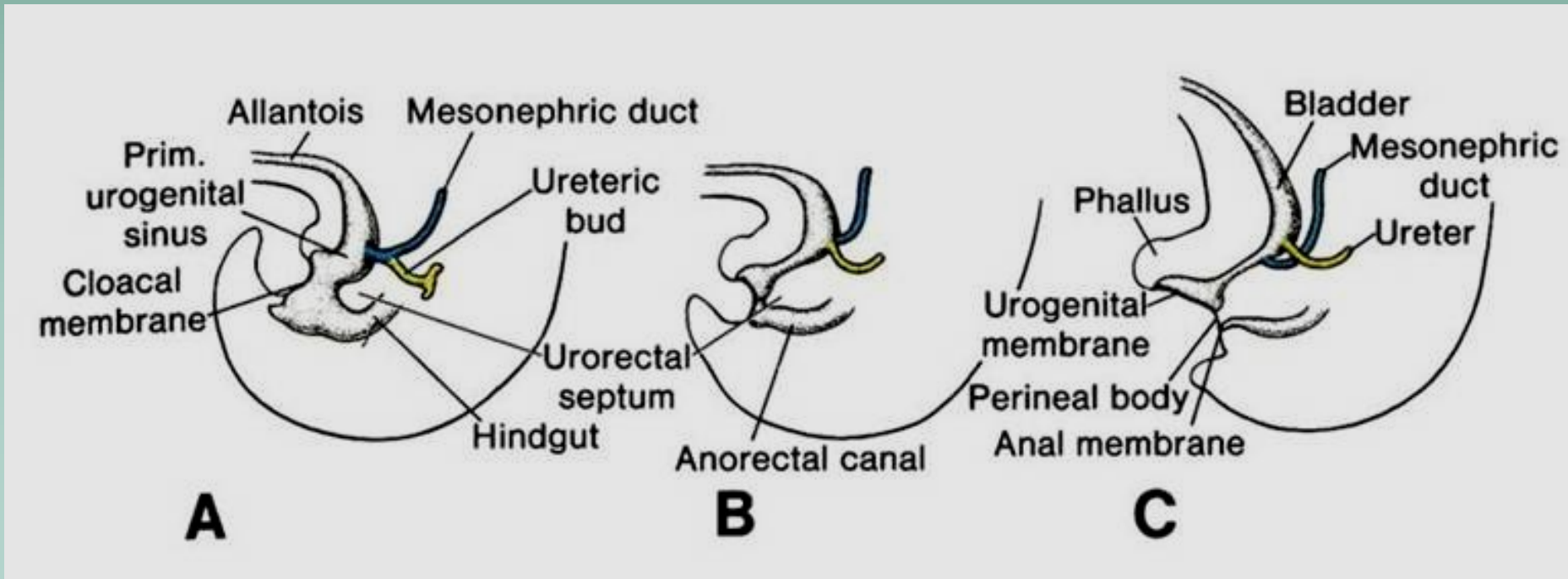
the **cloaca** is the most caudal part of the gut which is ventrally sealed off by a membrane composed of the ectoderm and endoderm - known as the **cloacal membrane**

cranially, the cloaca continues as the allantois that enters the connecting stalk

in higher vertebrates including the human, the cloaca soon divides with the **urorectal septum** (oriented frontally) into 2 portions :

- the **anorectal canal** situated dorsally - rectum,
- the **primitive urogenital sinus** situated ventrally - bladder + urethra.

the caudal part of the urorectal septum then fuses with the cloacal membrane: a part covering anorectal canal is the **anal membrane**, a part covering the primitive urogenital sinus is the **urogenital membrane**



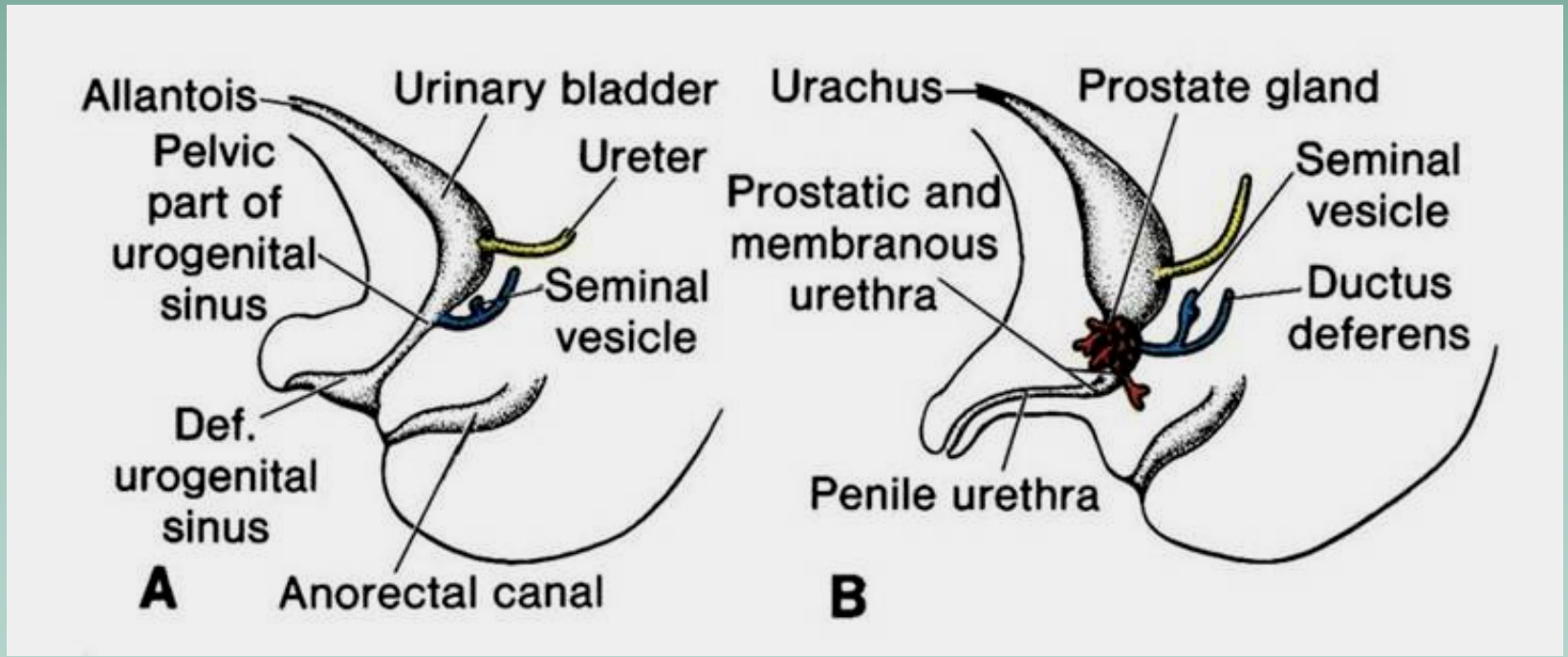
the urogenital sinus includes three parts:

- **vesical segment** (presumptive bladder - there is a wide cranial part
- **pelvic segment** - middle narrow
- **phallic segment** - it appears wide

the **vesical segment develops into the definitive bladder** - in both sexes

the pelvic segment becomes
the definitive urethra in females but **the prostatic urethra in males**

the phallic segment of the urogenital sinus becomes
the vestibule of the vagina in females but **the penile urethra in males**

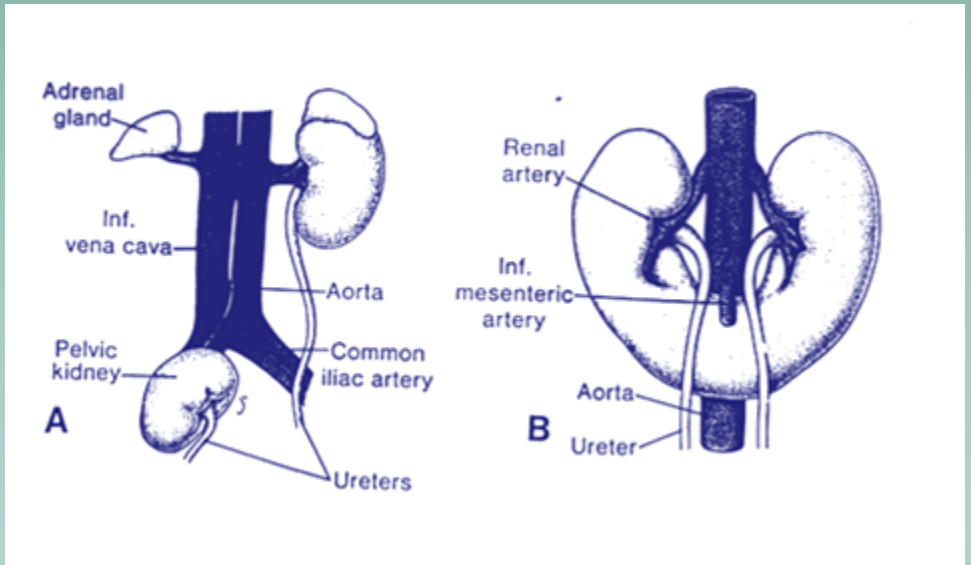


CONGENITAL MALFORMATIONS OF KIDNEYS AND URETERS

Renal agenesis = absence of a kidney
it results from failure of the ureteric bud to growout and is accompanied with an absence of the ureter
it may be uni- or bilateral
(unilateral agenesis is characterised by compensatory hypertrophy of the kidney that is present; bilateral agenesis is incompatible with survival after birth)
incidence is about 2 (3) per 10 000; is more frequent in males than females (3:1)
clinically, it is always accompanied by **oligohydramnios** which results from failure of urine production

Pelvic kidney = a kidney (s) is located in pelvis,
this malformation results from failure of the kidney to ascend

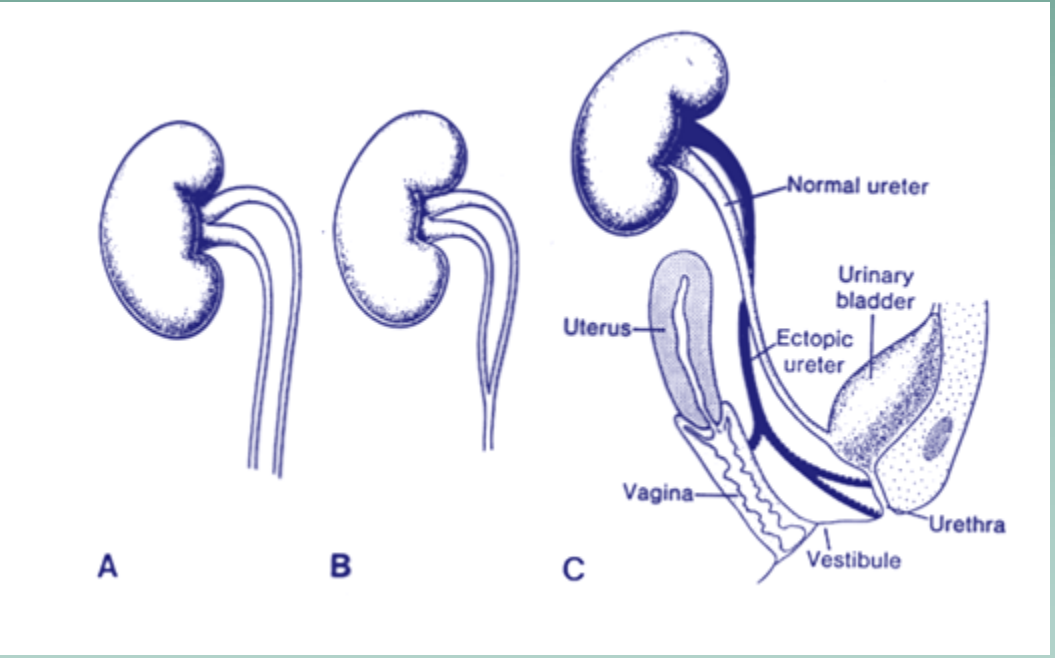
Horshoe kidney - both kidneys are fused at their inferior poles and located in pelvis (failure of kidneys ascend)
horshoe kidney is often symptomless and occurs 1 per 600 live birth.



Polycystic kidney disease = hereditary disease characterised by that one or both kidneys contain numerous small, medium - sized or large urine-filled cysts inhibiting its normal function
polycystic kidney disease may be uni- or bi-lateral
bilateral p. k. d. has almost bad prognosis because it is incompatible with survival after birth

P. k. d. is believed to result from failure of collecting tubules and uriniferous tubules to join up.
Polycystic kidney disease occurs in two hereditary forms. One is autosomal recessive or **infantile**, the other is autosomal dominant, or **adult**.

Duplication of the ureter -
ureter duplex
and **bifid ureter** (ureter fissus)

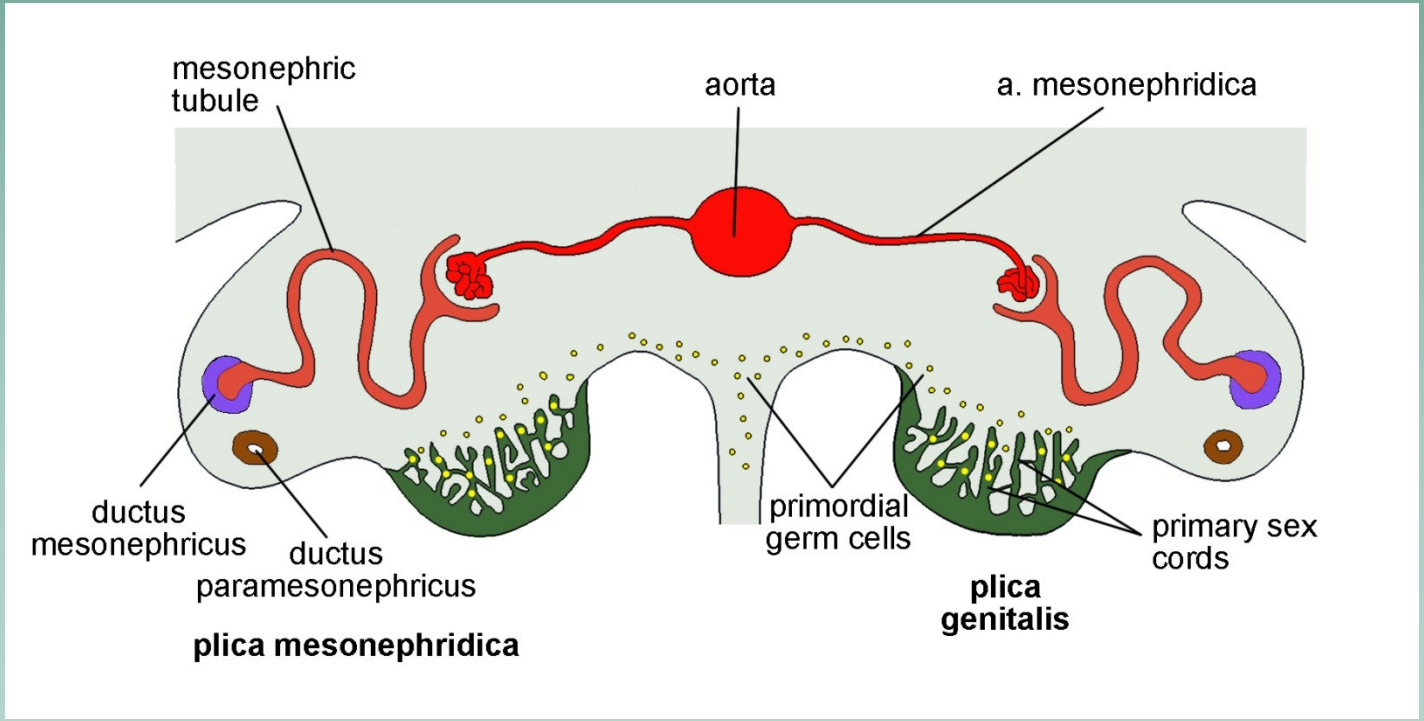


DEVELOPMENT OF INTERNAL SEXUAL ORGANS (gonads and ducts)

the early genital system is similar in both sexes, and this initial period is referred to as **the indifferent stage**
it lasts approximately up to the first half of the 3rd month (10th week) of the fetal development

the stage is characterized by presence of 3 embryonic organs:

- **the indifferent gonad anlage**
- **the mesonephric duct (Wolffian duct) + remnants of mesonephric tubules**
- **the paramesonephric duct (Müllerian duct)**



The indifferent gonad anlage lies within the **gonadal (genital) ridge** that is bilateral organ

the gonadal ridge is a mesenchymal structure located on the medial side of the mesonephros (urogenital ridge); initially is of the same length as the mesonephros, but portion from C_6 to L_2 then rapidly degenerates, the caudal part (S_1-S_3) is transformed in the gubernaculum

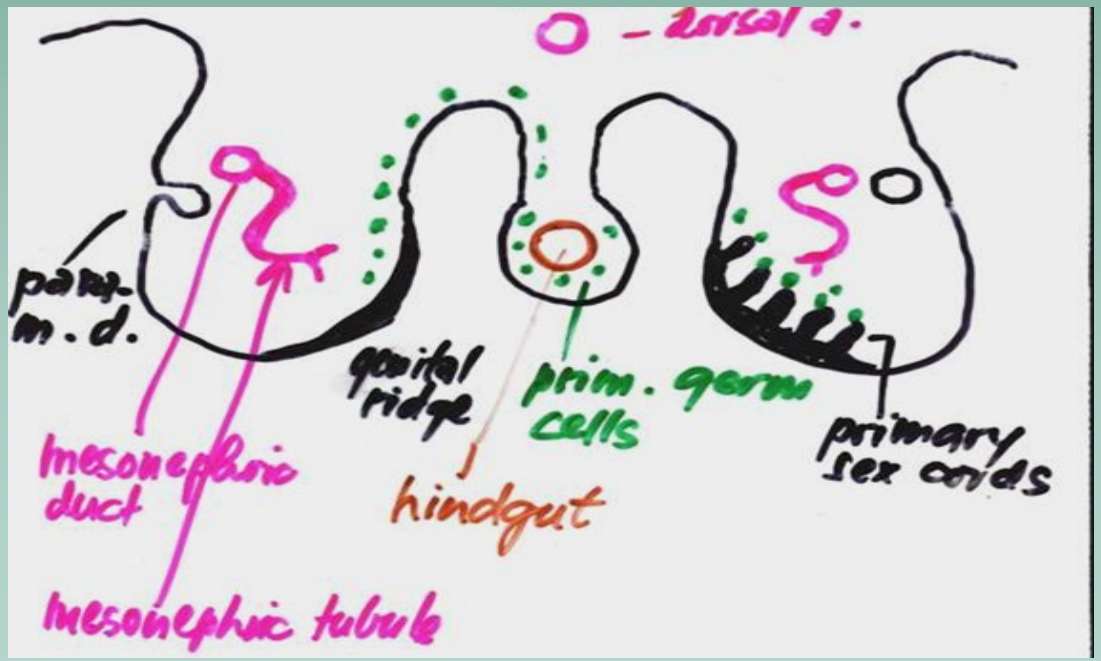
a segment of the ridge extending between **L_3-L_5** forms an **anlage of the future gonad** and is early invaded with **primordial germ cells** (PGCs)

PGCs differentiate outside the body (in the **yolk sac** and the gut) and migrate into indifferent gonad anlage by week 6

a surface of the future gonad is covered with a coelomic epithelium that thickens and proliferates in the underlying mesenchyma in the form finger-like epithelial cords - called **primary sex cord**

the indifferent gonad consists of an outer cortex and an inner medulla

The mesonephric duct and remnants of mesonephric tubules - persist from the "midkidney" stage.

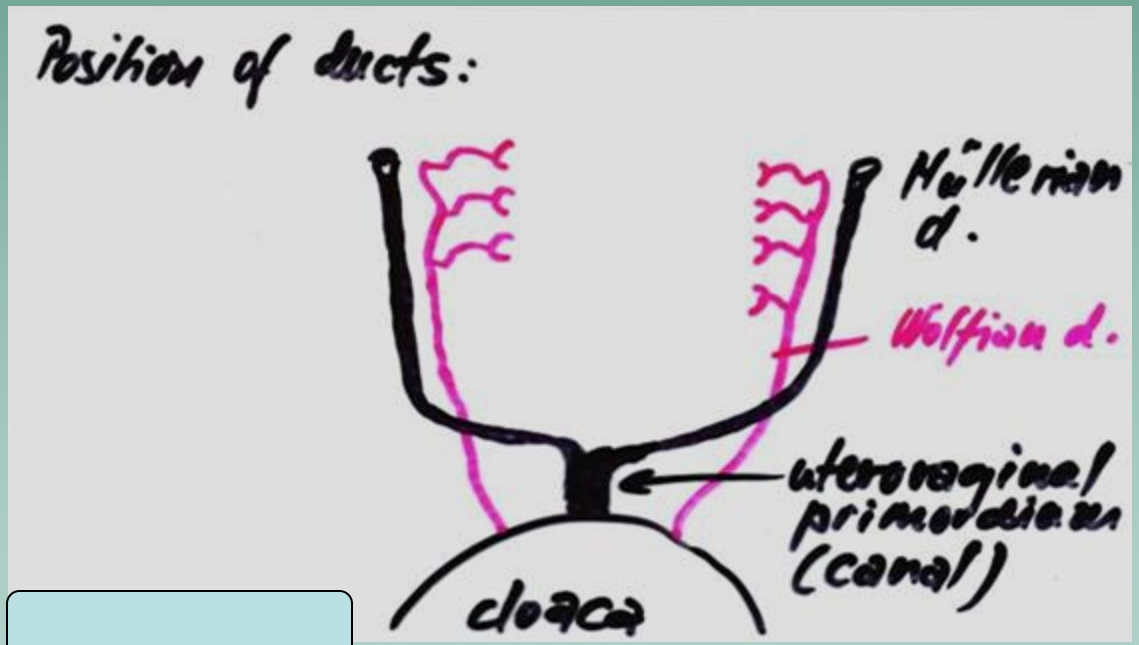


The paramesonephric duct is primitive genital duct that develops from the longitudinal invagination of coelomic epithelium covering the lateral aspect of the genital ridge (on each side)

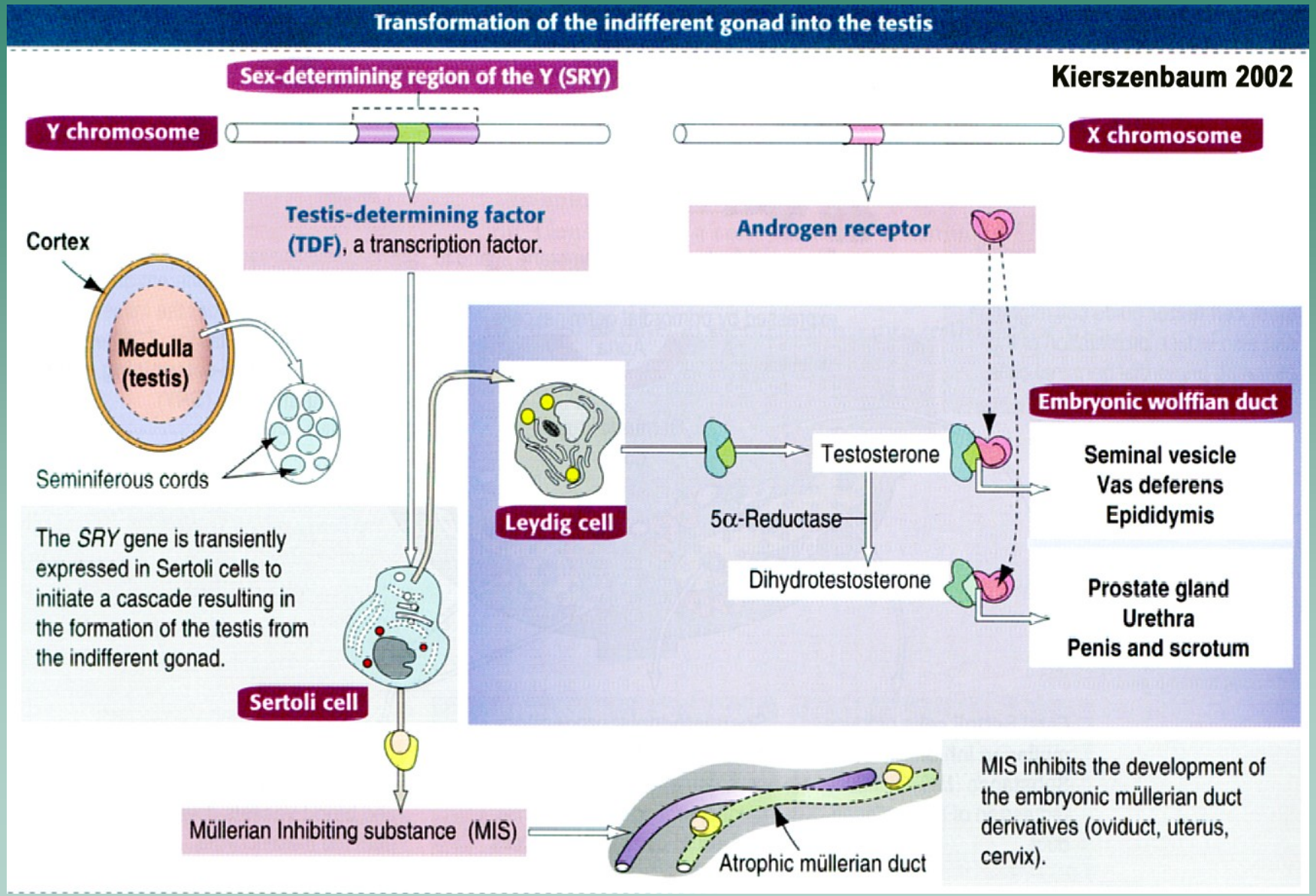
the proximal end opens into the coelomic, future peritoneal, cavity, the caudal end runs parallel to the mesonephric duct

in the small pelvis ducts cross ventral to the mesonephric ducts, come together in the midline, and fuse into Y-shaped **uterovaginal primordium** or **canal**

(the primordium projects into the dorsal wall of the urogenital sinus and produces an elevation, called the sinus tubercle)

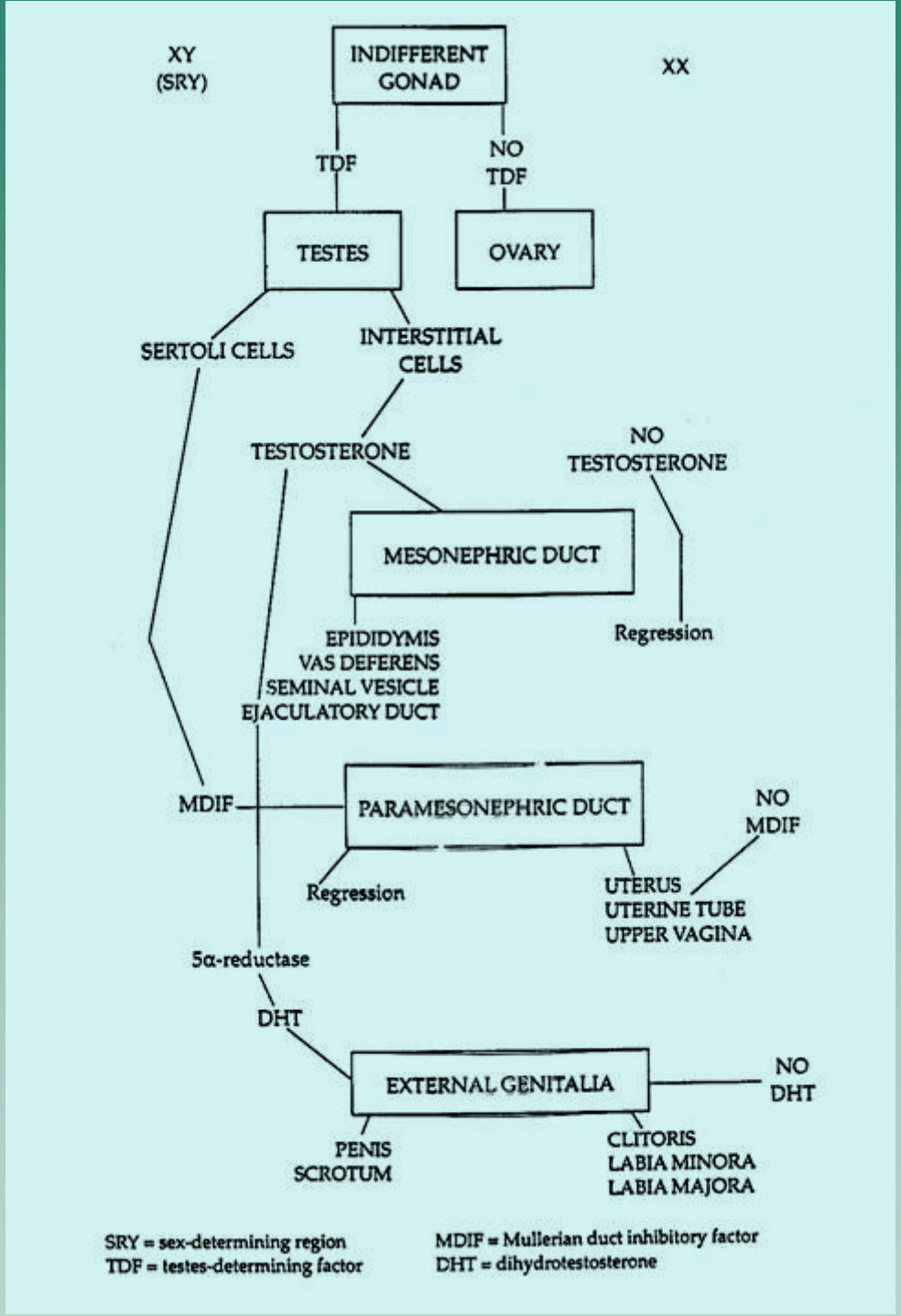


if the indifferent gonad anlage will develop in the testis or ovary, depends on the presence or absence of a Y chromosome



in presence of a Y chromosome, the **gonad anlage differentiates into the**

testis



the absence of a Y chromosome results in differentiation of the

ovary

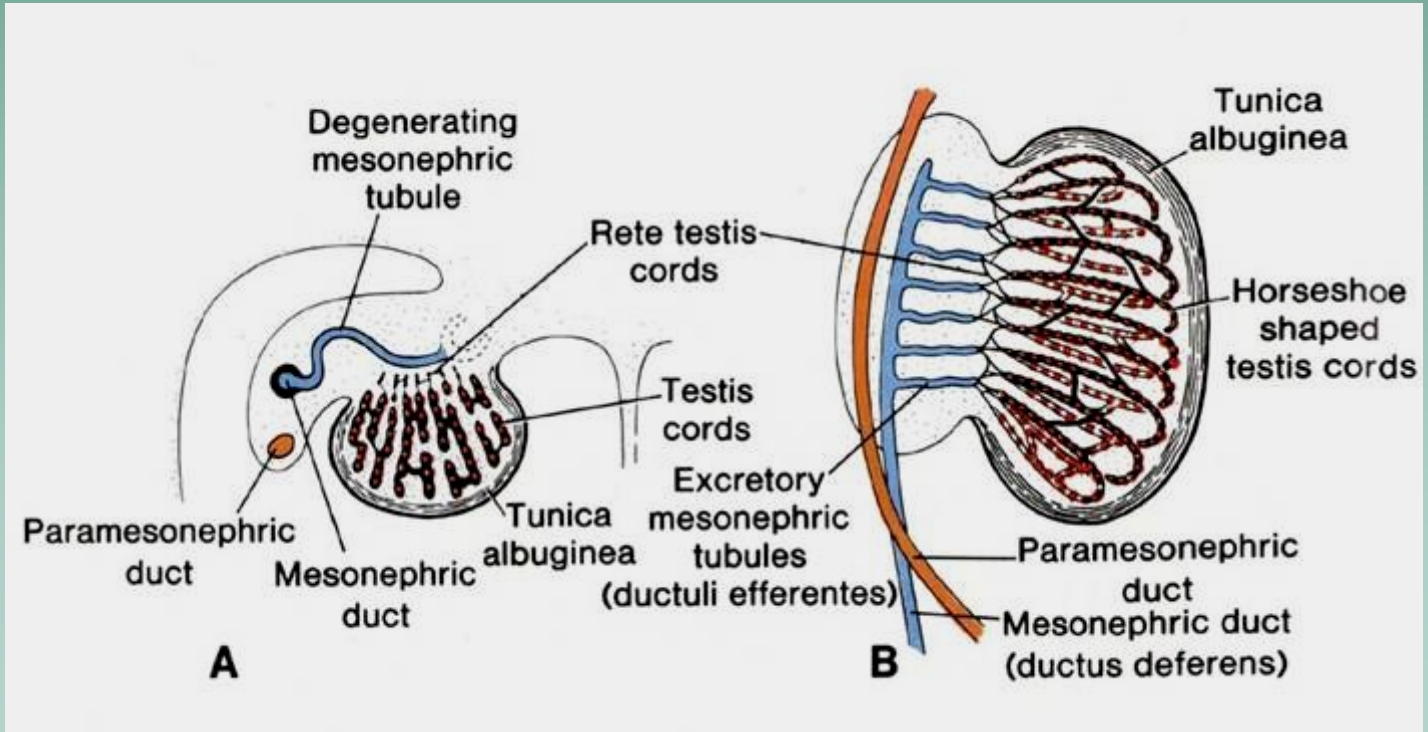
Development of testes

in embryos with a Y chromosome, the primary sex cords lose their connections with the coelomic epithelium and persist as the **testicular cords** that soon undergoe transformation into the **seminiferous tubules**

cells of the seminiferous tubules differentiate in the Sertoli cells, PGCs give rise to spermatogonia

the interstitial (Leydig) cells arise from the mesenchyma of indifferent gonad anlage

the tunica albuginea is developed early as a condensation of the mesenchyma lying between the coelomic epithelium and seminiferous tubules



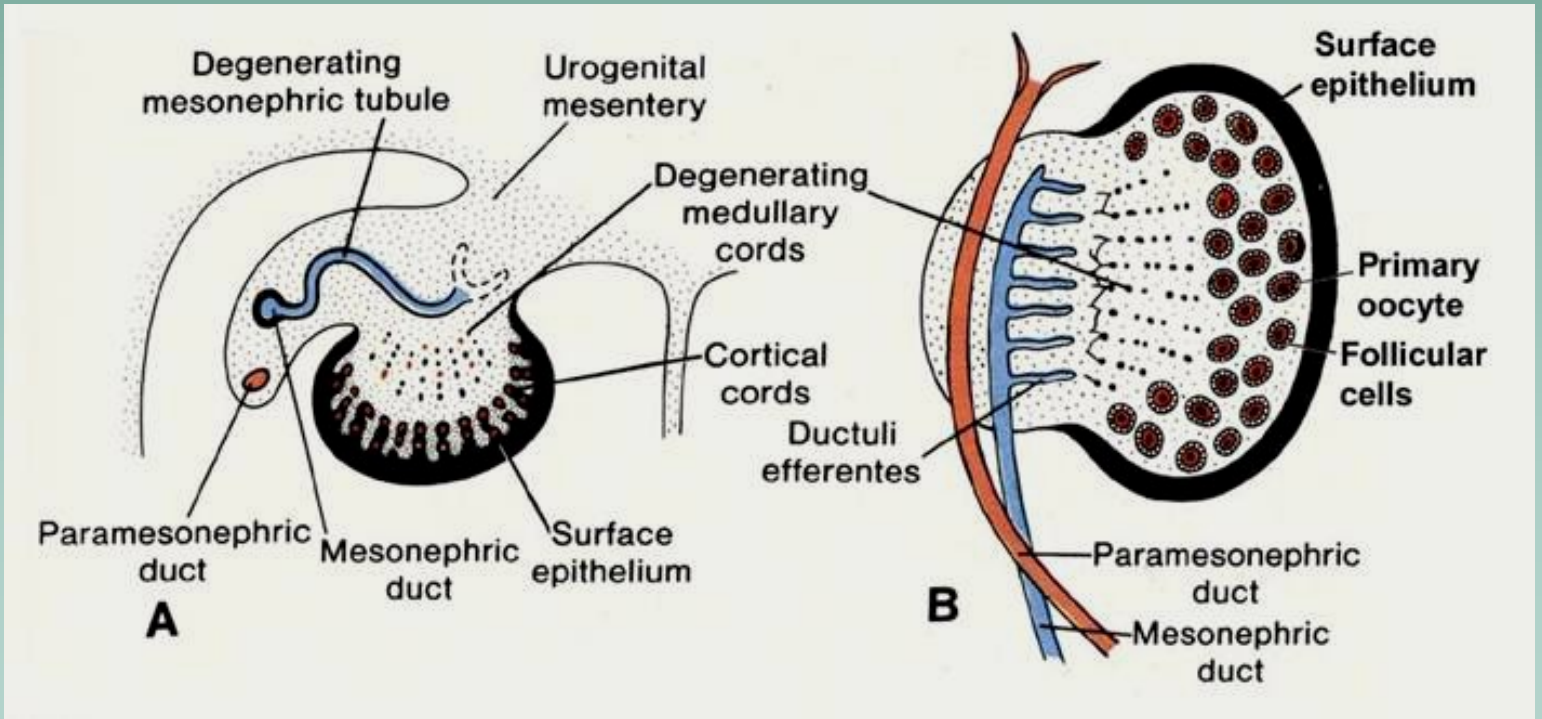
Development of ovaries

in embryos lacking a Y chromosome, the primary sex cords degenerate and migrate in the medulla in which form a rudimentary rete ovarii

the superficial coelomic epithelium sends off new sex cord, called **secondary** or **cortical sex cords**

these separate from it and are differentiated into the **follicular cells** which, in association with PGCs, form the **primordial ovarian follicles**

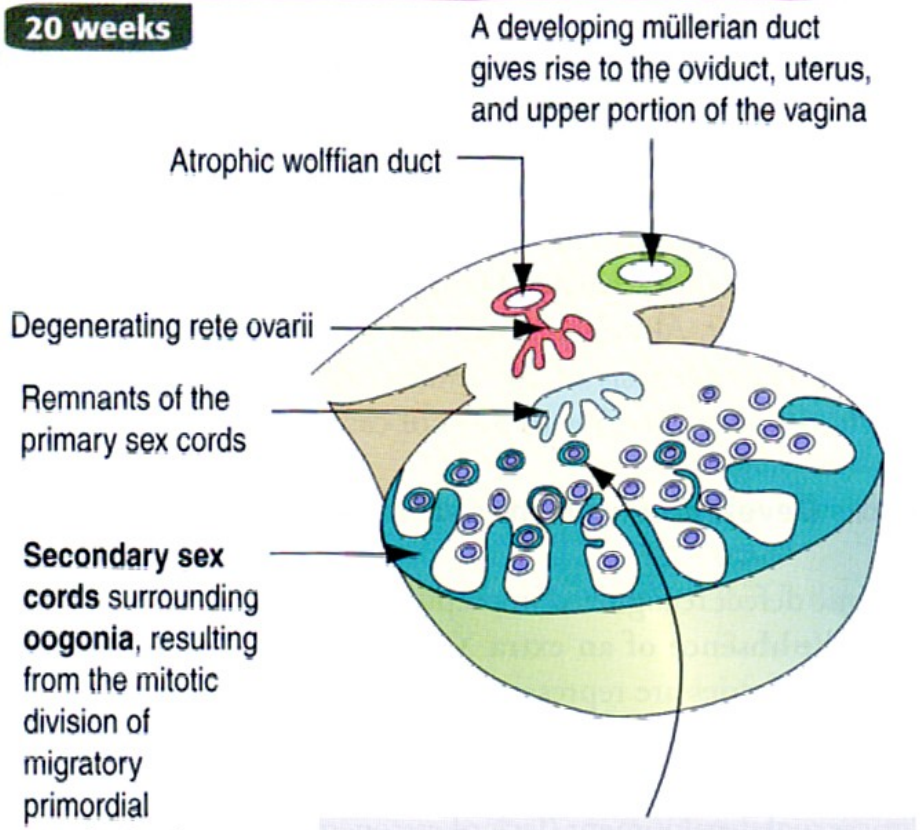
the mesenchyma extending between the surface epithelium and ovarian follicles gives rise to the thin fibrous capsule - tunica albuginea



From the indifferent gonad to the ovary and testis

Development of the ovary: Absence of TDF and müllerian inhibiting factor

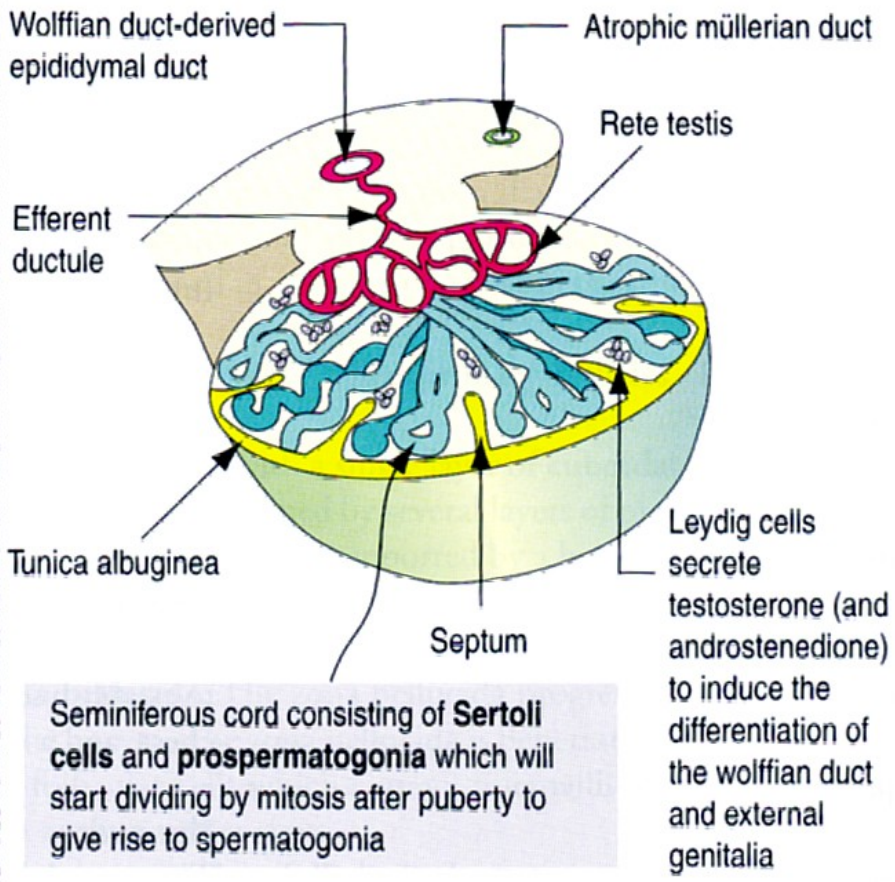
20 weeks



Development of the testis: Presence of both TDF and müllerian inhibiting factor

20 weeks

Kierszenbaum 2002



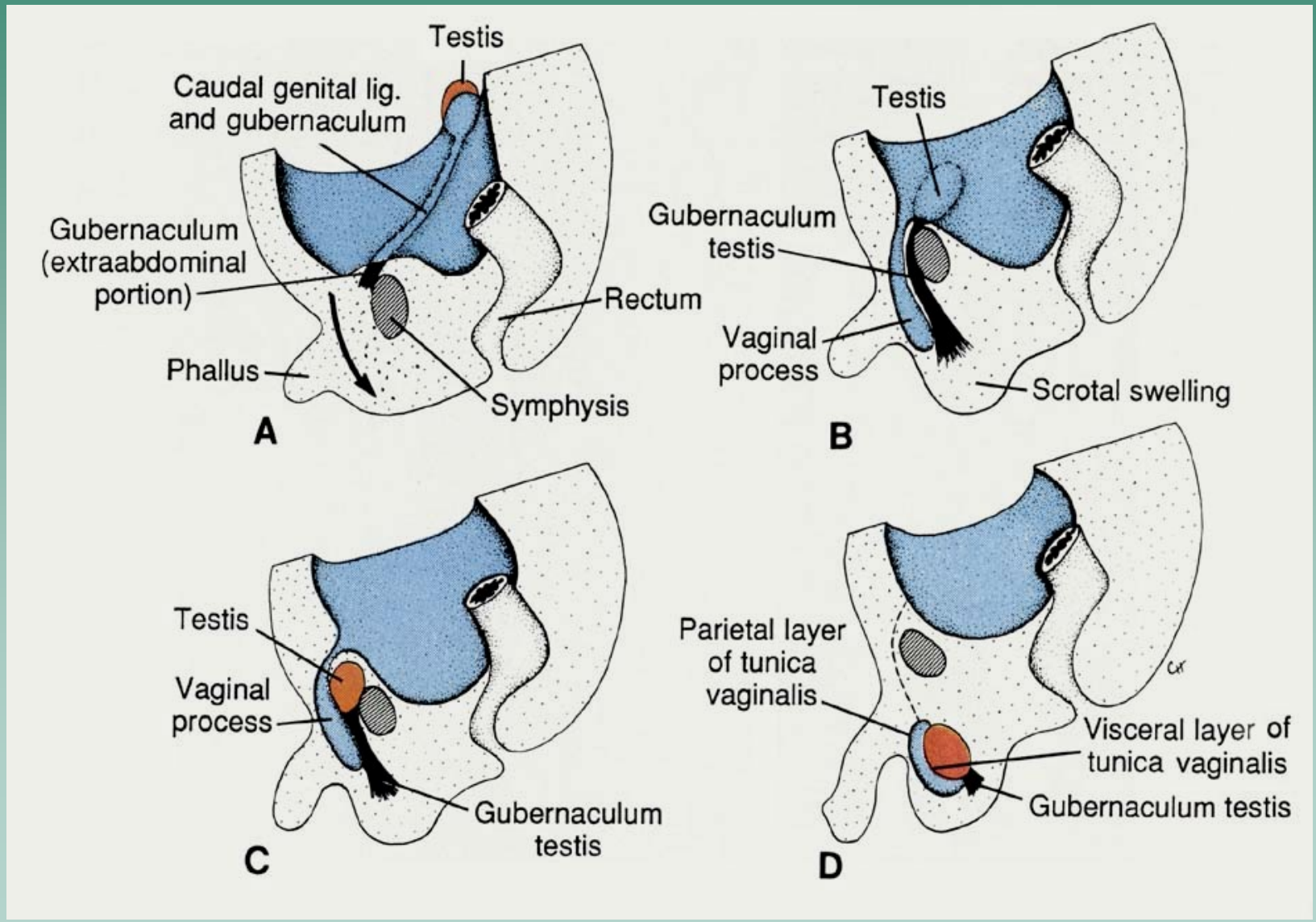
Descent of testis

by the 28th week

from the peritoneal cavity to the scrotum

Descent of ovary

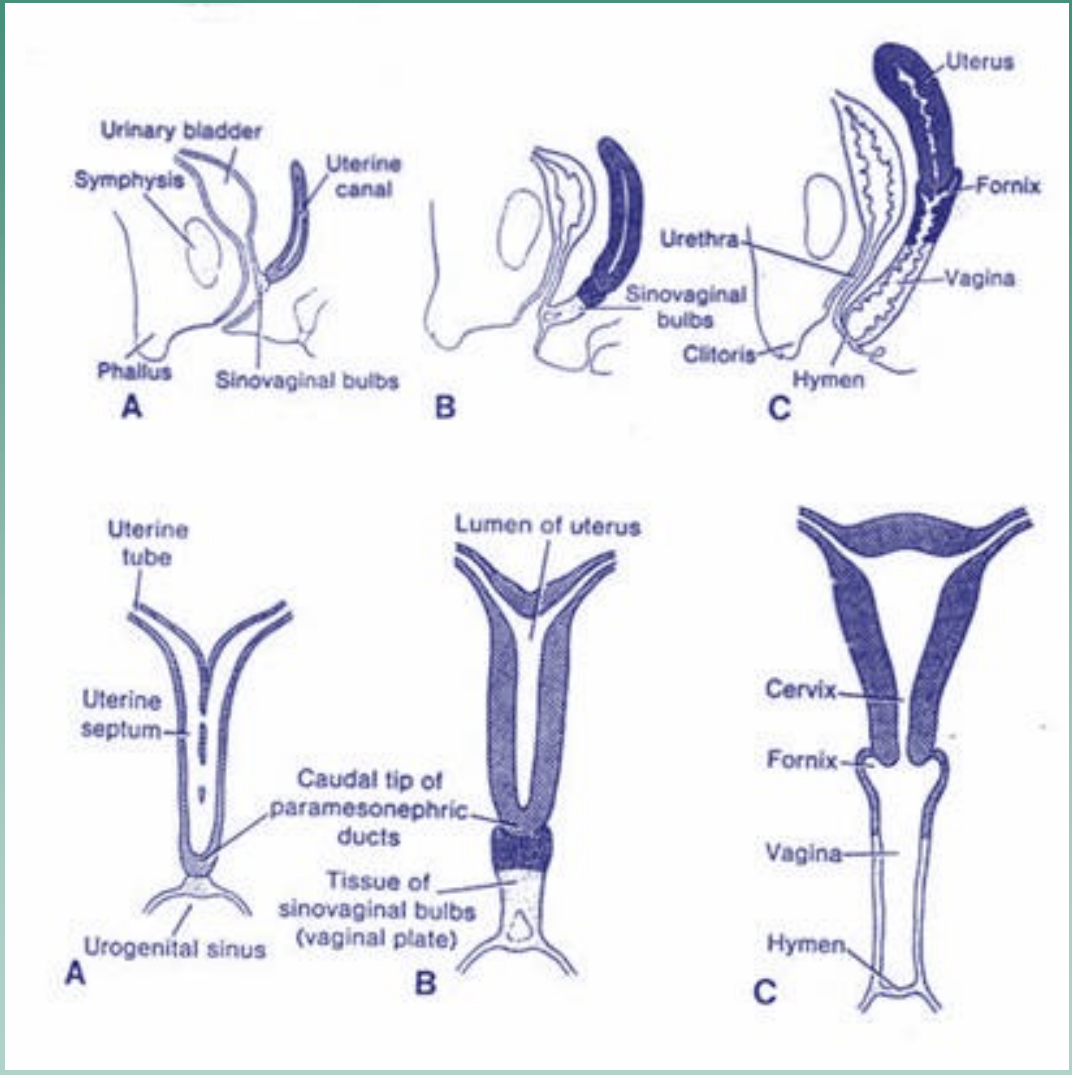
to the small pelvis



Development of genital ducts

in the presence of a Y chromosome **male sex**	**indifferent stage**	the absence of a Y chromosome **female sex**
are transformed into **efferent ductuli** (ductuli efferentes)	**remnants of mesophric tubules**	regress (tubules may persist as **epoophoron** and **paroophoron**)
becomes the **ductus epididymidis**, **ductus deferens** and **ejaculatory duct**	the **mesonephric (Wolffian) duct**	regresses cranial end of the duct may persists as appendix vesiculosa, caudal part as the **duct of Gartner**
regresses (rarely it may give rise to a rudimentary **appendix testis**)	the **paramesonephric duct** **unfused portion**	the **oviduct** (fallopian tube)
regresses (rarely **utriculus prostaticus**)	**the uterovaginal primordium**	the **uterus** + **cranial part of the vagina**

Derivatives of the paramesonephric duct:

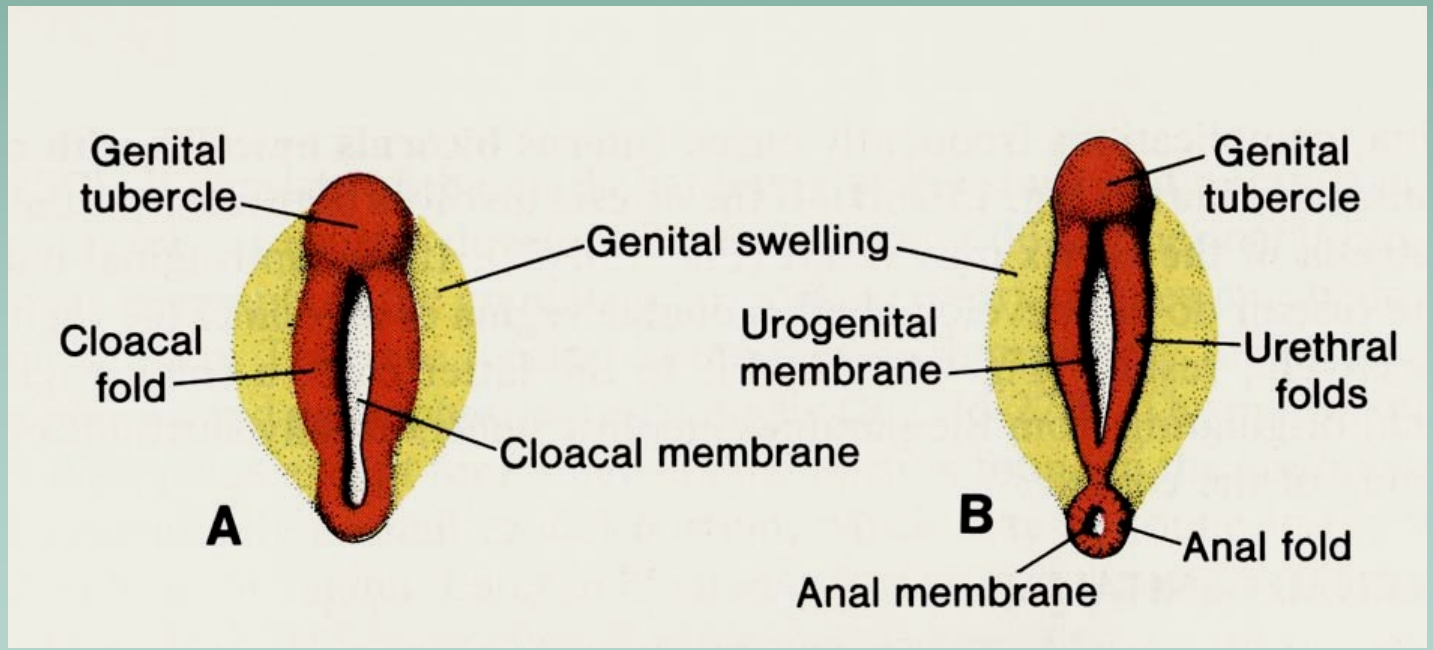


Development of external genitalia - indifferent stage

external genitalia undergoe the indifferent stage similar as gonads and genital ducts

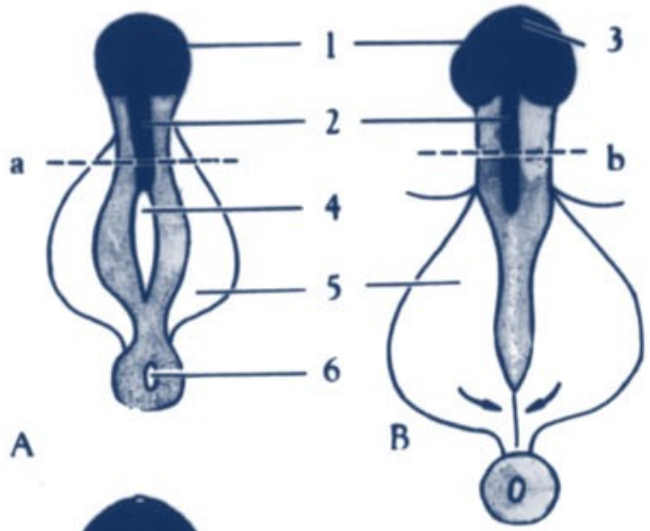
the indifferent stage is characterised by

- a **genital tubercle** - is situated at the cranial end of the cloacal membrane
  it rapidly grows and elongates to form the **phallus**
- the **cloacal** (**urogenital) folds** - are paired and demarcate the urogenital orifice
- the **labioscrotal swellings** - are located laterally to the urogenital folds on each side

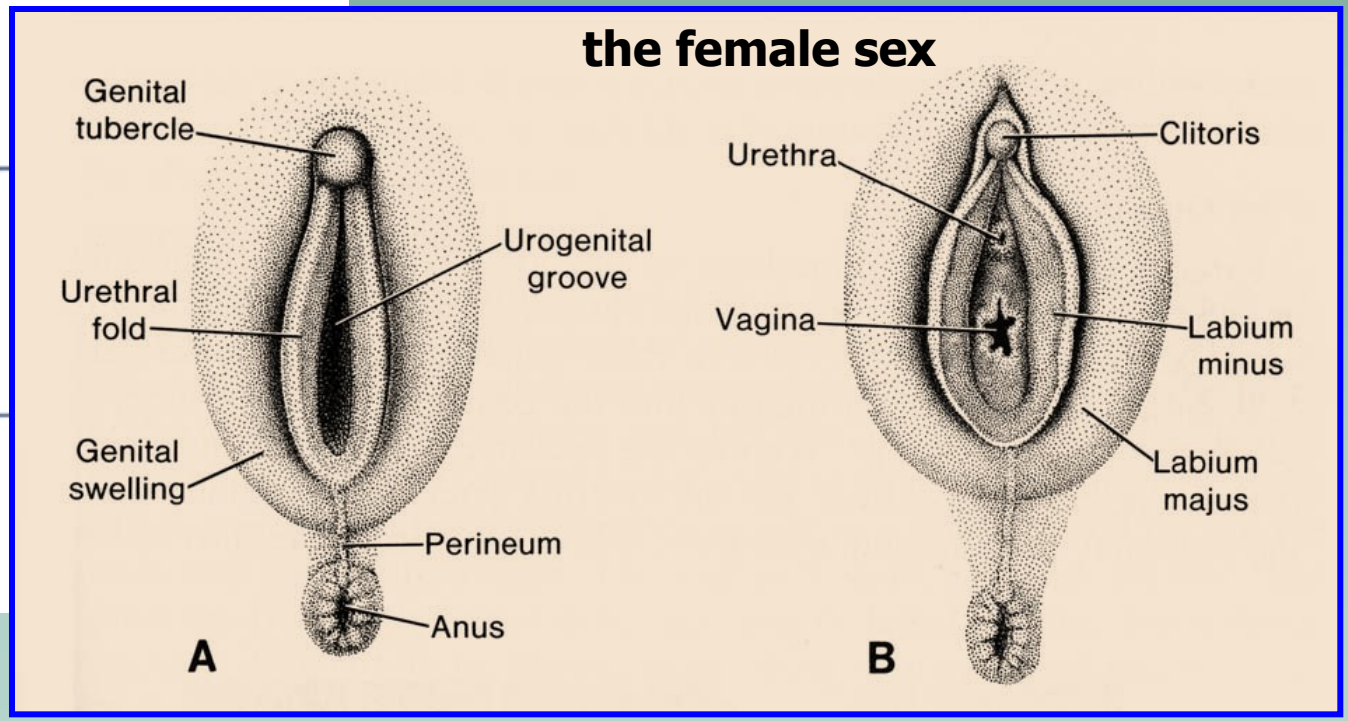


male sex	indifferent stage	female sex
gives rise to **the penis**	**the phallus**	grows slowly and is transformed in **the clitoris**
fuse in midline and close the urogenital orifice – **the cavernous urethra**	**urogenital folds**	do not fuse and form the **labia minora**
grow toward each other and fuse to form **the scrotum**	**labioscrotal swellings**	remain unfused similar to folds and form the labia majora

the male sex



the female sex



OVERVIEW OF CONGENITAL MALFORMATIONS OF GENITAL ORGANS

because an early embryo has the potential to develop as either a male or a female, errors in sex development may result in intermediate sex, a condition known as **intersexuality**, or **hermaphroditism**

a person with ambiguous external genitalia is called **intersex**, or a **hermaphrodite**

true hermaphrodites - have both ovarian and testicular tissue (ovotestis)
occur extremely rare

false hermaphrodites or **pseudohermaphrodites** - occur about once in 25,000 birth

two forms are distinguished:

- **female pseudohermaphrodites** - have 46,XX karyotype and ovaries, but external genitalia resemble masculine genitalia (hypertrophied clitoris, the labia majora are partially fused, the persistent urogenital sinus)

  malformation mostly occurs in the form of the **adrenogenital syndrome**, resulting from congenital virilizing adrenal hyperplazia

- **male pseudohermaphrodites** - 46,XY constitution, they have testes, but external genitalia resemble in various degree of female genitalia

  is caused by inadequate production **of testosterone, androgen receptor disorders, 5-α reductase deficiency** or **MDIF deficiency**

Malformations occuring in males:

cryptorchidism - (undescended testes) - is found in one in three premature male babies or in one in 30 full-term males

testes are retained in the abdominal cavity or in the inguinal canal

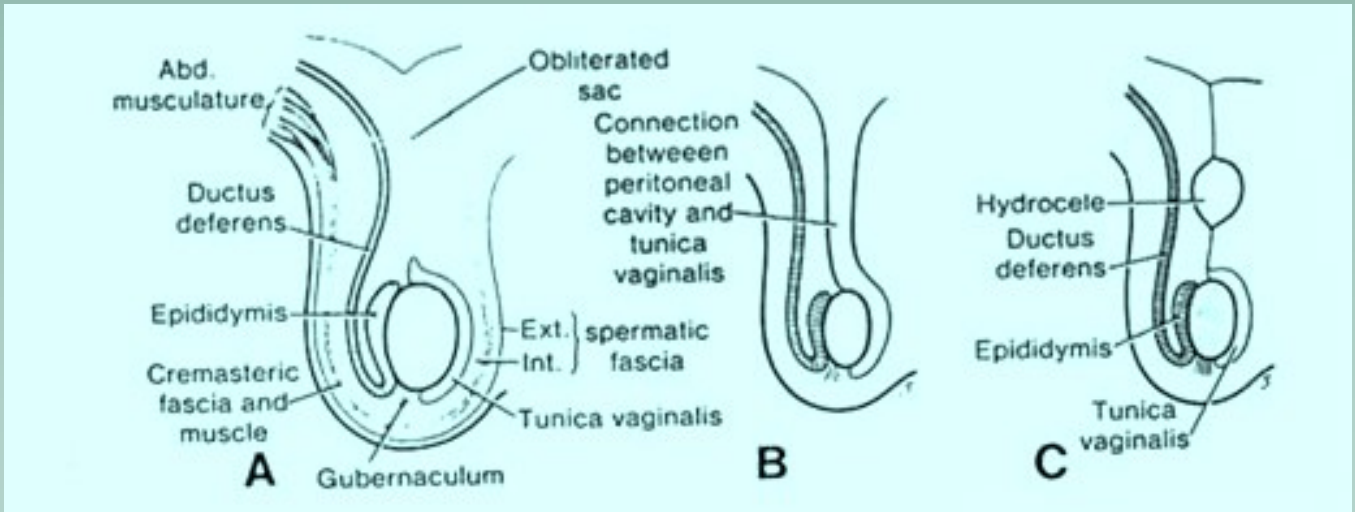
sterility is resulting if the condition persists to the puberty

anomaly may repair spontaneously, if not, the surgical treatment must follows

congenital inguinal hernia - occurs in the case of **unclosed processus vaginalis**, which connects the tunica vaginalis with the peritoneal cavity

if the abdominal pressure is increased, then intestinal loops herniate through it into the scrotum (rarely labium majus), congenital inguinal hernia is often accompanied with cryptorchidism

hydrocele - if the abdominal end of the processus vaginalis remains open, the peritoneal fluid passes into it and forms a hydrocele of the testis and spermatic cord



hypospadias - a malformation in which the external urethral orifice is on the ventral surface of the penis instead of at the tip of the glans

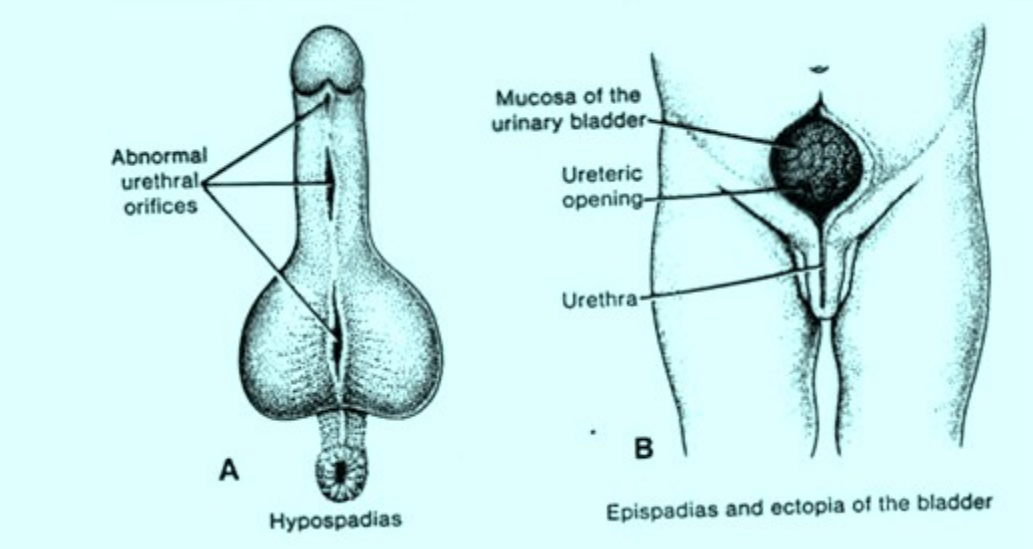
it occurs one in about every 300 males

4 types of hypospadias: glandular, penile, penoscrotal, and perineal

(the glandular and penile constitute about 80 per cent of cases)

epispadias - is a malformation in which the urethra opens on the dorsal aspect of the penis and is often associated with **extrophy of the bladder**

it occurs once in about 30,000 male infants



agenesis of the penis - extremely rare malformation results from failure of the genital tubercle to develop

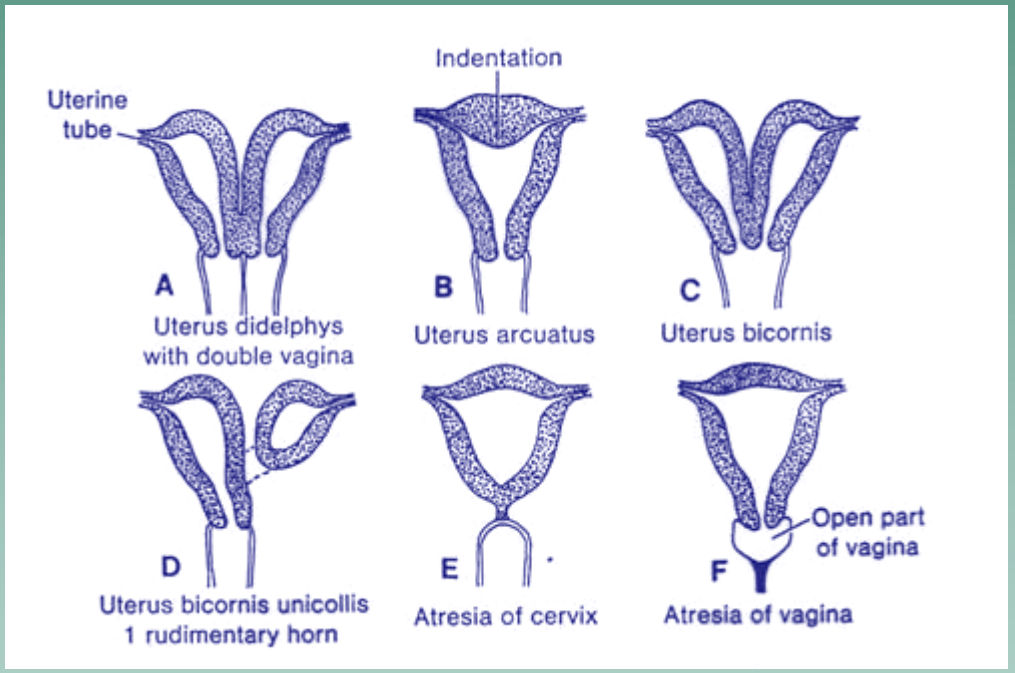
bifid penis and double penis - very rare - distal part of the penis is divided into two portions, it results from failure of fusion of two parts of the genital tubercle (if two genital tubercles do not fuse - it develops **double penis)**

micropenis - the penis is so small that it is almost hidden by the suprapubic pad of fat ; it is usually associated with hypopituitarism and hormonal deficiency of the fetal testes

Malformations occuring in females:

ectopic ovary - the ovary shows abnormal location, rare
uterovaginal malformations - result from
(1) improper fusion of both paramesonephric ducts
(2) incomplete development of one paramesonephric duct
(3) failure of parts of one or both ducts to develop
(4) incomplete canalization of the vaginal plate

- *double uterus (uterus didelphys)*
- *bicornuate uterus*
- *unicornuate uterus with one uterine tube*
- *absence of the uterus*
- *absence of the vagina - once in about every 4000 females*
- *vaginal atresia - results from failure of canalization of the vaginal plate*



anorectal agenesis and fistulas - the rectum ends well above the anal canal and is connected to the vagina with a fistula (rectovaginal fistula)
is the most common type of anorectal malformations