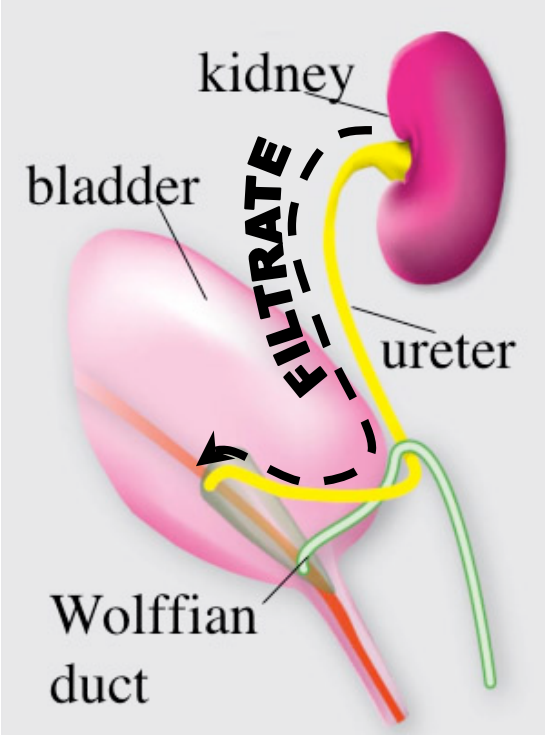
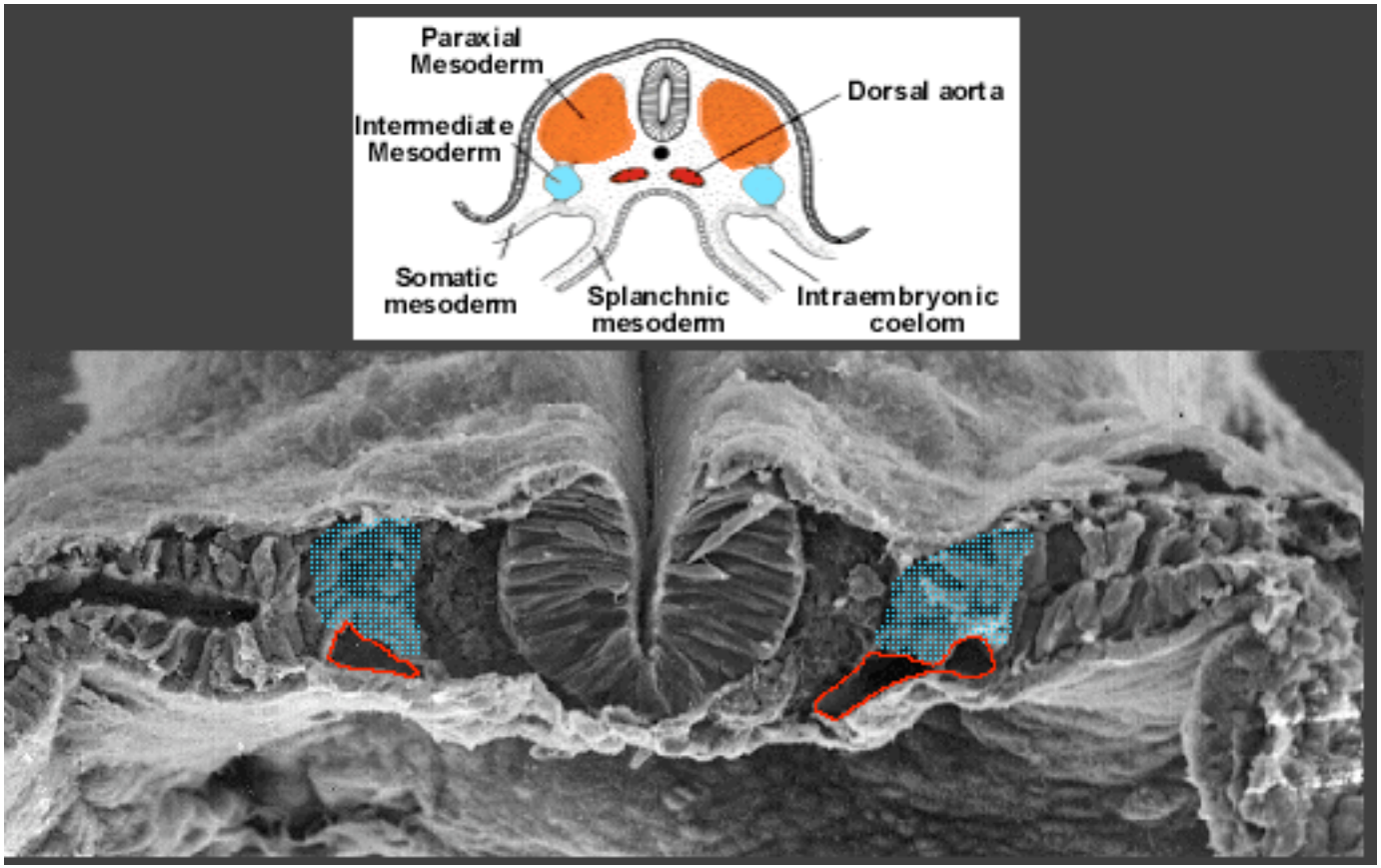


nephrons in the kidney generate urine that is propelled
to the ureters and then to the bladder for storage and excretion

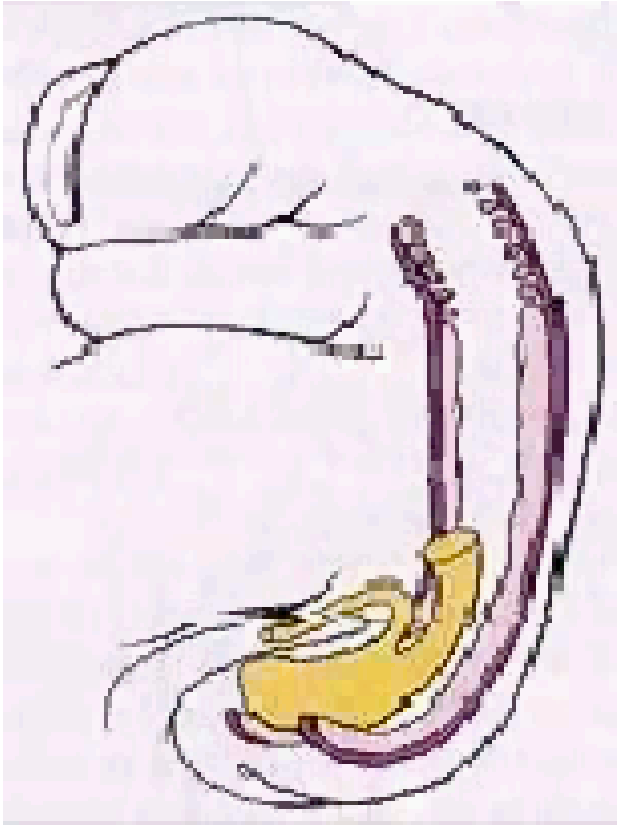
The Urinary outflow tract:

- 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

The urogenital system derives predominantly from intermediate mesoderm



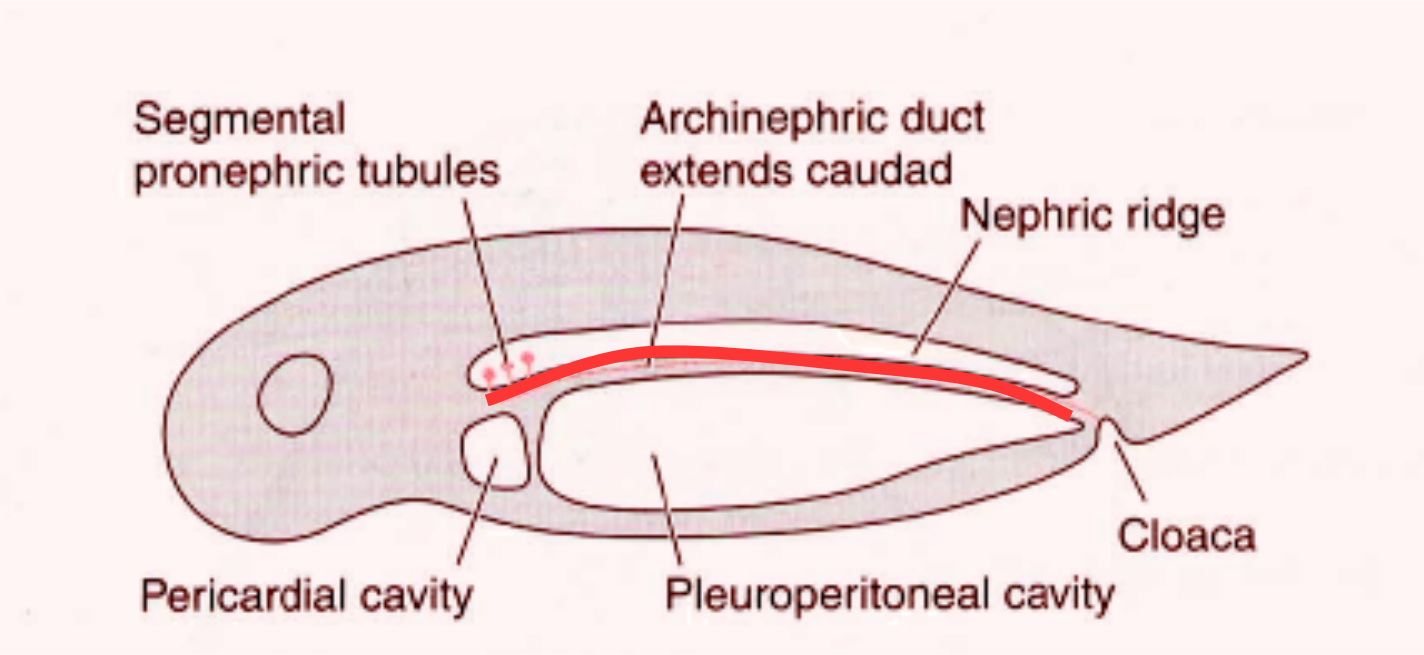
During development, 3 successive kidneys form:



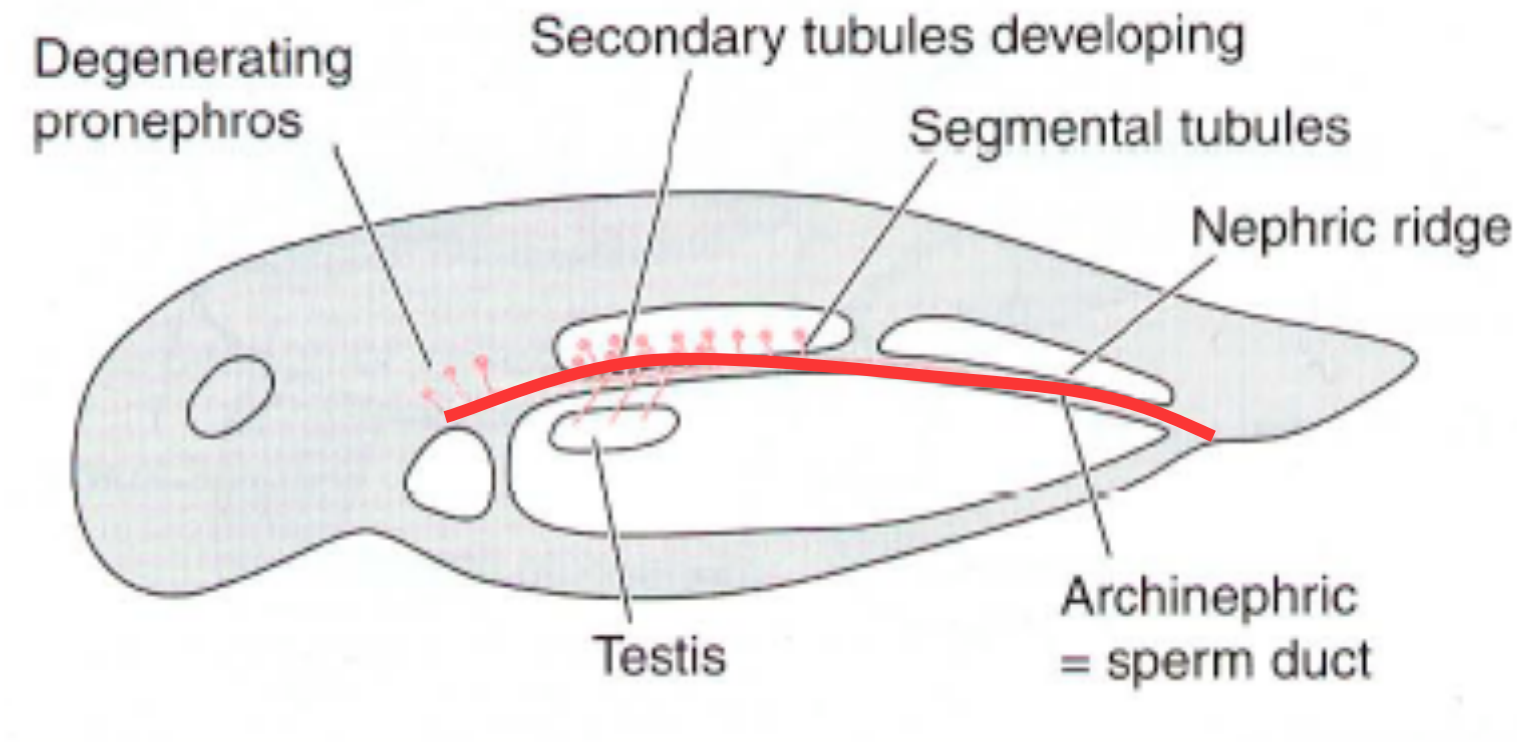
Pronephros
(head kidney)

Mesonephros
(middle kidney)

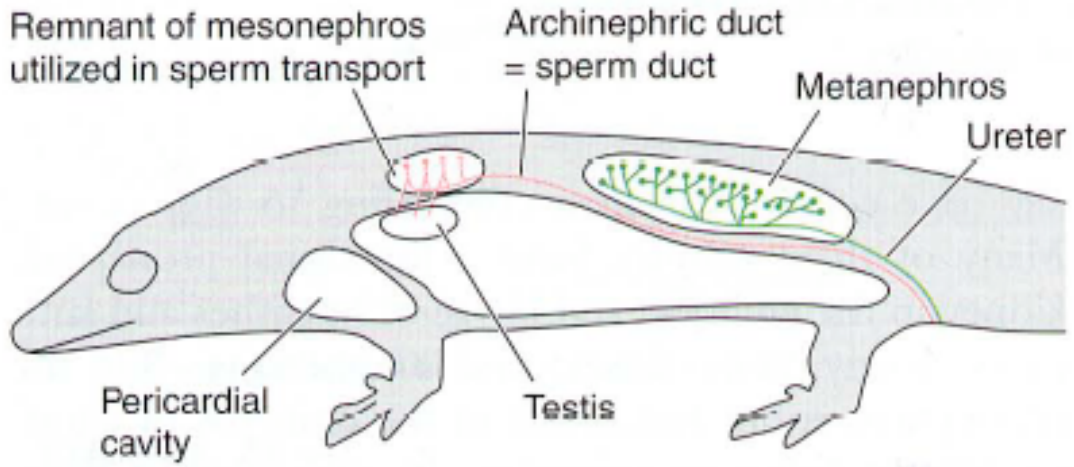
Metanephros
(definitive kidney)



pronephros in an early embryo



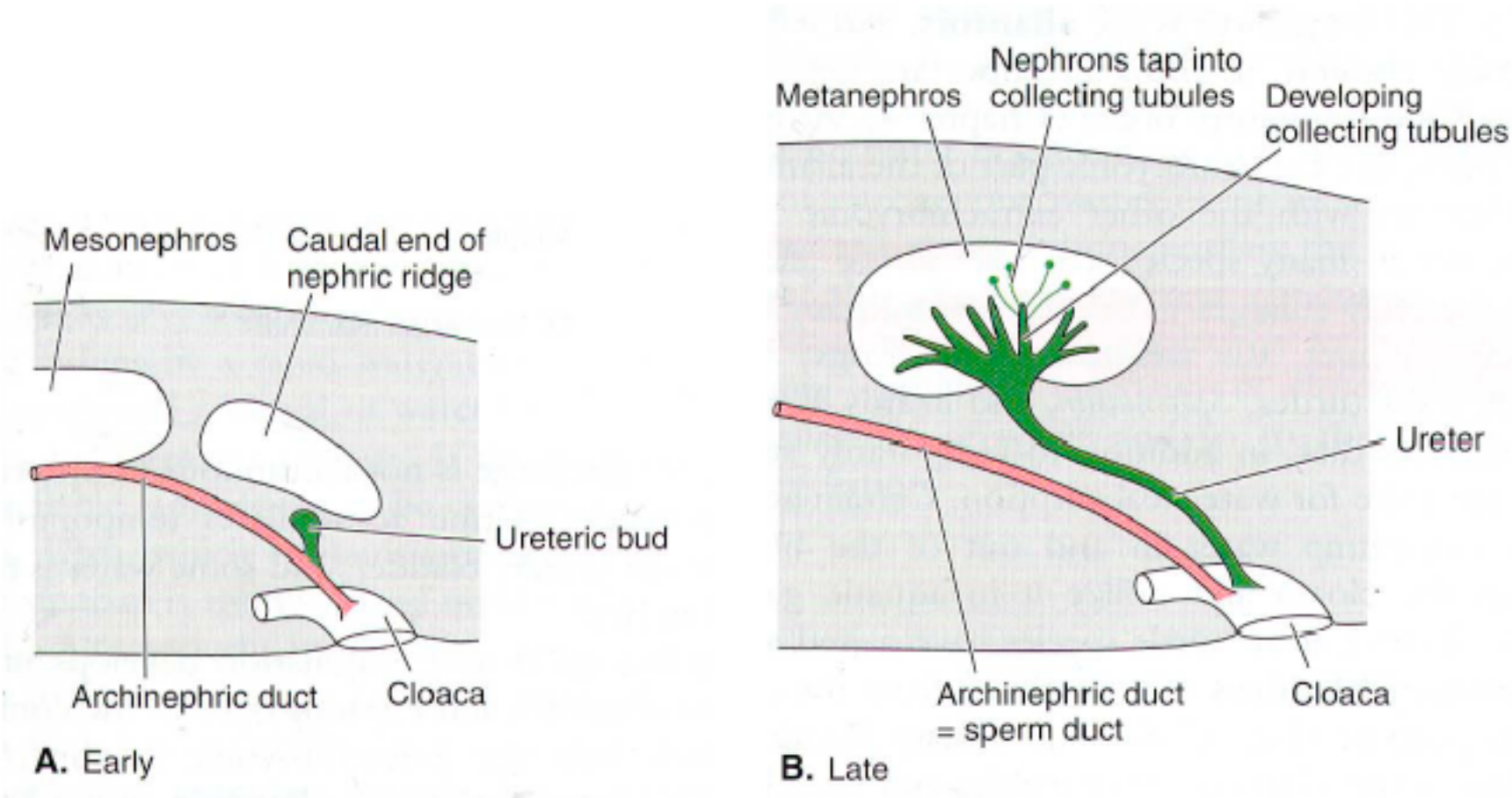
Mesonephros in intermediate embryo



C. Metanephros in late embryo and adult

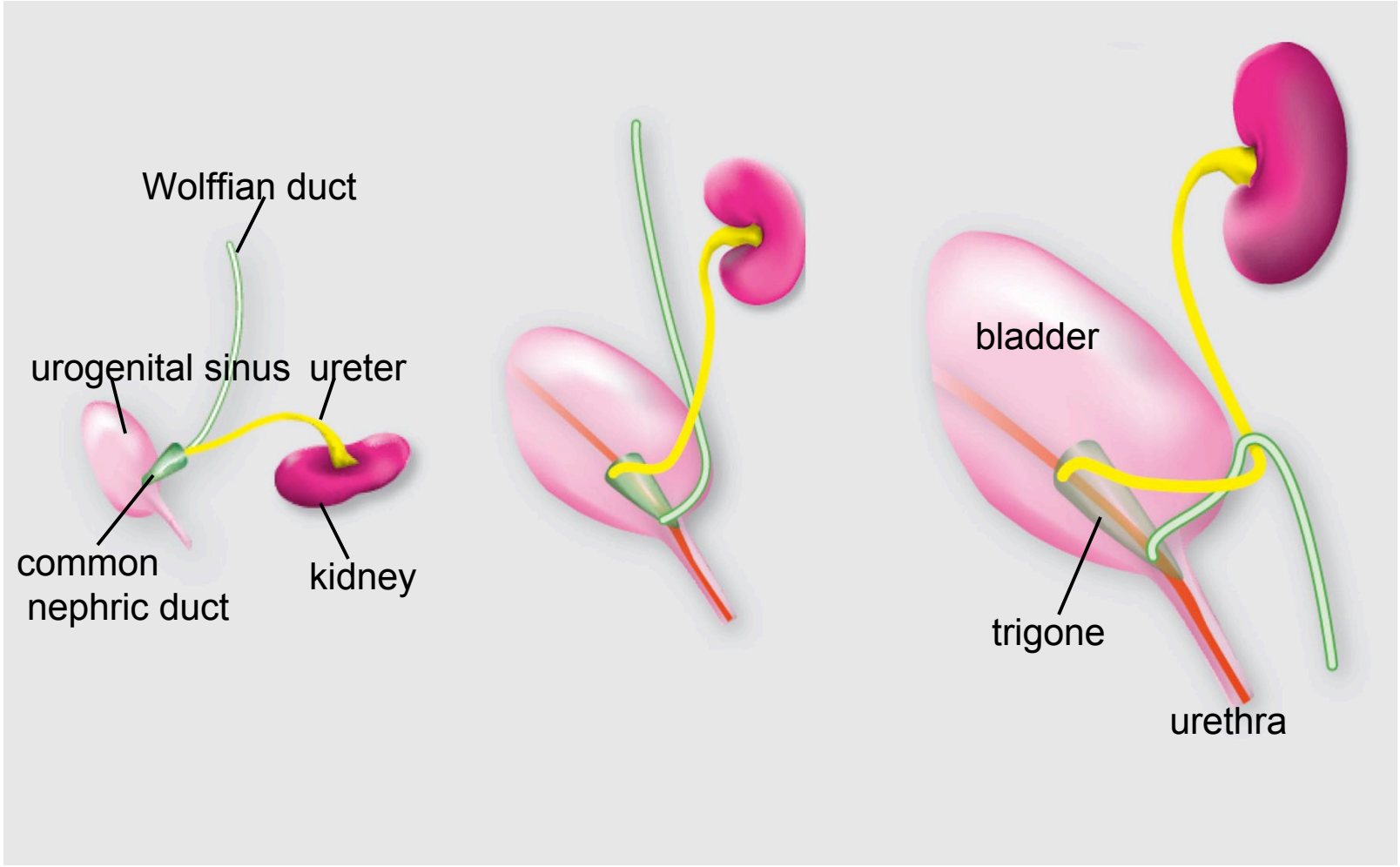
A **metanephros** is always drained exclusively by one duct, the ureter.

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

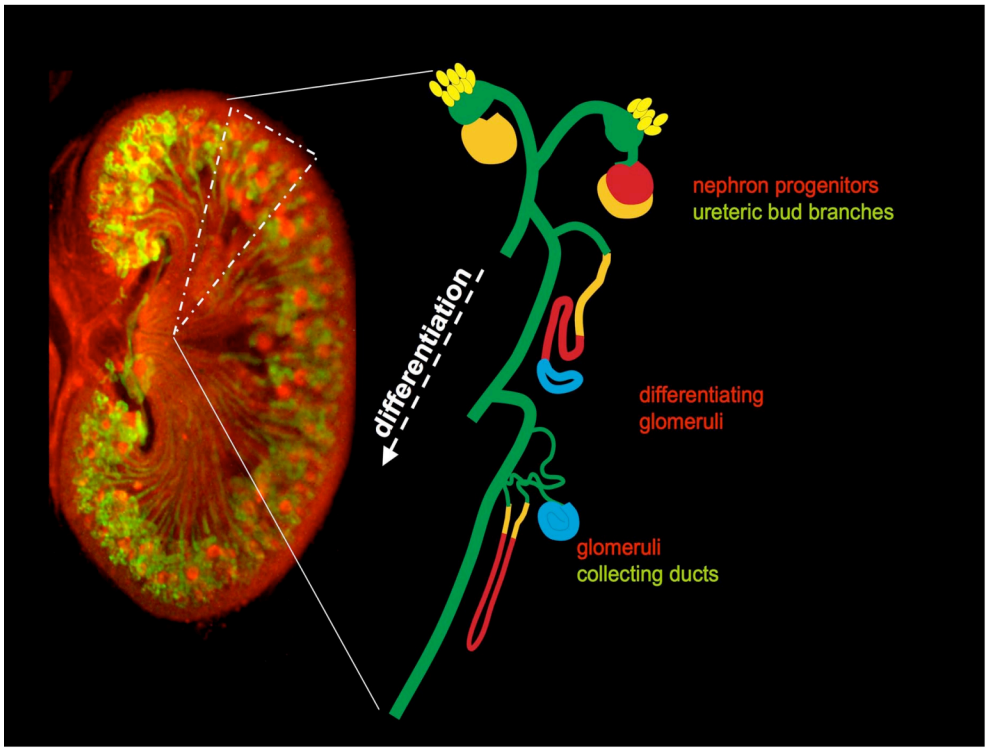


renal development begins when the ureteric bud invades kidney mesenchyme (**the metanephric blastema**)

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

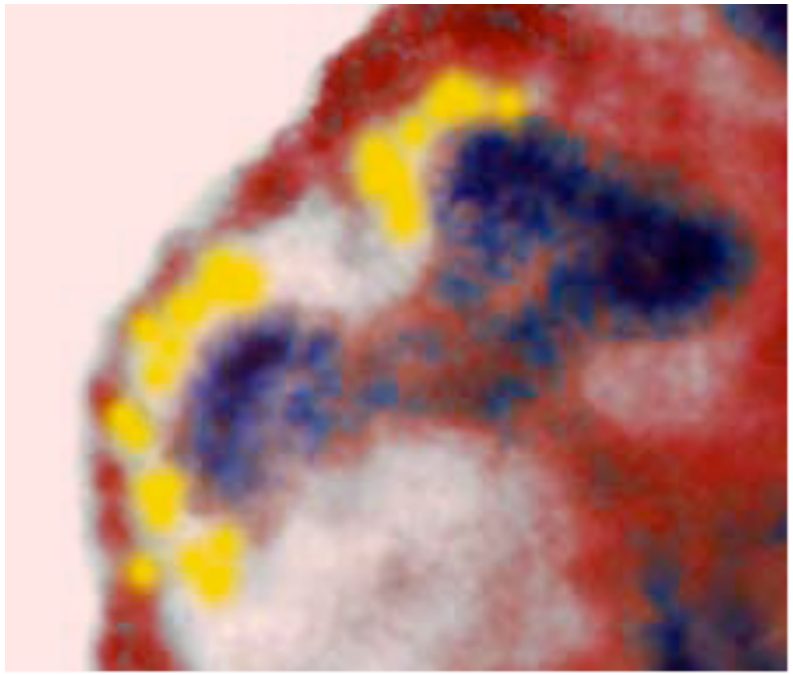


The kidney is radially patterned



- 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

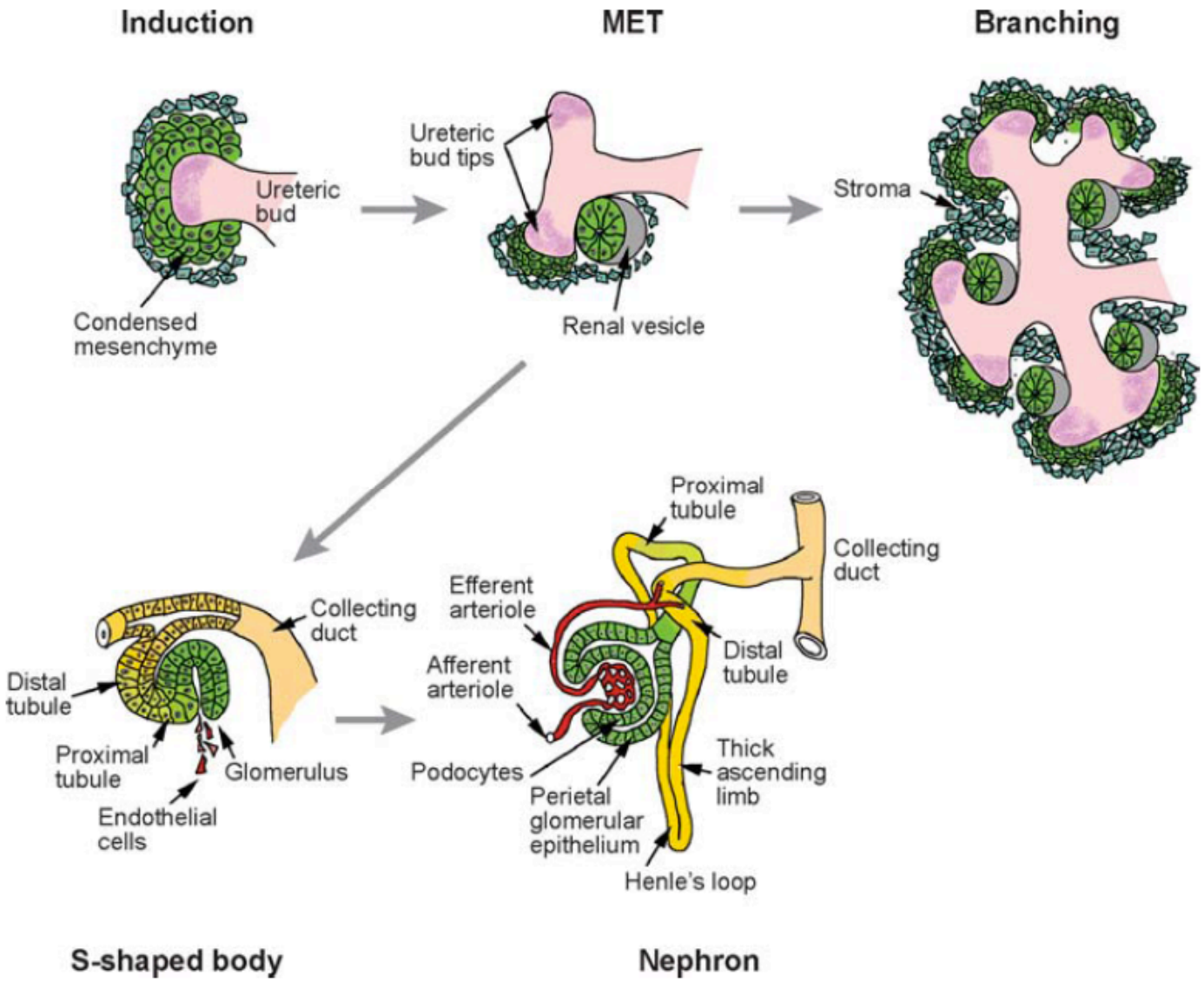
RECIPROCAL SIGNALING BETWEEN STROMA, NEPHRON PROGENITORS AND URETERIC BUD TIPS GIVES RISE TO CELL TYPES IN THE MATURE KIDNEY



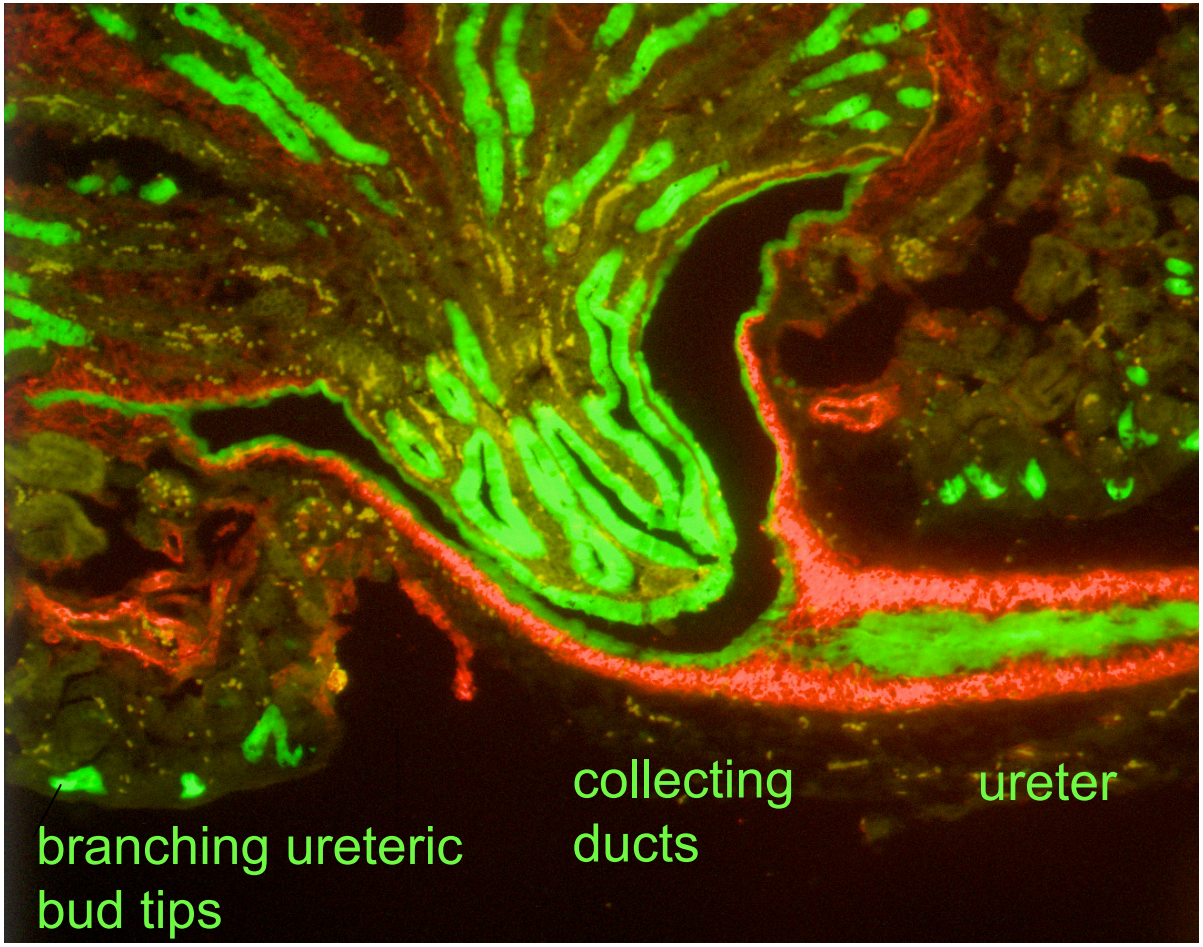
nephron progenitors **NEPHRONS**

ureteric bud tips **COLLECTING DUCT SYSTEM**

stroma CAPSULE/INTERSITIUM

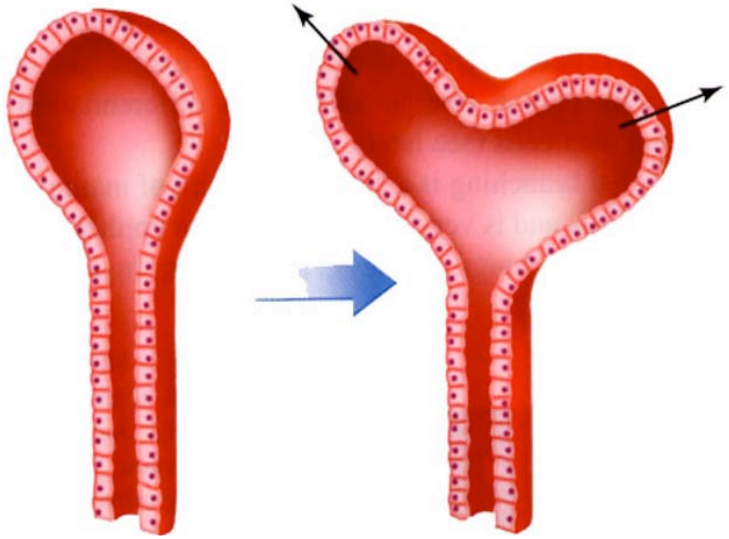

Induction
MET
Branching
Ureteric bud
Condensed mesenchyme
Ureteric bud tips
Renal vesicle
Stroma
Collecting duct
Distal tubule
Proximal tubule
Glomerulus
Endothelial cells
Proximal tubule
Collecting duct
Efferent arteriole
Distal tubule
Afferent arteriole
Thick ascending limb
Podocytes
Perietal glomerular epithelium
Henle's loop
S-shaped body
Nephron

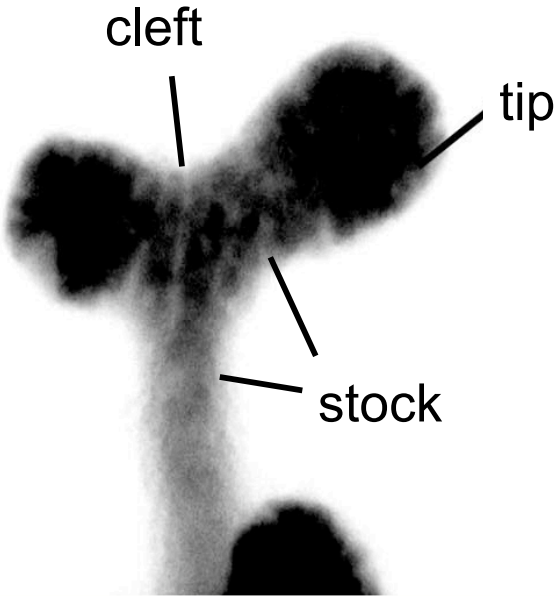
the collecting duct system and ureter are derived from the ureteric bud



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

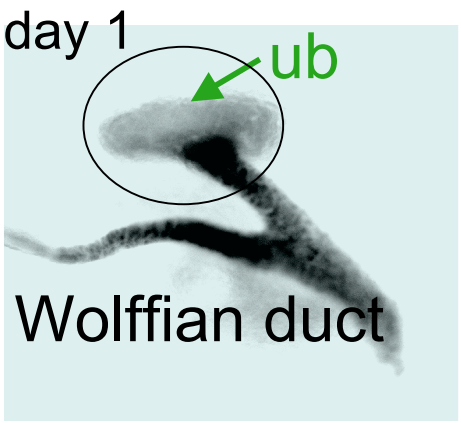
shape changes and local proliferation at ureteric bud tips forms an ampulla

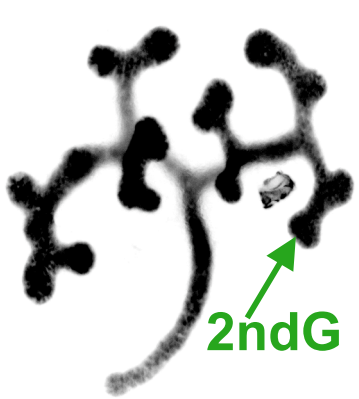


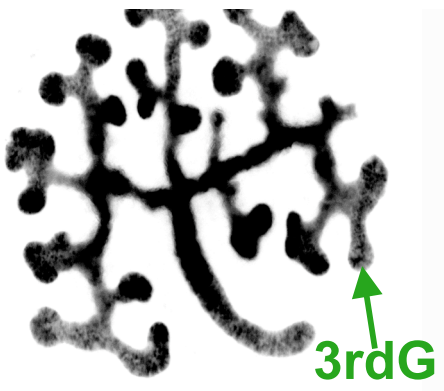


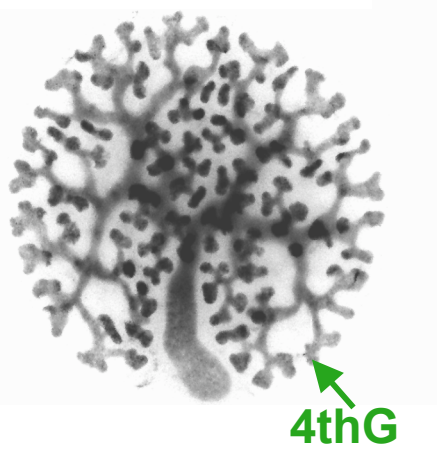
Branching morphogenesis:

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



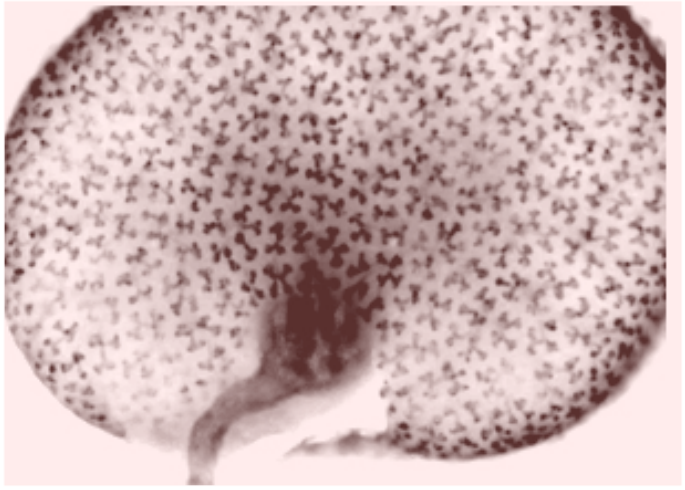


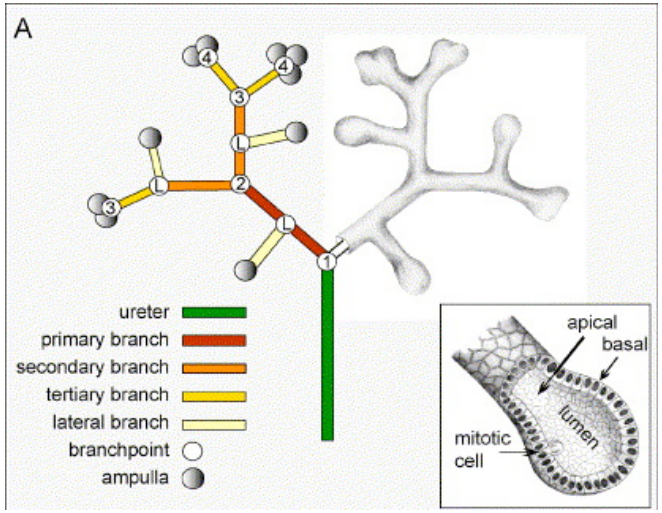


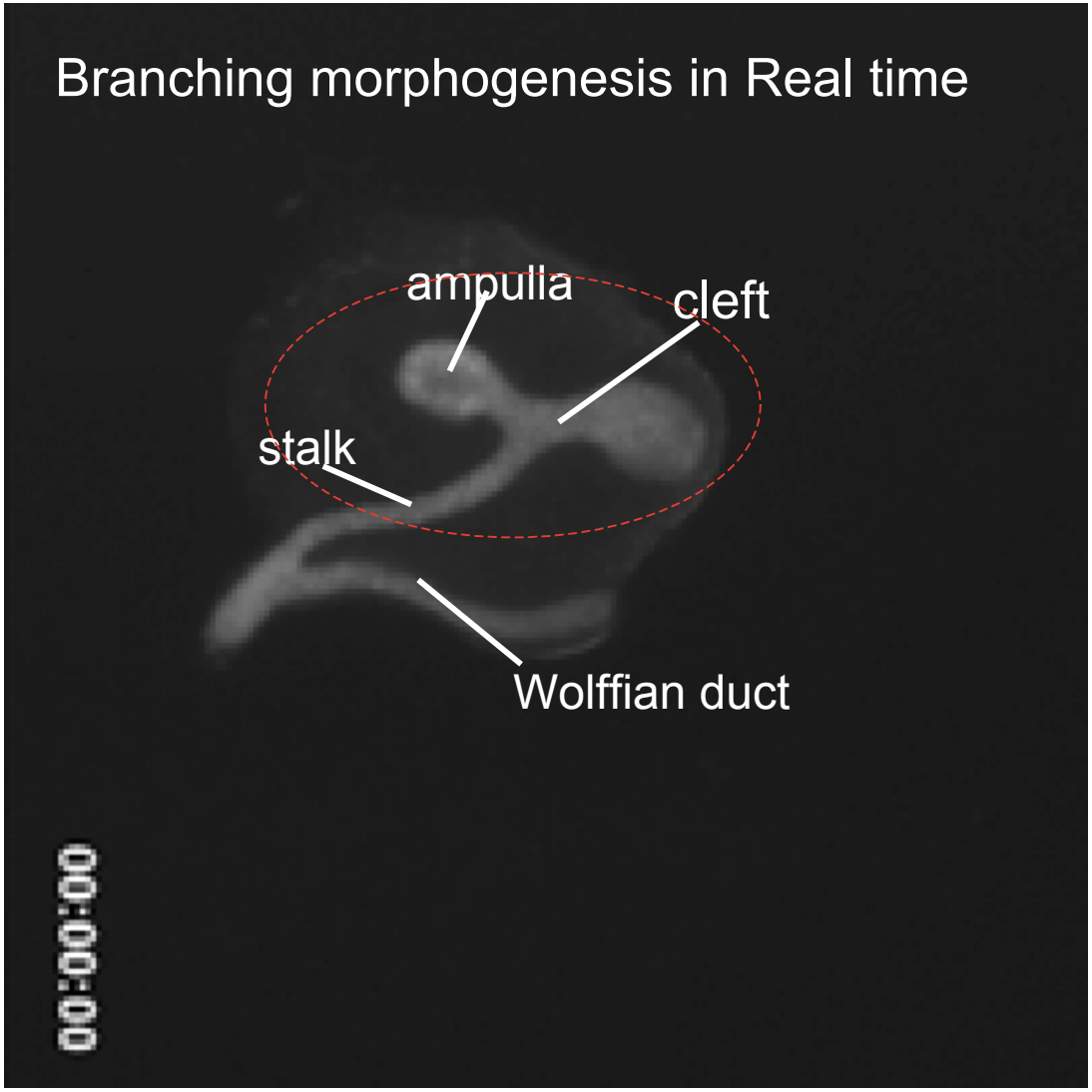


The collecting duct system grows from the periphery by **dichotomous branching**

at birth:

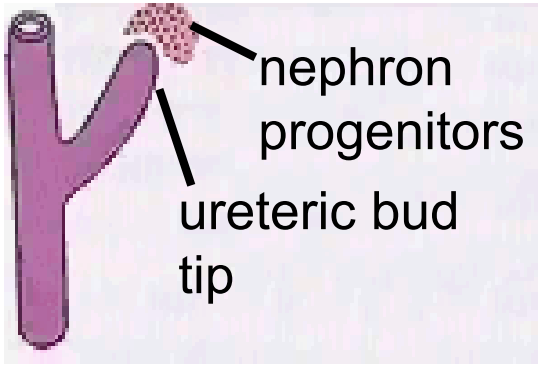




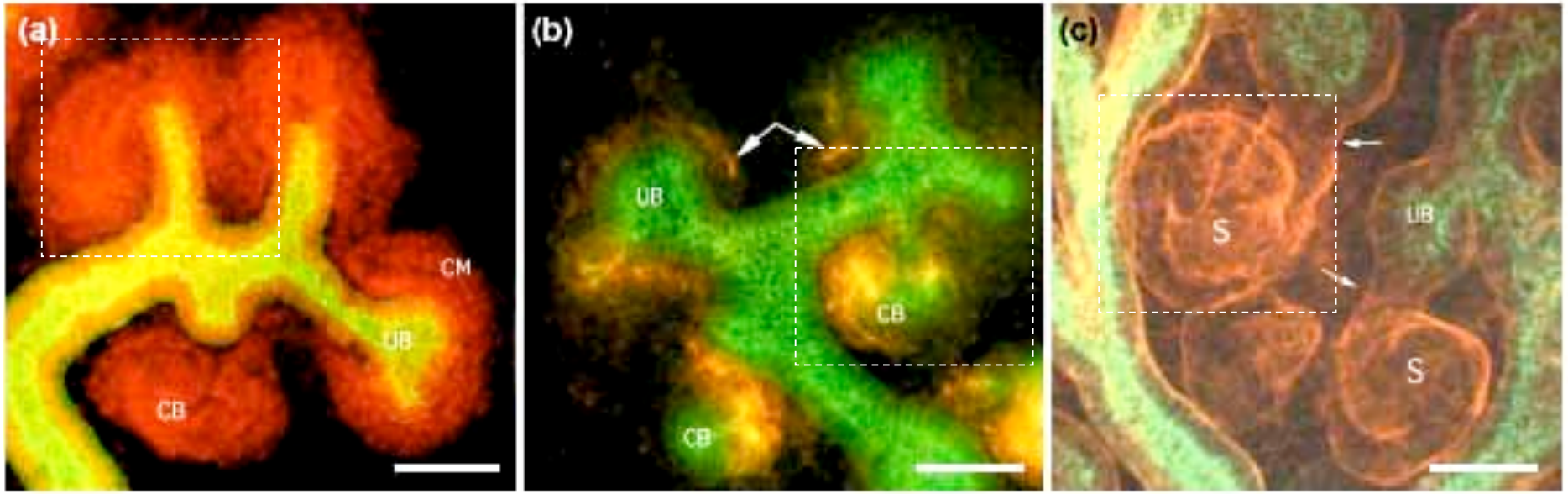


Costantini Lab
Columbia University, Dept. of Genetics & Development

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



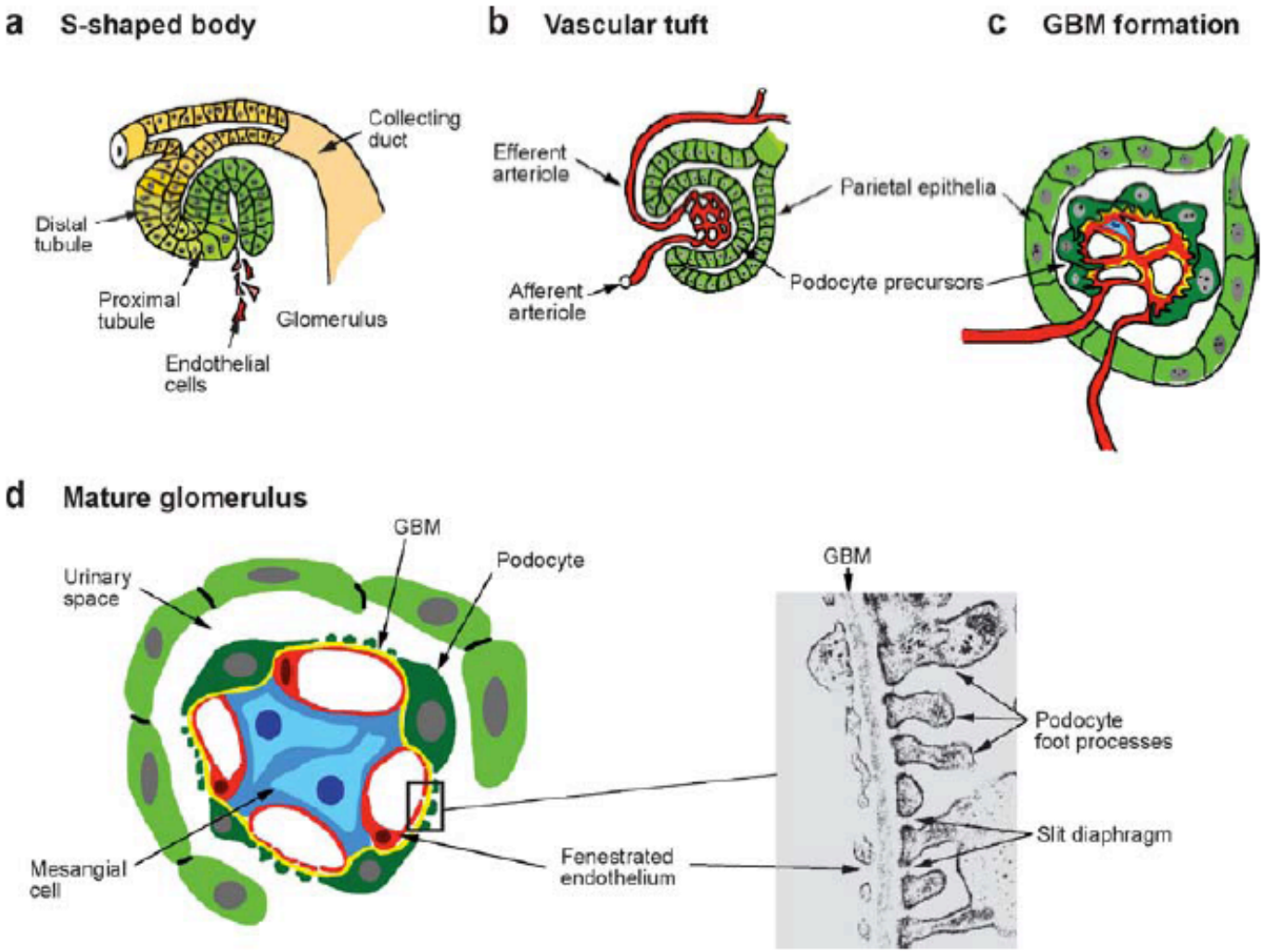
Nephron
progenitors condense at ub tips, aggregate



TRENDS in Cell Biology

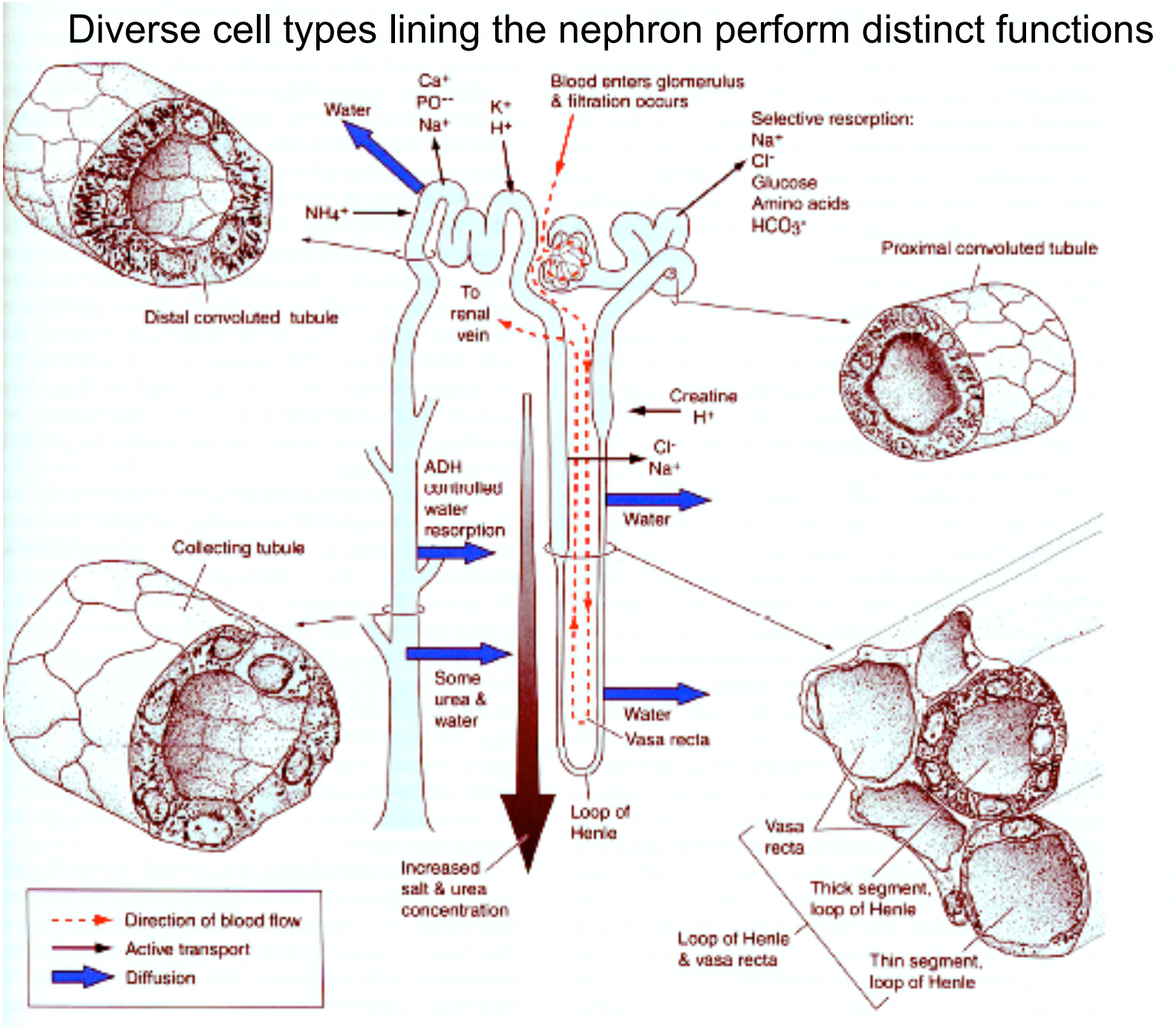
and **trans-differentiate** into epithelial cells
that make up the renal vesicle, **Comma** and **S-shaped bodies**

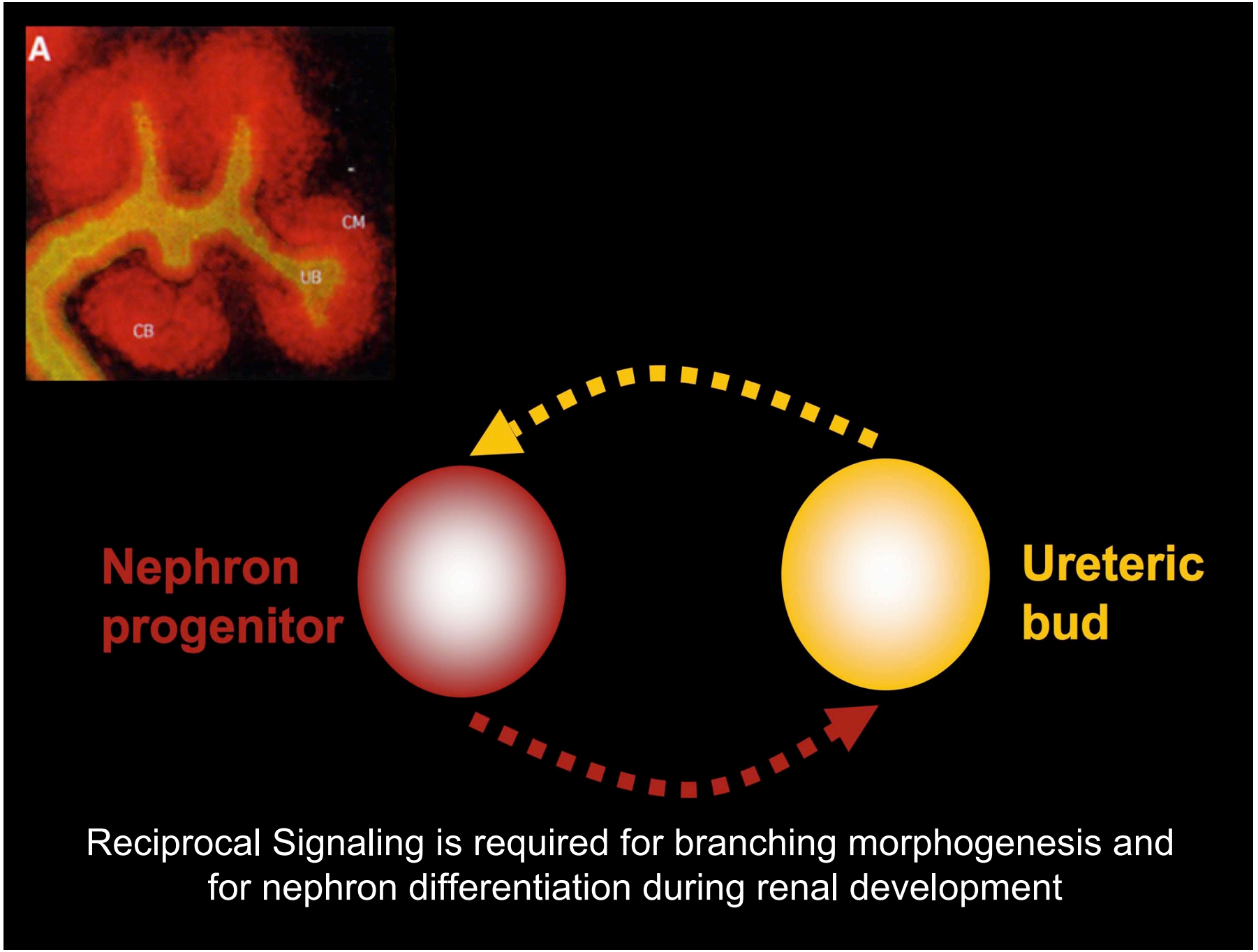
from: The kidney: Eds, Vize et al., 2003)



- Endothelial cells infiltrate the cleft of the s-shaped body
- Podocyte precursors in contact with endothelial cells begin to differentiate
- The glomerular basement membrane forms between podocytes and endothelial cells
- Podocytes extend foot processes

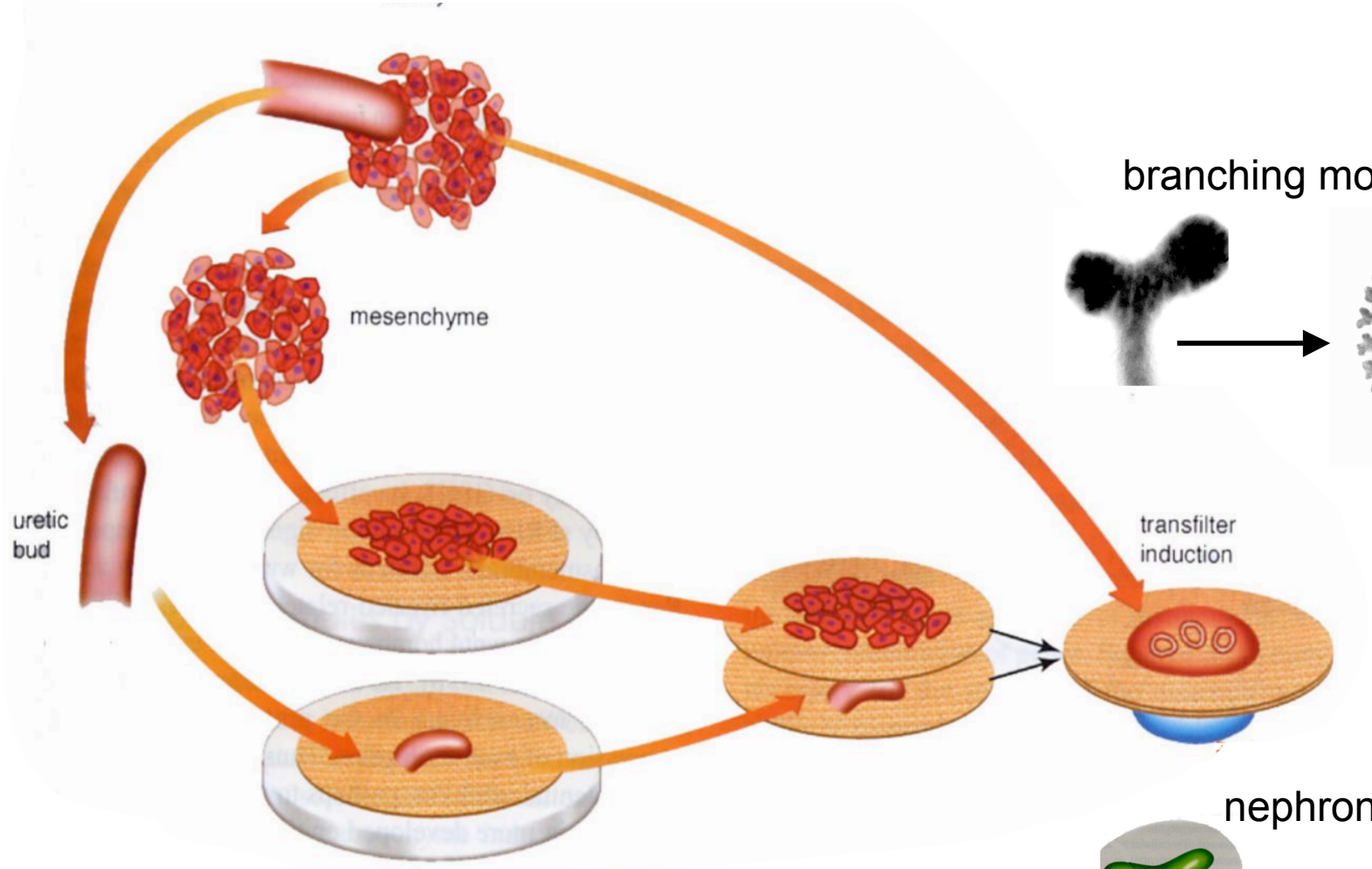
Diverse cell types lining the nephron perform distinct functions





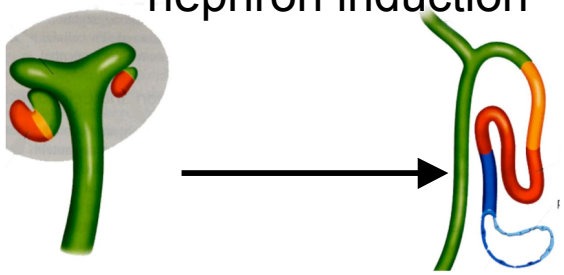
Reciprocal Signaling is required for branching morphogenesis and for nephron differentiation during renal development

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



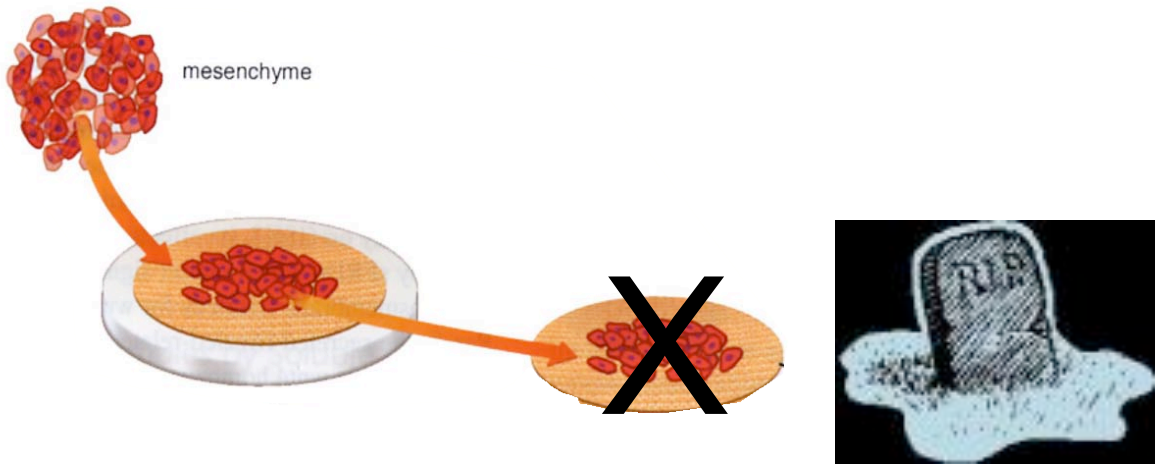
branching morphogenesis

nephron induction



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

•no ureteric bud, nephron progenitors undergo apoptosis



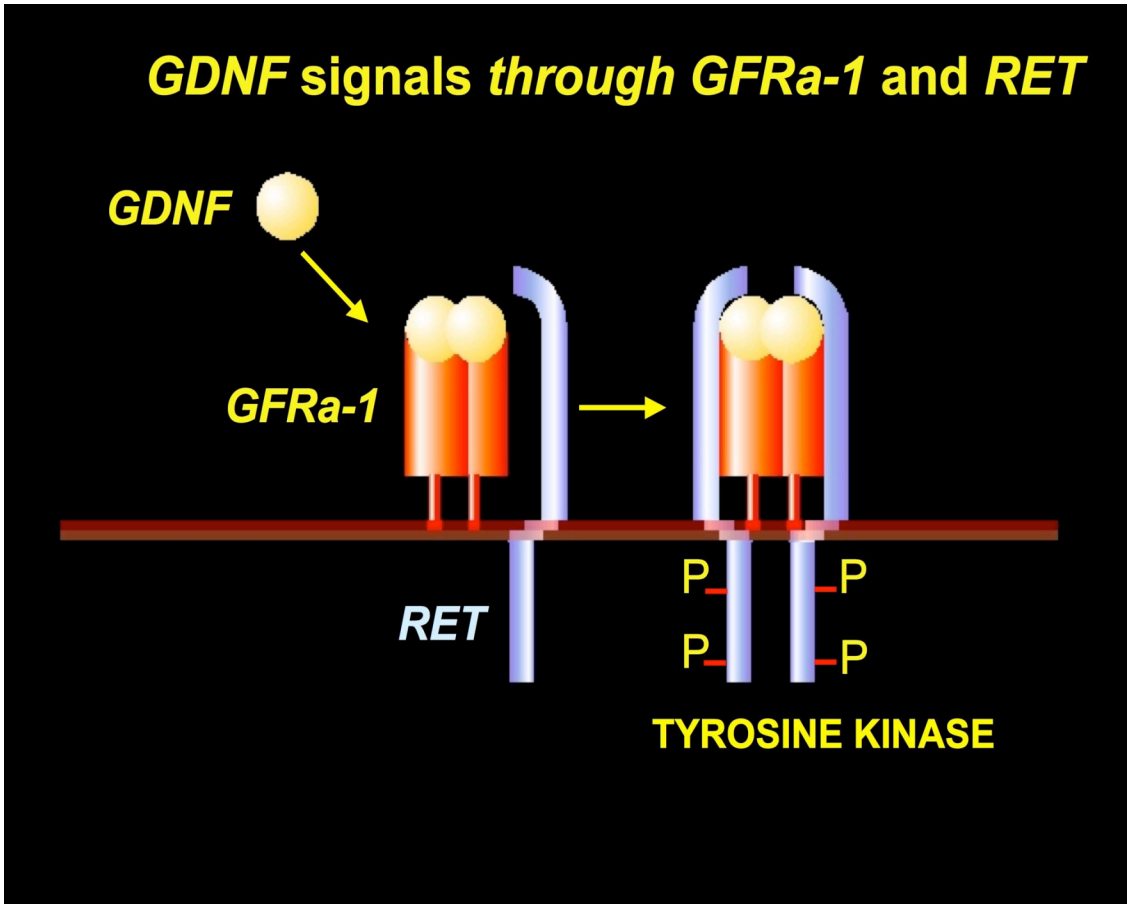
from: The kidney: Eds, Vize et al., 2003)

•no nephron progenitors, no branching morphogenesis

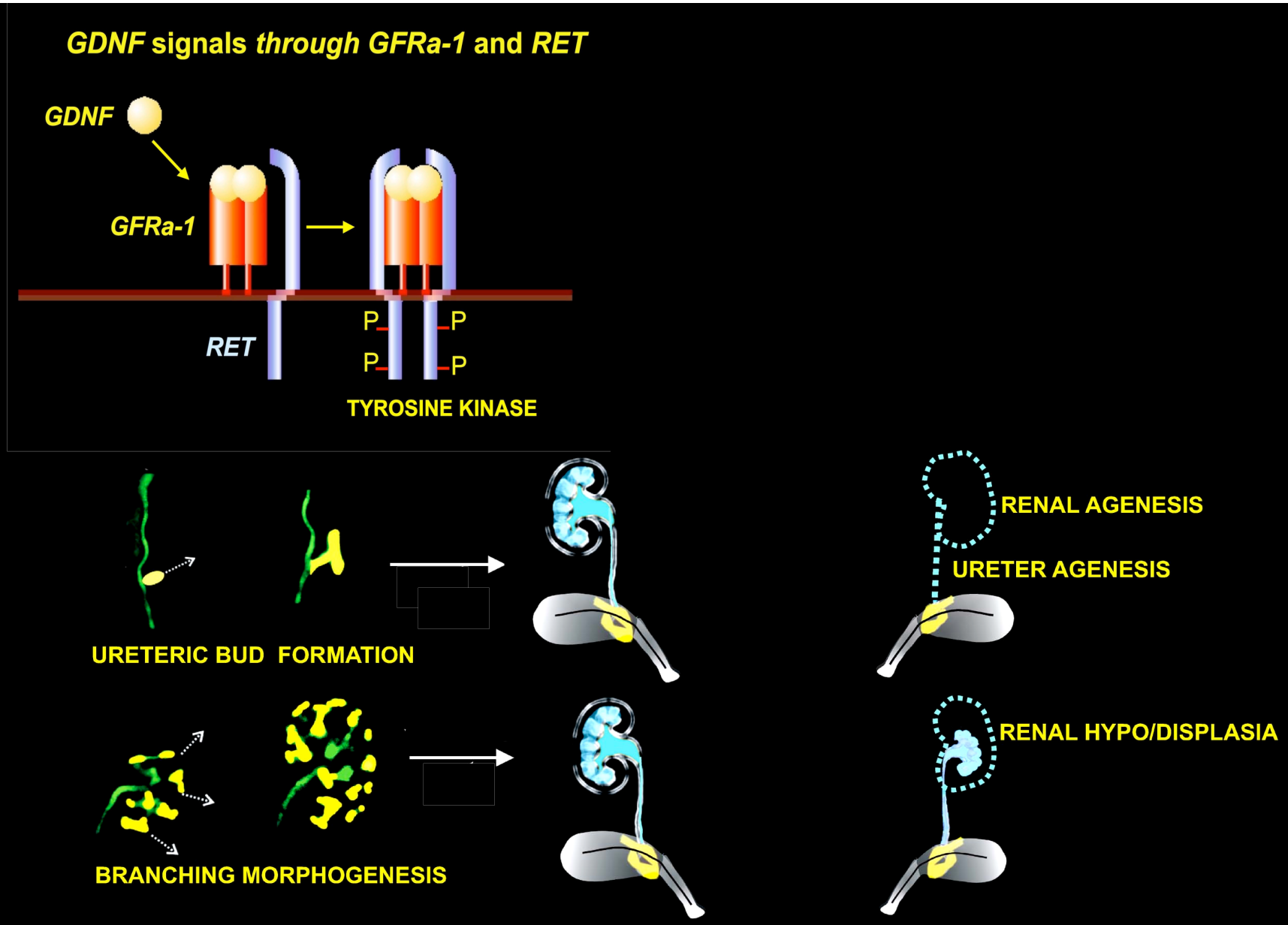
signals from the ureteric bud control nephron induction

signals from nephron progenitors control branching morphogenesis

RET-Gdnf signaling is crucial for branching morphogenesis

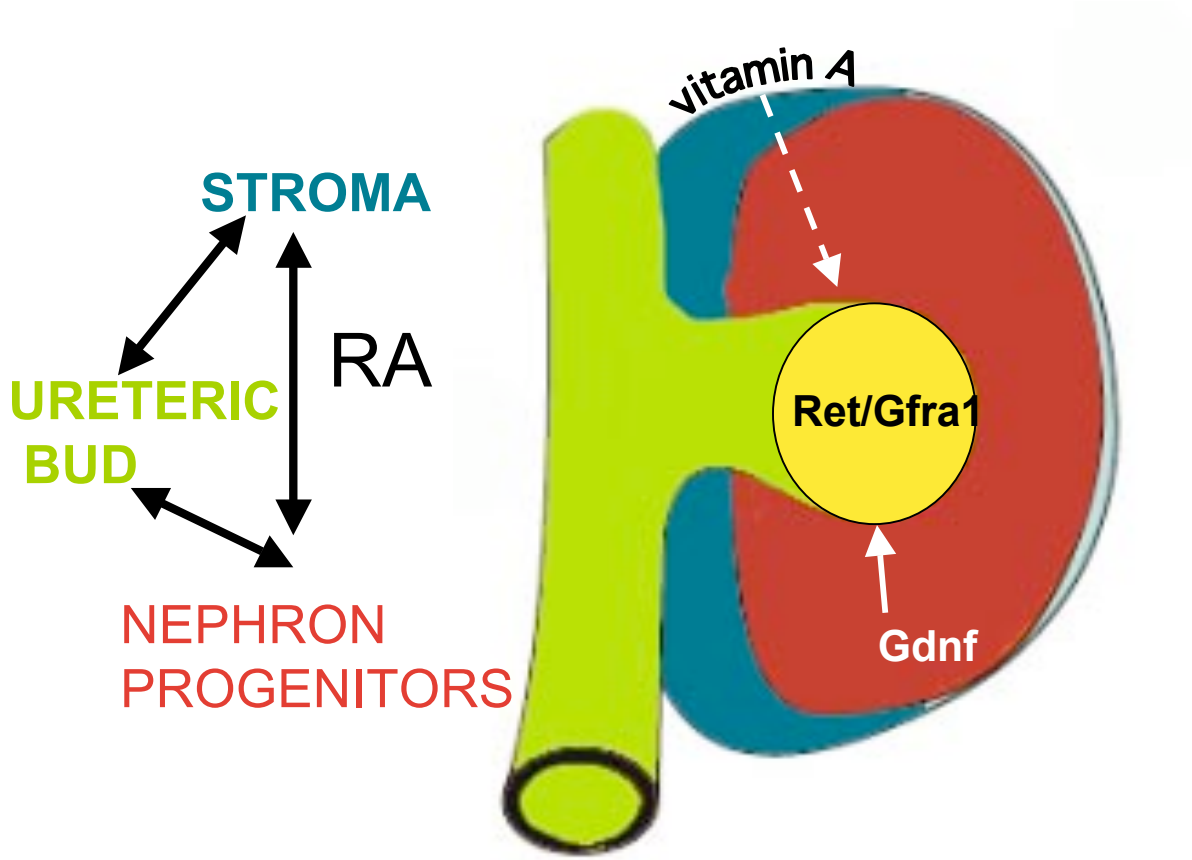


Ret mutations in humans cause renal abnormalities, Hirschsprung's disease and cancer



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

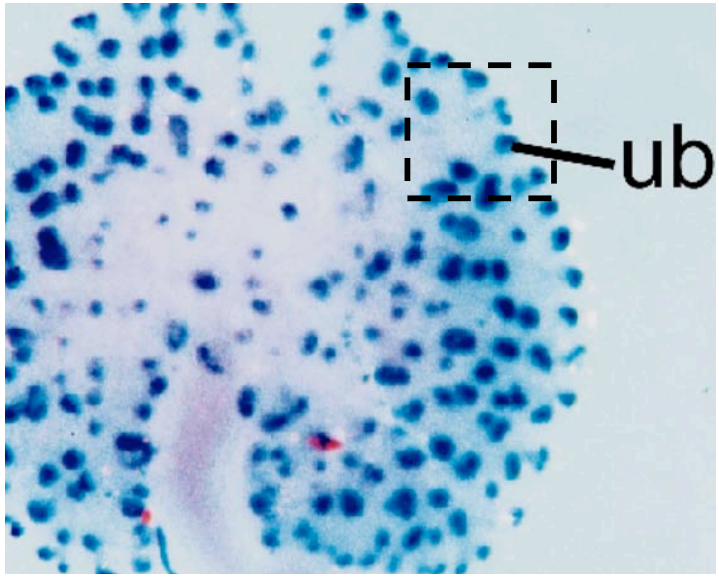
STROMAL CELL SECRETE RETINOIC ACID, THE ACTIVE FORM OF VITAMIN A
VITAMIN A INDUCES RET EXPRESSION IN NEARBY URTERIC BUD CELLS

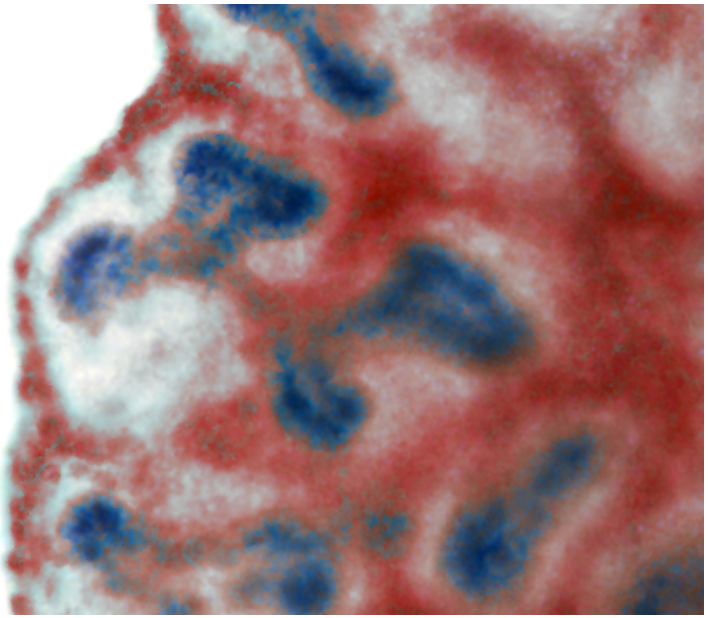


Gdnf secreted by nephron progenitors binds to Ret via the Ret co-receptor (Gfra1) inducing branching morphogenesis

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

ureteric bud (RET)
stroma (vitamin A)

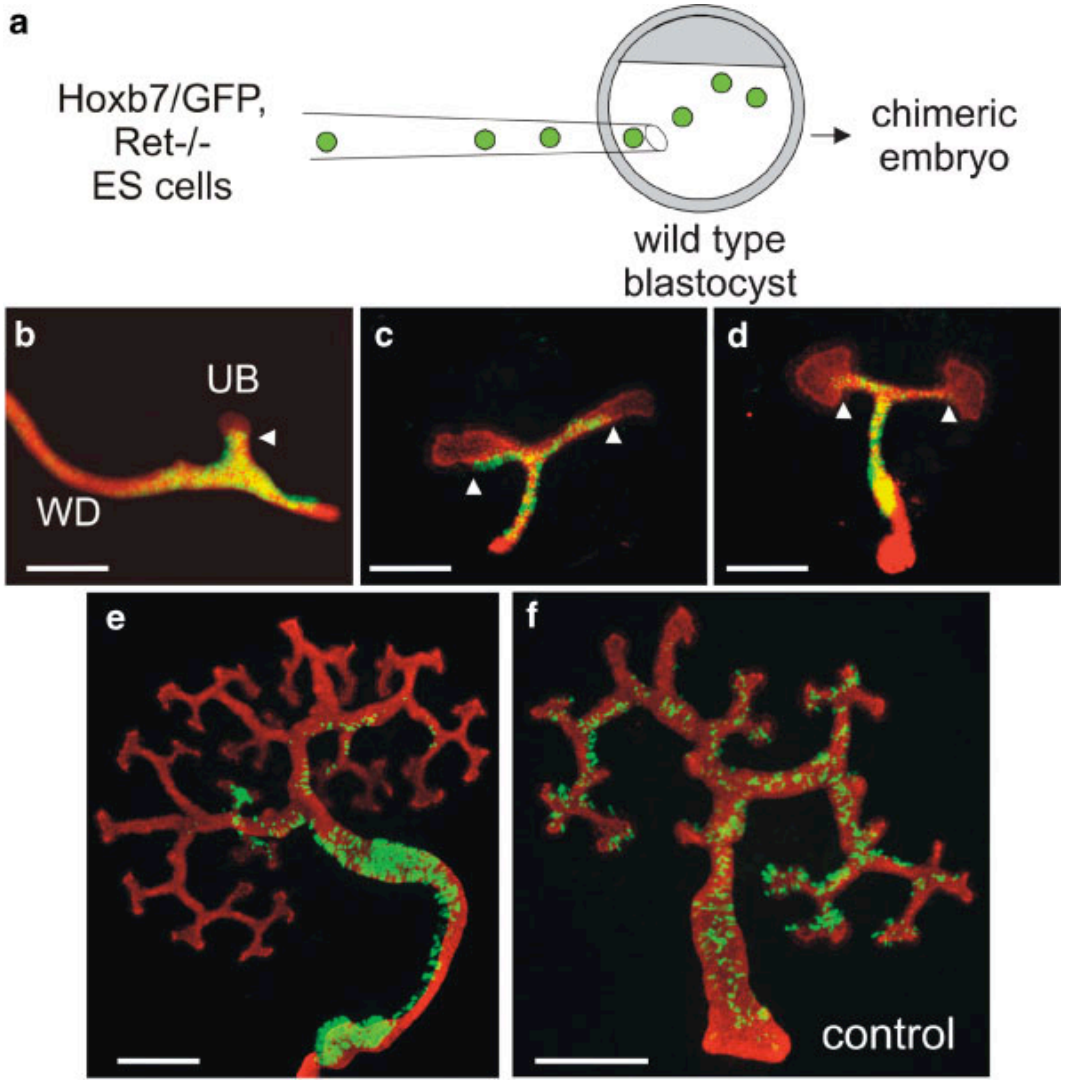




Vitamin A from Stromal cells controls Ret expression in ureteric bud cells

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

ureteric bud cells must express Ret to contribute to a tip



What cellular processes are stimulated by GDNF to promote branching of the ureteric epithelium? Some candidates are:

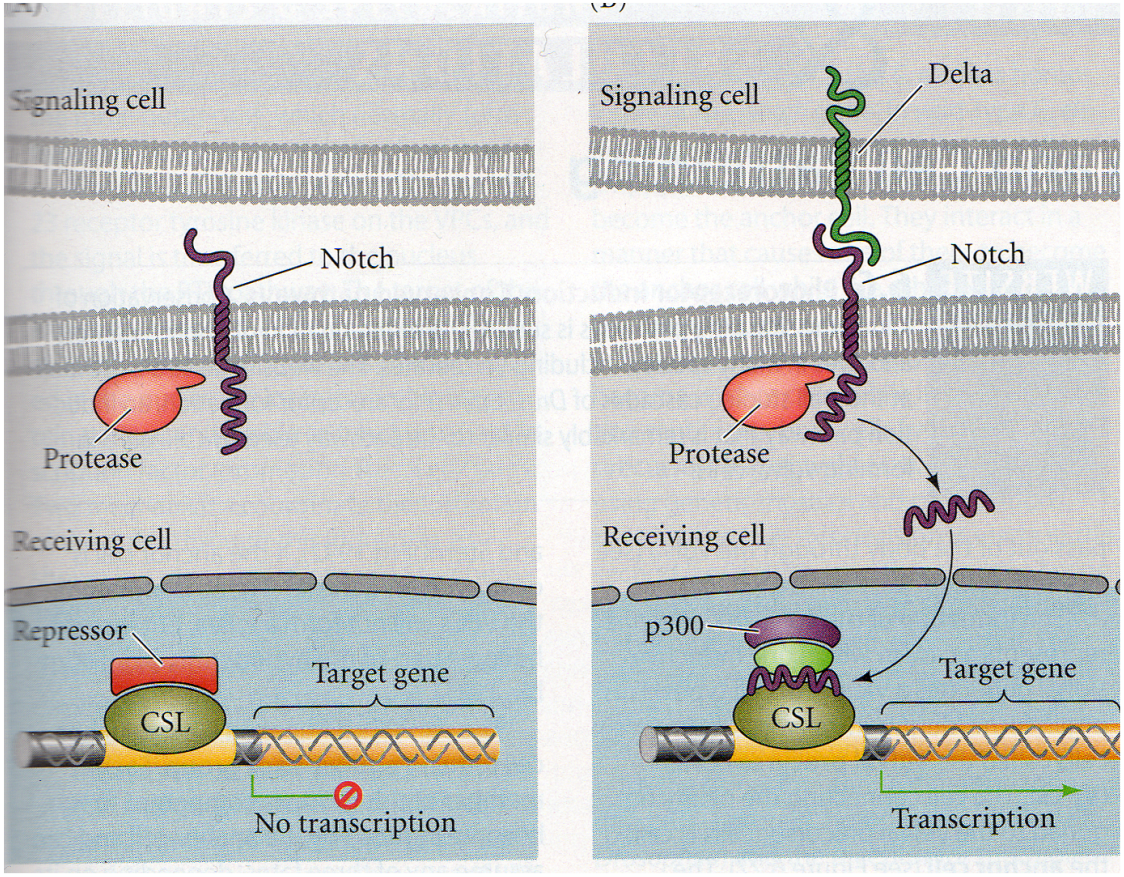
localized cell proliferation

changes in cell shape

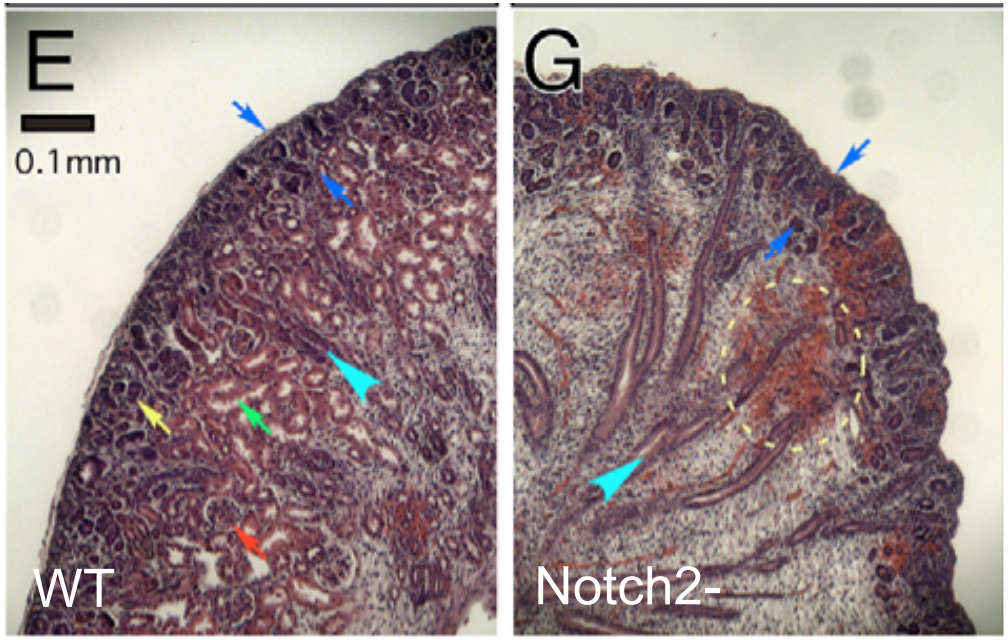
migration

differential cell–cell adhesion

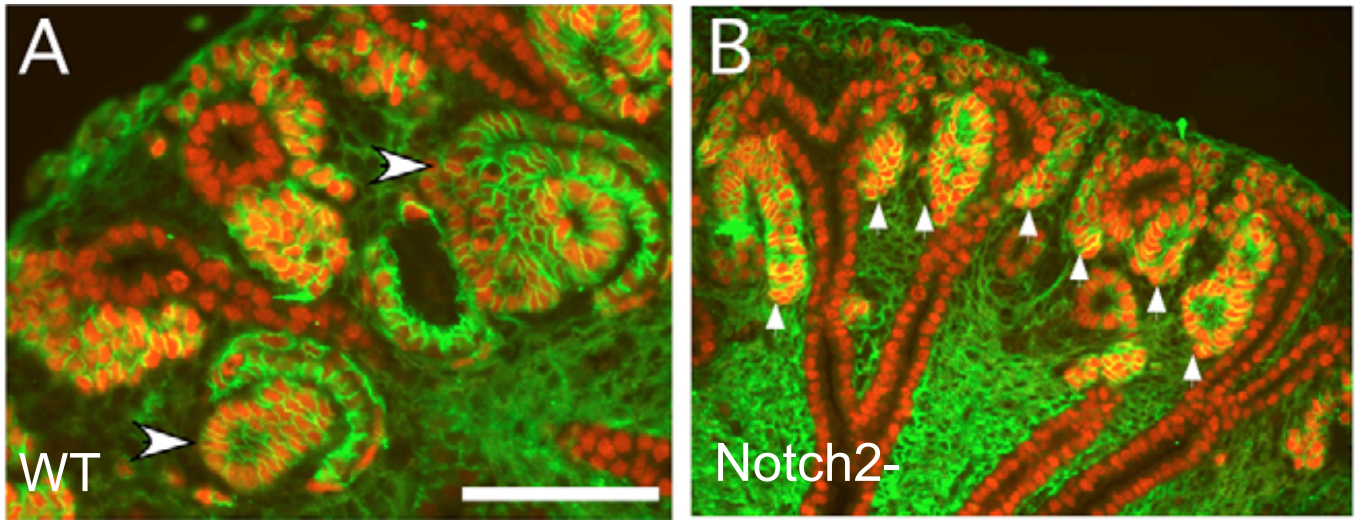
localized remodeling of the extracellular matrix



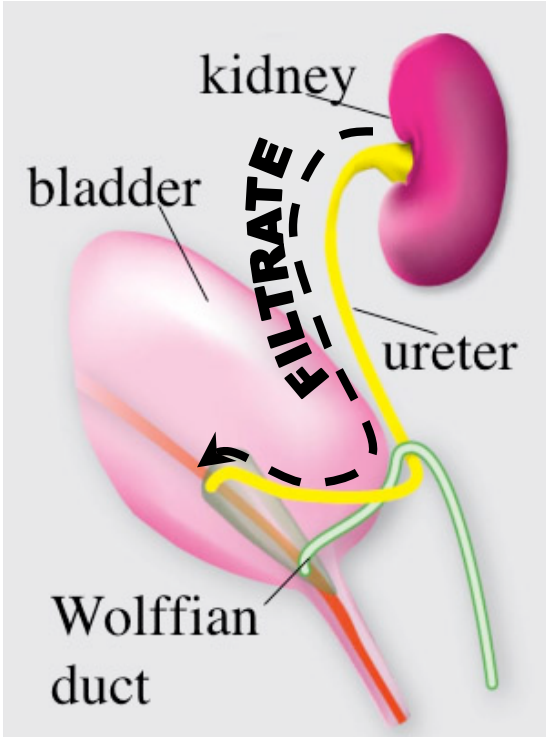
Notch activation: Delta, jagged or serrate ligands on an adjacent cell bind Notch
The intracellular domain of Notch is cleaved, goes to the nucleus and induces transcriptional activation of Notch target genes.



Cheng et al, 2007

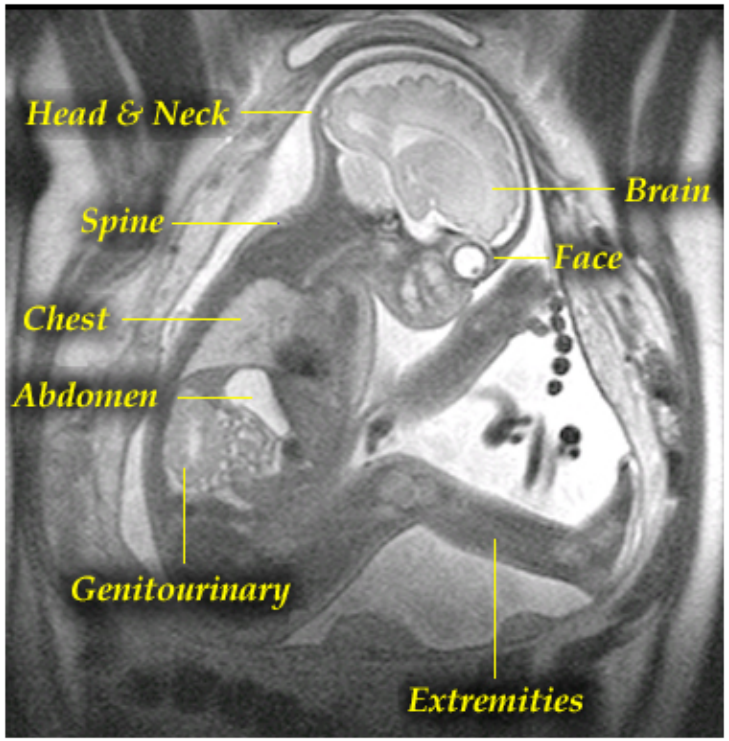


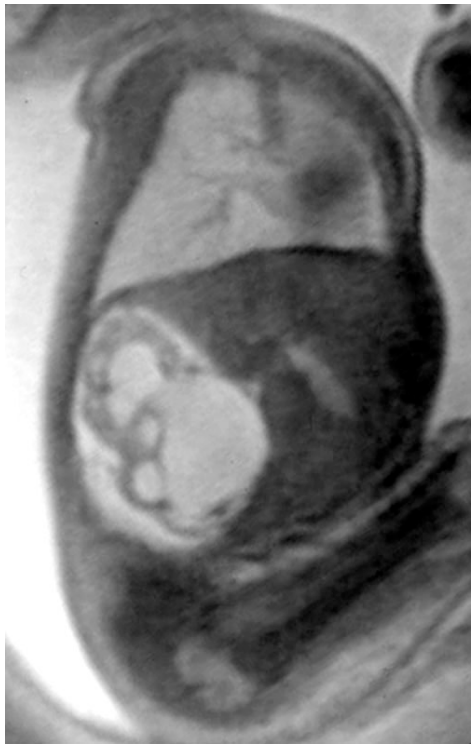
Notch2 is expressed in the developing nephron;
Glomerular differentiation is arrrested in Notch 2 mutant mice



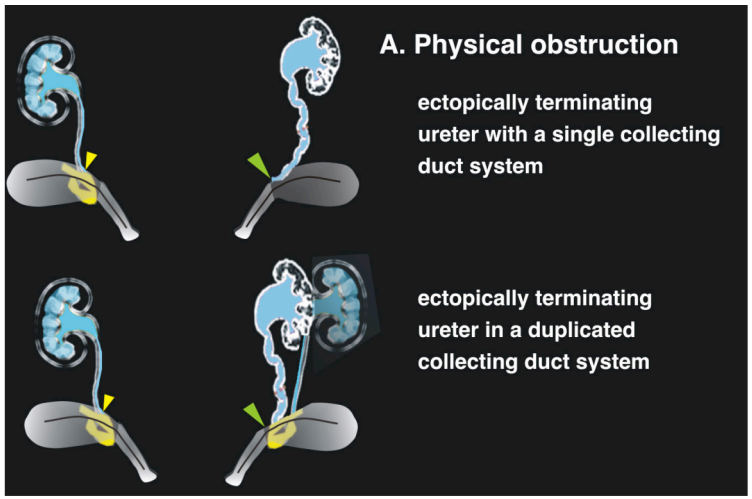
nephrons in the kidney generate urine that is propelled
to the ureters and then to the bladder for storage and excretion

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





hydronephrosis *in utero*

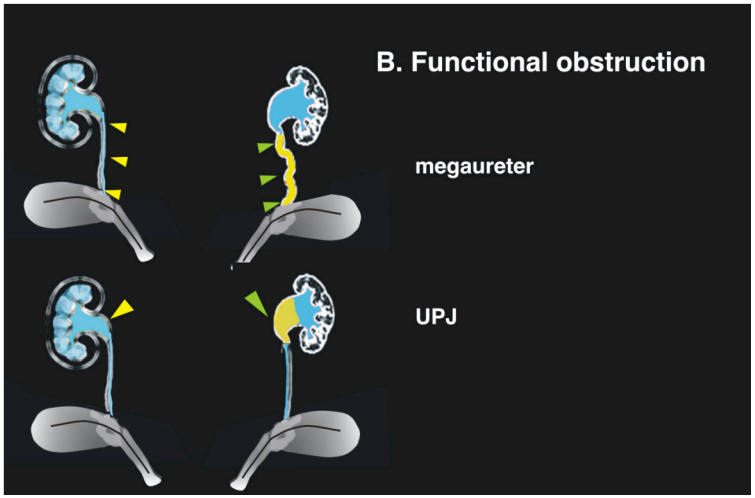


abnormal position of the ureter orifice

vitamin A deficiency, Ret

sprouty, slit-2, retinoid excess

Physical vs Functional obstruction



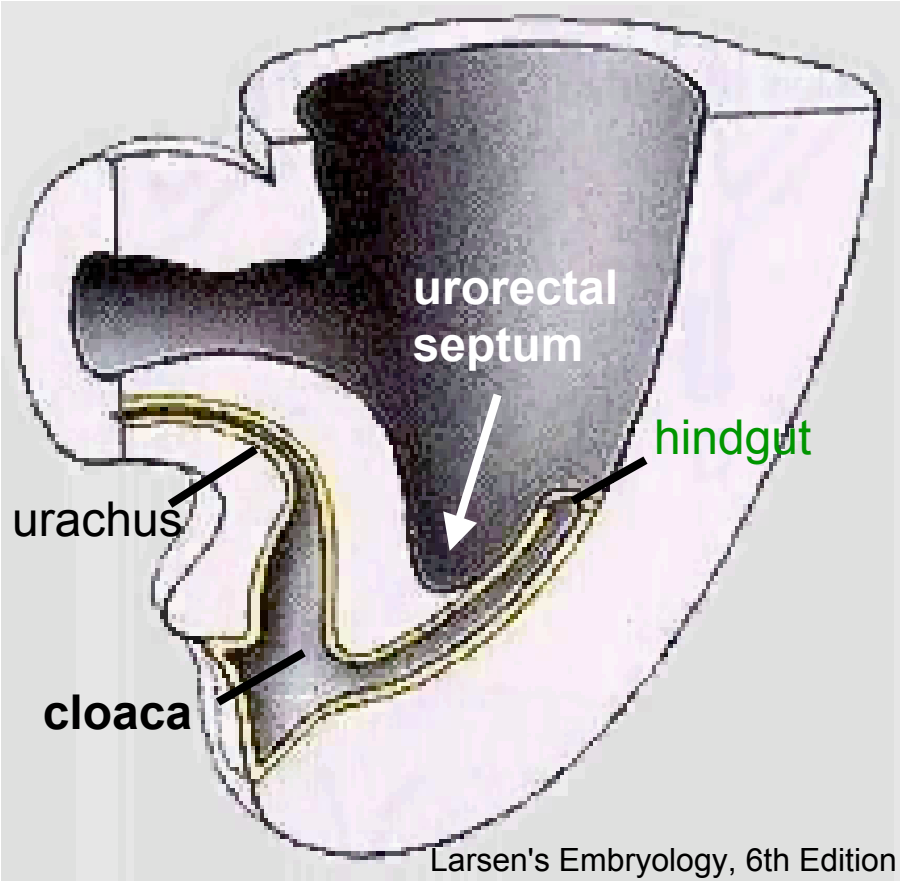
abnormal peristalsis

sonic hedgehog (muscle)

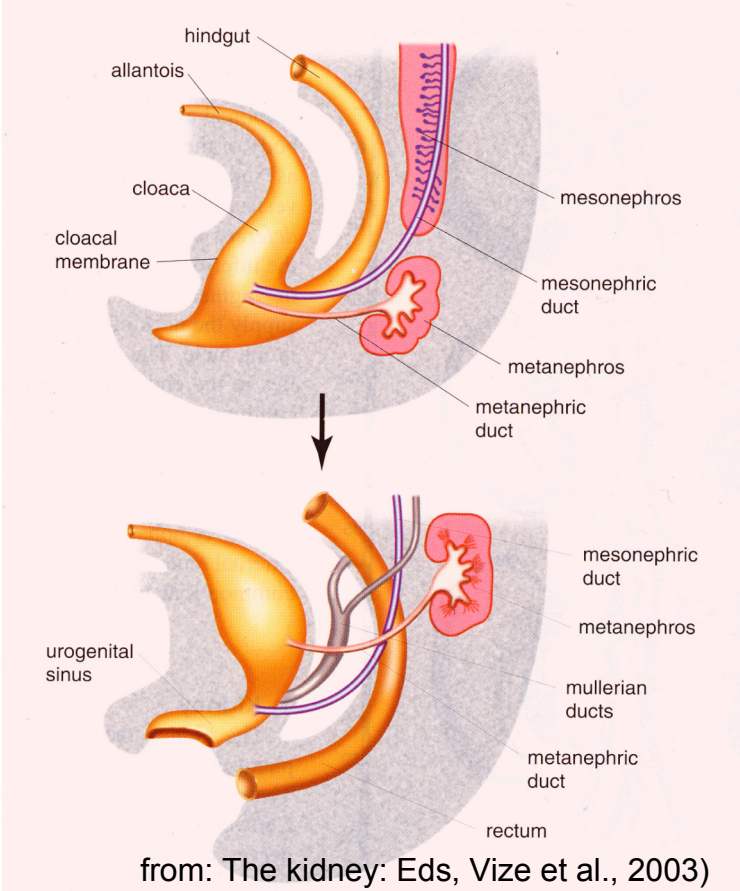
Calcineurin B (peristalsis)

uroplakin (epithelium)

Tbx18?



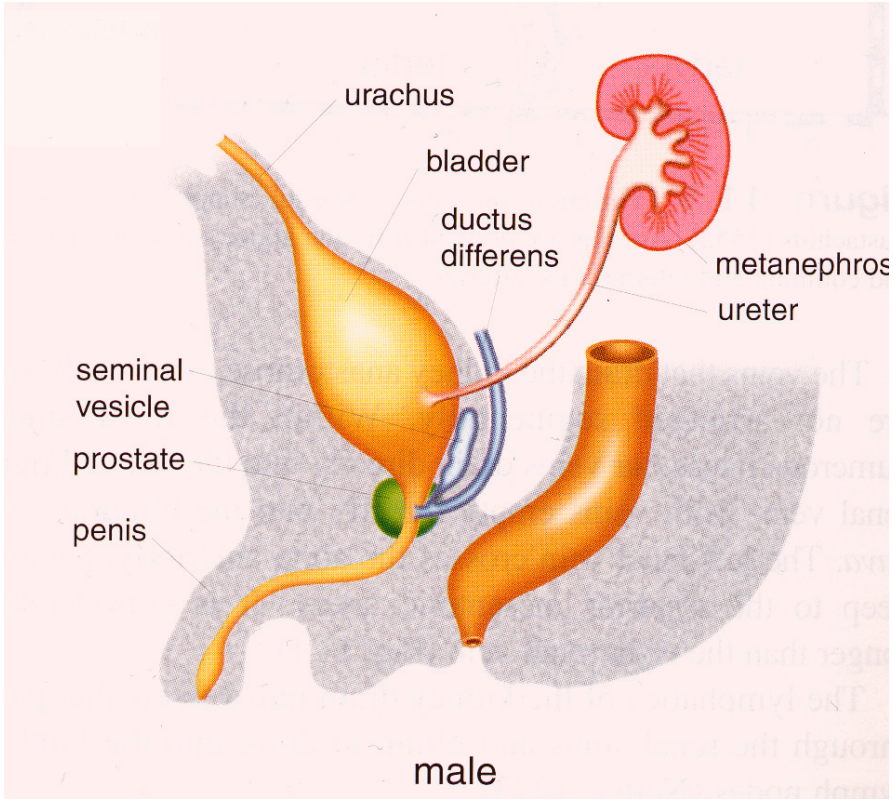
Larsen's Embryology, 6th Edition



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

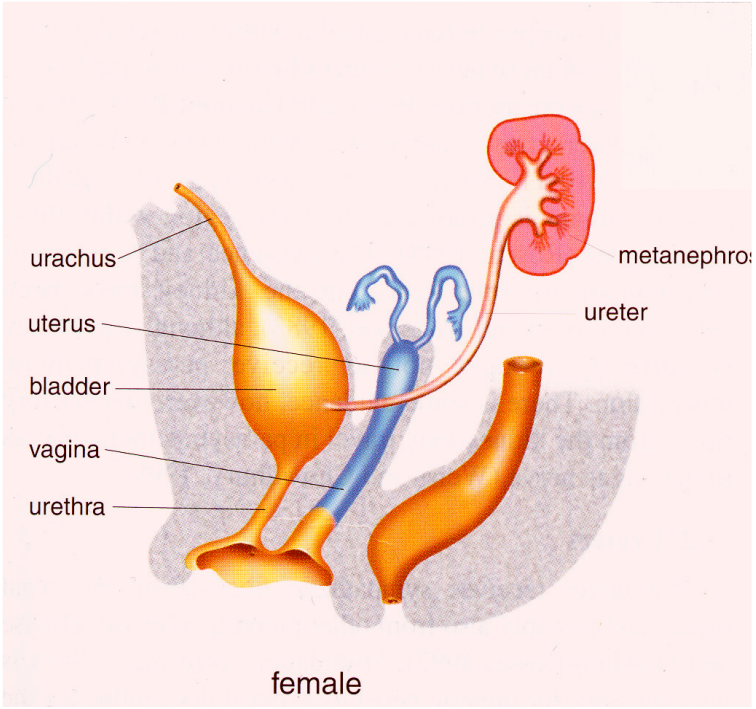
The urorectal septum partitions the cloaca ("sewer") into the urogenital sinus (ventral) and hindgut (dorsal)

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 males

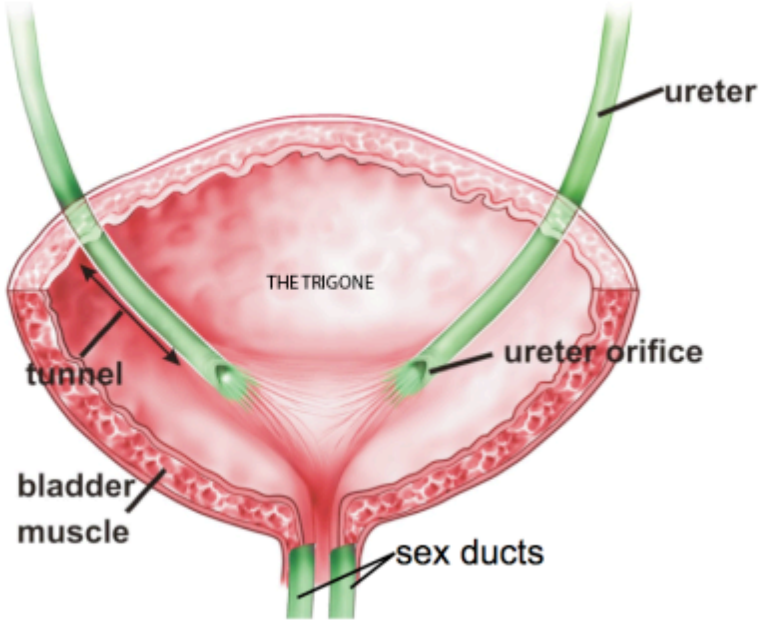
from: The kidney: Eds, Vize et al., 2003)

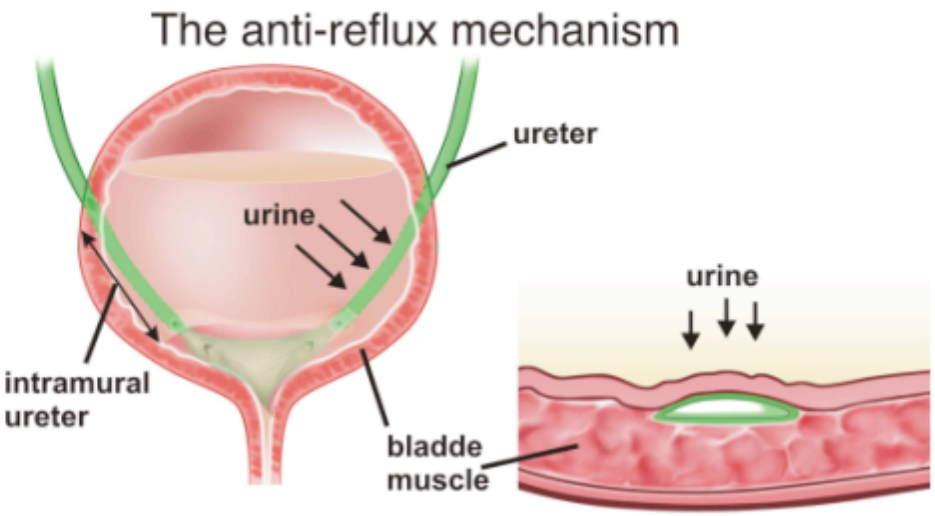


- in females the urogenital sinus forms the bladder, urethra and vagina
- Mullerian (paramesonephric ducts) differentiate into the uterus and upper vagina
- Wolffian (mesonephric ducts) regress

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

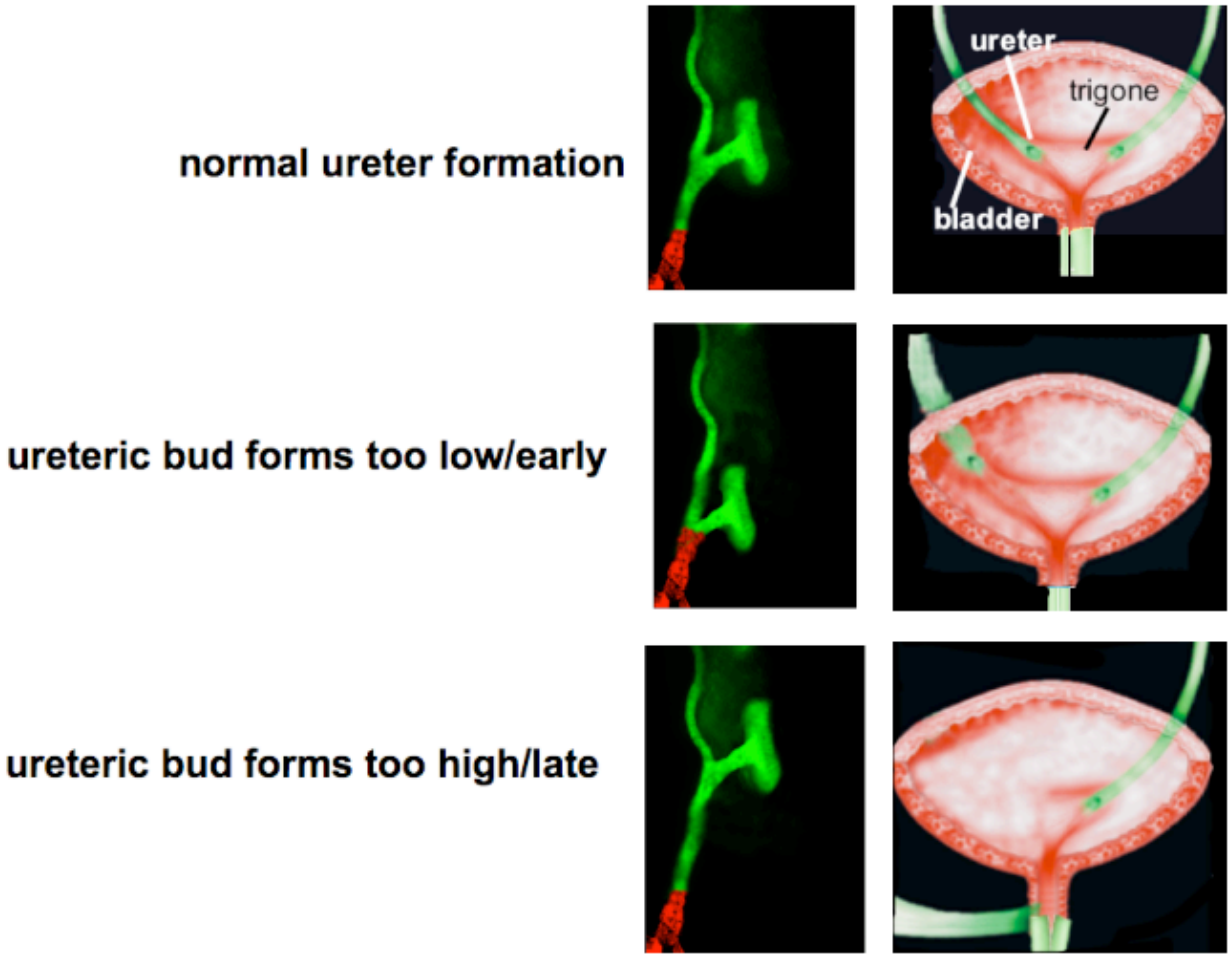
The trigone is the center of the anti-reflux mechanism

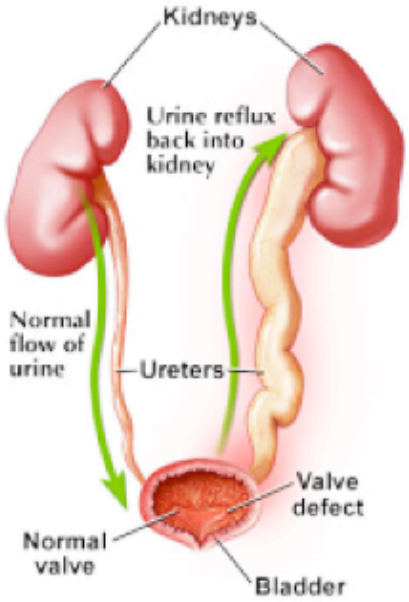




The trigone is bounded by the ureter orifices at its lateral edges and the sex ducts, at the apex

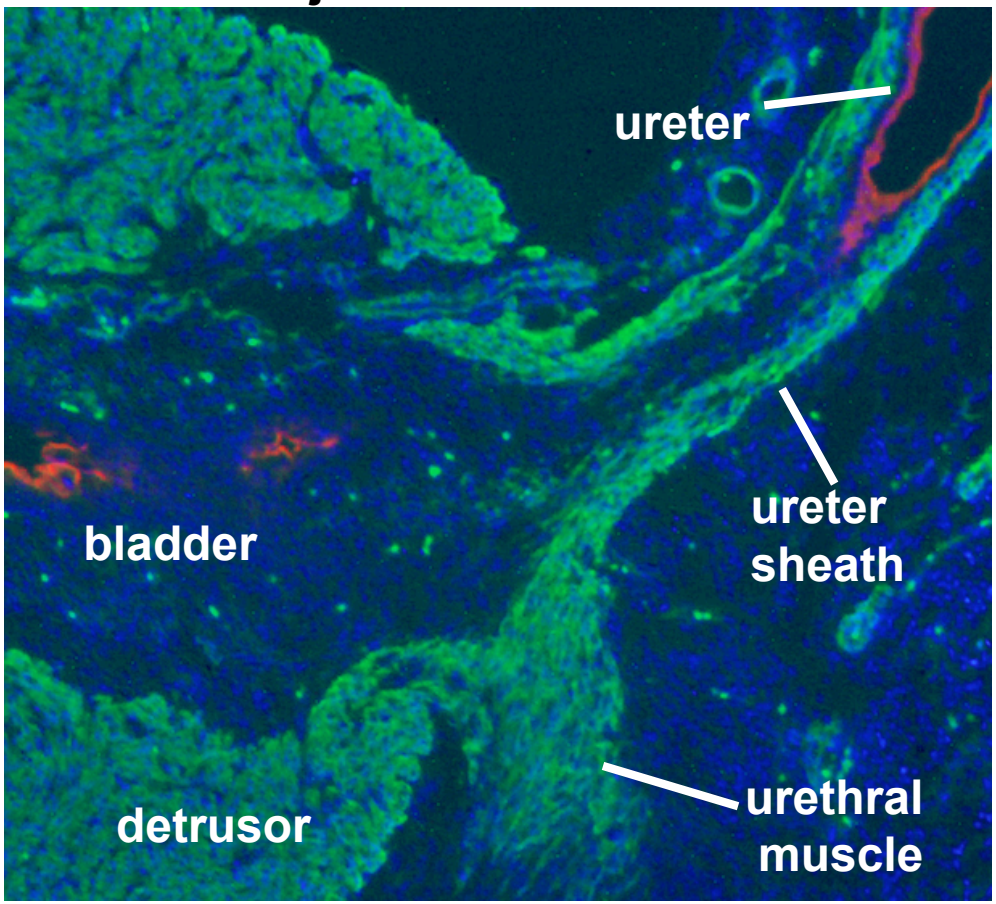
Abnormal connections between the ureter orifice and trigone are associated with vesicoureteral reflux and obstruction





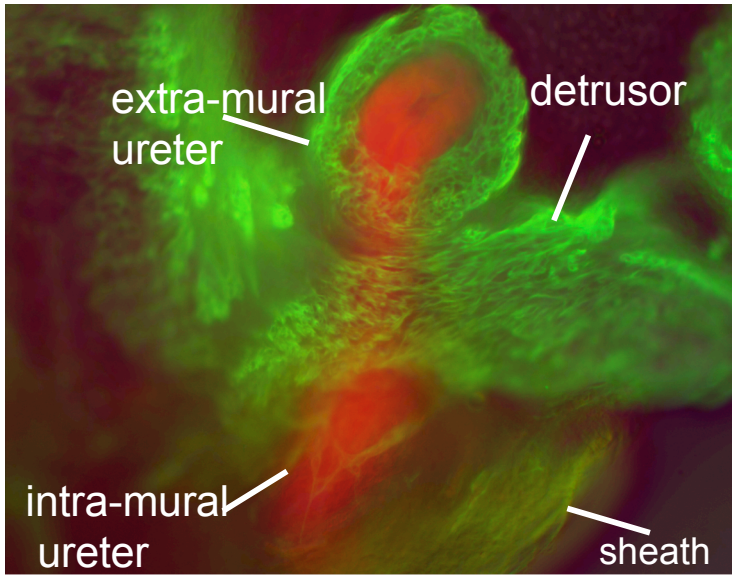
Mackie-Stephens hypothesis: the final position of the ureter with respect to the Trigone depends on the site of its formation on the Wolffian duct

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



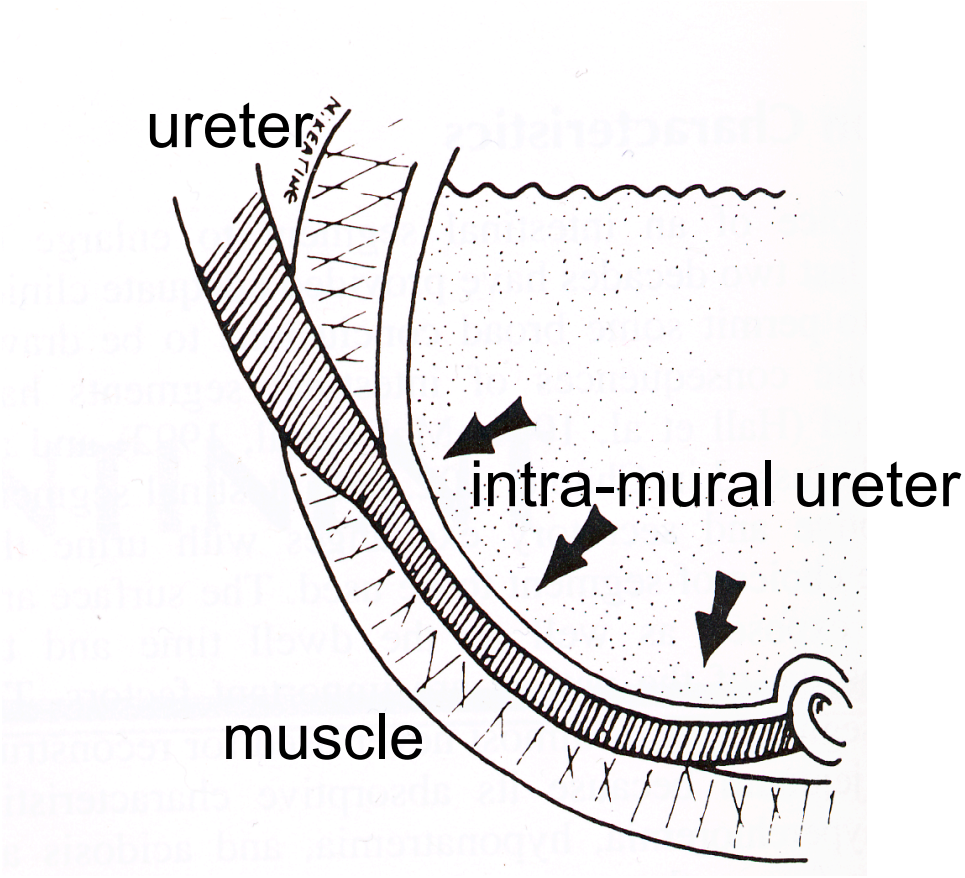
proper configuration of muscle groups that form the trigone is likely to be important for urinary tract function

the **ureteral valve** is part of the trigone and is an **anti-reflux** mechanism that prevents urine back flow (reflux)

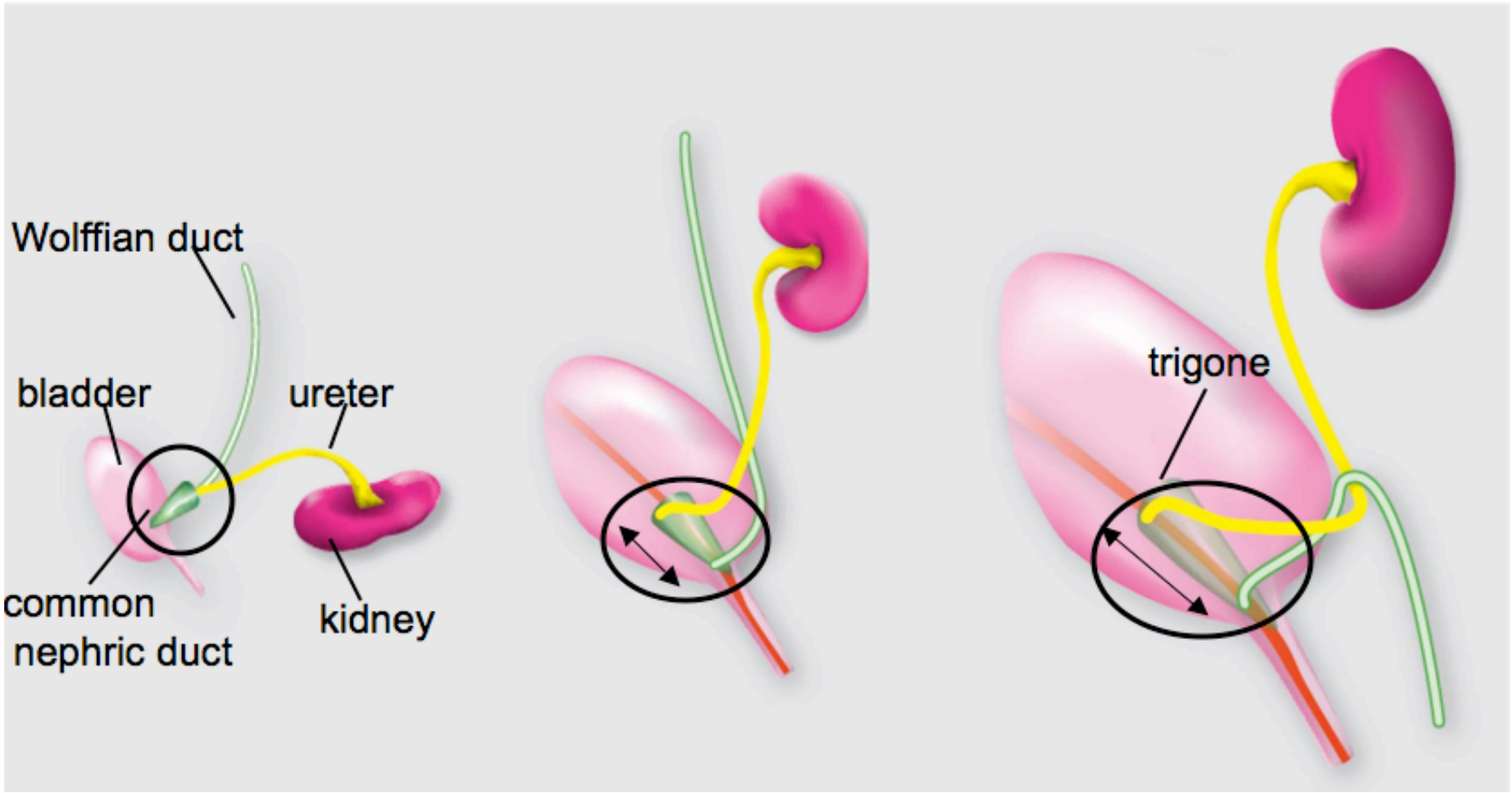


smooth muscle actin

ureter epithelium

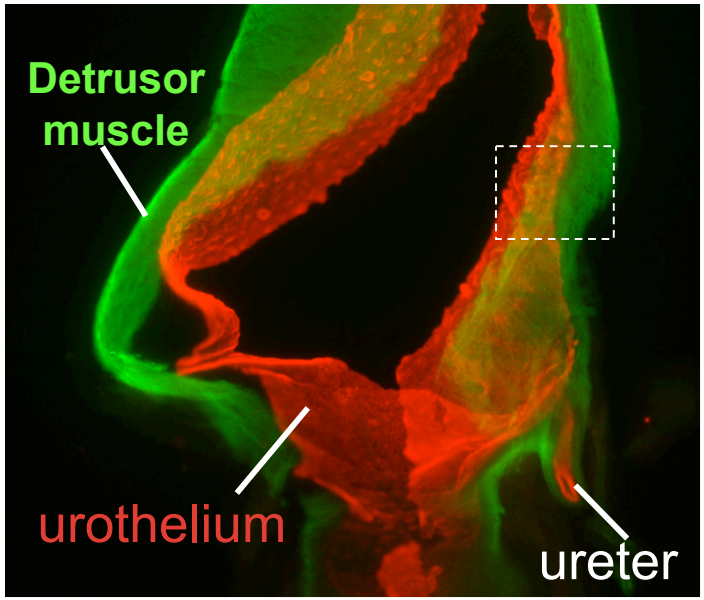


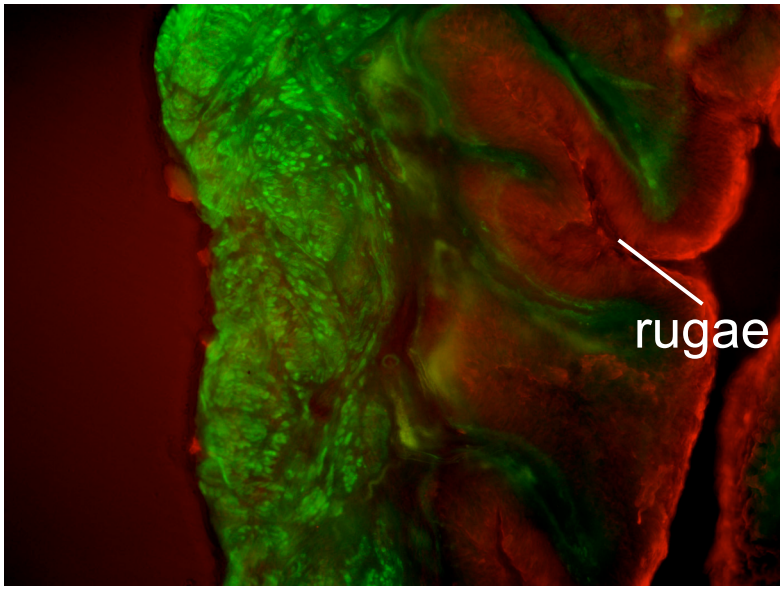
Ureterl valve function depends on insertion of the ureter orifice at the proper position in the bladder neck (trigone)



THE **TRIGONE** IS MORPHOGLOGICALLY DISTINCT FROM THE BLADDER AND IS THOUGHT TO BE DERRIVED FROM THE COMMON NEPHRIC DUCT

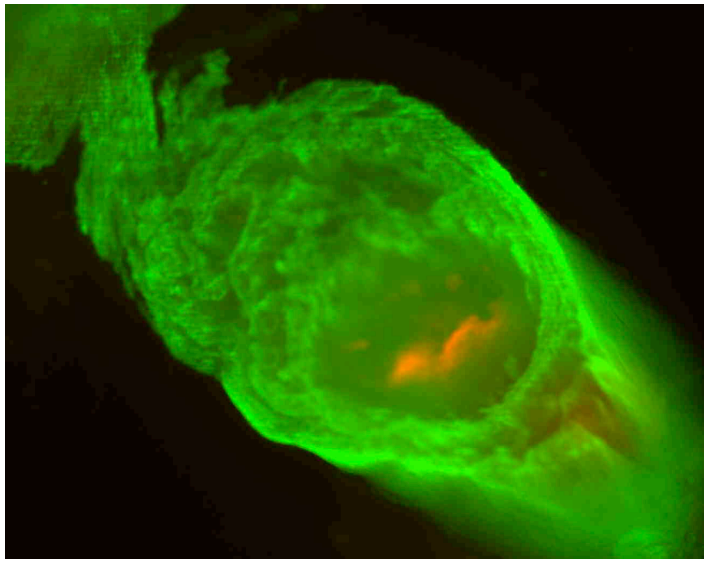
The bladder epithelium is lined with
plaques made from **uroplakins** that form a water-proof barrier

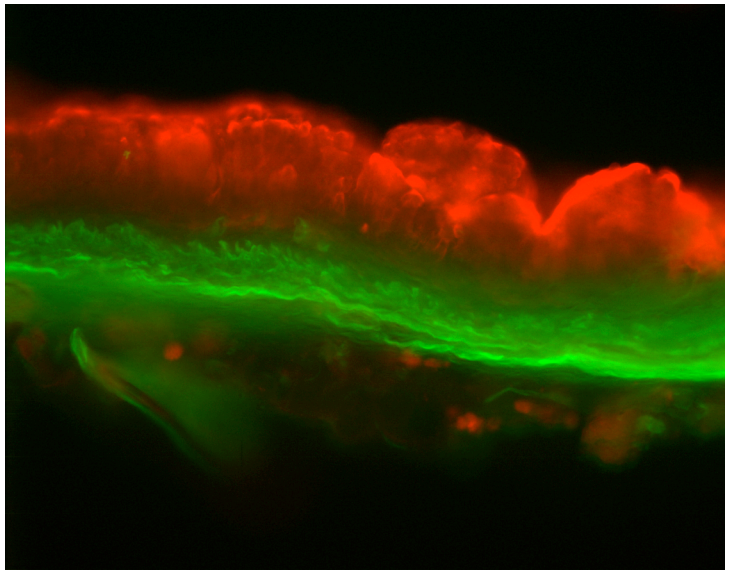




smooth muscle of the detrusor and rugae (folds) in the urothelium
allow the bladder to expand and contract

- 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

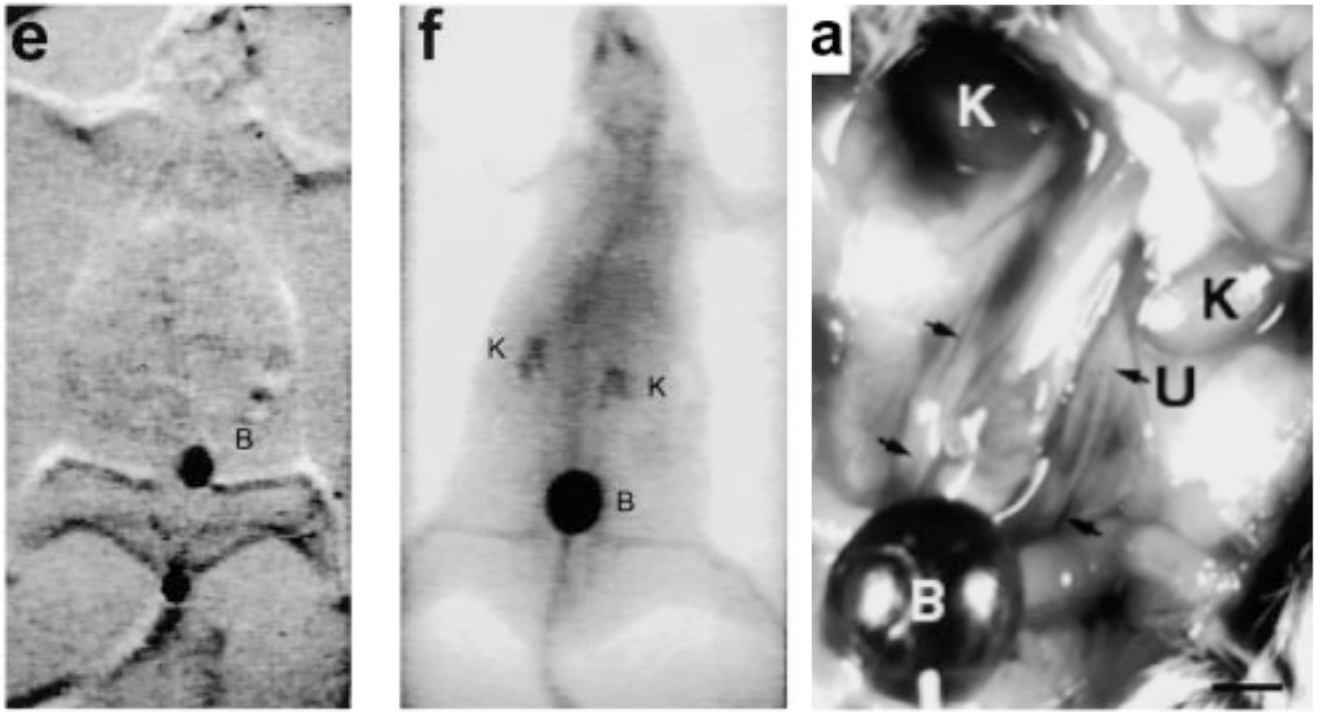




smooth muscle actin
uroplakin

Inactivation of uroplakins results in vesicuureteral reflux in mice

India ink injections into the bladders of wt and uroplakin3- mice

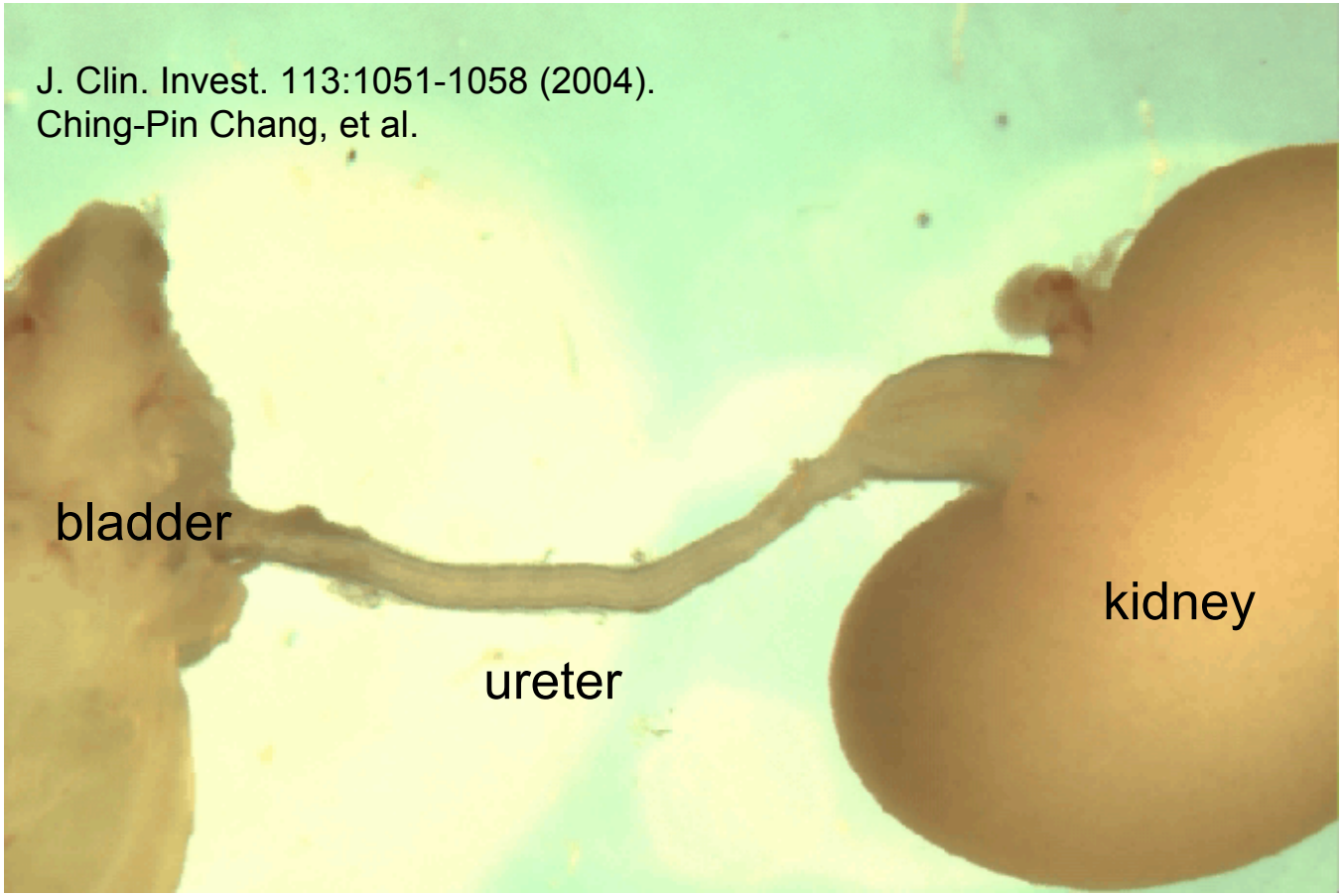


wild type

uroplakin3 mutants

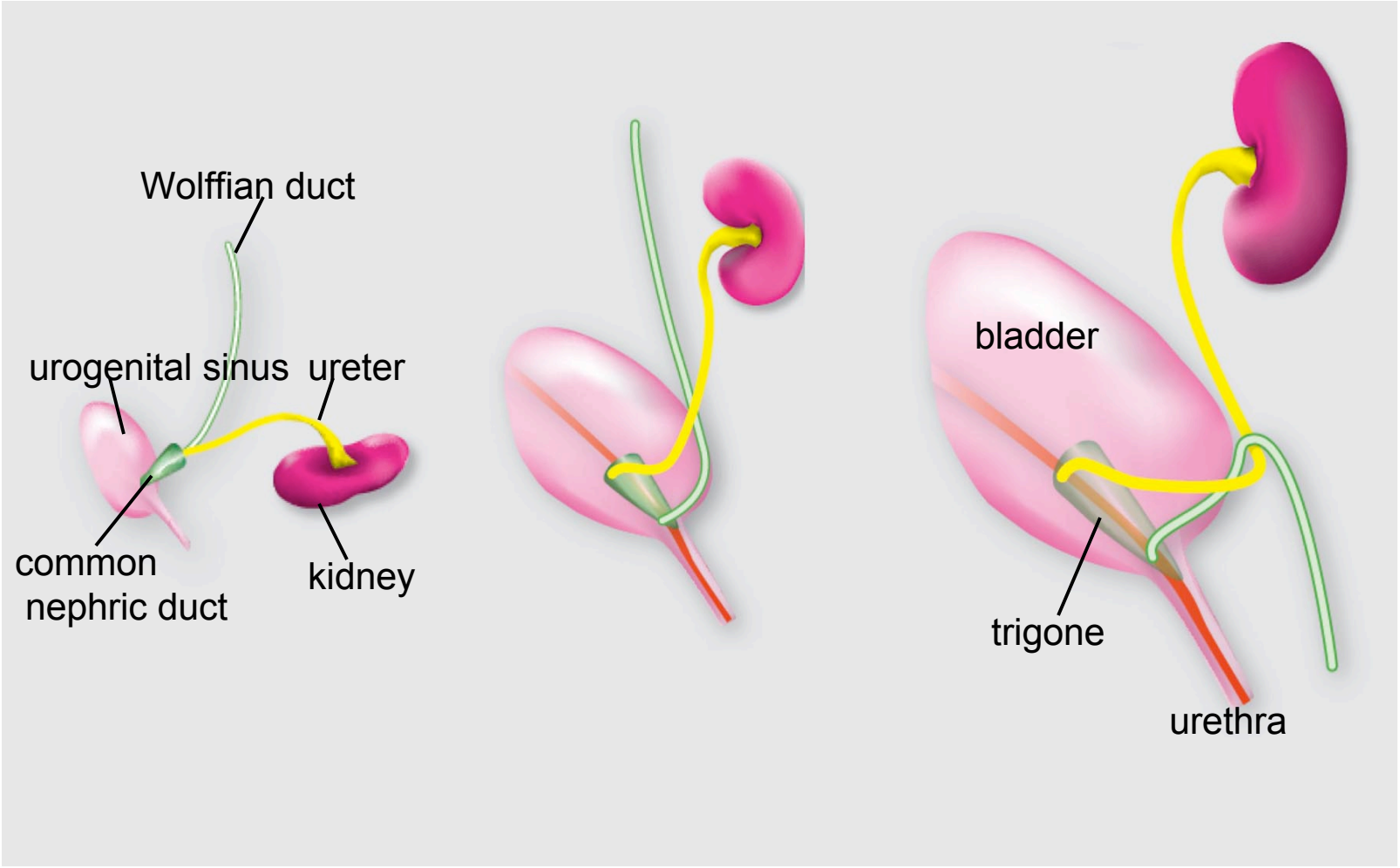
retrograde urine flow in uroplakin3 ko mice

URETER PERISTALSIS IN VITRO (E15 mouse embryo):



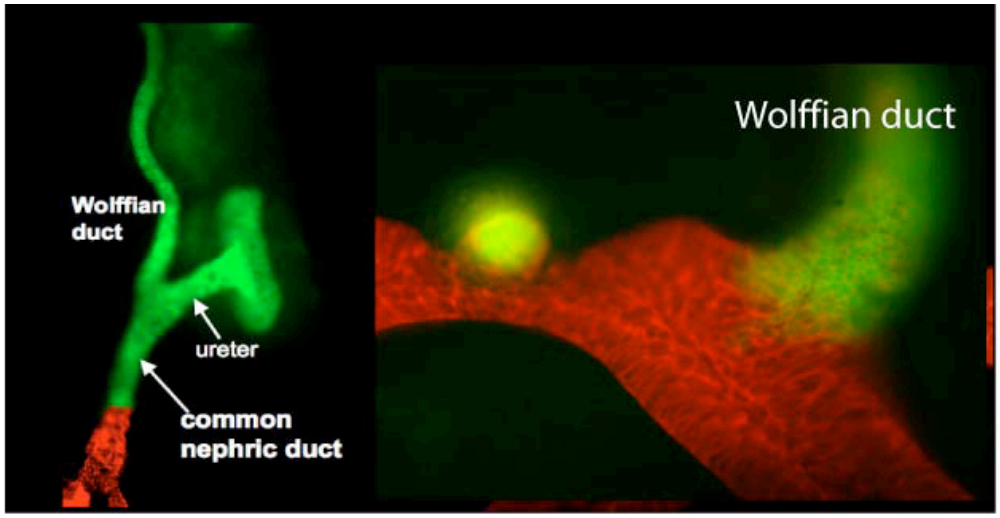
Impaired peristalsis is a cause of obstruction
(functional obstruction)

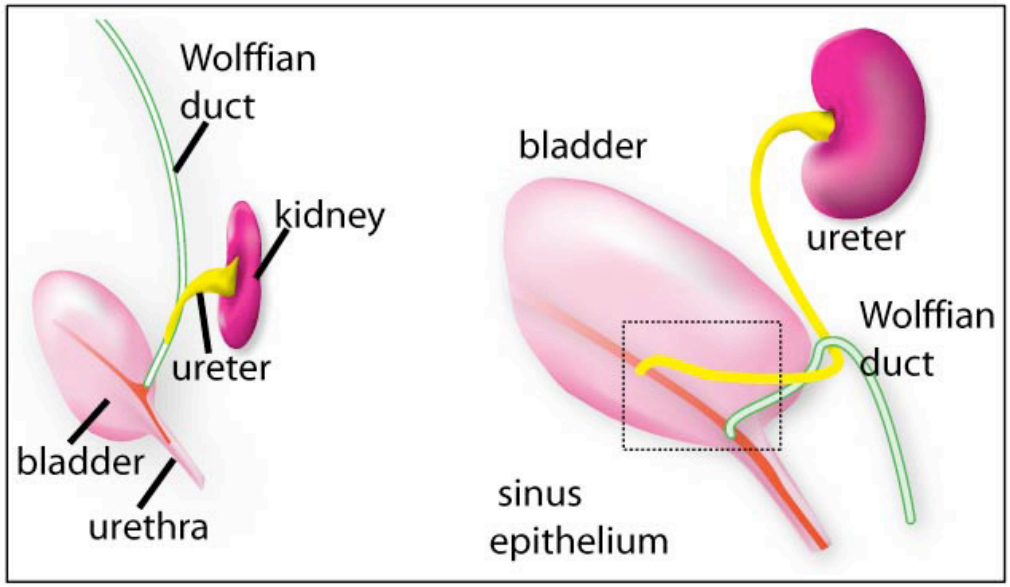
The ureter is initially joined to the Wolffian duct (future vas-deferens) not to the bladder



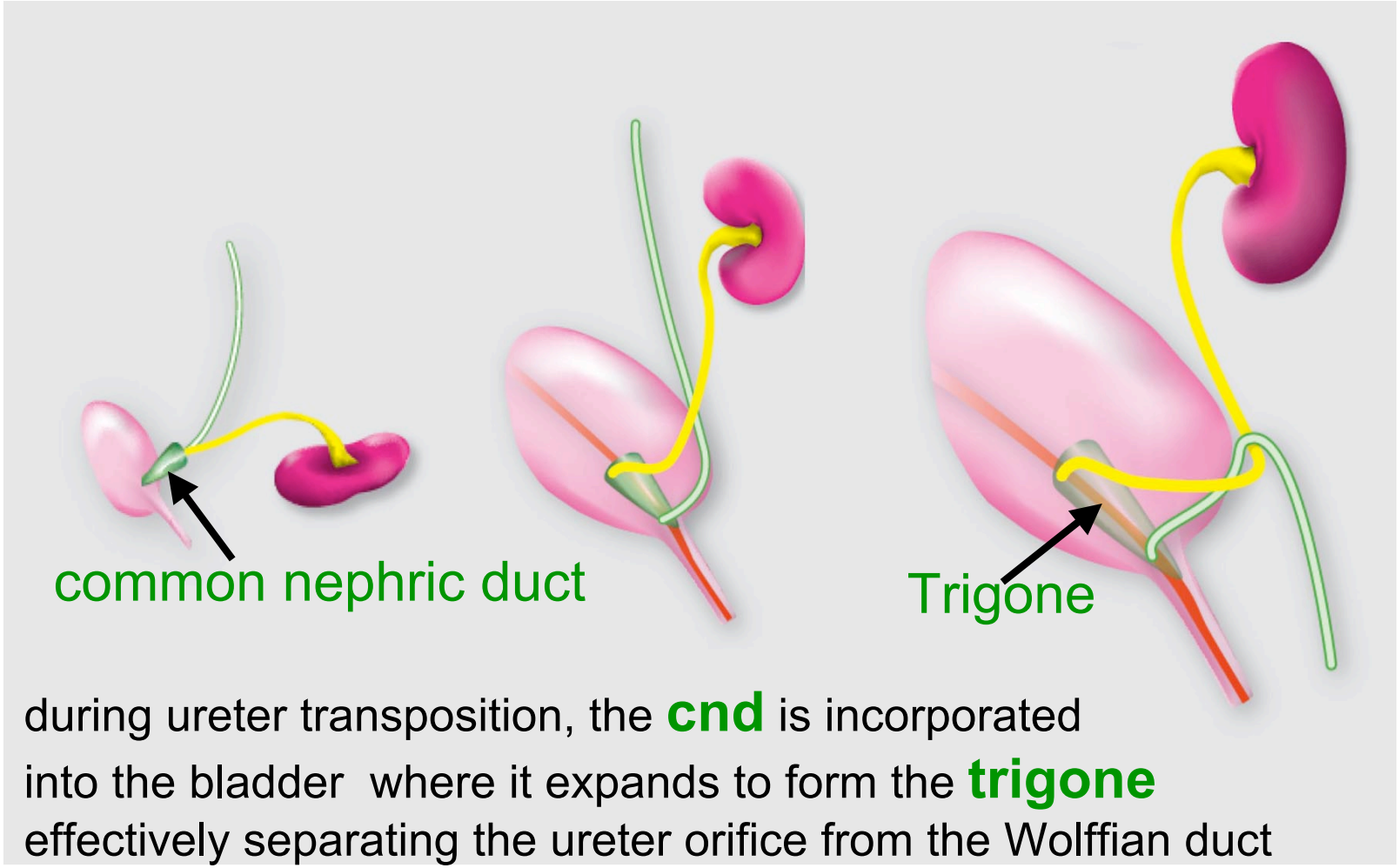
Mature connections are established when the ureter orifice is **transposed** from the posterior Wolffian duct (**the common nephric duct)** to the bladder

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



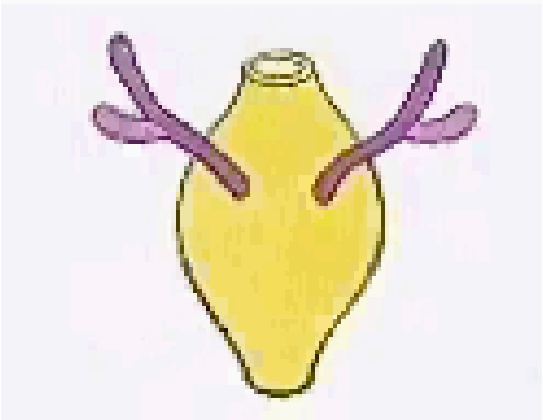


According to the accepted model, trigone formation is considered to be crucial for repositioning the ureter orifice



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

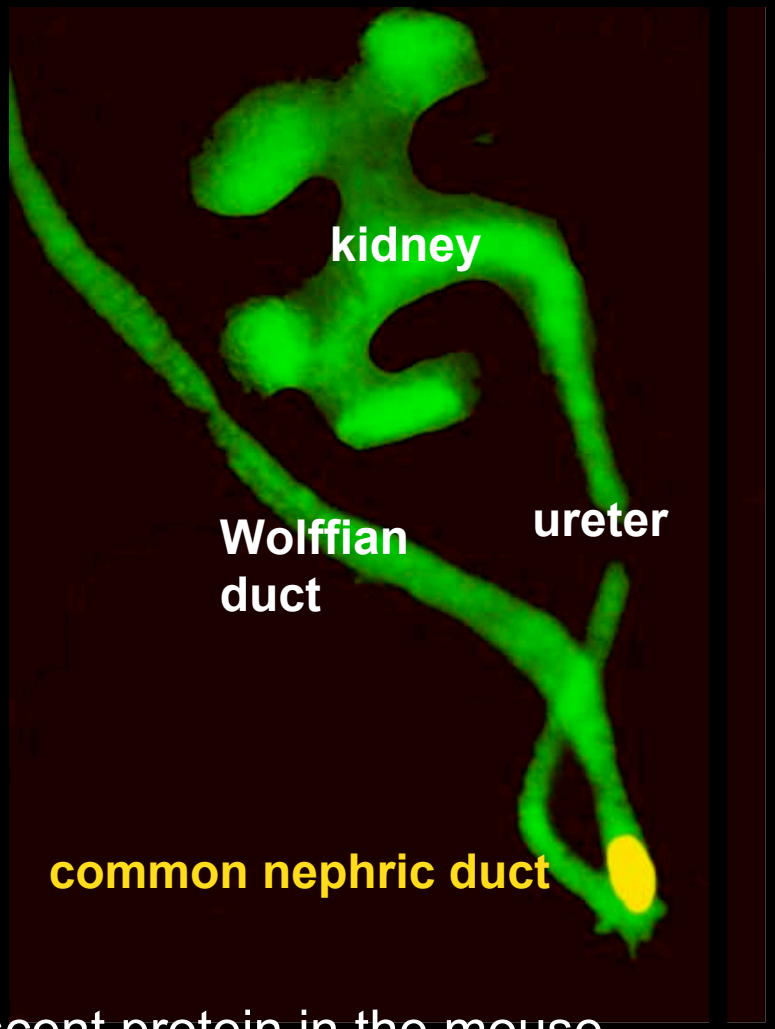
Accepted model of ureter transposition



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

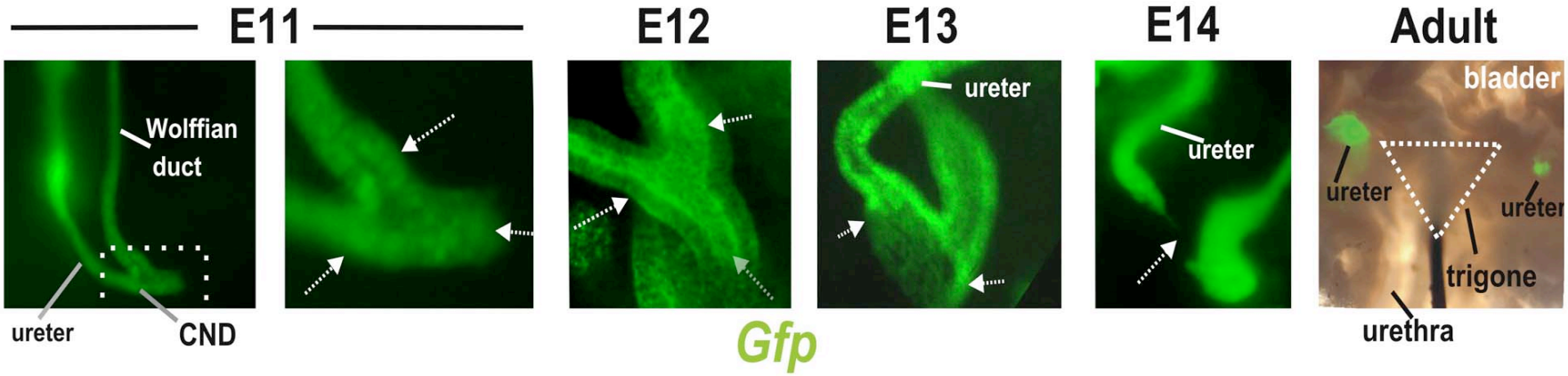
Larsen's Embryology

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



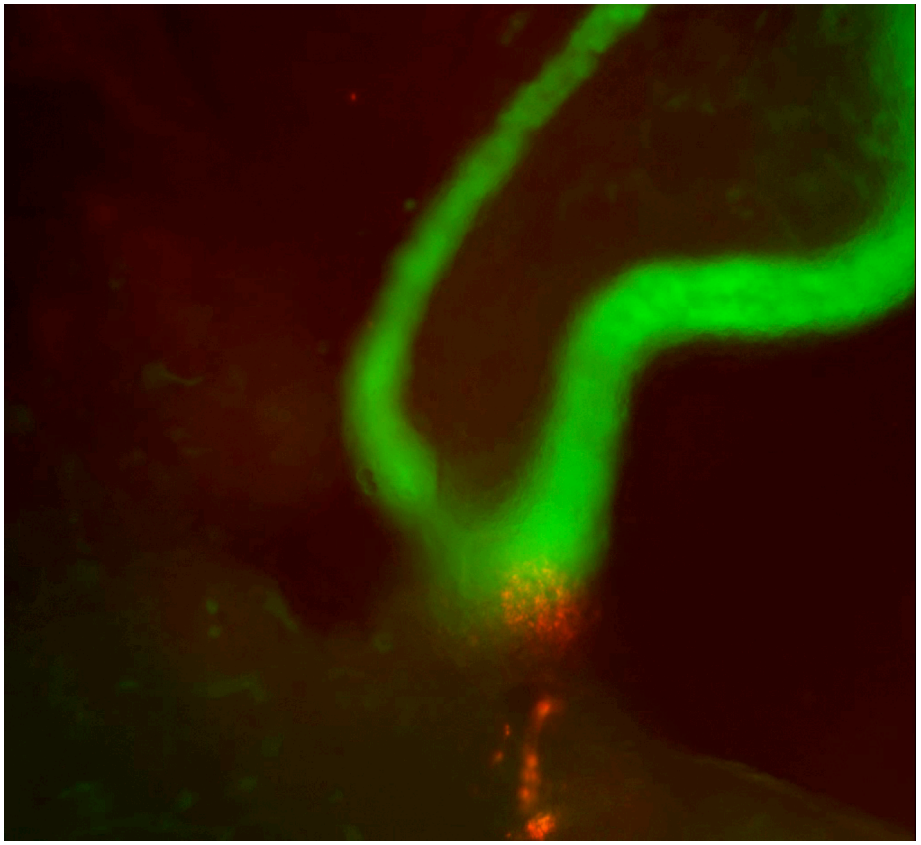
expression of Jelly Fish green fluorescent protein in the mouse common nephric duct of this transgenic mouse enables us to follow its fate during ureter insertion

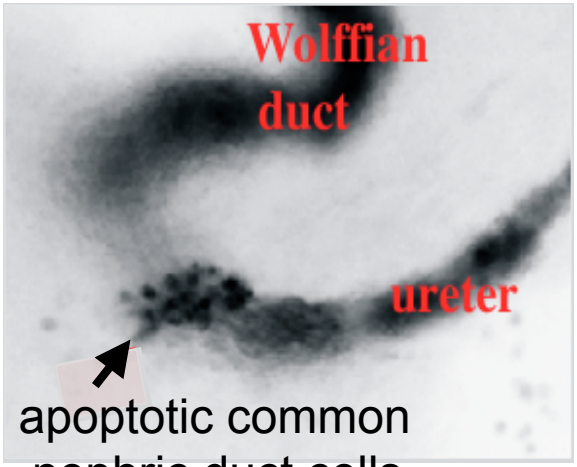
what happens to the common nephric duct
during ureter transposition?



The common nephric duct appears to regress rather than expand

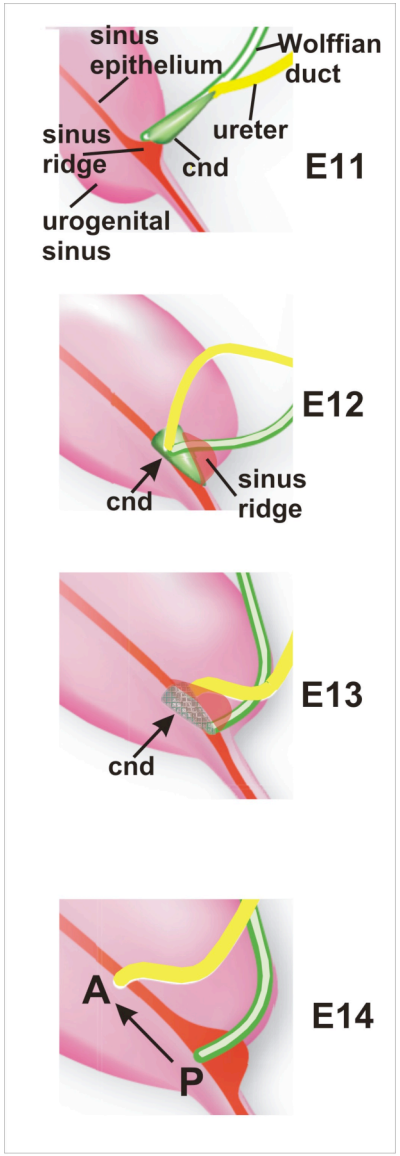
Ureter transposition depends on apoptosis of the
common nephric duct





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