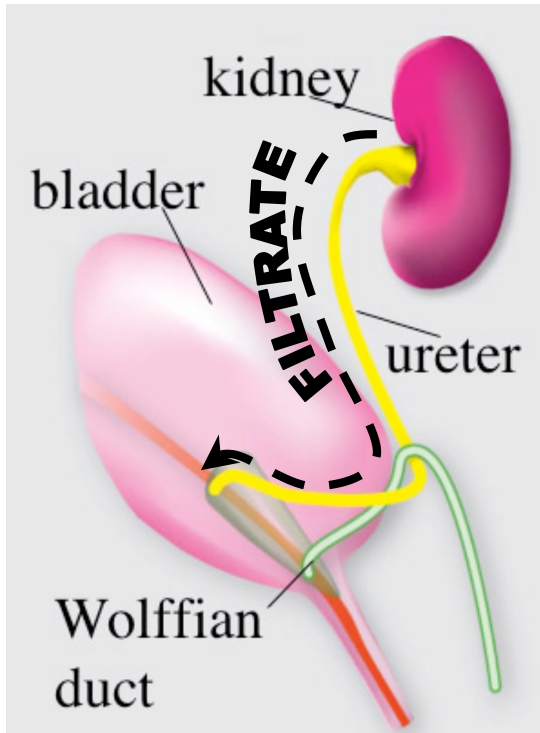


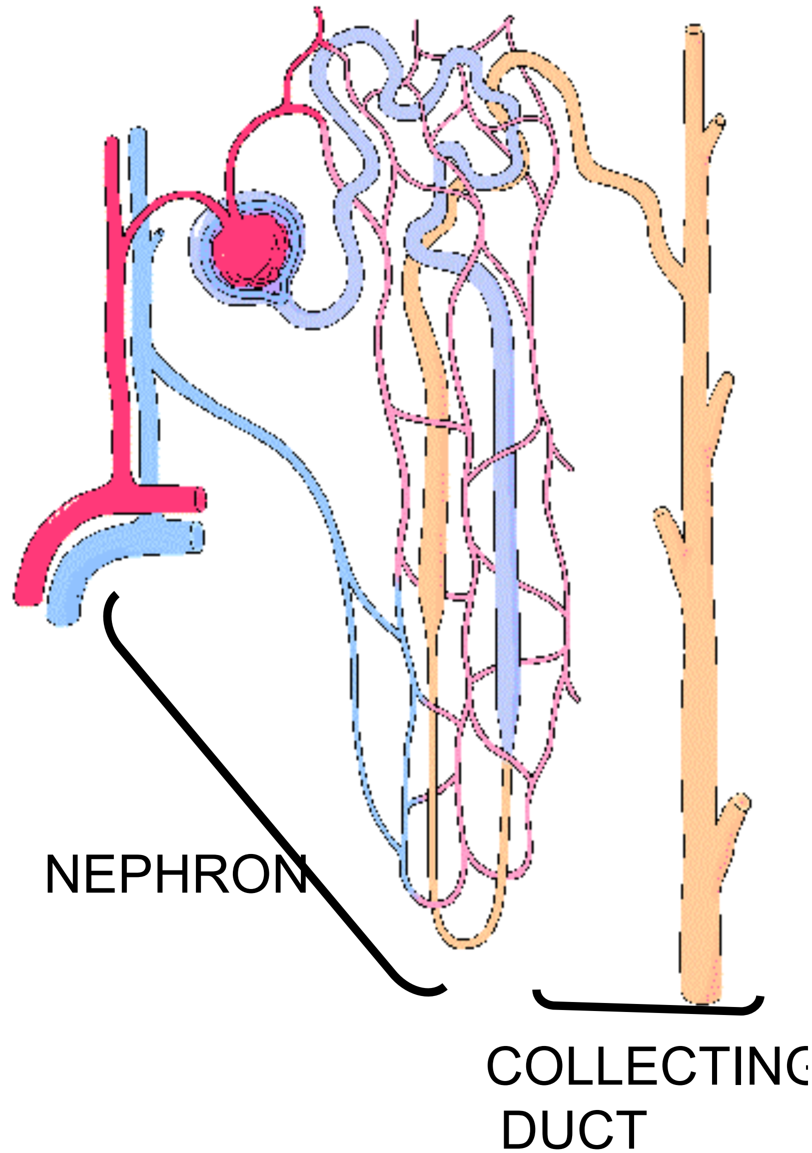
nephrons in the kidney generate urine that is propelled
to the ureters and then to the bladder for storage and excretion

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:

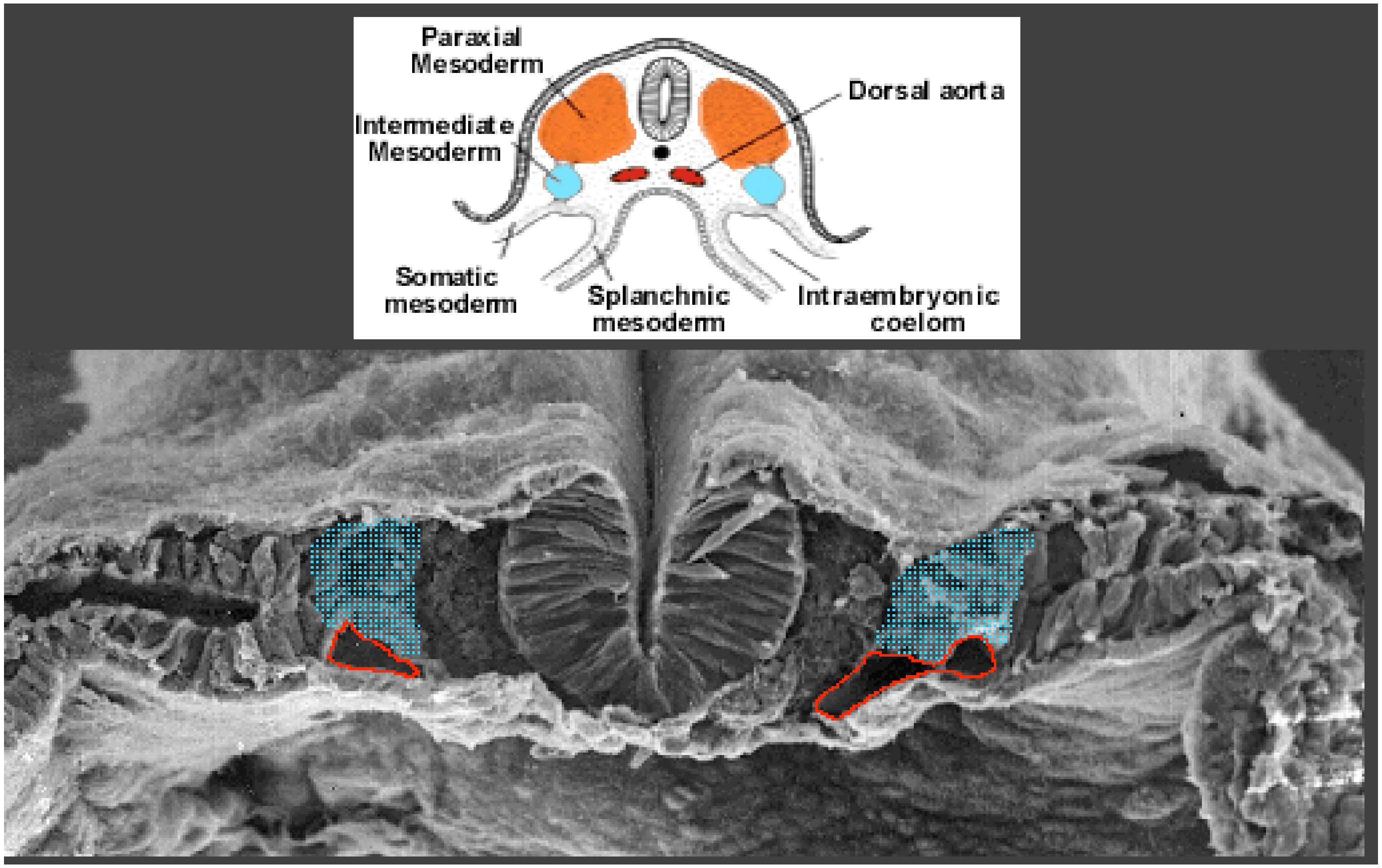
- nitrogen-containing waste products of protein metabolism, urea and creatinine, pass on through tubules to be excreted in urine
- urine from all collecting ducts empties into renal pelvis
- urine moves down ureters to bladder

  empties via urethra

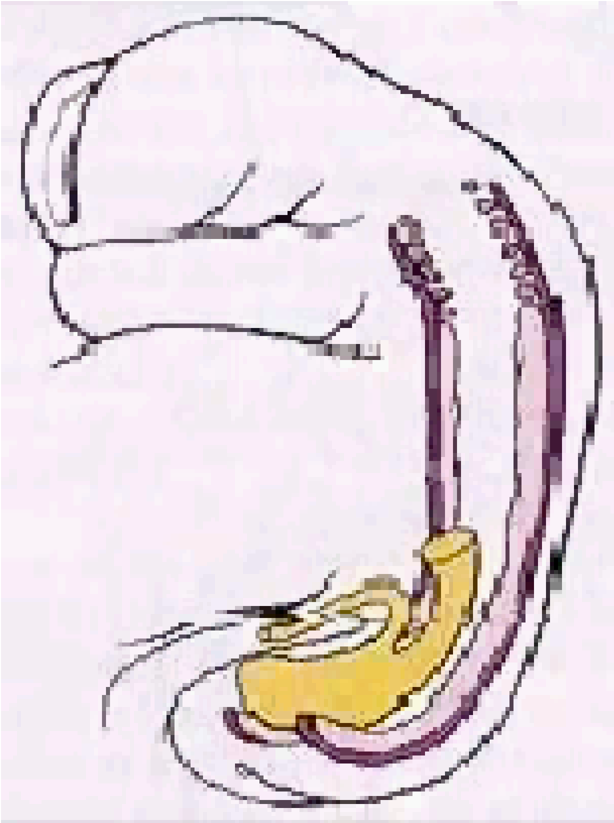
Formation of Urine:

- 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



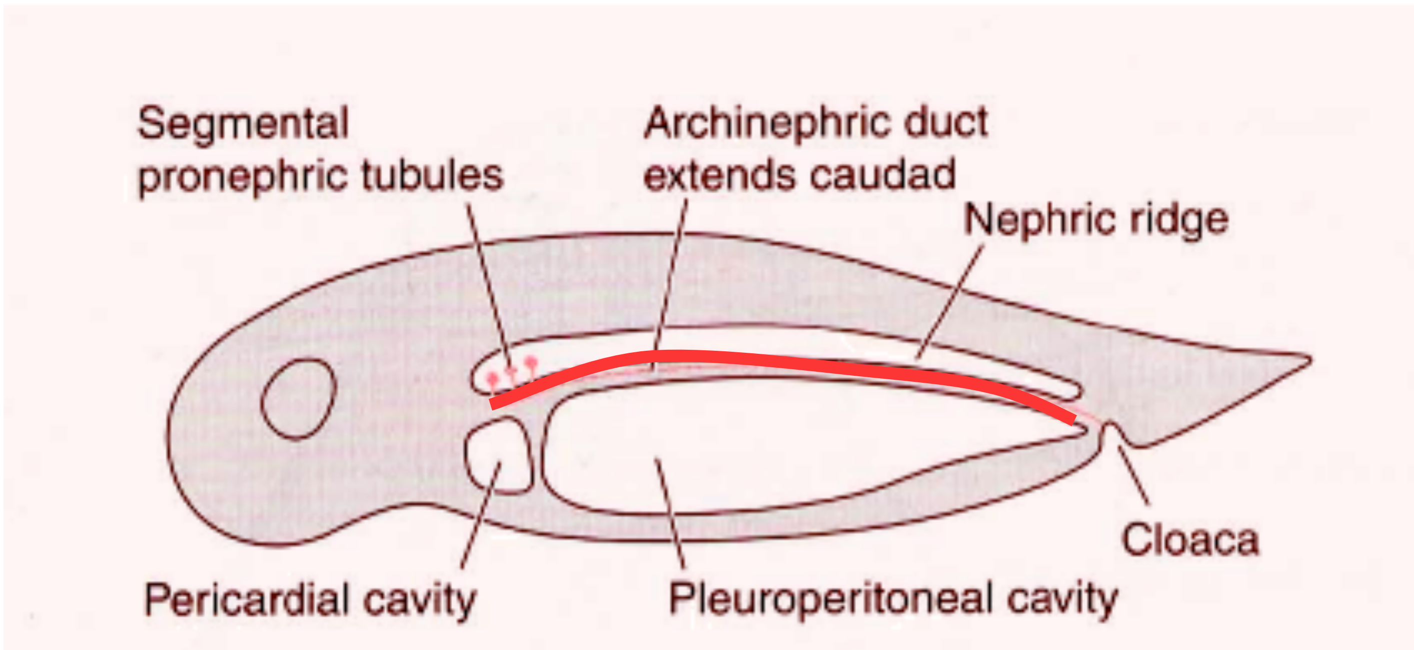
During development, 3 successive kidneys form:



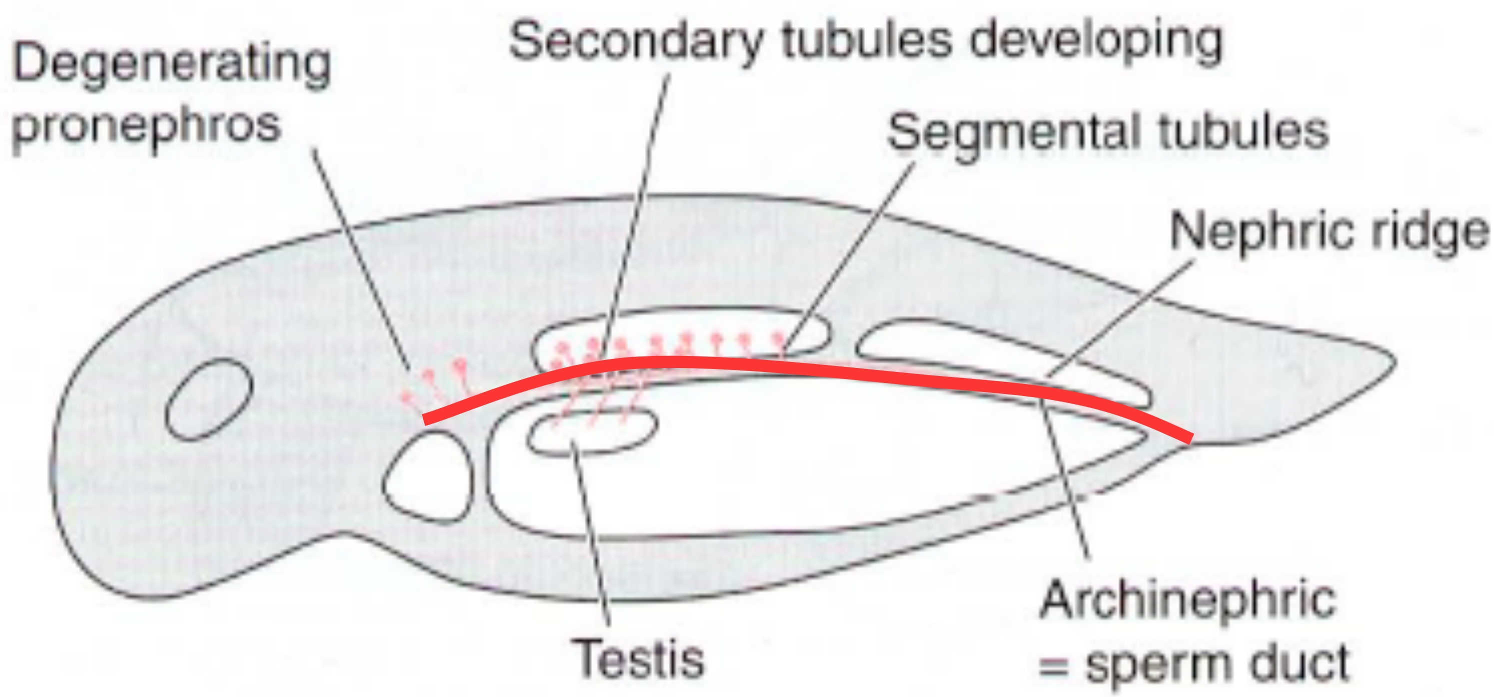
Pronephros
(head kidney)

Mesonephros
(middle kidney)

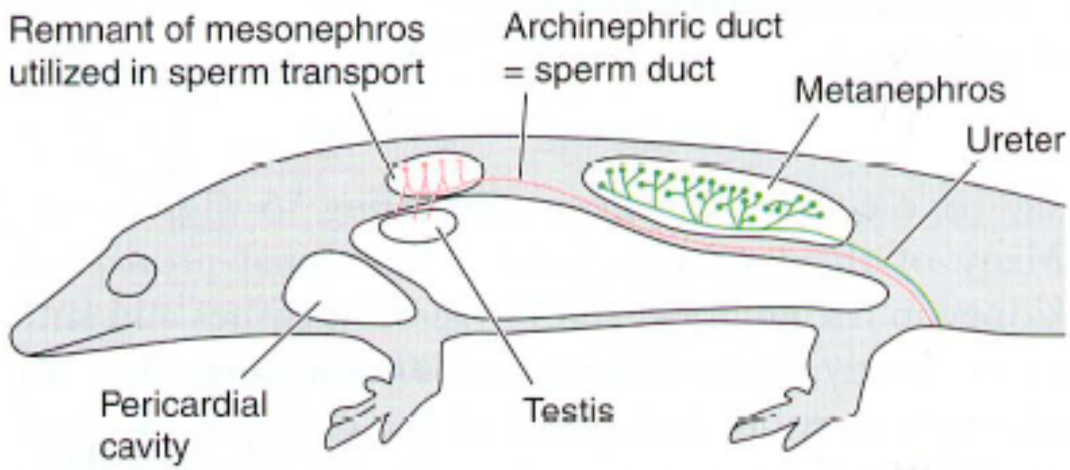
Metanephros
(definitive kidney)



pronephros in an early embryo



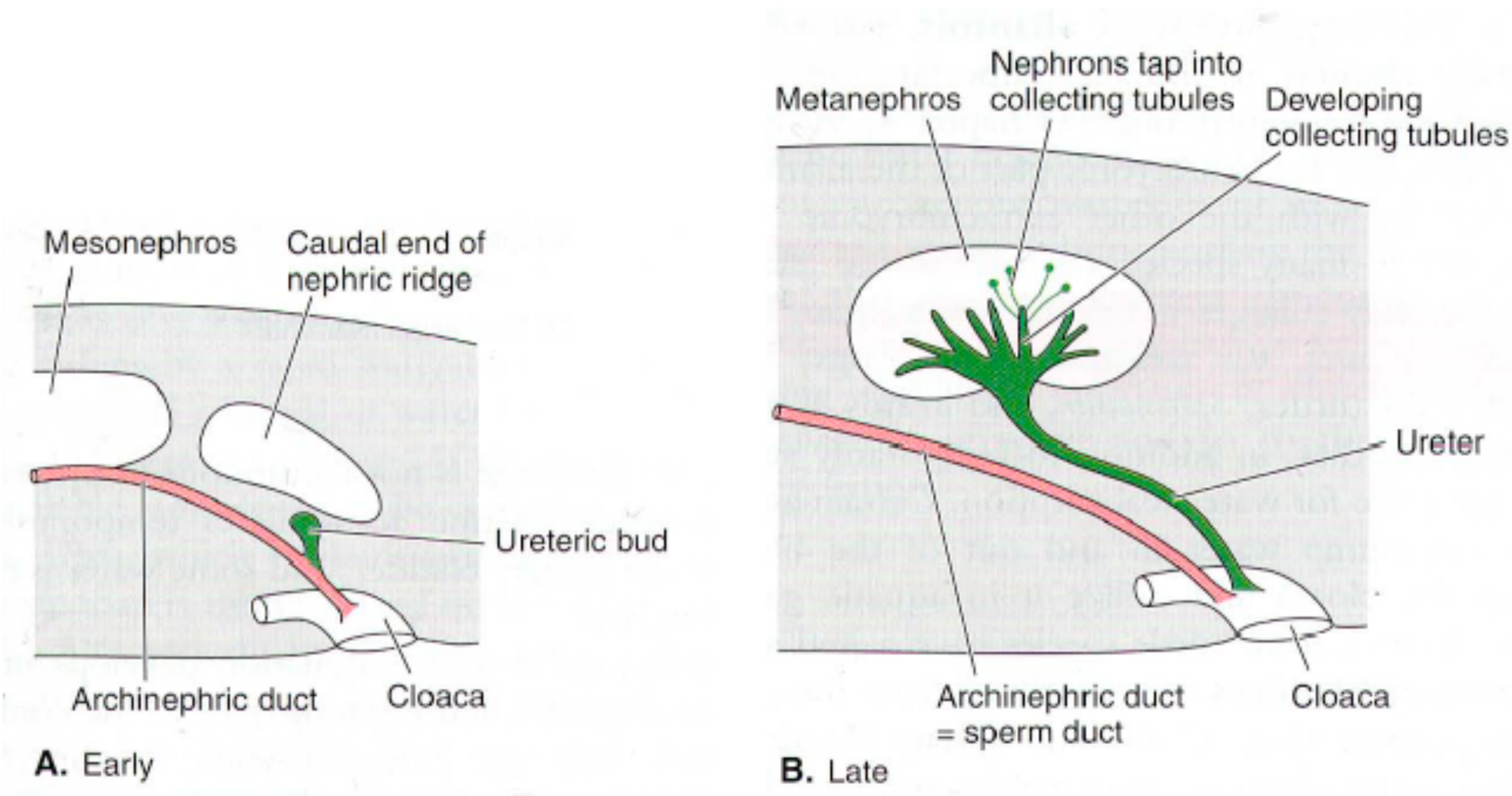
Mesonephros in intermediate embryo



C. Metanephros in late embryo and adult

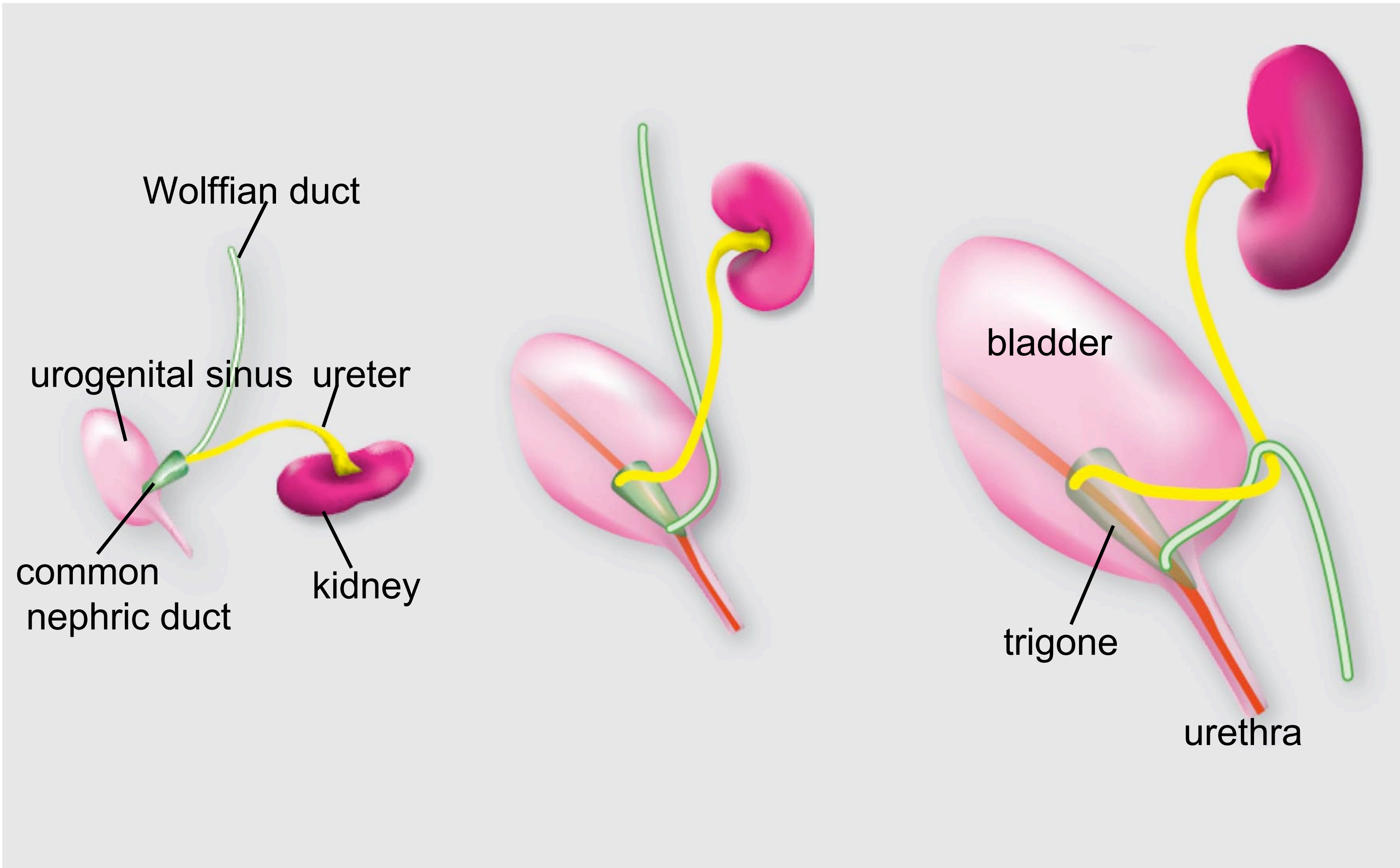
A **metanephros** is always drained exclusively by one duct, the ureter.

In birds in 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



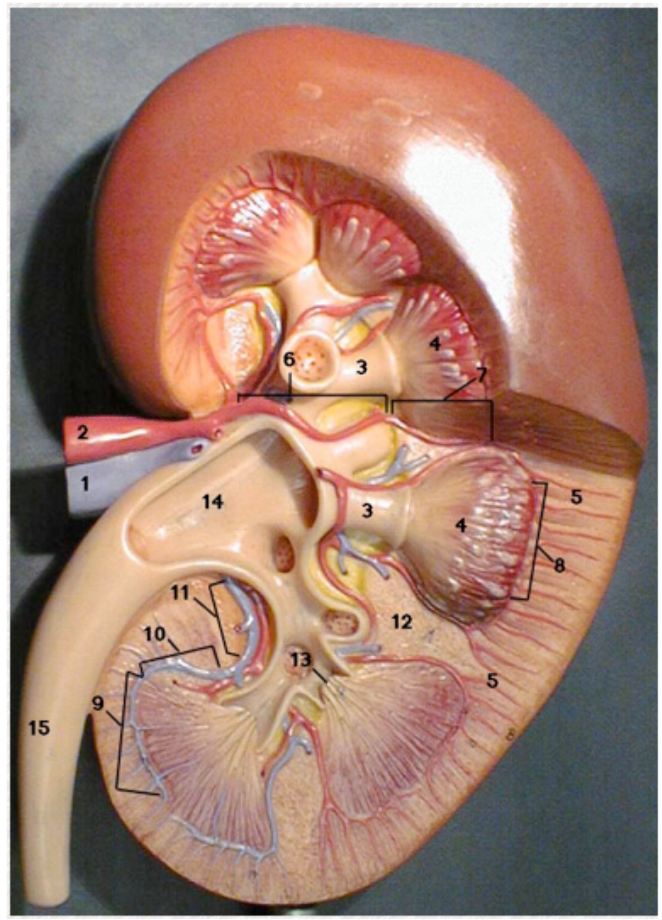
renal development begins when the ureteric bud invades kidney mesenchyme (**the metanephric blastema**)

As the embryo grows, the **ureters lengthen**, and the **kidneys rotate** and **ascend** along the dorsal body wall

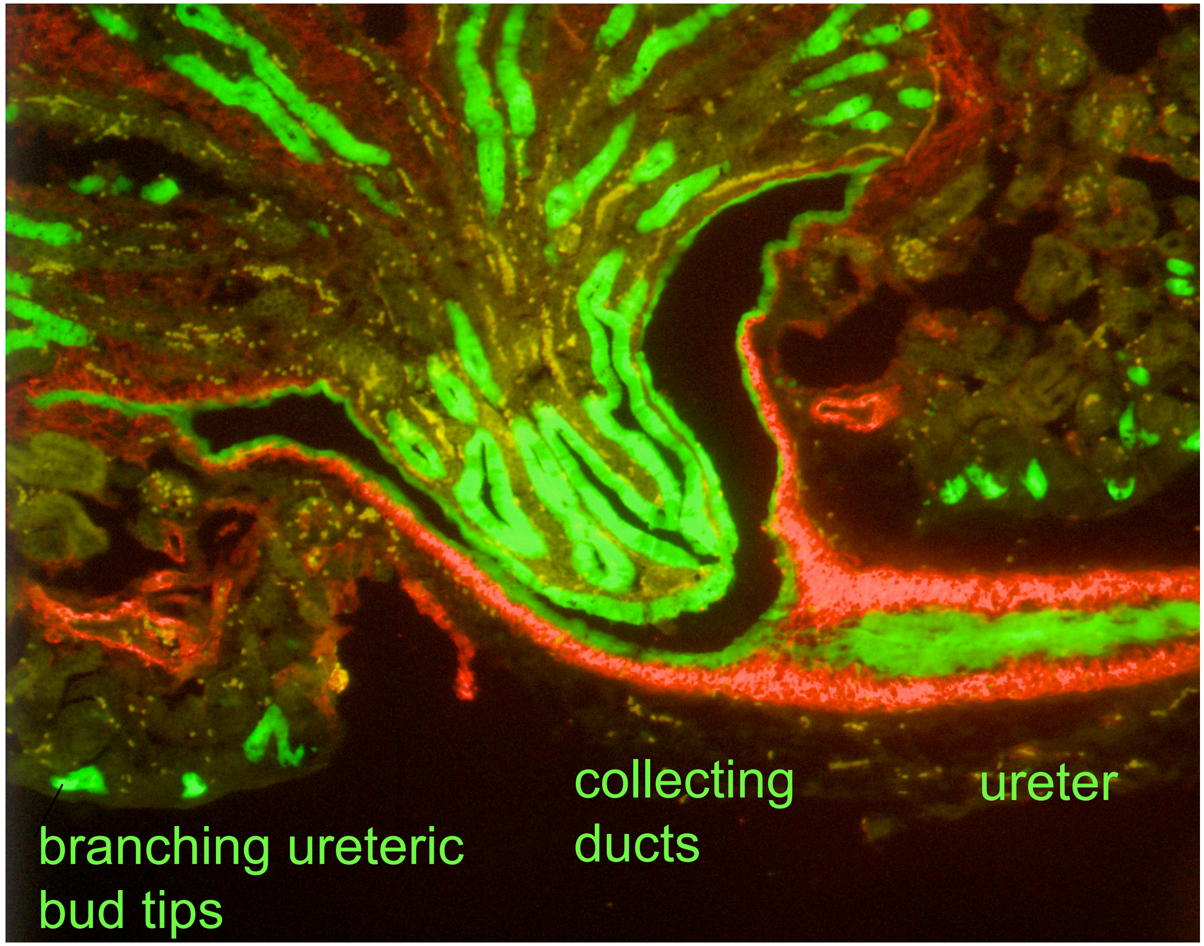


Part I. Making a kidney

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 collecting duct system and ureter are derived from the ureteric bud



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

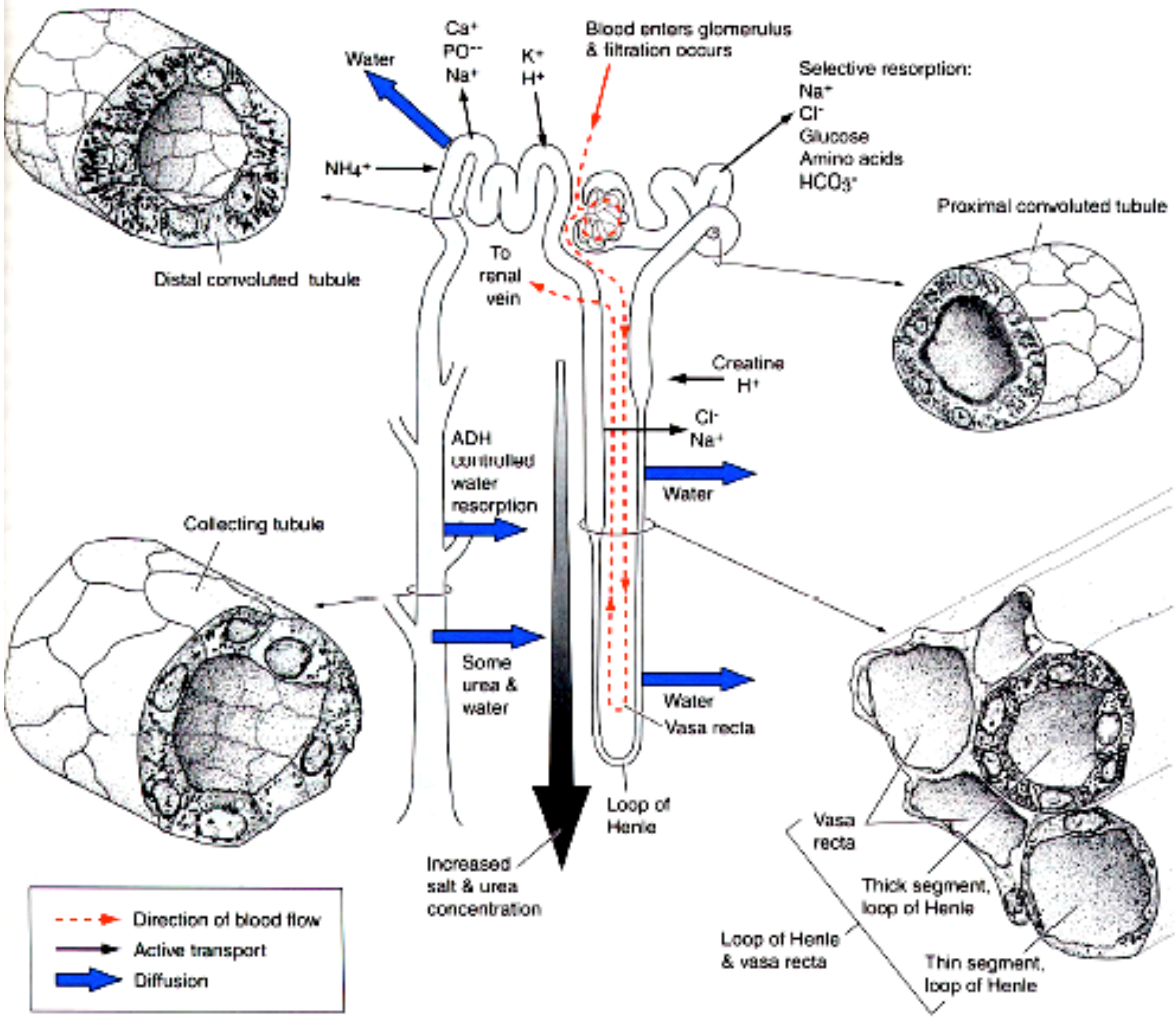
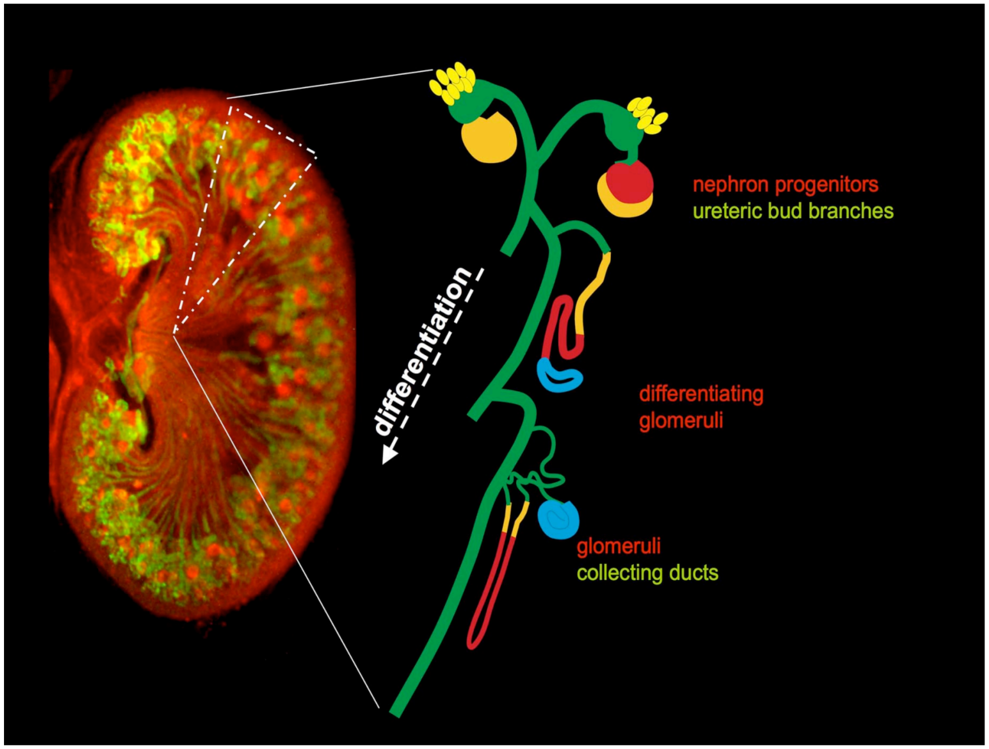


FIGURE 20-14
A mammalian nephron. Dashed red arrows represent blood flow. The regions where materials are exchanged by active transport (*narrow black arrows*) or by passive diffusion (*wide blue arrows*) are shown. The combined result of kidney action is the production of a hypertonic urine. *(Modified from Williams et al.)*

The kidney is radially patterned



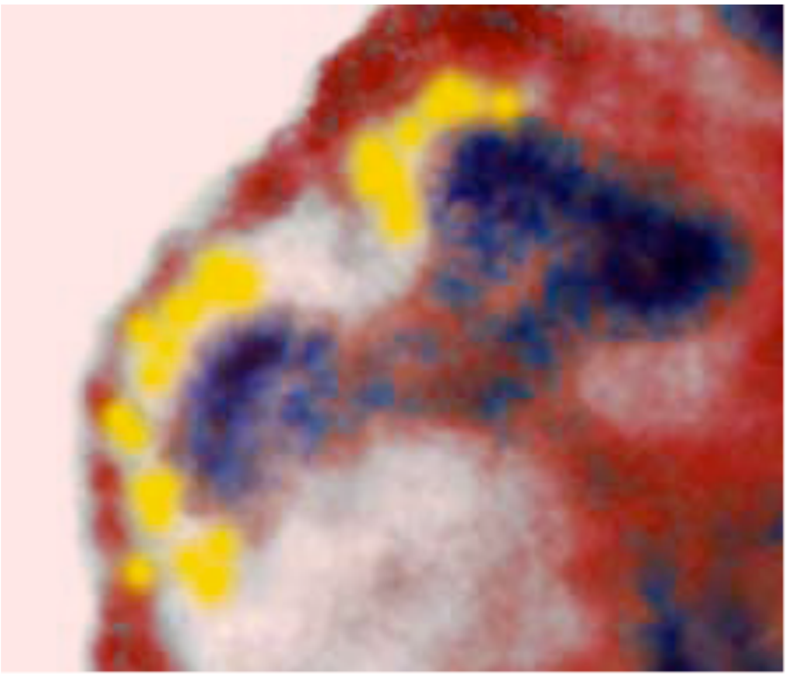
•branching morphogenesis and nephron formation last until just after birth

•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

RECIPROCAL SIGNALING BETWEEN STROMA, NEPHRON PROGENITOF
URETERIC BUD TIPS GIVES RISE TO CELL TYPES IN THE MATURE K

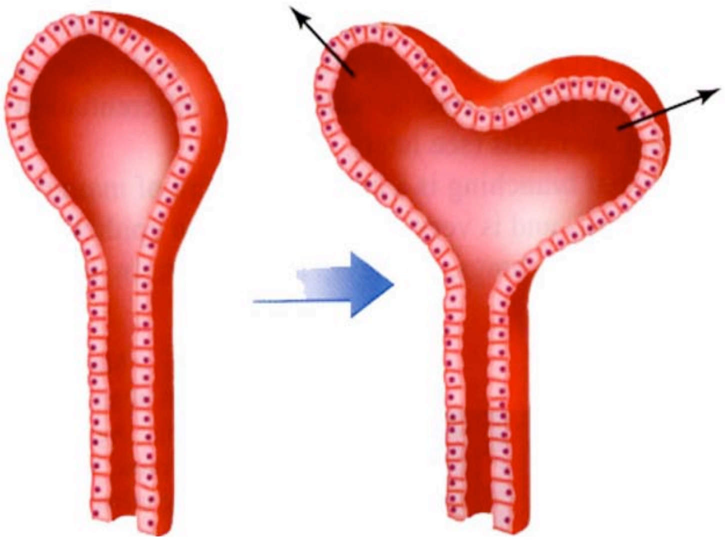


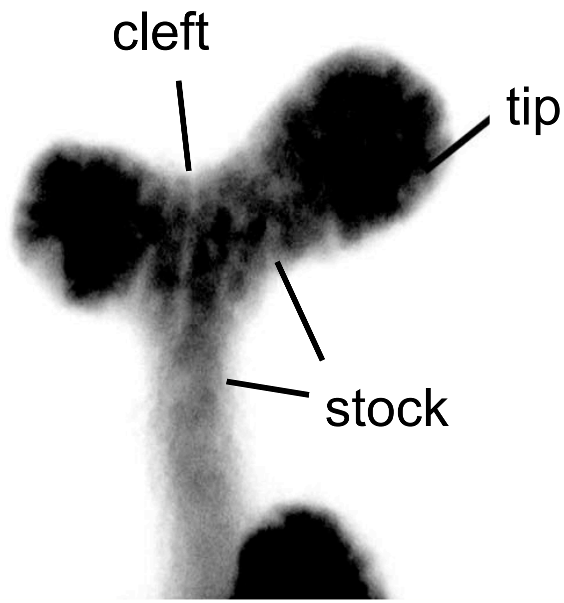
nephron progenitors **NEPHRONS**

ureteric bud tips **COLLECTING DUCT SYSTEM**

stroma CAPSULE/INTERSITIUM

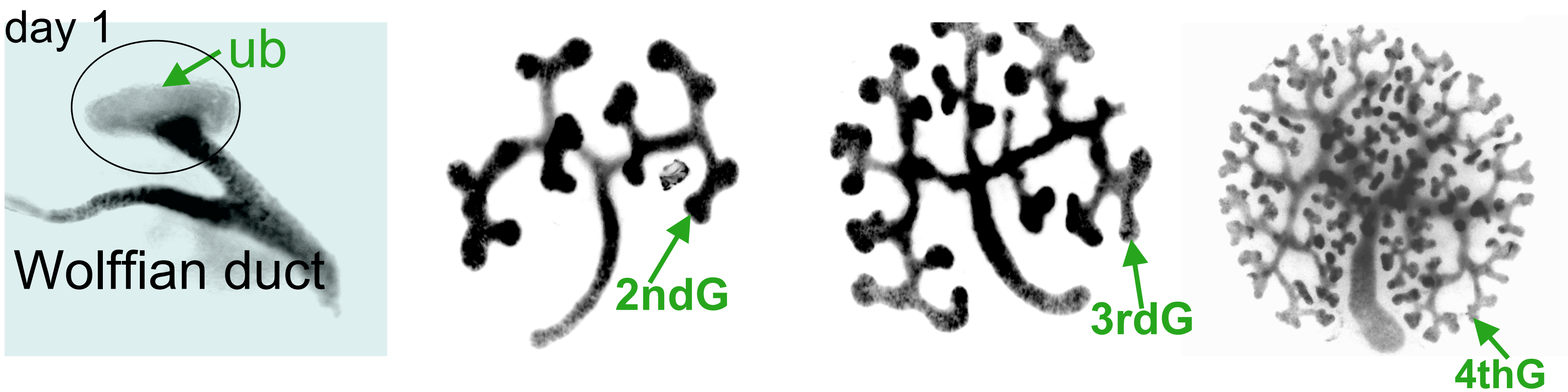
shape changes and local proliferation at ureteric bud tips forms an ampulla





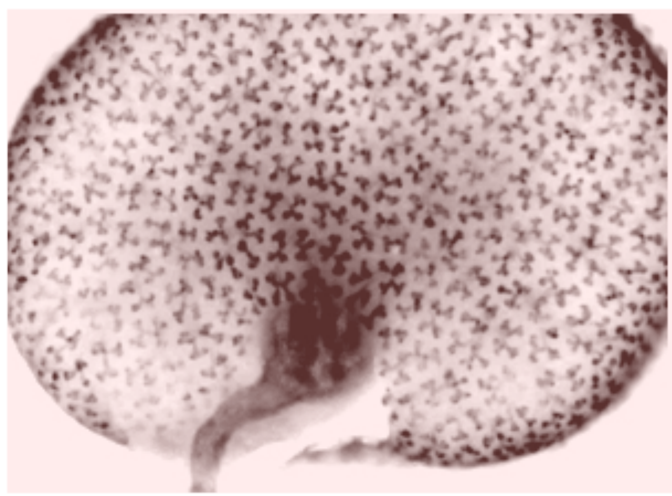
Branching morphogenesis:

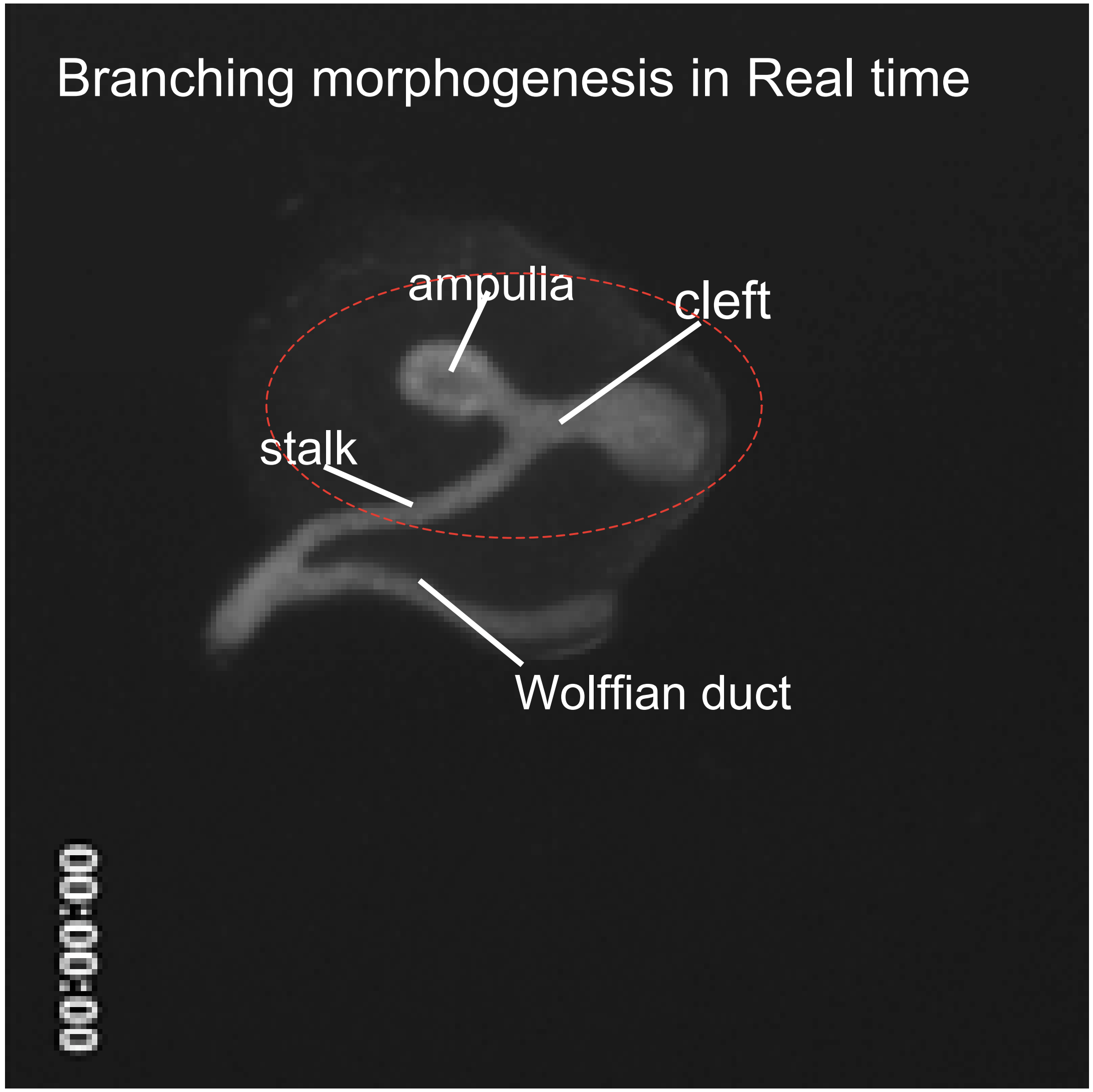
- ampullae form at ureteric bud tips
- a cleft forms and the tips begin to bifurcate
- the tips elongate
- new ampullae form



The collecting duct system grows from the periphery by **dichotomous branching**

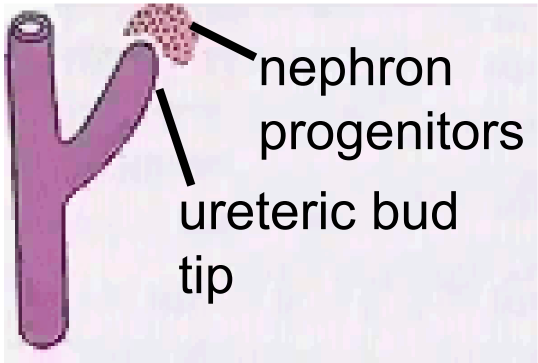
at birth:

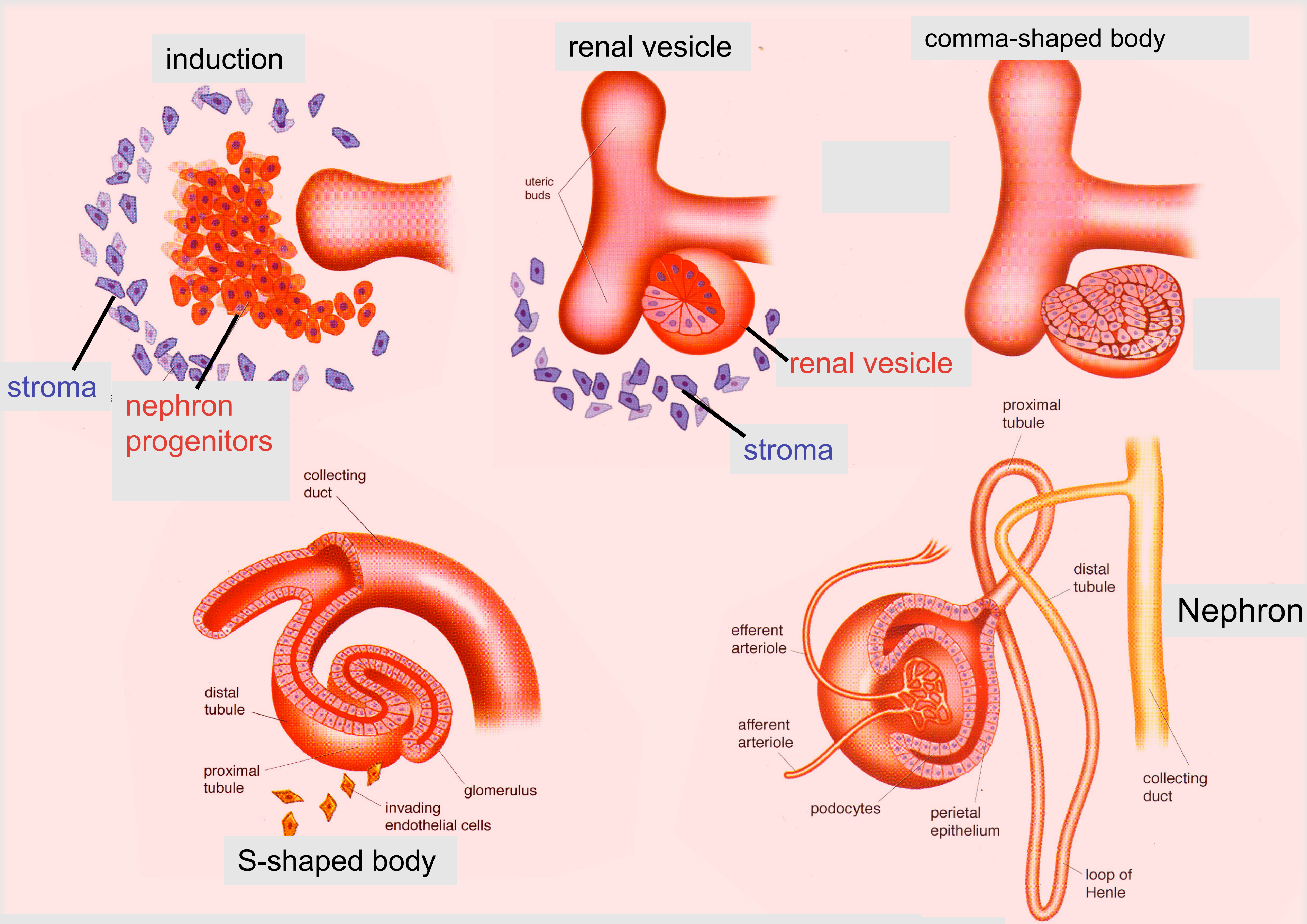




Costantini Lab
Columbia University, Dept. of Genetics &
Development

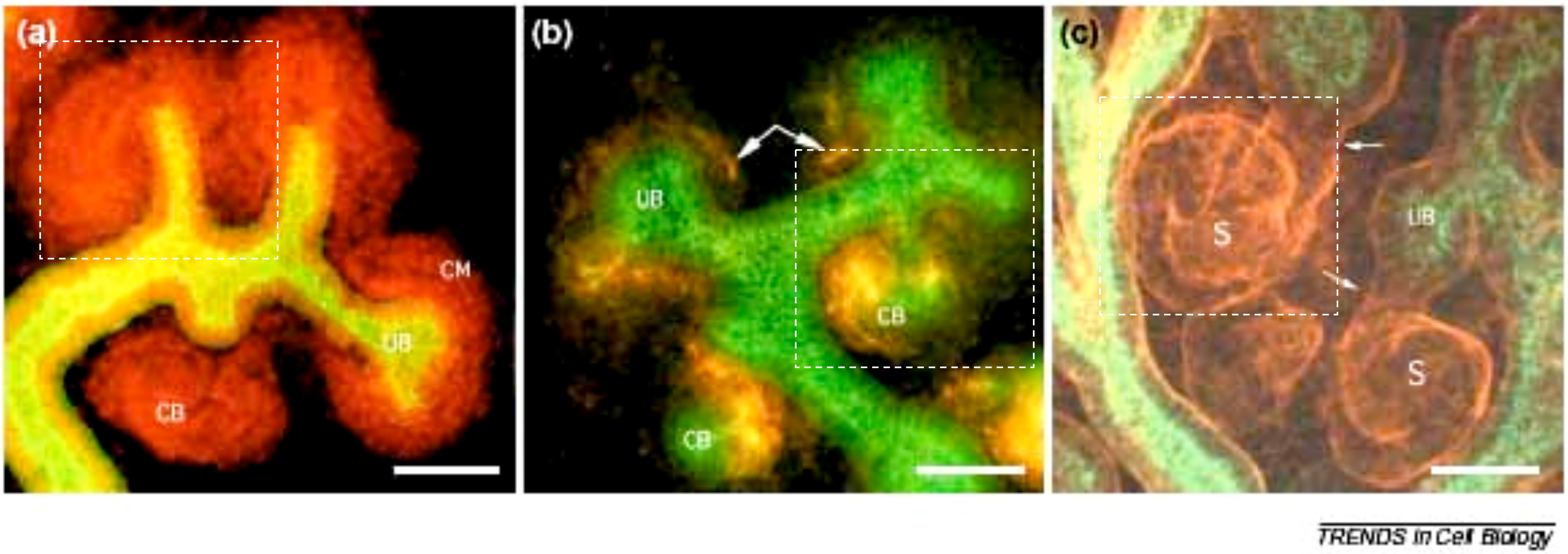
IEPHRONS FORM EXCLUSIVELY AT **URETERIC BUD TIPS** IN RESPONSE TO LOCAL SIGNALS FROM URETERIC BUD CELLS





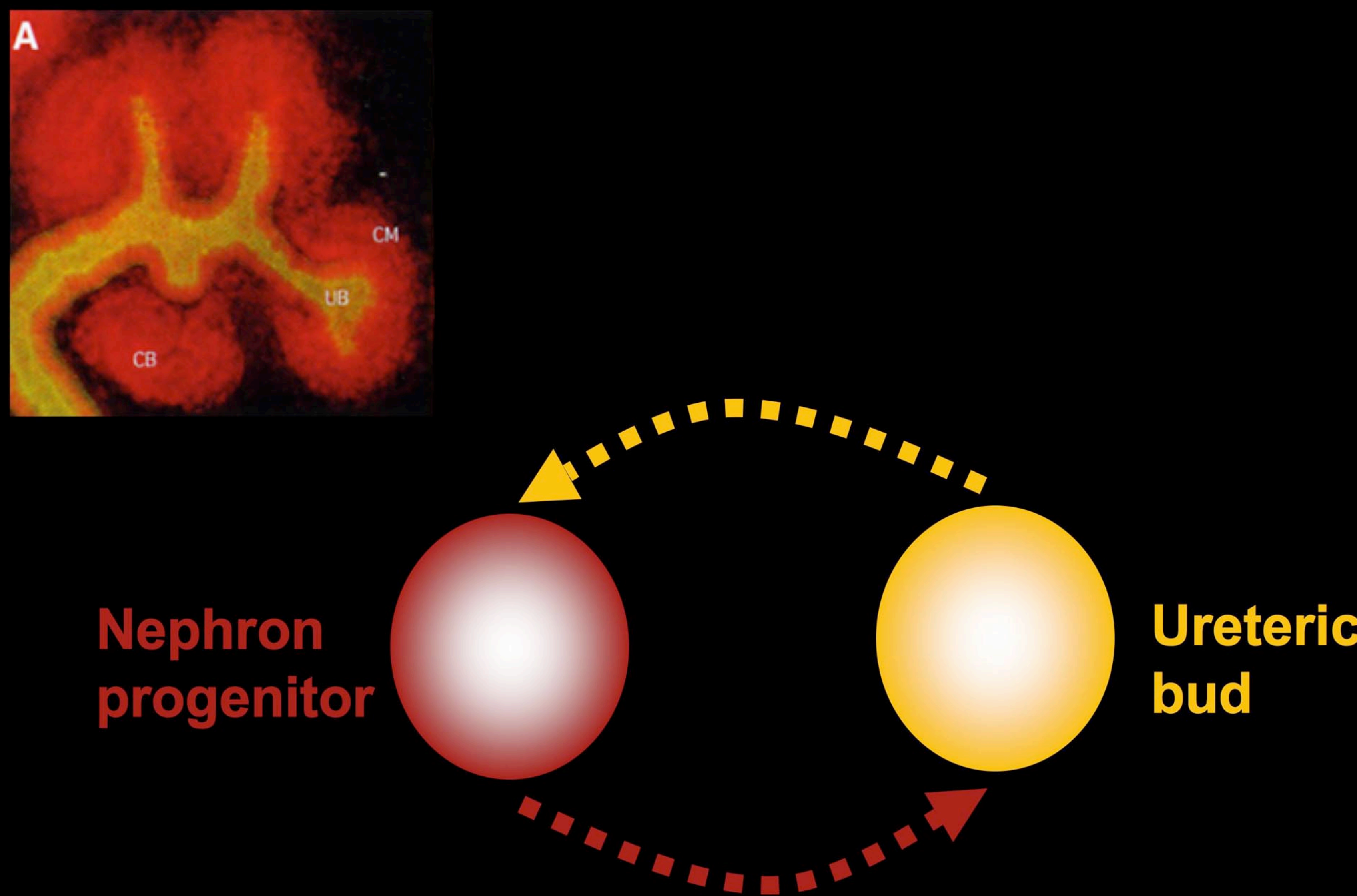
from "The Kidney: From normal development to congenital disease". 2003. Eds Vize, et al.

Nephron progenitors condense at ub tips, **aggregate**



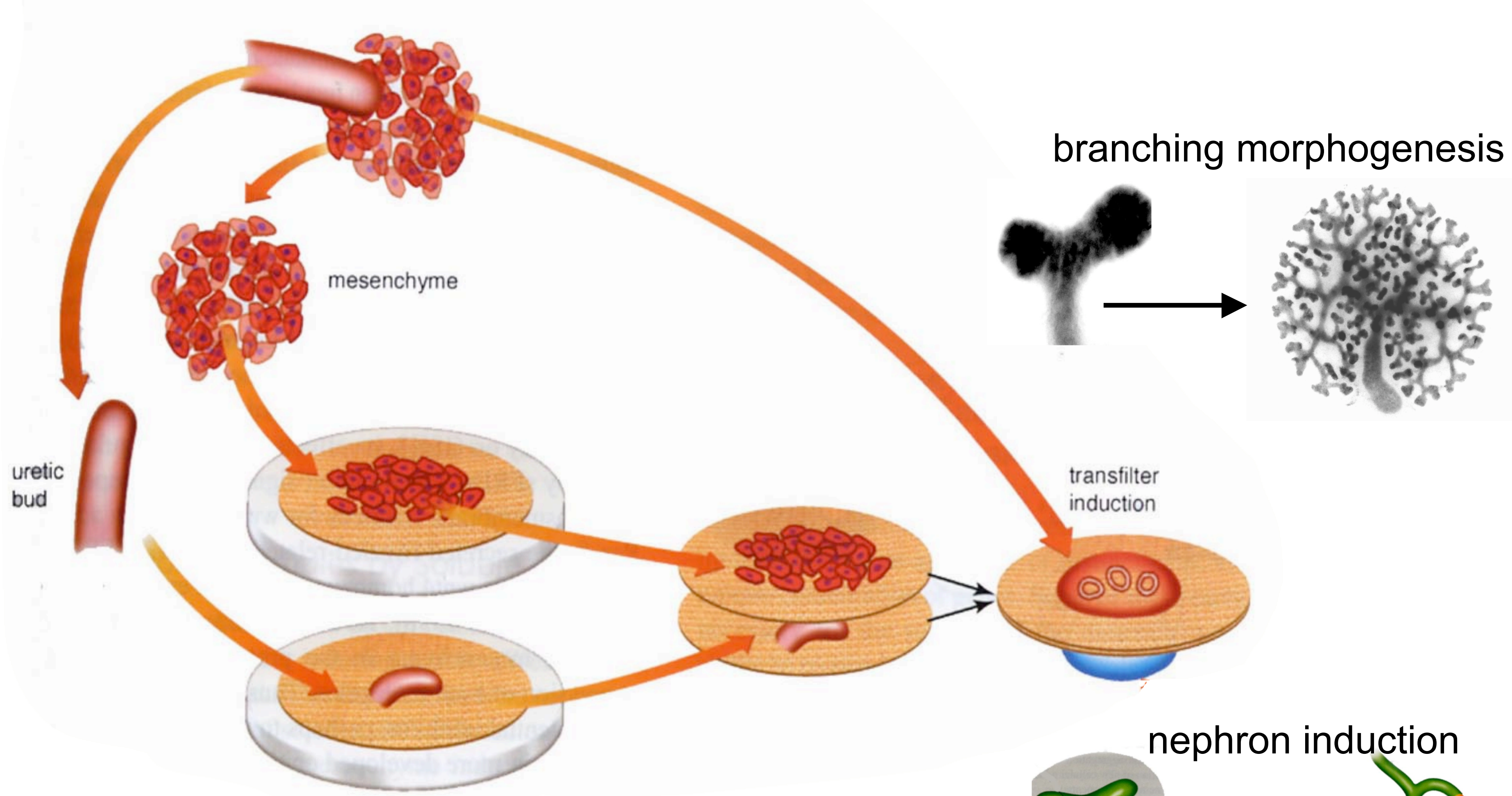
and **trans-differentiate** into epithelial cells that make up the renal vesicle, **Comma** and **S-shaped bodies**

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

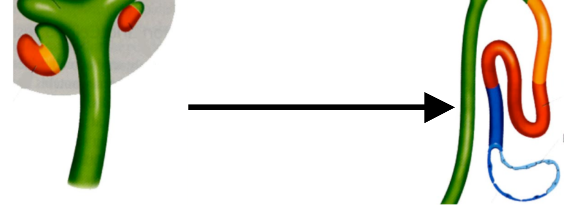


Reciprocal Signaling is required for branching morphogenesis and for nephron differentiation during renal development

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

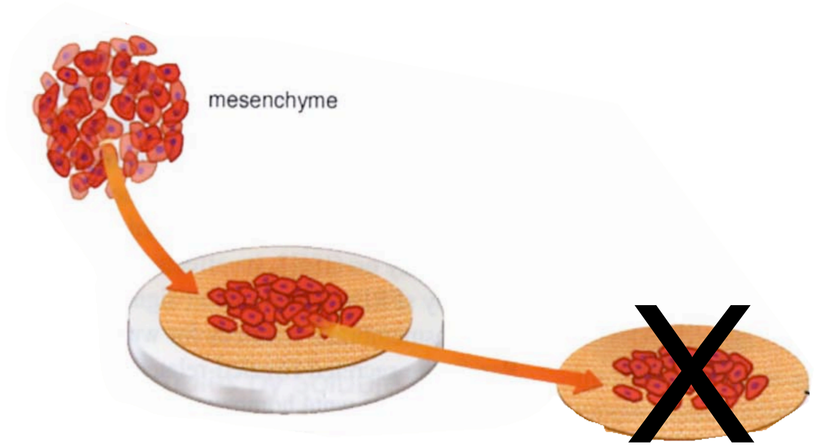


nephron induction



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

•no ureteric bud, nephron progenitors undergo apoptosis



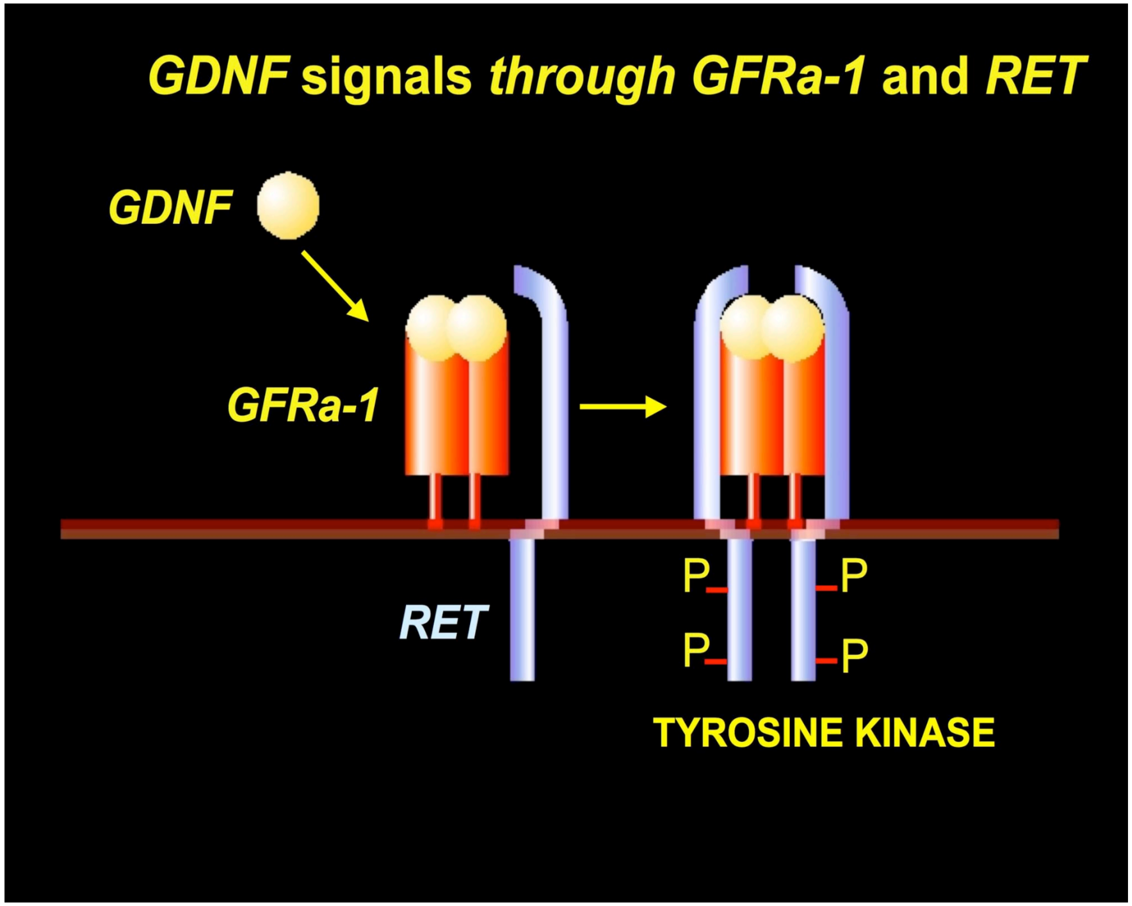
from: The kidney: Eds, Vize et al., 2003)

•no nephron progenitors, no branching morphogenesis

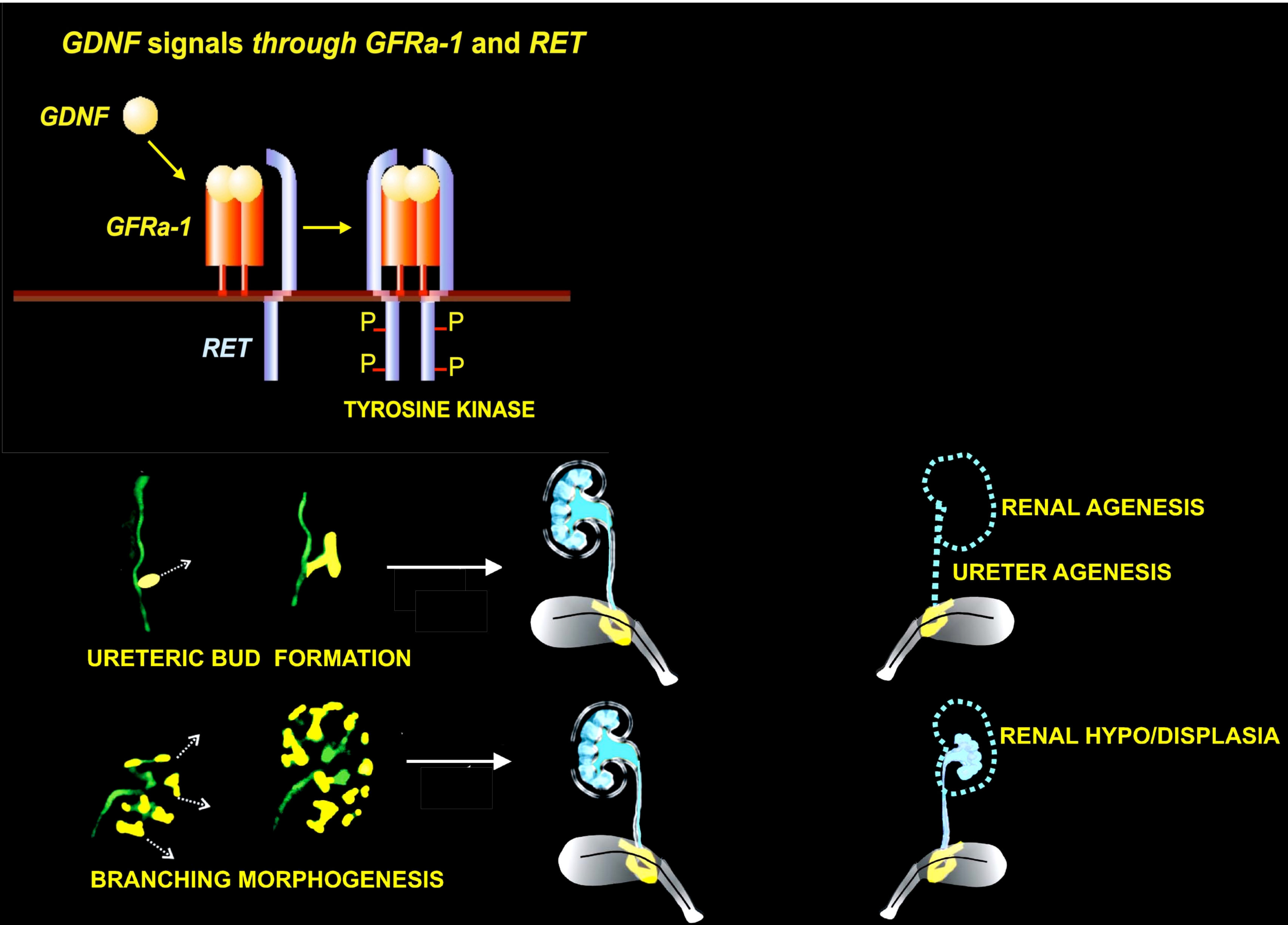
signals from the ureteric bud control nephron induction

signals from nephron progenitors control branching morphogenesis

RET-GDNF SIGNALING EXEMPLIFIES A RECIPROCAL
⁻HELIAL-MESENCHYMAL PATHWAY THAT IS CRUCIAL FOR RENAL DEVELOPMENT

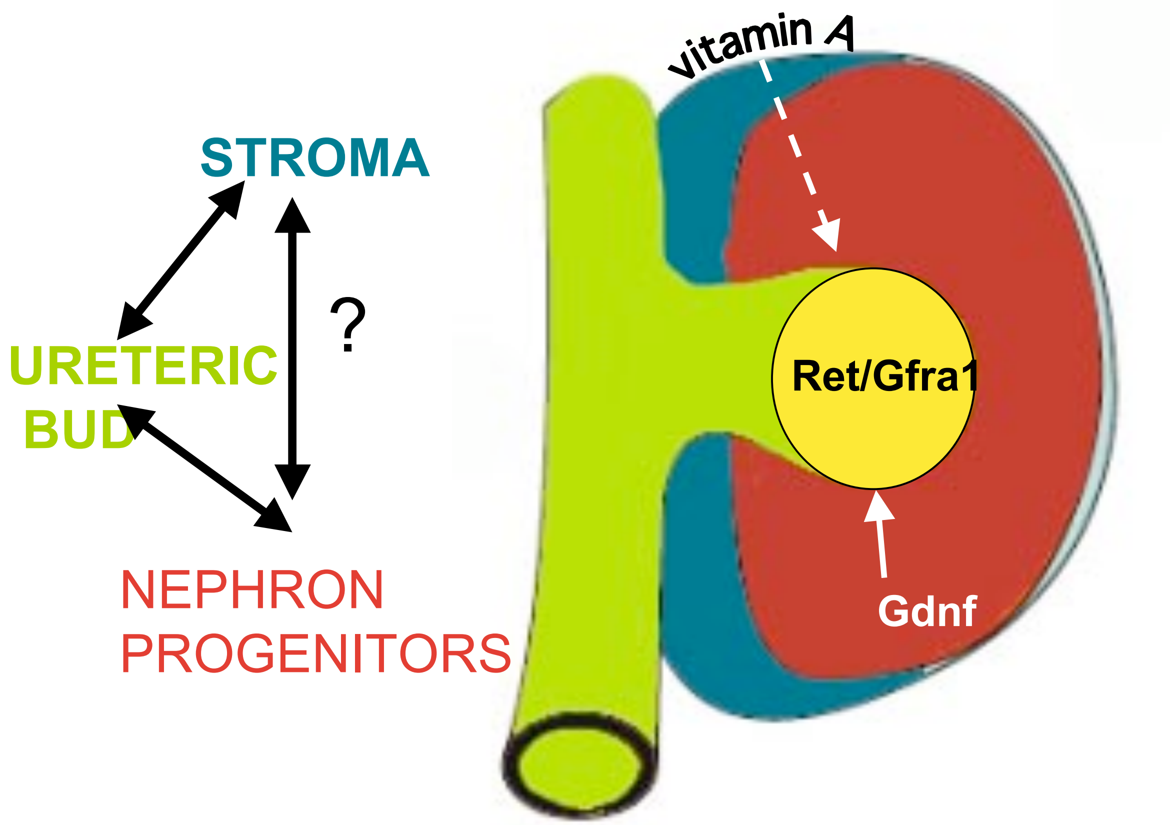


Ret mutations in humans cause renal abnormalities, Hirschsprung's disease and cancer



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

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

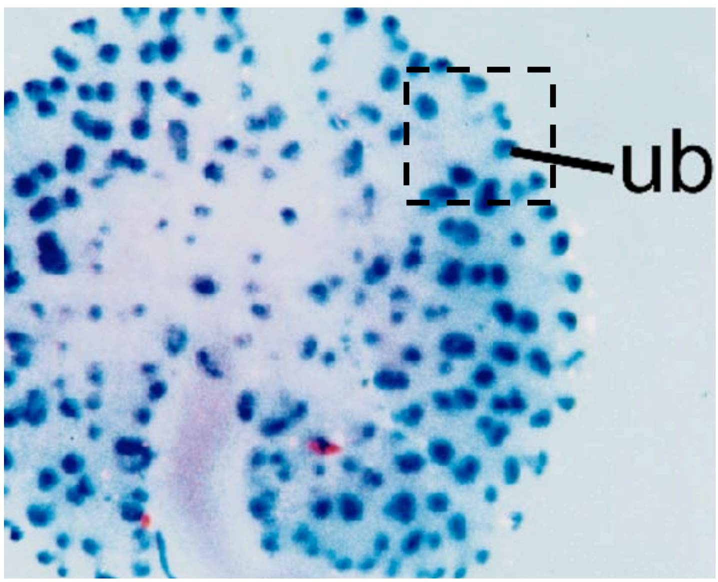


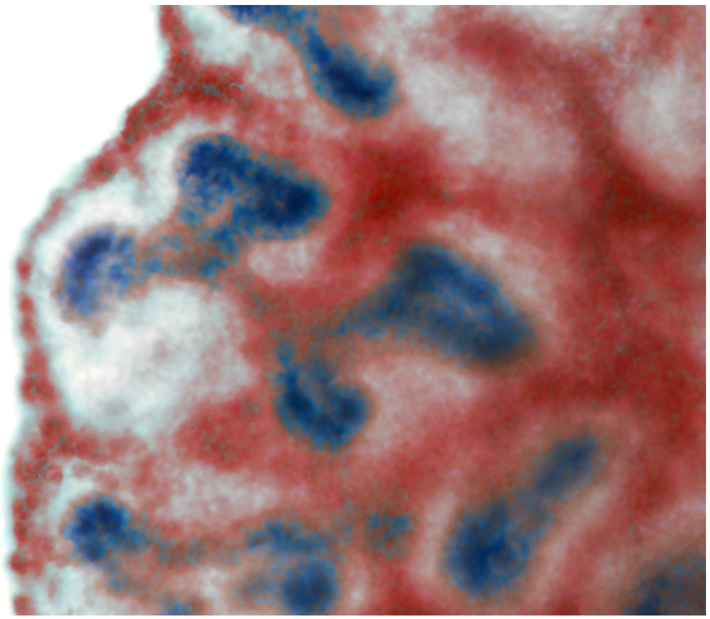
STROMAL CELL SIGNALS CONTROL RET EXPRESSION IN URTERIC BUD

The *Ret* receptor is expressed in ureteric bud tips and control branching morphogenesis

ureteric bud (RET)

stroma (vitamin A)

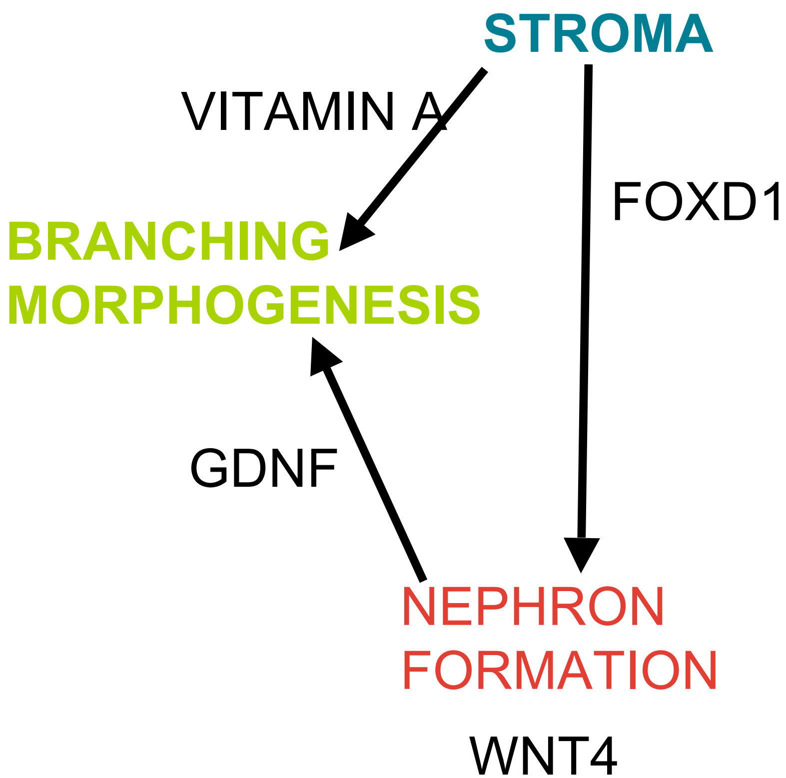




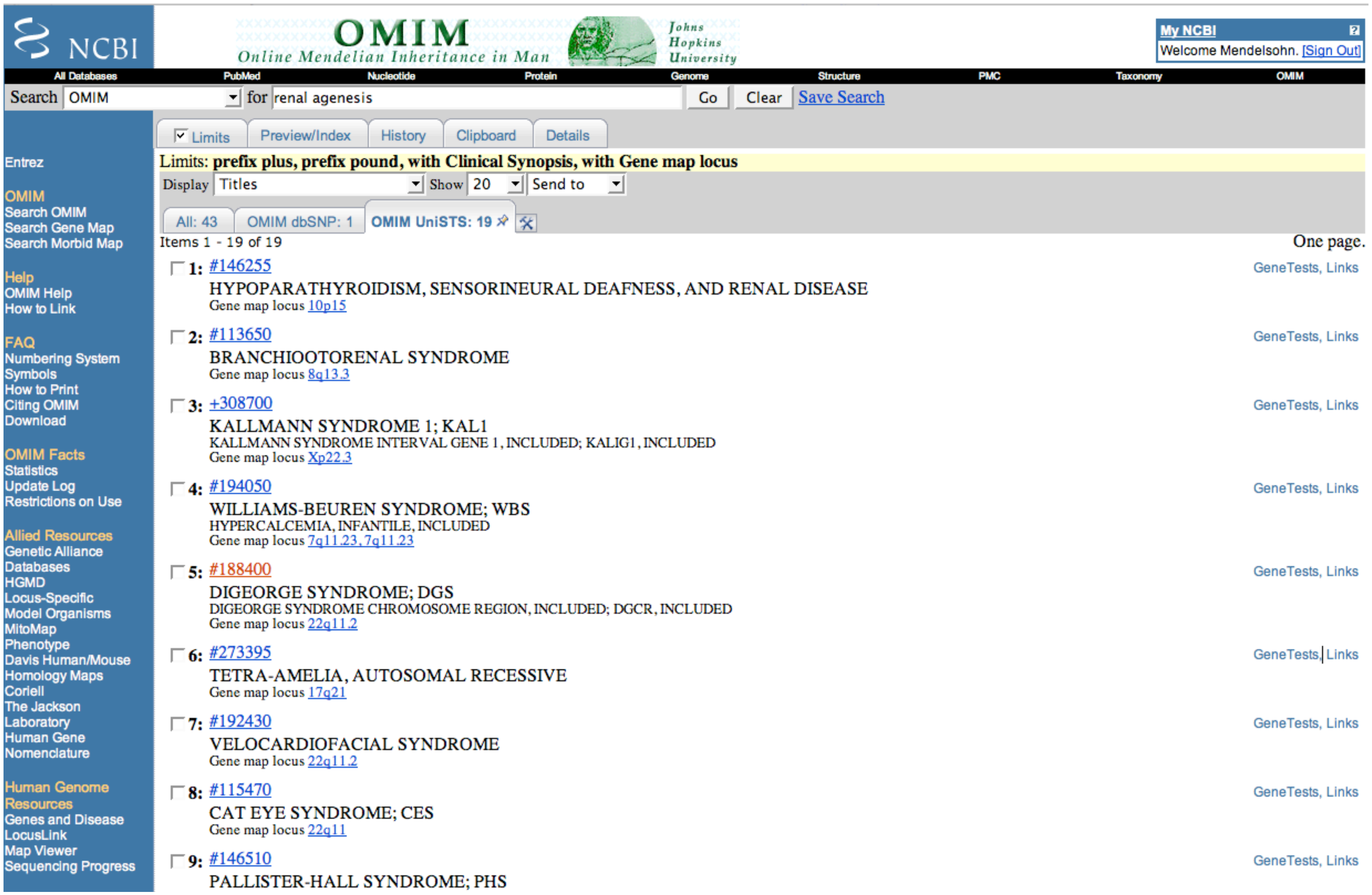
Vitamin A from Stromal cells controls Ret expression in ureteric bud cells

Vitamin A deficiency generates renal malformations similar to those induced by Ret mutations

MANY GENES ARE NOW KNOWN THAT REGULATE RENAL DEVELOP

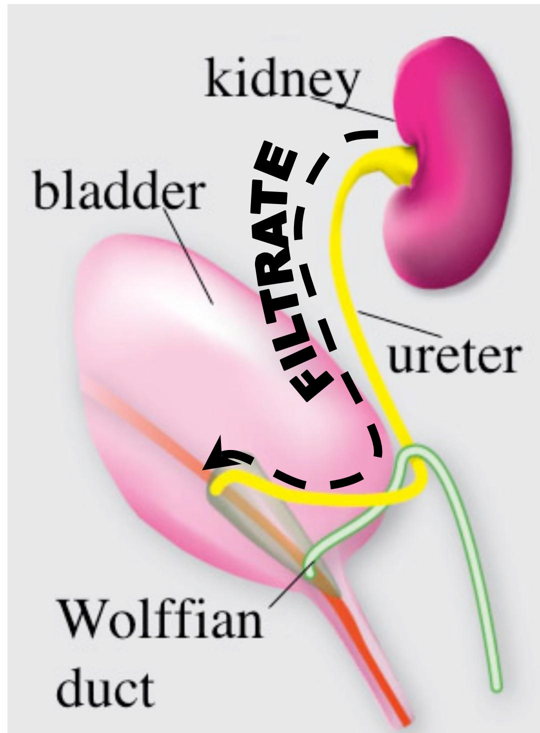


Mouse models and human genetics have identified genes that when deleted in humans result in renal abnormalities



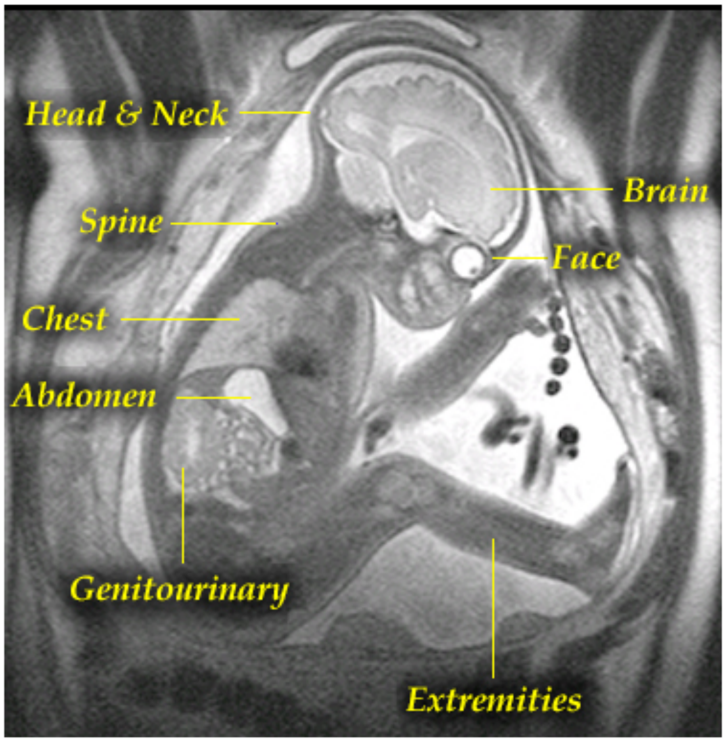
but in most cases, the genetic basis of renal defects is still unknown

Part II. The lower urinary tract



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

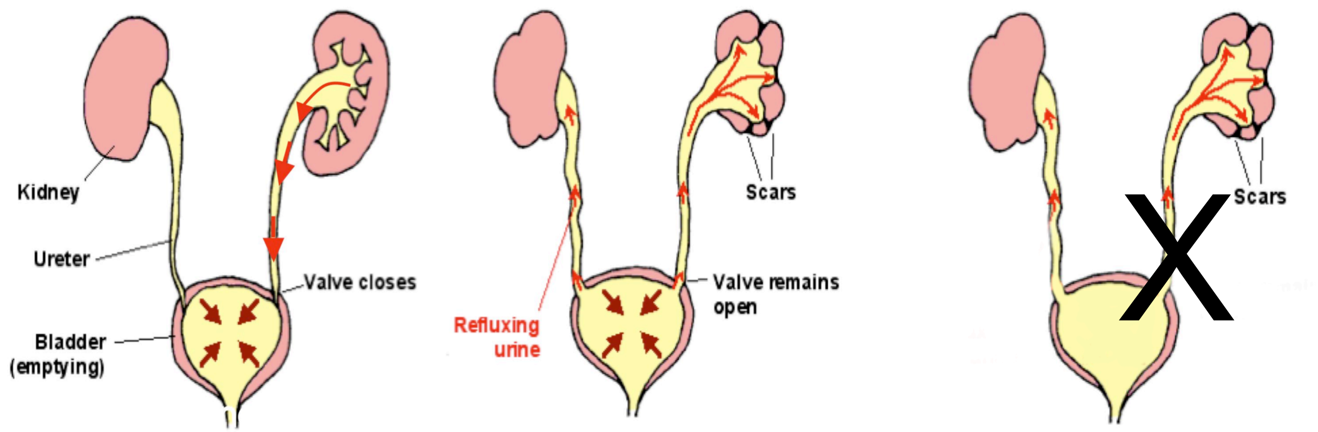
physical or functional blockage that impedes urine flow can cause renal scarring, hydronephrosis or end state renal disease



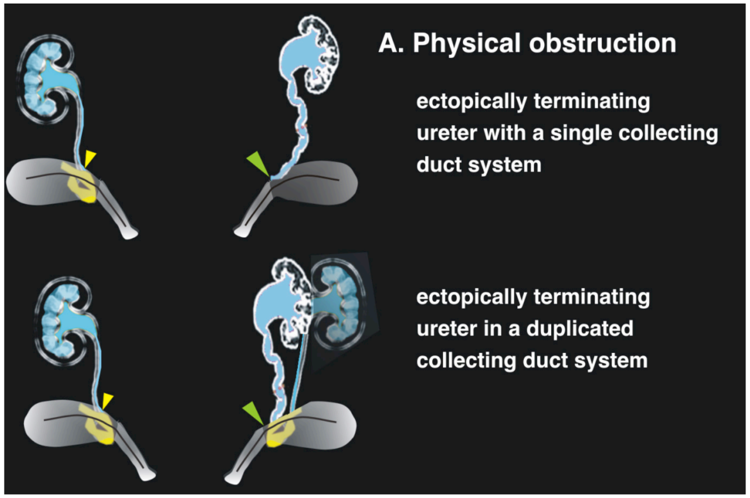
hydronephrosis *in utero*

proper positioning of the ureter orifice is necessary for:

- formation of patent connections along the outflow tract
- preventing reflux



normal reflux obstruction

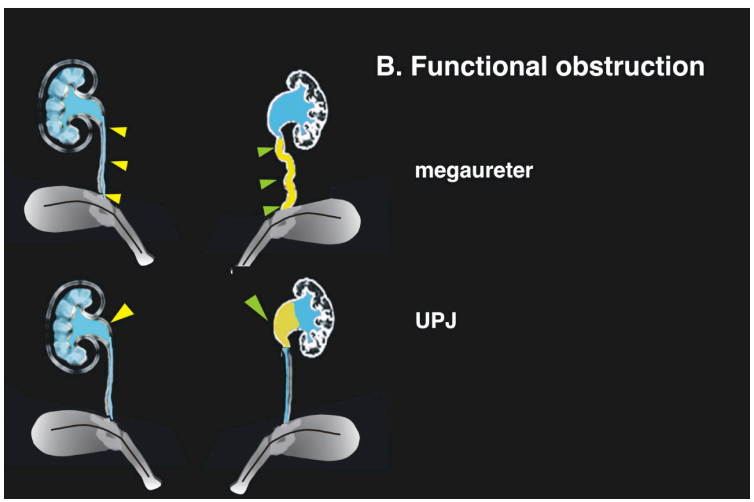


abnormal position of the ureter orifice

vitamin A deficiency, Ret

sprouty, slit-2, retinoid excess

Physical vs Functional obstruction

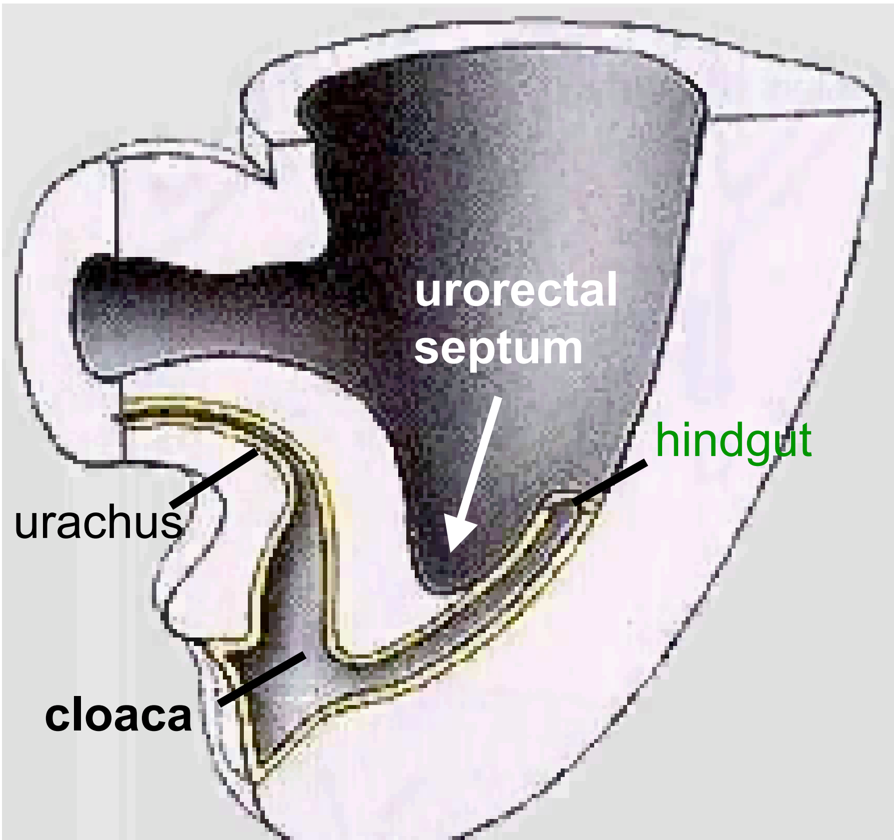


abnormal peristalsis

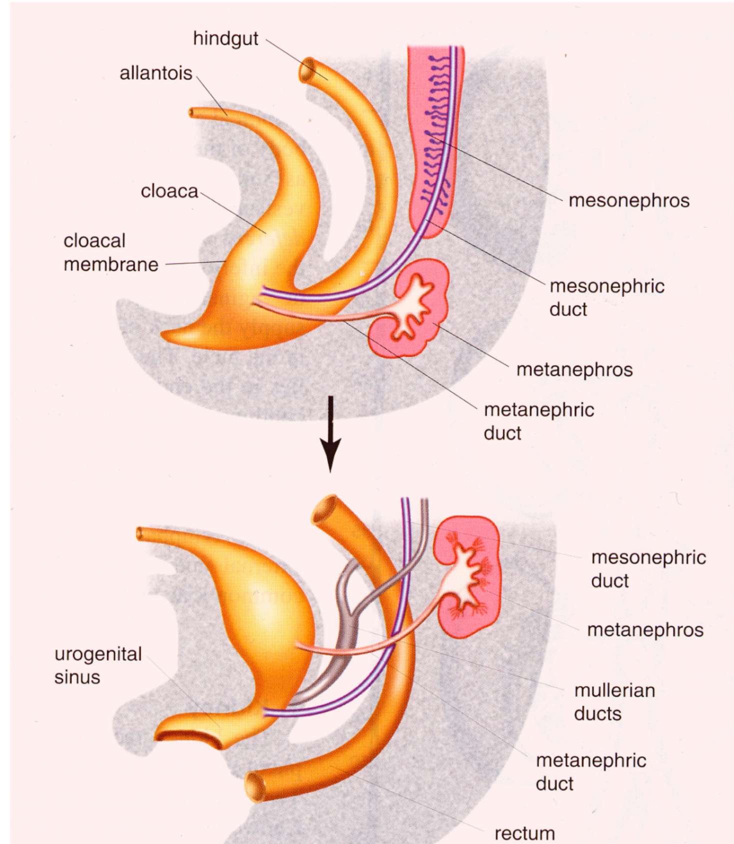
sonic hedgehog (muscle)

Calcineurin B (peristalsis)

uroplakin (epithelium)



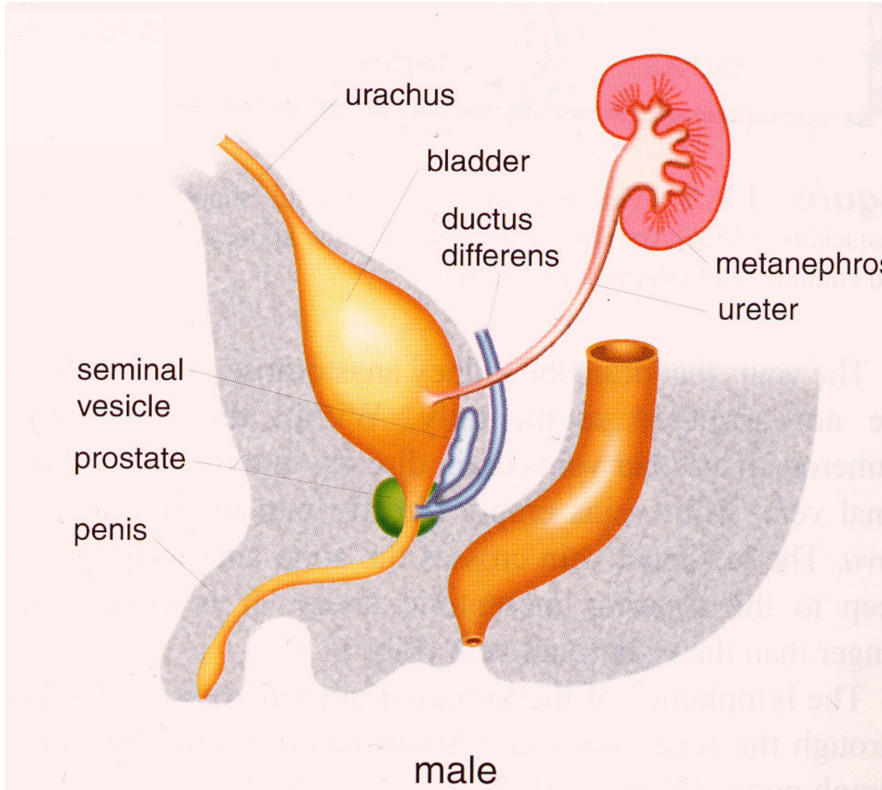
Larsen's Embryology, 6th Edition



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

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

The urogenital sinus forms the bladder and urethra in both sexes

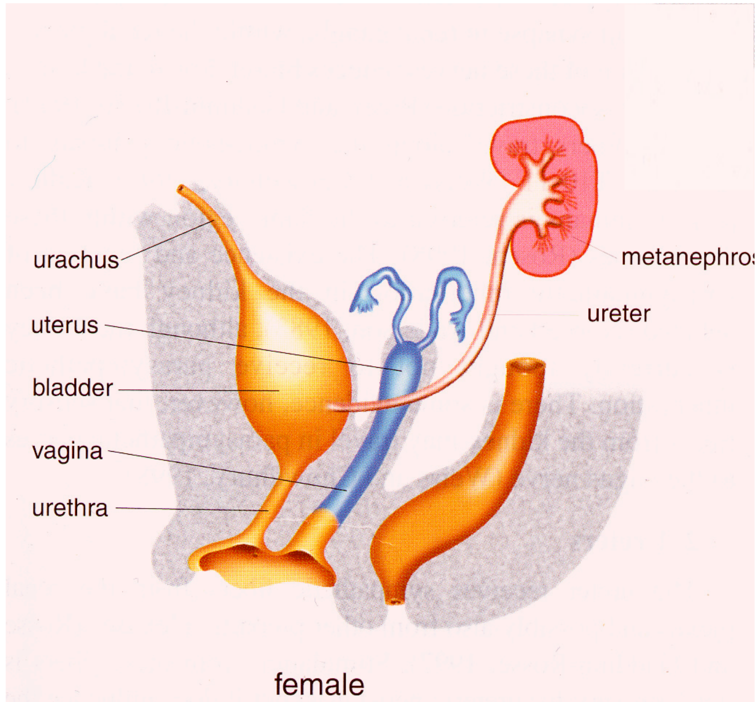


•The urogenital sinus forms the bladder, urethra (including the prostate and penis)

•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)



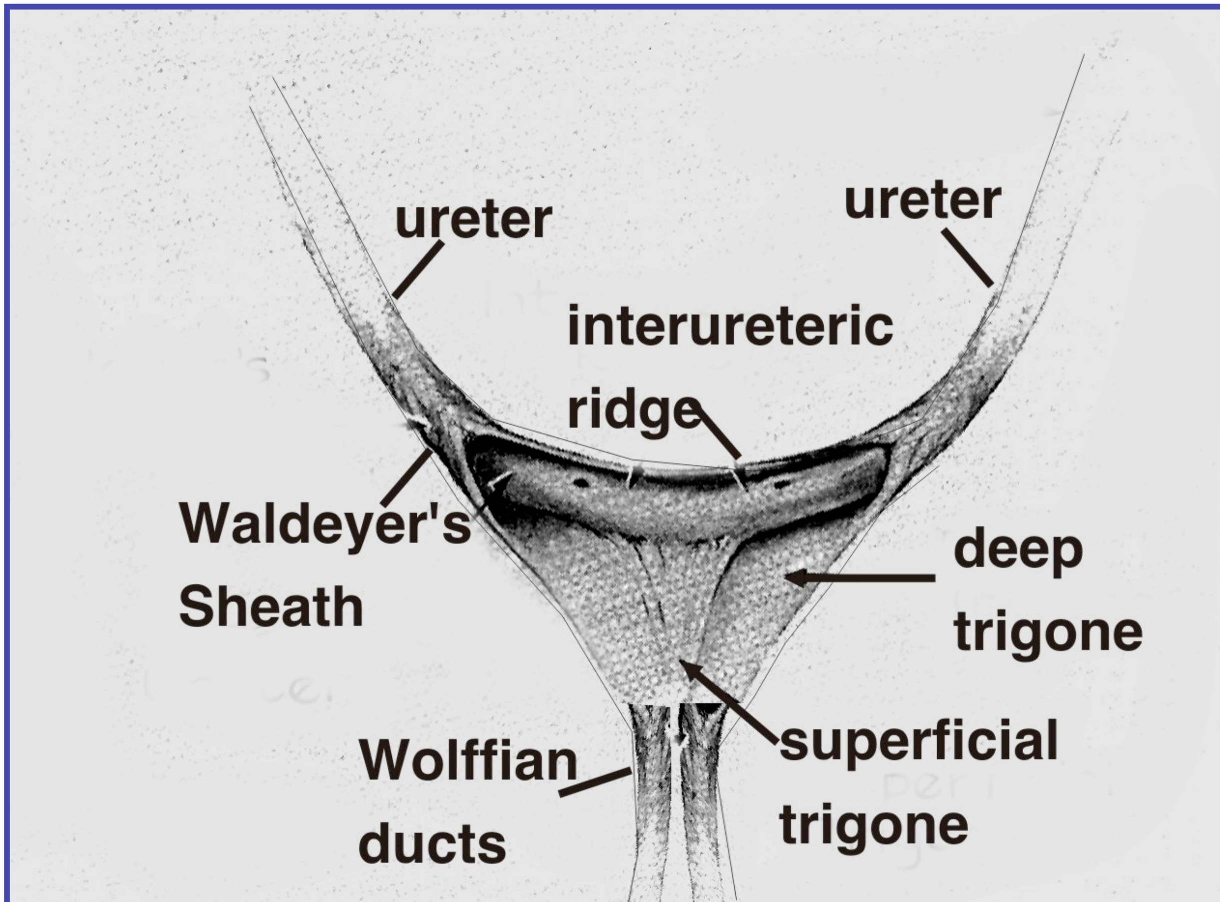
•in females the urogenital sinus forms the bladder, urethra and vagina

•Mullerian (paramesonephric ducts) differentiate into the uterus and upper vagina

•Wolffian (mesonephric ducts) regress

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

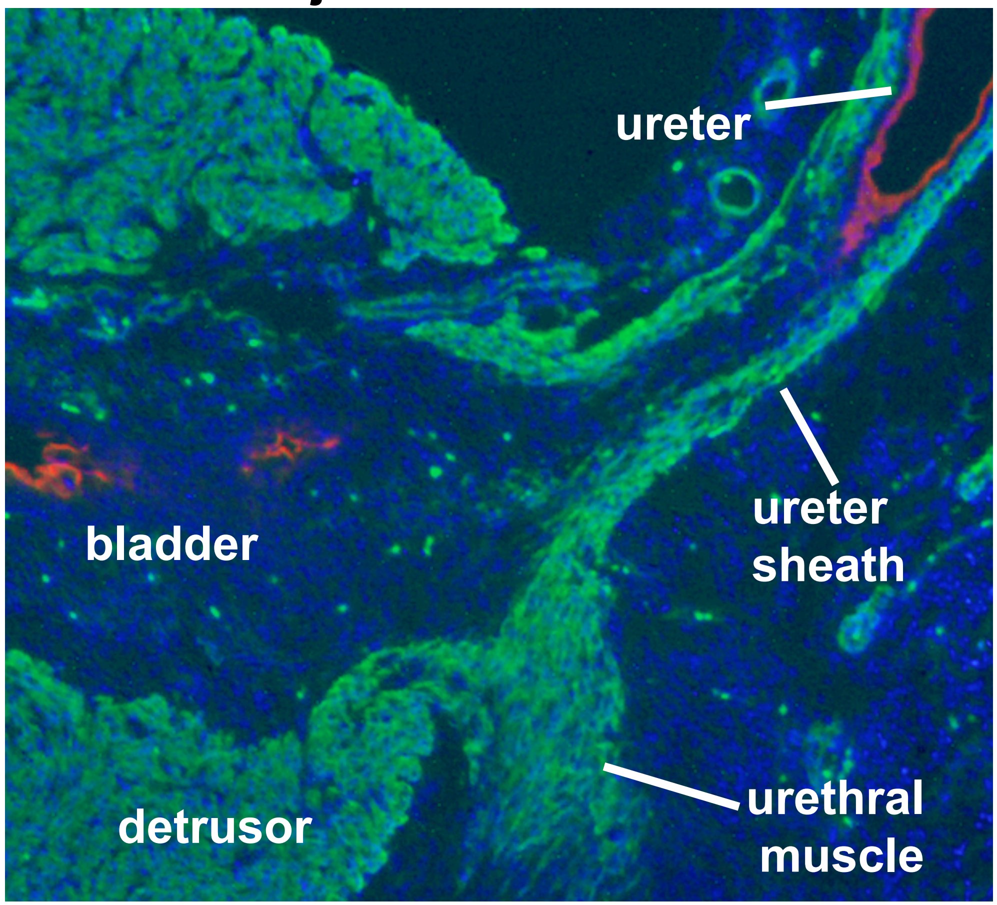
Urine transport depends on proper connections between the ureters and the **bladder trigone**



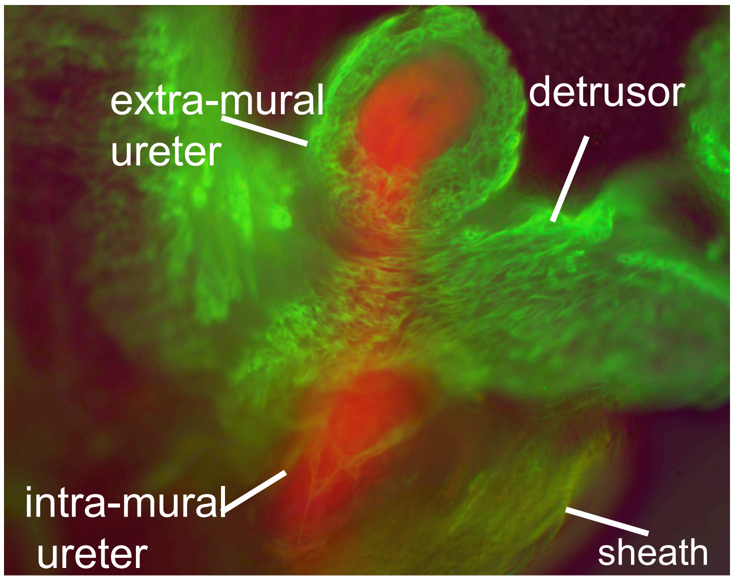
The **trigone** is defined as the portion of the urogenital sinus that lies between the ureters and sex ducts

after: Hutch, J.A. Anatomy and physiology of the bladder, trigone and urethra, xv, 180, [2] p. (Butterworths Appleton-Century-Crofts, London, New York,, 1972).

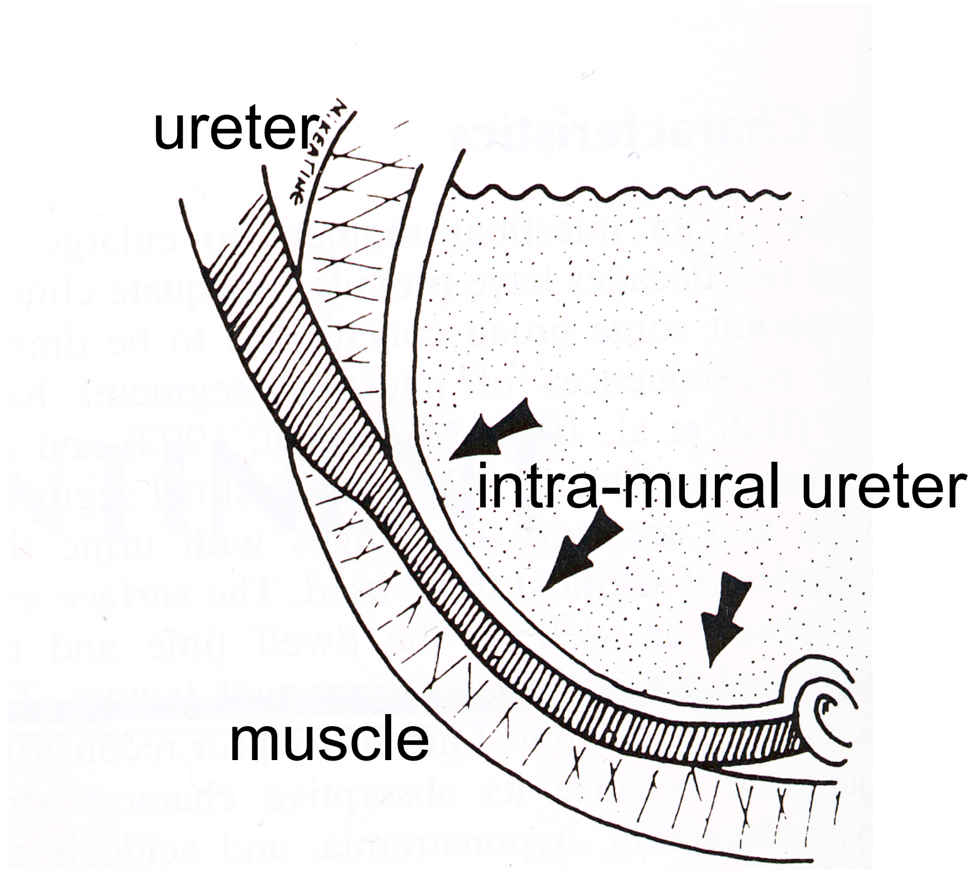
The trigone is a region where the detrusor and urethral muscle join the ureteral fibers



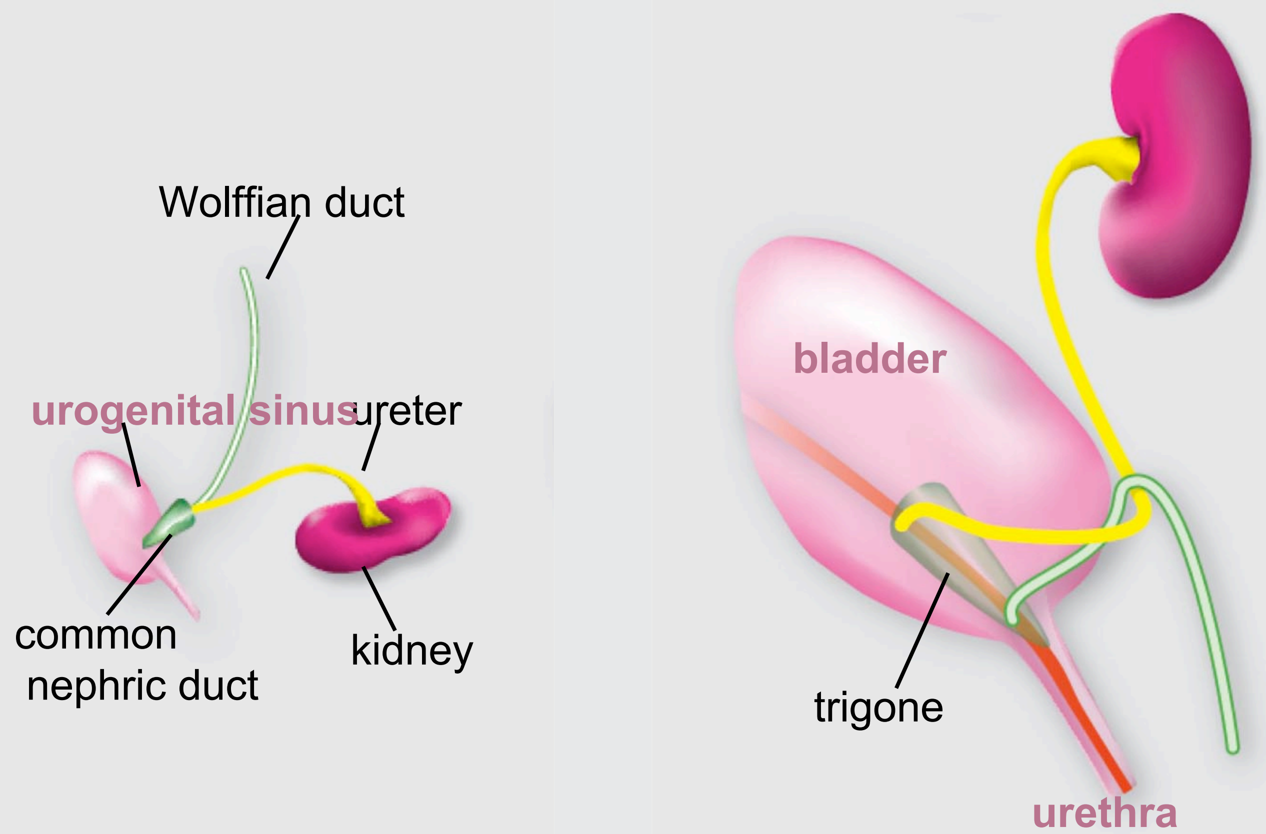
proper configuration of muscle groups that form the trigone is likely to be important for urinary tract function the **flap valve** is part of the trigone and is an **anti-reflux** mechanism that prevents urine back flow (reflux)



smooth muscle actin
ureter epithelium

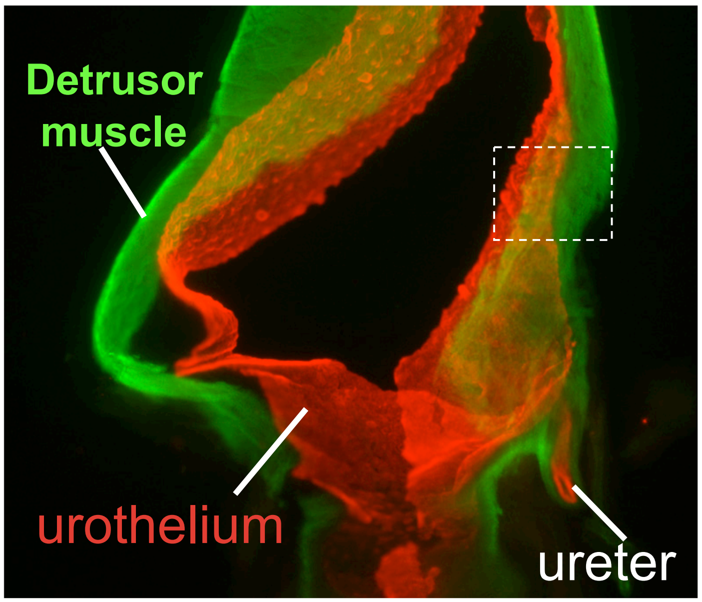


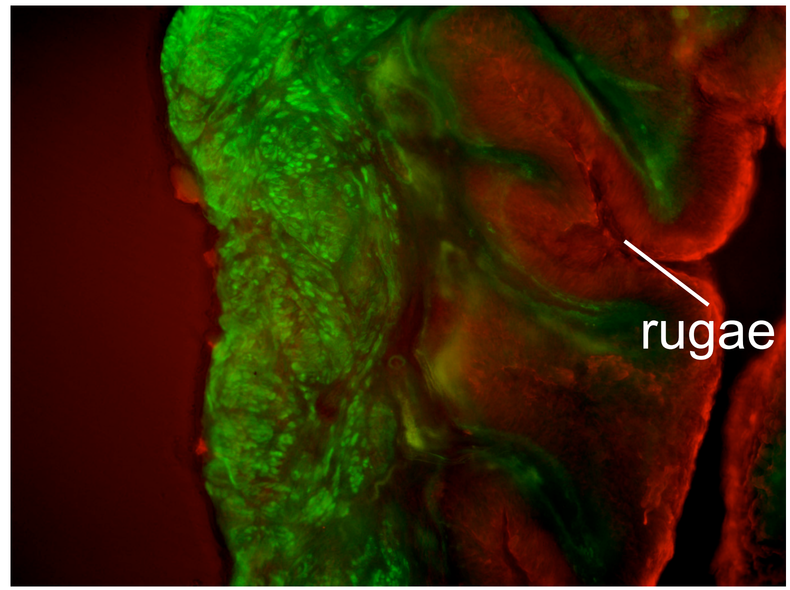
Flap-valve function depends on insertion of the ureter orifice at the proper position in the bladder neck (trigone)



THE **TRIGONE** IS MORPHOGLOGICALLY DISTINCT FROM THE BLADD
AND IS THOUGHT TO BE DERRIVED FROM THE COMMON NEPHRIC D

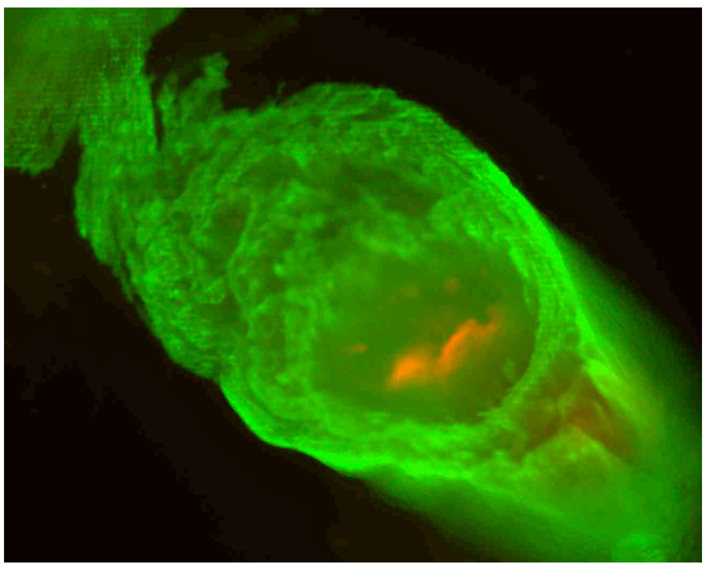
The bladder epithelium is lined with
plaques made from **uroplakins** that form a water-proof barrier

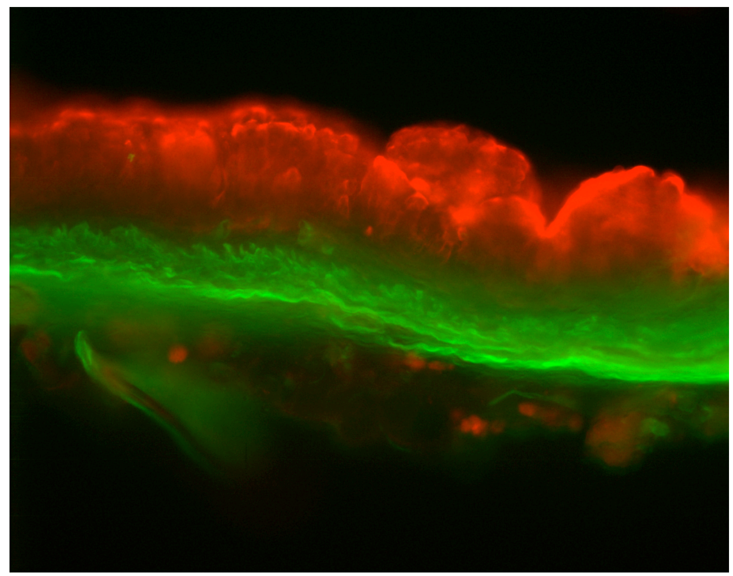




smooth muscle of the detrusor and rugae (folds) in the urothelium
allow the bladder to expand and contract

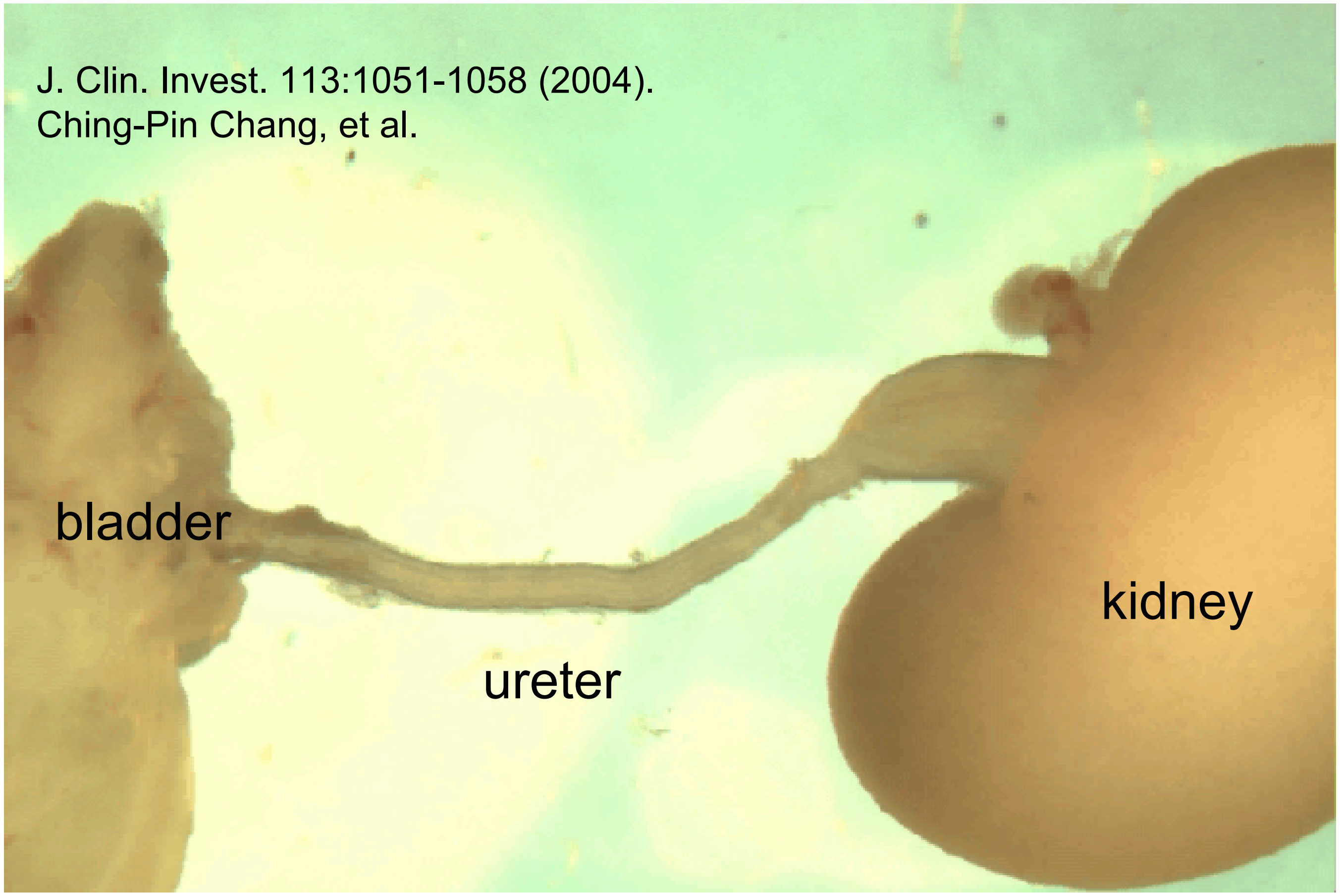
- a transitional epithelium expressing uroplakin also lines the ureters
- The ureter smooth muscle coat mediates myogenic peristalsis
- defective smooth muscle formation or mutations in uroplakins cause functional obstruction





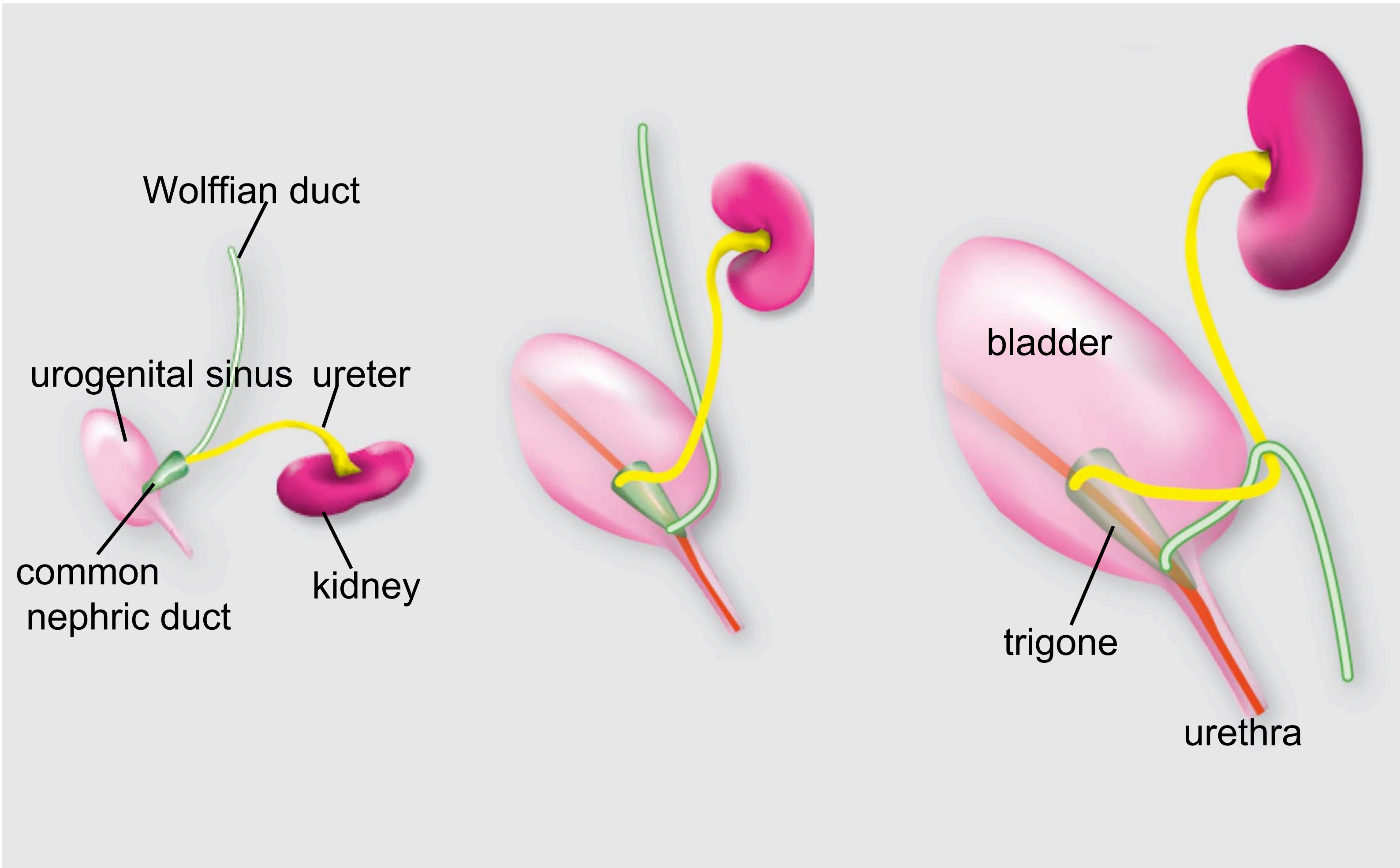
smooth muscle actin
uroplakin

URETER PERISTALSIS IN VITRO (E15 mouse embryo):



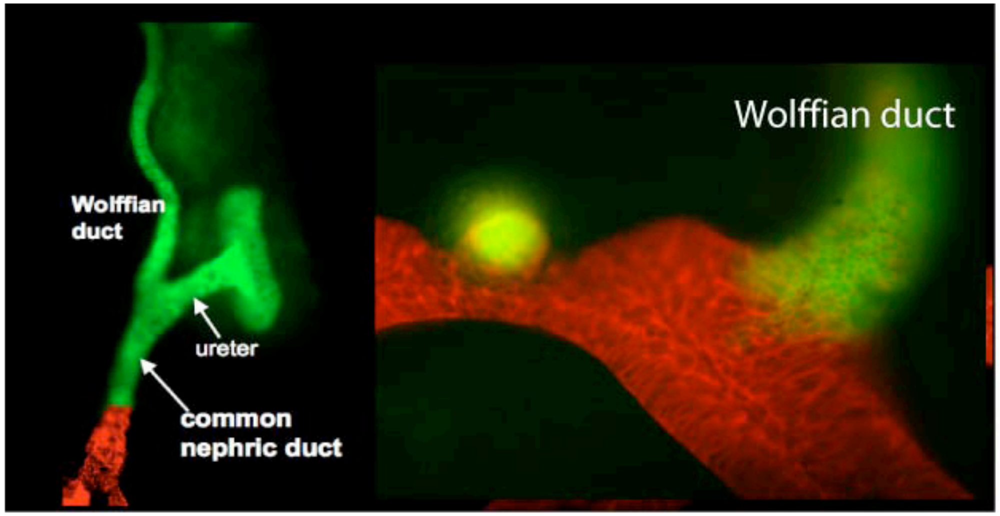
Impaired peristalsis is a cause of obstruction (functional obstruction)

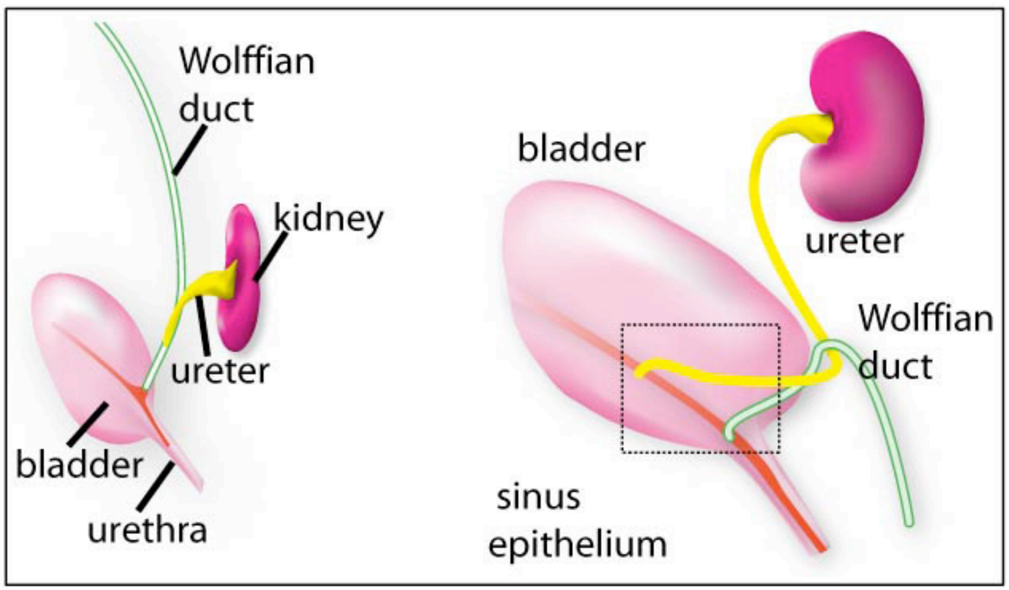
The ureter is initially joined to the Wolffian duct (future vas-deferens) not to the bladder



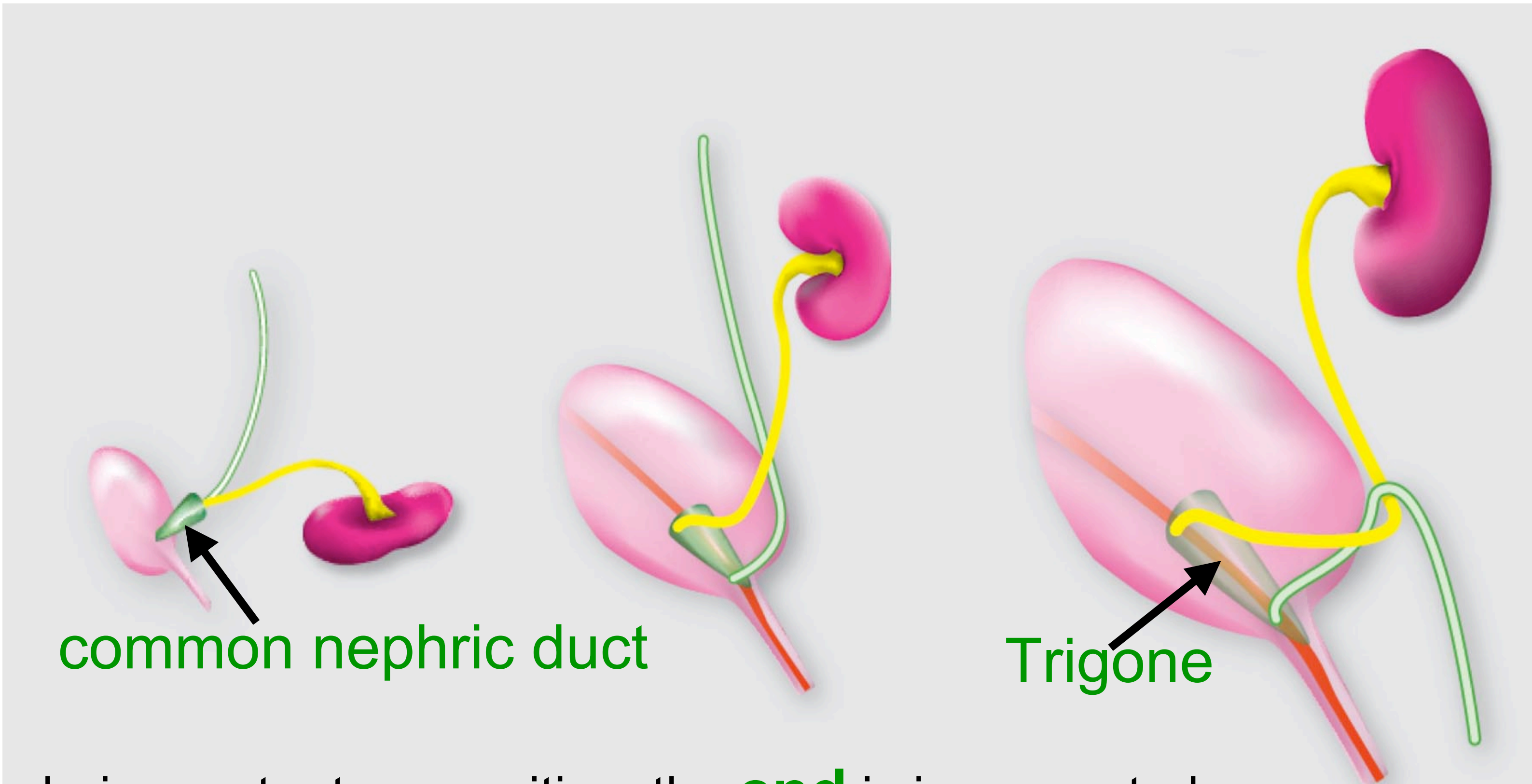
Mature connections are established when the ureter orifice is **transposed** from the posterior Wolffian duct (**the common nephric duct)** to the bladder

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



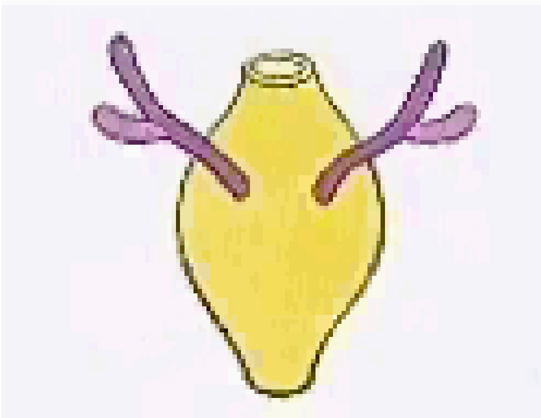


According to the accepted model, trigone formation is considered to be crucial for repositioning the ureter orifice



during ureter transposition, the **cnd** is incorporated into the bladder where it expands to form the **trigone** effectively separating the ureter orifice from the Wolffian duct

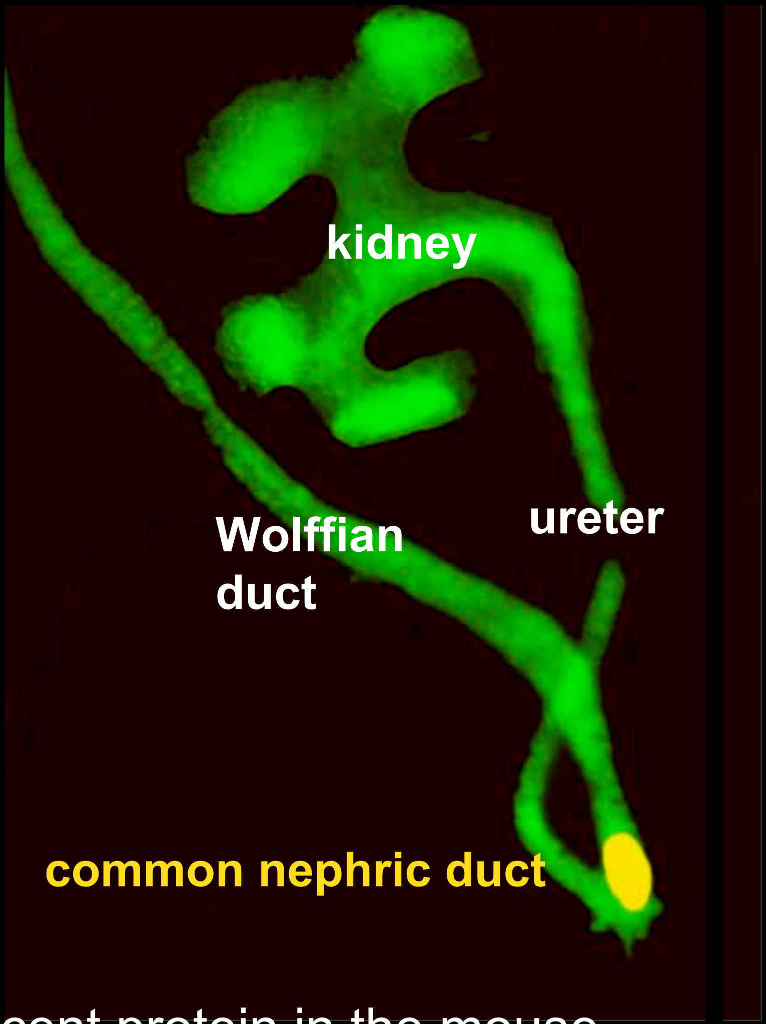
Accepted model of ureter transposition



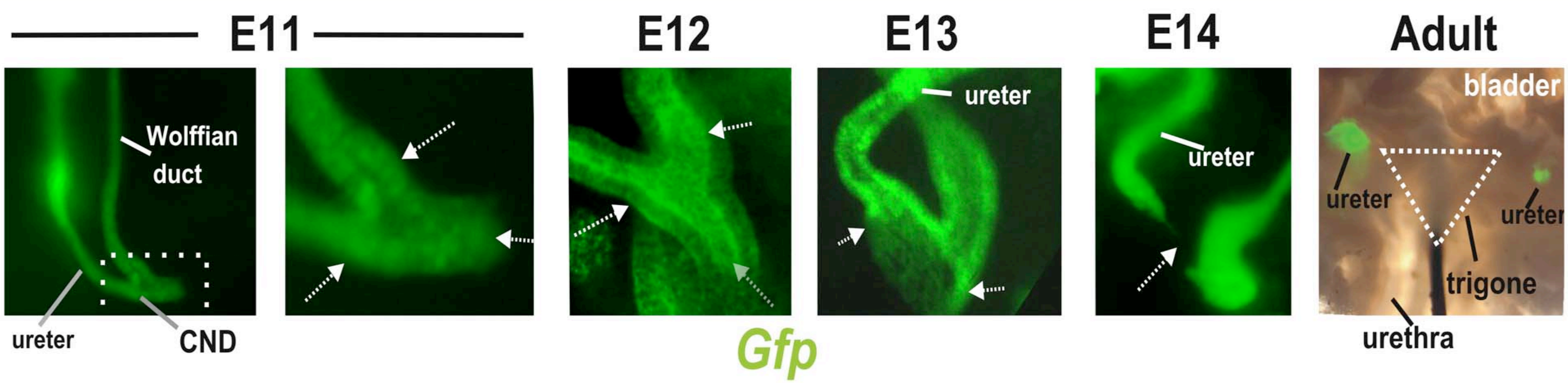
formation of the **trigone** from the **common nephric duct** repositions the ureters in the bladder

Larsen's Embryology

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

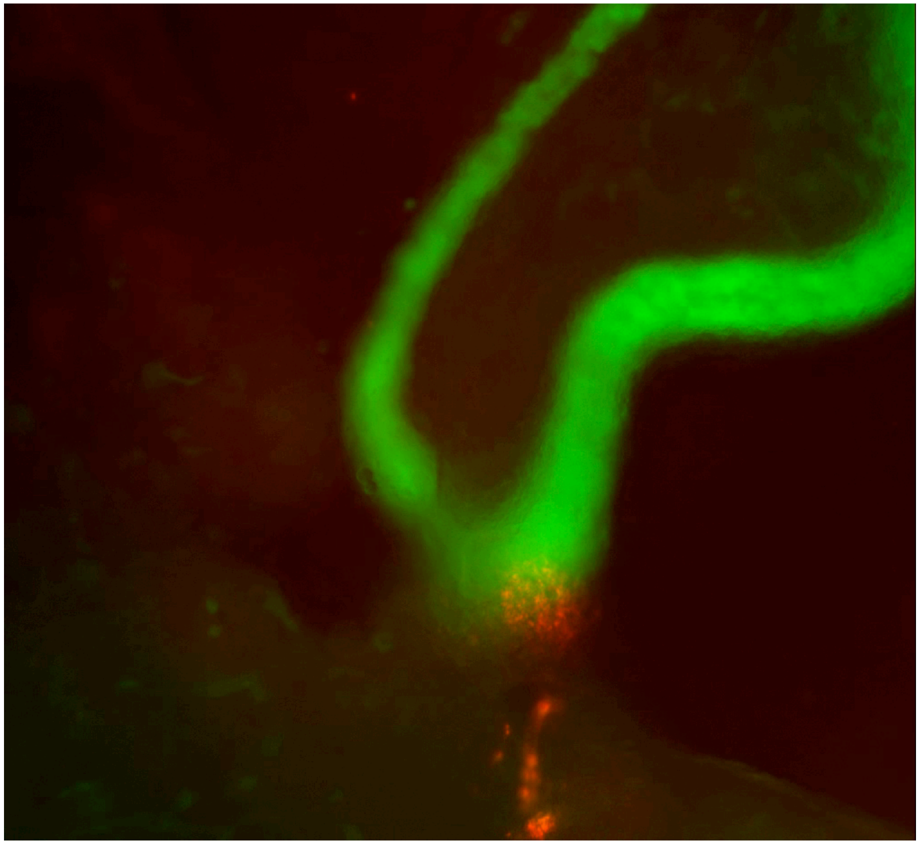


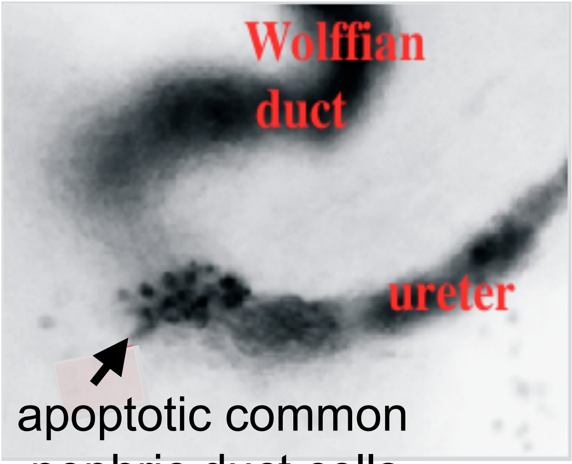
expression of Jelly Fish green fluorescent protein in the mouse common nephric duct of this transgenic mouse enables us to follow its fate during ureter insertion what happens to the common nephric duct during ureter transposition?



The common nephric duct appears to regress rather than expand

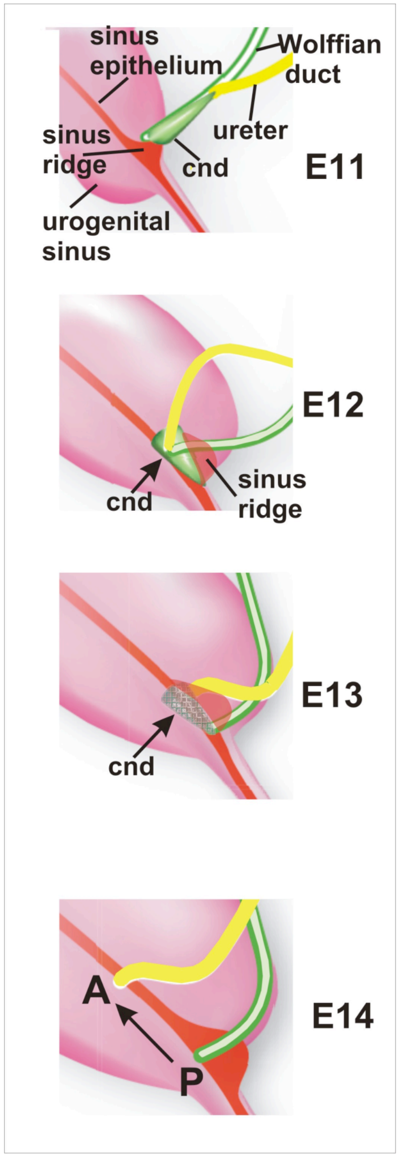
Ureter transposition depends on apoptosis of the **common nephric duct**





apoptotic common nephric duct cells

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