nephrons in the kidney generate urine that is propelled to the ureters and then to the bladder for storage and excretion

The Urinary outflow tract:
- monitors and regulates extra-cellular fluids
- excretes harmful substances in urine, including nitrogenous wastes (urea)
- returns useful substances to bloodstream
- maintain balance of water, electrolytes (salts), acids, and pH in the body fluids

Formation of Urine:
- blood is filtered to the glomerulus
- capillary walls are thin
- blood pressure is higher inside capillaries than in Bowman’s capsule

Formation of Urine:
- nitrogen-containing waste products of protein metabolism, urea and creatinine, pass on through tubules to be excreted in urine
- urine from all collecting ducts empties into renal pelvis
- urine moves down ureters to bladder empties via urethra

Formation of Urine:
- in healthy nephron, neither protein nor RBCs filter into capsule
- in proximal tubule, most of nutrients and large amount of water reabsorbed back to capillaries
- salts selectively reabsorbed according to body’s needs
- water reabsorbed with salts

The urogenital system derives predominantly from intermediate mesoderm
During development, 3 successive kidneys form:

- **Pronephros** (head kidney)
- **Mesonephros** (middle kidney)
- **Metanephros** (definitive kidney)

A **metanephros** is always drained exclusively by one duct, the ureter. In birds and reptiles, the ureter separates from the nephric duct (Wolffian duct) and enters the cloaca. In mammals, the ureter separates from the nephric duct and enters the bladder.

Renal development begins when the ureteric bud invades kidney mesenchyme (the metanephric blastema). As the embryo grows, the ureters lengthen, and the kidneys rotate and ascend along the dorsal body wall.
Part I. Making a kidney

1. Renal vein
2. Renal artery
3. Renal calyx
4. Medullary pyramid
5. Renal cortex
6. Segmental artery
7. Arcuate artery
8. Arcuate vein
9. Interlobar vein
10. Segmental vein
11. Renal column
12. Renal papilla
13. Renal pelvis
14. Ureter

The distinct cellularity of the collecting duct system and ureter depends on developmental signals from surrounding mesenchyme.

Diverse cell types lining the nephron perform distinct functions.

- Branching morphogenesis and nephron formation last until just after birth
- Occur exclusively in the peripheral domain beneath the renal capsule
- New generations of nephrons and ureter branches displace older generations inward
- Further differentiation occurs in inner domains at a distance from the renal capsule

The kidney is radially patterned.

Reciprocal signaling between stroma, nephron progenitors and ureteric bud tips gives rise to cell types in the mature kidney.

Shape changes and local proliferation at ureteric bud tips forms an ampulla.

Branching morphogenesis:
- Ampullae form at ureteric bud tips
- A cleft forms and the tips begin to bifurcate
- The tips elongate
- New ampullae form
The collecting duct system grows from the periphery by **dichotomous branching** at birth.

Nephrons form exclusively at ureteric bud tips in response to local signals from ureteric bud cells.

Nephron progenitors condense at ub tips, aggregate and trans-differentiate into epithelial cells that make up the renal vesicle, Comma and S-shaped bodies.

Co-culture experiments demonstrate reciprocal signaling between ureteric bud epithelial and nephron progenitors.

- No ureteric bud, nephron progenitors undergo apoptosis.
- No nephron progenitors, no branching morphogenesis.

Signals from the ureteric bud control nephron induction.
Signals from nephron progenitors control branching morphogenesis.

RET-GDNF SIGNALING EXEMPLIFIES A RECIPROCAL EPITHELIAL-MESENCHYMAL PATHWAY THAT IS CRUCIAL FOR RENAL DEVELOPMENT.

GDNF secreted by nephron progenitors binds to Ret via the Ret co-receptor (Gfra1) inducing branching morphogenesis.

Mutations in Ret, Gdnf or Gfra1 result in renal agenesis or hypoplasia.

Ret mutations in humans cause renal abnormalities, Hirschsprung’s disease and cancer.
The *Ret* receptor is expressed in ureteric bud tips and controls branching morphogenesis. Vitamin A from stromal cells controls *Ret* expression in ureteric bud cells. Vitamin A deficiency generates renal malformations similar to those induced by *Ret* mutations.

Many genes are now known that regulate renal development.

Mouse models and human genetics have identified genes that when deleted in humans result in renal abnormalities, but in most cases, the genetic basis of renal defects is still unknown.

Part II. The lower urinary tract.

Physical or functional blockage that impedes urine flow can cause renal scarring, hydronephrosis or end stage renal disease.
proper positioning of the ureter orifice is necessary for:
• formation of patent connections along the outflow tract
• preventing reflux

abnormal position of the ureter orifice
vitamin A deficiency, Ret sprouty, slit-2, retinoid excess

Physical vs Functional obstruction
abnormal peristalsis
sonic hedgehog (muscle)
Calcineurin B (peristalsis)
uroplakin (epithelium)

The urogenital sinus forms the bladder, urethra in both sexes

The urogenital sinus forms the bladder and urethra in both sexes

The urorectal septum partitions the cloaca ("sewer") into
the urogenital sinus (ventral) and hindgut (dorsal)

Larsen's Embryology, 6th Edition

• The mesonephric duct (aka Wolffian duct) forms the vas (ductus) deferens, seminal vesicle and epididymis in males
• Mullerian ducts (paramesonephric ducts) degenerate in females

from: The kidney: Eds, Vize et al., 2003)

Urine transport depends on proper connections between the
ureters and the bladder trigone

The trigone is defined as the portion of the urogenital sinus
that lies between the ureters and sex ducts

from: The kidney: Eds, Vize et al., 2003)
The trigone is a region where the detrusor and urethral muscle join the ureteral fibers. Proper configuration of muscle groups that form the trigone is likely to be important for urinary tract function.

The flap valve is part of the trigone and is an anti-reflux mechanism that prevents urine back flow (reflux). Flap-valve function depends on insertion of the ureter orifice at the proper position in the bladder neck (trigone).

The Bladder epithelium is lined with plaques made from uroplakins that form a water-proof barrier. Smooth muscle of the detrusor and rugae (folds) in the urothelium allow the bladder to expand and contract.

A transitional epithelium expressing uroplakin also lines the ureters. The ureter smooth muscle coat mediates myogenic peristalsis. Defective smooth muscle formation or mutations in uroplakins cause functional obstruction.

Impaired peristalsis is a cause of obstruction (functional obstruction).
Mature connections are established when the ureter orifice is transposed from the posterior Wolffian duct (the common nephric duct) to the bladder.

How do ureters move from the Wolffian duct to the bladder?

According to the accepted model, trigone formation is considered to be crucial for repositioning the ureter orifice during ureter transposition, the common nephric duct is incorporated into the bladder where it expands to form the trigone, effectively separating the ureter orifice from the Wolffian duct.

Accepted model of ureter transposition

formation of the trigone from the common nephric duct repositions the ureters in the bladder

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using mouse models to re-assess the mechanism of ureter transposition:

expression of Jelly Fish green fluorescent protein in the mouse common nephric duct of this transgenic mouse enables us to follow its fate during ureter insertion

what happens to the common nephric duct during ureter transposition?

The common nephric duct appears to regress rather than expand
Ureter transposition depends on apoptosis of the common nephric duct.

A revised model of ureter transposition:

- The common nephric duct is absorbed into the expanding urogenital sinus. The ureter makes direct contact with and inserts into the urogenital sinus.
- Apoptosis of the common nephric duct enables the ureter orifice to detach from the Wolffian duct.
- Continued growth and expansion of the urogenital sinus moves the ureter orifice further anterior to the bladder neck.