ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

WELCOME TO

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: 10 March 2020

Topic: Congenital Anomalies of the Kidney and Urinary Tract

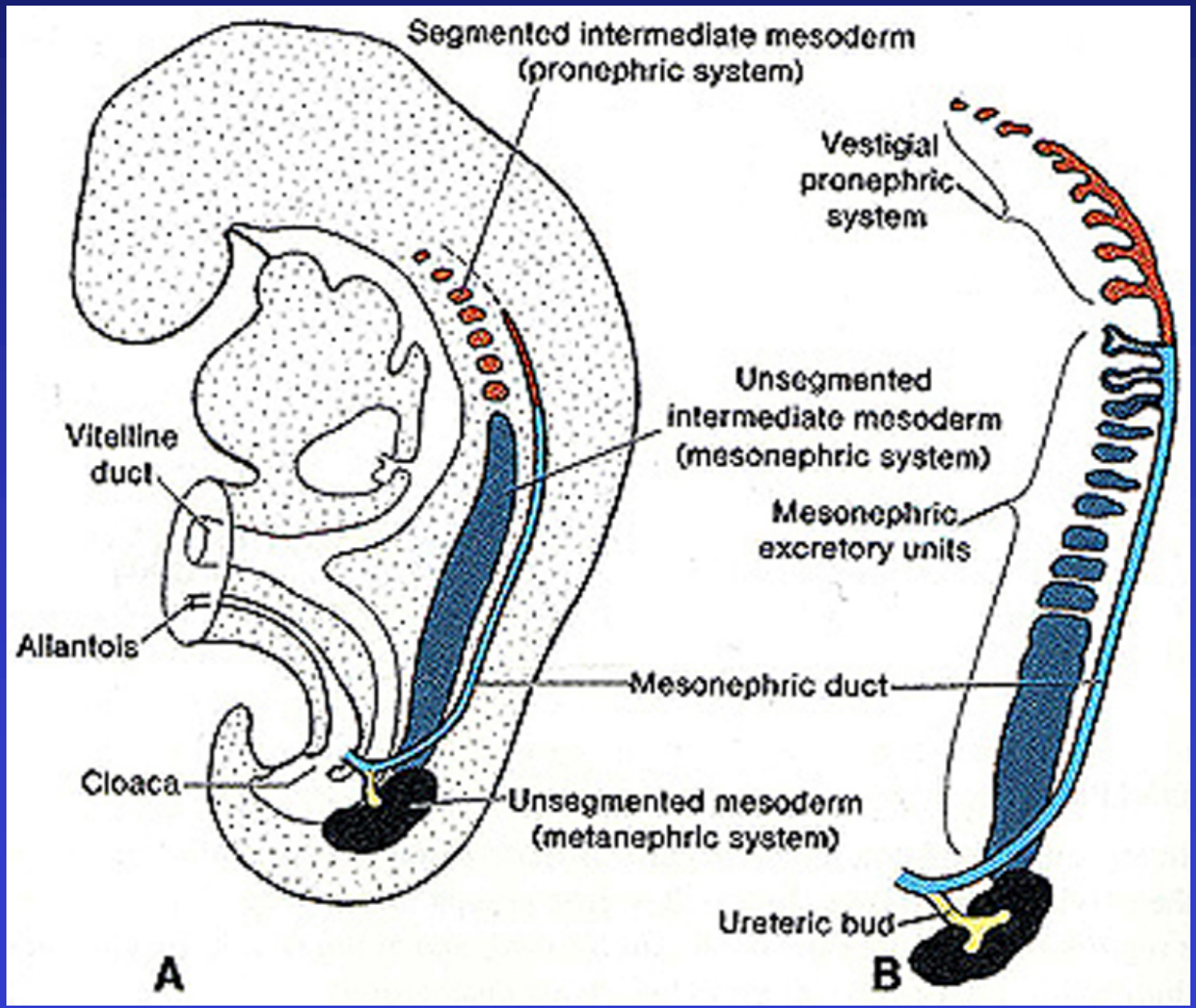
Speaker: Carl Bates

Moderator: Francesco Emma

Kidney development

- 3 kidneys form during embryogenesis (all from the intermediate mesoderm)
  - **Pronephros**
  - **Mesonephros**
  - **Metanephros**
- Kidney development progresses rostral to caudal

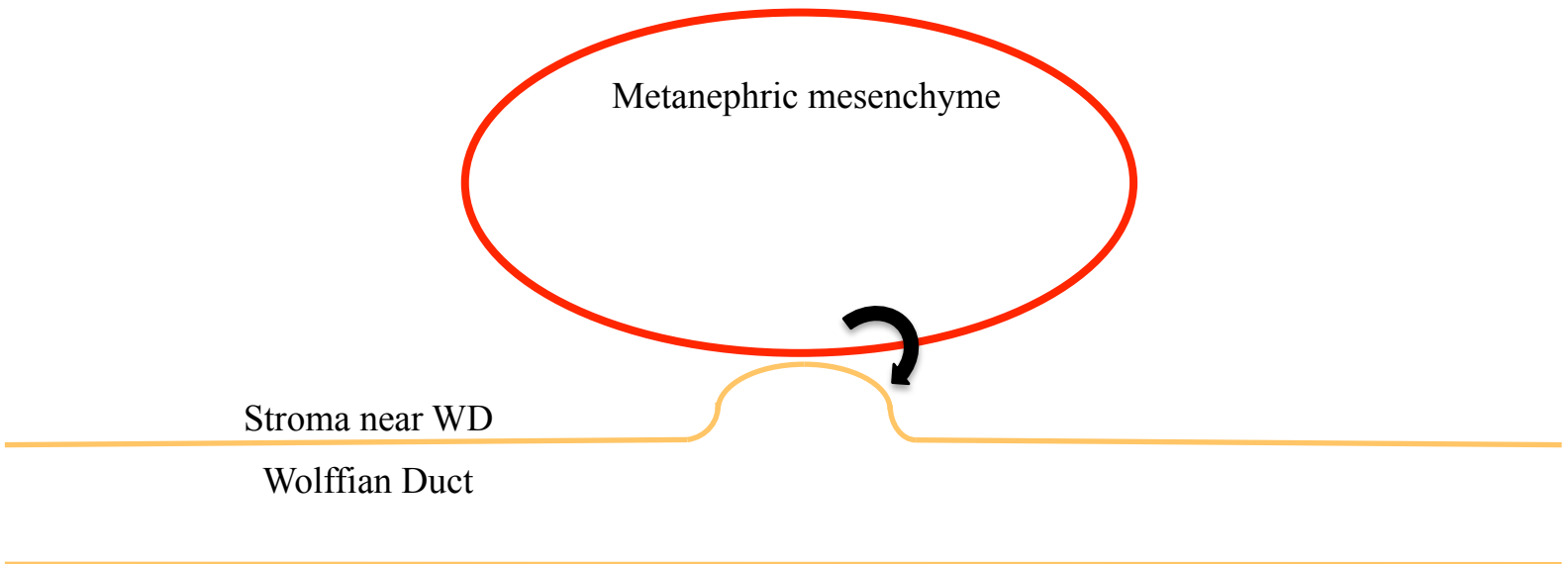
Kidney Development



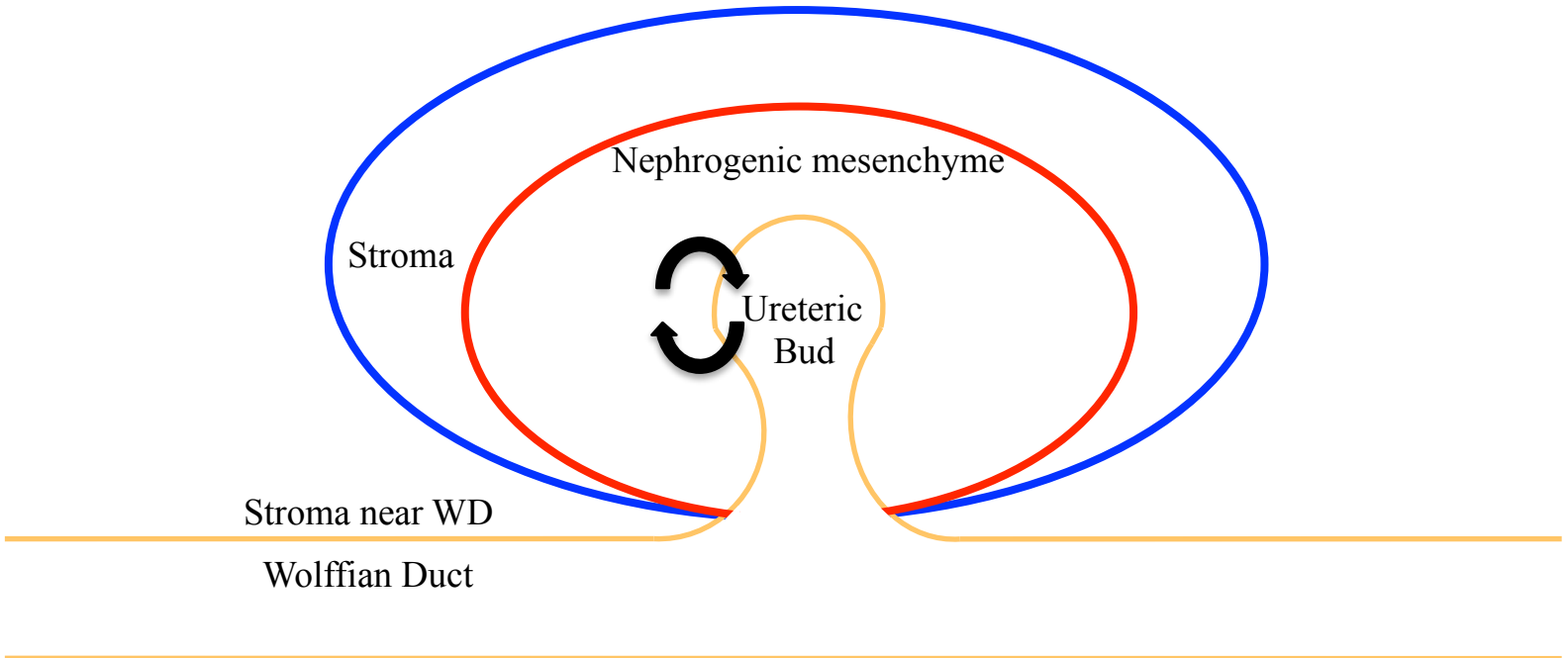
Metanephric Kidney Development

- Reciprocal inductive signaling between 2 tissues:
  - **Ureteric Bud**
  - **Metanephric mesenchyme**
- Starts at 5th week of gestation
- Ends at ~34 weeks of gestation

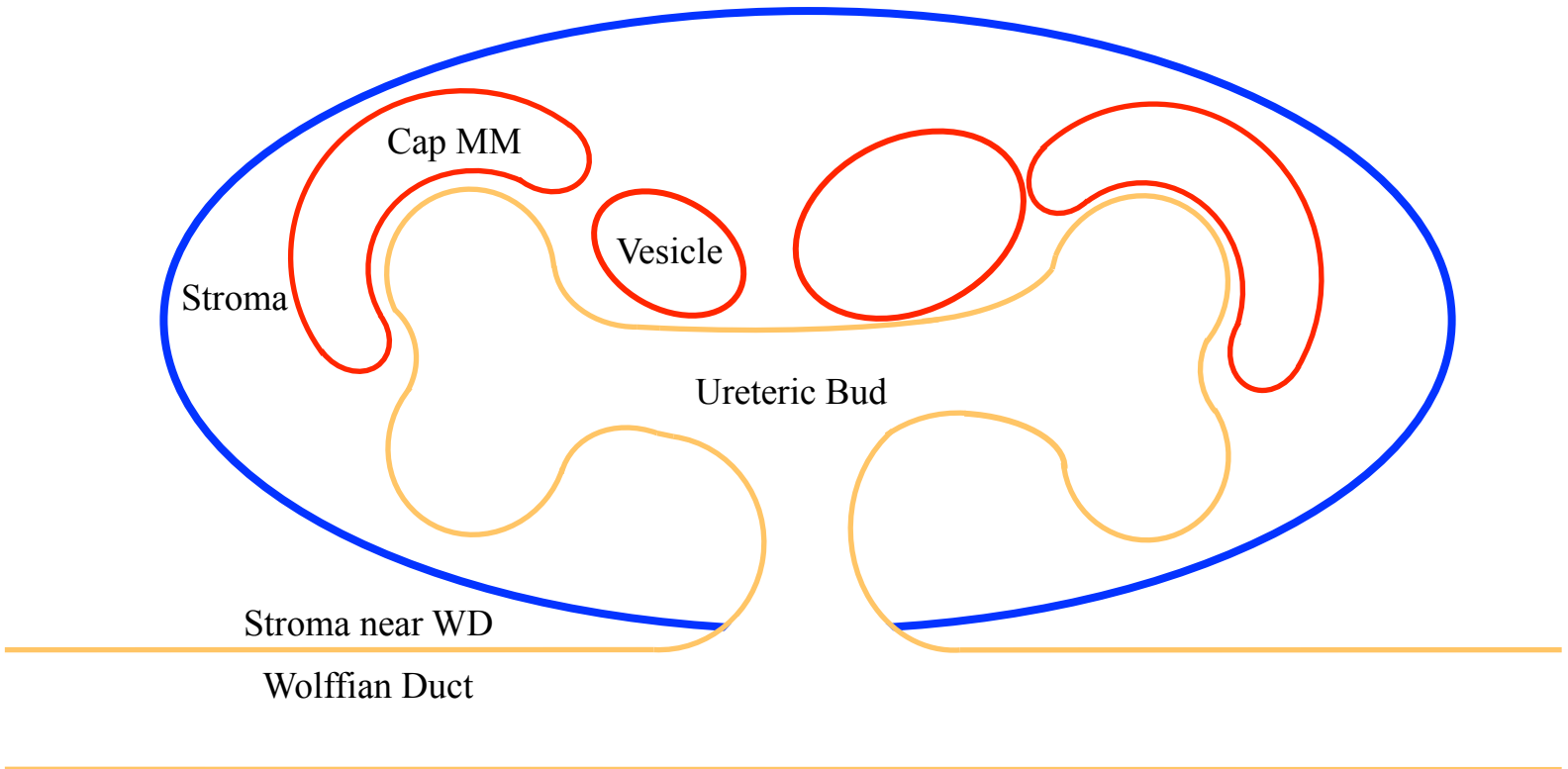
Metanephros: E10.0-10.5



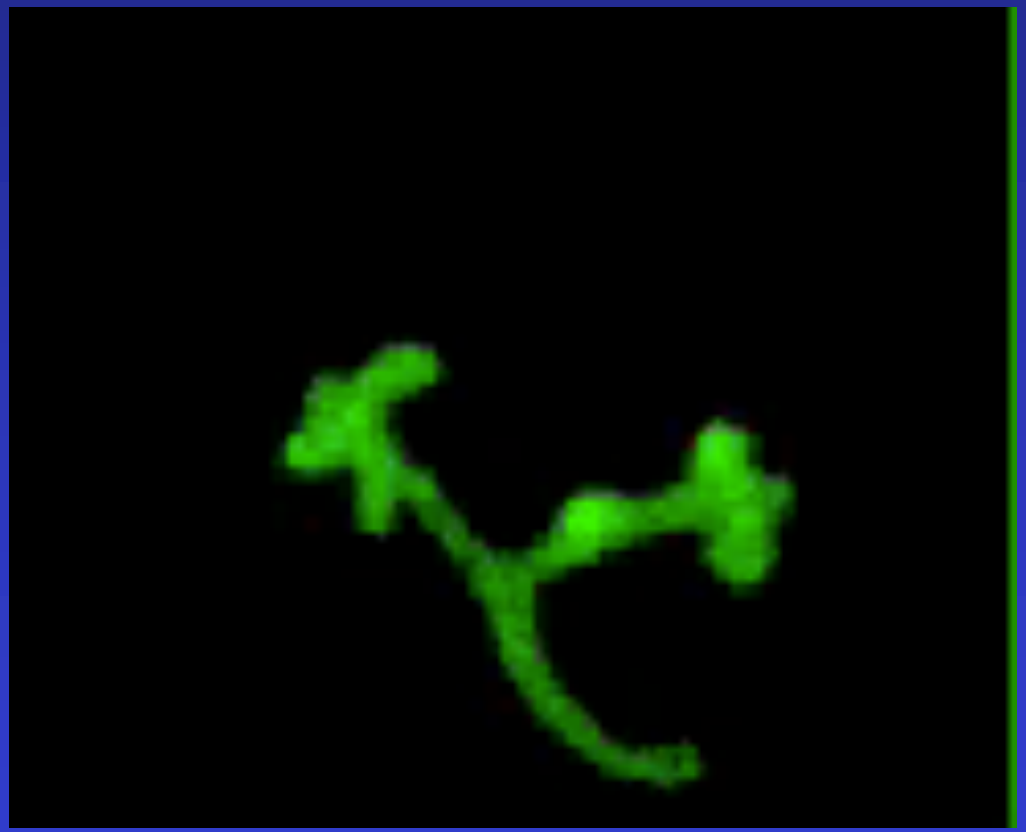
Metanephros: E11.0-11.5



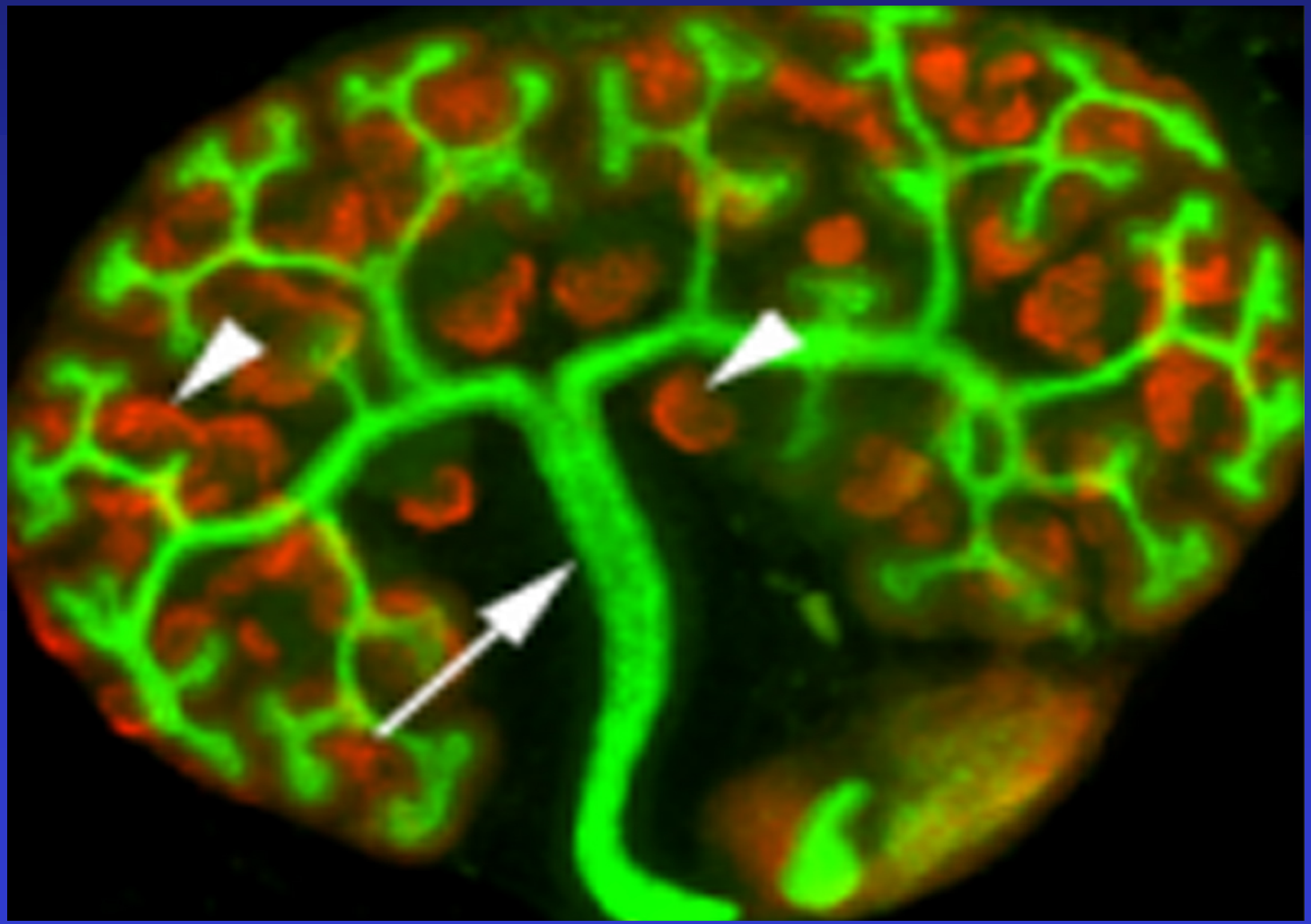
Metanephros: E12.5-13.5



Ureteric bud branching in a mouse explant



Ureteric bud and developing nephrons in an explant



Nephron Formation

a) induction of a condensate

b) pretubular cells aggregate and start to epithelialise

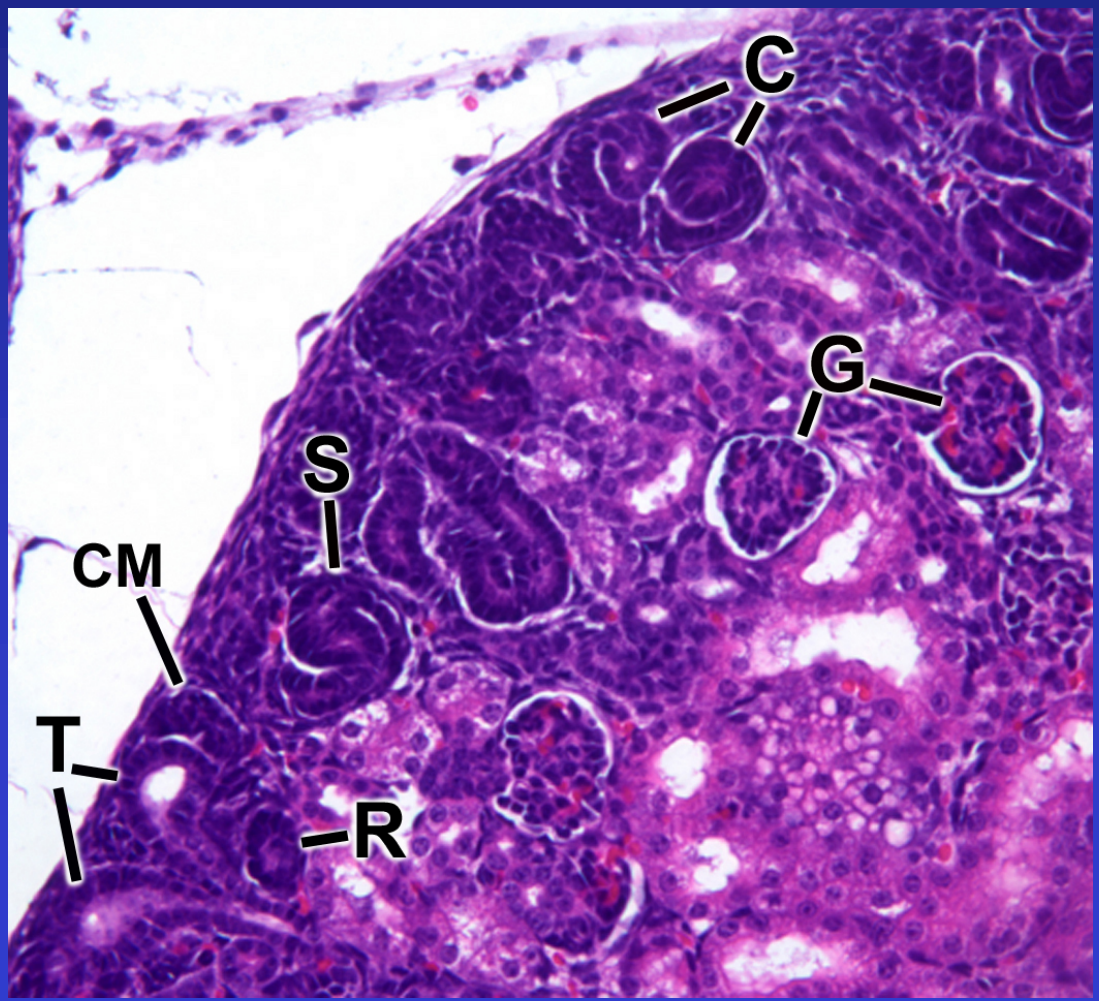
c) Comma-shape body

d) S-shape body

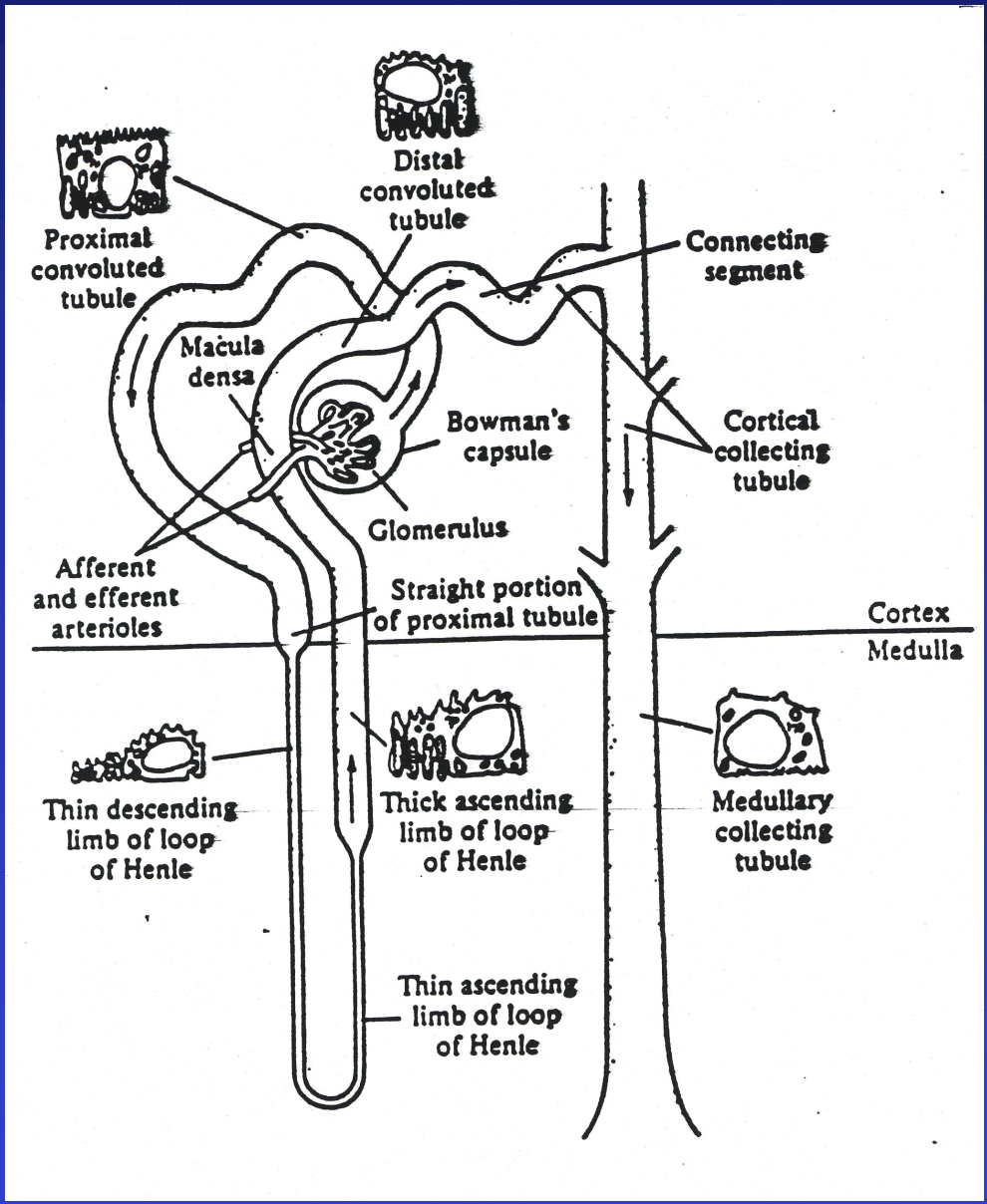
e) migration of endothelial cells

f) glomerulogenesis

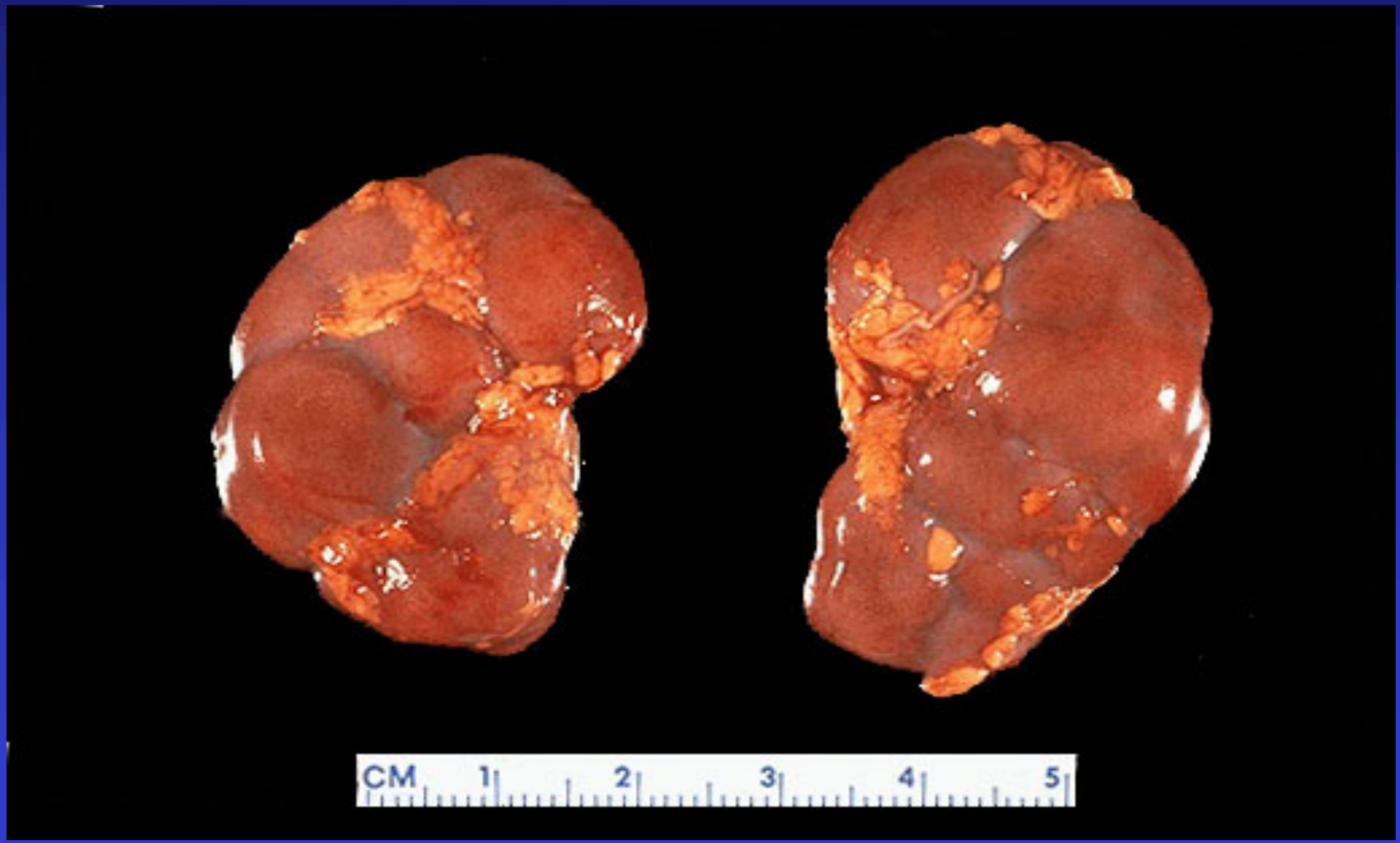
Different stages of nephron formation: E16.5 mouse kidney H&E



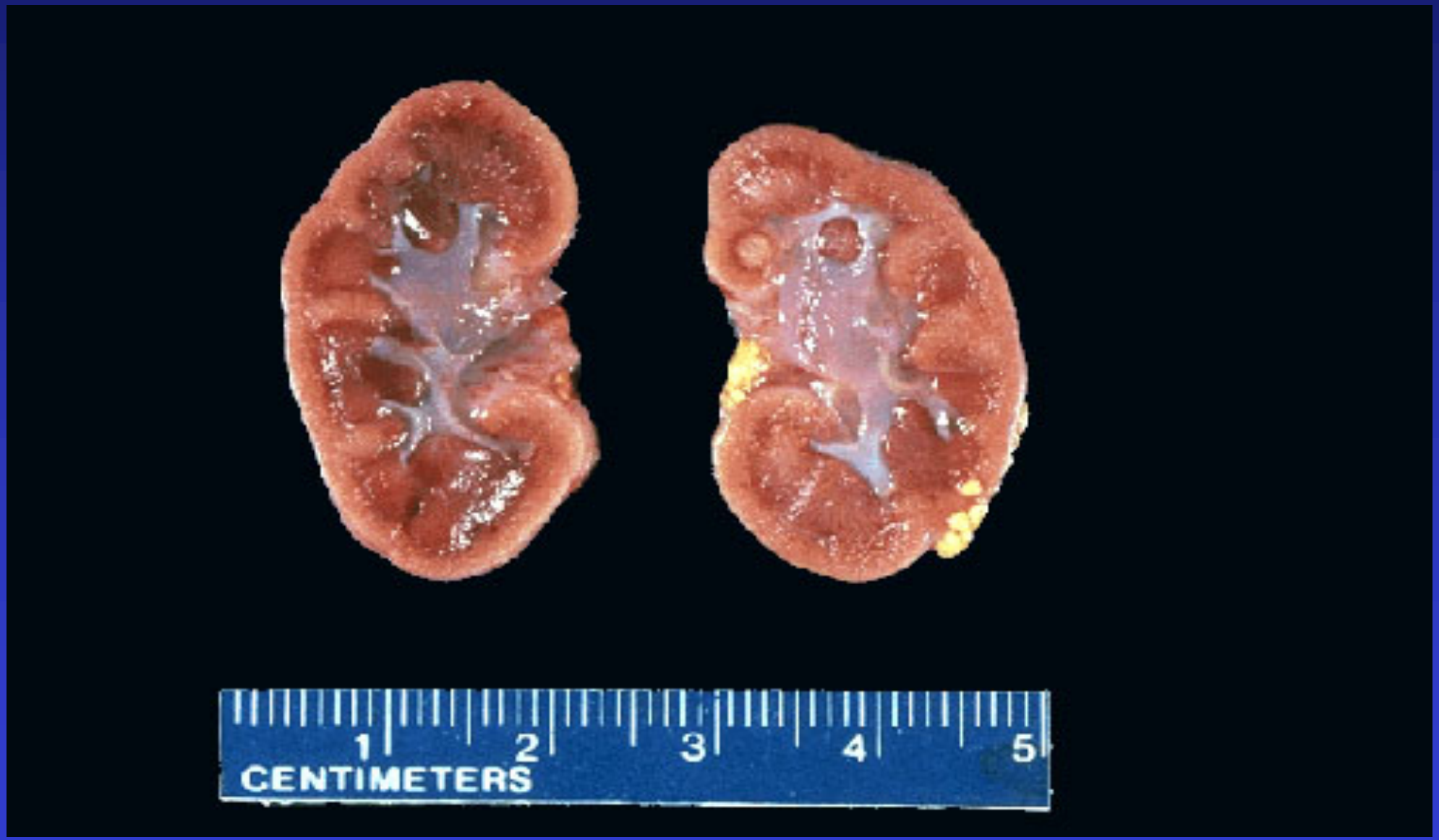
Mature Nephron and Collecting Ducts



Newborn Kidney-Whole



Newborn Kidney-Cut



Congenital kidney disease

Epidemiology of ESRD

- Incidence of pediatric ESRD has decreased from 2008- 2014
  - ~1700 in 2008 and ~1400 as of 2014
- 40% of children with new ESRD are 18-21 yo
  - 6.8/million are 5-9 yo
  - 30.6/million are 18-21 yo

Distribution of ESRD type by age: 2012-2016

Primary Cause	0-4	5-9	10-13	14-17	18-21
CAKUT	46.3	33.4	24.2	23	8.4
Primary Glom Disease	7.5	19.4	21.6	23.9	28.1
Secondary Glom Disease/Vasculitis	2.5	7.0	8.8	11.0	15.2
Cystic/Hereditary/ Congenital	19.1	13.3	14.7	11.2	7.8
Other	24.7	26.8	30.9	30.8	40.5

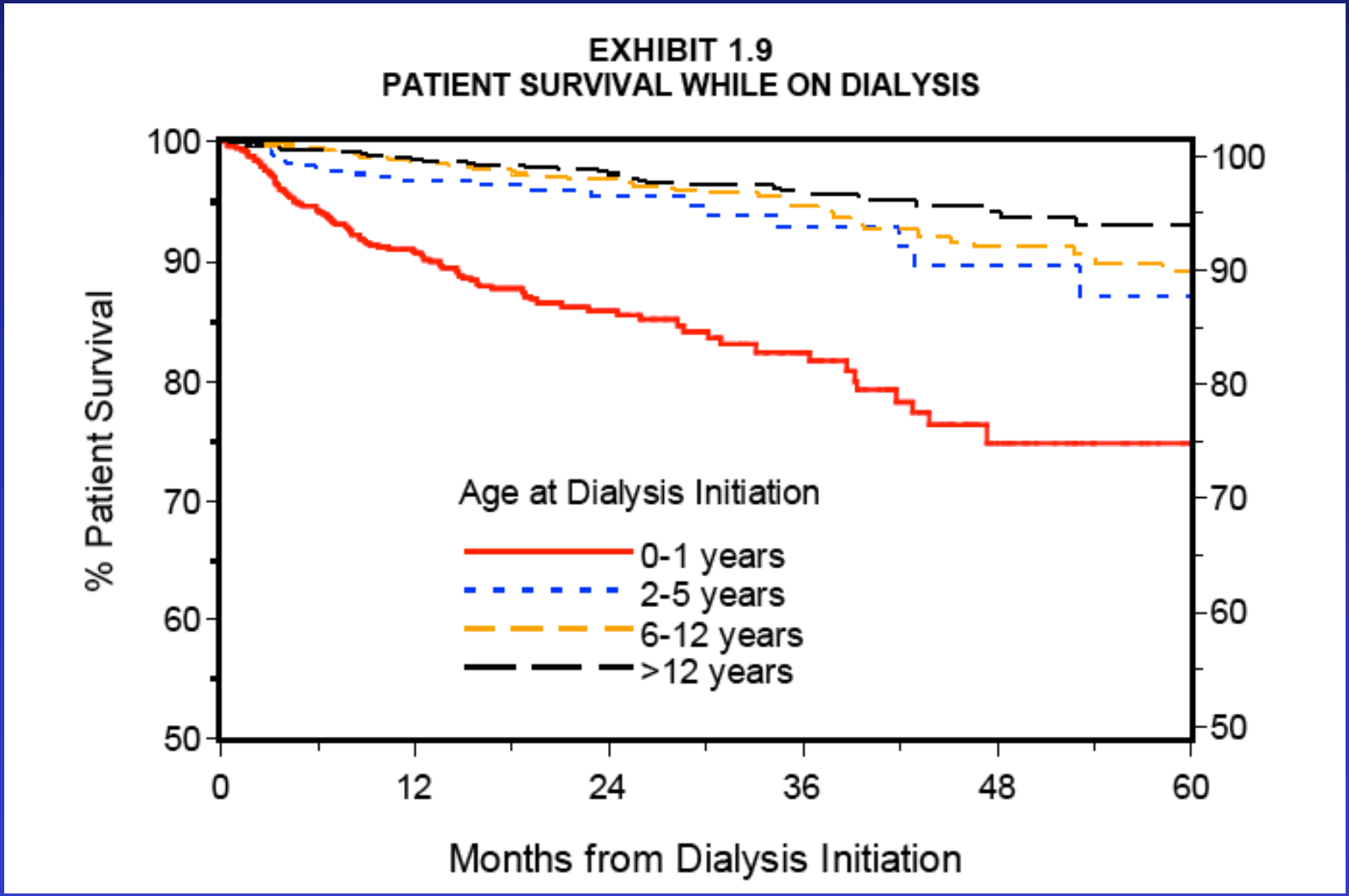
2018 USRDS ANNUAL DATA REPORT

Distribution of CAKUT type : 2012-2016

Type of CAKUT	Total patients	Percent incidence	Median age	Percent males
Obstructive Uropathy	665	9.3	10	83.2
Renal aplasia/hypoplasia/dysplasia, oligonephronia	744	10.4	9	59
Reflux nephropathy/chronic pyelonephritis	165	2.3	16	54.5

2018 USRDS ANNUAL DATA REPORT

Consequences of End Stage Renal Disease

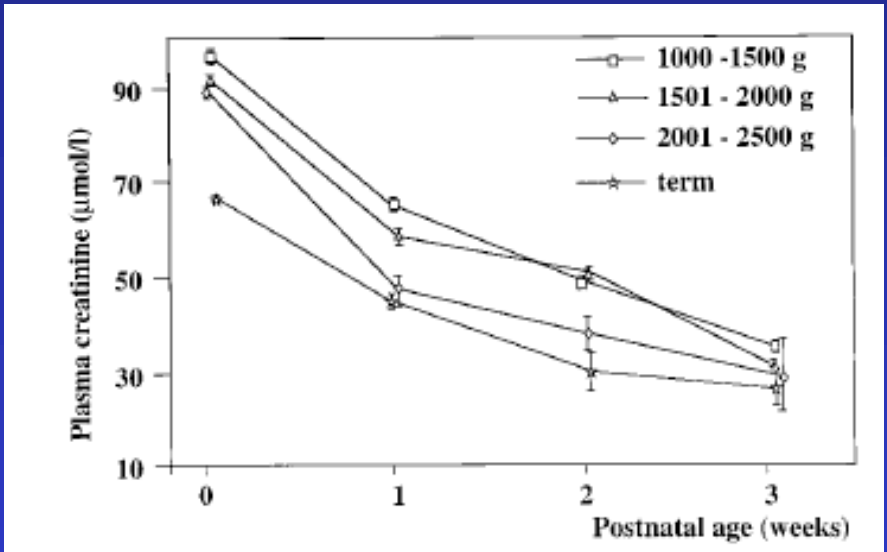


2011 NAPRTCs Annual Report

Maturational changes in kidney function:

- Normal adult GFR: 100 ml /min/1.73m^2
- Term neonates
  - Fetal to day 1: 1.7 $\rightarrow$ 5.8 ml /min/1.73m^2
  - Newborn to 2 m: 6 $\rightarrow$ 75 ml /min/1.73m^2
  - 2 m to 1-2 years: 75 $\rightarrow$ 100 ml /min/1.73m^2
- 28 wk preterm, day 1: 2.9 ml /min/1.73m^2
- Redistribution of renal blood flow from juxtamedullary nephrons out toward superficial nephrons = $\uparrow$ GFR

Change in creatinine after birth



Guignard, et.al., Pediatrics 1999;103;e49

Neonatal vs. adult tubular function:

- Neonatal kidneys are less efficient at:
  - Acid excretion (hence lower [serum bicarbonate])
  - Potassium excretion (hence higher [potassium])
  - Sodium excretion
  - Concentrating ability
  - Diluting ability (although efficient enough to tolerate hypotonic fluid- human milk)

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- Neonatal kidneys are more efficient at:
  - Phosphate reabsorption (hence higher [$PO4^-$])

Congenital kidney / urinary tract diseases

1. **Obstructive Uropathy**
2. **Aplasia/Dysplasia/Hypoplasia**
3. **Reflux nephropathy**

Congenital kidney / urinary tract diseases

1. **Obstructive Uropathy**
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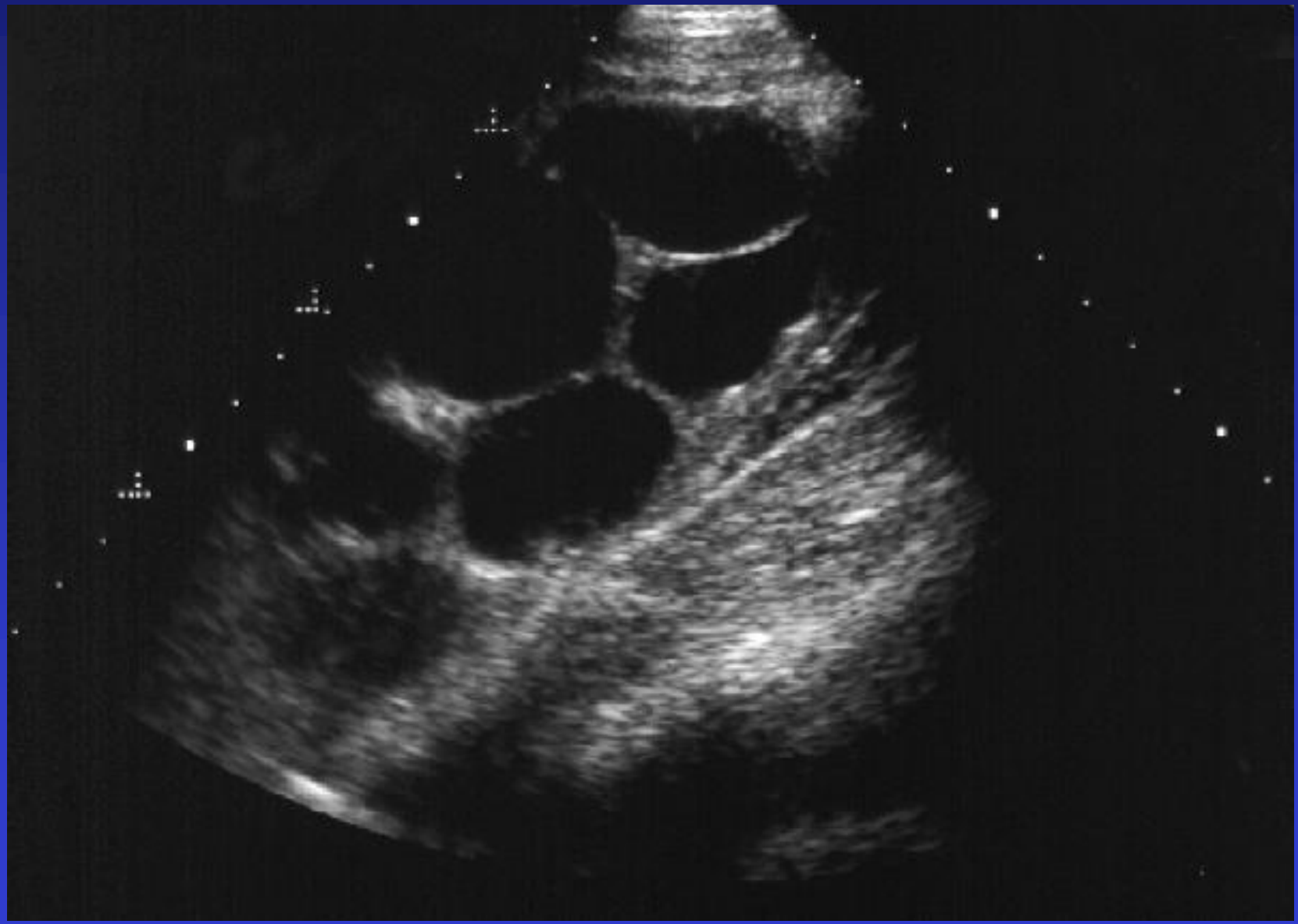
Case 1

- Ex-33 week 4 day old infant male infant in Neonatal ICU (s/p 3 days of amp/gent) has a creatinine of 3.0 mg/dl.
- You decide to to a renal ultrasound test

Case 1



Case 1: Differential diagnosis

1. **Bilateral Obstruction:** (likely with ↑ Creat)
   - **Posterior Urethral valves**
   - **Prune Belly syndrome**
   - **Myelomeningocele**

   → Lower tract
   - **Bilateral UPJ obstruction**
   - **Bilateral UVJ obstruction**
   - **Bilateral Ureterocele**

   → Ureteral dysgenesis
2. **Vesico-ureteric reflux**
3. **High in utero urine flow rates** (mild)
4. **Partial obstruction** (uni- or bilateral)

Major Causes of Pediatric Obstructive Uropathy: Lower urinary tract obstruction

- Posterior urethral valves
  - 1:5000 - 1:8000 births and in males only
  - most common cause of lower urinary tract obstruction
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- Myelomeningocele (with neurogenic bladder)
  - 1:1000 births
  - most common cause of Pediatric neurogenic bladder
  - due to disordered innervation of detrusor muscle and external sphincter
  - leads to varying degrees of functional obstruction

Major Causes of Pediatric Obstructive Uropathy: Ureteral Dysgenesis

- Ureteropelvic junction (UPJ) obstruction
  - incidence 1:1500- 1:2000 births
  - 75% are unilateral
  - Male predominence

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- Ureterovesical junction obstruction
  - male predominance
  - 75% are unilateral
- Ureterocele (intravesicle ureter)
  - female predominance
  - 1:5000 births
  - 80-90% unilateral

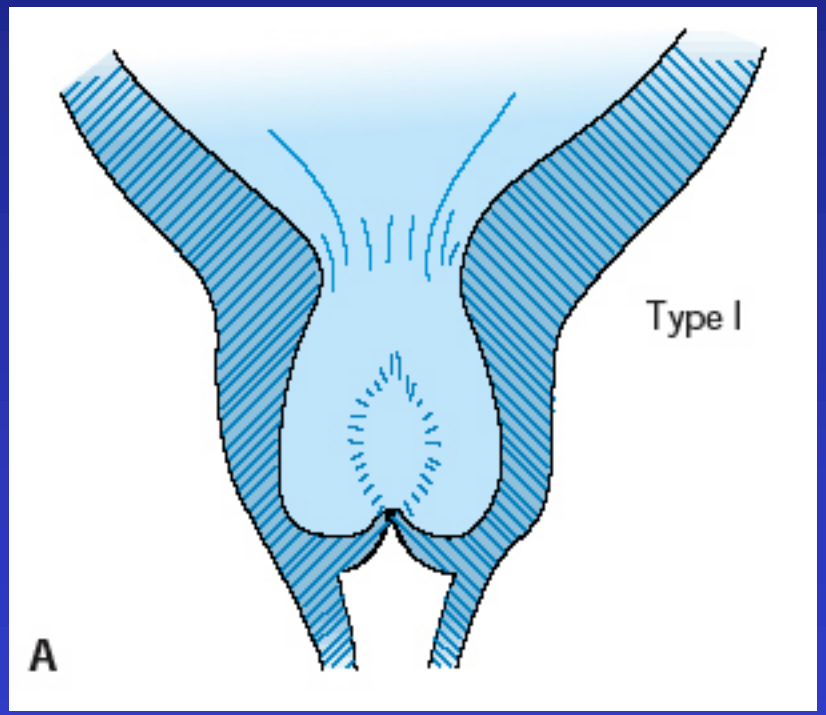
Case 1: next test?

- Nuclear cystogram?
- Voiding cystourethrogram?

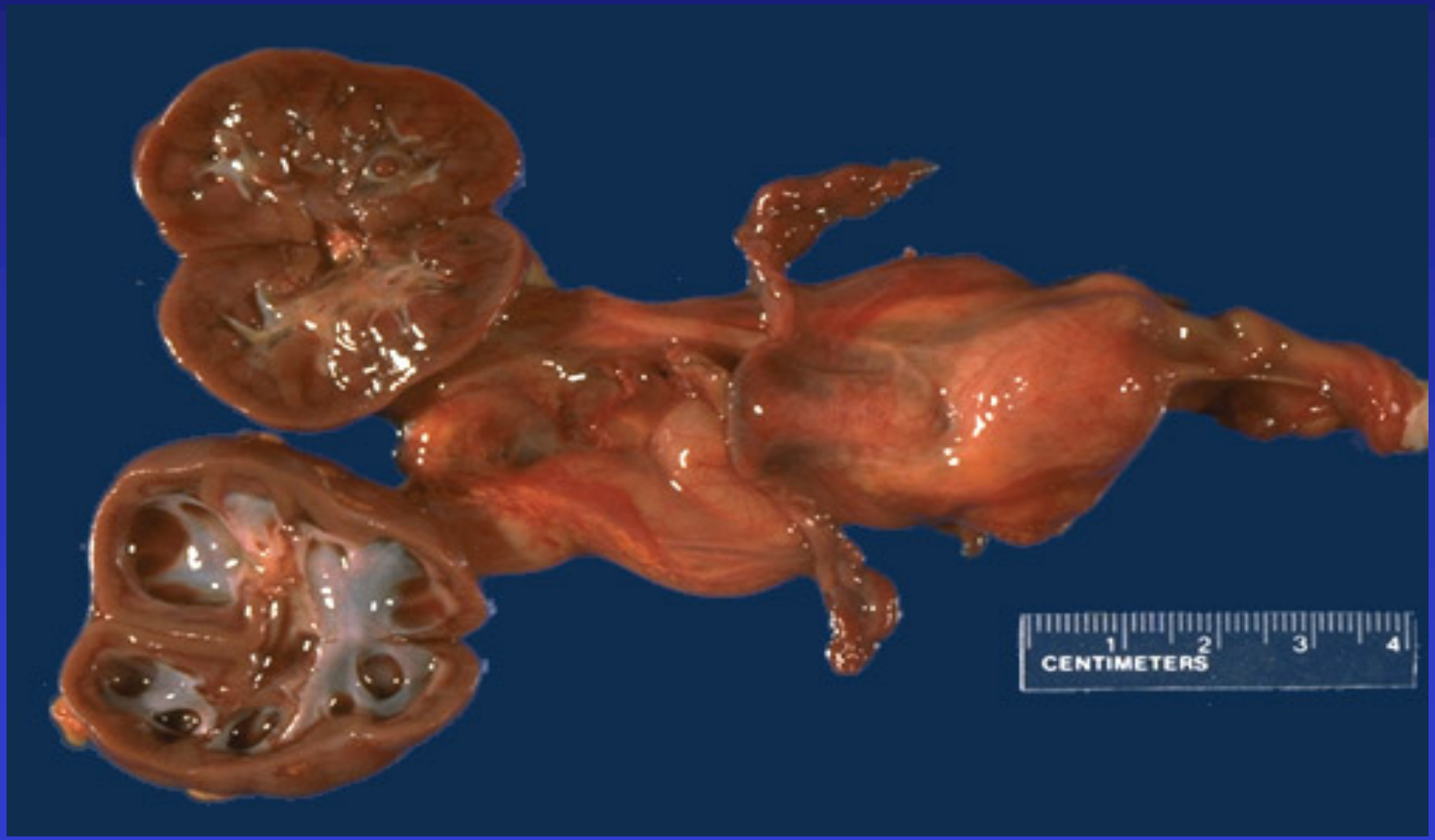
VCUG-need to rule out posterior urethral valves

Case 1: VCUG

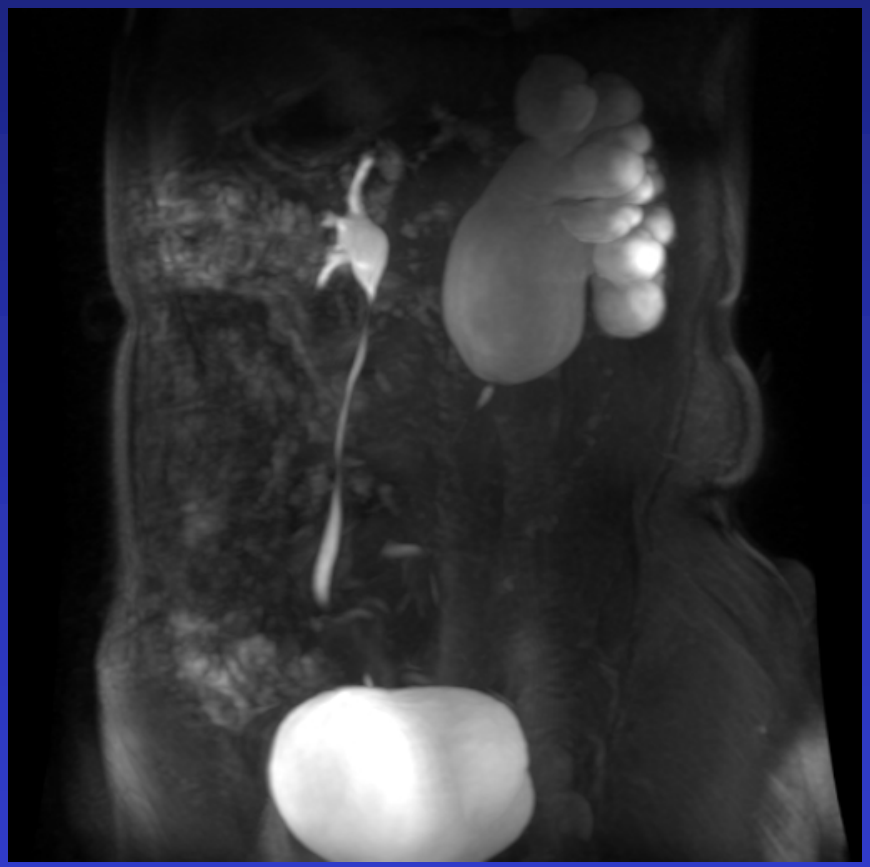
Obstructive Uropathy-PUV



Obstructive Uropathy-PUV



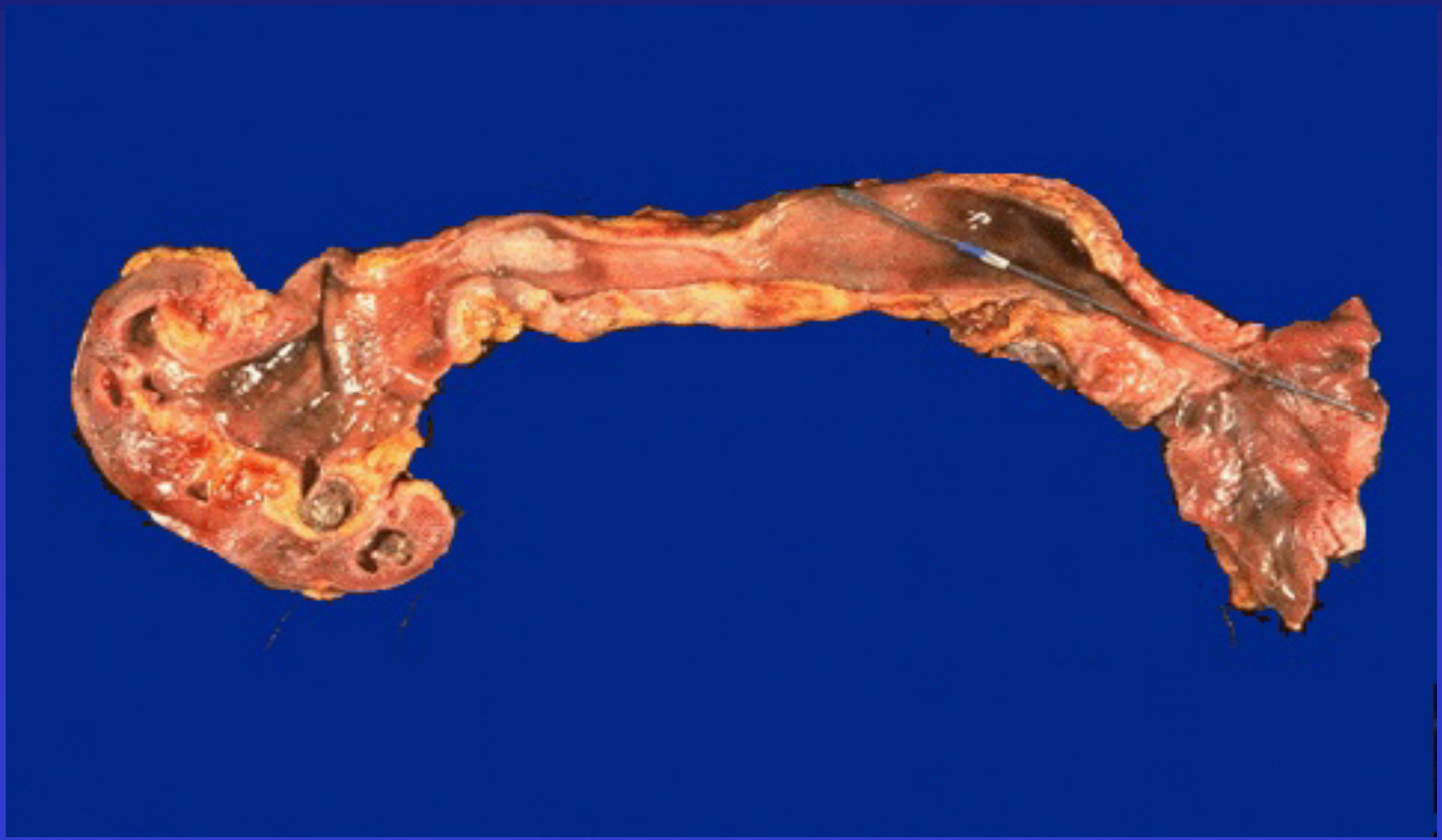
Obstructive Uropathy-UPJ obstruction



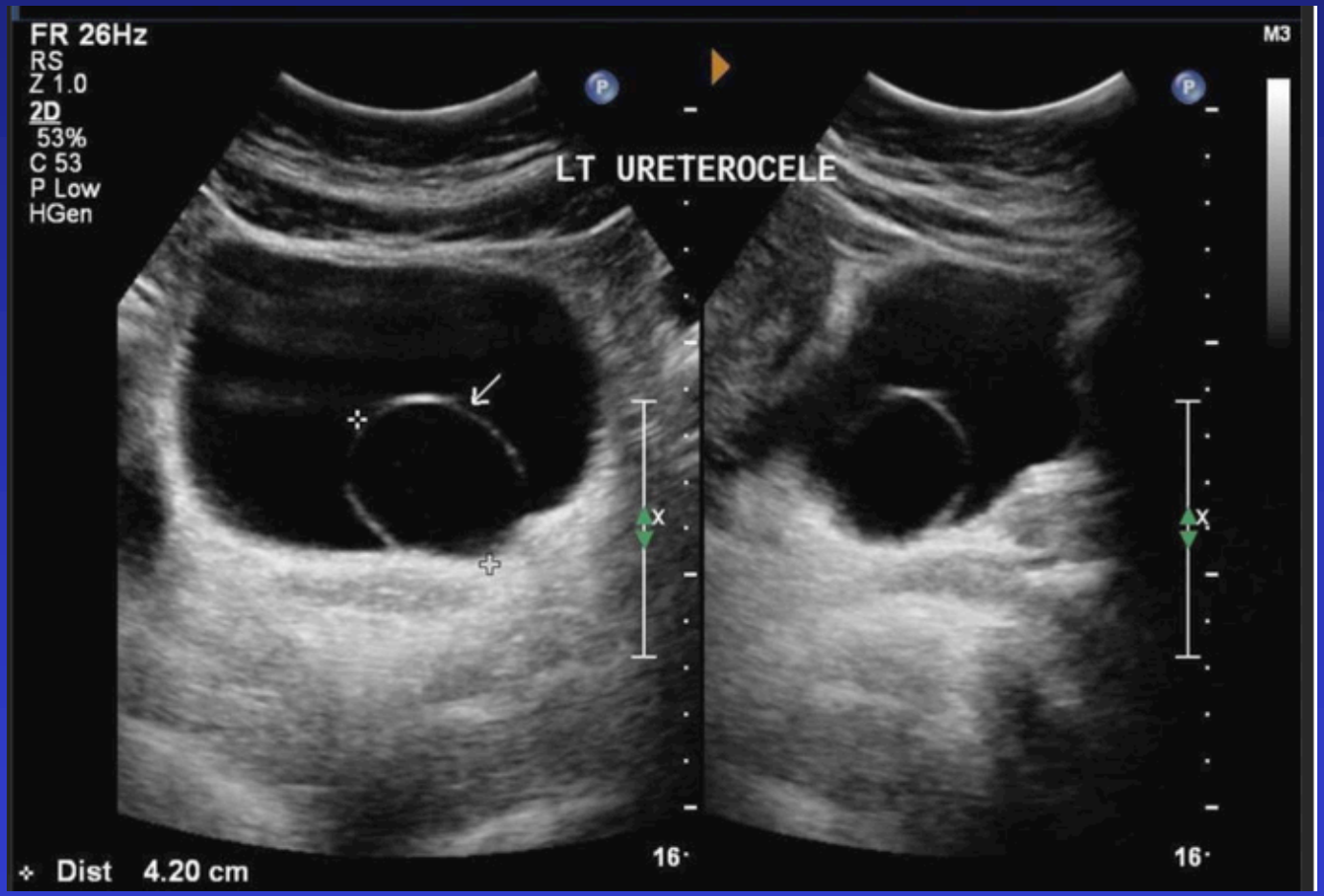
MR Urogram

radiopaedia.org

Obstructive Uropathy-UVJ obstruction



Obstructive Uropathy-Ureterocele

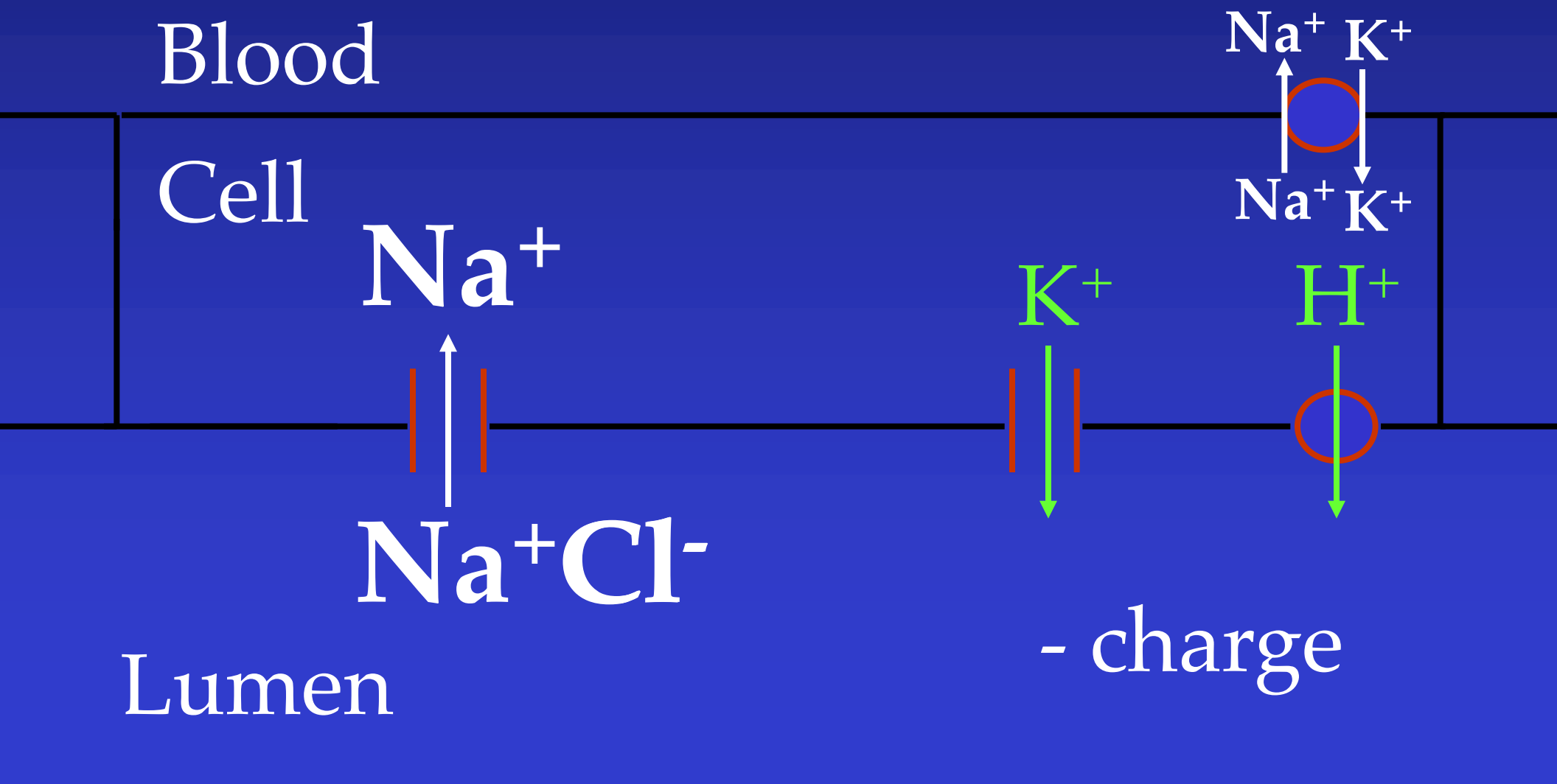


Bladder US

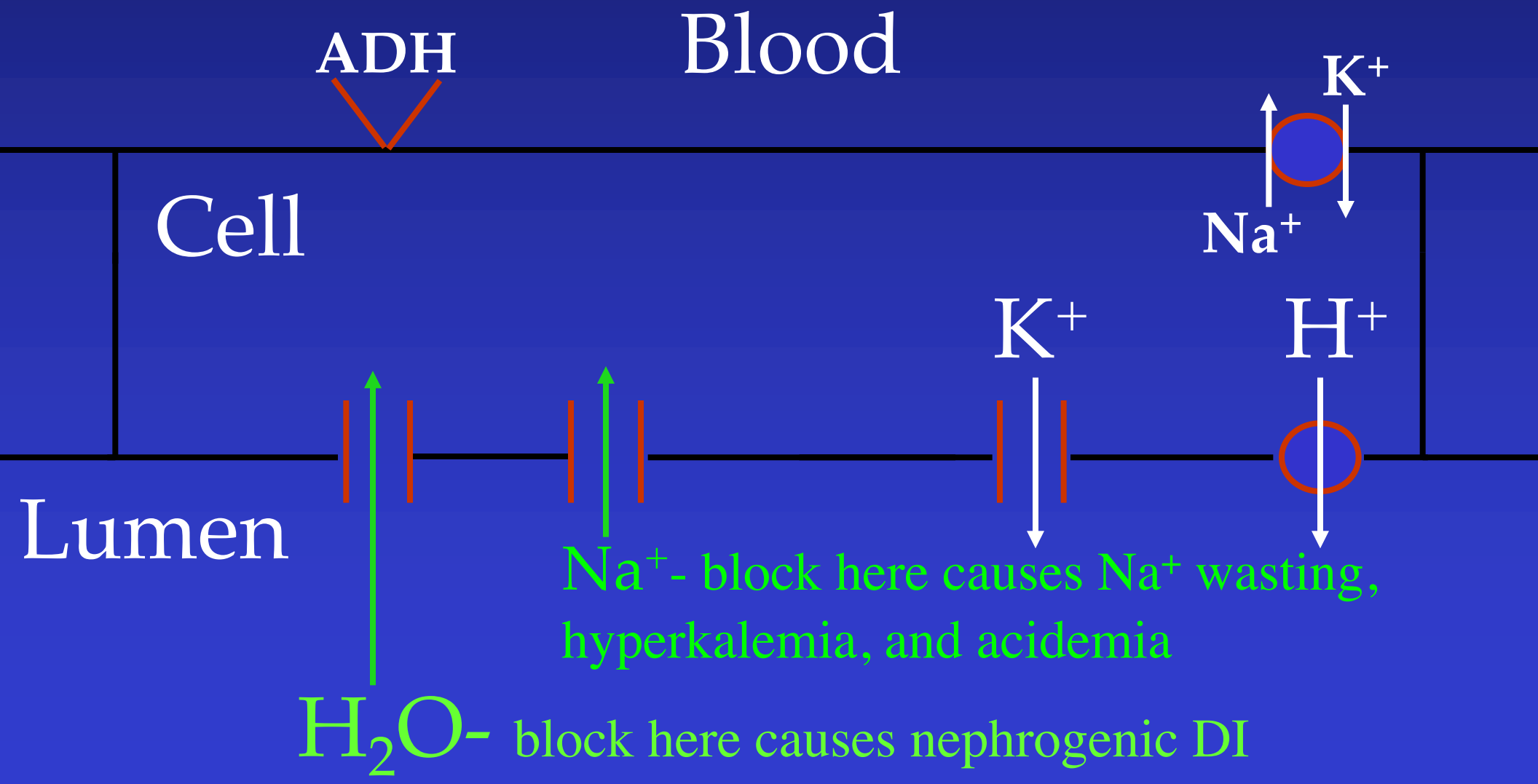
Ultrasound-images.com

Complications of Obstructive Uropathy?

H^+ and K^+ in the cortical collecting ducts



Collecting Duct Transporters



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  - Growth hormone (when older)

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- Other problems with CKD ($\uparrow PO_4^-$, rickets, anemia)

CKD management

- Hyperphosphatemia
  - Dietary phosphate binders
- Renal osteodystrophy
  - 1, 25 dihydroxyvitamin D (or analogs)
- Anemia
  - Erythropoietin, Iron

- Failure of medical management → dialysis, transplantation

Statistics on renal failure in obstructive nephropathy:

- 30-70% will progress to chronic renal failure/end stage renal disease after surgical repair

  Pediatrics 107:1004-1010, 2001; Pediatr 113:793-800, 1988.

- A predictive biomarker is creatinine at age 1 year
- Creatinine < 0.8 at 12 months = no significant increases in creatinine over next 5 years
- Creatinine > 0.8 at 12 months = progressive renal disease in most and some on dialysis in 5 years

  J Urol 133(2): 240-3, 1985

Lower urinary tract obstruction

- High rates of ESRD after surgical correction at birth are likely because…
- Irreversible injury to nephrons happens in utero
- Bladder/smooth muscle remodeling occurs leading to ongoing obstruction, infections, and renal injury after birth

Congenital kidney / urinary tract diseases

1. Obstructive Uropathy
2. **Aplasia/Dysplasia/Hypoplasia**
3. Reflux nephropathy

Case 2

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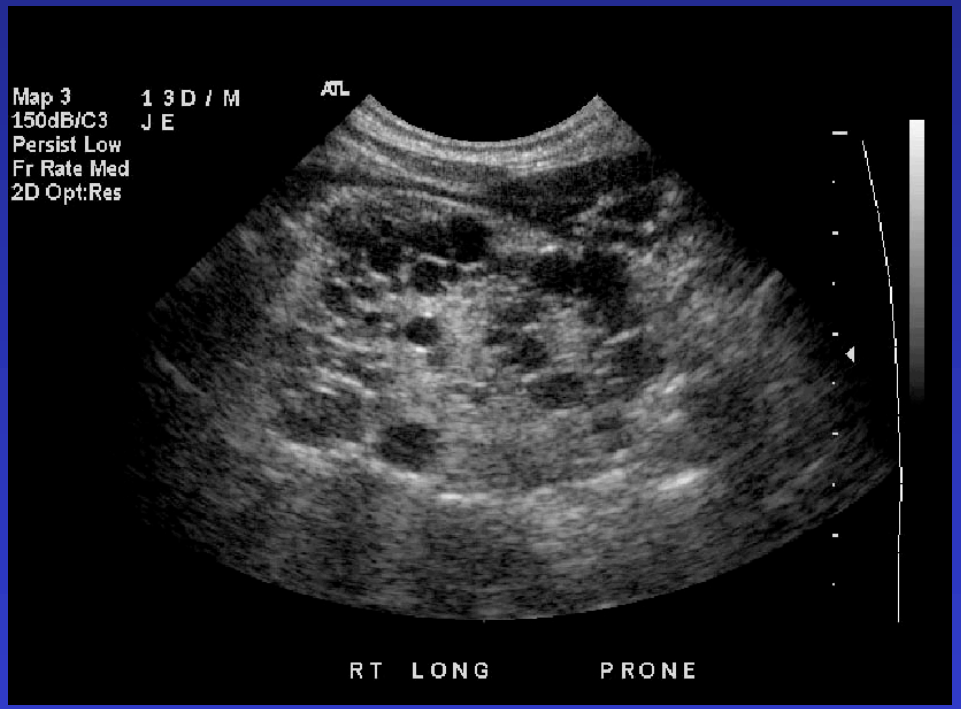
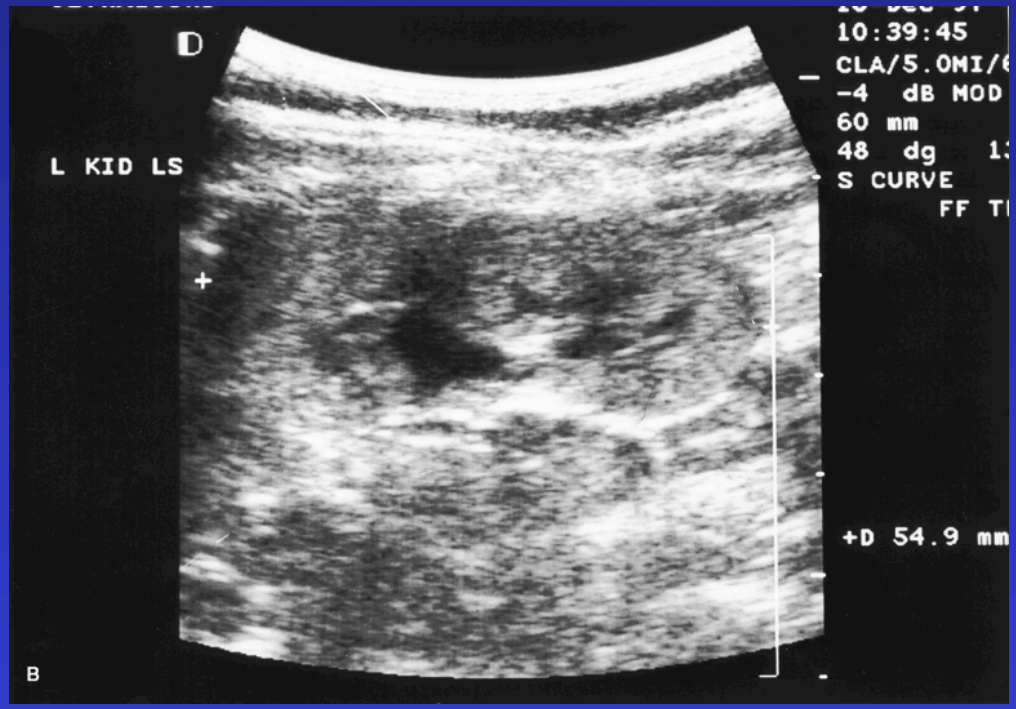
Renal Ultrasound images:



Multicystic dysplastic kidney (non functional)

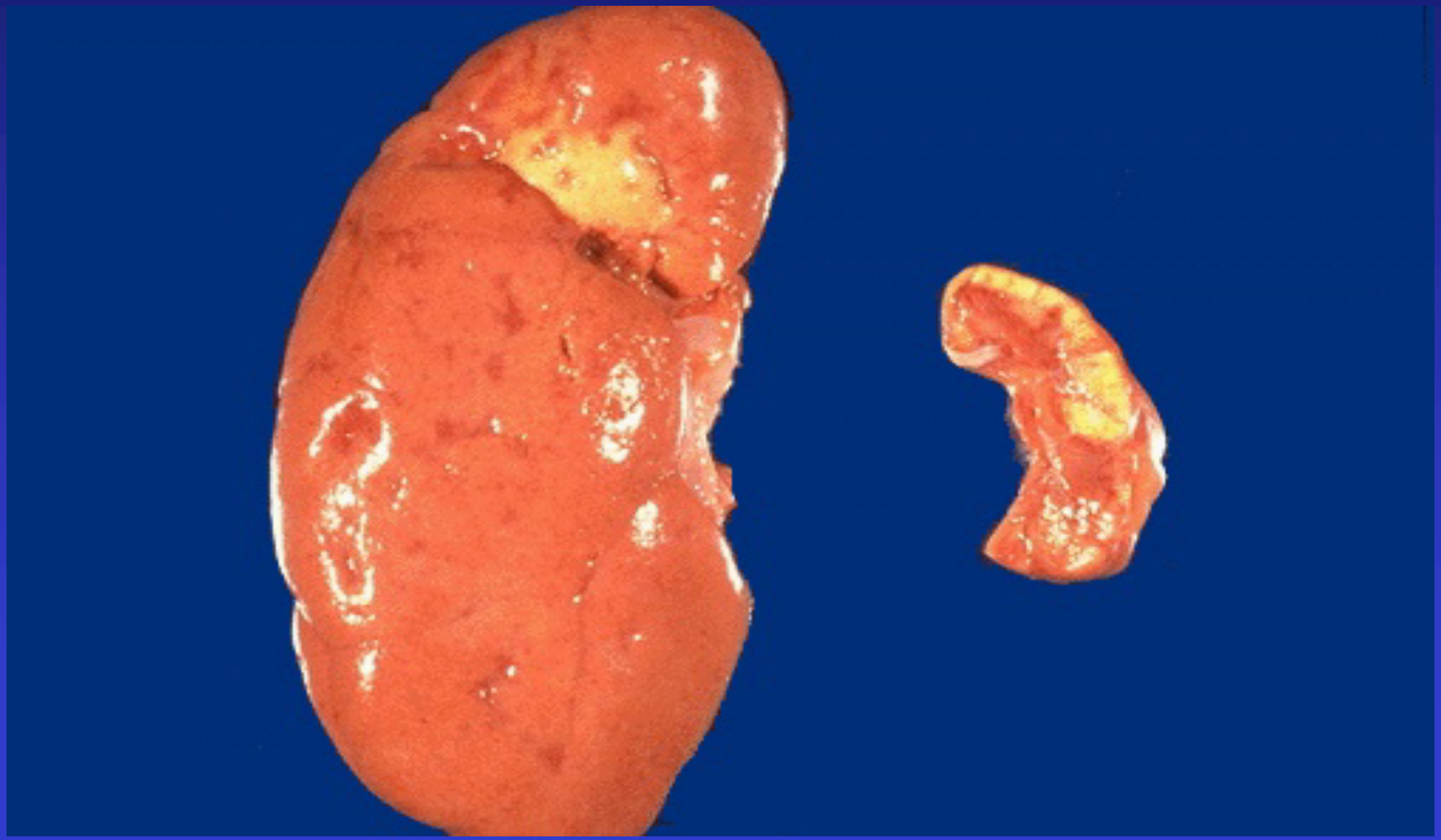


Hypoplastic / dysplastic kidney

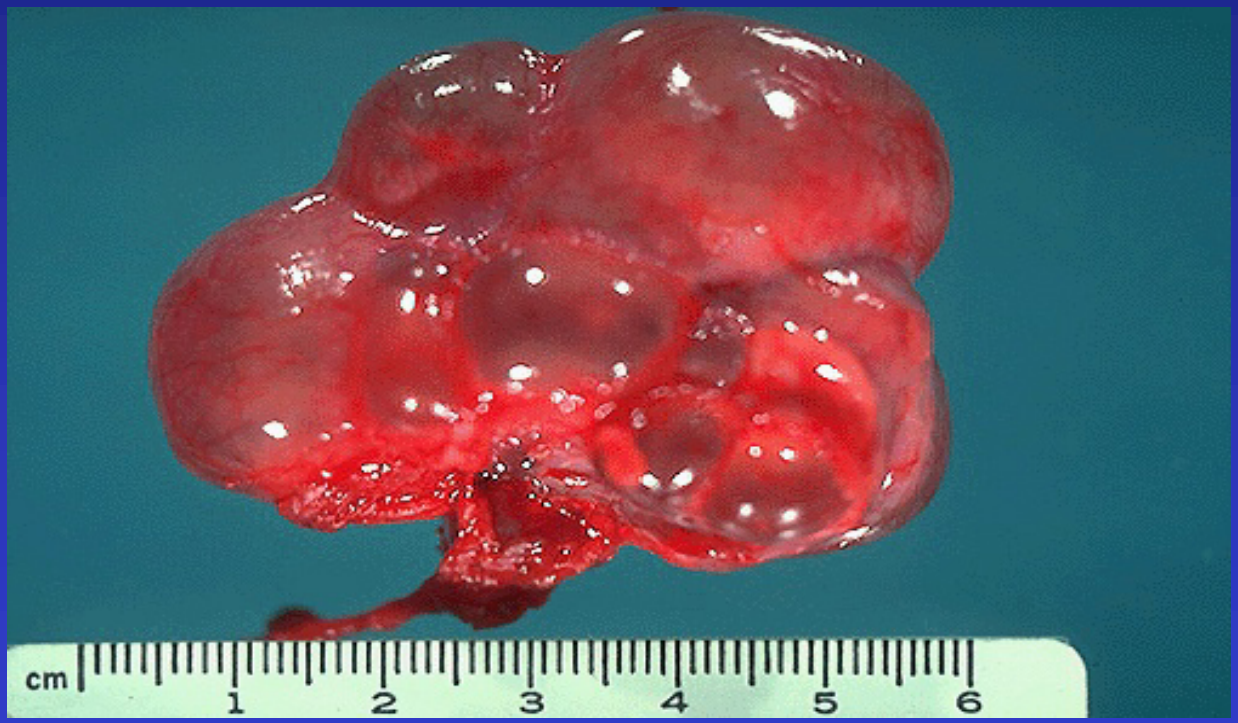
Aplasia/dysplasia/hypoplasia

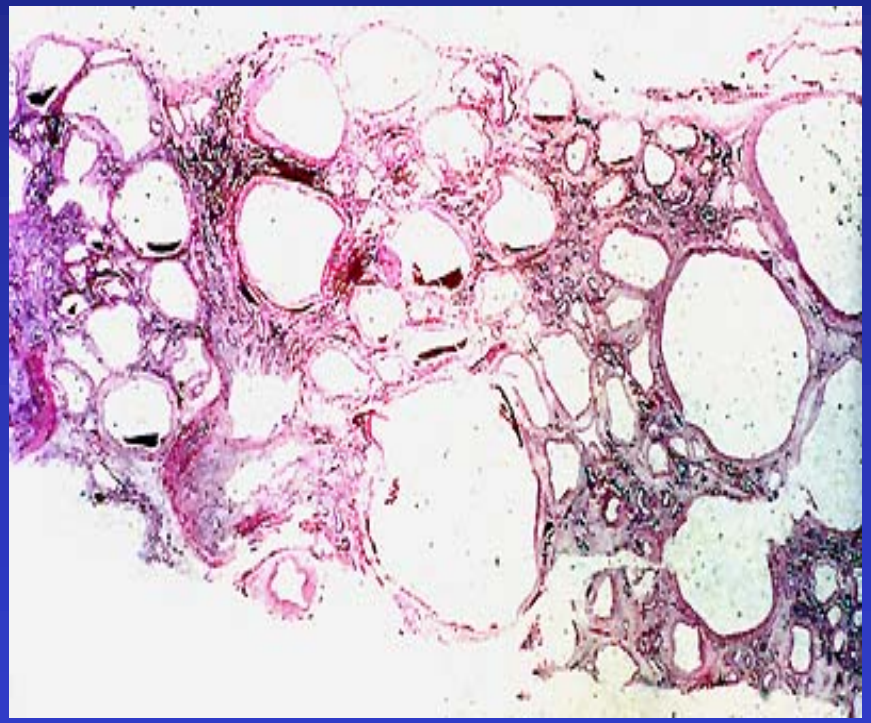
- Aplasia-absent kidney
  - Agenesis- never kidney tissue at all (probably very rare)
  - Involution of kidney from severe/early fetal hypo-dysplasia
- Dysplasia- abnormal kidney structures
  - aberrant ureteric bud/metanephric mesenchyme interaction
  - Complete (no kidney function), partial (some function)
  - Cystic (MCDK) and non-cystic
- Hypoplasia- normal kidney structures, just smaller/fewer
  - Often combined with dysplasia

Aplasia (hypoplasia)



Multicystic Dysplasia





Aplasia/dysplasia/hypoplasia

- Incidence:
  - Difficult to determine (bilateral disease often likely leads to fetal demise)
  - 1/3 fetal ultrasound abnormalities = anomalies of the kidney and urinary tract
- Unilateral
  - Most common presentation
  - Increased risk of proteinuria/hypertension/CKD later in life
  - 20-40% incidence of VUR in contralateral kidney
- Bilateral
  - Live born are are risk for lung hypoplasia (oligohydramnios)

Aplasia/Dysplasia: potential complications

- Concentrating defects (disruption of hypertonic medulla)
- Salt wasting (poor collecting duct formation)
- Hypertension (renin driven)
- Poor growth
- Chronic kidney disease

Genetics of aplasia/hypo-dysplasia:

RUS of 1st degree relatives of proband with bilateral renal aplasia/dysplasia.

Abnormality	Parents age 19-46	Sibs	Controls age 19-46	Controls all ages	Prevalence in other studies
Solitary kidneys	4.2%	5%	0.4%	0.3%	0.16%
Double ureter	2.8%	0	0	0	0.85%
Multicystic kidney	1.4%	0	0	0	0.02%

from: N Engl J Med 1984; 310:1341-1344.

GU Anomalies in Family Members with a Proband with Bilateral Renal Aplasia / Dysplasia

- Study group (N=34) 14.7% incidence of GU anomalies in relatives.
- Control group (N=68) 2.4% incidence of GU abormalities in relatives.

Schwaderer AL, Bates CM, McHugh KM, McBride KL. Pediatr Nephrol, 22: 52-56, 2007.

- This points to potential autosomal dominant gene mutations contributing to CAKUT

Genetics of aplasia/hypo-dysplasia: Syndromes with identified genetic mutations

- ***HNF1β***: Renal Cysts and Diabetes Syndrome (RCAD)
  - AD with variable penetrance
  - wide spectrum of phenotypes, most commonly renal cysts and early onset diabetes mellitus
  - Renal anomalies are variable and include:

    dysplasia, hypoplasia, aplasia, cysts, duplex collecting systems, hydronephrosis

    Nat Rev Nephrol. 2015;11(2):102-112.
- ***PAX2***: Renal Coloboma Syndrome
  - AD with variable penetrance
  - optic disc coloboma (less common: hearing loss, seizures, Arnold Chiari malformation)
  - Renal anomalies are variable and may predominate:

    hypoplasia, aplasia, multicystic dysplasia, reflux.

    Semin Cell Dev Biol. 2015;44:97-106

Genetics of aplasia/hypo-dysplasia: Syndromes with identified genetic mutations

- ***EYA1, SIX2, SIX5***: Branchio-Oto-Renal (BOR) syndrome
  - AD with variable penetrance
  - bilateral renal aplasia and hearing loss

    Int J Pediatr Otorhinolaryngol. 2014;78(8):1201-1210
- ***SALL1***: Townes-Brocks Syndrome
  - AD with variable penetrance
  - Wide spectrum of renal anomalies and imperforate anus, malformed ears, and thumb defects

    Am J Med Genet A. 2012;158A(3):533-540.
- ***GLI3***: Pallister-Hall syndrome
  - AD with variable penetrance
  - Renal aplasia, hypoplasia, dysplasia and polydactyly, syndactyly, imperforate anus, hypothalamic hamartoma

    Gene. 2016;589(2):100-103.

Genetics:
Non-syndromic aplasia/hypo-dysplasia:

- ***HNF1B, PAX2, EYA1, SIX1,* and *SALL1***
  - 17% of unrelated families had mutations in one of these genes
  - Most were in *HNF1B* or *PAX2* *J Am Soc Nephrol. 2006;17(10):2864-2870*

- ***RET/GDNF***: *Am J Hum Genet.* Feb 2008;82(2):344-351.
  - 7 of 19 stillborn fetuses with bilateral renal aplasia and 2 of 10 fetuses with unilateral aplasia had mutations in *RET*
  - 1 of 10 with unilateral aplasia had *GDNF* mutations

- ***BMP4, SIX2***: *J Am Soc Nephrol.* Feb 27 2008; 891-903.
  - 10 unrelated kids (of 250) with a/hypo-dysplasia had mutations

- ***FGF20***: *Dev Cell.* 2012;22(6):1191-1207
  - Consanguineous patients had two mutations in FGF20

Genetics:
Non-syndromic aplasia/hypo-dysplasia:

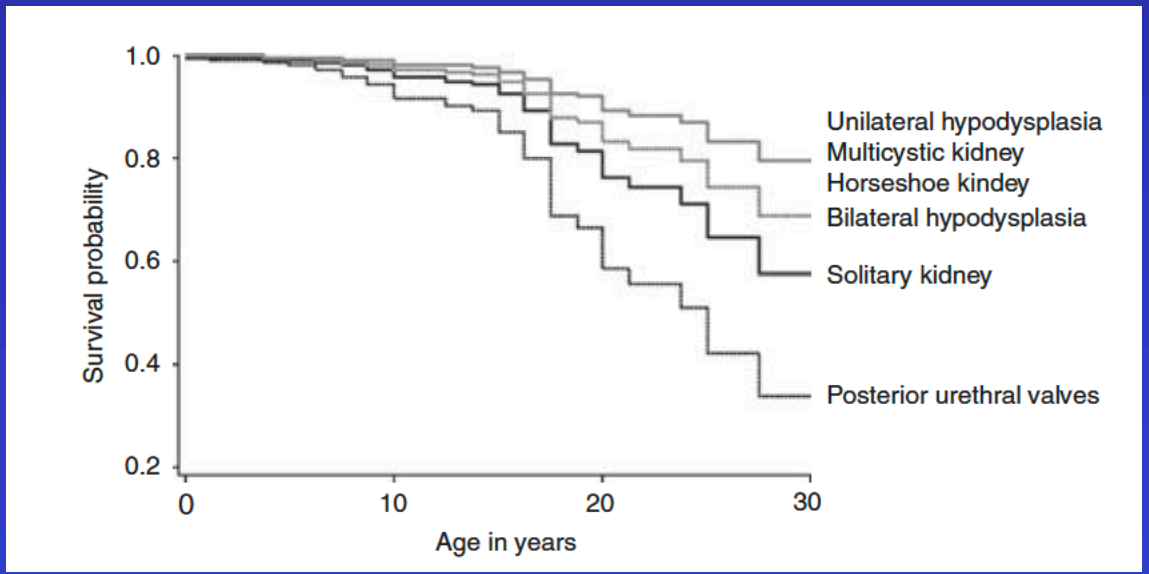
- Study examining 749 families with isolated kidney disease for candidate AD gene mutations *Kidney Int*. 2014;85(6):1429-1433.
  - 37 single allele mutations found in 47 patients (41 families)
  - *BMP7 (1), CDC5L (1), CHD1L (5), EYA1 (3), GATA3 (2), HNF1B (6), PAX2 (5), RET (3), ROBO2 (4), SALL1 (9), SIX2 (1), SIX5 (1)*

- Study in 574 patients with isolated kidney disease for candidates: J Am Soc Nephrol. 2014;25(9):1917-1922
  - 15 mutations in: *FRAS1, FREM2, GRIP1, FREM1, ITGA8, GREM1*

- Whole exome sequencing in 33 consanguineous families with isolated renal hypo/dysplasia J Am Soc Nephrol. 2017;28(1):69-75.
  - 9 families with recessive mutations in: *ZBTB24, WFS1, HPSE2, ATRX, ASPH, AGXT, AQP2, CTNS, PKHD1*

A final word about congenital single kidney long term prognosis

Several studies have shown that having unilateral CAKUT does confer increased risks of proteinuria, hypertension and chronic kidney disease…..mostly showing up later in life…see below



Kidney International (2009) 76, 528–533

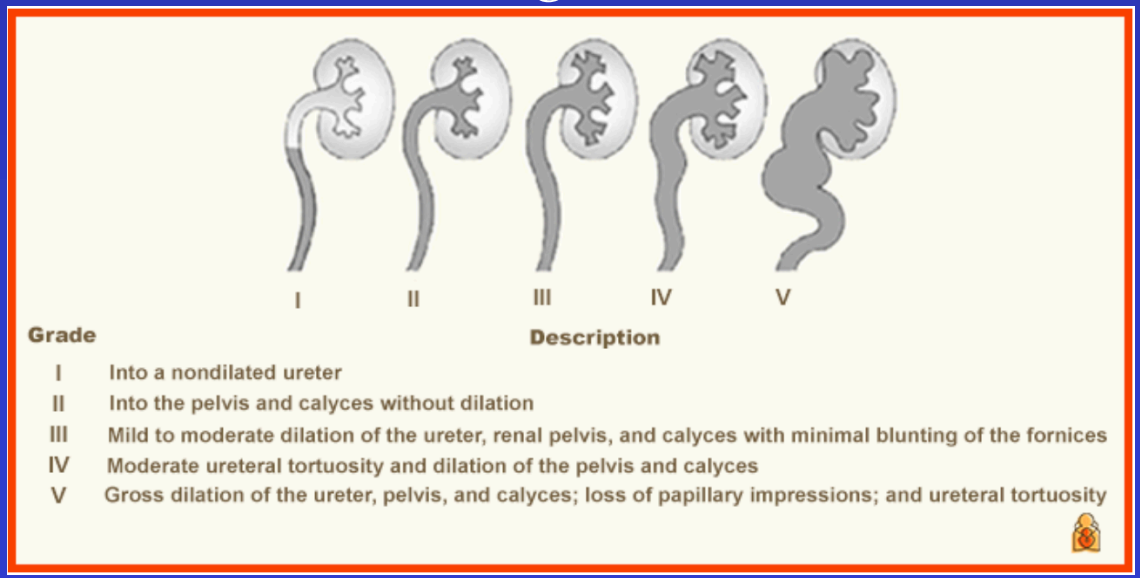
Congenital kidney / urinary tract diseases

1. Obstructive Uropathy
2. Aplasia/Dysplasia/Hypoplasia
3. **Reflux nephropathy**

Vesico-ureteric reflux (VUR)

- In development, the ureteric bud may arise from the wrong position along the mesonephric duct.
- This leads to an incorrect ureteral insertion site in the bladder and an incompetent "valve."

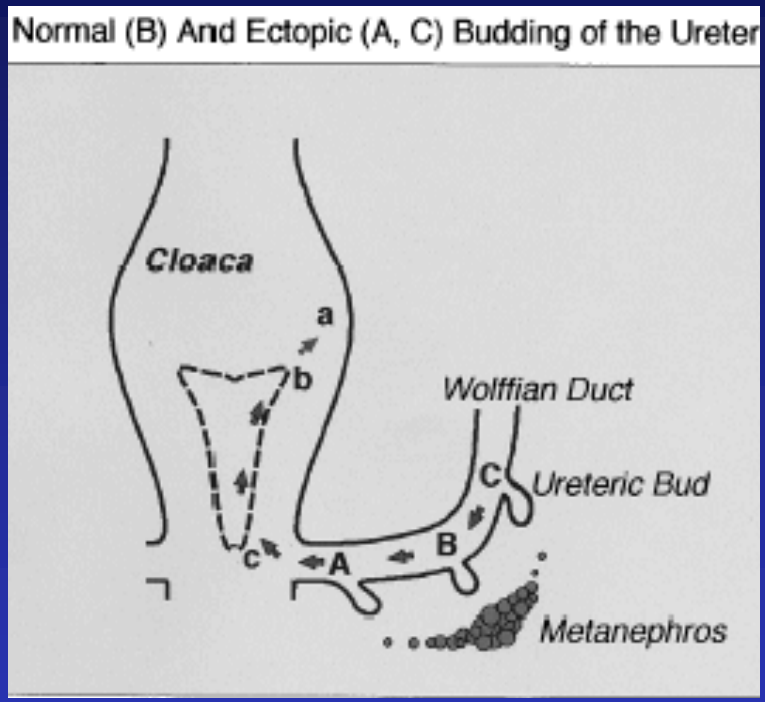
VUR grades

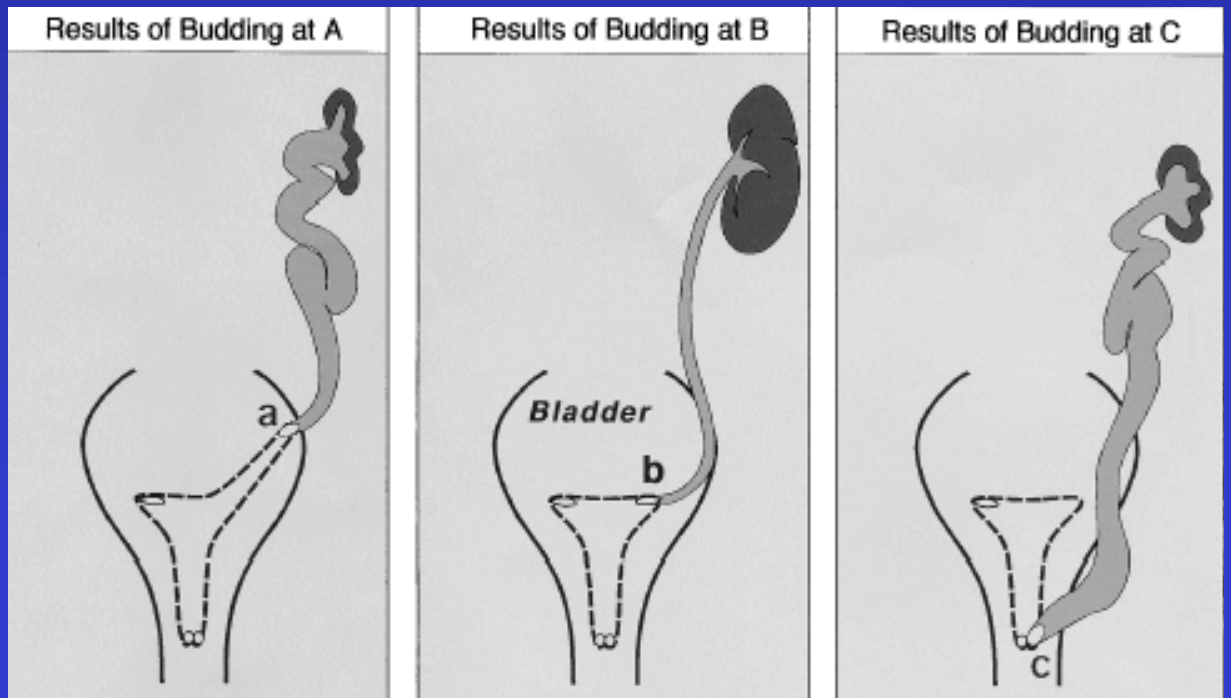


How incorrect ureteric bud sites can lead to reflux:

The Mackie-Stephens Hypothesis

Mackie & Stephens, J Urol. 114, 274-280, 1975





Vesico-ureteric reflux (VUR)

- Affects 1-2% of the population with a higher incidence in females versus males (most common congenital urological abnormality)
- Appears to be autosomal dominant (no major gene identified that causes most cases although genes within families have been identified)
- Peak incidence is in early childhood with gradual resolution
- Majority of patients do well
- Others develop Reflux nephropathy
  - Scarring, inflammation, fibrosis associated with VUR

What causes reflux nephropathy?

RN can be divided into two types: congenital vs acquired:

	Acquired RN	Congenital RN
Time of occurrence	Postnatal	Prenatal
UTI prior to Dx	Common	Uncommon
Age distribution	All pediatric ages	Mostly younger children
Gender distribution	Mostly female	Mostly male
VUR grades	Mostly lower	Mostly high
Dysplastic features	No	Yes

Adapted from Adv Chronic Kidney Dis. 2011 18(5): 348–354

- May misclassify a congenital as acquired as there could have been a scar prior to the UTI
- Congenital forms may reflect renal dysplasia and associated VUR
- Some ”sterile” acquired forms could happen in younger males who void under high pressure

Relationship of VUR, UTI and renal scarring

- 10-15% of patients with VUR and UTI develop scars

  Pediatrics. 2010; 126:1084-91; NEJM. 2014; 370 (25) 2367-2376

- Mechanisms underlying scar formation is unknown
  - ? Immune dysregulation, vascular defects, mesangial abnormalities
- Higher grades of VUR associated with increased scars
  - Unclear if this is a causal relationship an association only
- Scar risks increase with bowel and bladder dysfunction
- A delay in febrile UTI treatment increases risks of scarring
- Younger age with UTI confers a higher risk of scarring

  Pediatrics. 2010; 126:1084-91

Complications of reflux nephropathy

- Hypertension
  - Occurs in 17-30% of children and 33-38% of adults with scarring (often presents years after the preceding UTI and presumed scar)
  - Often responds to ACEi or ARBs
- Proteinuria
  - Microalbuminuria occurs in ~50% of pediatric patients
  - Overt proteinuria occurs in 21% of adults
- Focal and segmental glomerular sclerosis
  - One study noted 21% of patients with RN developed FSGS
- Chronic kidney disease
  - In NA, it is the 4th leading cause of CKD in children
  - Undiagnosed hypertension likely causes/exacerbates CKD

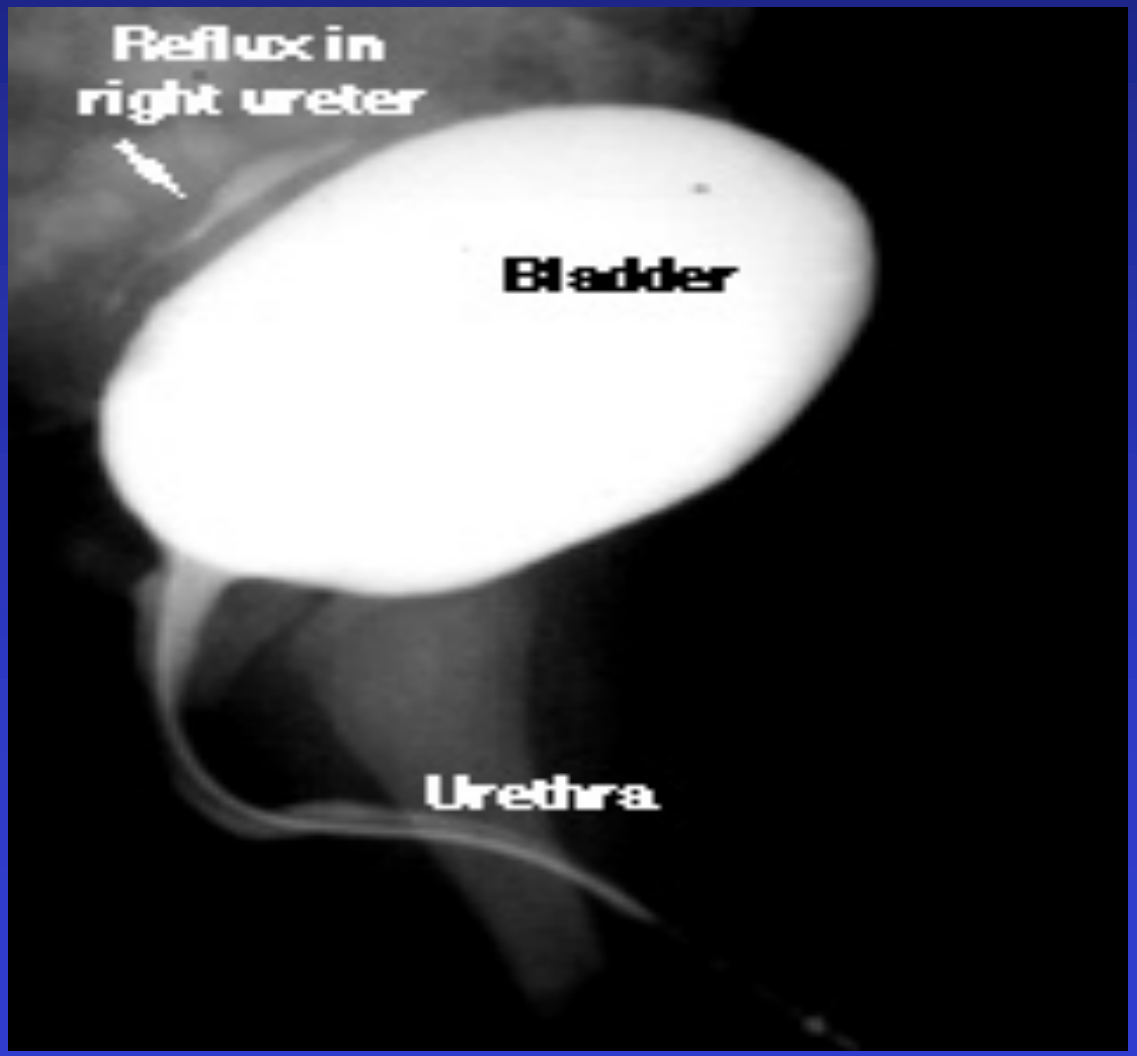
Pediatrics. 2010; 126:1084-91

Management of VUR/RN

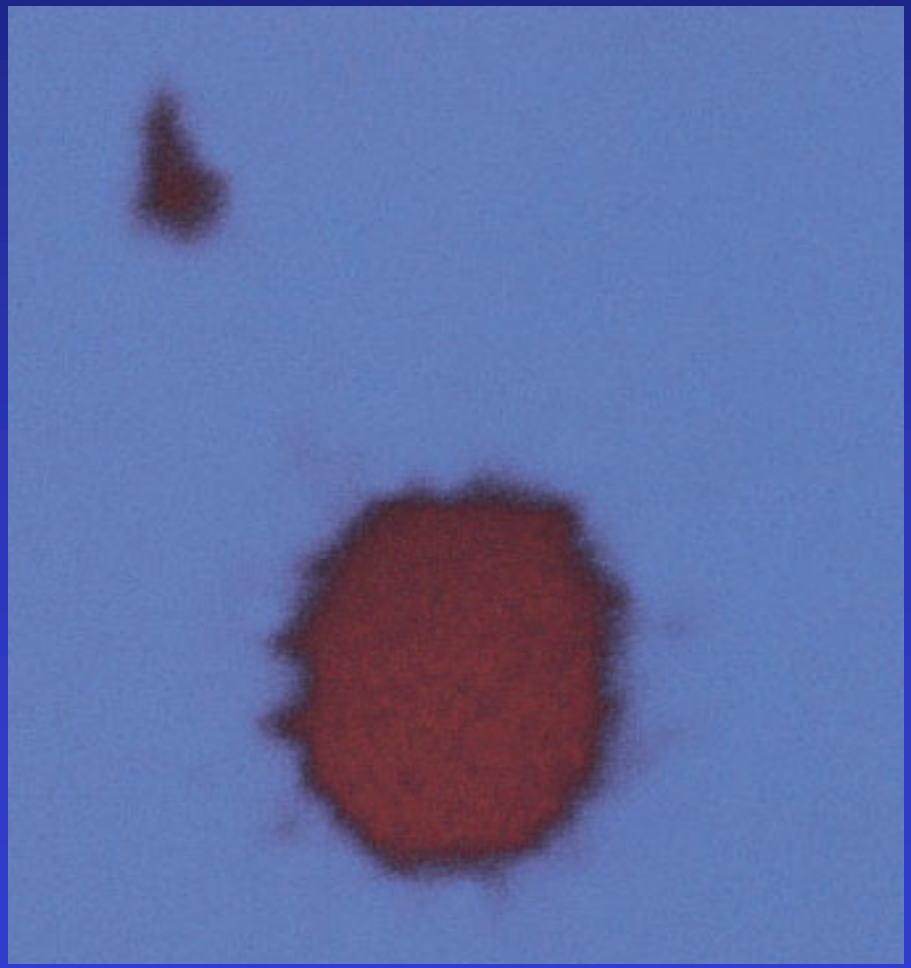
- Antimicrobial prophylaxis:
  - 6 studies have examined prophylaxis (2 most recent only including those with VUR and UTI, while the others were +/- VUR)
  - Some (including the latter two) showed prophylaxis decreased risks of subsequent UTI
  - None showed a reduction in scarring (although were not powered)

    Pediatrics. 2010; 126:1084-91; NEJM. 2014; 370 (25) 2367-2376
  - AUA recommends prophylaxis for:
    - Children < 1 yo with febrile UTI/VUR or grade III-V VUR and no UTI ("optional" for patients with lower grades and no UTI)
    - Children > 1 yo with BBD ("optional" for patients with UTI/VUR without BBD)
- Treat any bowel-bladder dysfunction
- Surgical correction….controversial as studies conflict on whether surgical correction (open or endoscopic) is better than antibiotic prophylaxis for recurrent UTI or scarring

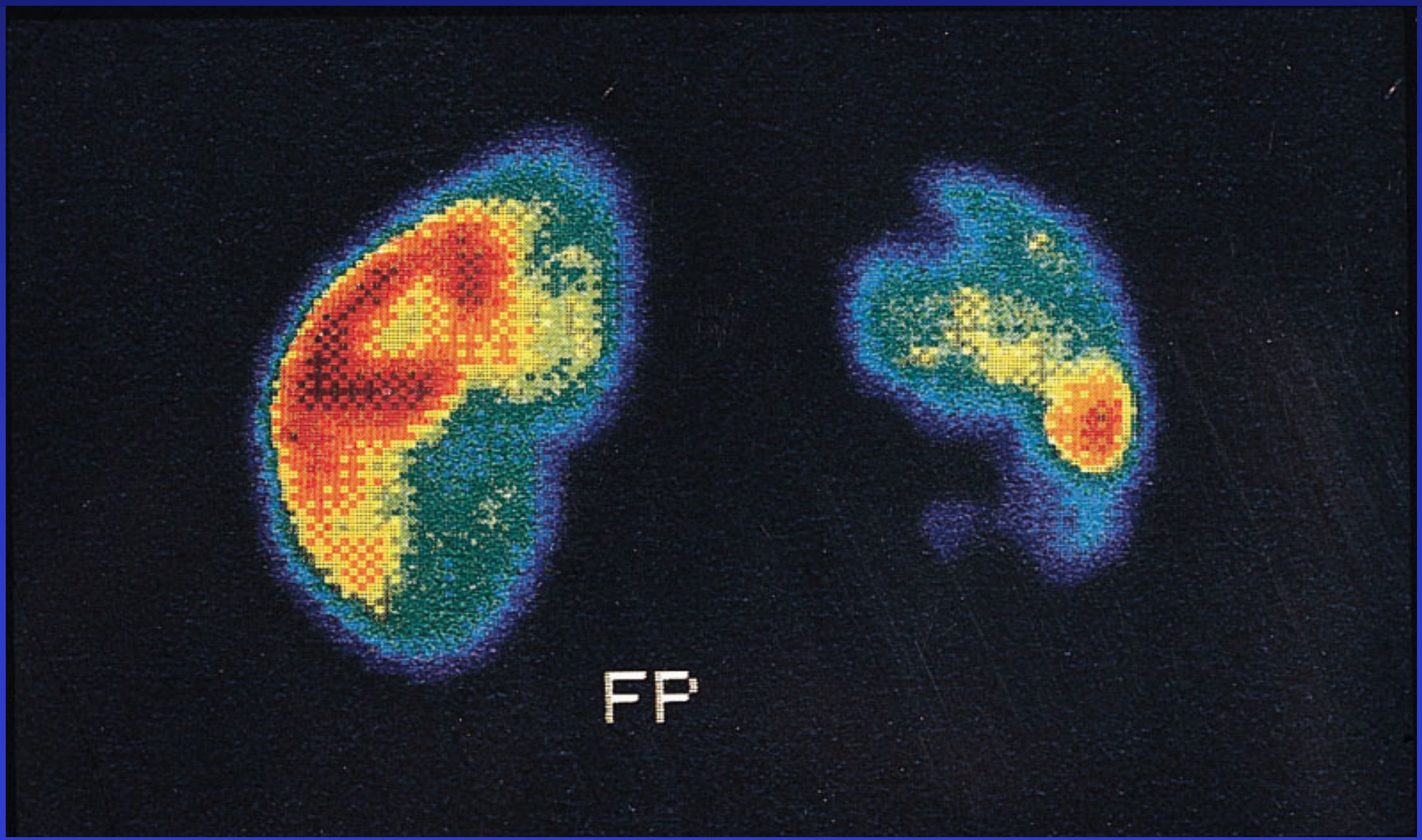
Reflux- diagnostic test 1: Voiding cystourethrogram (VCUG)



Reflux- diagnostic test 2: Nuclear cystogram



Reflux nephropathy-DMSA scan



Summary

- Congenital kidney diseases are leading causes of chronic kidney disease in children, especially in the very young
- Obstructive nephropathy is a leading cause of chronic kidney disease and can result from either lower urinary tract obstruction or bilateral ureteral dysgenesis
- Although aplasia/hypo/dysplasia is most often unilateral, bilateral disease is a leading cause of end stage renal failure
- VUR is the most common congenital urogenital anomaly and may lead to reflux nephropathy
- Animal models are valuable in elucidating molecular control of kidney development and in generating biomarkers of progressive structural CKD in children

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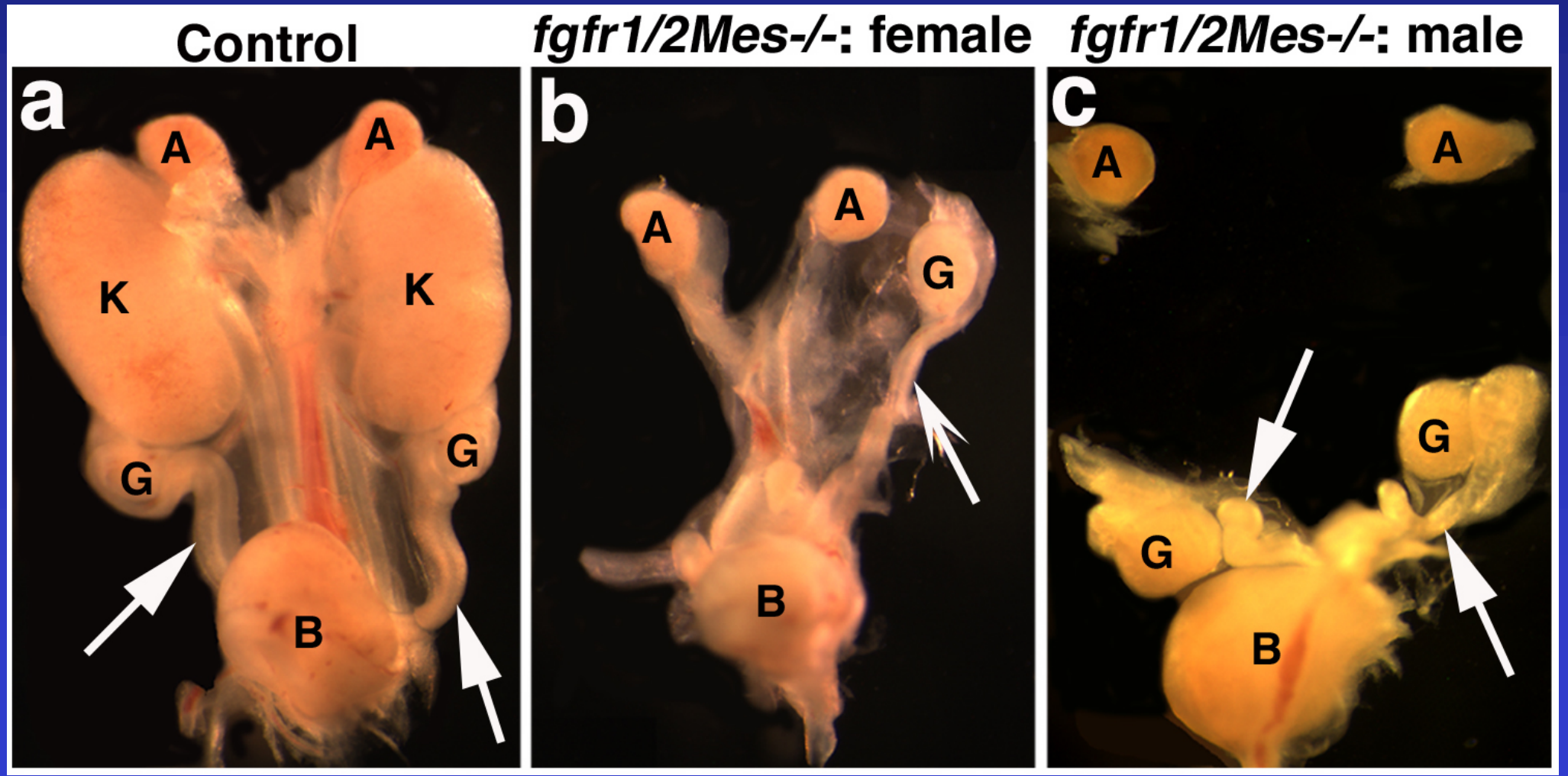
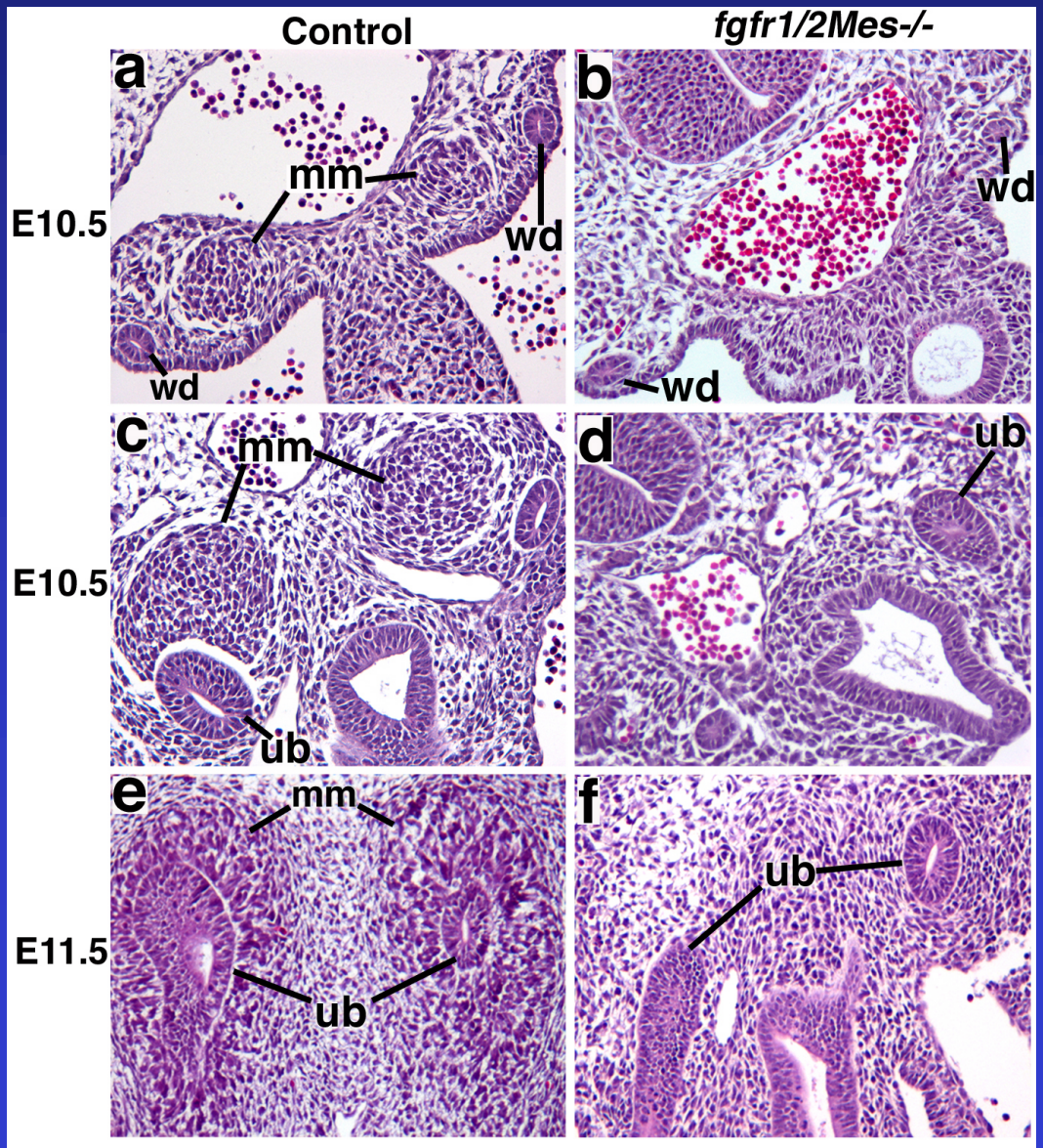
Aplasia: mouse model (E16.5 urogenital systems in *fgfr1/2*$^{Mes-/-}$ mice)

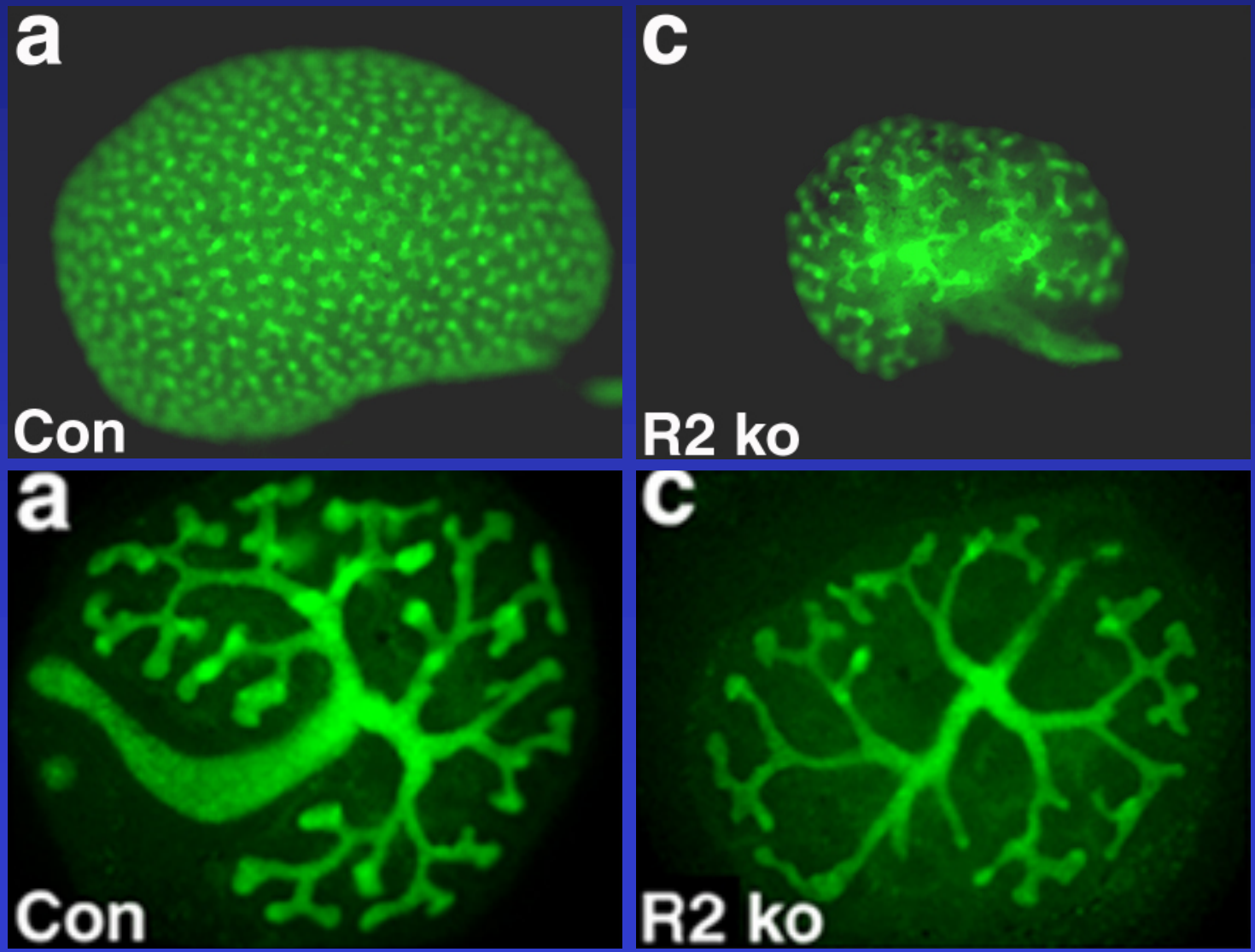


Aplasia: mouse model
(Early kidney H&E in *fgfr1/2*$^{Mes-/-}$ mice)

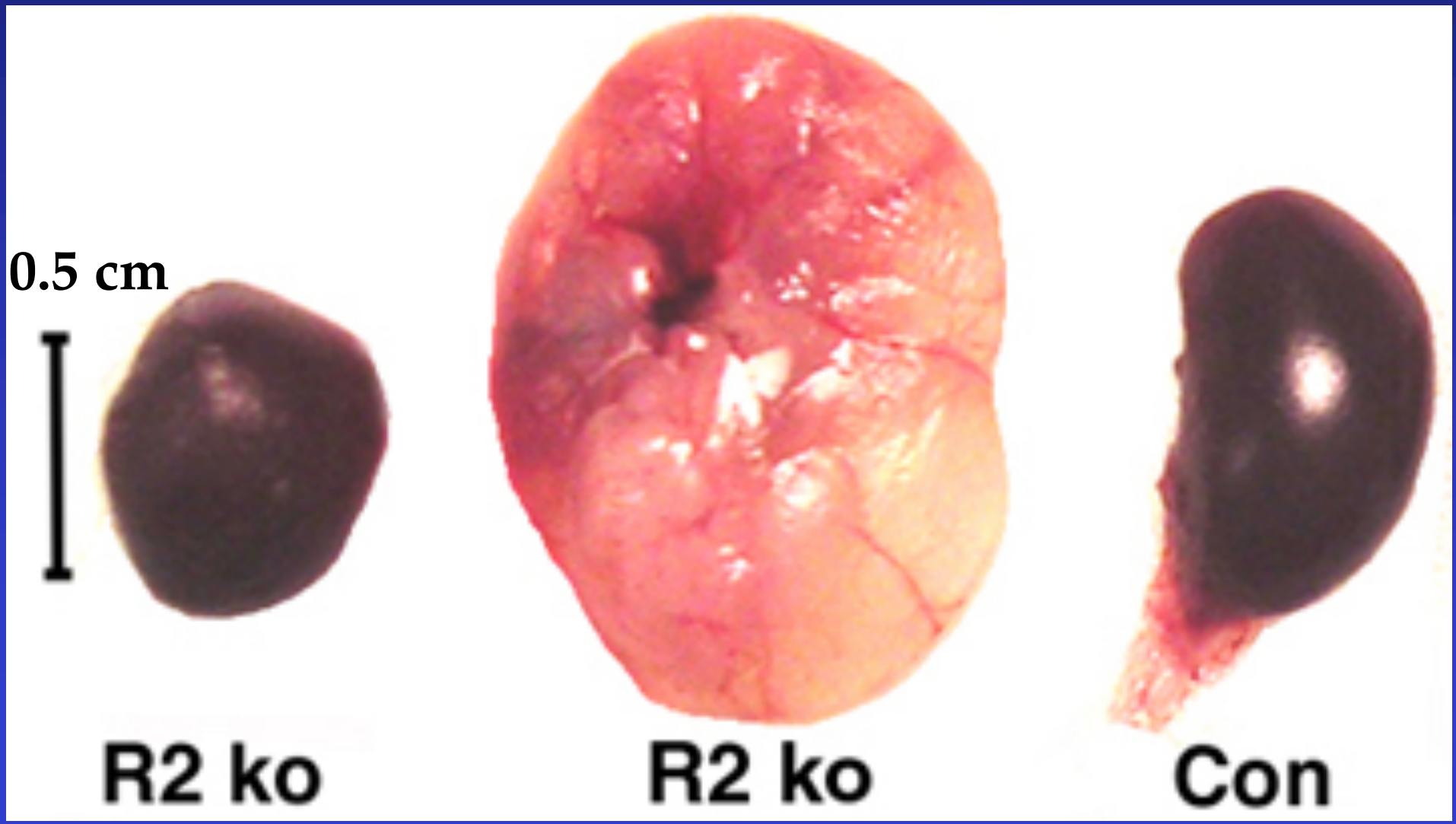


Hypoplasia / dysplasia: mouse model

E11.5 explants and 16.5 kidneys: control and *fgfr2*$^{UB-/-}$

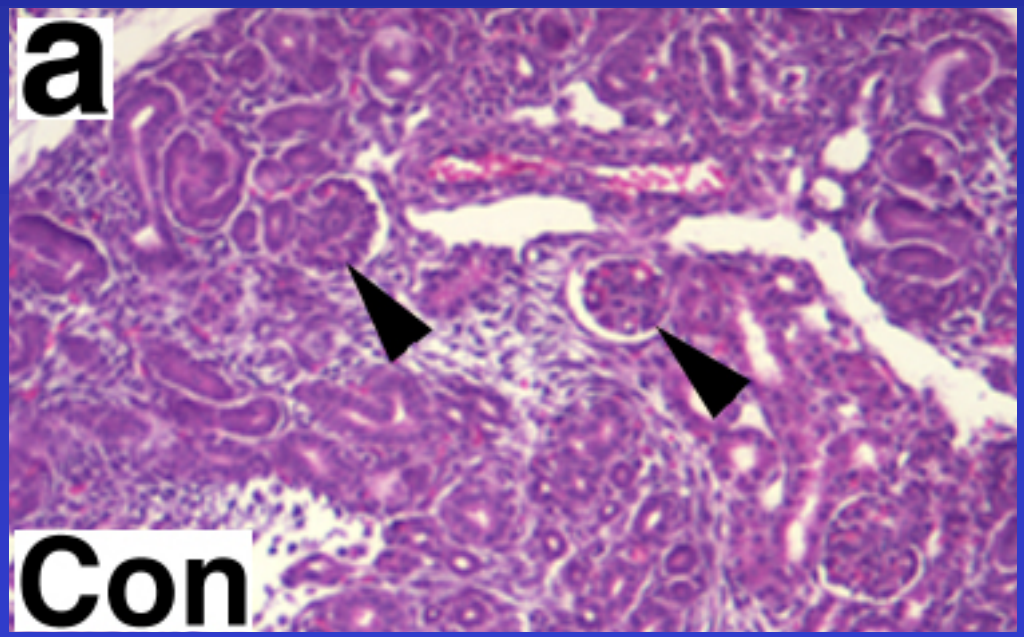


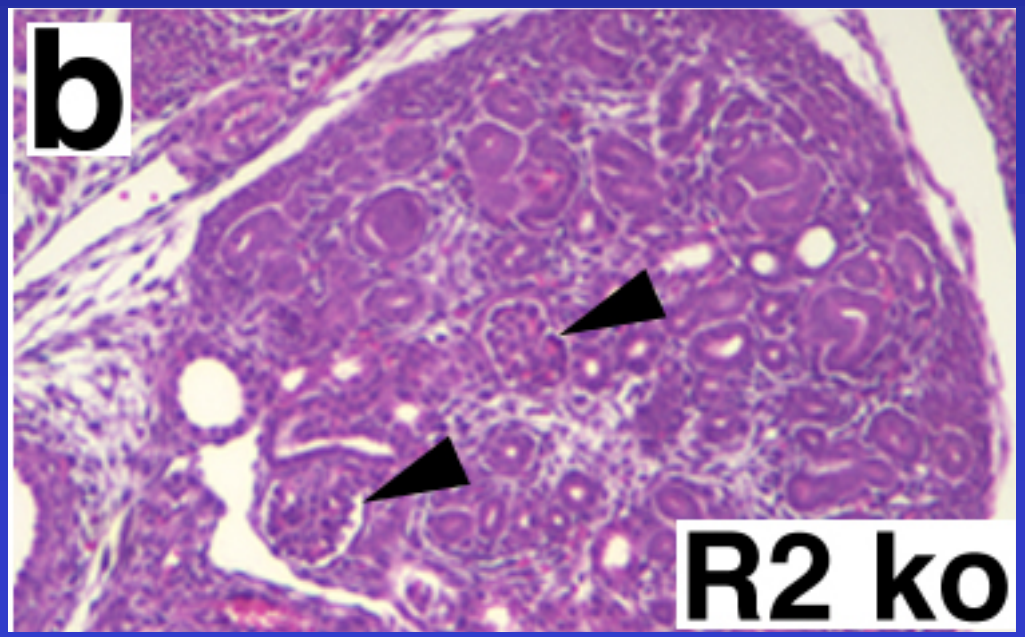
Hypoplasia / dysplasia: mouse model
Adult mouse kidneys: *fgfr2*$^{UB-/-}$ vs controls



Hypoplasia / dysplasia: mouse model

E16.5 kidneys H & E: control vs *fgfr2*$^{UB-/-}$





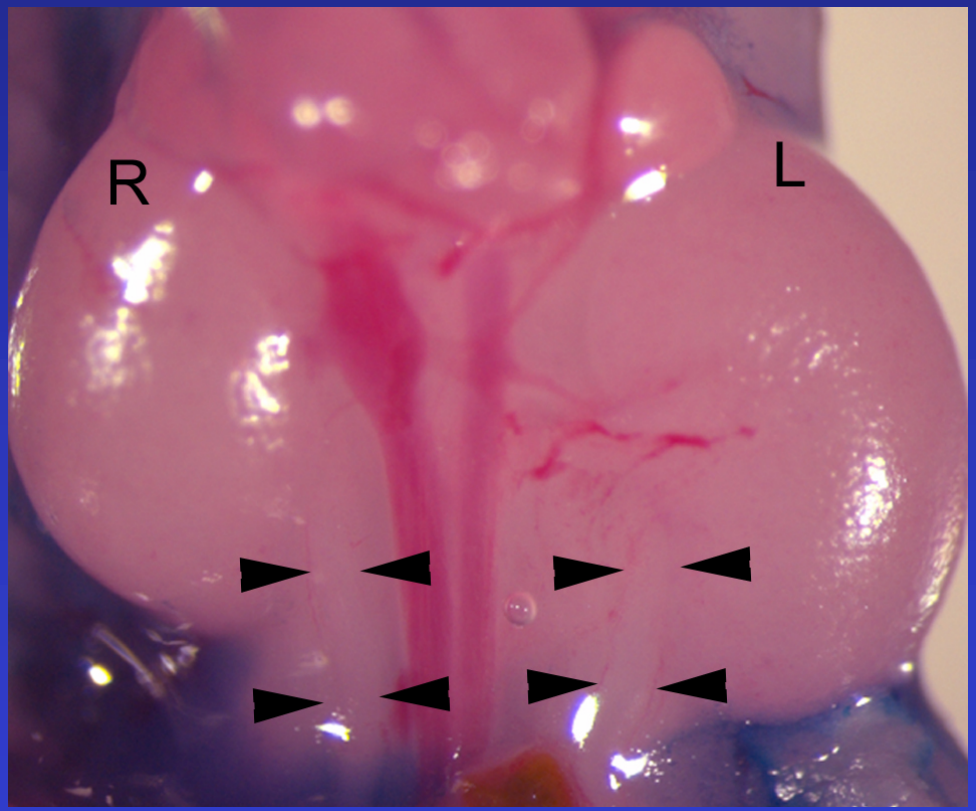
Congenital kidney diseases

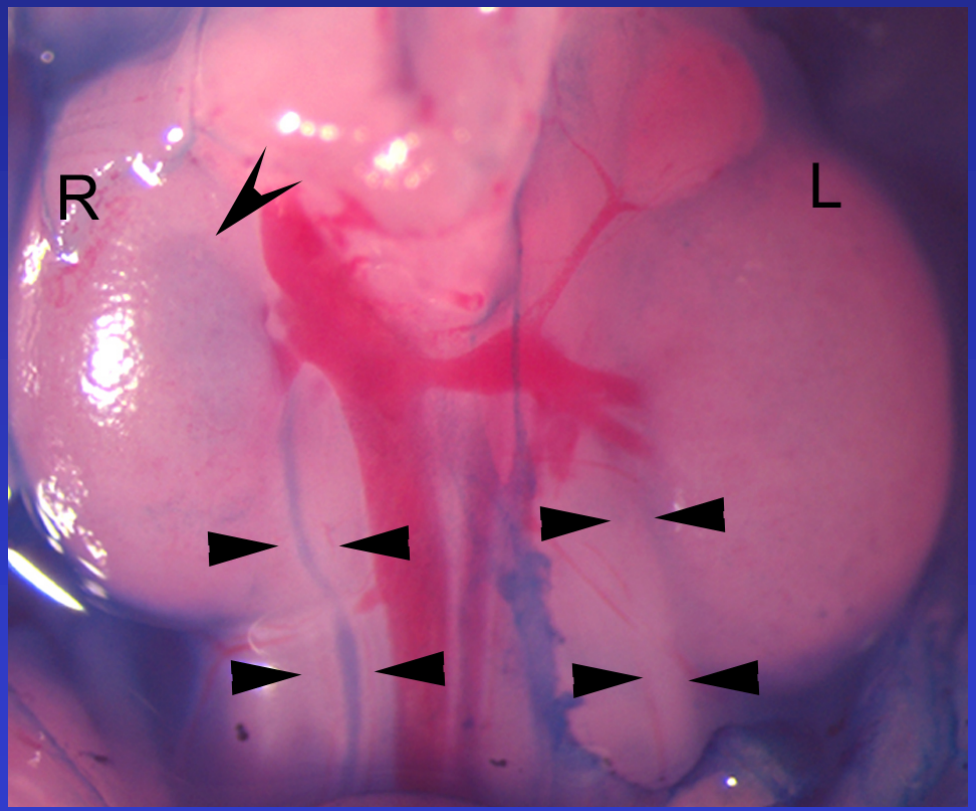
1. Obstructive Uropathy
2. Aplasia/Dysplasia/Hypoplasia- mouse models
3. **Reflux nephropathy- mouse models**
4. Polycystic kidney disease

Cystograms in P1 *Fgfr2*$^{Mes-/-}$ mice:

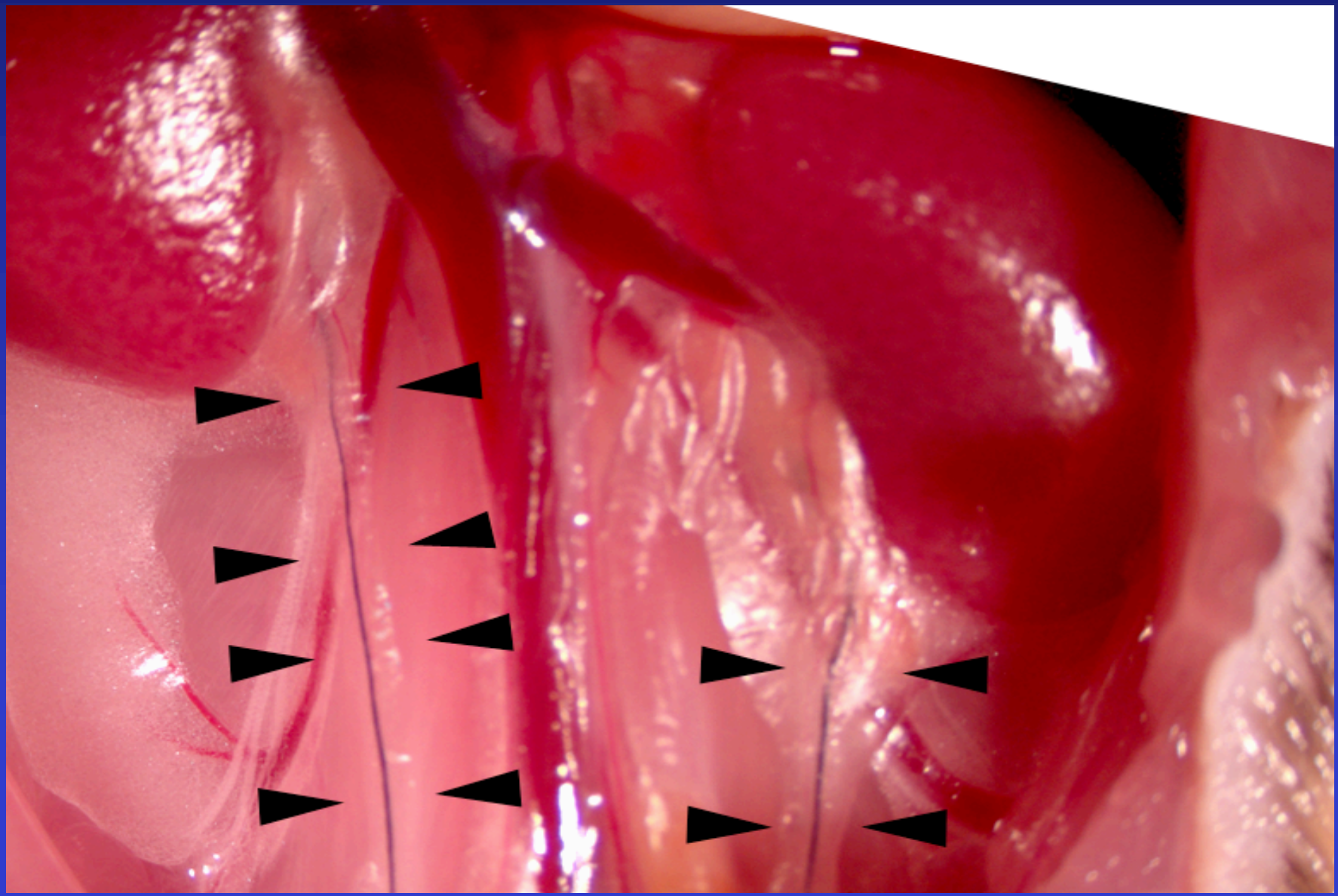
Control

Fgfr2$^{Mes-/-}$

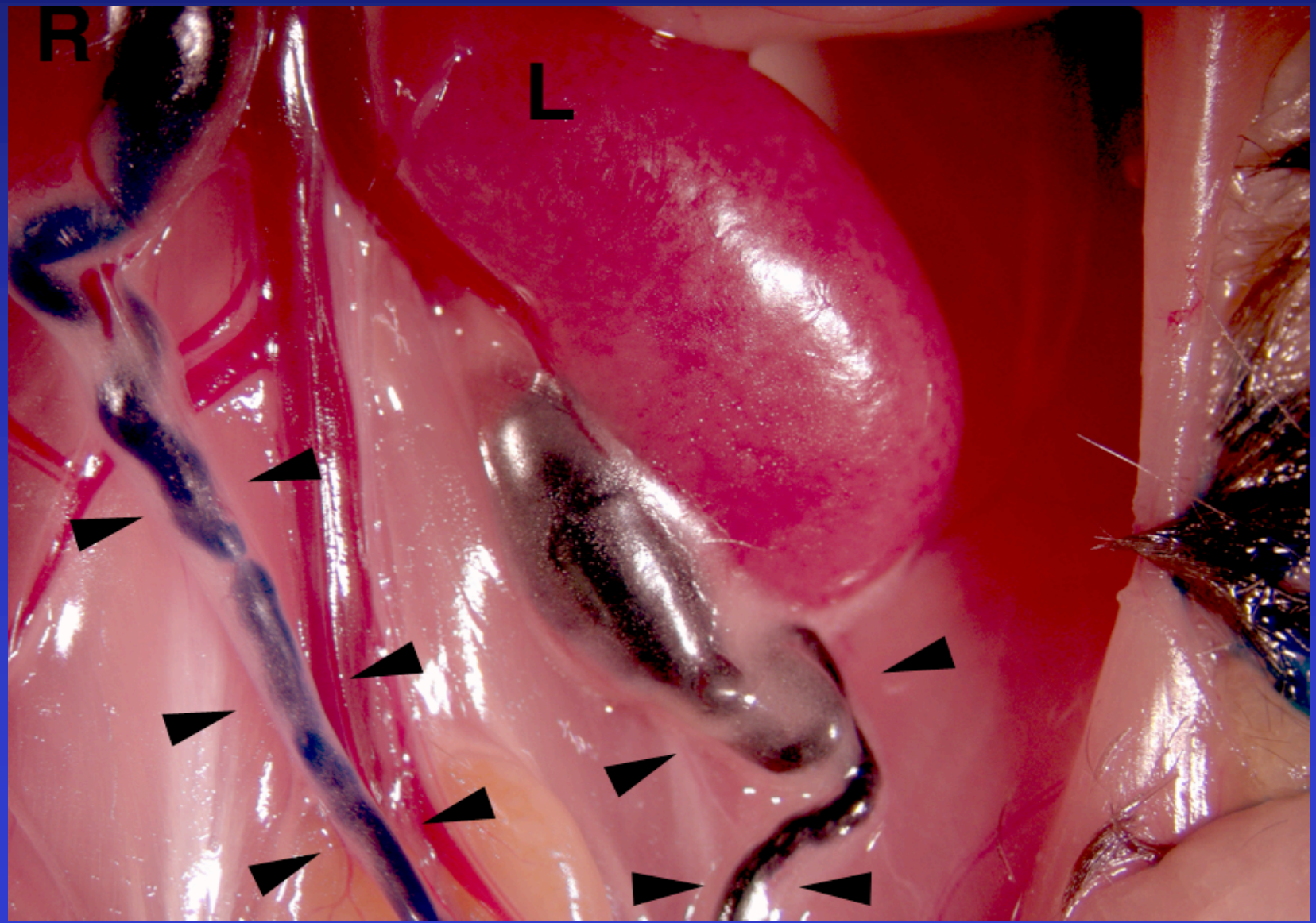




Grade I VUR in adult



Grade IV-V bilaterally



Obstructive Uropathy: mouse model (adult male *mgb* mutant mouse)

Obstructive Nephropathy: mouse model (embryonic control vs *Fgfr2*$^{Mes-/-}$)