Renal Development

Including the development of the associated ducts and the bladder

The urinary system includes:

Kidneys which produces and excretes urine – also have a gland function

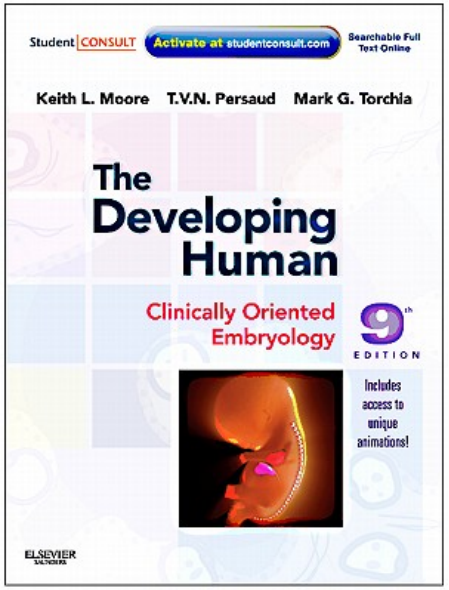
Ureters, which convey the urine to the bladder

Bladder, which stores the urine

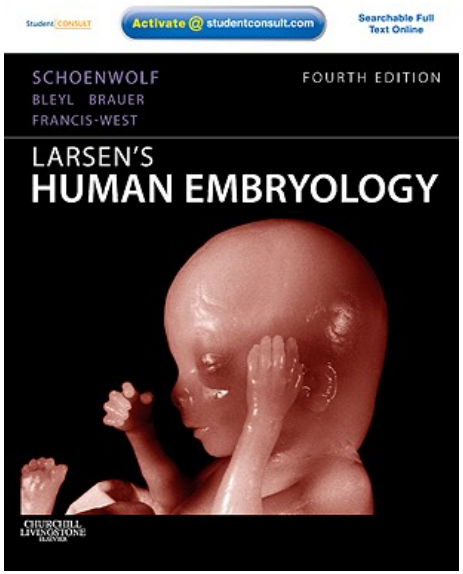
Urethra, connection from the bladder to external

Objectives

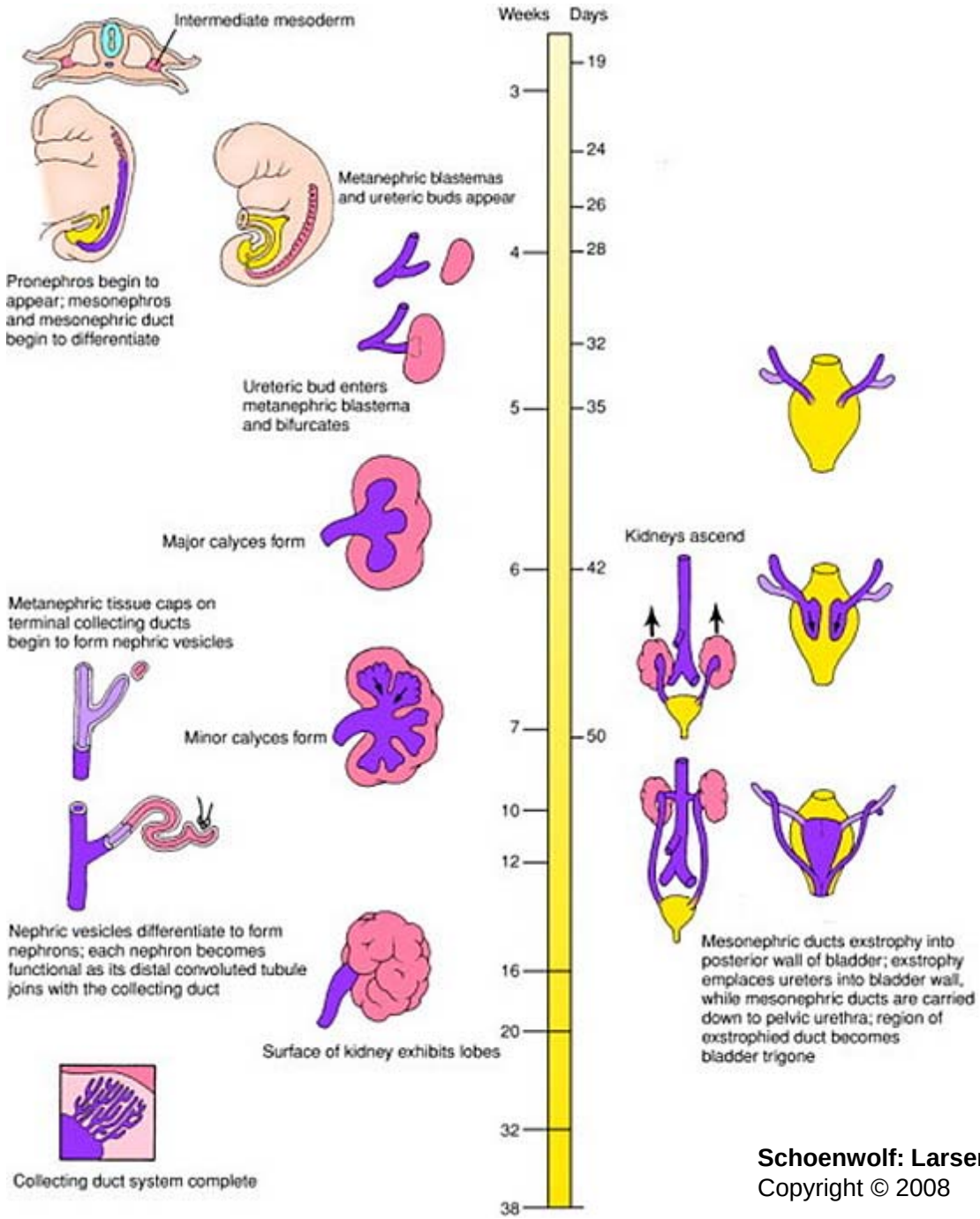
- The origin of kidneys
- Understand the 3 main stages of kidney development.
- Understand development of the nephron.
- Brief understanding of the mechanisms of nephron development.
- Understand the development of the cloaca, ureter and bladder.



Citation: The Developing Human: clinically oriented embryology 9th ed. Keith L. Moore, T.V.N. Persaud, Mark G. Torchia. Philadelphia, PA: Saunders, 2011.
Chapter 12 - Urogenital System



Citation: Larsen's human embryology 4th ed. Schoenwolf, Gary C; Larsen, William J, (William James). Philadelphia, PA : Elsevier/Churchill Livingstone, c2009.
Chapter 15 - Development of the Urogenital System



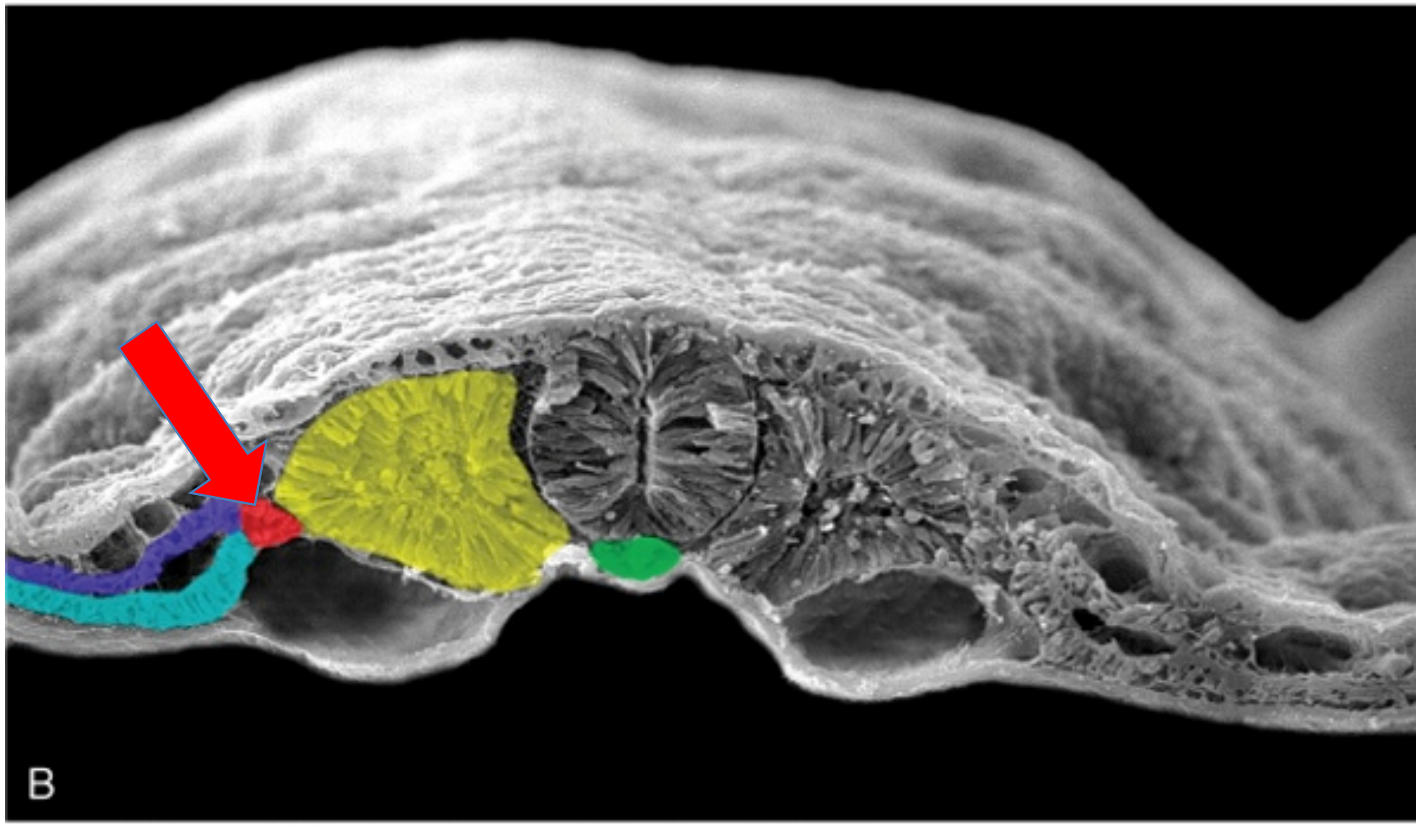
Overview and timeline of Kidney, duct and bladder development

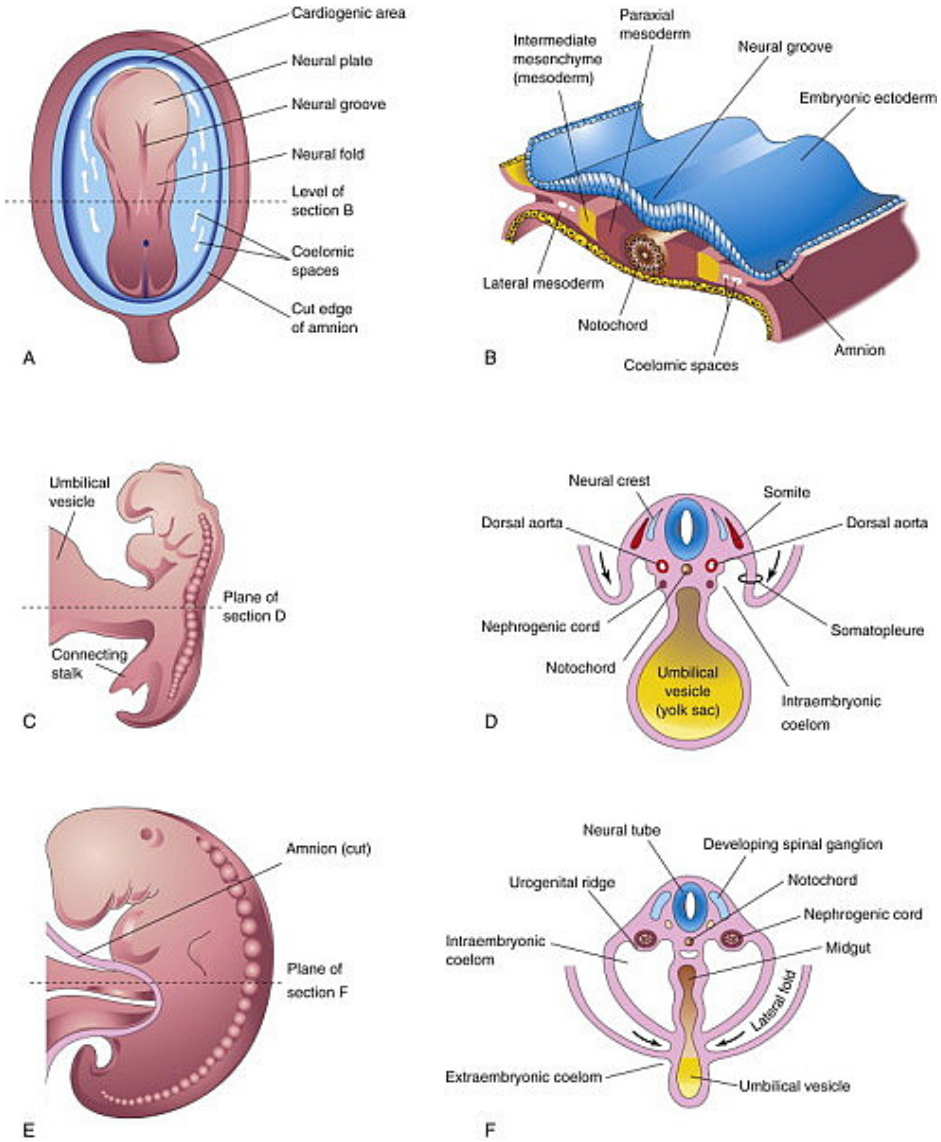
Like lung development, much of the cellular changes occur during the fetal stages.

Kidney function is provided by the placenta before birth.

Schoenwolf: Larsen's Human Embryology, 4th ed.

Intermediate mesoderm





The urogenital system arises within the intermediate mesoderm

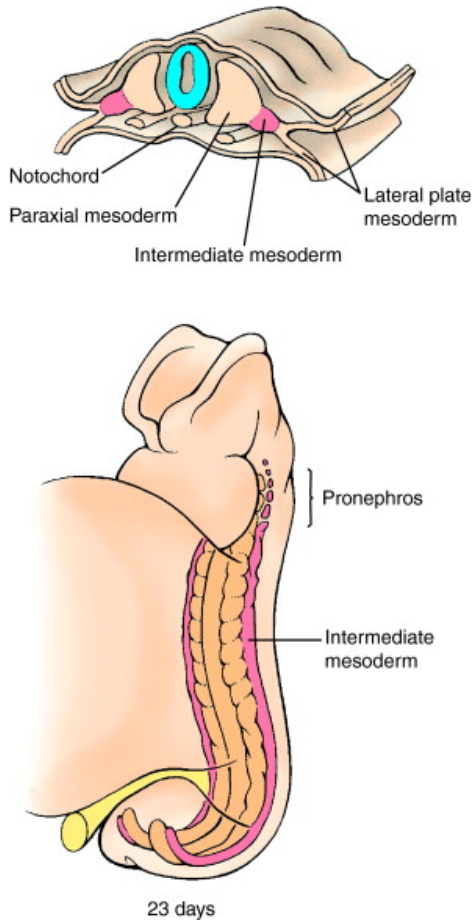
At later stages the intermediate mesoderm bulges into the coelomic cavity to form a **urogenital ridge**

Urinary system forms retroperitonealy from the **nephrogenic cord**

Gonads from from the **genital ridge**

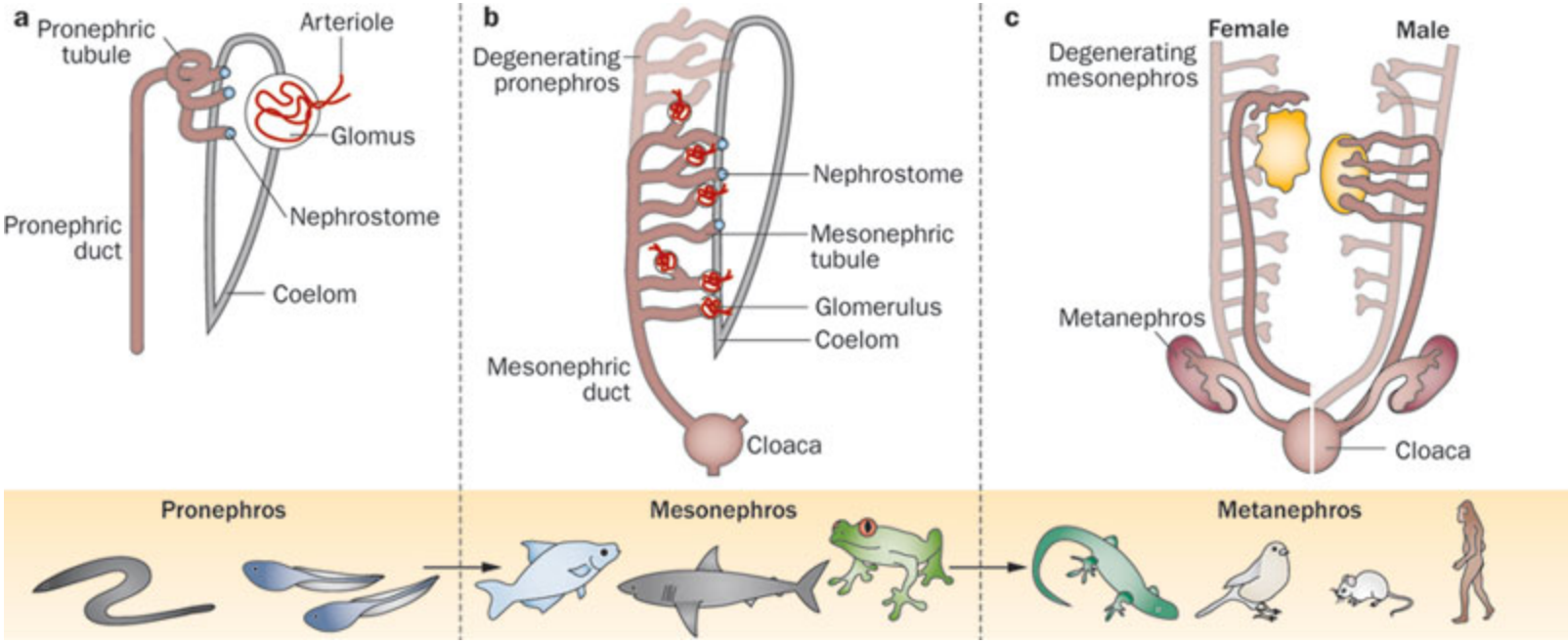
From Moore KL, Persaud TVN, Shiota K: Color Atlas of Clinical Embryology, 2nd ed. Philadelphia, WB Saunders, 2000.

The urogenital system involves the formation of 3 sets of kidneys in succession
Pronephros>Mesonephros>Metanephros



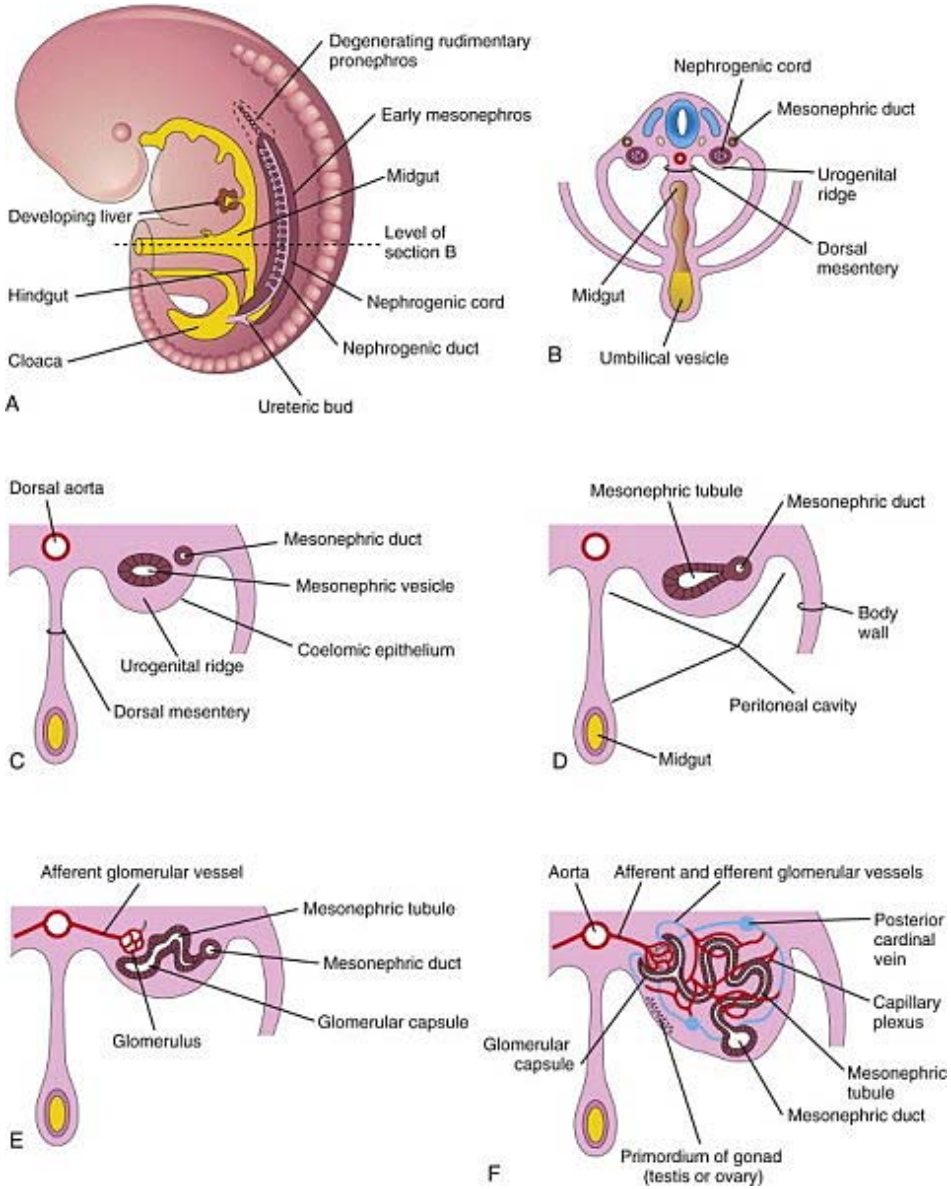
Pronephros (pronephroi) begins 23 days
Cervical nephrotomes form in 5-7 cervical segments
Transient and nonfunctional disappear by day 24-25
Forms the origin of the **mesonephric duct** – sometimes called **Wolffian duct** (Caspar Friedrich Wolff, Embryologist 1733-1794)

Schoenwolf: Larsen's Human Embryology, 4th ed.



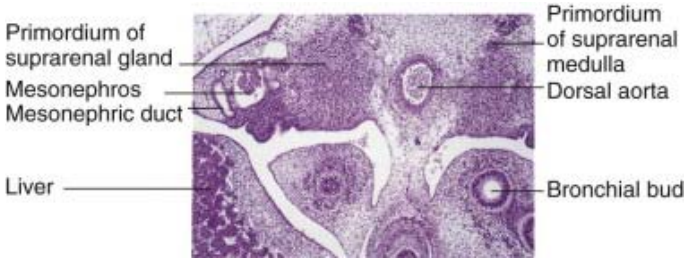
a. The pronephros is the most immature form of kidney; it represents the first stage of kidney development in most animal species, but became functional only in ancient fish, such as lampreys or hagfish, or during the larval stage of amphibians.
b. The mesonephros represents the second stage of kidney development in most animal species, and represents the functional mature kidney in most fish and amphibians. It is made up of an increased number of nephrons, usually dozens to hundreds.
c. The metanephros represents the last stage of kidney development after degeneration of the pronephros and mesonephros in reptiles, birds and mammals, where it persists as the definitive adult kidney; it consists of a substantially increased number of nephrons, usually from thousands to millions.

Paola Romagnani, Laura Lasagni & Giuseppe Remuzzi
Nature Reviews Nephrology 9, 137-146 (March 2013)



The mesonephros (mesonephroi)

Develops early 4th week
Upper thoracic to 3rd lumbar
About 40 tubules altogehter
More cranial ones regress
Form primitive nephrons
These connect with the mesonephric duct
Become moderately functional at week 6 and then regress week 10



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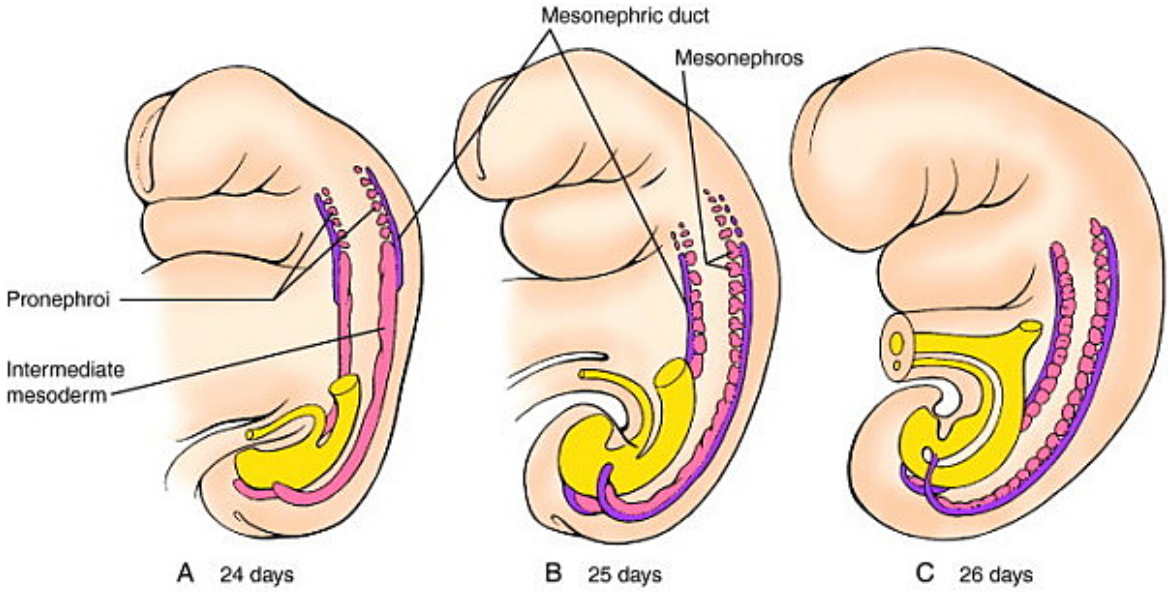
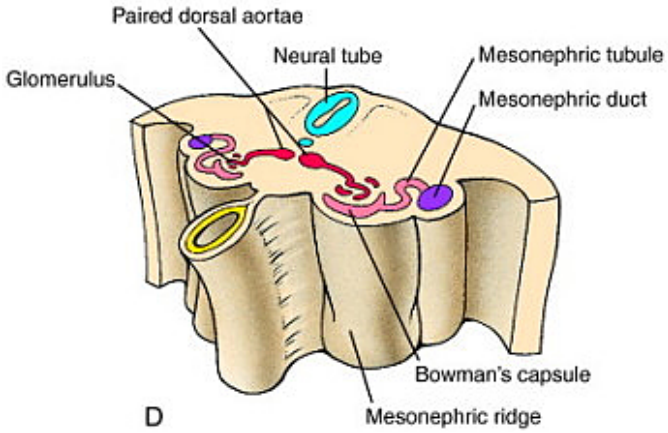
Mesonephroi seen as a mediolateral view





Note the development of the mesonephric ducts

- 1st appears at 24 days as solid longitudinal rods
- Fuses with the ventrolateral walls of the cloaca day 26
- Fusion begins a process of canalization at the distal end

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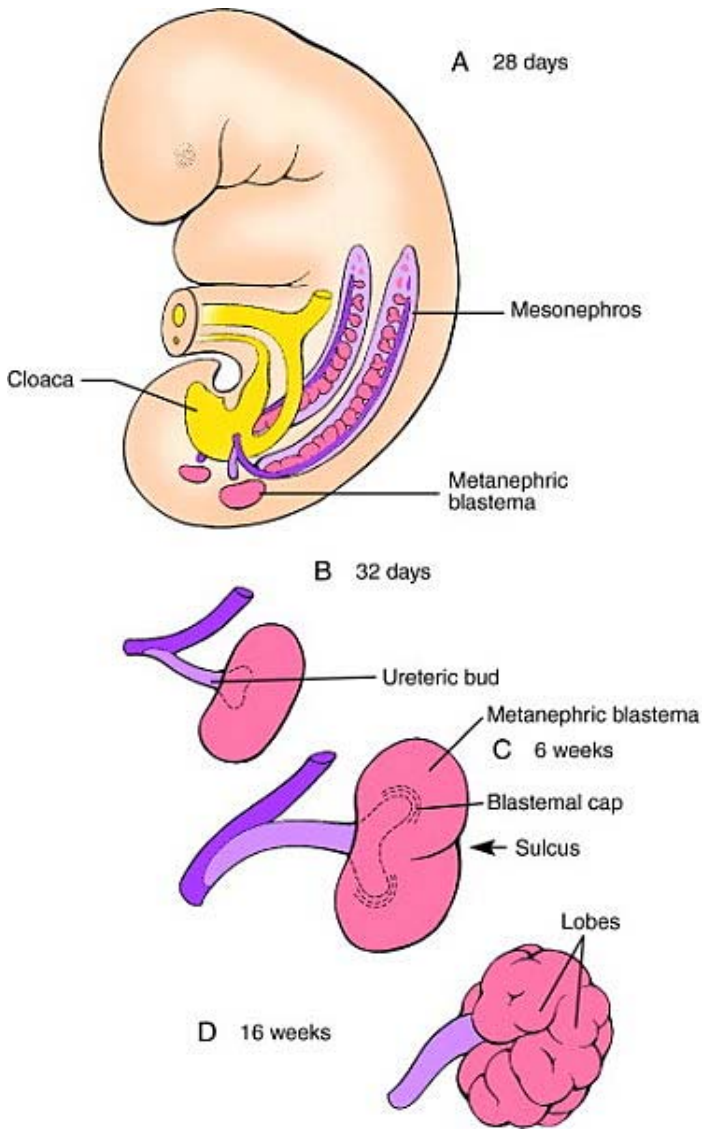
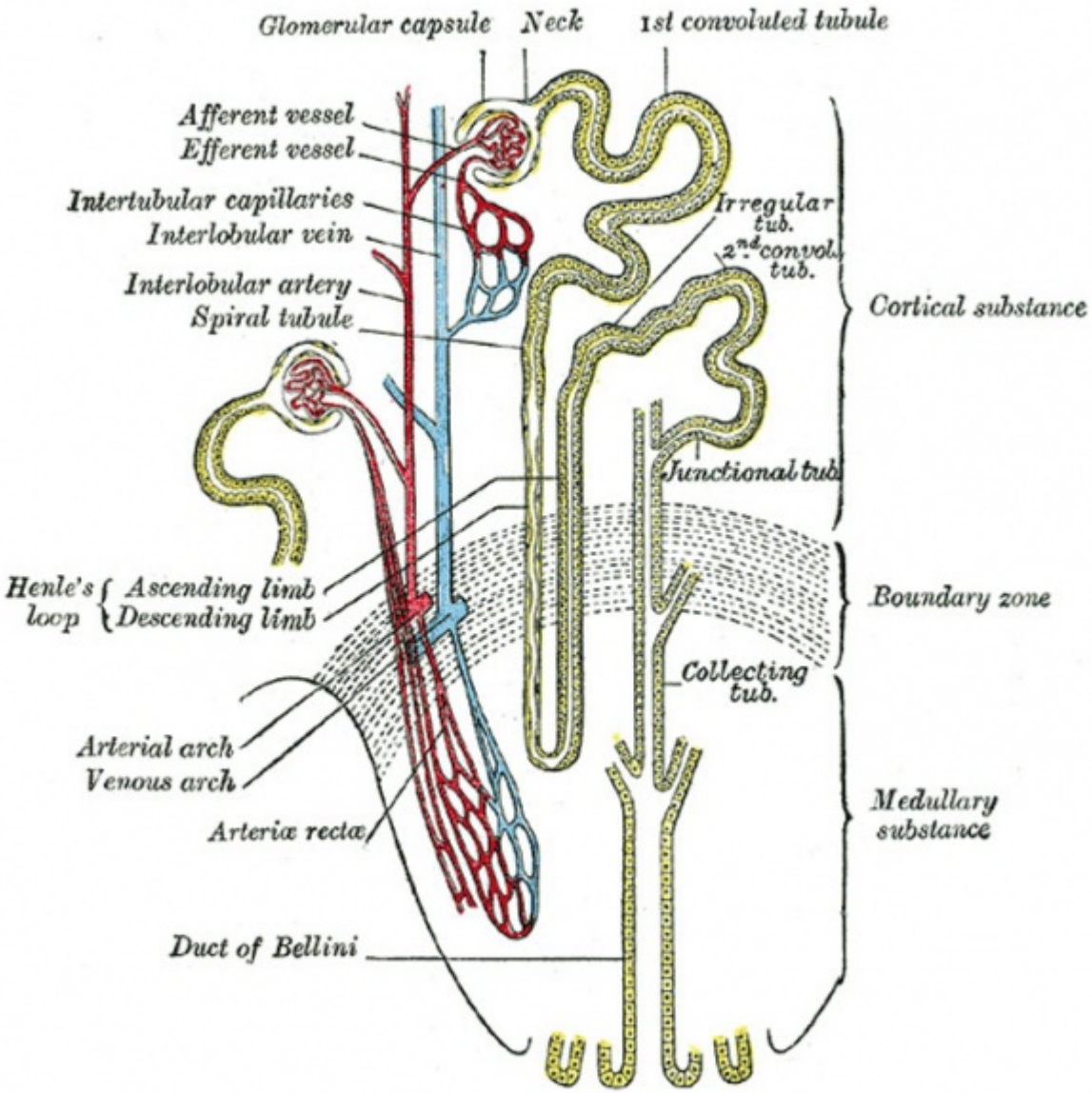


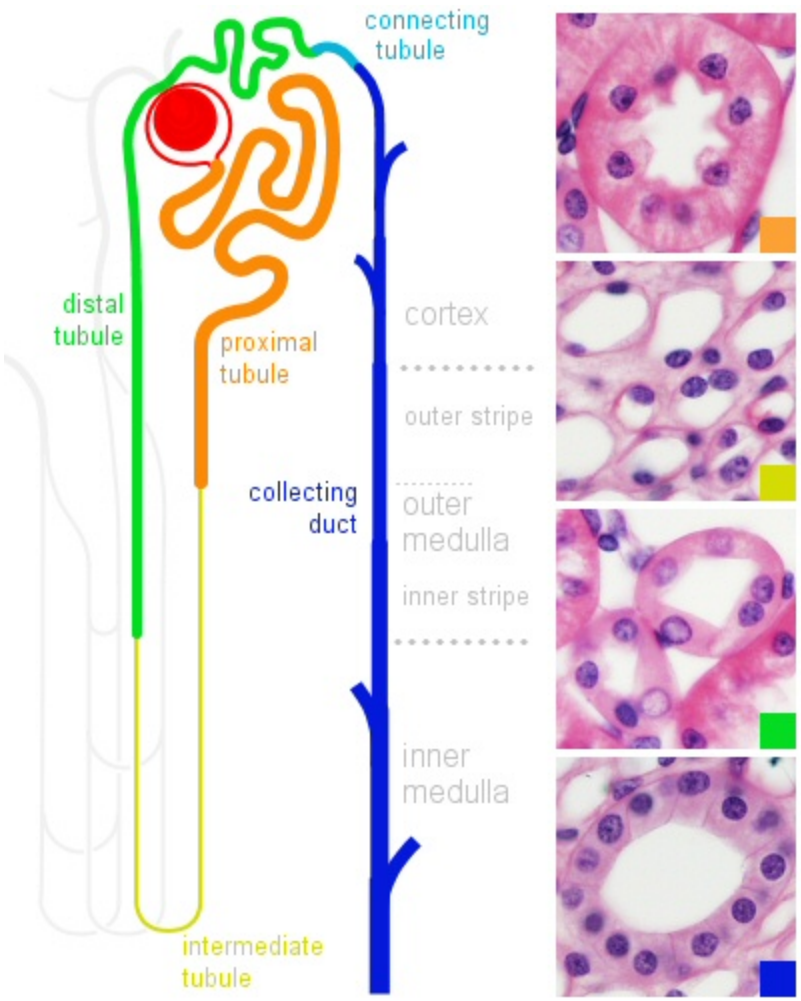
Metanephros (metanephroi)

- The definitive kidney
- Is formed through an interaction between the ureteric buds and the metanephric blastema
- The bud branches to form new tips – ampulla and the blastema forms a cap around each bud
- 16 weeks – 14-16 lobes formed
- Ureters and collecting ducts> ureteric buds
- Nephrons> blastema
- Reciprocal inductive signalling required

Schoenwolf: Larsen's Human Embryology, 4th ed.

Constructing nephrons, the functional units of the kidney





Origin of the parts of the nephric ducts

Collecting Portion (Ureteric Bud)

Ureter

Renal pelvis

Major and minor calyces

Collecting ducts

Collecting tubules

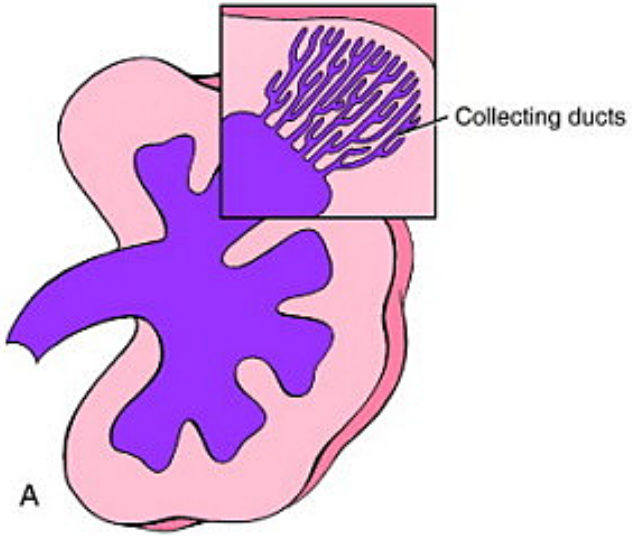
Excretory Portion (or Nephron) (Metanephric Blastema)

Bowman's capsule

Proximal convoluted tubule

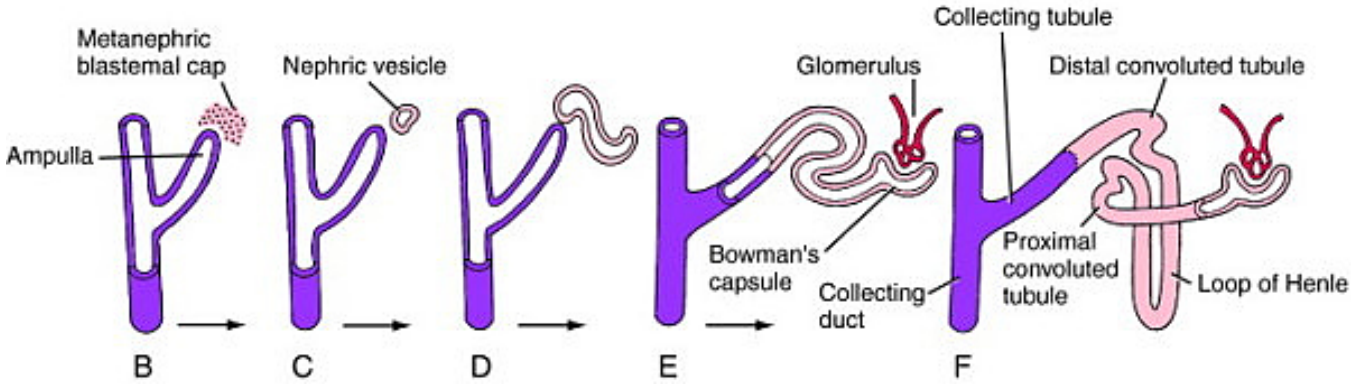
Loop of Henle

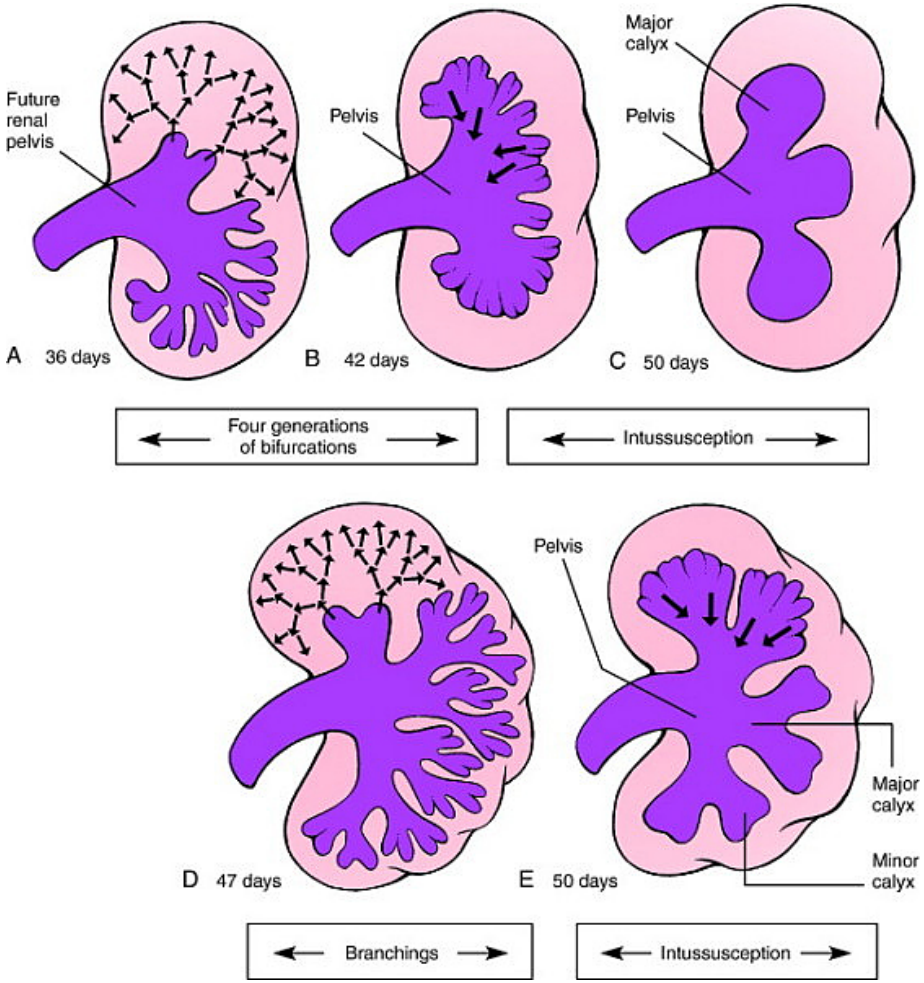
Distal convoluted tubule



Four stages of nephron development

- **vesicle** (V) stage (13-19 weeks)
- **S-shaped body** (S) stage (20-24 weeks)
- **capillary loop** (C) stage (25-29 weeks)
- **maturation** (M) stage (infants aged 1-6 months)





Branching of the ureteric bud creates the pelvis and the calyces

6th week – bud splits 4 times to give 16 branches that coalesce to give the major calyces

By 7 weeks the next four generations coalesce to make the minor calyces

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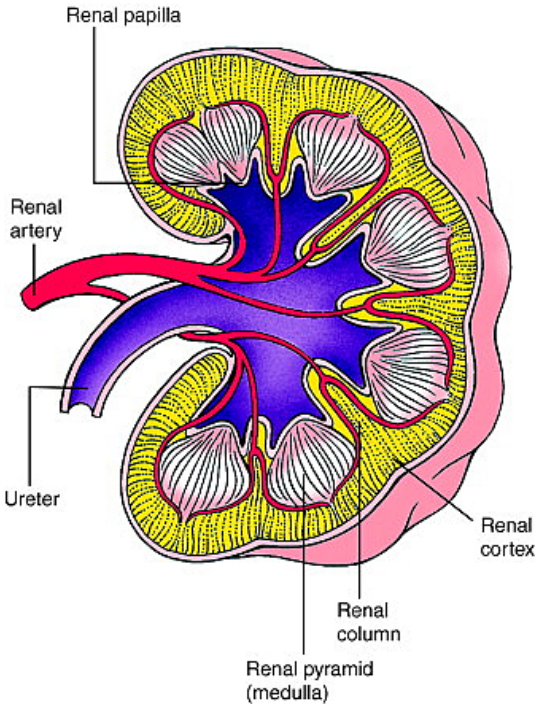
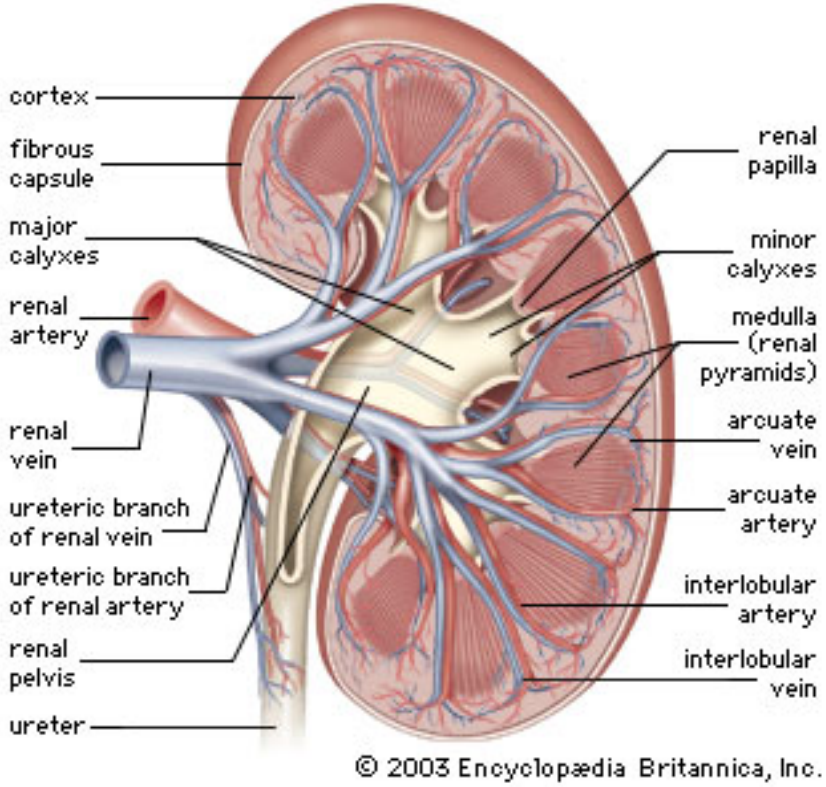
10 weeks



Adult human kidney



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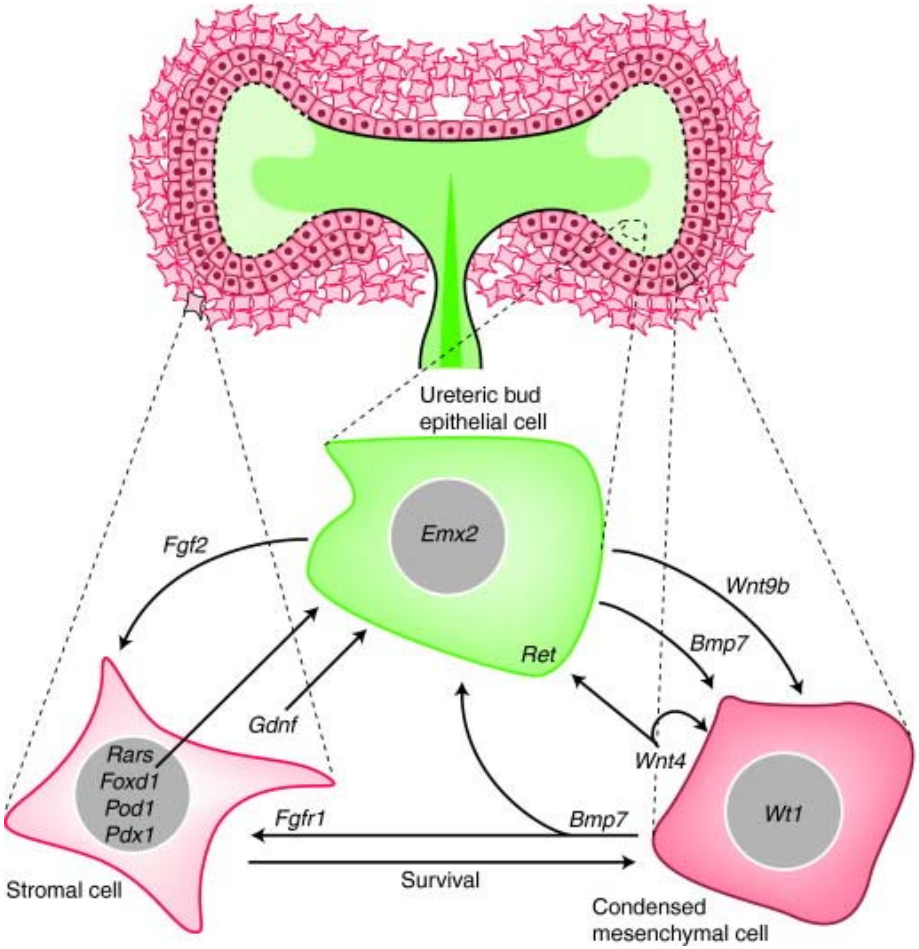

Kidney patterning depends on interactions between the ureteric branches, condensing nephrogenic mesenchyme, and interstitial stromal cells. *Wt1* expression is upregulated in the metanephric mesenchyme, making the mesenchyme receptive to ureteric bud induction. *Wnt4* released by the condensed mesenchyme induces continual ureteric bud branching and growth. *Wnt9b,* expressed by ureteric buds, promotes Wnt4 expression within the condensing mesenchyme; *Wnt4* is necessary for maintaining the survival of this mesenchyme and for subsequent nephron differentiation. Stromal cells express *Foxd1, Pod1*, and *Pdx1* and the retinoic acid receptors, *RARα* and *RARβ2*, necessary for balancing stromal and nephron progenitor specification and survival. The growth factors *Fgf2* and *Bmp* promote stromal cell differentiation at the expense of the nephron mesenchymal population.

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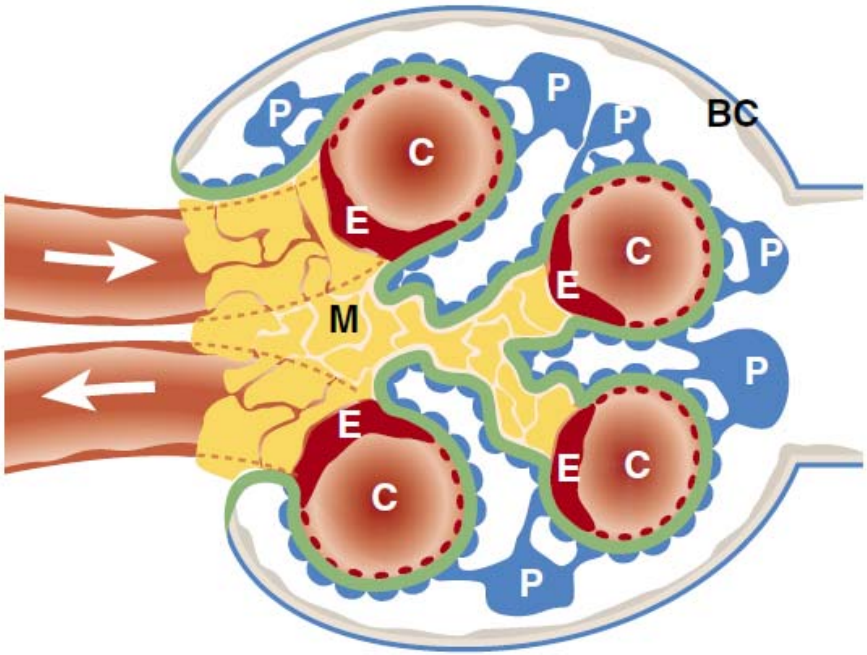
Formation of the glomerulus

A single capillary loop grows into the glomerular cleft of the S shaped body

Angiogenesis is mechanism but experiments show that kidney mesenchyme is capable of vasculogenesis too.

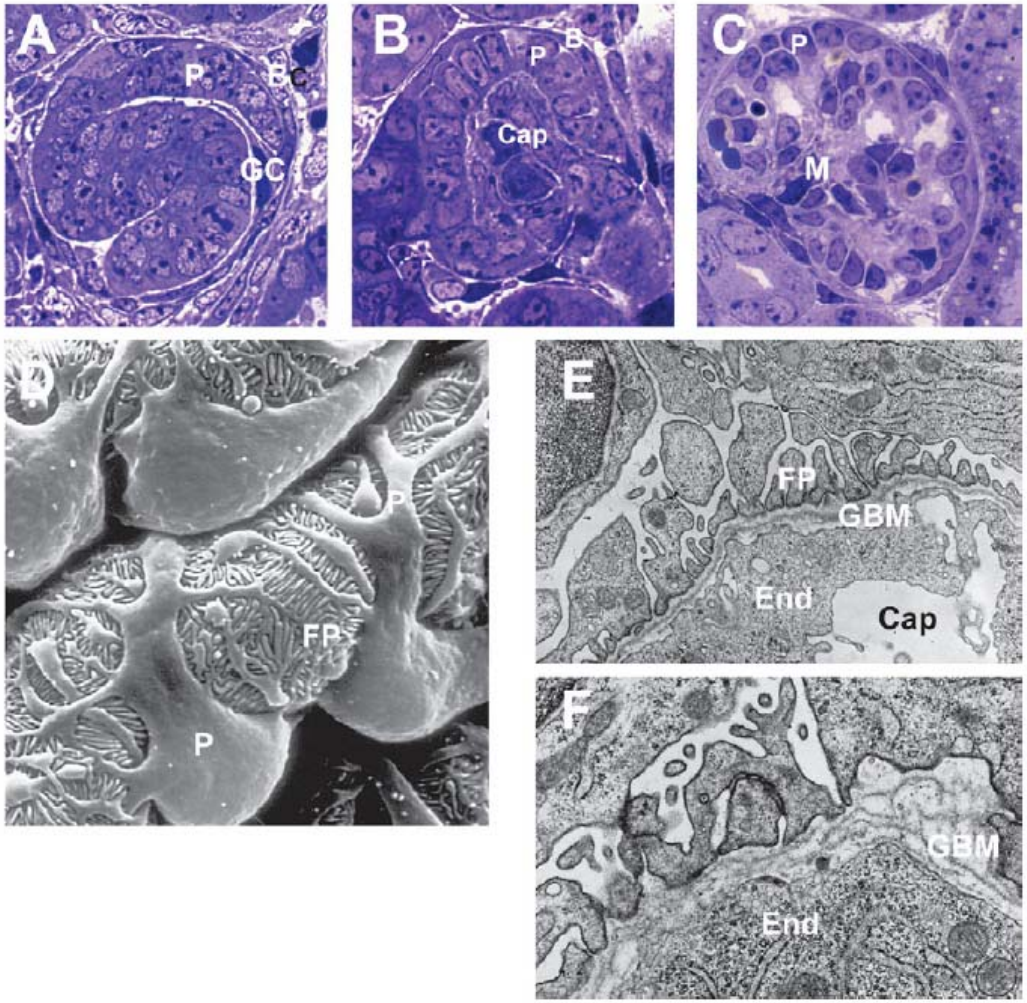


Schematic of a mature glomerulus in cross section. The four major cell types of the glomerulus are the Bowman's capsule (BC) or parietal epithelium (gray), podocytes (P, blue) or visceral epithelium, mesangial cells (M, orange) and endothelial cells (E, red). The mature glomerulus is encompassed by the Bowman's capsule. The glomerulus comprises a self-contained network of capillary loops (C, red), with mesangial cells forming a nexus at the base of the capillary network. The glomerular basement membrane (GBM, green) divides the glomerulus into two compartments, an inner one containing the capillaries and the mesangial cells, and an outer one containing podocytes and the space into which the filtrate passes. The glomerulus remains connected to the remainder of the nephron through an opening in the Bowman's capsule that connects the glomerulus to the proximal tubule, shown on the right. The arrows in the capillaries indicate the flow of blood in and out of the glomerulus.

Development of the renal glomerulus: good neighbors and good fences

Susan E. Quaggin[1] and Jordan A. Kreidberg[2,*]

Development 135, 609-620 (2008) doi:10.1242/dev.001081



Histology of glomerular development.
(**A-C**) Toluidine blue-stained sections from newborn mouse kidneys. (A) S-shaped body. P, podocyte progenitors; GC, glomerular cleft. A capillary loop is present in the cleft. B, Bowman's capsule.

(B) Immature glomerulus showing the 'bowl'-shaped arrangement of the podocytes. Cap, capillary loops.

(C) Mature glomerulus. P, podocytes; M, mesangial cells.

(**D**) Scanning electron micrograph of the interior of an adult rat glomerulus showing interdigitating foot processes (FP) encompassing capillary loops. P, podocyte cell body.

(**E**) Transmission electron micrograph of a newborn mouse glomerulus. FP, foot processes; GBM, glomerular basement membrane; End, endothelial cell; Cap, capillary lumen.

(**F**) Transmission electron micrograph from an 3 integrin mutant newborn mouse kidney, showing malformed foot processes and fragmented glomerular basement membrane.

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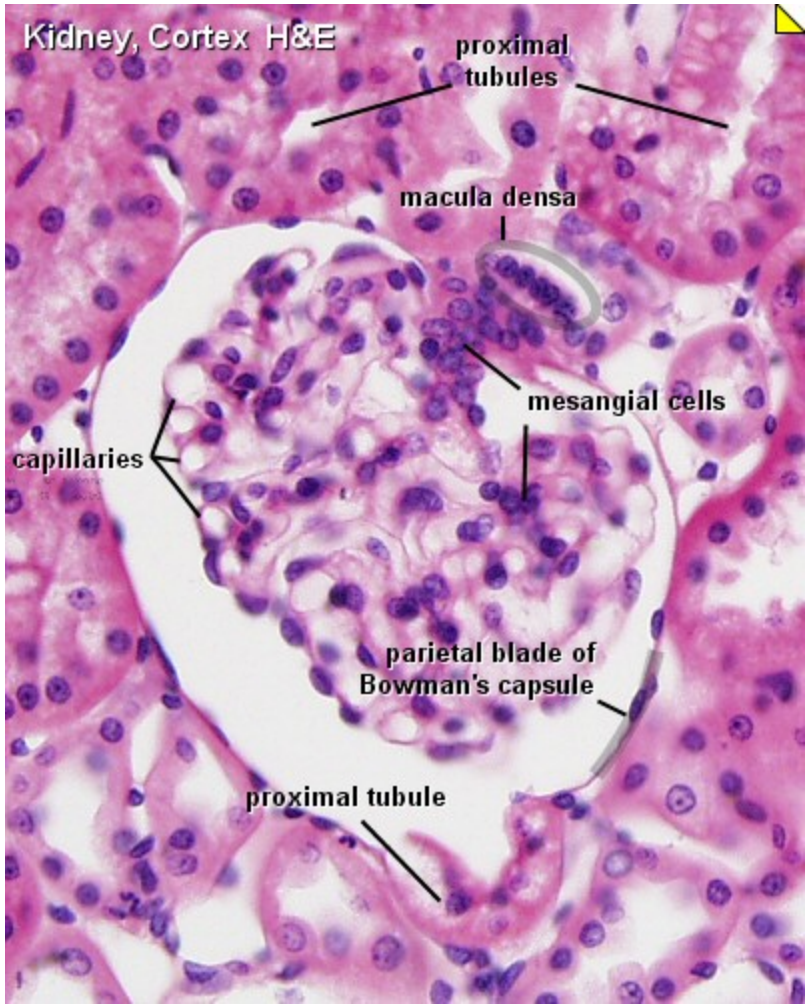


Adult nephron structure

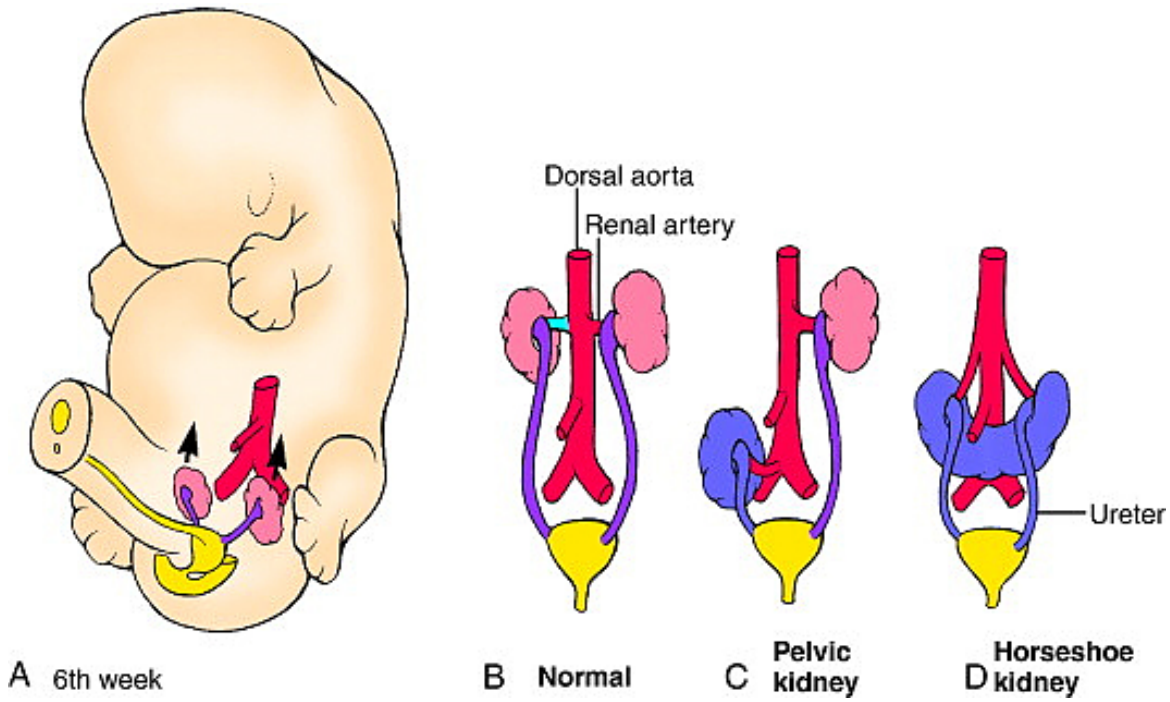
mean glomerular number shown to level at 36 weeks

about 15,000 at 15 weeks

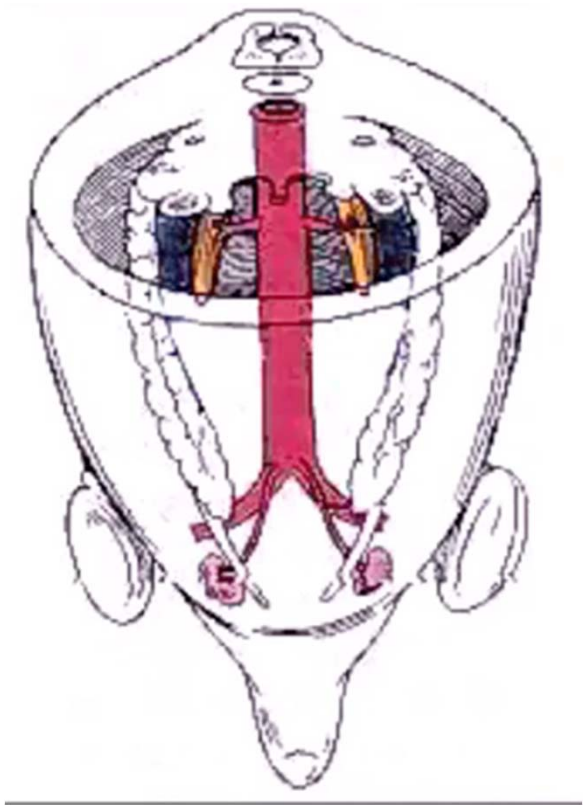
about 740,000 at 40 weeks.

Ascent of the kidneys

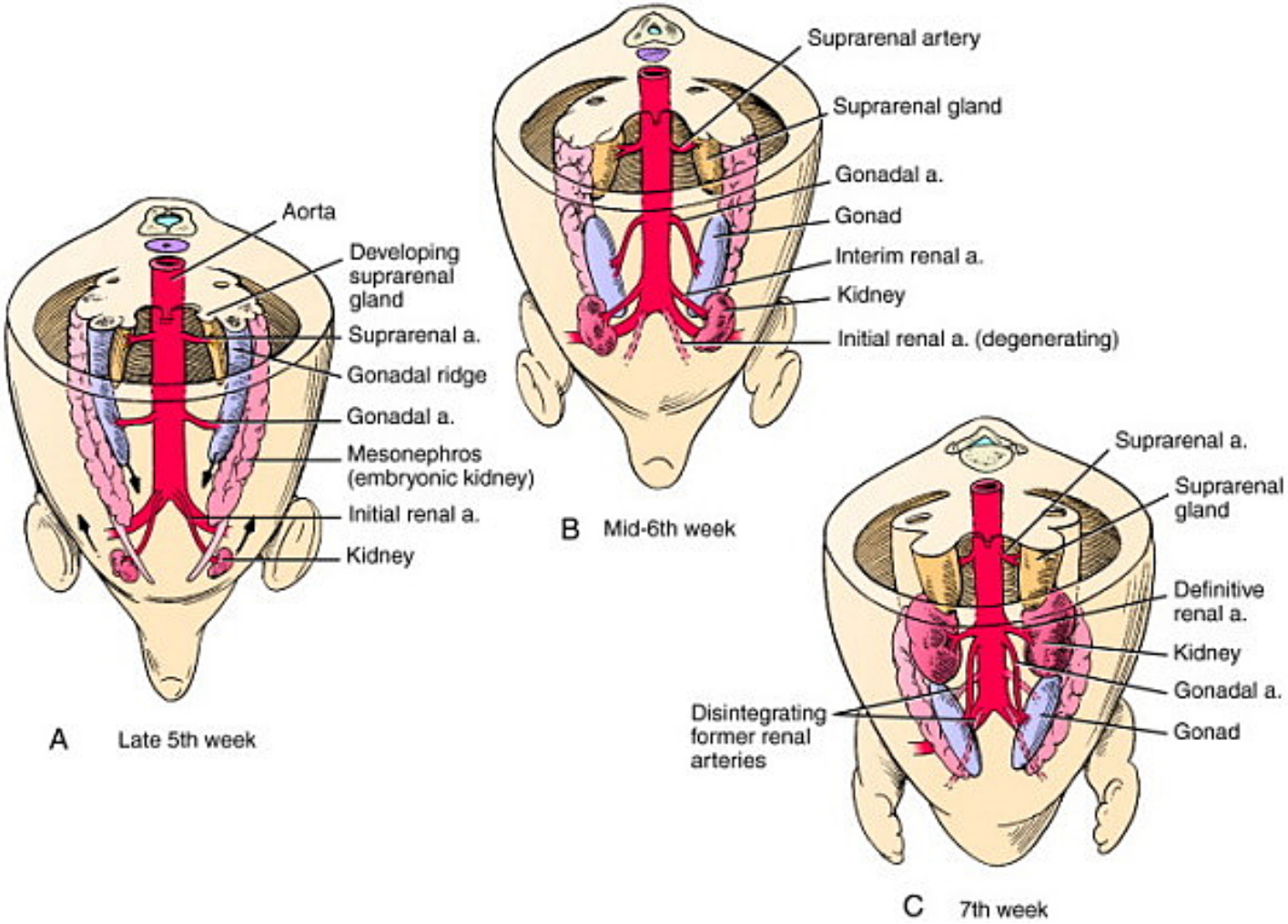
6-9 weeks kidneys ascend to just below suprarenal glands
Differential growth of lumbar and sacral regions may play a role
Ascending kidney is progressively revascularized
Anomalies
Failure of regression – accessory renal arteries
Failure to ascend – pelvic kidney
Fusion of the metanephroi during ascent – horseshoe kidney
Right usually lower due to the liver



As the kidneys ascend they are progressively revascularized by a series of temporary sprouts from the dorsal aorta. The final pair form the renal arteries



Aortic branches supplying the suprarenal gland, kidneys and gonads



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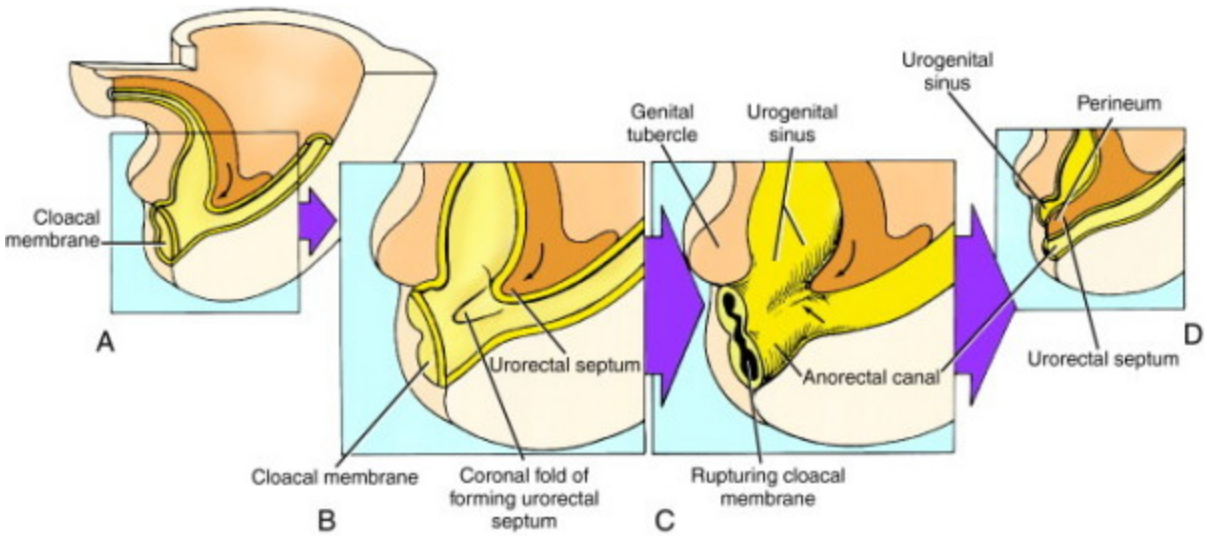
Hindgut

- Forms the - distal transverse colon, descending colon, sigmoid colon, rectum and cloaca.
- The **cloaca** subdivides into the ventral urogenital sinus and a posterior anorectal canal.



4-6 weeks The urorectal septum divides the cloaca, the cloacal membrane ruptures and the tip of the urorectal septum forms the perineum

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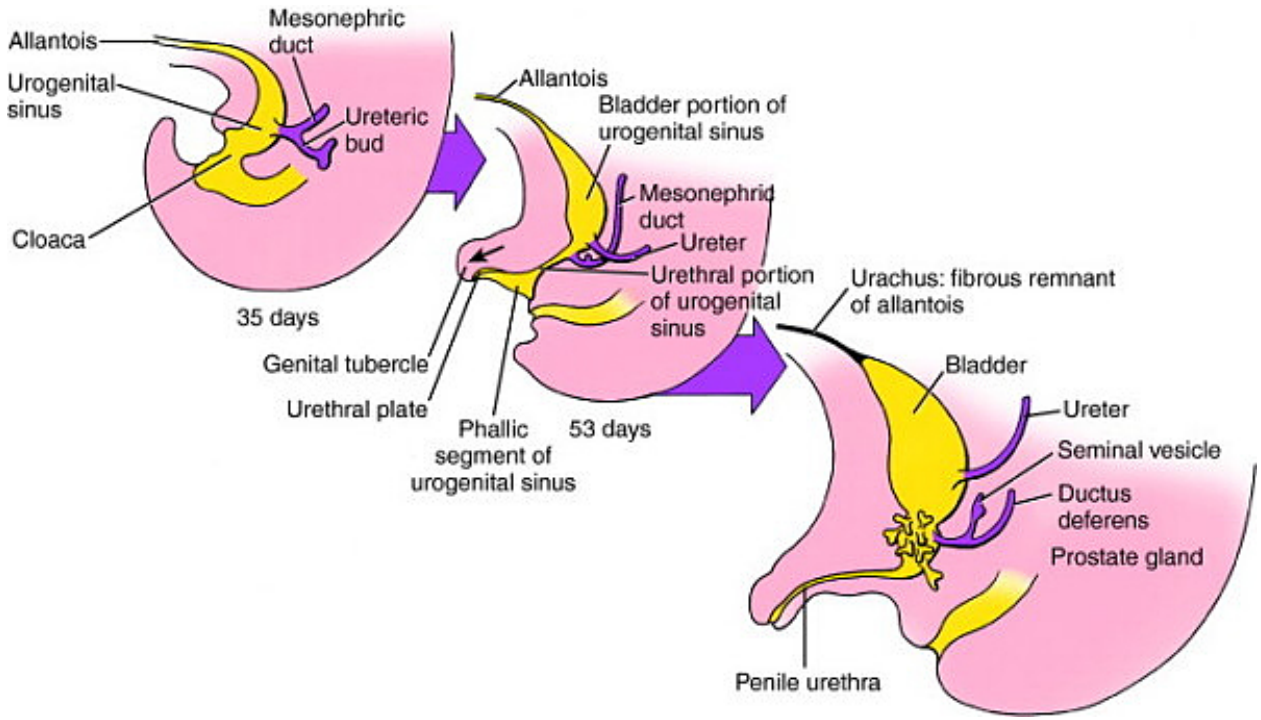
Rearrangement of the mesonephric and ureteric duct openings



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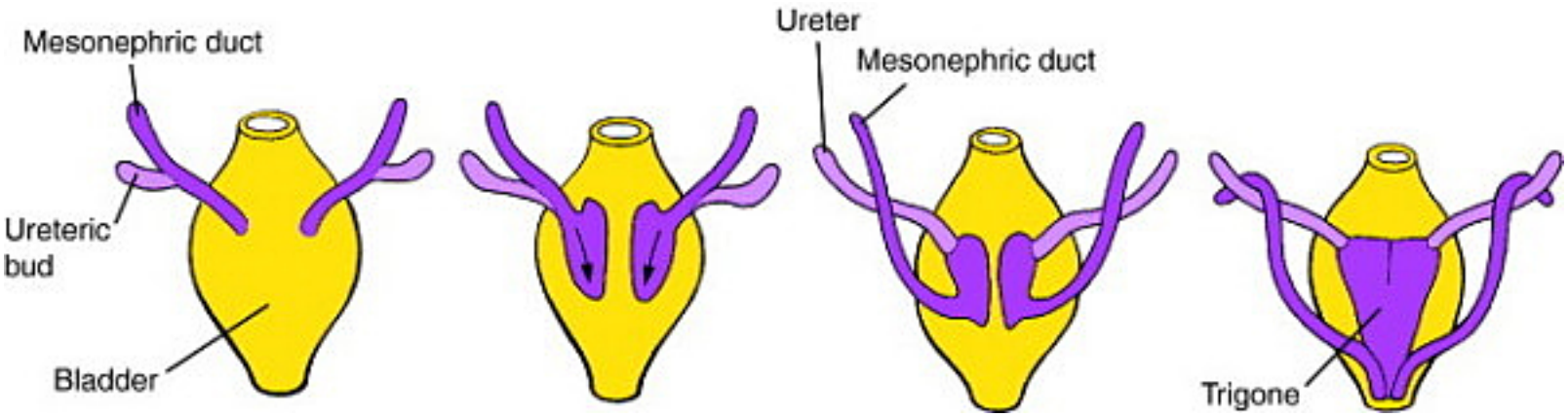
Wk 4-6 **Exstrophy** (turning inside out) of the mesonephric ducts and ureters into the bladder wall creates the **trigone** (smooth triangular region) of the bladder



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Kidneys are also endocrine organs

- Covered also in Endocrine Development lecture
- Renin - Increase Angiotensin-aldosterone system (juxtaglomerular cells)
- Prostaglandins - decrease Na+ reabsorption (mesangial cells)
- Erythropoietin (EPO)- Increase Erythrocyte (rbc) production (interstitial fibroblasts)
- 1,25 (OH)2 vitamin D - Calcium homeostasis
- Prekallikreins - (plasma protein inactive precursor of kallikrein) Increase kinin production (altered vascular permeability)