0:00

Urinary Tract Pathology
Lecture 1:
Non-neoplastic Kidney

APPROVED

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Spring, 2010

1:18

A **lot** of diseases affect the kidneys!

He can't discuss all of the non-neoplastic kidney diseases in 50 minutes! This lecture focuses on the most common and severe diseases which we're likely to see in practice.

1:43

There is an enormous differential diagnosis of diseases which can affect the kidney.
A good strategy to remember these diseases is to categorize them based on locations, clinical presentations, or etiologies.

Physiologic-anatomic view

2. Intra-renal diseases are due to actual functional or morphological disruption of structures inside the kidney. These are the diseases we'll discuss in this lecture.

3. Post-renal diseases affect morphology and function of the tubing downstream of the kidney. These will be discussed in a later lecture.

- Pre-renal
  - Renal bloodflow
- Intra-renal
  - Vessels
  - Glomeruli
  - Tubules
  - Interstitium
- Post-renal
  - Urinary obstruction

1. These diseases are primarily due to disruptions in bloodflow to the kidney (such as chronic hypotension or myocardial infarction). There is not much associated microscopic pathology and they will not be discussed in this lecture.

Another trick to complicated organ pathology is to break the structure down into its individual parts. Each of these components of the kidney is preferentially affected by different disease processes.

5:34

1. Acute renal diseases occur over the course of a few hours, days, or weeks and result in compromised renal function. They are often reversible.

Clinical view:
Acute vs. Chronic and Mild vs. Severe

2. In contrast, **chronic** renal diseases occur over periods of months or years.

RIFLE: Acute Renal Failure			
Category	Duration	Cr	GFR
~	acute	normal	normal
Risk	acute	>1.5	<75%
Injury	acute	>2	<50%
Failure	acute	>3	<25%
Loss	>4 wk		minimal
End-stage	>12 wk		minimal

K/DOQI: Chronic Renal Failure	
Category	GFR
Stage 1	normal
Stage 2	<100%
Stage 3	<67%
Stage 4	<33%
Stage 5	<15%

3. Acute and chronic diseases can also be sub-categorized into **mild** and **severe** forms. These are differentiated by the degree to which GFR is compromised (mild <50% compromise, severe >50% compromise).

Etiologic View: VINDICATE

- **V**ascular
- **I**nfectious
- **N**eoplastic
- **D**egenerative/
  Deficiency/
  Deposition/(**D**rugs)
- **I**diopathic/
  Iatrogenic
- **C**ongenital/
  Chromosomal/
  Geneti**C**
- **A**utoimmune/
  Allergic
- **T**oxic/**T**raumatic
- **E**ndocrine/
  m**E**tabolic

9:29

Today's Lecture

- Selected renal diseases with distinctive pathologies that are:
  - Intrinsic (intra-renal), mostly involving vessels & tubules
  - All potentialy severe; some acute, some chronic
  - Predominantly vascular, toxic, congenital/genetic
- Autoimmune renal disease (which is mostly glomerular) will be discussed by Dr. Howell
- Renal neoplasms will be discussed on Thursday

8:39

Etiologic View: VINDICATE

We will be discussing renal diseases of the circled etiologies in this lecture.

- **V**ascular
- **I**nfectious
- **N**eoplastic
- **D**egenerative/ **D**eficiency/ **D**eposition/(**D**rugs)
- **I**diopathic/ **I**atrogenic
- **C**ongenital/ **C**hromosomal/ Geneti**C**

These are predominately the cystic diseases.

- **A**utoimmune/ **A**llergic

There are *many* autoimmune diseases which affect the kidney. They usually affect the glomerular compartment.

- **T**oxic/**T**raumatic
- **E**ndocrine/ m**E**tabolic

I. Selected non-neoplastic renal diseases
    A. Non-progressive acute renal injury
        1. Acute tubular necrosis
            a. Ischemic type
            b. Toxic type
        2. Acute interstitial nephritis
    B. Progressive to chronic renal failure (ESRD)
        1. Renovascular disease
            a. Diabetic nephropathy
            b. Hypertensive nephropathy
                i. Ordinary type
                ii. Malignant hypertension
        2. Renal cystic disease
            a. Adult polycystic kidney disease
            b. Dialysis-associated cystic disease
            c. Pediatric cystic diseases & others
II. Selected renal neoplasms (next lecture...)

10:21

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The first thing we'll discuss are the acute renal diseases. These are often reversible but are very common and can cause a great deal of morbidity.

10:56

Acute renal failure in general is common in hospitalized patients.

Acute renal failure in hospitalized patients:

Most common intrarenal causes

- Acute tubular necrosis
- Acute interstitial nephritis
- Glomerulonephritis

11:20

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There are TWO potential causes of acute tubular necrosis.

11:46

Acute tubular necrosis (ATN)

Most patients entering the hospital have bloodflow compromise to the kidneys for prerenal reasons (chronic heart failure, hypotension, MI). This degree of compromise is not enough to cause visible pathology.

- Second most common cause of acute renal failure (after prerenal azotemia)
- Most common intrarenal cause of acute renal failure in hospitalized patients (15% of ICU admissions)
- 50% episode survival, 30% 1-year survival

ATN occurs with sudden and severe compromise in bloodflow to the kidneys which results in visible pathological injury. This is the second most common cause of acute renal failure (ARF) in the hospital.

Likely because many of these patients have many other diseases.

Acute tubular necrosis (ATN)

- Ischemic
- Toxic

13:24

Causes of ischemic ATN

The renal tubules have a very high metabolic rate and require a large supply of oxygen.
If there is a sudden decrease in oxygen by any cause the tubules can die or be severely injured.

- Sudden decreased renal oxygenation from any cause
  - Hypotension
  - Blood loss
  - Myocardial infarction
  - Obstetric complications
  - Sepsis
  - Surgery

14:01

Causes of toxic ATN

- Drugs
  - Aminoglycosides
  - Amphotericin B
  - Cytotoxic drugs
    - Cisplatin
  - Cyclosporine
- Radiographic contrast media
- Myoglobinuria
- Ethylene glycol
- Heavy metals
- Organic solvents

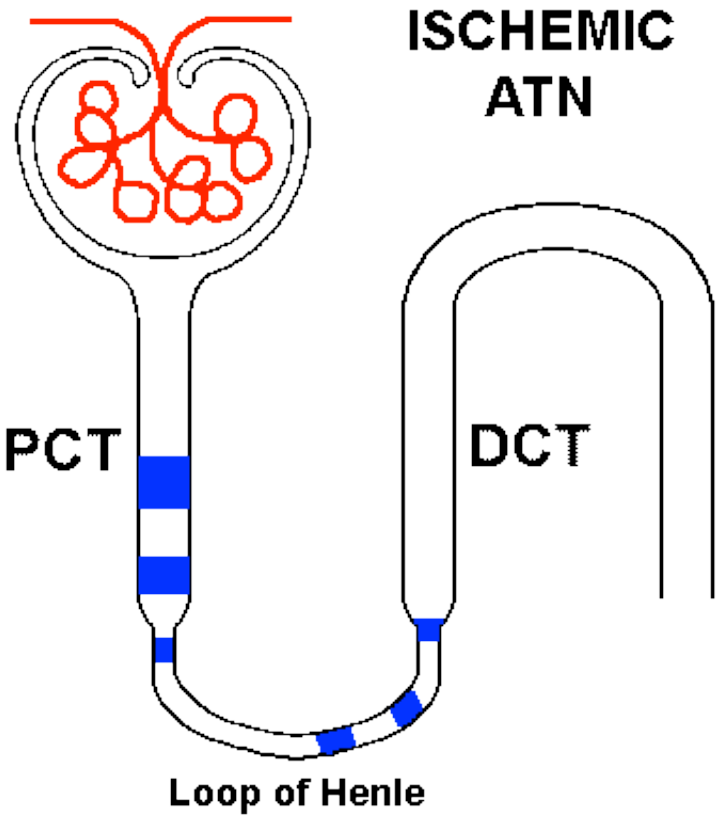
Such as lead

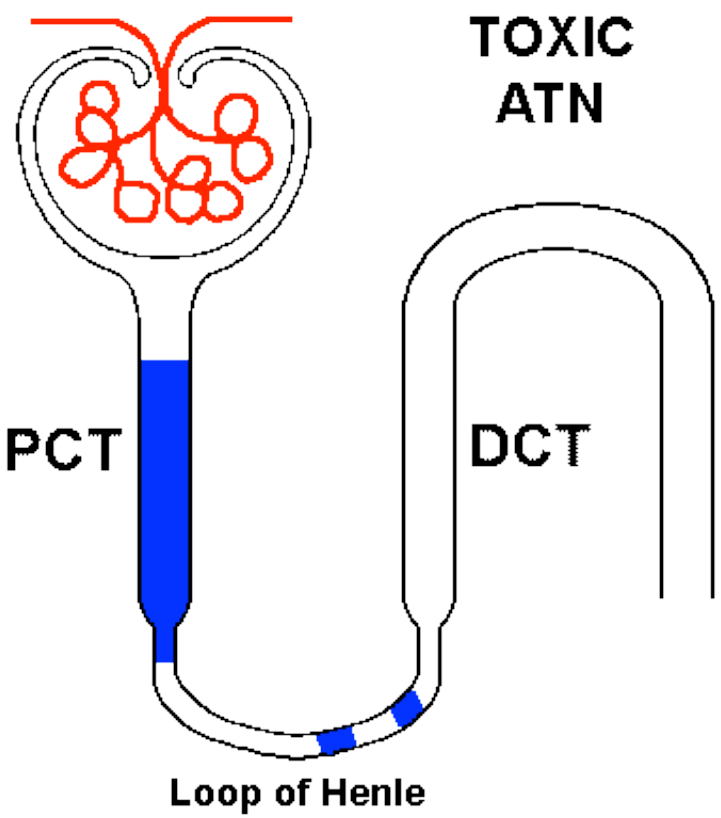
Such as chloroform

14:48

Acute tubular necrosis

The most metabolically active tubules are the **proximal tubules** and the **ascending loop of Henle tubules**. These are the most susceptible to damage in both ischemic and toxic ATN.





In ischemic ATN, the visible damage to both the proximal tubule and ascending loop of Henle is **patchy and has skip lesions**.

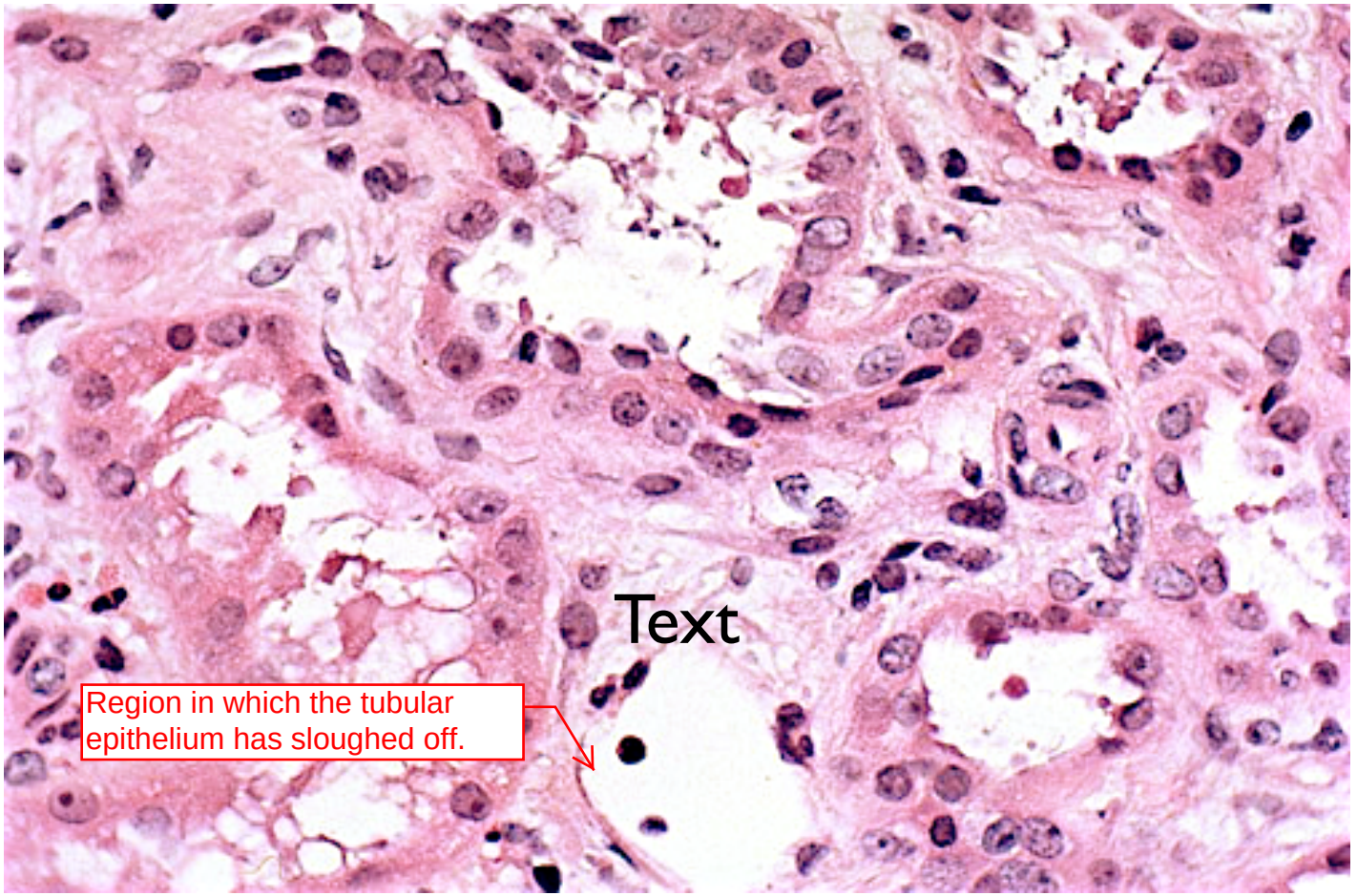
In toxic ATN, the damage is characteristically **contiguous**.

Gross pathology

- Pale, swollen kidney

15:47

A normal tubule should have a clear lumen and cuboidal to columnar epithelium which isn't heavily vacuolated or filled with debris.



Region in which the tubular epithelium has sloughed off.

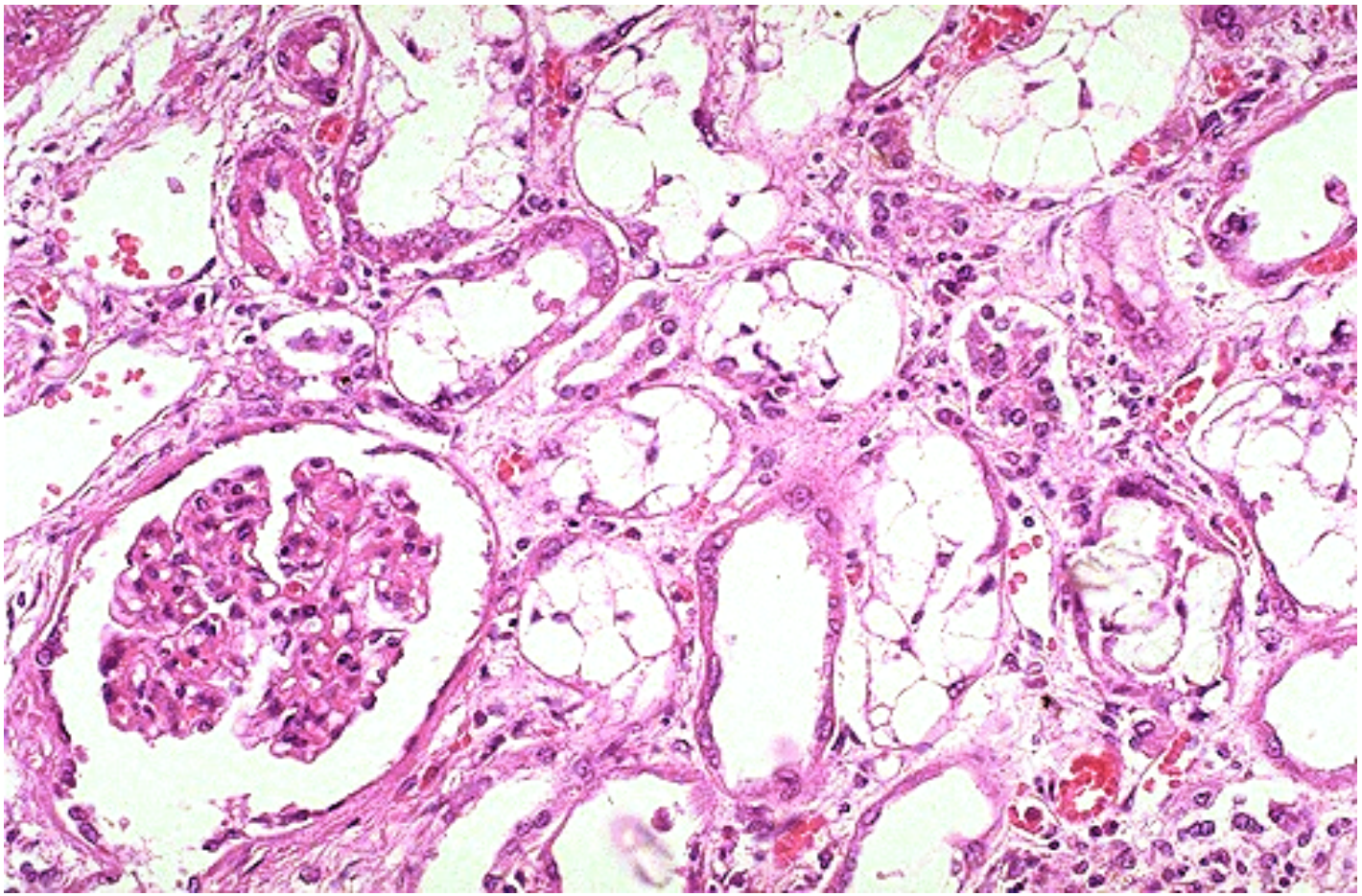
This patient had a hypotensive episode which resulted in ATN

Ischemic ATN: Loss of tubular epithelium, tubular dilatation, cellular debris (casts) in lumens, little or no inflammation, often patchy (skip lesions)

This can be important to consider when assessing a renal biopsy.

17:20

The basic picture is very similar:
- tubular dilatation
- sloughing of epithelium
- cast formation



Toxic ATN: Ballooning degeneration of tubular epithelium, some toxins → crystals in tubules, diffuse

Such as ethylene glycol

Specifically oxalate crystals

18:00

- Extent of tubular epithelial cell injury biopsy correlates poorly with clinical renal impairment. Why?
  - ? Patchiness (in ischemic ATN)
  - ? Medullary tubule damage more important than proximal tubule damage
  - ? Functional subcellular damage (e.g. brush border loss) more important than frank necrosis?
  - ? Local mediator release (*many* investigated) with even sublethal hypoxia may disrupt microcirculation or cause other functional problems

Kidney needle core biopsies mostly sample the cortex. However, the damage to the ascending loop of Henle (medulla) may be more important than damage to the proximal tubule (cortex).

This can only be seen wtith electron microscopy

The visible pathologic damage to the tubules may be less important than invisible damage to renal microcirculation caused by local mediator release.

19:56

Natural history of ATN

- **Initiation (onset) phase**
  - Rapid decline of GFR over hours
- **Maintenance (oligo-anuric) phase**
  - Low GFR, low urine output lasting 5-10 days
- **Recovery (diuretic) phase**
  - Often sudden recovery of GFR, profuse diuresis lasting several days
- **Late recovery (convalescent) phase**
  - In pts without pre-existing disease, complete functional and histologic recovery
  - Many patients suffer ATN on background of other diseases, long-term survival varies

Once the insult has resolved, it takes 5-10 days for the tubular epithelium to re-generate. During this period, patients require support and often dialysis.

Over the next weeks or months

21:23

Treatment of ATN

- For toxic ATN, remove offending agent
- Supportive
  - Volume management
  - Hyperkalemia
  - Loop diuretics
- Dialysis frequently required

These patients often have hyperkalemia due to low GFR

21:48

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II. Selected renal neoplasms (next lecture...)

This is the second most common intrinsic cause of acute renal injury.

22:02

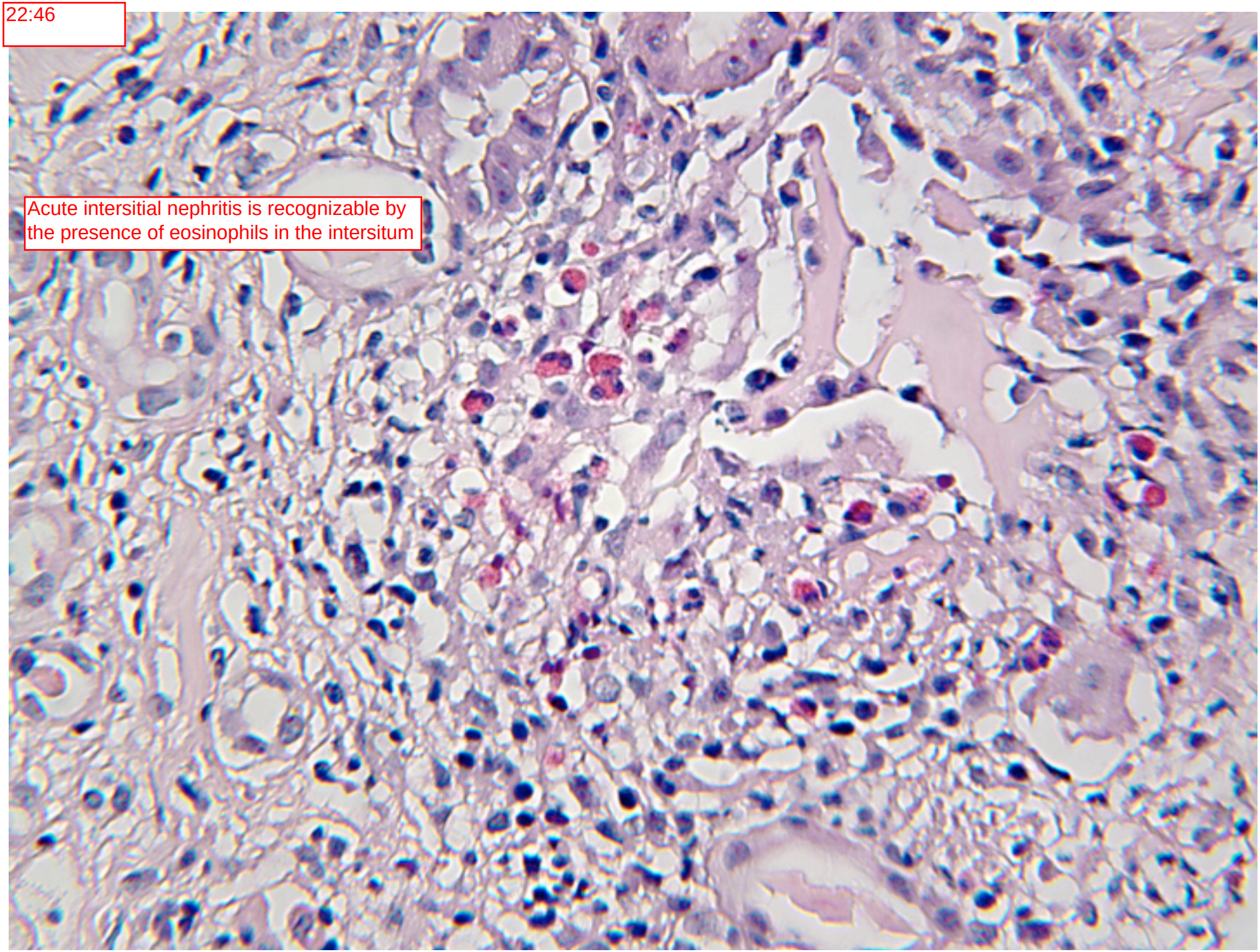
Acute Interstitial Nephritis

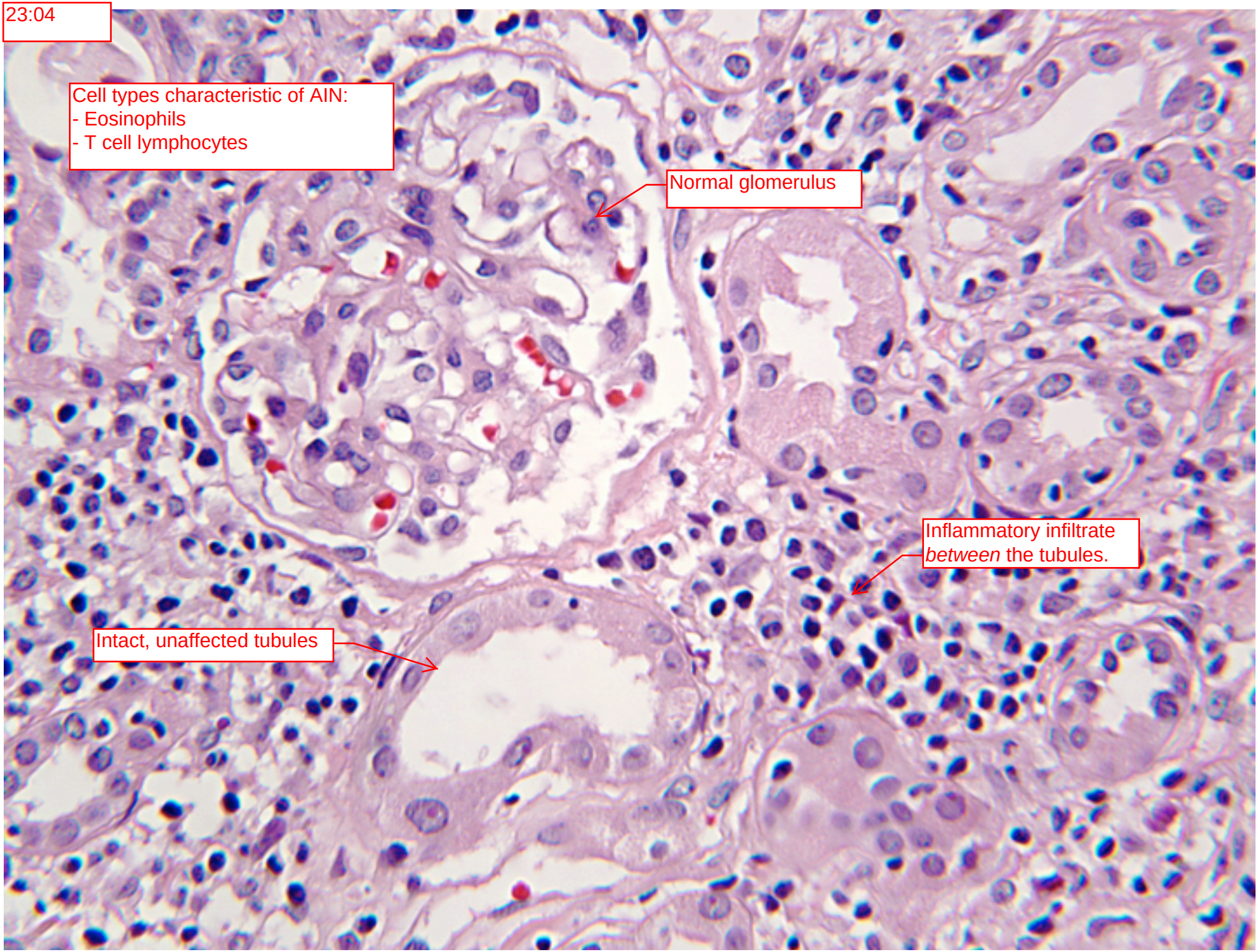
- Second most common intrarenal cause of acute renal failure
- Pathology: Eosinophil-rich interstitial inflammatory infiltrate and edema
- Etiology: Cell-mediated hypersensitivity reaction
  - Drug-induced >75%

Acute tubular necrosis is a disease that occurs *within* the tubules. Acute intersitial nephritis occurs *between* the tubules, in the intersitum.

The vast majority of these are iatrogenic.

22:46


Acute intersitial nephritis is recognizable by
the presence of eosinophils in the intersitum


23:04
Cell types characteristic of AIN:
- Eosinophils
- T cell lymphocytes
Normal glomerulus
Inflammatory infiltrate
between the tubules.
Intact, unaffected tubules

23:48

Drugs associated with AIN

- Antibiotics
  - beta-lactams, sulfonamides, rifampicin, fluoroquinolones, vancomycin, acyclovir
- NSAIDs
- Famotidine, omeprazole
- Allopurinol
- Phenytoin
- Furosemide

The *most common* class of drugs associated with AIN

The second most common drug-induced cause of AIN

26:16

Clinical

- Delay between drug exposure and renal failure averages 10 days (range: 1 d to several months)
- Arthralgia, fever, skin rash, eosinophilia in 20-40%
- Most have hematuria
- ~40% require dialysis
- Up to 50% have some longterm loss of GFR
- Treatment: withdrawal of drug + steroids

These are all typical manifestations of T-cell hypersensitivity reactions

So be sure to get a thorough history of drug exposure!

Treatment with steroids has helped reduce the percentage of patients with longterm complications.

24:24

Pathogenesis

1. It is thought that in most cases the drug haptenizes (forms an immune-sensitive complex) with an endogenous protein antigen in the TBM or renal intersitum. This neo-antigen can elicit an immune response from sensitized T effector cells in the intersitium.

tubular basement membrane

- Drug or derivative haptenizes to endogenous TBM or interstitial component or complexes deposit in interstitium

2. In other cases the drugs may form immune complexes in the periphery and deposit in the intersitum. However, this is thought to be less common.

- Immunologic predisposition (sensitized T-effector cells, weak T-suppressor response
- Cell-mediated (non-humoral) mechanism
- Release of fibrogenic cytokines can rapidly (1-2 weeks) induce irreversible fibrosis

3. T cells can release fibrogenic cytokines as they react in the intersitum. While some patients recover completely from AIN, others can have irreversible renal compromise due to this fibrosis.

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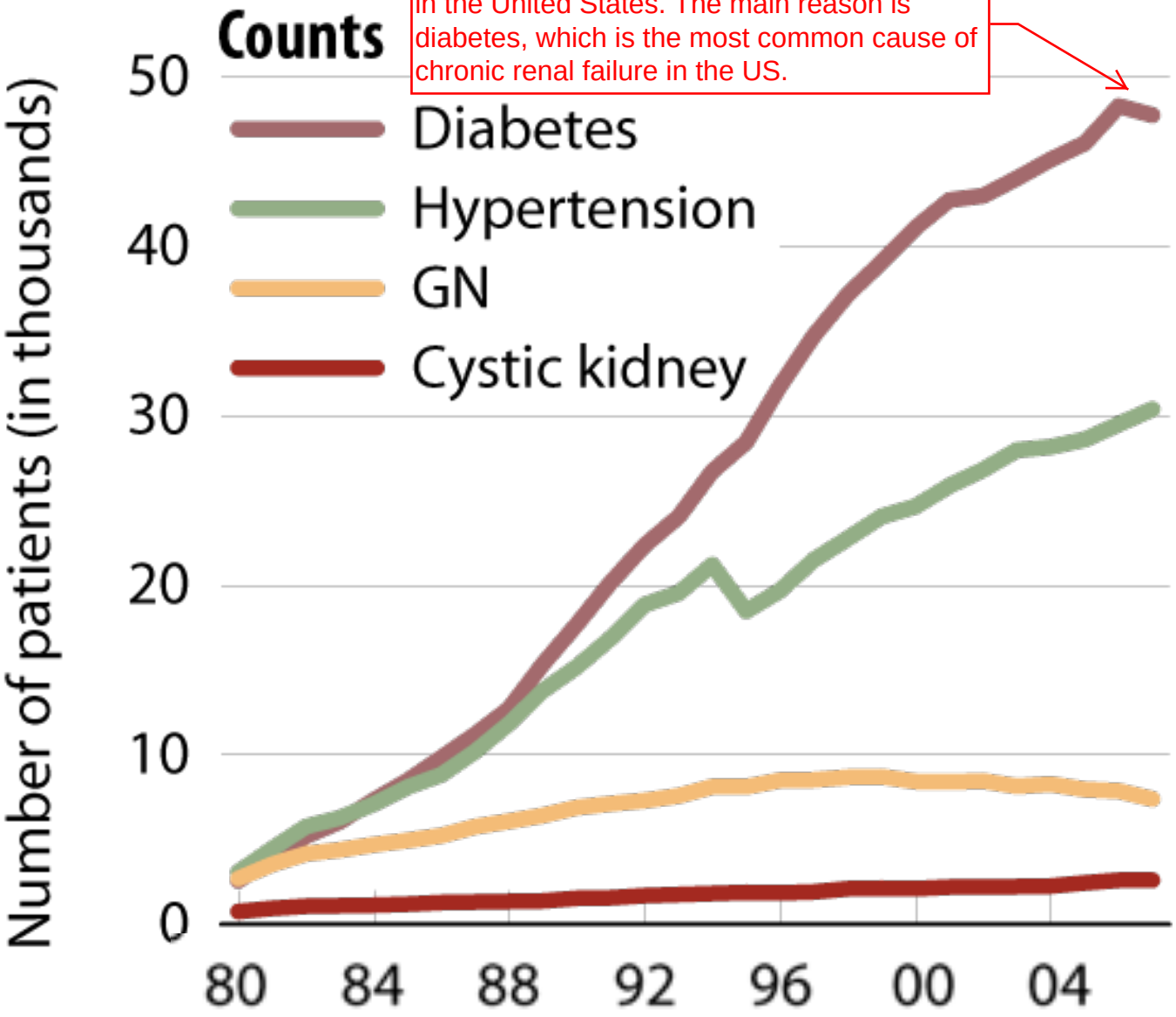
End Stage Renal Disease

28:03

Remember, prevalence is a number. This shows how many patients with current chronic renal failure have each etiology.

ESRD Prevalence

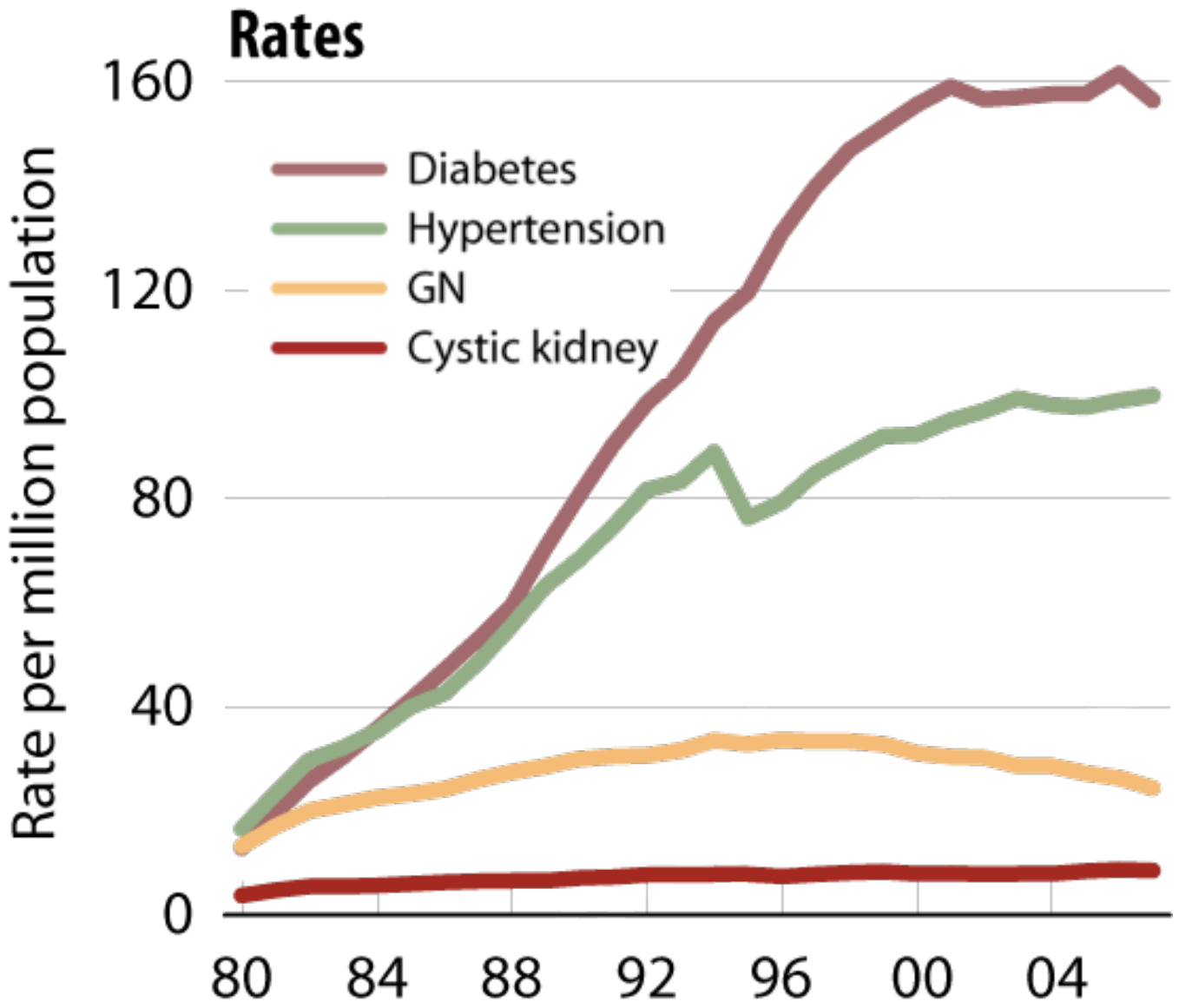
Chronic renal failure is an increasing problem in the United States. The main reason is diabetes, which is the most common cause of chronic renal failure in the US.



29:03

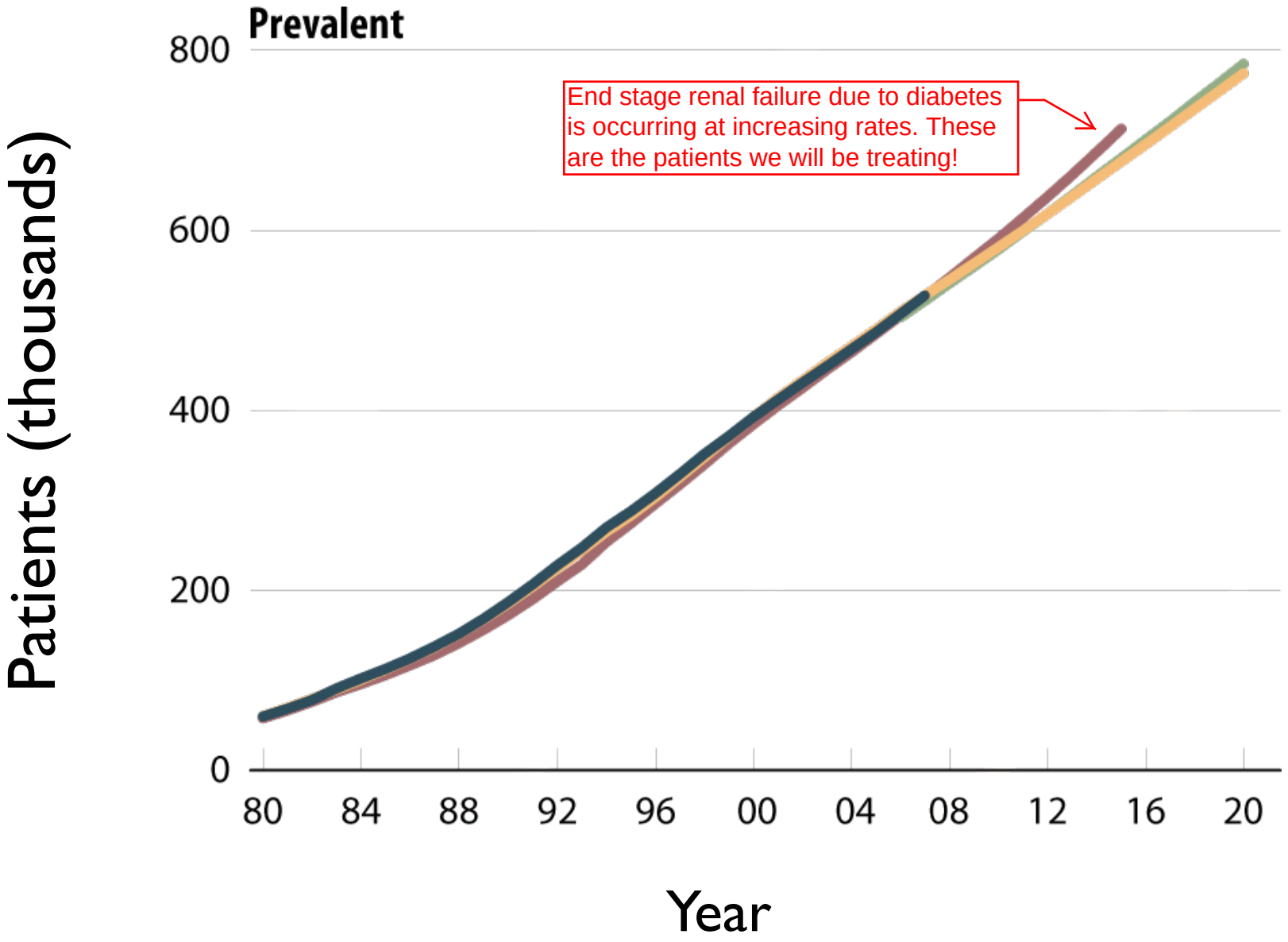
ESRD

INCIDENCE
This shows how many new cases of chronic renal failure occur per year from each etiology. Note that diabetes is also causing the most new cases of chronic renal failure per year.



29:31

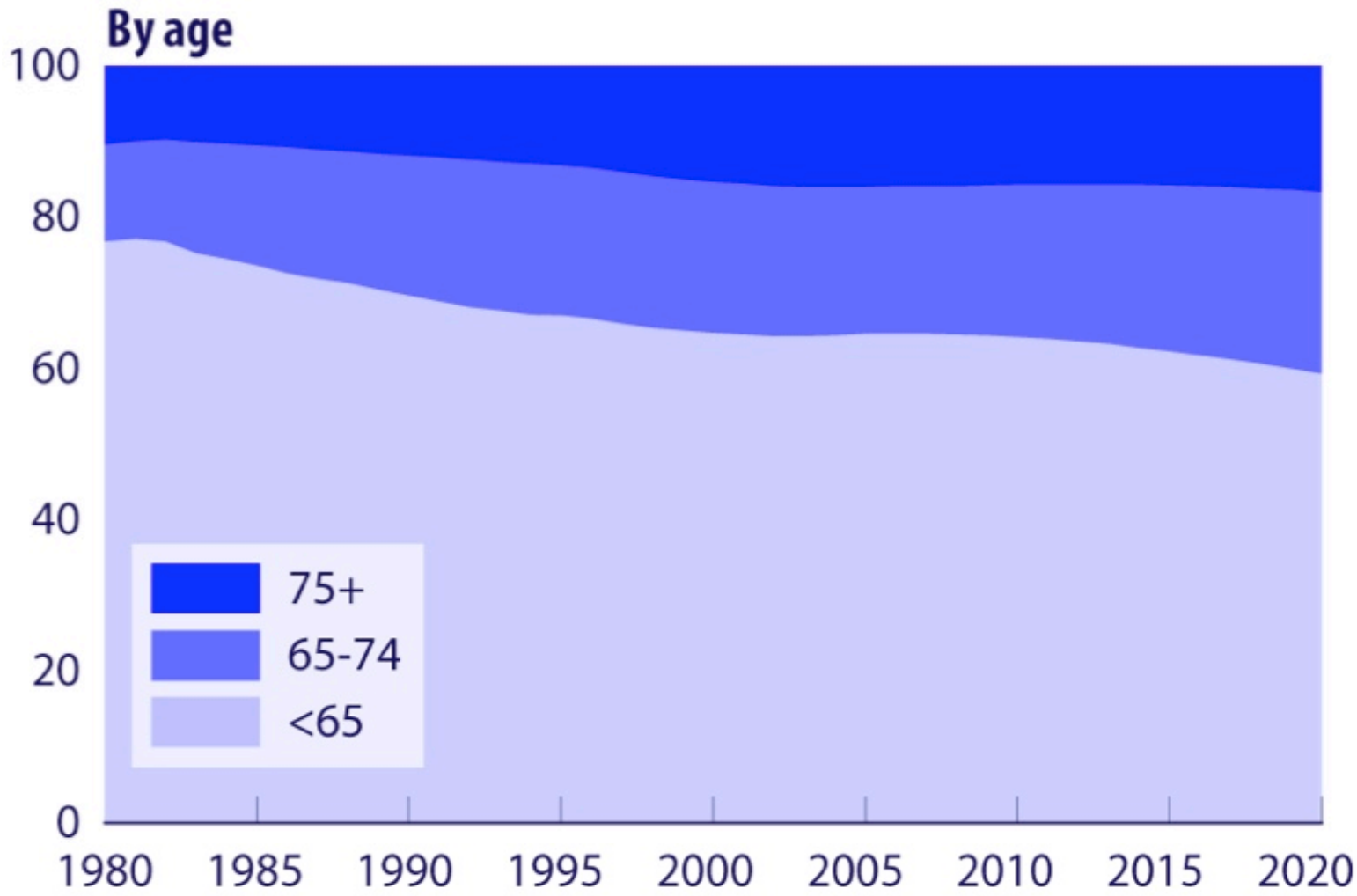
Historical & Projected Prevalence of ESRD



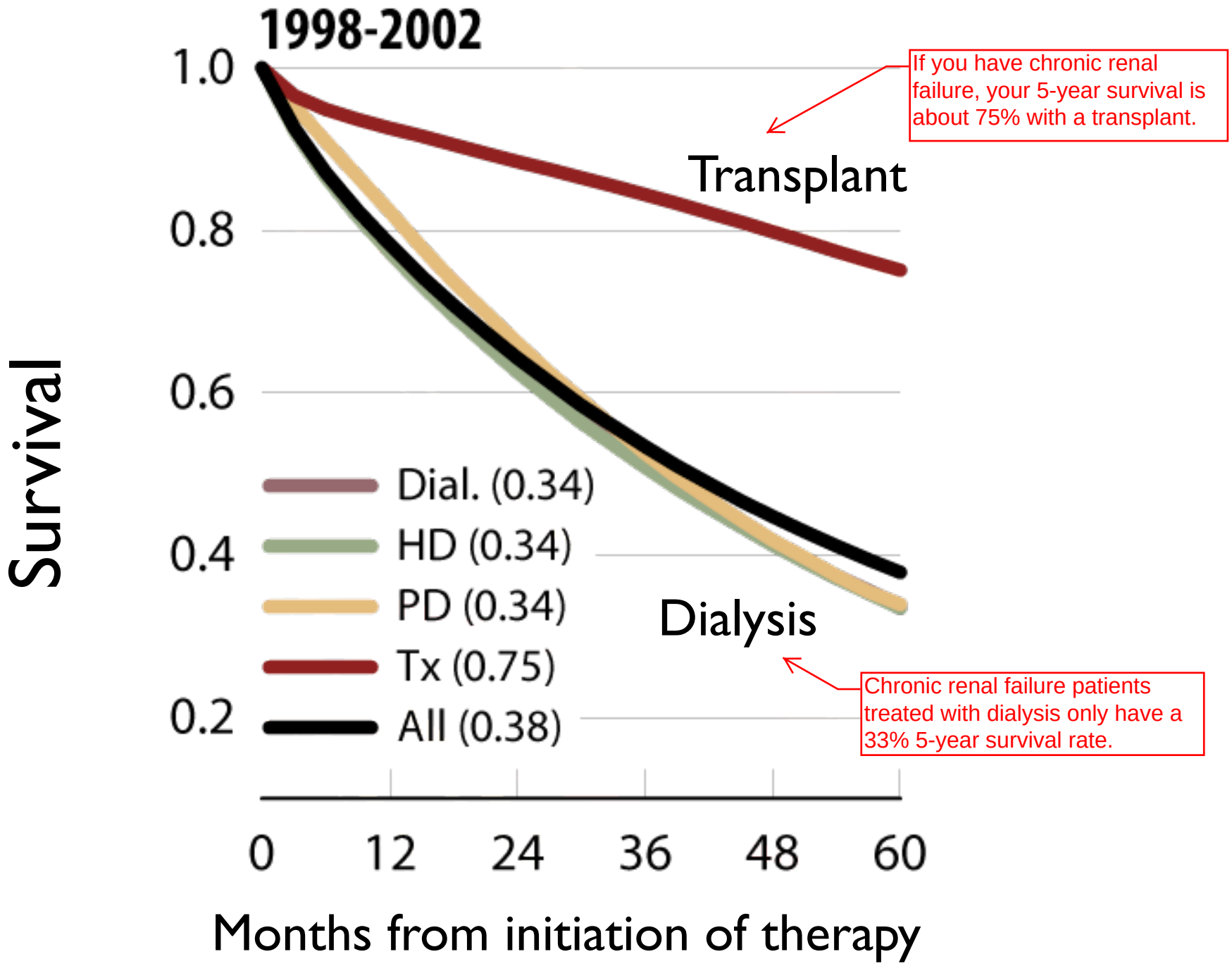
30:00

End stage renal disease used to be a disease of younger patients due to causes other than diabetes and hypertension.
Because diabetes and hypertension have become more common causes of ESRD, the patient population is now older.

"Graying" of ESRD population

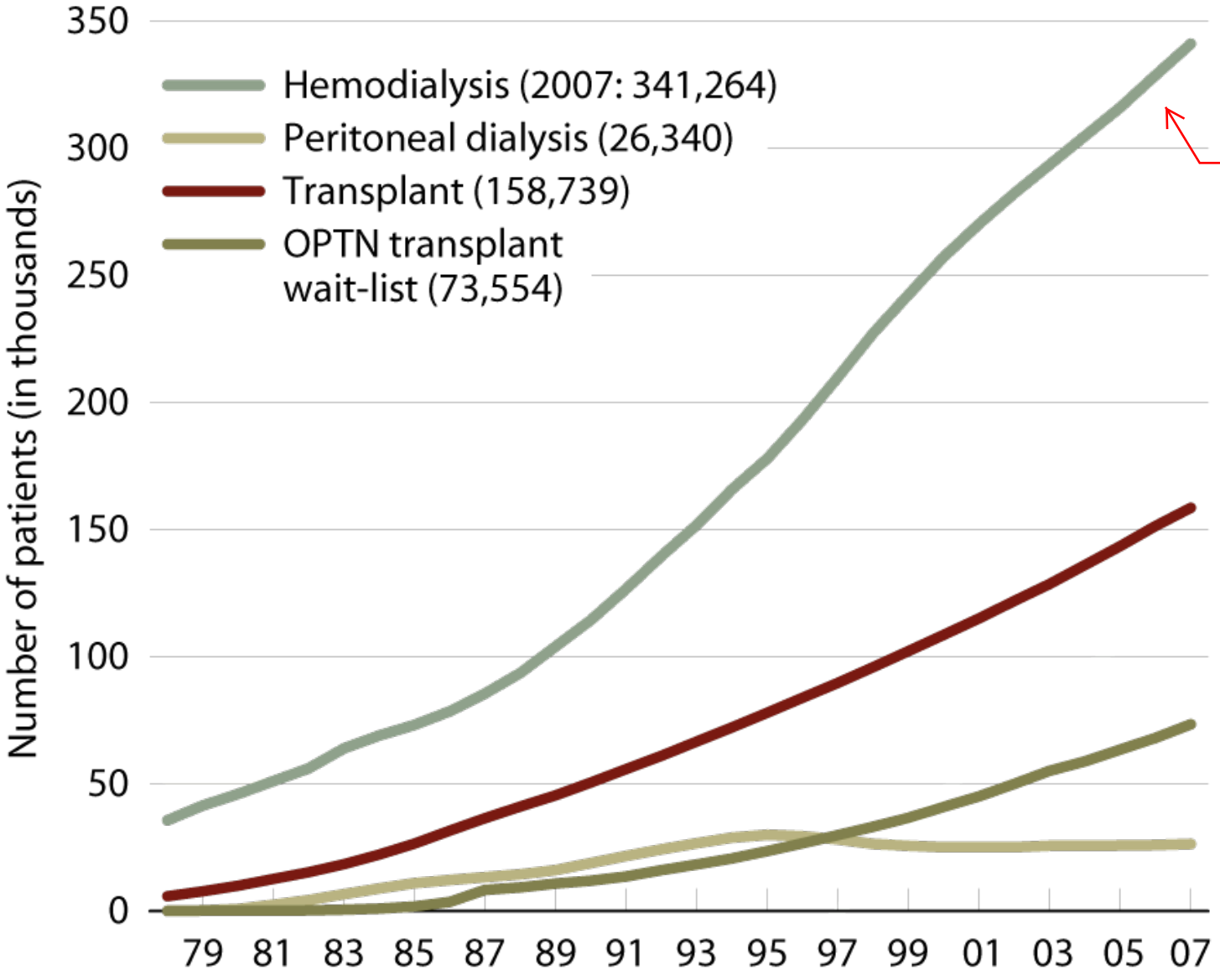


30:35


1998-2002
1.0
0.8
0.6
0.4
0.2
Survival
Dial. (0.34)
HD (0.34)
PD (0.34)
Tx (0.75)
All (0.38)
Transplant
Dialysis
0
12
24
36
48
60
Months from initiation of therapy
If you have chronic renal failure, your 5-year survival is about 75% with a transplant.
Chronic renal failure patients treated with dialysis only have a 33% 5-year survival rate.

31:03

Prevalence by treatment

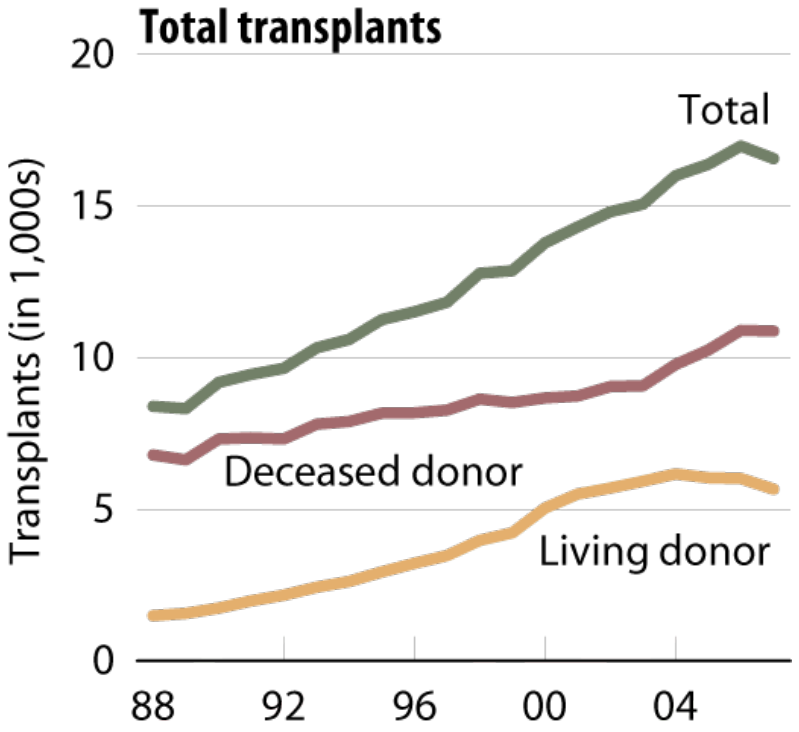


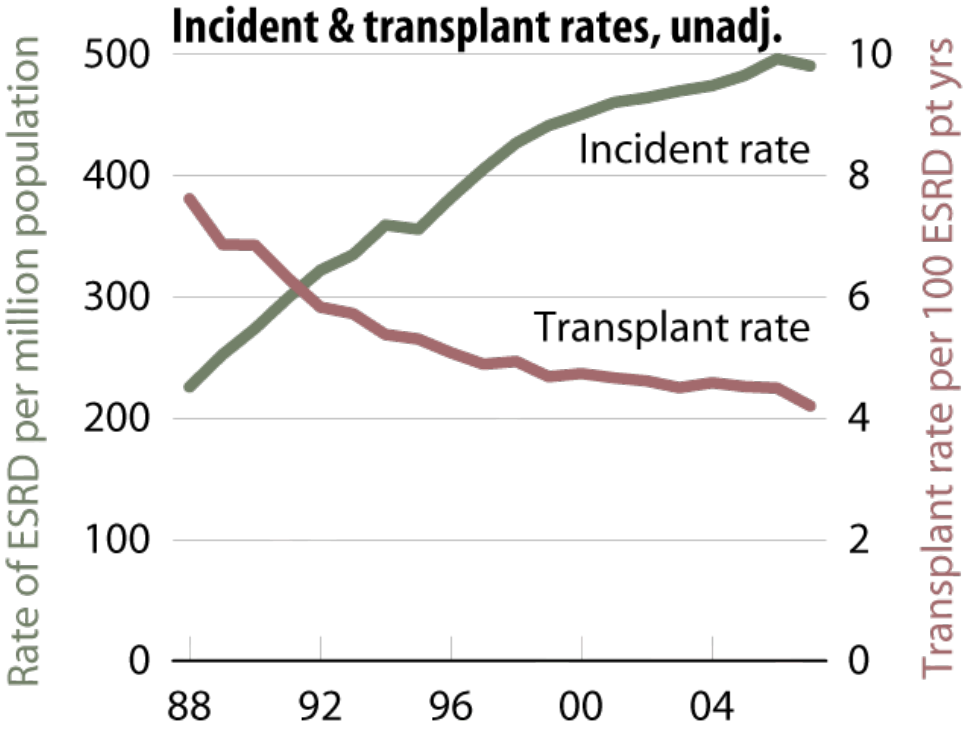
Unfortunately, most patients with chronic renal failure are being treated with dialysis.

31:12

Total Transplants and Transplant Rates

As a side note, you should be aware that the total number of transplants being given is increasing. However, the total number of patients who need transplants is increasing at a faster rate.





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Renovascular disease

- Most common cause of End Stage Renal Disease (ESRD)
- Major causes:
  - Diabetes mellitius
  - Hypertension

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Diabetic nephropathy: clinical

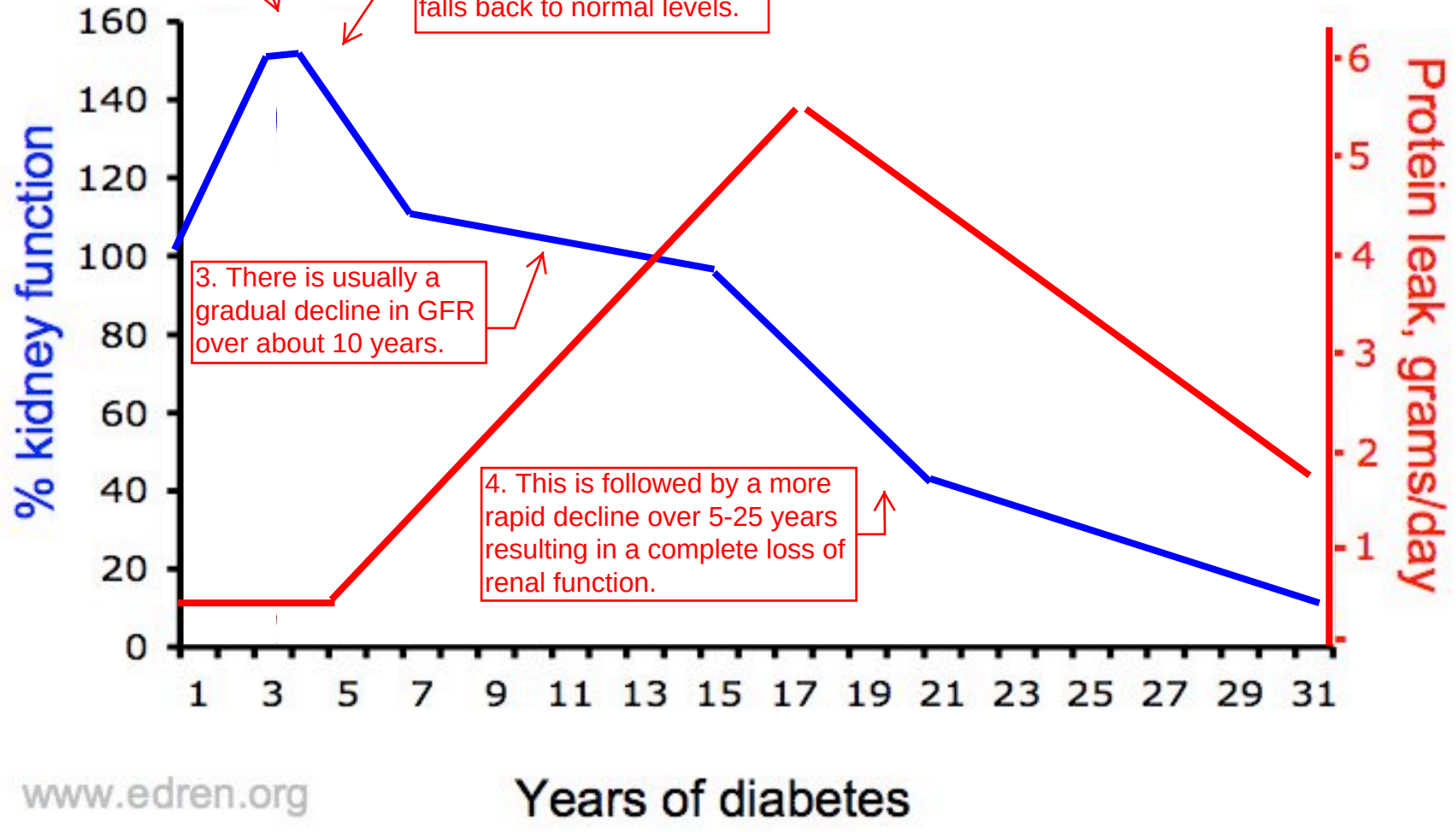
- Persistent albuminuria, relentless decrease in GFR, hypertension (i.e. nephrotic syndrome)
- Both IDDM (~30%) & NIDDM (~15%)
- Better control → lower risk
- Untreated mortality 100%
- Rx: ACE inhibitors, dialysis, transplantation

33:00

Evolution of diabetic nephropathy

1. In the early phase of diabetic nephropathy, GFR compensatory increases. The patient will be asymptomatic.

2. After this period, the GFR falls back to normal levels.



3. There is usually a gradual decline in GFR over about 10 years.

4. This is followed by a more rapid decline over 5-25 years resulting in a complete loss of renal function.

34:20

Natural History of Diabetic Nephropathy

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased	Type 1 normal Type 2 normal hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickend BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300 mg/d	Type 1 normal Type 2 normal hypertension	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d	Type 1 increased Type 2 normal hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>380 mg/d	Hypertension	15-25 years
Stage 5	Uremic	ESRD	0-10	Decreasing	Hypertension	25-30 years

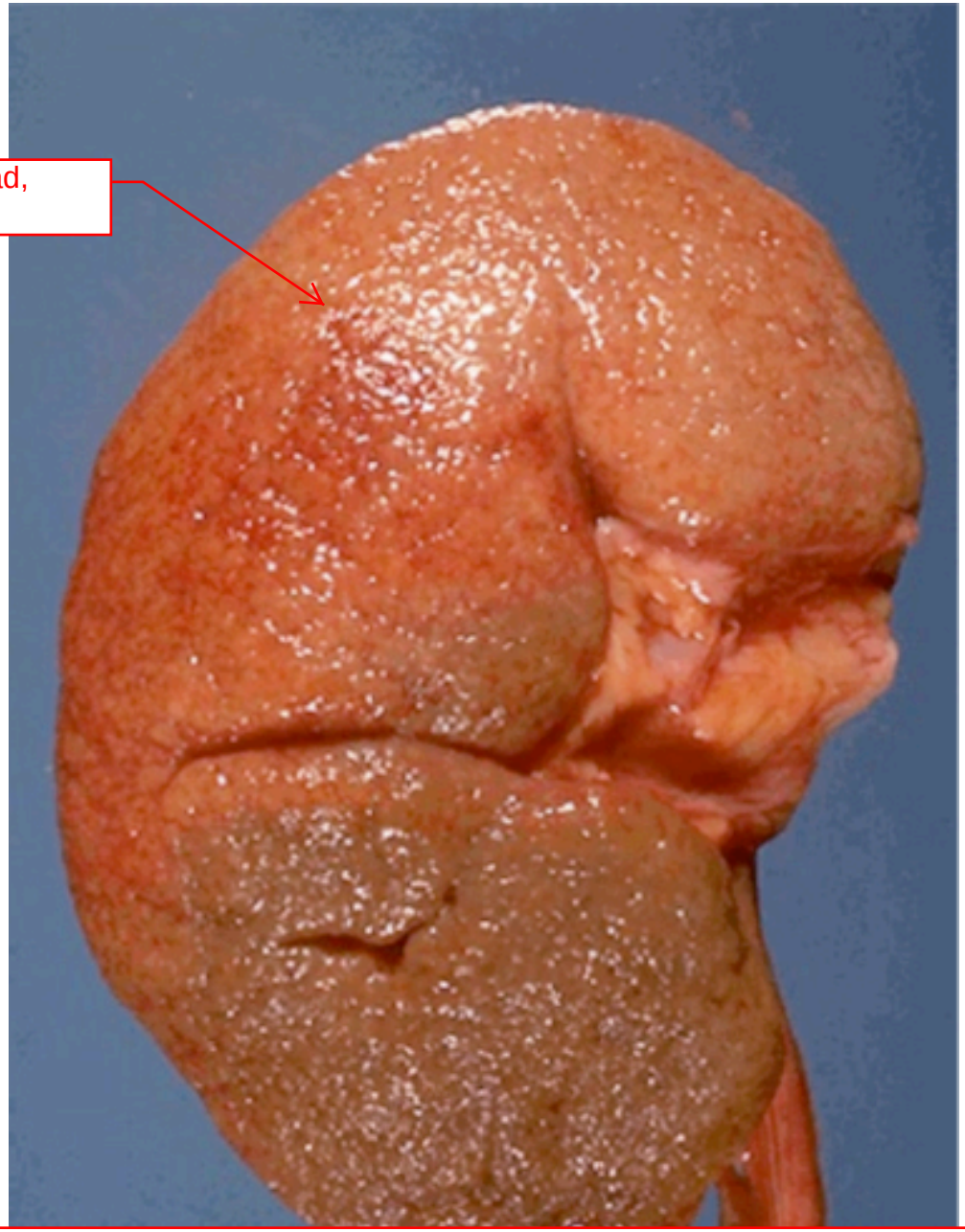
The asymptomatic stage

There are changes on biopsy but the disease is still clinically silent.

The disease is clinically recognized at this stage.

Patients excrete increasing amounts of albumin in their urine throughout stage 3.
During stage 4, albumin excretion *decreases* because of the fall in overall GFR.
By stage 5, these patients are no longer able to excrete urine at all.

35:43



Explanation:
- Each tubuloglomerular unit has its own blood supply which radiates from the glomerulus in the cortex, follows the loop of Henle and distal tubule into the medulla, and returns back to the glomerulus.
- When the glomerulus dies, the entire unit, including the proximal tubule, loop of Henle, and distal tubules all die off.
- This results in a linear scar from the cortex to the medulla.
- The scar becomes fibrotic and pulls the parenchyma inwards, resulting in the characteristic pock marks.

37:20

FYI: the **mesangium** is the central part of the renal glomerulus within the basement membrane and surrounding the capillaries.

Diabetic nephropathy

Diabetic nephropathy occurs in the small vessels and the glomeruli.
It has three main components:

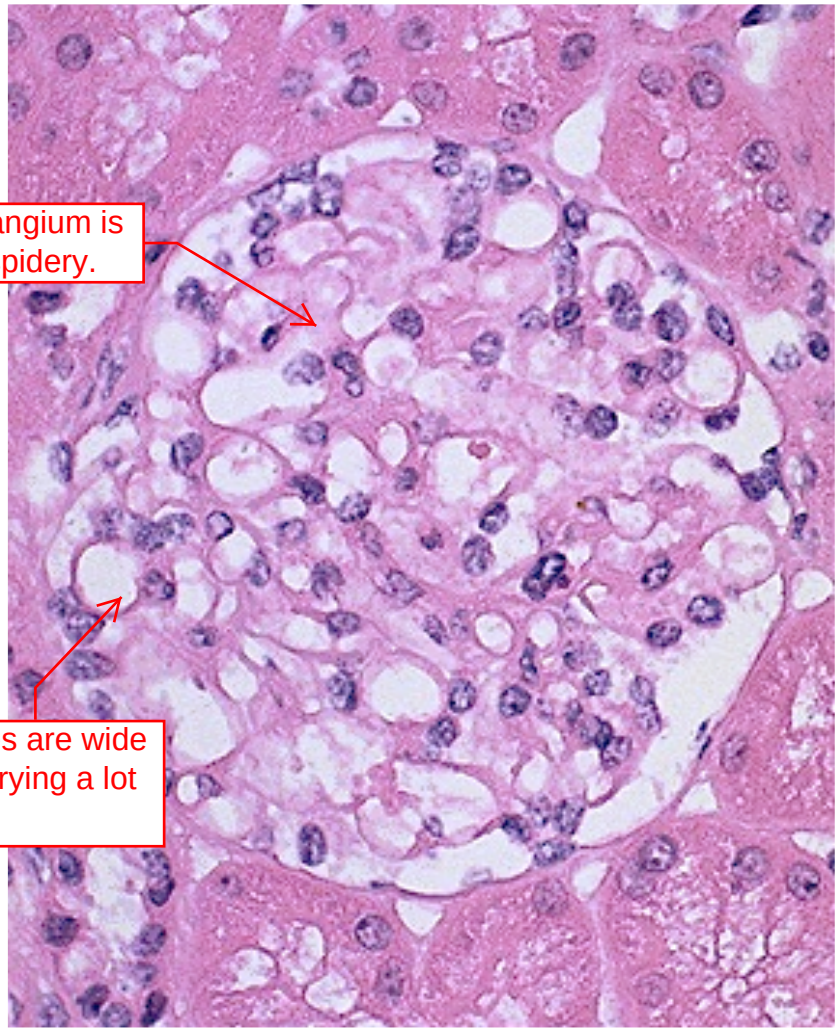
- Glomerulosclerosis
  - Nodular lesion ("Kimmelstiel-Wilson disease")
  - Diffuse mesangial expansion
  - Exudative lesions ("fibrin cap","capsular drop")
- Arterial damage
  - Hyalinosis of small arteries
  - Accelerated atherosclerosis
- Tubulointerstitial changes
  - Tubular dropout
  - Interstitial fibrosis
  - Papillary necrosis

Due to depositions within the mesangium

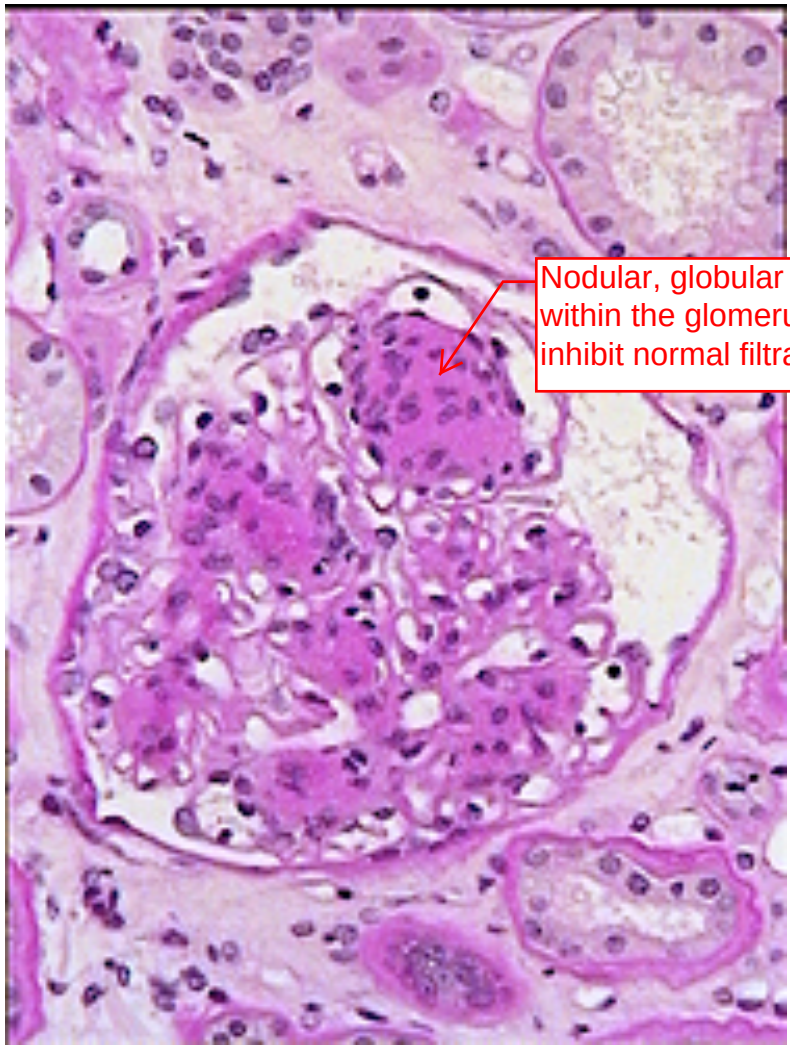
In diabetic neuropathy, the glomerular capillaries lose their integrity. Serum and fibrin leak from these capillaries and result in adhesions and fibrin accumulation between the glomerulus and Bowman's capsule.

These occur because of loss of blood supply to the tubuloglomerular unit.

39:01

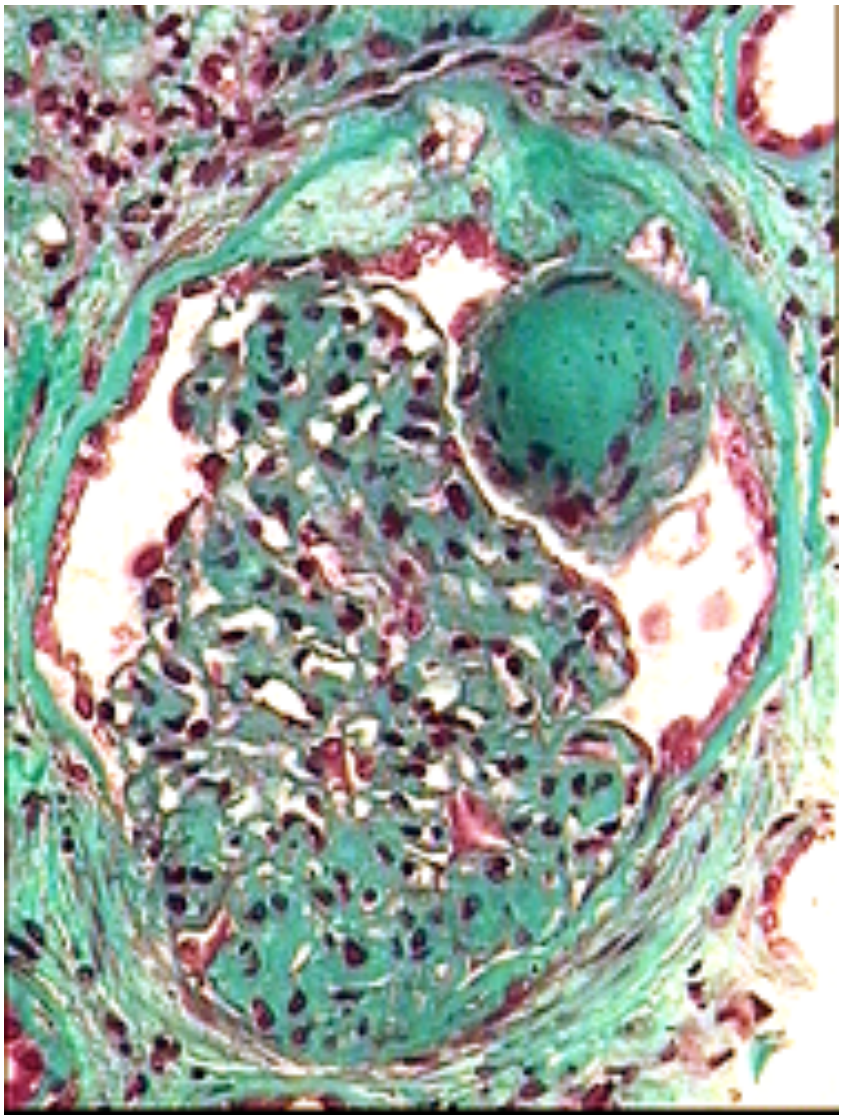


Normal

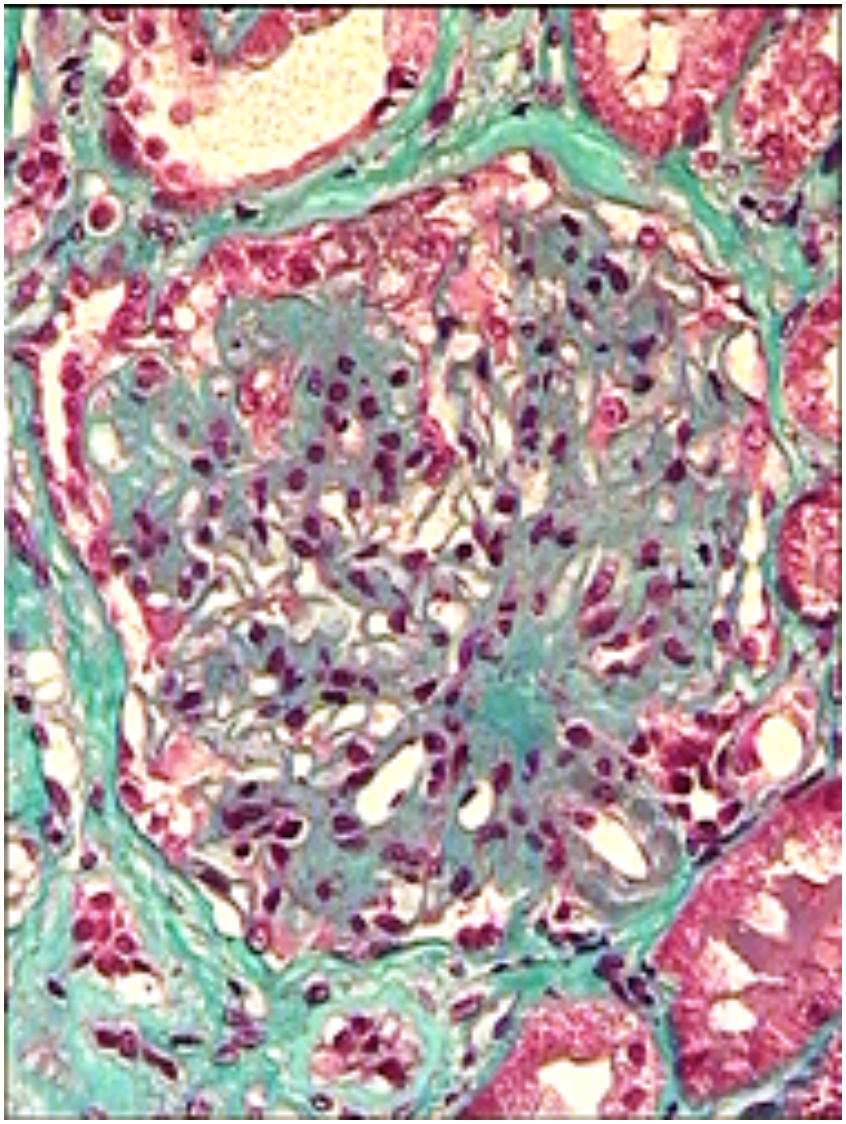


Nodular glomerulosclerosis

39:48



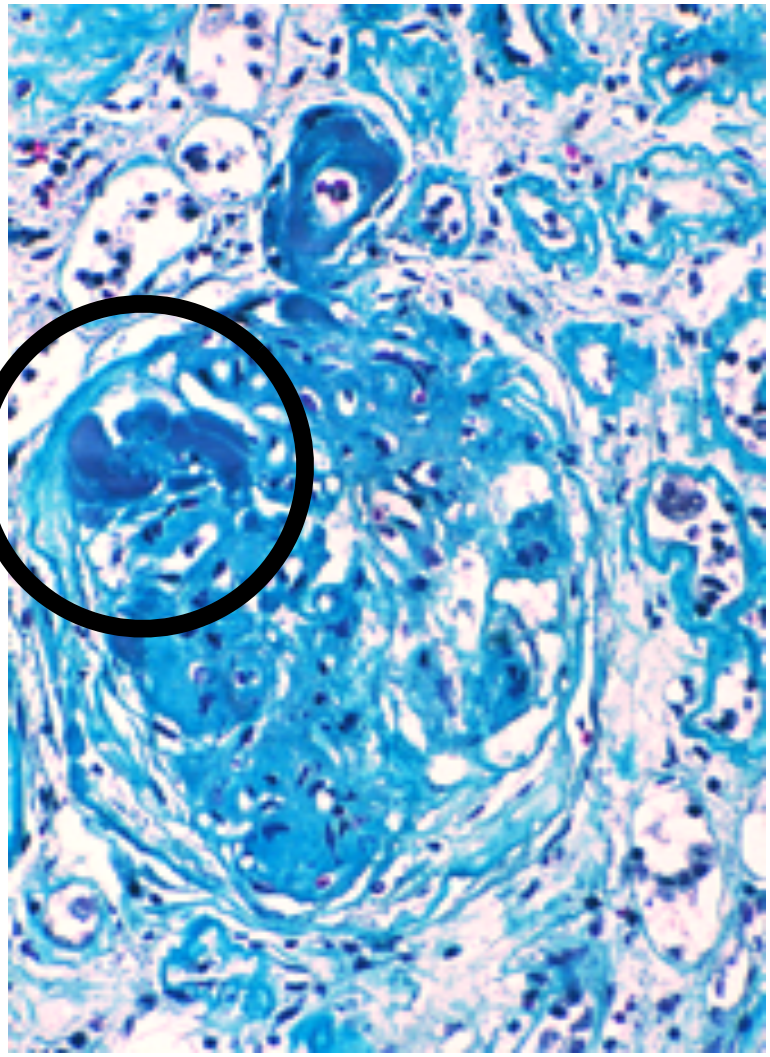
Nodule formation

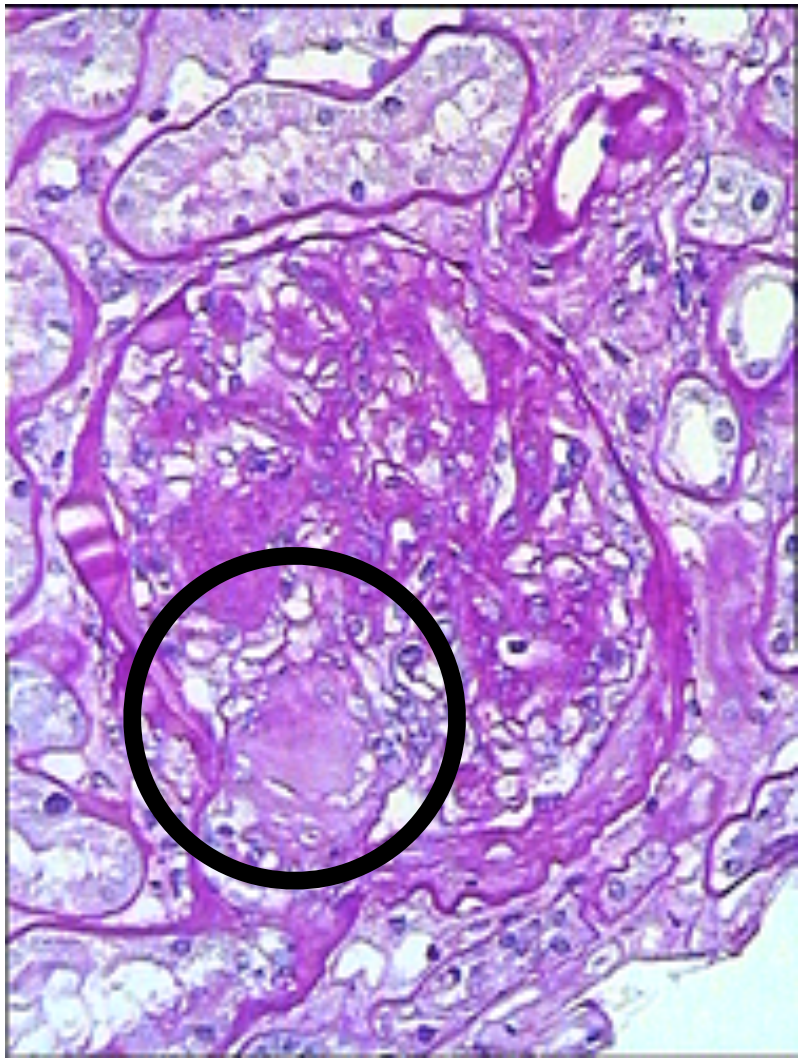


Diffuse mesangial expansion

This stain colors collagen green.
Collagen is seen in the nodular lesions and deposited diffusely throughout the mesangium.

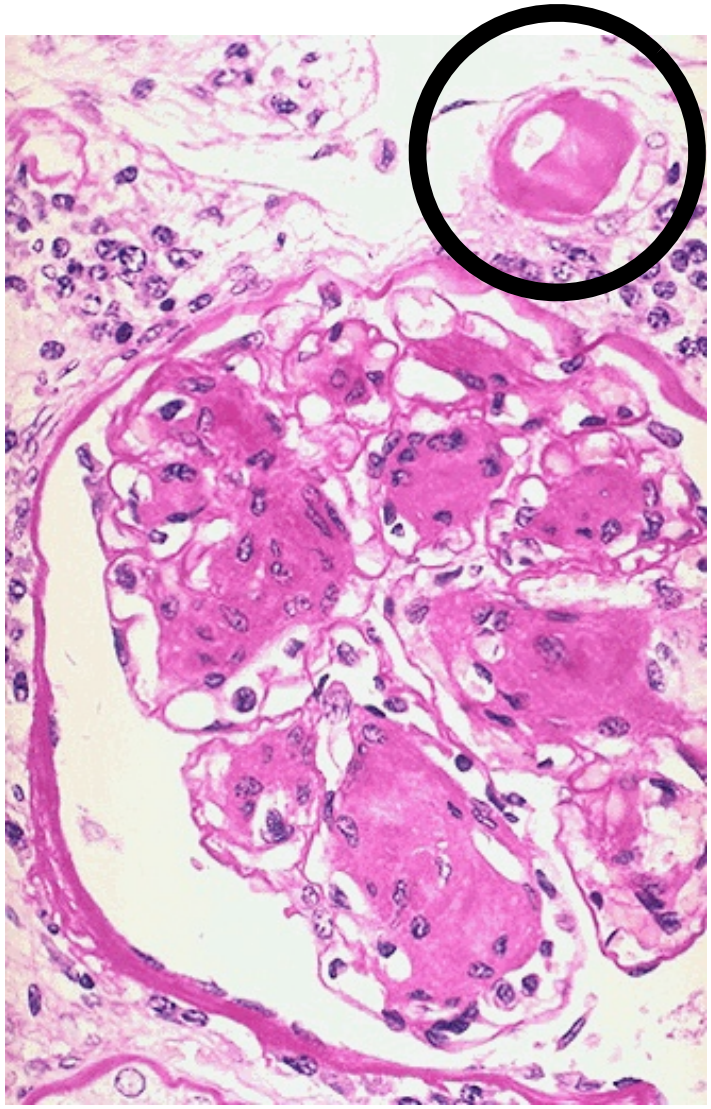
40:10

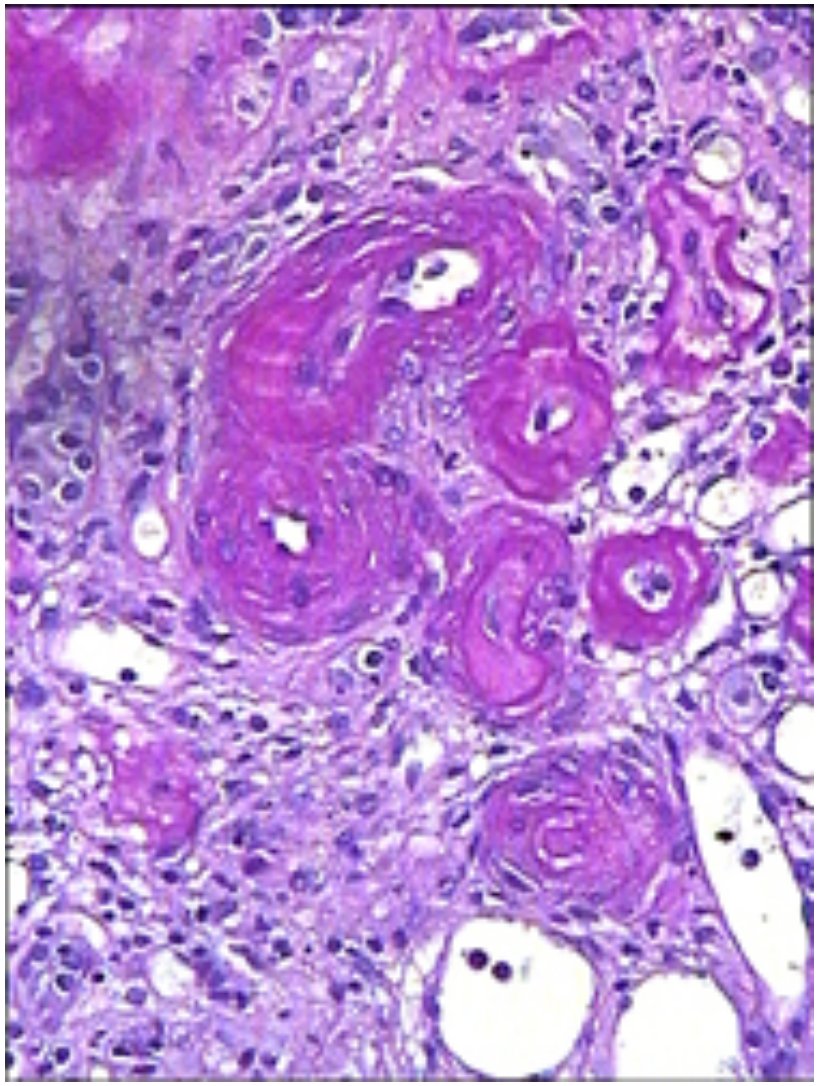




“Exudative Lesions”

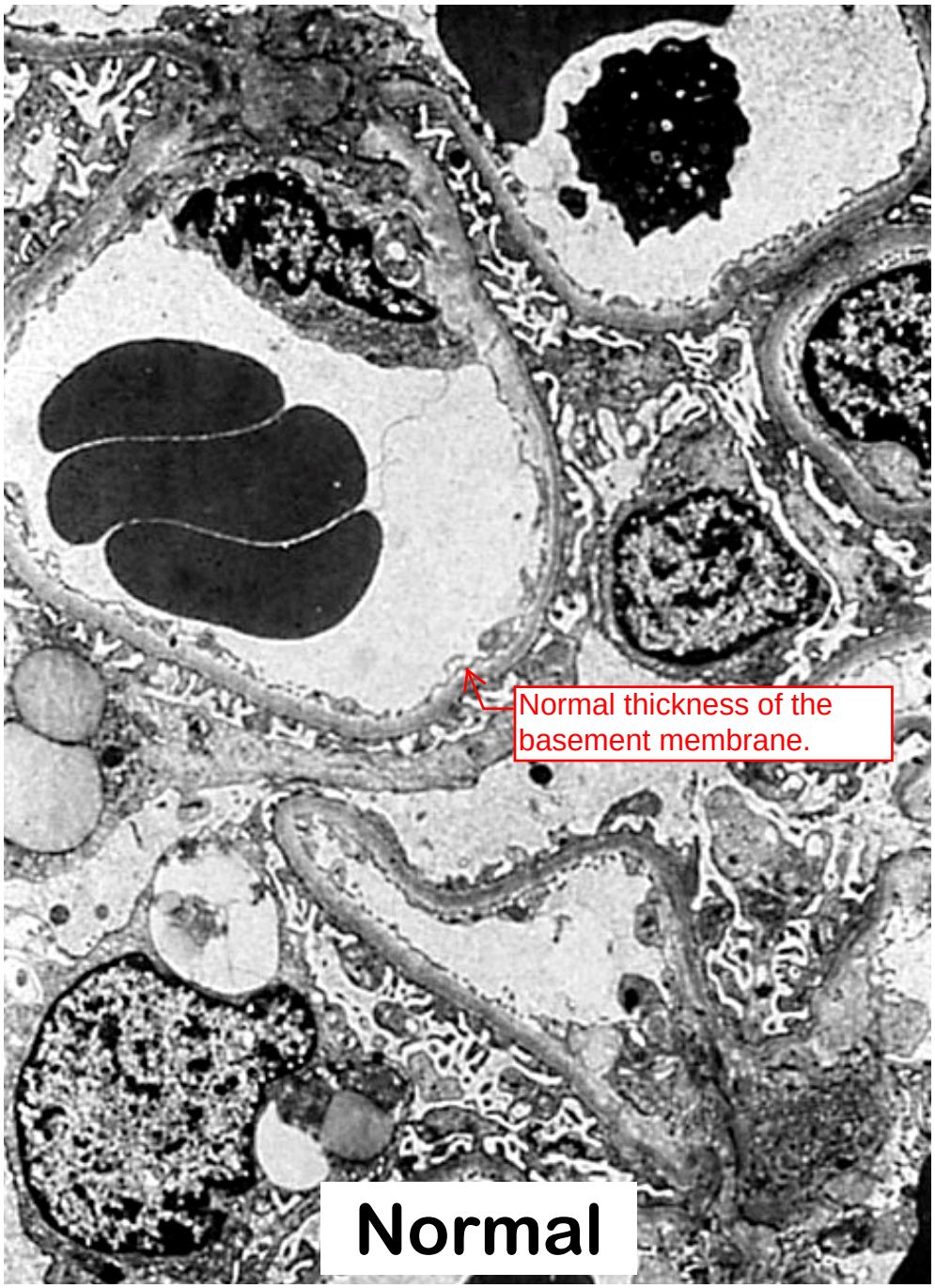
These other stains show the fibrin and serum material exuding from capillaries and depositing between the glomerulus and Bowman's capsule.

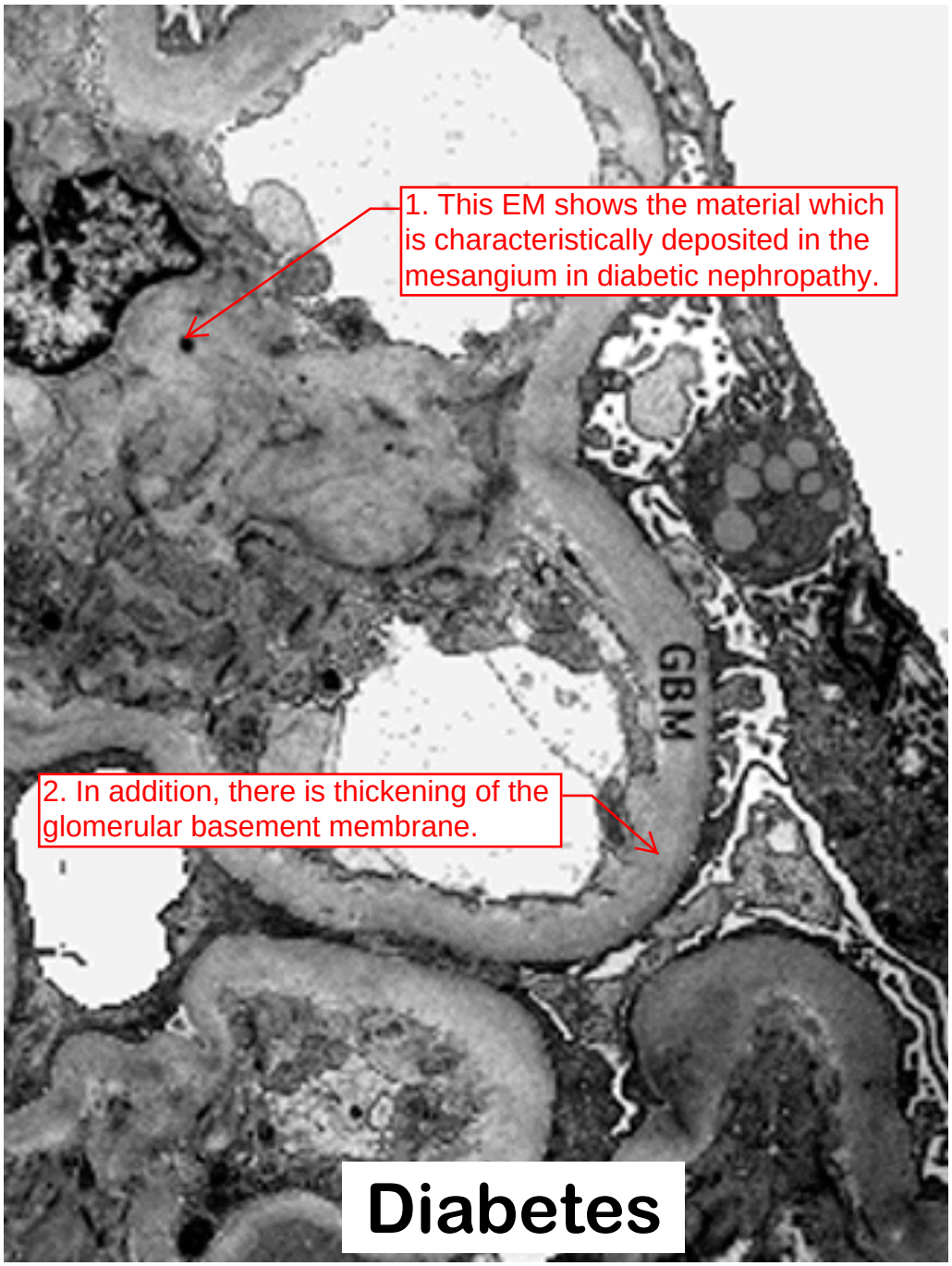




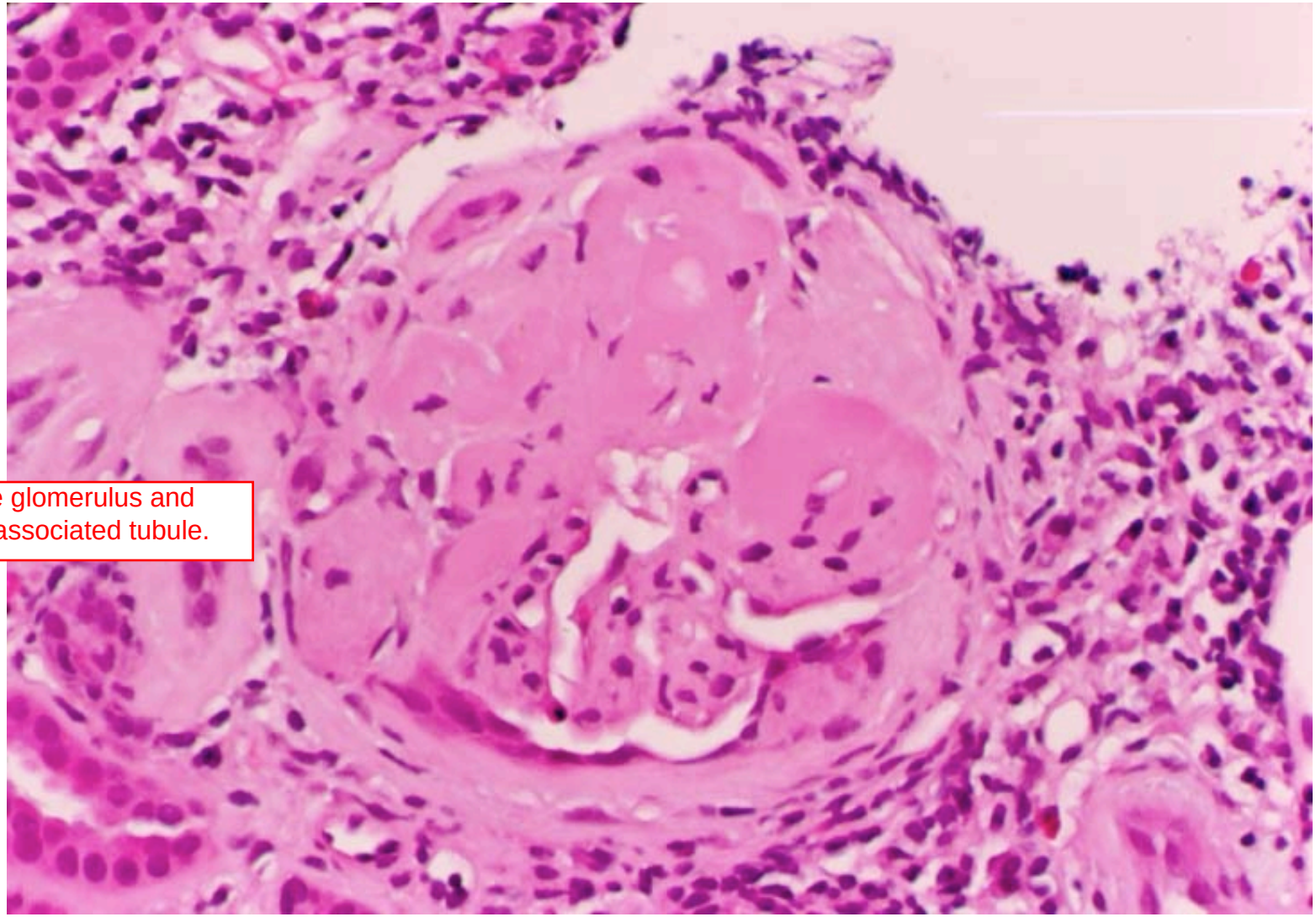
Hyaline arteriolosclerosis

40:42


Normal thickness of the basement membrane.
Normal


1. This EM shows the material which is characteristically deposited in the mesangium in diabetic nephropathy.
GBM
2. In addition, there is thickening of the glomerular basement membrane.
Diabetes

41:12



An end-stage glomerulus and death of the associated tubule.

End stage glomerulus

41:23

What is the stuff that's being deposited???
Quick answer: no one knows...

Pathogenesis of diabetic nephropathy

- Not comprehensively understood
  - Early changes relate to mesangial hypertrophy
  - Mesangial hyalinois, but chemical composition of deposits unclear
  - Late physiologic changes ← massive glomerular loss

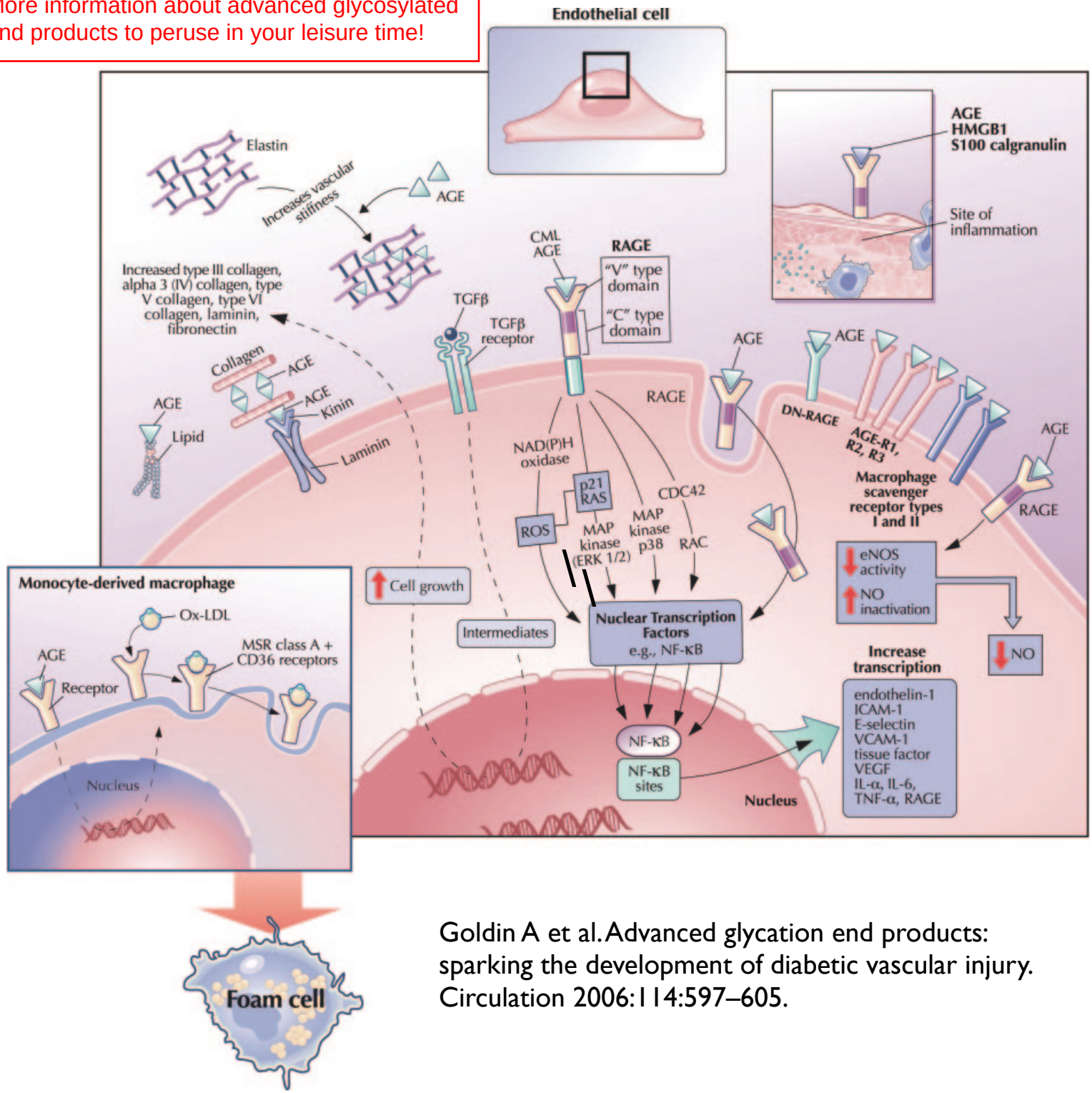
- Implicated factors:
  - Hyperfiltration → mechanical glomerular injury (glomerular microaneurysms)
  - Advanced glycosylation end products (AGE)
  - Cytokine pathway activation → mesangial hypersecretion
  - IGF-1, SPARC, other mediators

These are protein materials with arginines which have been spontaneously glycosylated, resulting in precipitation.

It is possible that the depositions result in secondary cytokine activation and subsequent fibrosis.

42:20

More information about advanced glycosylated end products to peruse in your leisure time!



Goldin A et al. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation 2006:114:597–605.

42:40

I. Selected non-neoplastic renal diseases
  A. Non-progressive acute renal injury
    1. Acute tubular necrosis
      a. Ischemic type
      b. Toxic type
    2. Acute interstitial nephritis
  B. Progressive to chronic renal failure (ESRD)
    1. Renovascular disease
      a. Diabetic nephropathy
      b. Hypertensive nephropathy
        i. Ordinary type
        ii. Malignant hypertension
    2. Renal cystic disease
      a. Adult polycystic kidney disease
      b. Dialysis-associated cystic disease
      c. Pediatric cystic diseases & others
II. Selected renal neoplasms (next lecture...)

This is the second most common cause of chronic renal failure.

43:00

Hypertension & the kidney

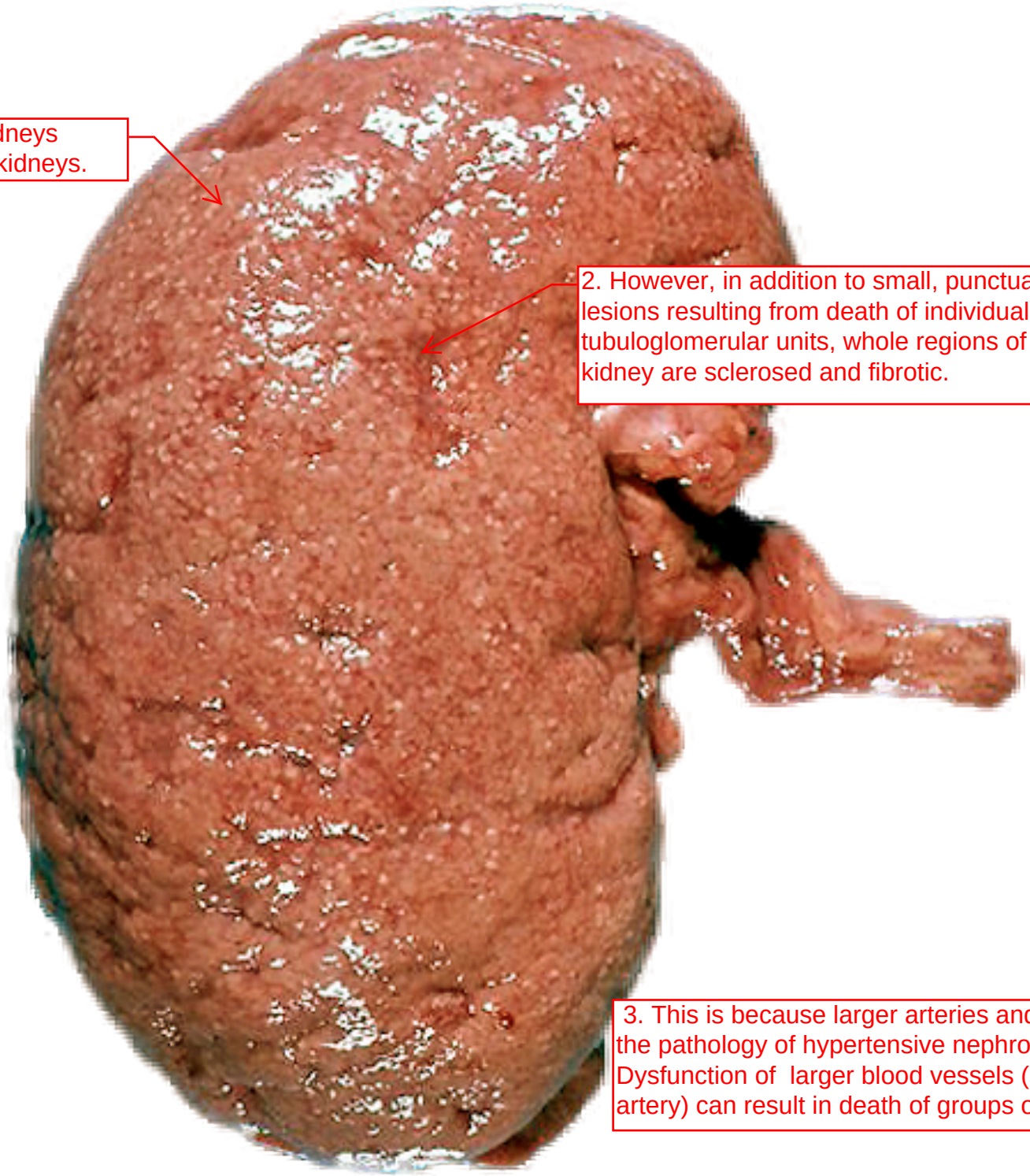
- Clinical: long-term (systolic) hypertension, retinopathy, LV hypertrophy, mild proteinuria, progressive renal insufficiency
- Risk factors: black race, diabetes, smoking, obesity, low HDL

Risk factors for hypertensive nephropathy tend to be the same as for hypertension in general.

- Reduction in blood pressure partially protective against development of hypertensive ESRD
- Remember: hypertension both *cause* and *effect* of renal disease

Hypertension is a cause of renal disease. However, once renal disease has been established, it can lead to further aggravation of hypertension, causing a downward spiral of disease.

43:48



1. Hypertensive kidneys resemble diabetic kidneys.

2. However, in addition to small, punctuate lesions resulting from death of individual tubuloglomerular units, whole regions of the kidney are sclerosed and fibrotic.

3. This is because larger arteries and arterioles are involved in the pathology of hypertensive nephropathy.
Dysfunction of larger blood vessels (such as an entire lobar artery) can result in death of groups of tubuloglomerular units.

44:38

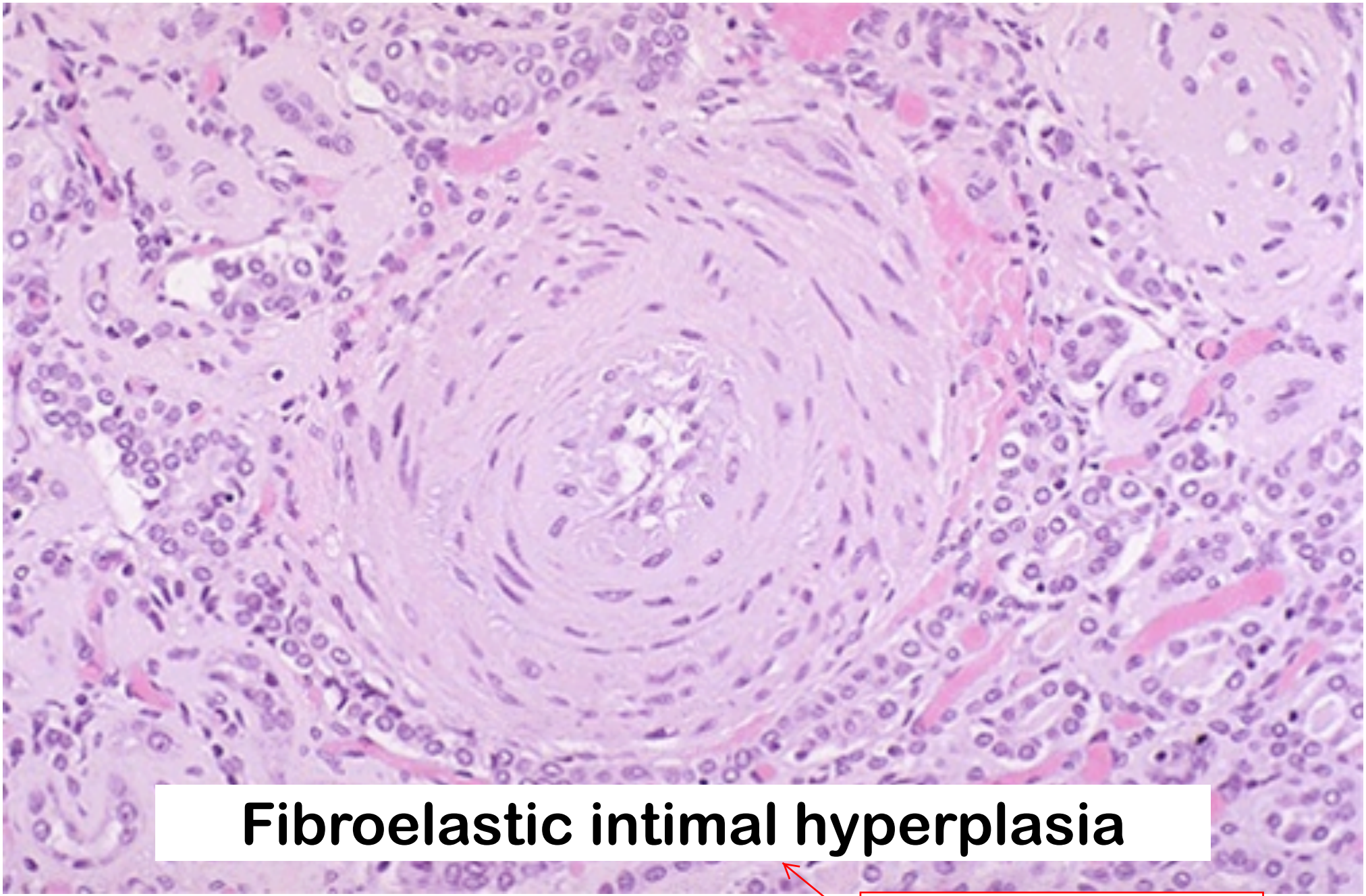
(Chronic) hypertensive nephrosclerosis

- Medial thickening and intimal fibrosis of medium-sized and larger arteries

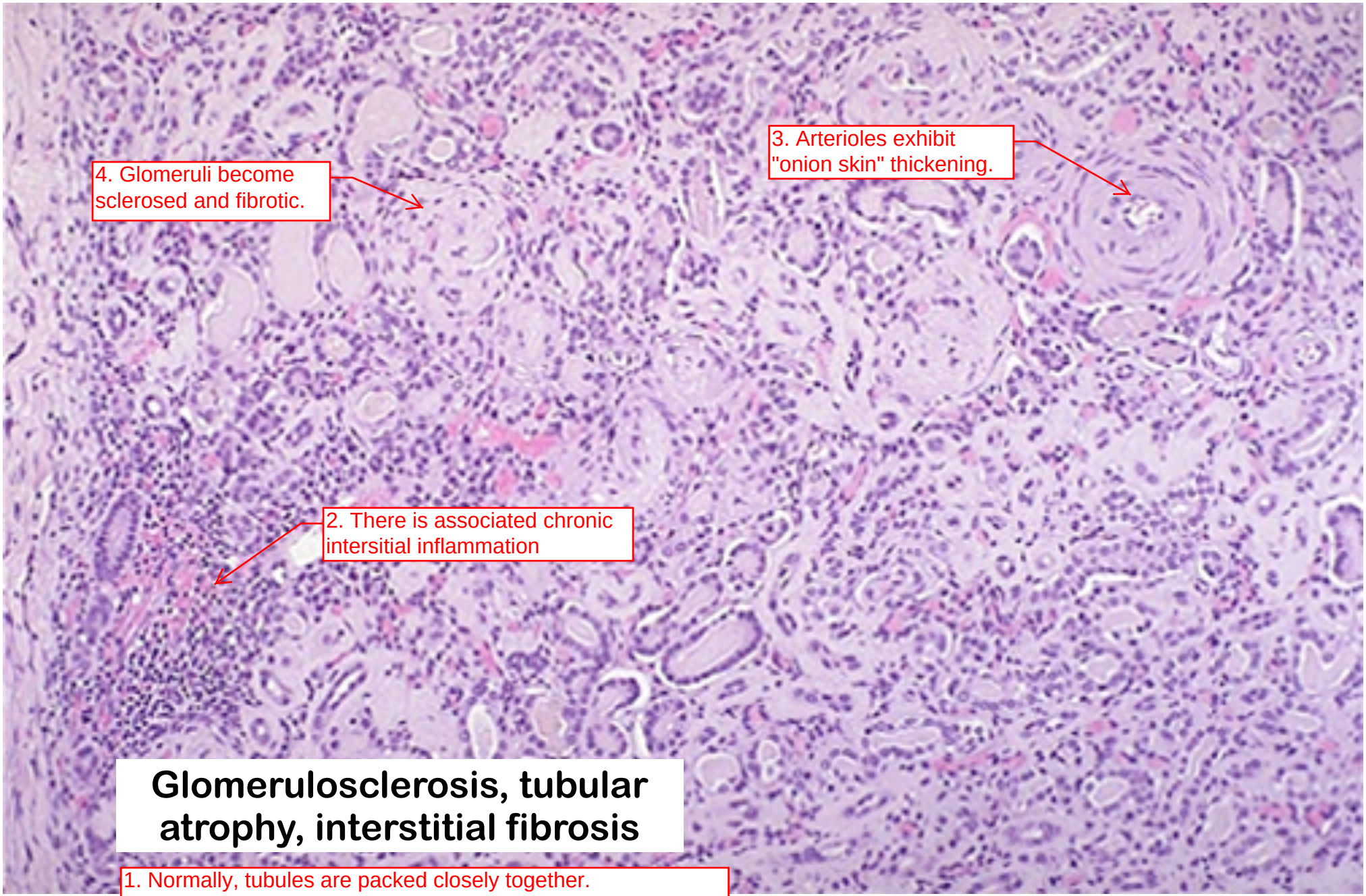
There is more medium and large-sized artery disease in hypertensive nephropathy than is typically seen in diabetic nephropathy.

- Arteriolar thickening and hyalinosis
- Global glomerulosclerosis
- Tubulointerstitial fibrosis

45:02

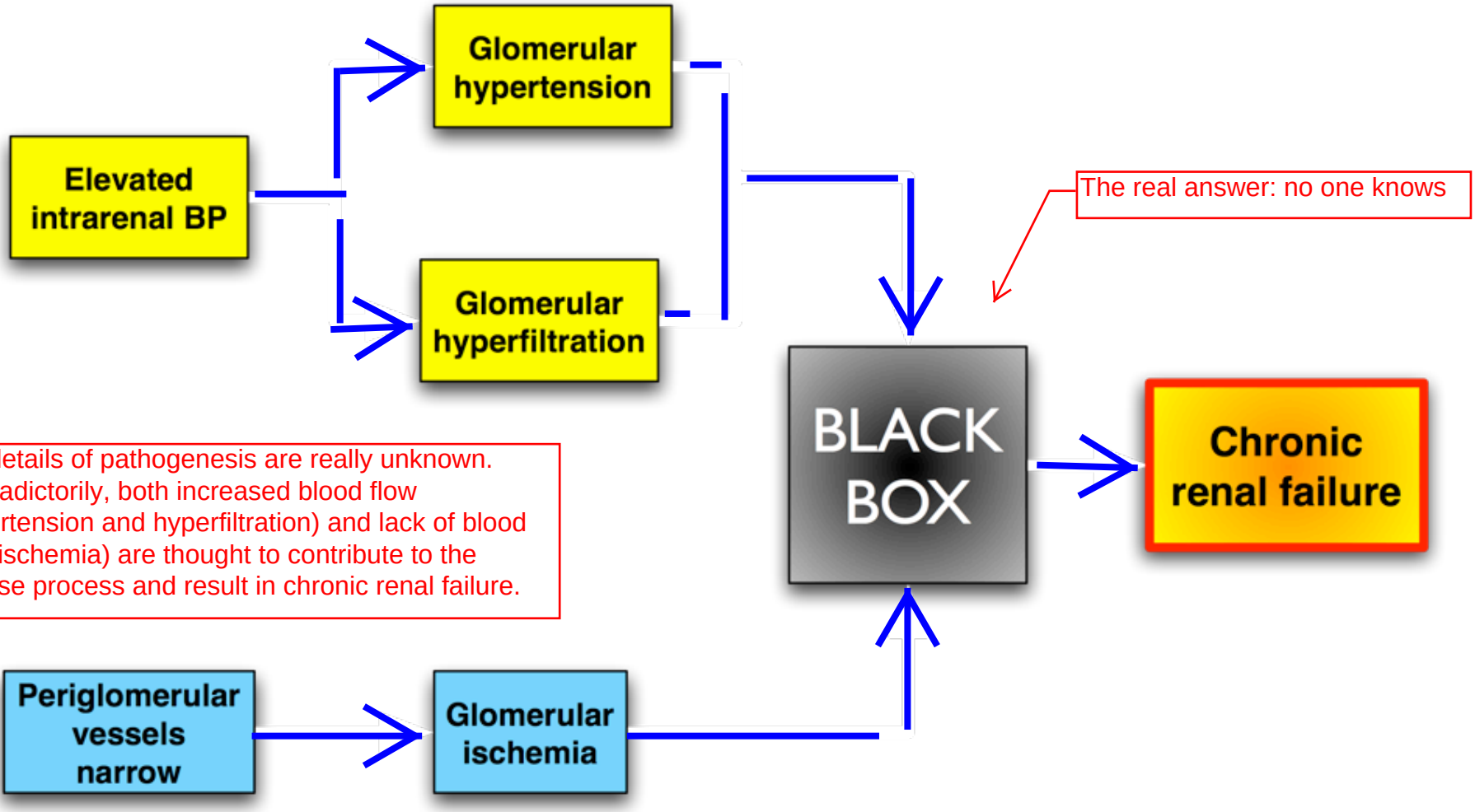

Fibroelastic intimal hyperplasia
Due to severe hypertensive nephropathy

45:18


4. Glomeruli become sclerosed and fibrotic.
3. Arterioles exhibit "onion skin" thickening.
2. There is associated chronic intersitial inflammation
Glomerulosclerosis, tubular atrophy, interstitial fibrosis
1. Normally, tubules are packed closely together.
This shows expansion of the intersitum and loss of tubules.

46:03

Pathogenesis



The real answer: no one knows

The details of pathogenesis are really unknown. Contradictorily, both increased blood flow (hypertension and hyperfiltration) and lack of blood flow (ischemia) are thought to contribute to the disease process and result in chronic renal failure.

47: 07

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        i. Ordinary type
        ii. Malignant hypertension
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      a. Adult polycystic kidney disease
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      c. Pediatric cystic diseases & others
II. Selected renal neoplasms (next lecture...)

Acute hypertensive nephropathy ("Malignant hypertension")

- Acute onset of SBP>160 with acute end-organ damage
- About 1% of essential hypertension
- Most common in young-middle aged males, black > white
- Untreated (historical) 1-year survival 25%
- Modern 1-year survival >90%

This may occur with background pre-existing essential hypertension or in patients without any history of hypertension.

48:10

Pathology of "malignant hypertension" (I)

With a very sudden increase in pressure, arterioles become functionally incompetent and die.

- Arteriolar damage
  - Fibrinoid necrosis
  - Proliferative endarteritis
    - "Onionskin" myointimal proliferation → Musculomucoid intimal hyperplasia → Obliterative fibrous endarteritis
  - "Sausuge-string" arteriolar ectasias

Definition: Dilation, distention, or expansion of the arterioles.
He describes these as "blow-outs" of arterioles.

Pathology of "malignant hypertension" (II)

- Secondary to arteriolar damage:
  - Nephropathy
  - Retinopathy
  - Encephalopathy
  - Other
    - Microangiopathic hemolytic anemia
    - Disseminated intravascular coagulation
    - Cardiac left ventricular ischemic dysfunction
    - GI hemorrhage, infarction
    - Ischemic pancreatitis

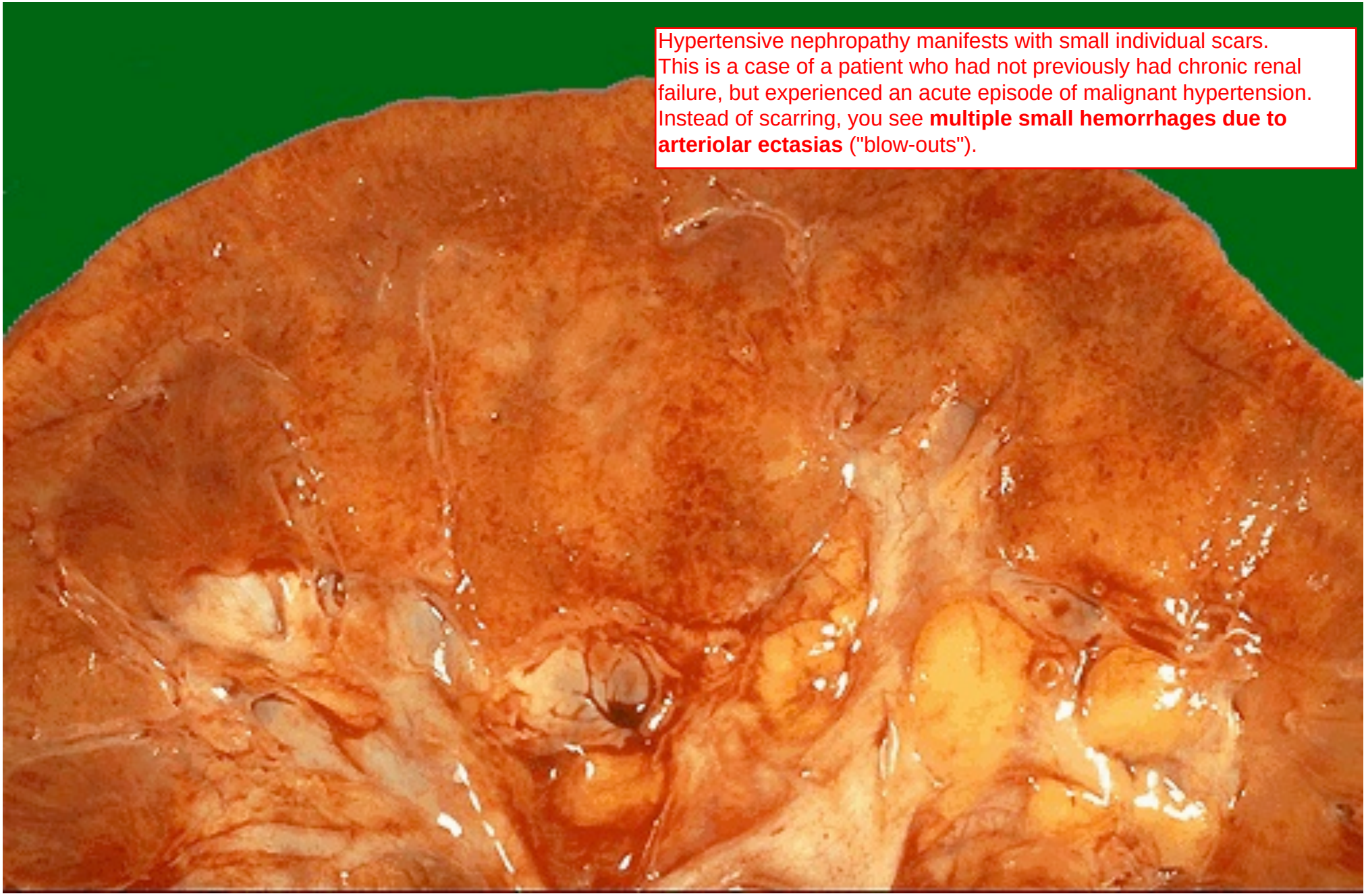
These patients also develop disease of other organs that are supplied by many small arterioles, such as the retina and the brain.

Pathology of "malignant hypertension" (III)

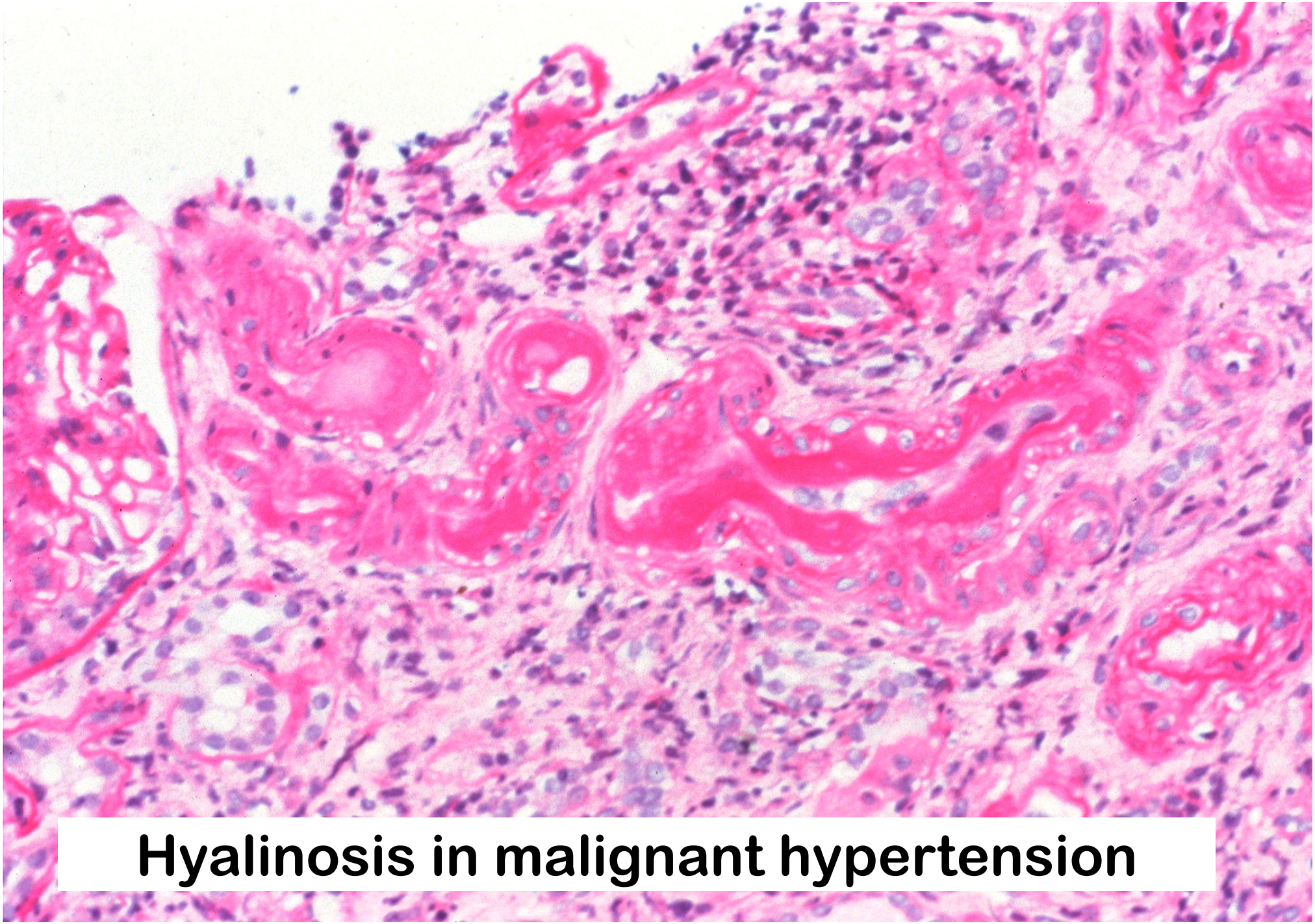
Even more disastrous effects of sudden severe hypertension:

- Mechanical effects:
  - Aortic dissection
  - Congestive heart failure
  - Pulmonary edema
  - Hemorrhagic stroke

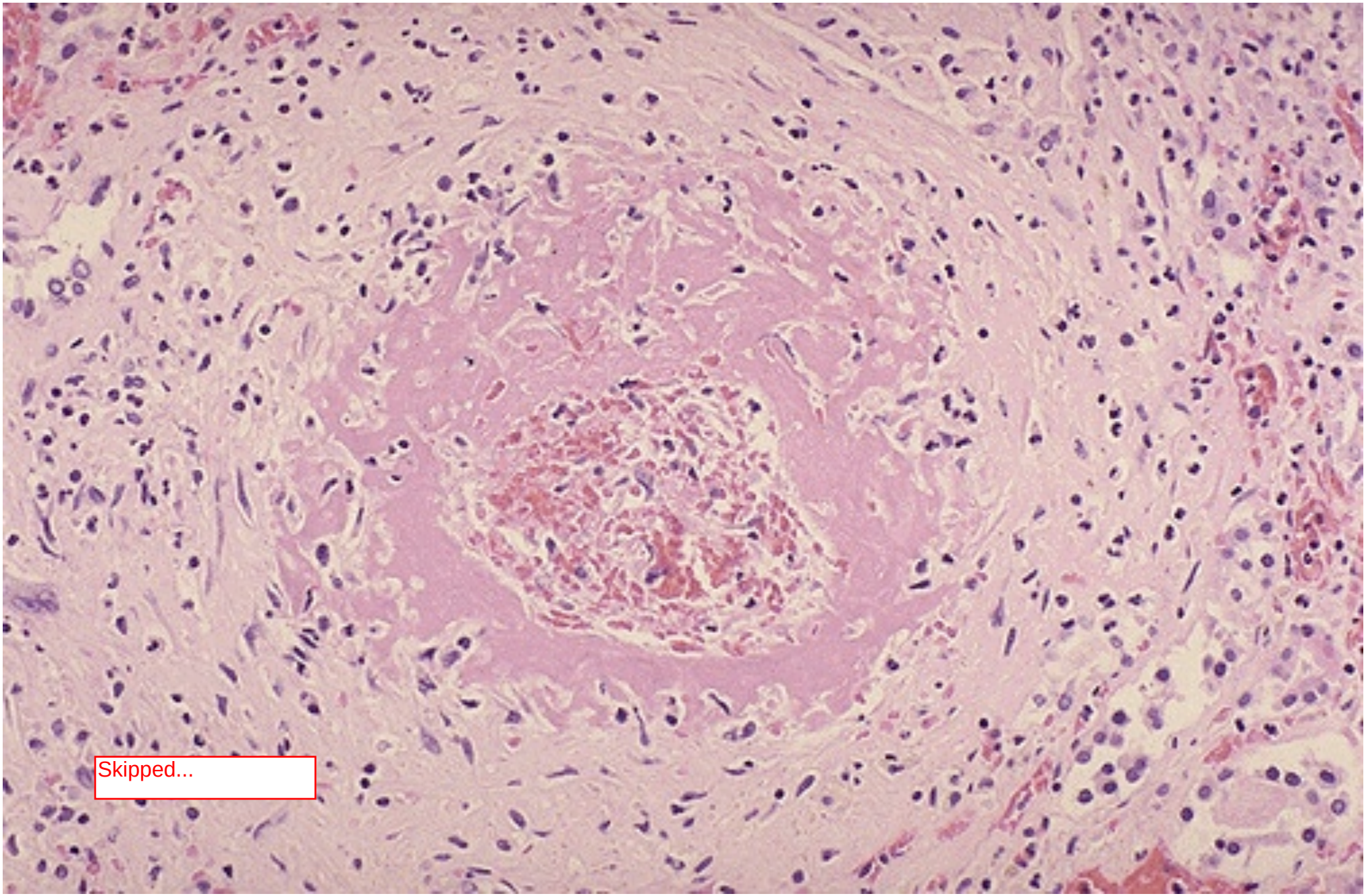
49:18



Hypertensive nephropathy manifests with small individual scars.
This is a case of a patient who had not previously had chronic renal failure, but experienced an acute episode of malignant hypertension.
Instead of scarring, you see **multiple small hemorrhages due to arteriolar ectasias** ("blow-outs").



Hyalinosis in malignant hypertension



Skipped...

49:59

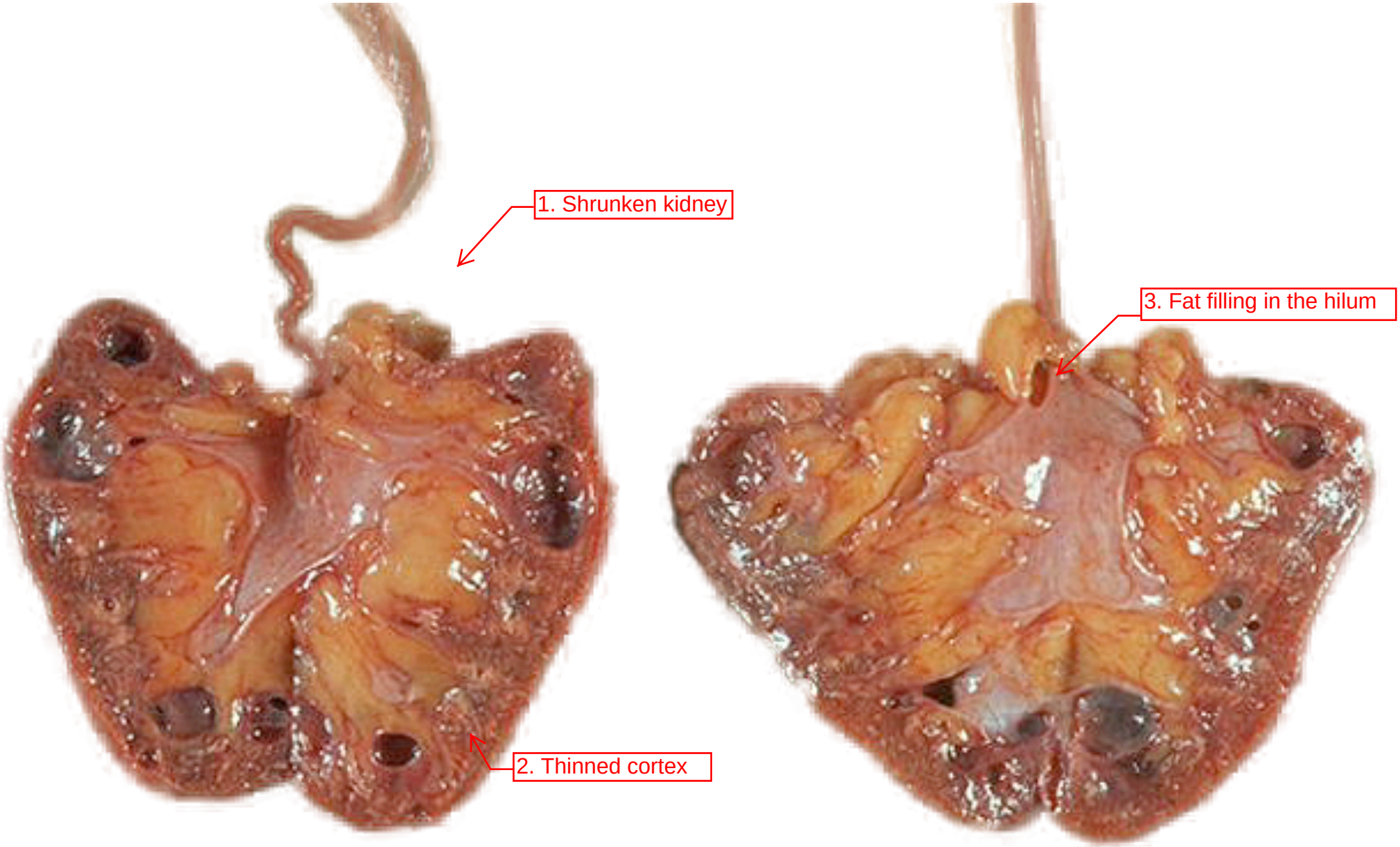
“End-stage kidney”

- End result of massive loss of glomerulotubular units, from whatever cause

Diabetes, hypertension, malignant hypertension, etc.

- Shrunken kidney, thinned cortex
- Fat fills in missing space in hilum
- Cystic change

50:18


1. Shrunken kidney
2. Thinned cortex
3. Fat filling in the hilum

50:45

I. Selected non-neoplastic renal diseases
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    2. Renal cystic disease
      a. Adult polycystic kidney disease
      b. Dialysis-associated cystic disease
      c. Pediatric cystic diseases & others
II. Selected renal neoplasms (next lecture...)

He didn't have time to finish this lecture. Stay tuned for more fun with kidneys on Thursday!

0:00

I. Selected non-neoplastic renal diseases
  A. Non-progressive acute renal injury
    1. Acute tubular necrosis
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II. Selected renal neoplasms (next lecture...)

this lecture will finish the topic of non-neoplastic renal disease (number 2 on the left) and discuss renal neoplasias

0:58

Cystic kidney disease

Includes a variety of diseases that do not have common etiologies or pathogenesis. The only thing in common is that the kidney ended up with several cysts on it.

- U.S. prevalence about 600,000 cases
- Fourth-leading cause of ESRD
- About 90% of cases are adult (autosomal dominant) polycystic kidney disease

Cystic kidney disease includes several diseases. What they have in common is the fact the kidney ended up with several cysts on it. The most important one is polycystic kidney disease that accounts for 90% of cases in adults.

1:35

Cystic kidney diseases

Mechanism	Age at presentation: Infant/child	Age at presentation: Adult
Hereditary	**Infantile PCKD** Juvenile nephronophthisis Glomerulocystic kidney	**Adult PCKD** VHL/TS Medullary sponge Glomerulocystic
Non-hereditary (developmental or acquired)	**Multicystic dysplastic kidney**	**Dialysis-associated cystic disease**

The more than dozen type of cystic diseases could be divided by their mechanism (hereditary and non-hereditary) and by their age of presentation: infant/child and adult). He will focus on adult polycystic disease (PCKD), which is a hereditary and adult target disease. The other ones in the same box (VHL//TS, medullary sponge,etc he will not talk about). He also did not talked about the other ones as well.

skipped

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II. Selected renal neoplasms (next lecture...)

2:32

He read every single bullet!

Adult polycystic kidney disease

APKD

- Hereditary basis
  - Frequency ~1:750
  - "Most common genetic disease"
  - Autosomal dominant ("ADult")
  - 25% no family Hx←new mutation
- Presents in adulthood
  - Widely variable expressivity ← some people will express it when they are in their 20's some people will not express until they are in their 70-80's
  - 100% penetrance by age 80
  - Most present in 30's to 40's

APKD is the most common genetic disease. It is Autosomal Dominant (ADult) and 1/4 of the people who develop have no family history. The disease has a variable expressivity and it is most present in 30's to 40'.

APKD: Clinical

- Symptoms
  - Flank pain, acute or chronic
  - Hematuria
  - Infection

Pain usually due to super infection of the cyst

it could be gross or microscopically

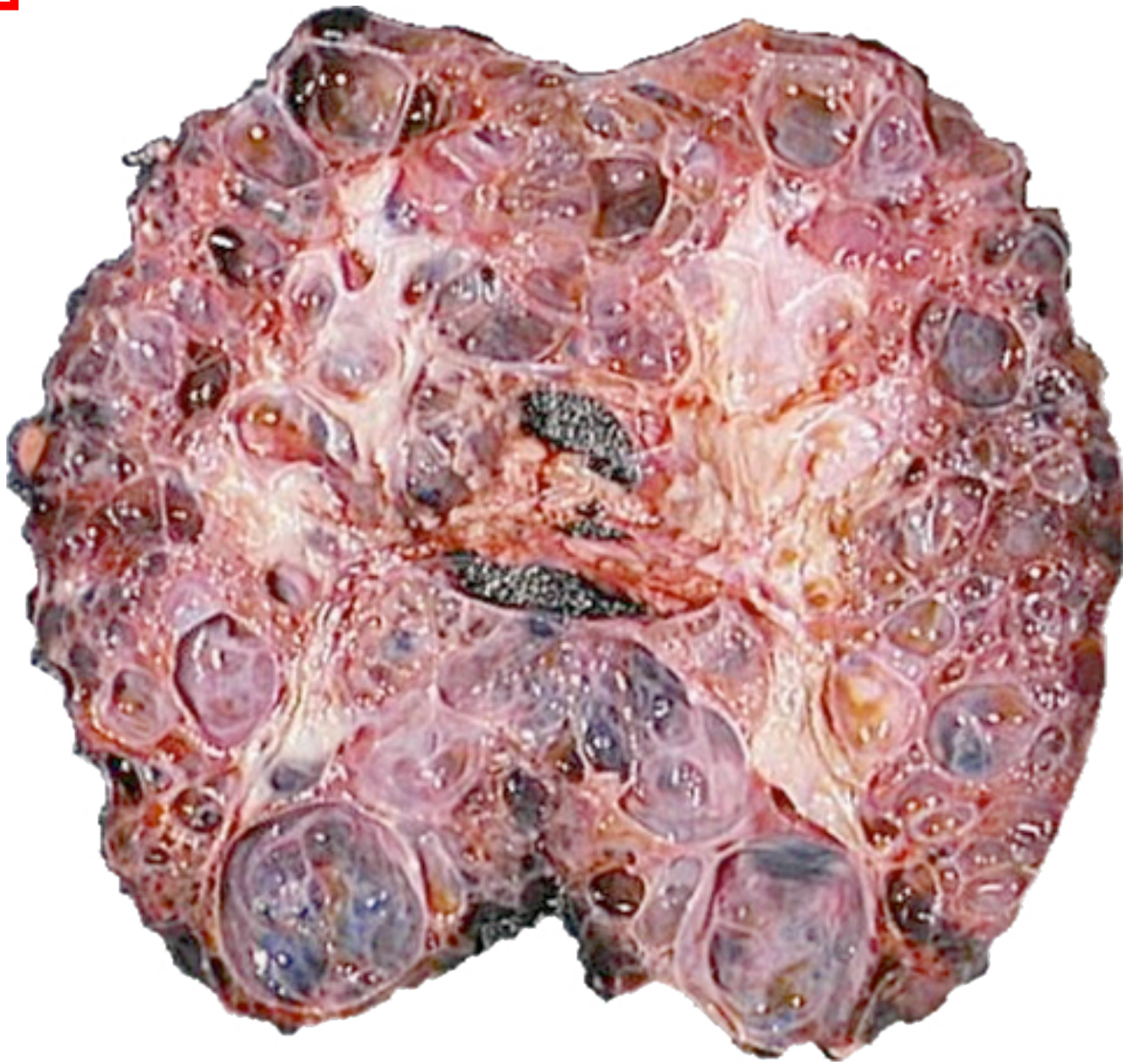
also kidney can become really enlarged

- Complications
  - Hypertension (10%)
  - Nephrolithiasis (10%)
  - Perinephric abscess
  - Renal cell carcinoma (up to 5%)

again because of the cysts they can get nephrolithiasis = kidney stones

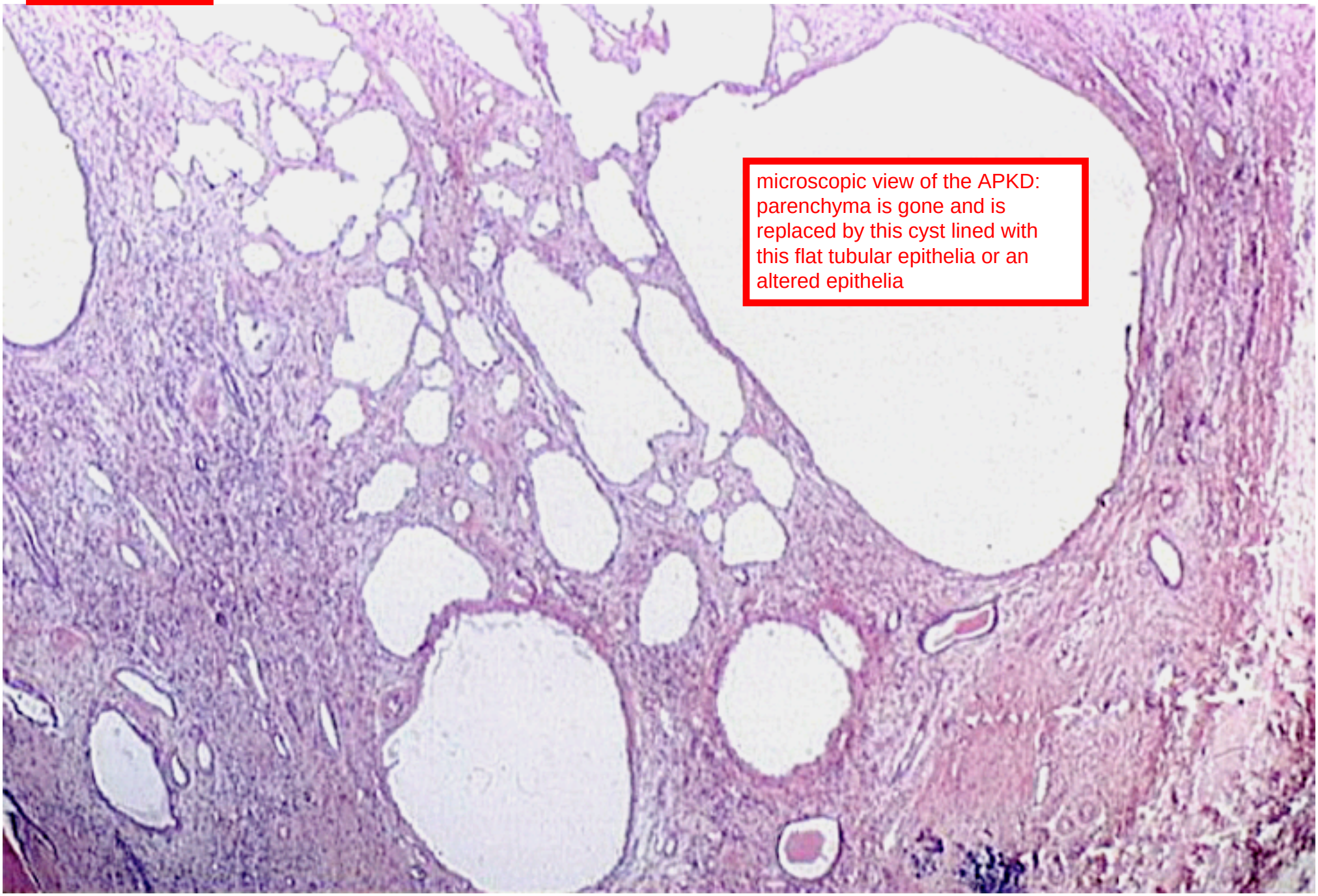
Symptoms of APKD includes pain (associated with infection), and blood in urine (hematuria). Complications involve hypertension (10%), kidney stones and an increase **risk** to develop renal cell carcinoma (up to 5%).

4:47



This is an example of APKD. Usually the kidney is removed when is causing symtomatology or some evidence it can have developed into a renal cell carcinoma. These kidney can get really large.

5:46


microscopic view of the APKD: parenchyma is gone and is replaced by this cyst lined with this flat tubular epithelia or an altered epithelia

6:05

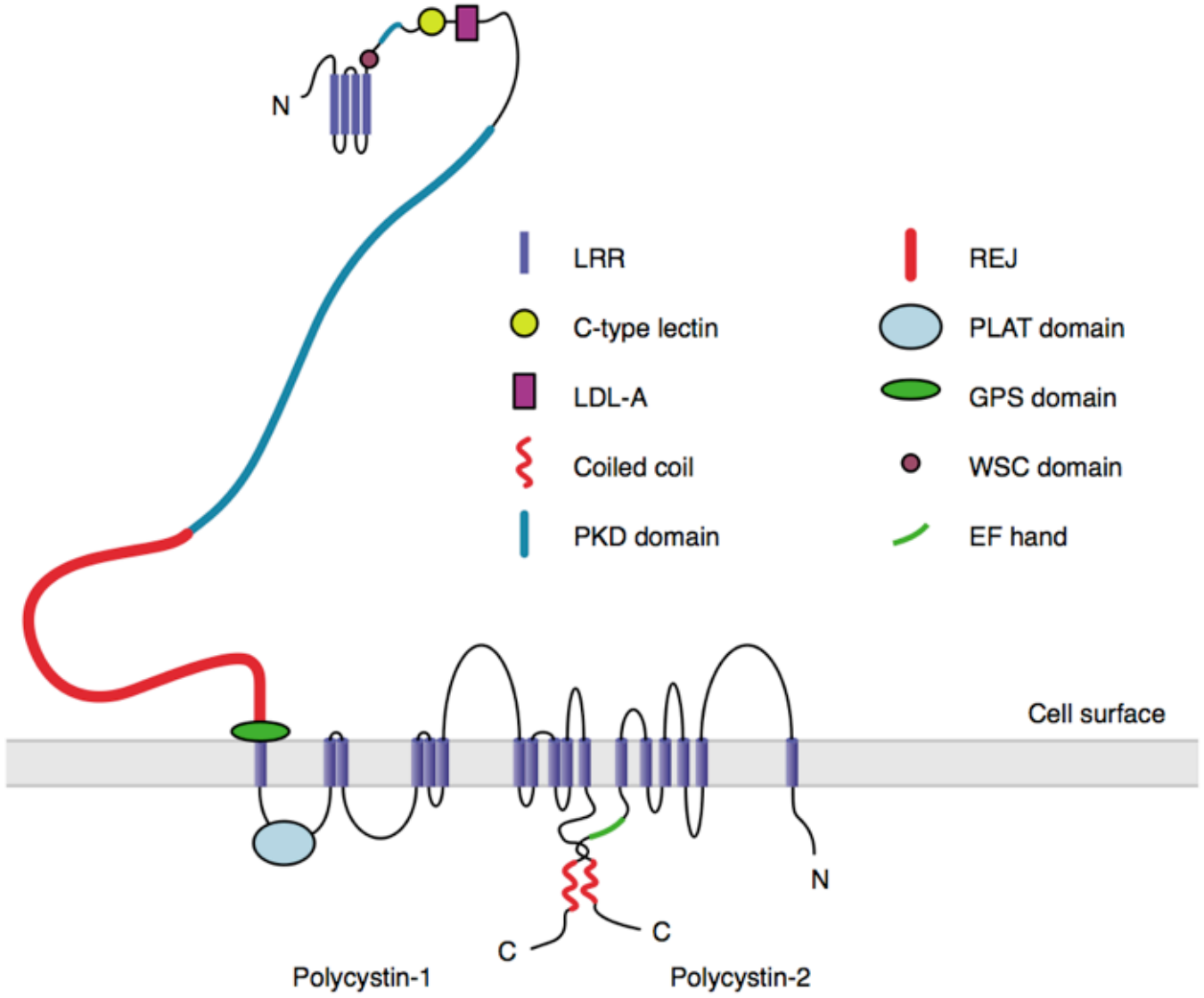
APKD: Molecular basis

- ***PKD1*** (16p13.3) → polycystin 1
  - 4302 AA transmembrane protein
  - Protein binding and ion channel regulatory domains
  - Mutation in 90% of cases
- ***PKD2*** (4q21) → polycystin 2
  - 968 AA transmembrane protein
  - Ca^{2+}-permeable nonselective cation channel
  - Mutation in remaining 10%

Molecular basis really well know. He talked very briefly about the polycystins. Here he just said that these polycystins could be an ion channel, calcium ion channels, or regulatory proteins and then (obviously) are expressed in the kidney

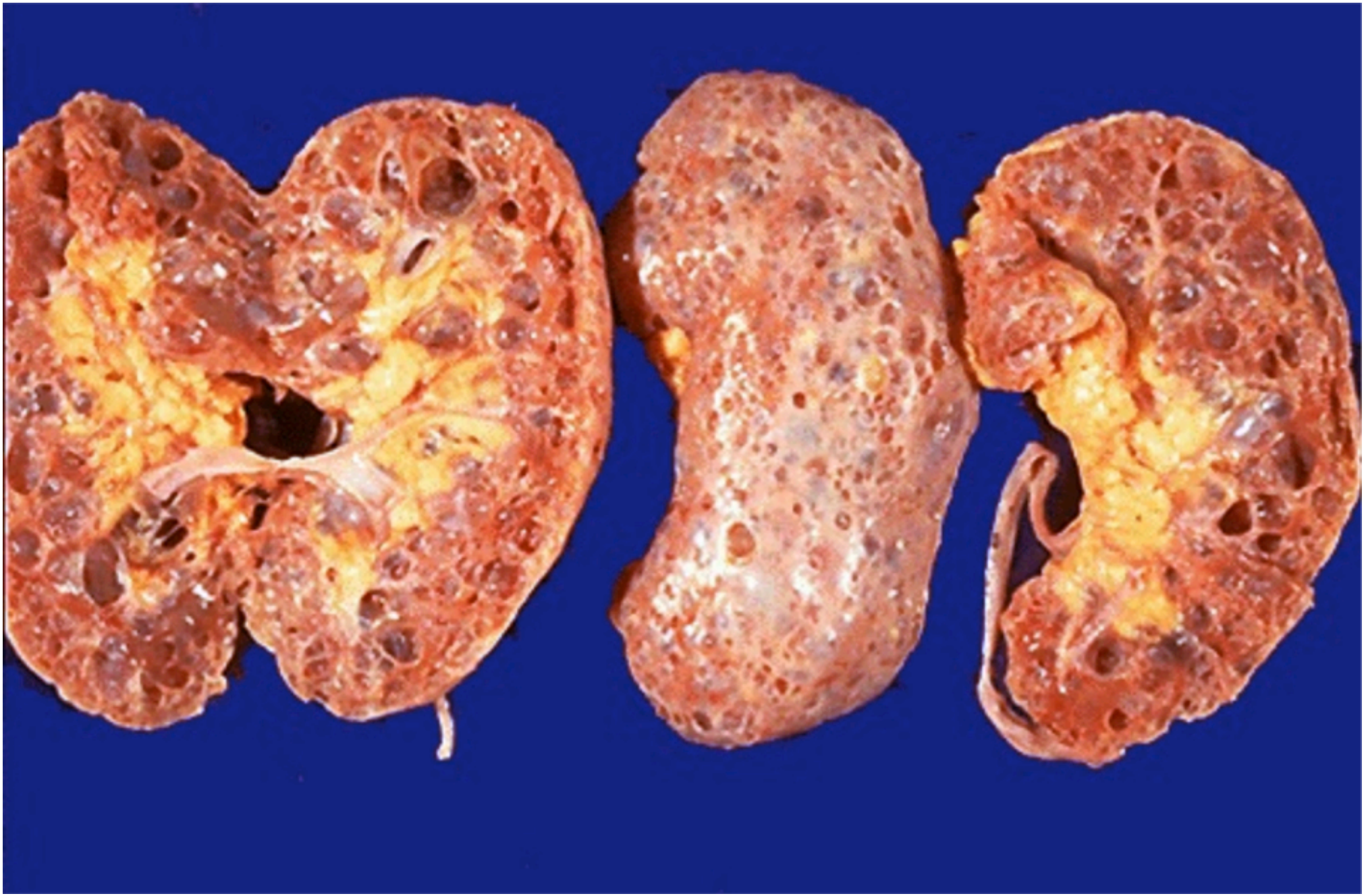
6:38

Domain structure of polycystins



Just showing the structure of the polycystins that he believed was obtained from sequence rather than from crystallization studies. This is a ion channel, when things go wrong with these polycystins we develop APKD. If you have forgotten already what APKD stands for = ADULT POLYCYSTIC KIDNEY DISEASE :)

7:09 - APKD !



7:22

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      c. Pediatric cystic diseases & others
II. Selected renal neoplasms (next lecture...)

people who undergo dialysis can develop cystic disease as well.

7:40 - READ!

Acquired cystic renal disease

- Chronically non-functioning kidneys in dialysis patients
- Undergo cystic transformation after many years
- Increased risk of renal cell carcinoma

People in dialysis for many years can also develop cystic renal disease and they are also at increased risk of renal cell carcinoma

skipped!

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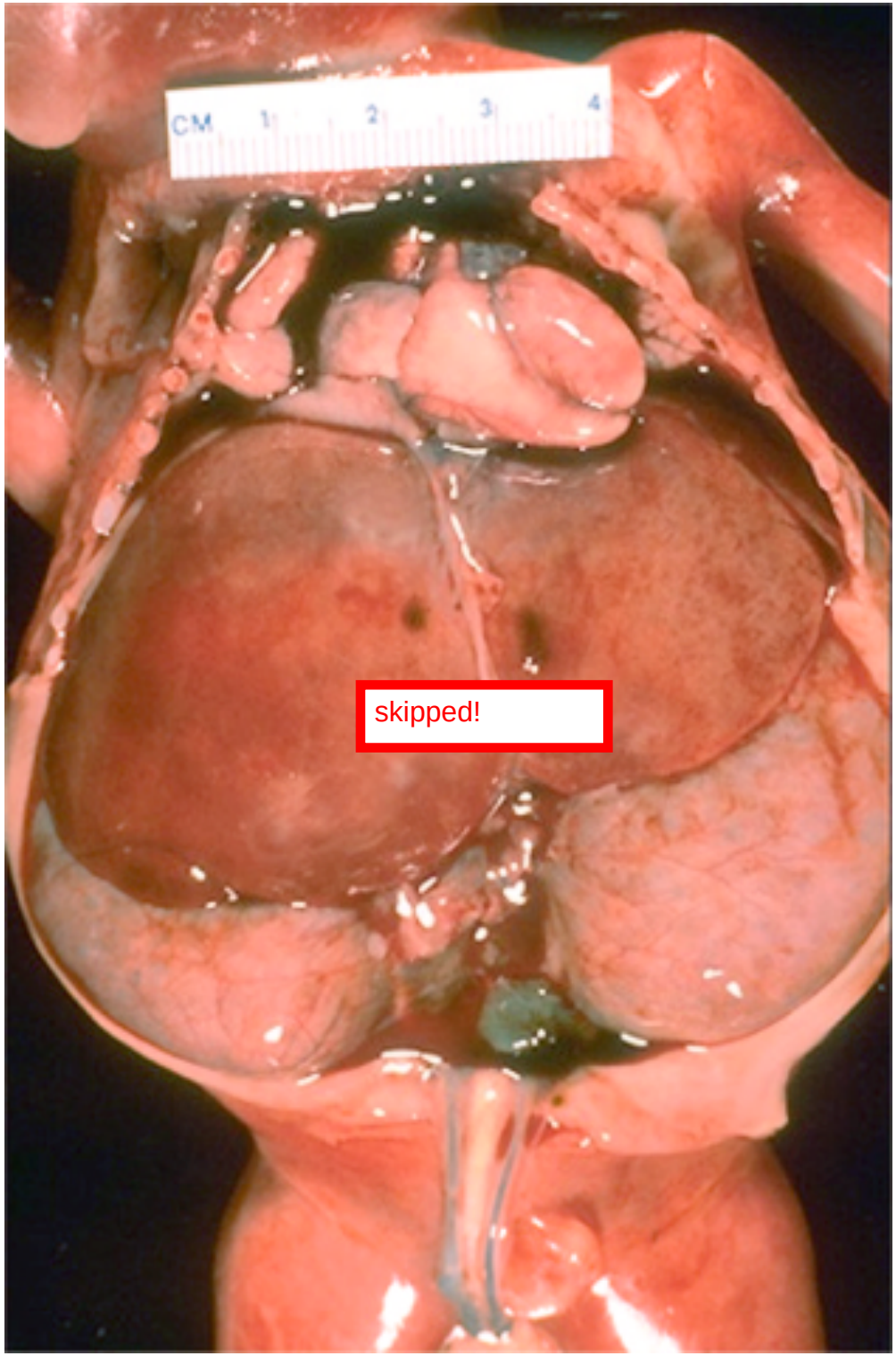
II. Selected renal neoplasms (next lecture...)

skipped!

Infantile polycystic kidney disease

- Autosomal recessive
  - PKHD1 located at 6p21
  - 1 in 20,000 pregnancies
- Multiorgan manifestations
  - Bilateral renal cysts
  - Liver cysts
  - Pulmonary hypoplasia (2°)
- Most die in utero or early infancy


CM
1
2
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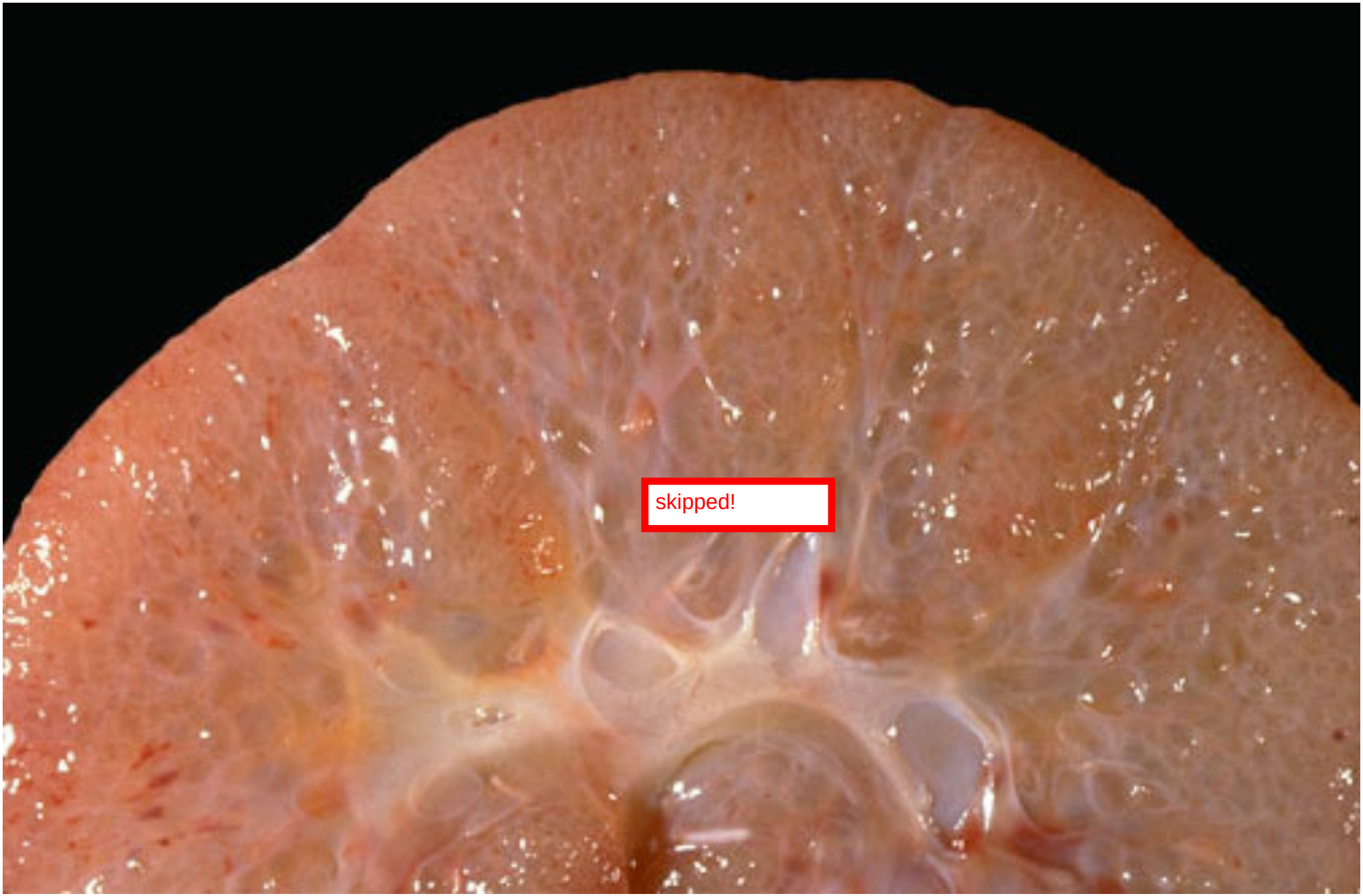
skipped!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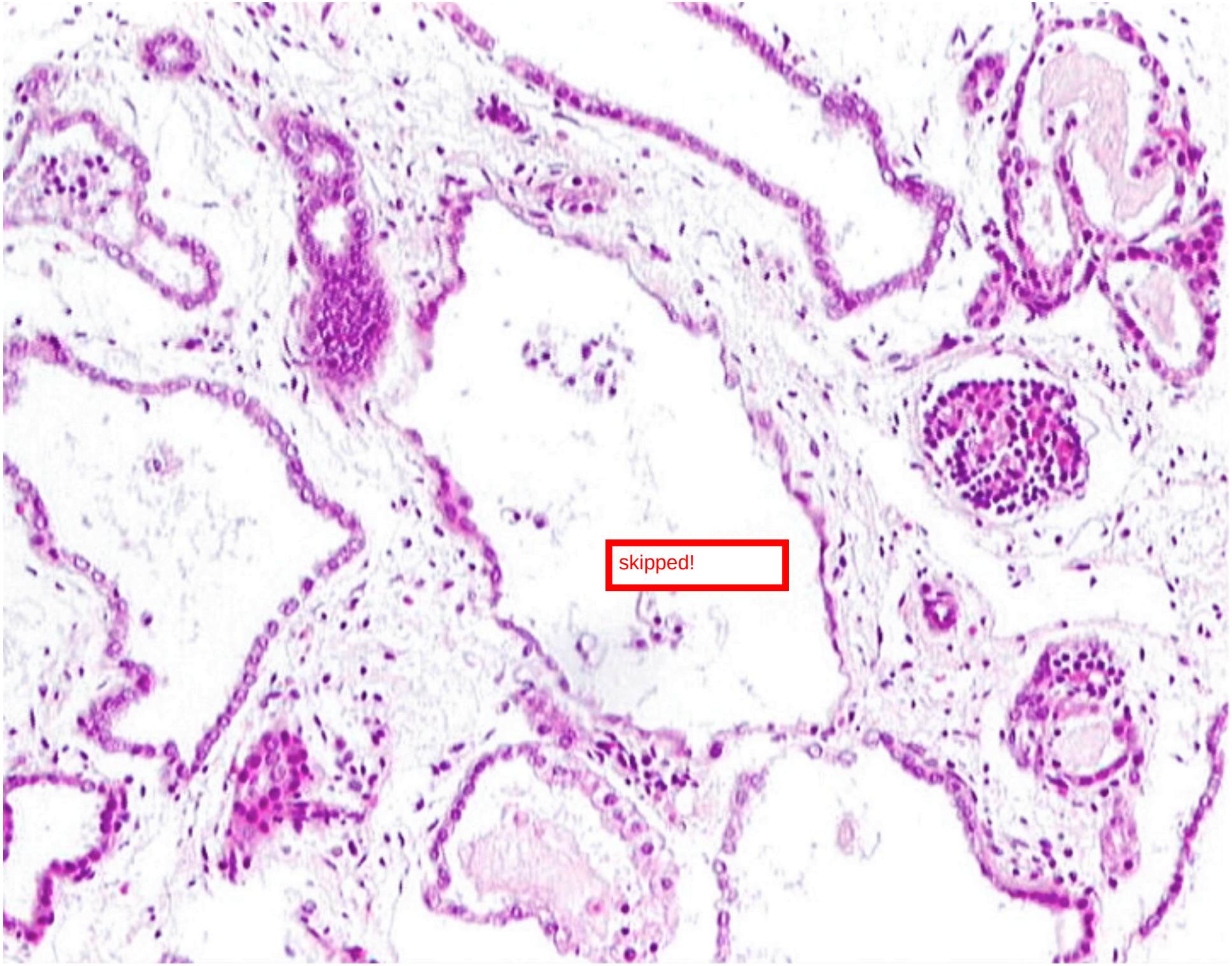
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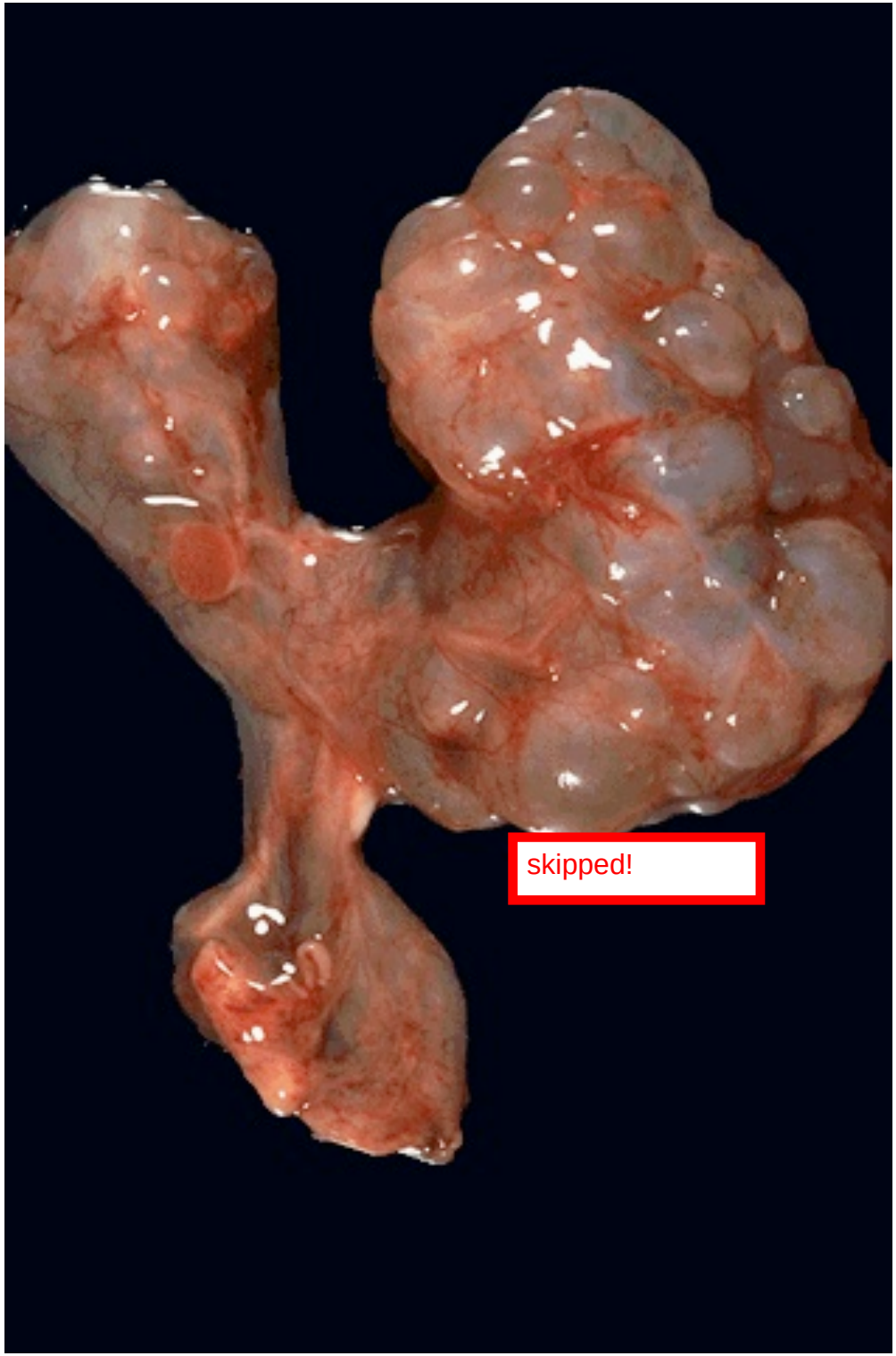
skipped!

Multicystic renal dysplasia

- Non-hereditary
  - May occur as one component of multiple malformation syndrome
- Congenital presentation
  - 1 in 1500 births
- Maldevelopmental basis
  - Obstructive ureteral anomaly (90%)
  - May have other malformations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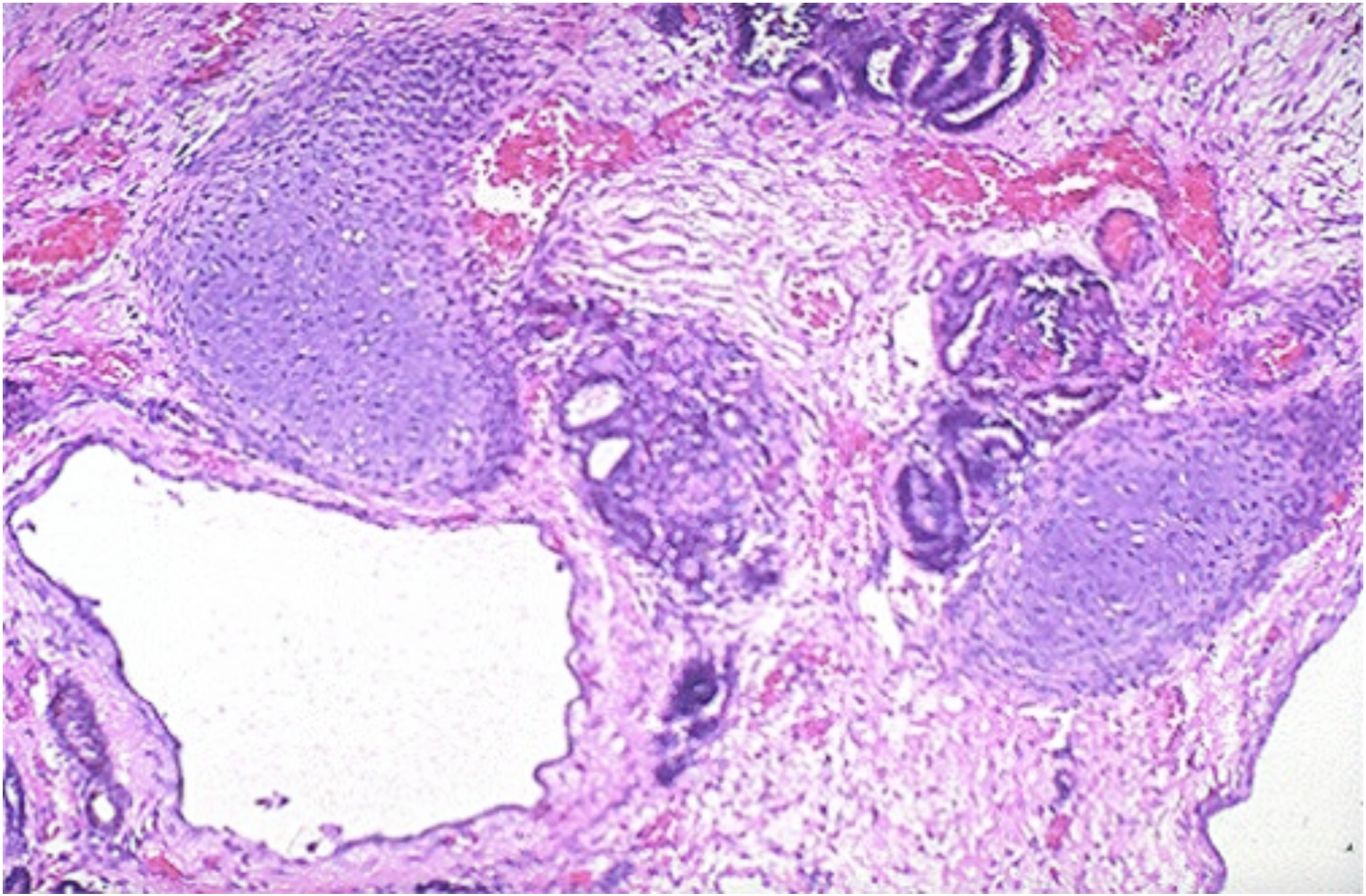

8:20 - he said the we need to know some other non-neoplastic kidney disease but my understanding is that from now on until slide 29 it will not be testable. However he emphasized that we will have to learn it at some point for our board exam and as physicians.

What important* non-neoplastic kidney diseases have we missed today, and what should you do about it?

*Could mean many things, but among them—for you at this stage in your training—might mean "board-testable"!

8:34 - read!

Pre-renal diseases

- Remember what you have learned about atherosclerosis, the Goldblatt kidney, low cardiac output states, hypovolemia, shock etc. in other pathology and physiology lectures.
- Keep an eye open for hepatorenal syndrome.

non-functional liver leading to a non-functional kidney

Intrarenal diseases

discussed the ones that were important

9:11 -read

Infectious

- Will say a bit about pyelonephritis next week in the bladder lecture
- For other infectious kidney diseases, check your Microbiology notes!
  - Tuberculosis
  - Polyomavirus

Neoplastic

- Next lecture

Deposition

- Read about kidney bladder stones (lithiasis) in your text
- Dr. Howell will talk about amyloidosis, myeloma kidney, etc.

9:57

Autoimmune

- Dr. Howell

9:58

Post-renal

- We will talk in bladder lecture next week about some obstructive diseases of urinary tract and their effects on the kidney.

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            b. Toxic type
        2. Acute interstitial nephritis
    B. Progressive to chronic renal failure (ESRD)
        1. Renovascular disease
            a. Diabetic nephropathy
            b. Hypertensive nephropathy
                i. Ordinary type
                ii. Malignant hypertension
        2. Renal cystic disease
            a. Adult polycystic kidney disease
            b. Dialysis-associated cystic disease
            c. Pediatric cystic diseases & others
II. Selected renal neoplasms (next lecture...)

Urinary Tract Pathology
Lecture 2:
Kidney Neoplasms

John F. Madden, M.D., Ph.D.

Spring 2010

OK guys, I took the background to make our lives easier. He follows a lot his bullet points so whatever you see a yellow highlight in his bullets = he talked about it.

10:49

Featured kidney neoplasms

- Benign
  - Angiomyolipoma
  - Renal oncocytoma
- Malignant
  - Renal cell carcinoma
  - Renal medullary carcinoma
  - Nephroblastoma

we are going to talk about benign and malignant tumors

10:58

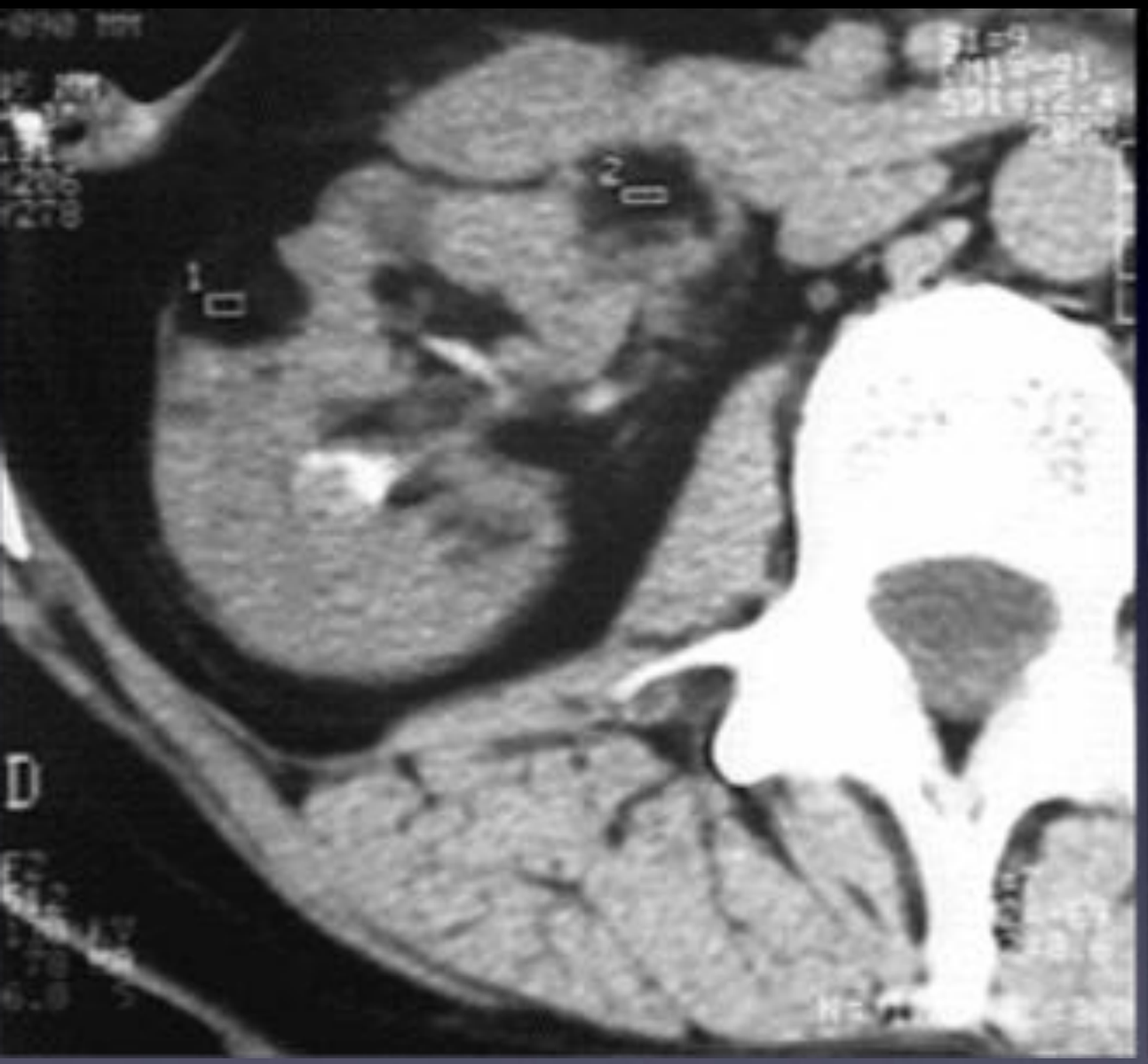
Angiomyolipoma

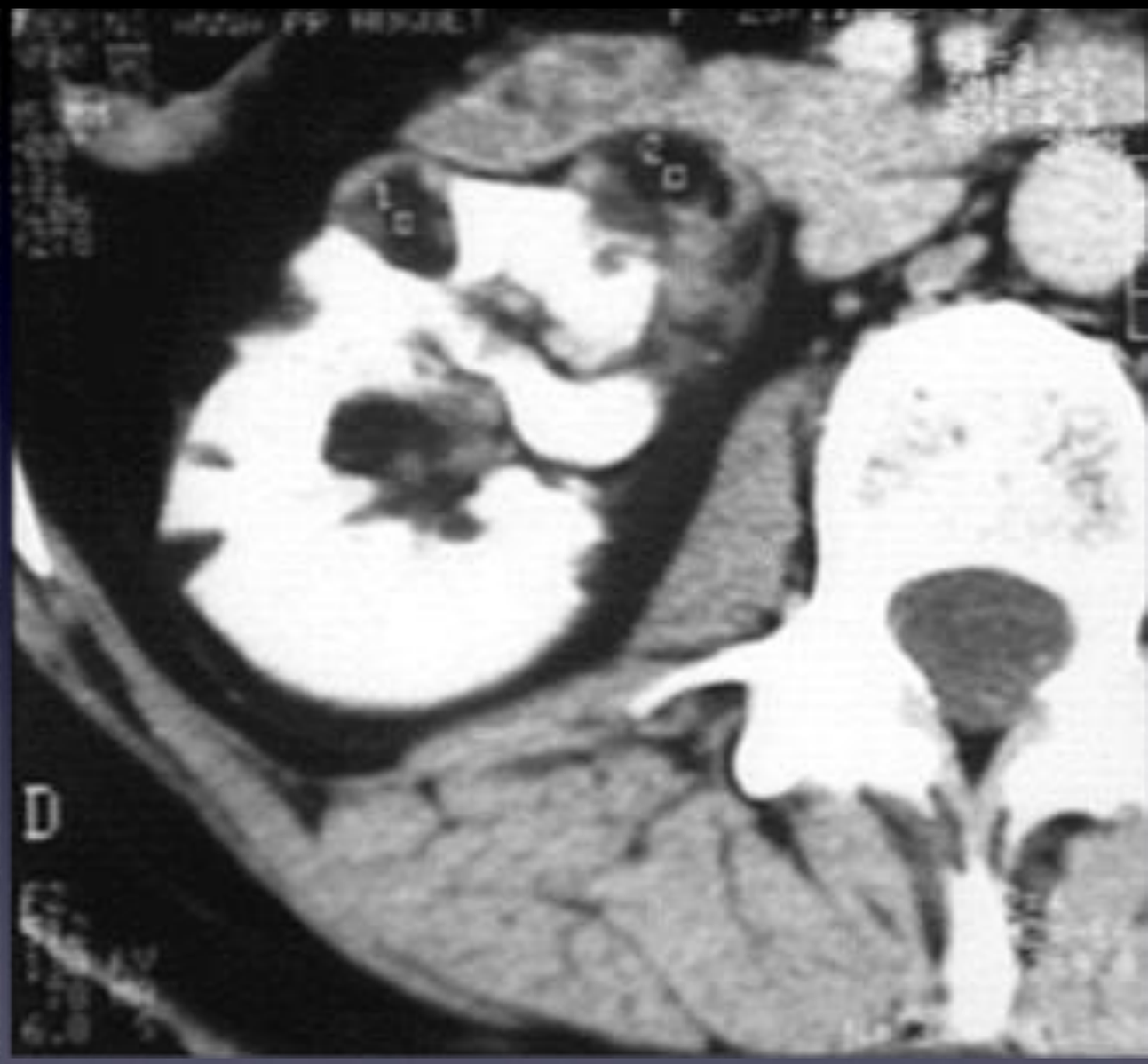
- About 2% of renal tumors
- Middle-age
- Females > males
- Association with tuberous sclerosis (TS)
  - —70% of TS pts have AML
  - —20% of AML pts have TS

often find incidentally during a CT scan. Clinically it presents with hematuria and pain

80% are sporadic AML. Do not present with TS

11:41

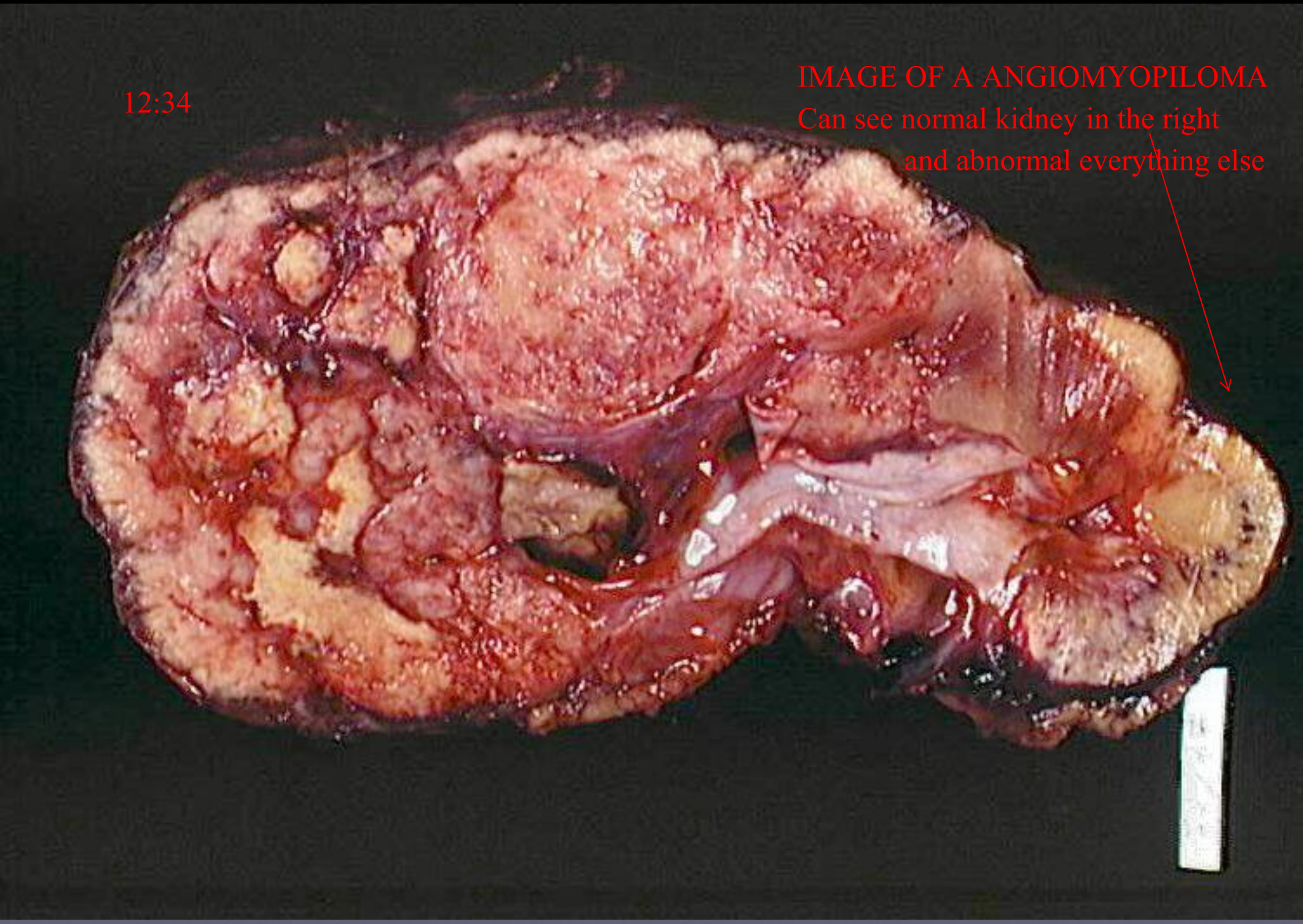




CT scan with and without contract of angiomyolipoma. He did know how to read the image and locate the tumor for us. Move it on!!

12:34

IMAGE OF A ANGIOMYOPILOMA
Can see normal kidney in the right
and abnormal everything else



12:55

Angiomyolipoma: clinical

Since there are a lot of blood vessels there, you will see the reddish areas. Even though this tumor is benign, it mimics renal cell carcinoma so you need to keep in mind for you differential.

- Larger tumors symptomatic, smaller tumors incidental
- Complications: hemorrhage, renal failure
- Radiographic differential diagnosis = renal cell carcinoma
- Therapy
  - —Symptomatic → nephrectomy
  - —Asymptomatic ?→ embolization
- Workup patient for tuberous sclerosis

He did not talk about anything else in this slide besides mention (in the next slide) that it is important to do a workup in the patient for tuberous sclerosis

13:18

LOTS OF FAT

Angiomyolipoma = microscopic view. As the name imples: angio = it has lots of abnormal vessels; myo = has a lot of muscle cells; lipoma =a lot of fat cells

ABNORMAL VESSEL

LOTS OF ABNORMAL MUSCLE CELLS

14:30

Angiomyolipoma: Pathology

- Benign tumor consisting of various proportions of:
  - —blood vessels
  - —proliferating smooth muscle
  - —fat
- Actually one cell type = “perivascular epithelioid cell” (PEC) you can see the muscle cells, the fat, all around the vessel (PEC)
  - —Myomelanocytic phenotype, expresses melanocytic and muscle markers simultaneously
- PEComa family of tumors (kidney, liver, lung, etc.)
- Relation with TS suggests invovlement of mTOR pathway lesions in these tumors
  - —Rapamycin has therapeutic potential, under investivation

16:17 this is the second benign tumor, again incidentally discovered but need to differentiate it from renal cell carcinoma, and as for angiomyolipoma you need to remove and ask the pathologist what it is.

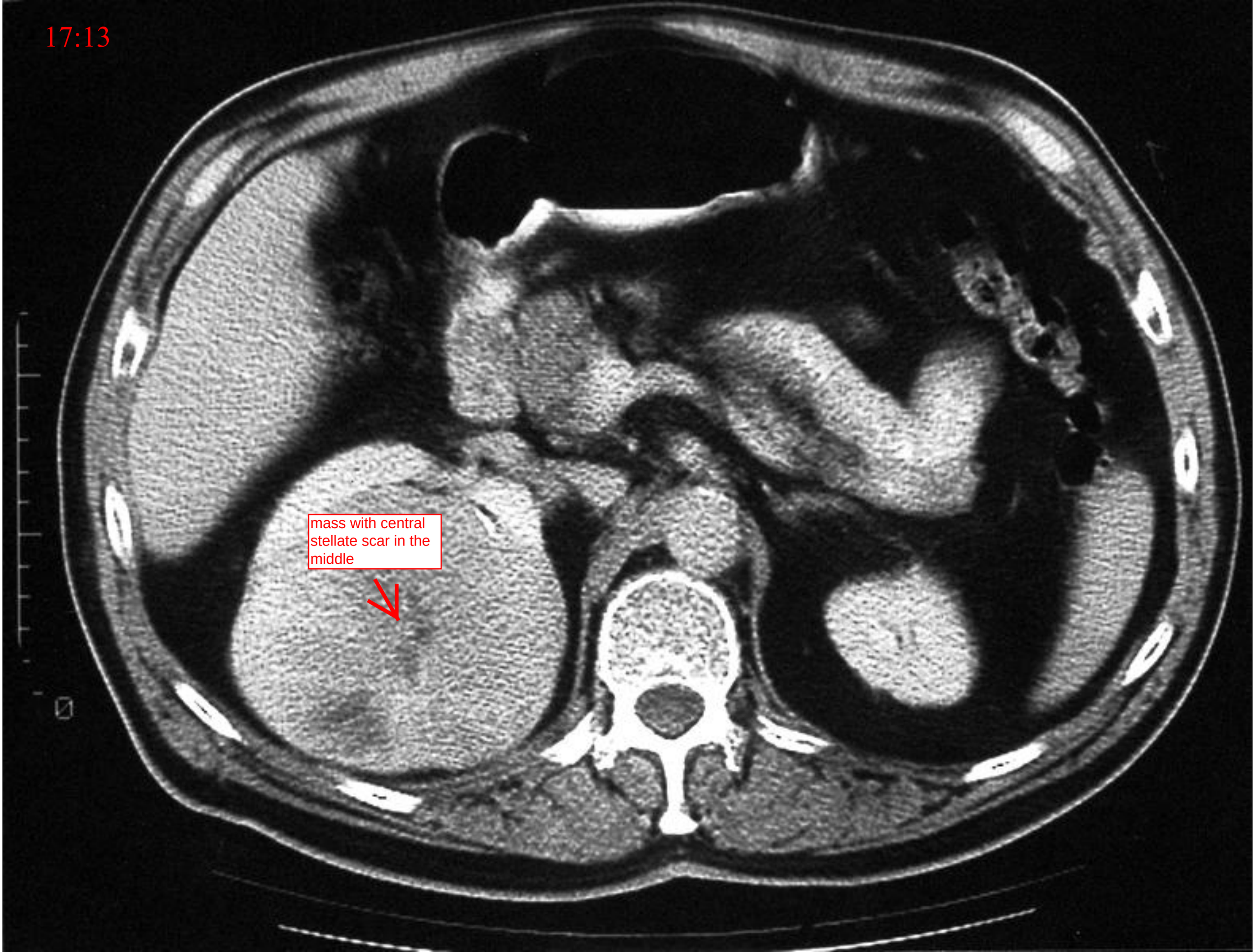
Renal oncocytoma

- Benign neoplasm consisting of "oncocytes"
- About 3% of nephrectomies for tumor
- Usually asymptomatic, incidental
  - —↑incidence ← ↑imaging

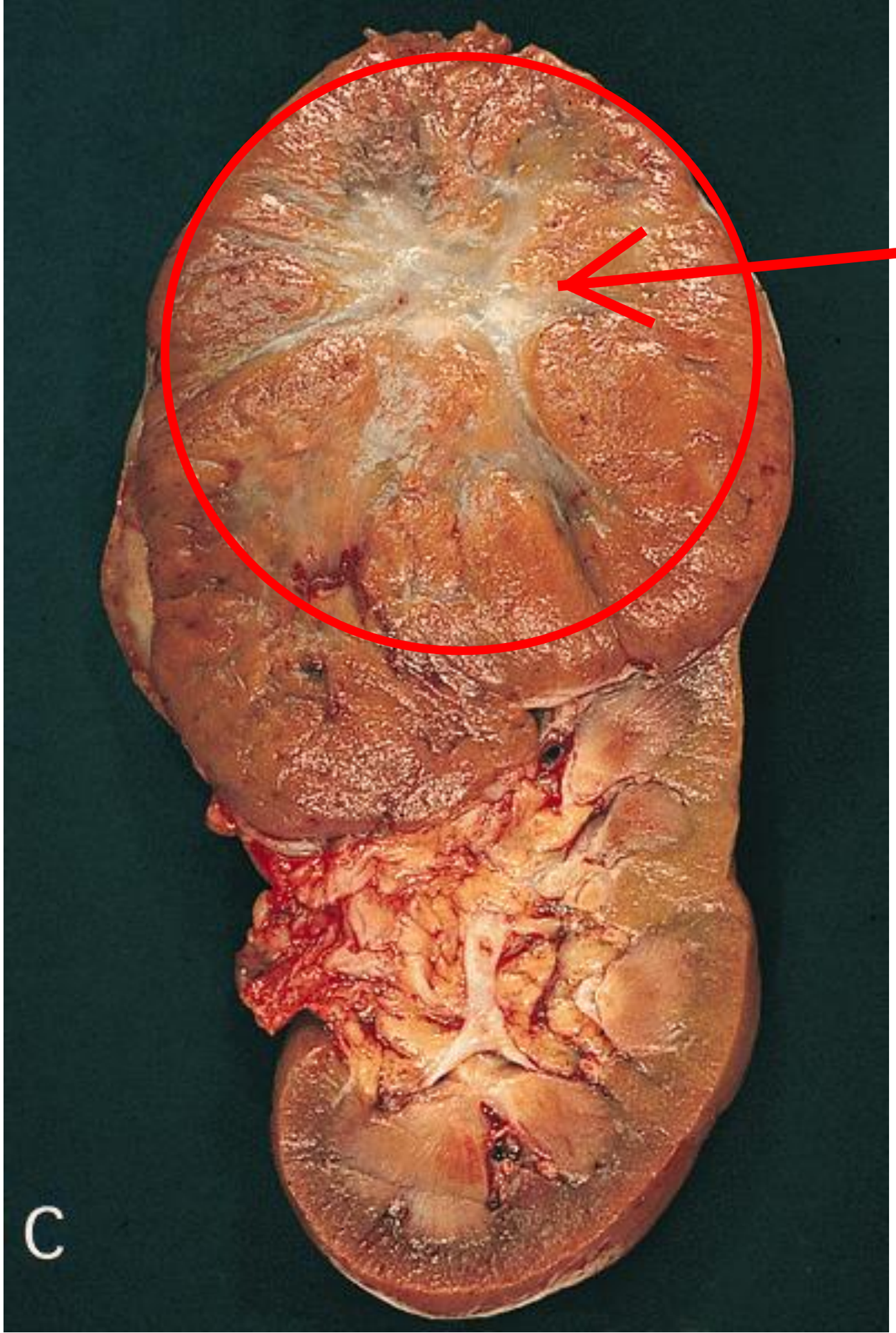
incidence is increasing because of better imaging

- Older adults
- Males > females
- Circumscribed cortical mass
- Central stellate scar

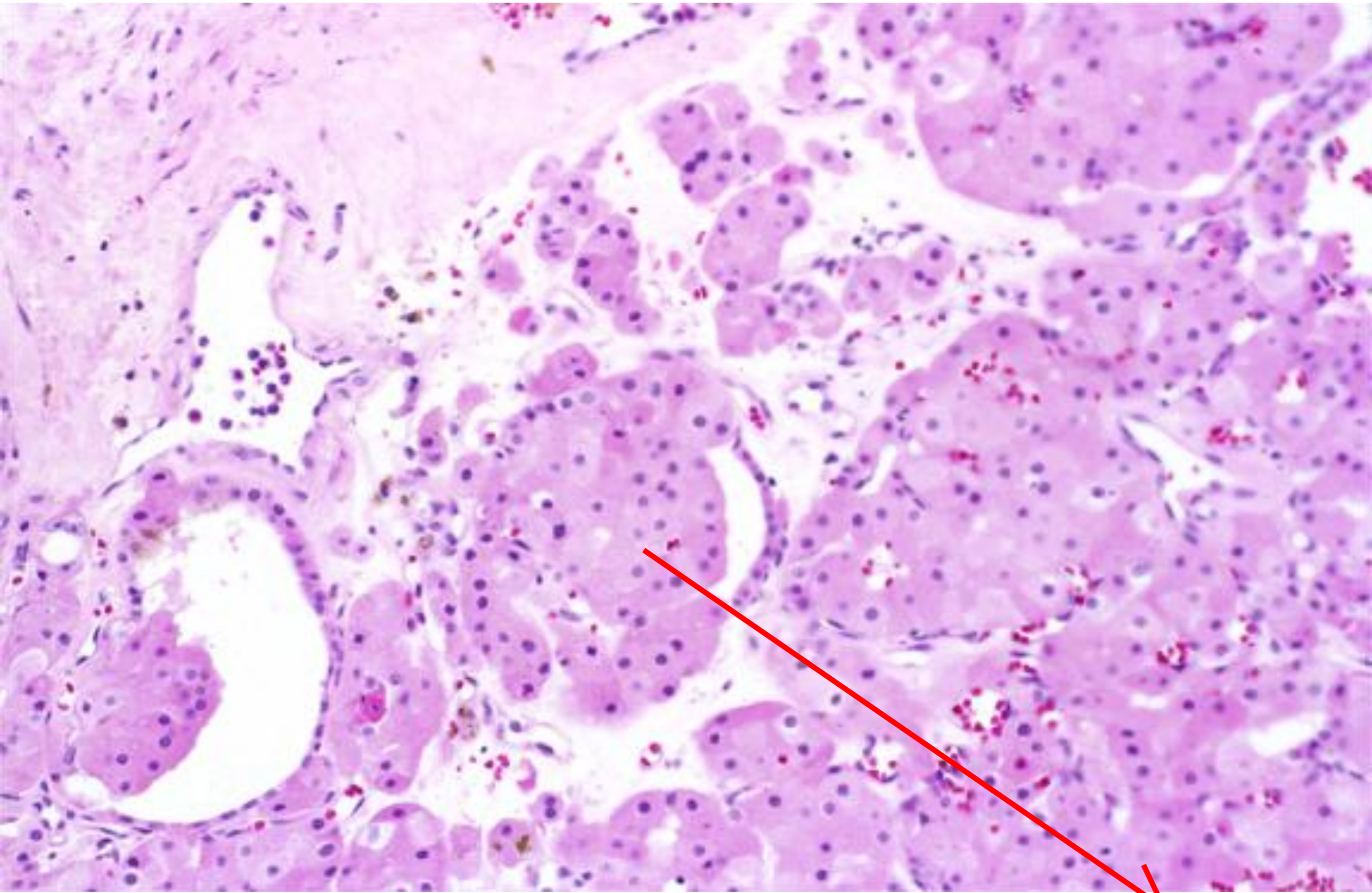
characteristic of this tumor is that it has a circumscribed cortical mass with a CENTRAL STELLATE SCAR. This is an important diagnostic tool for a radiologist to suggest a renal oncocytoma


17:13
mass with central stellate scar in the middle

17:30

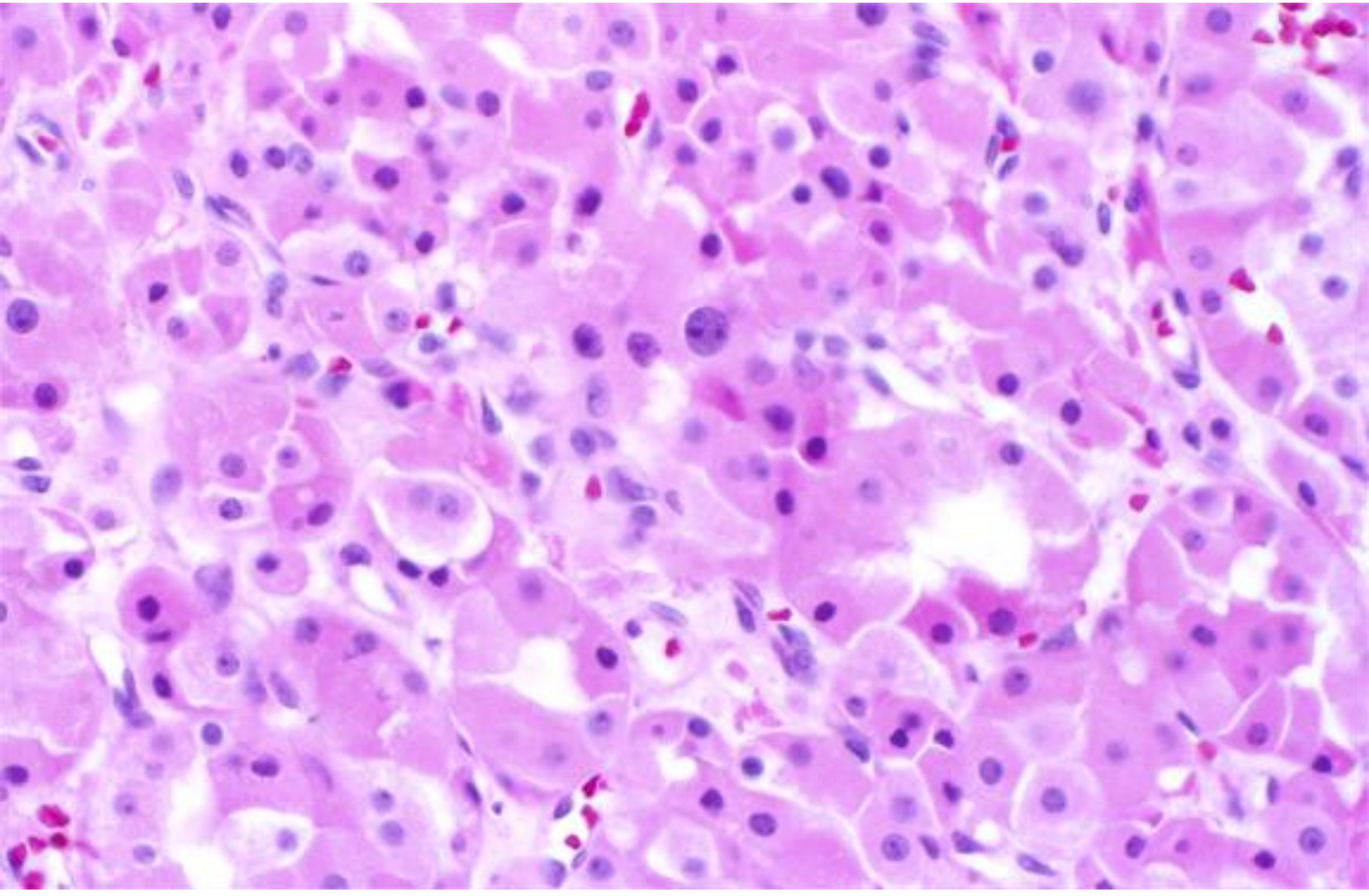


17:34 The cell type of this tumor is a "funny" "odd" shape =oncocyte.



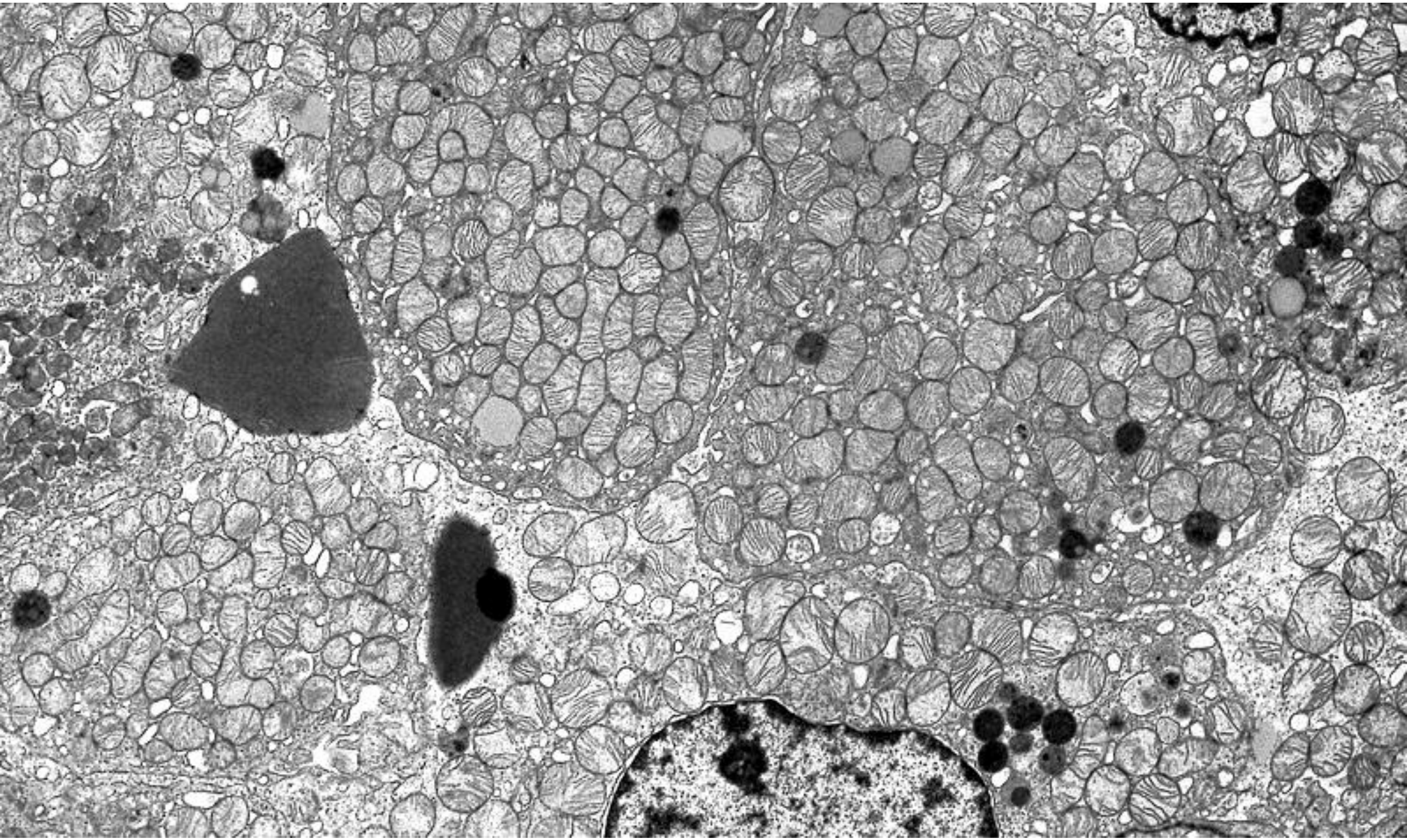
They occur in the kidney and endocrine system. It has a very abundant red staining cytoplasm.

18:01: Here a magnified view of oncocytoma. The reddish comes from the fact the cells are packed



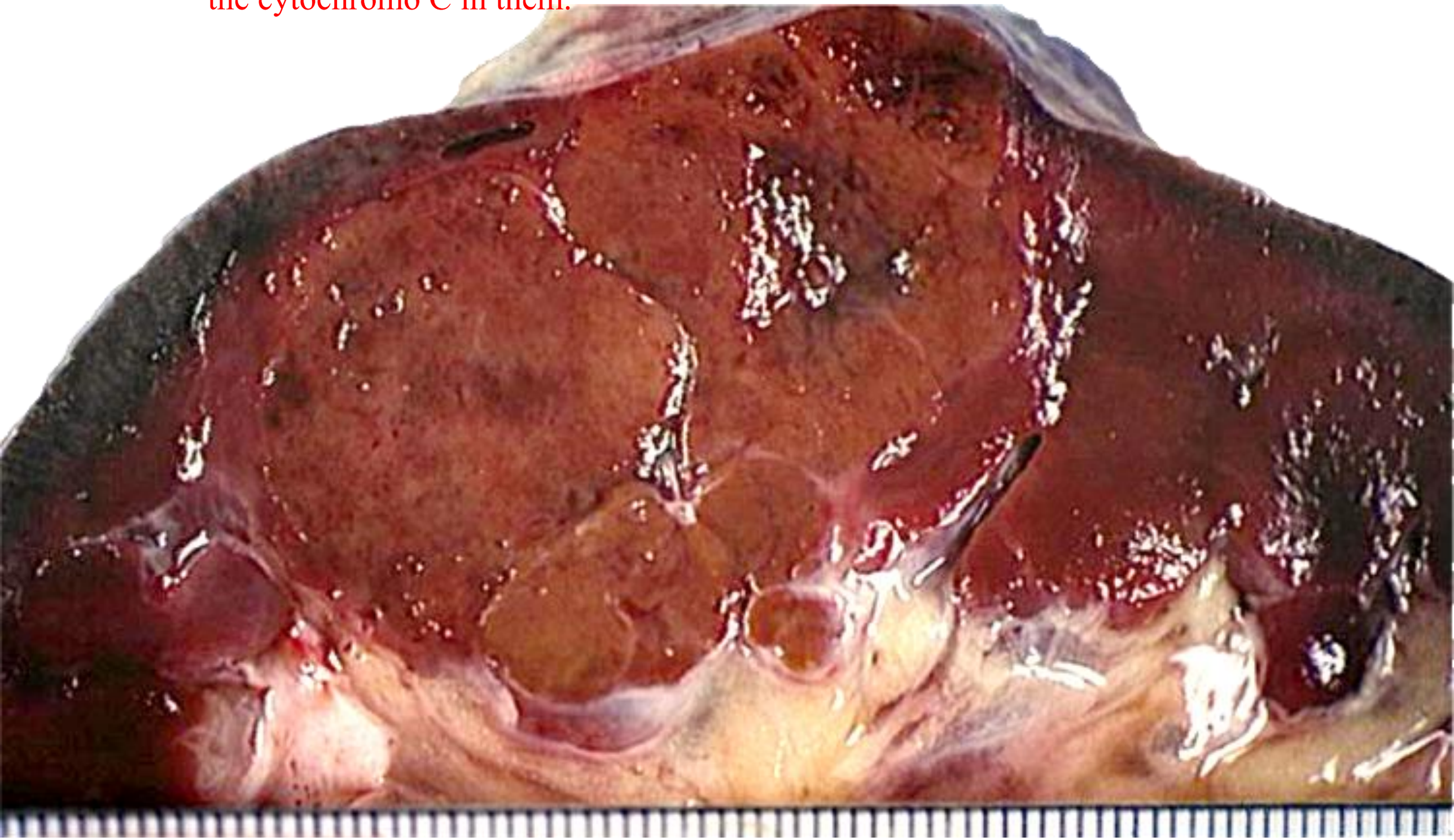
with mitochondria and mitochondria stain red.

18:10 Electron MI showing all the mitochondria that he was talking about it.



18:18

You can see the red color macroscopically as well. The mitochondria are red because all the cytochromo C in them.



You will not die because of Renal oncocytoma but you will undergo a biopsy to differentiate it from renal cell carcinoma, the "bad guy". (next slide)

18:44

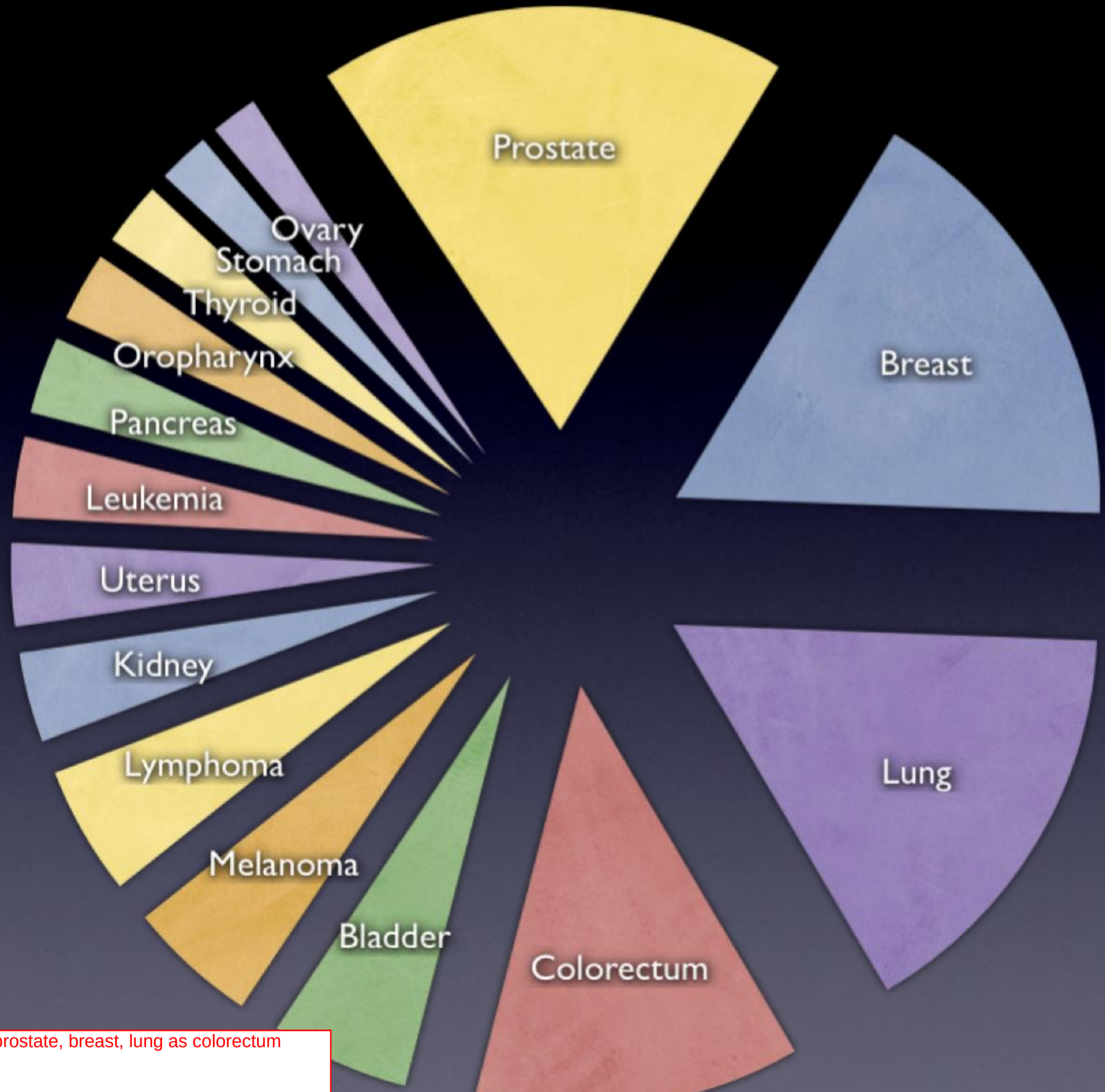
Renal cell carcinoma (RCC)

There are several subtypes of RCC

- Most common renal tumor
  —3% of adult malignancies
- Median age 55 years
- Male : female :: 1.6 : 1
- Risk factors
  —Tobacco
  —Hereditary/acquired cystic disease
  —von Hippel-Lindau syndrome

20:14

Relative US Cancer Incidence by Site, both sexes, all races, 2002-2006



Renal cell carcinoma is not as common as prostate, breast, lung as colorectum cancers but still it is a very common cancer.

20:58

RCC: Clinical

- Majority asymptomatic
- "Classic triad" ® advanced disease
  - —Hematuria
  - —Flank pain
  - —Flank mass
- Paraneoplastic syndromes
  - —Erythrocytosis
  - —Hypercalcemia
  - —Liver dysfunction

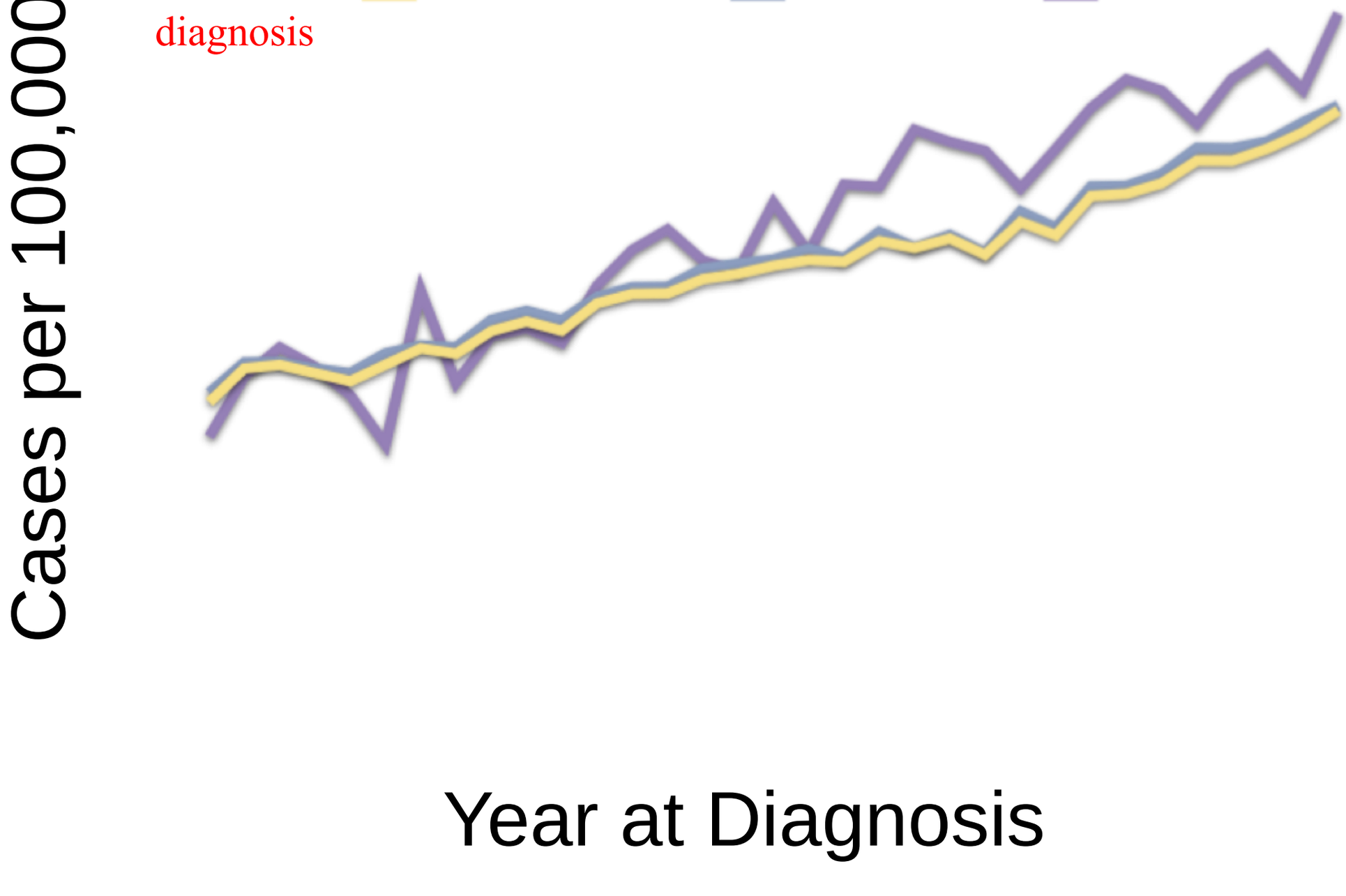
most of the times it is asymptomatic. In advanced disease it can show with the CLASSIC triad.

very often patients will come to you because of the paraneoplastic syndromes that often comes with RCC

21:50

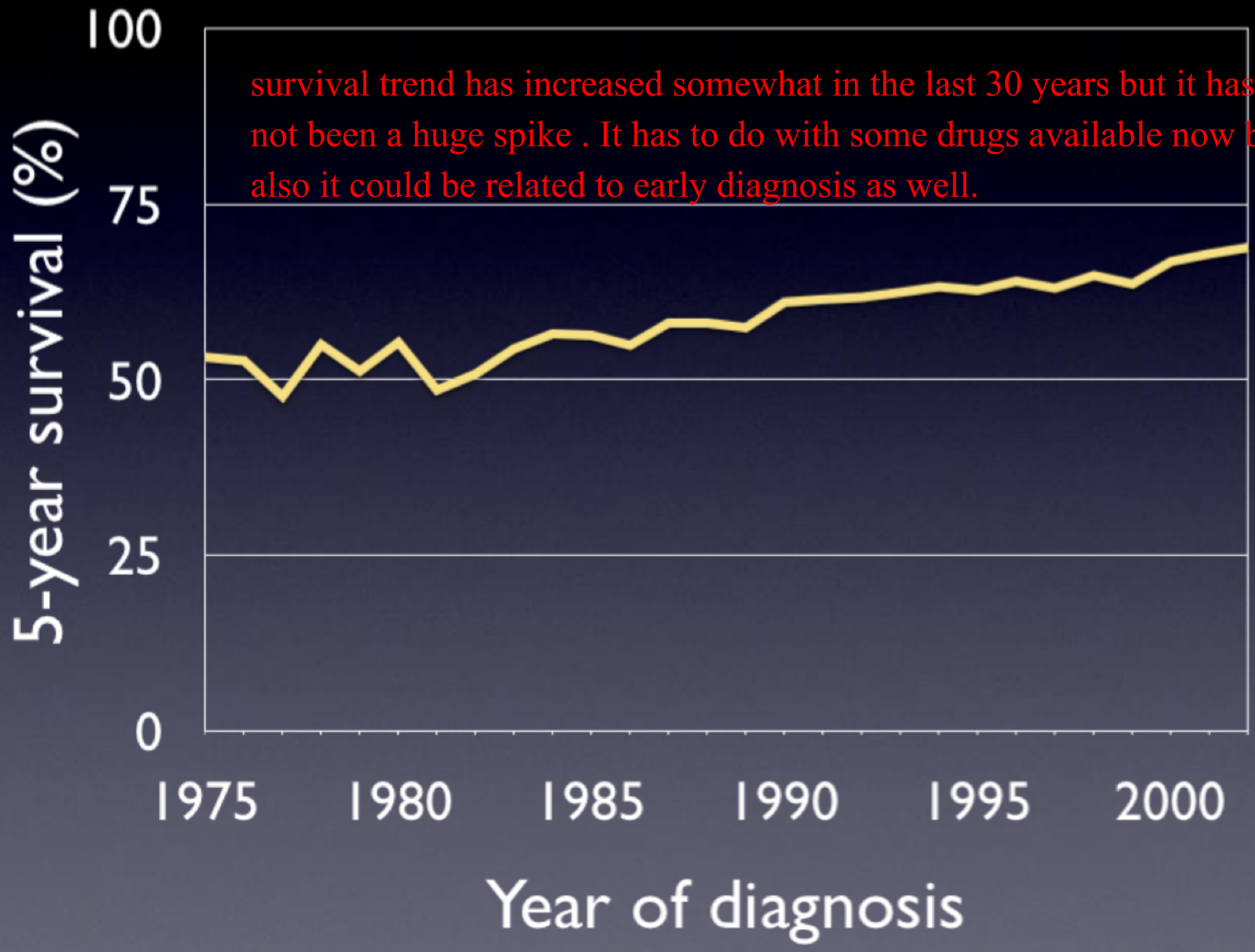
Kidney Cancer Incidence

I don't know why this graph is not showing correctly but each line represents a population: all races, white and black. He just mentioned that the incidence of kidney cancer is increasing but he believes it has to do with better imaging and diagnosis



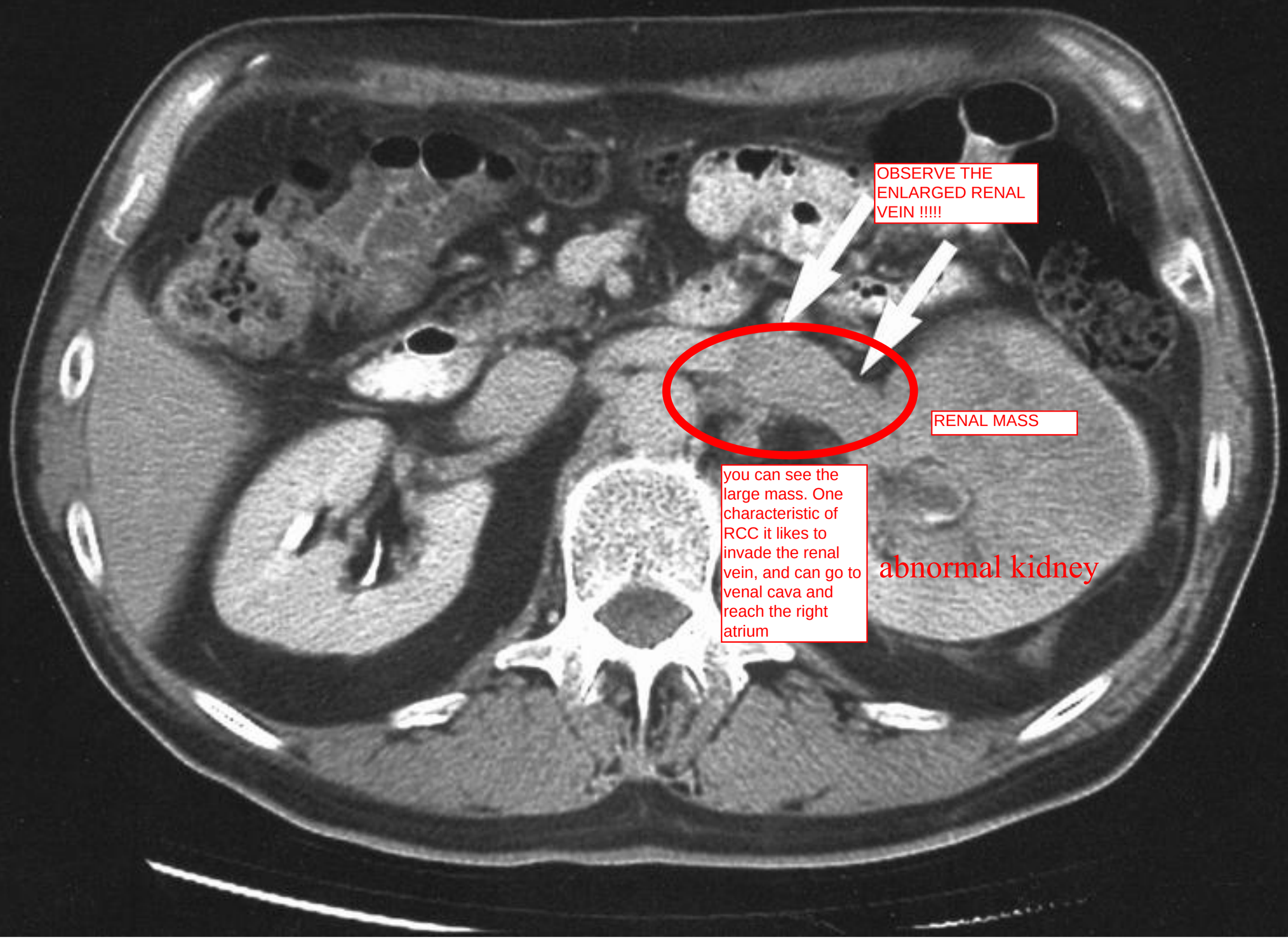
22:34

Kidney cancer survival trend



survival trend has increased somewhat in the last 30 years but it has not been a huge spike . It has to do with some drugs available now but also it could be related to early diagnosis as well.

23:04


OBSERVE THE ENLARGED RENAL VEIN !!!!!
RENAL MASS
you can see the large mass. One characteristic of RCC it likes to invade the renal vein, and can go to venal cava and reach the right atrium
abnormal kidney

24:20

RCC Staging

Depends on where it is located into the kidney or outside the kidney but within the retroperitoneal compartment, or if extent to other areas.

T1	Localized to kidney, δ7 cm
T2	Localized to kidney, >7 cm
T3	Local extension
T4	Wide extension
N	#/size of (+) nodes
M	Distant metastasis

24:21

RCC Subtypes

There is a half dozen subtypes well characterized. They are all different cancers but in terms of prognostic significance and treatment they are about the same.

- Characteristic cytogenetic abnormalities
- Prognostic significance
- Important for pathologic recognition

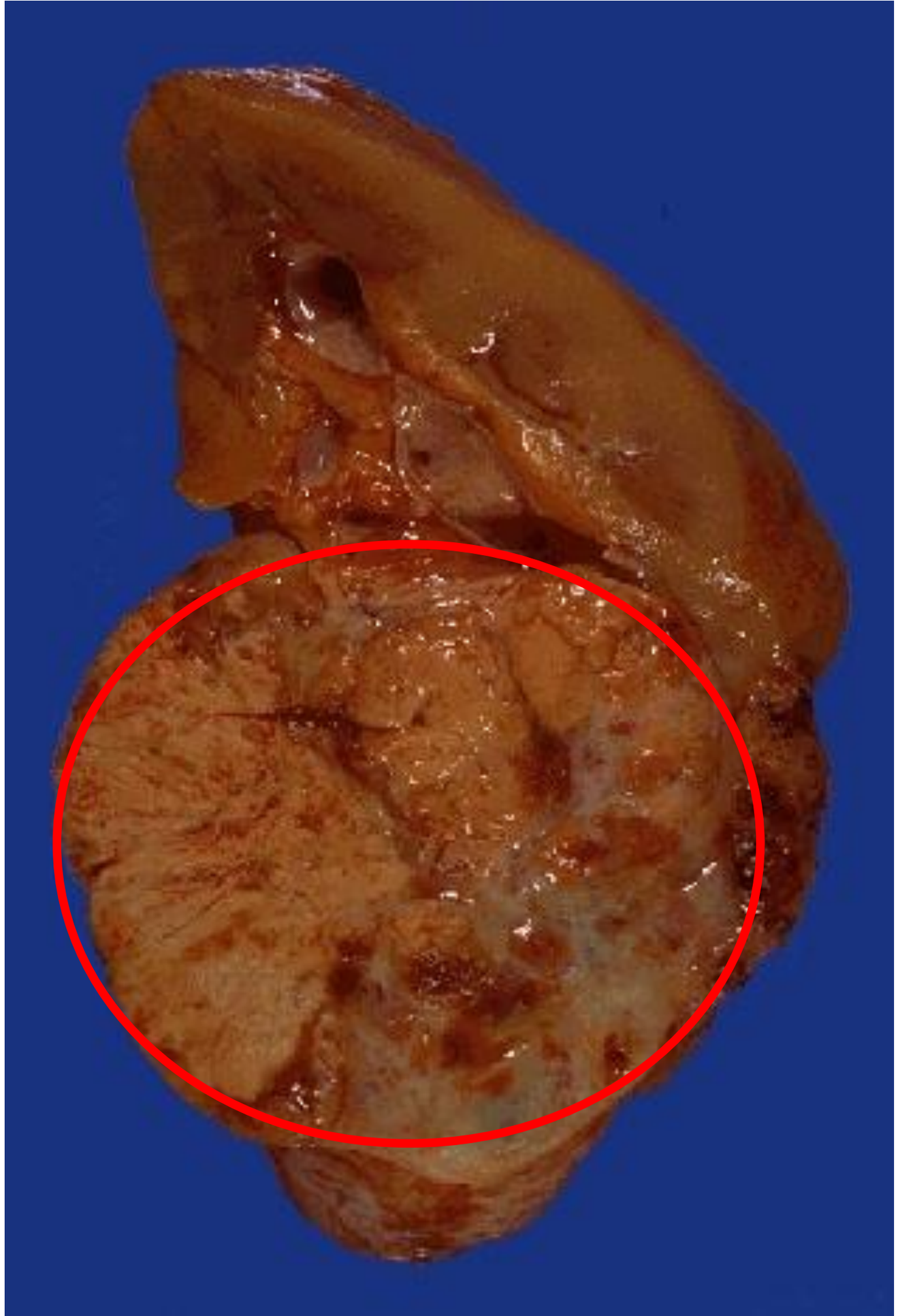
25:10

Conventional ("clear-cell") RCC

- Most common subtype (70%)
- Frequently has del 3p
- Characteristic appearance
  - —Rounded cortical mass
  - —Variegated cut surface
    Tan (viable tumor with lipid), yellow (necrosis), red (hemorrhage), white (calcification)
  - —Cystic areas (±)
  - —Extension into renal vein (±)

Here he just mentioned there is the most common. Go to next slide to see the characteristic appearance.

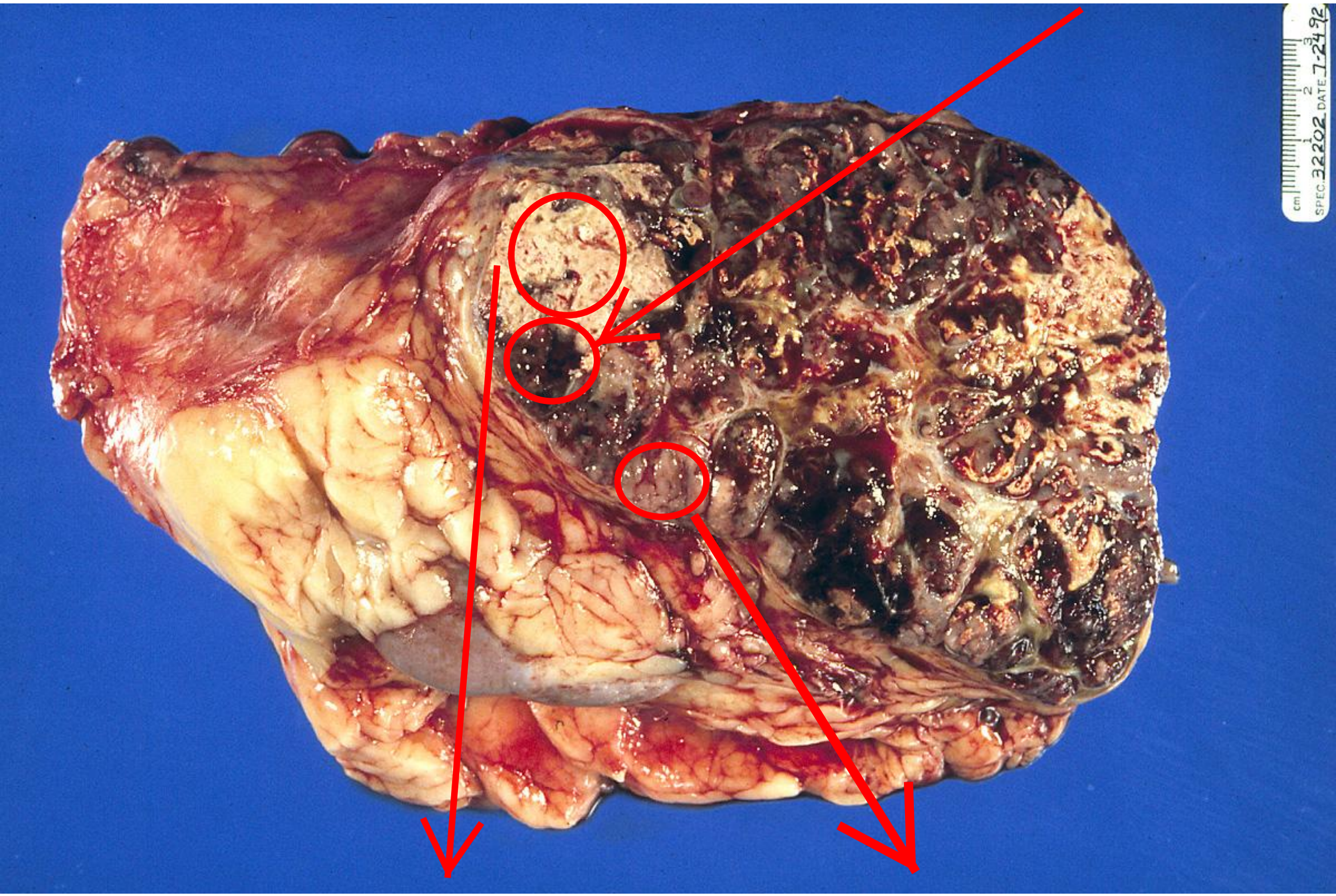
25:18



Conventional RCC:

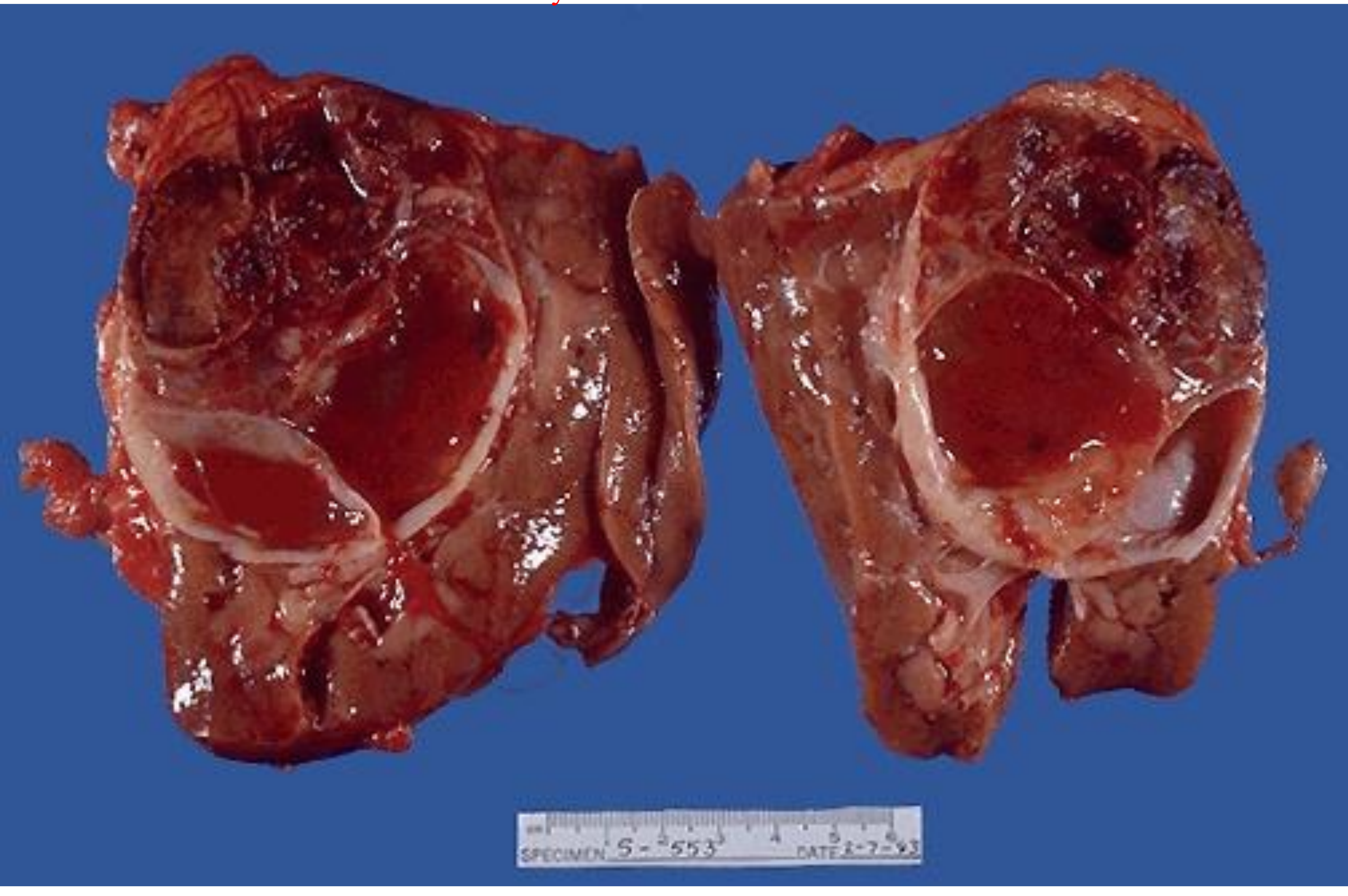
large mass with a heterogeneous pattern, intercalated with areas of hemorrhage and necrosis sometimes with areas of calcification, it has cystic areas and usually spreads into the renal veins

25:41 Picture of conventional RCC after fixation. The black areas are blood in the presence of formalin



White are indicative of areas of necrosis and tan areas are viable tumor.

26:12: another conventional RCC with cystic areas in it



26:17

Conventional RCC: microscopic

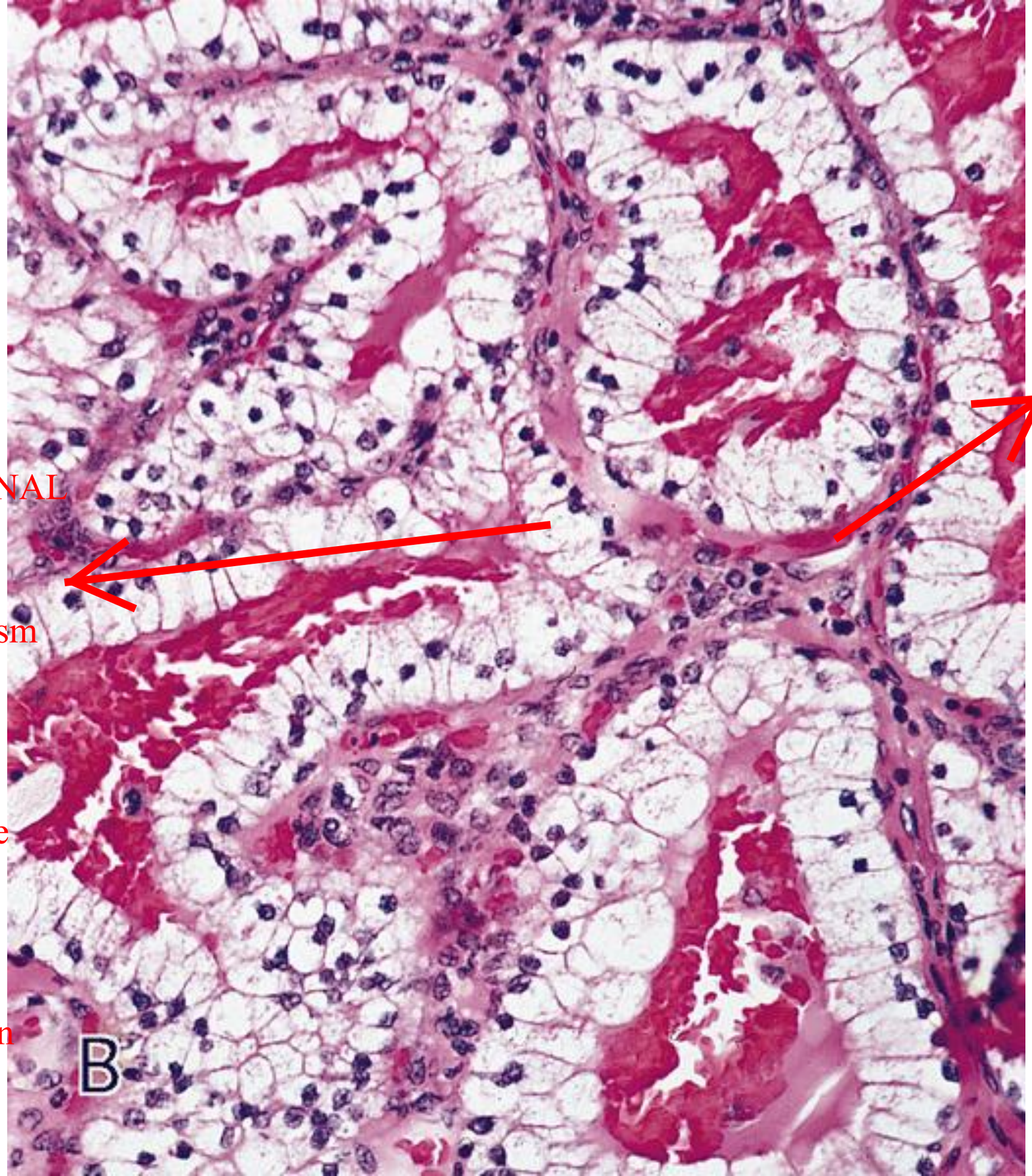
- "Clear cell" cells are clear because they are full of lipids and glycogen (next slide there is one example of clear cell)
- Cytoplasmic lipid and glycogen
- Solid or glandular
- Prominent capillary network
- Frequent hemorrhage and necrosis

26:20

Example of clear RCC microscopically.

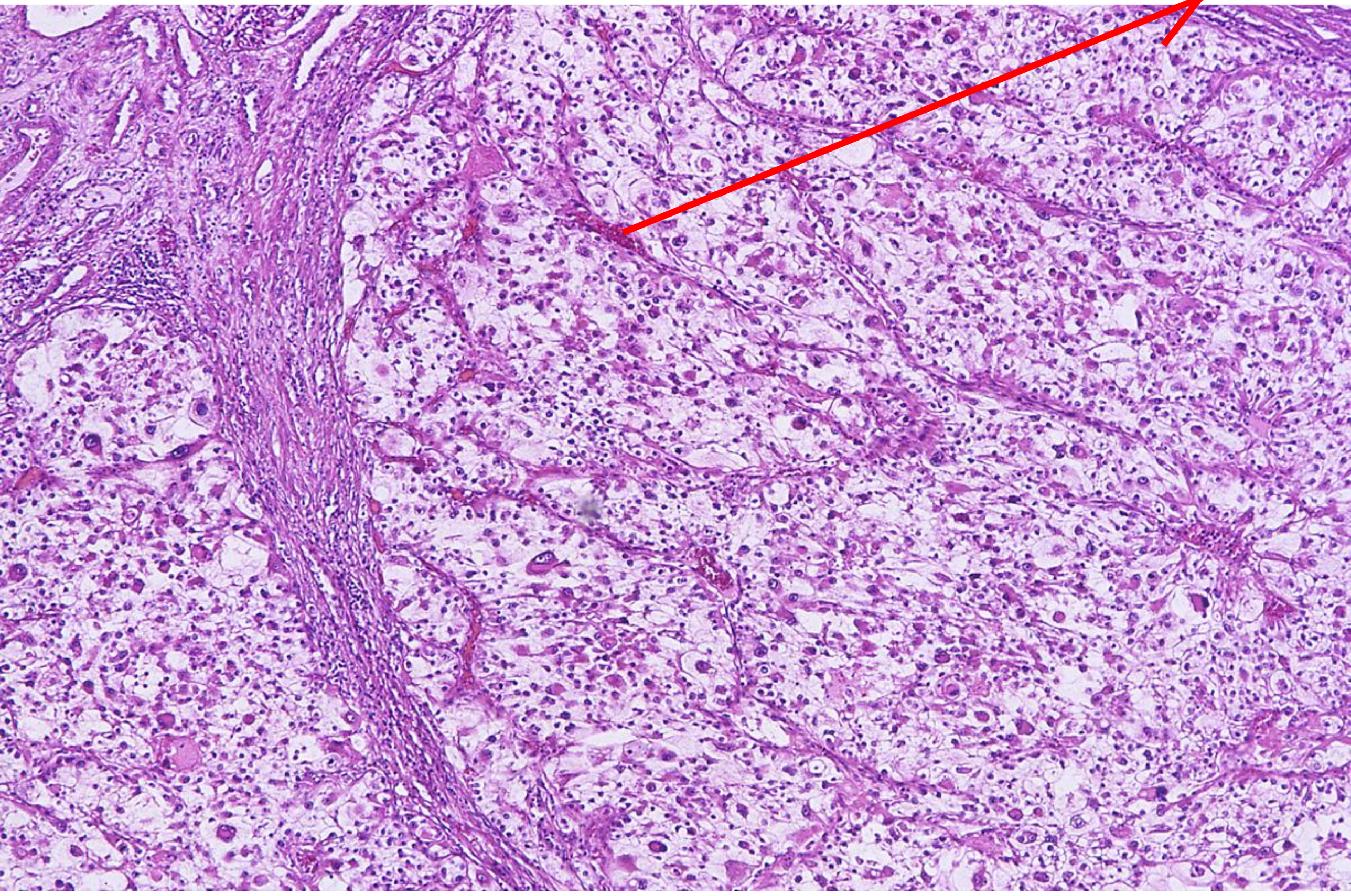
remember: CLEAR = CONVENTIONAL

Clear areas of the cytoplasm are filled with organeles, phagocytosed material, some mitochondria, some fat globules, some glycogen globules,etc



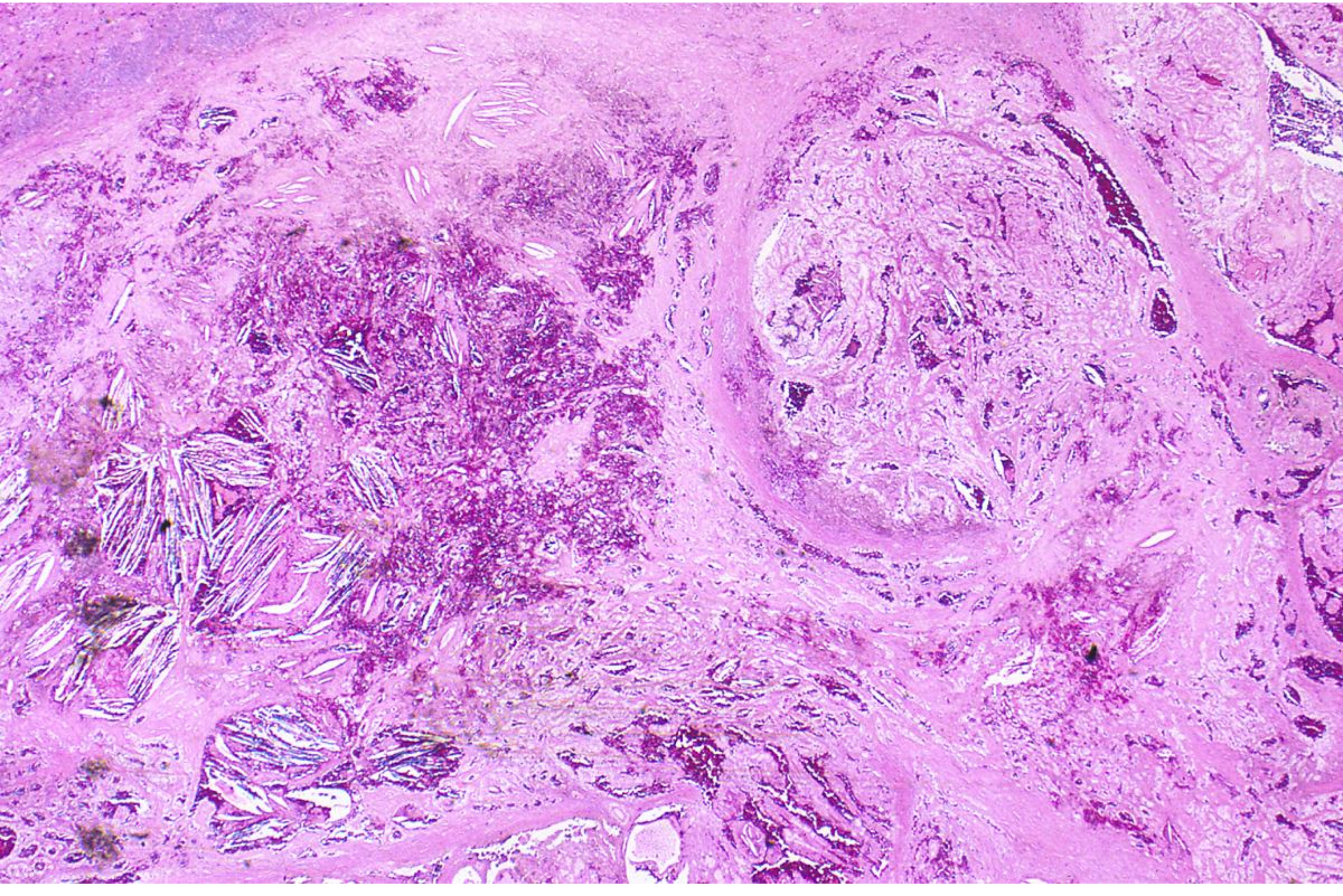
this tumor also has the ability to request a lot of blood supply so you will see a lot of blood vessels. The vessels are usually weak, so you see a lot of hemorrhage on it.

Clear RCC could present with glandular or solid areas. Example of a solid area with a lot of capillaries.

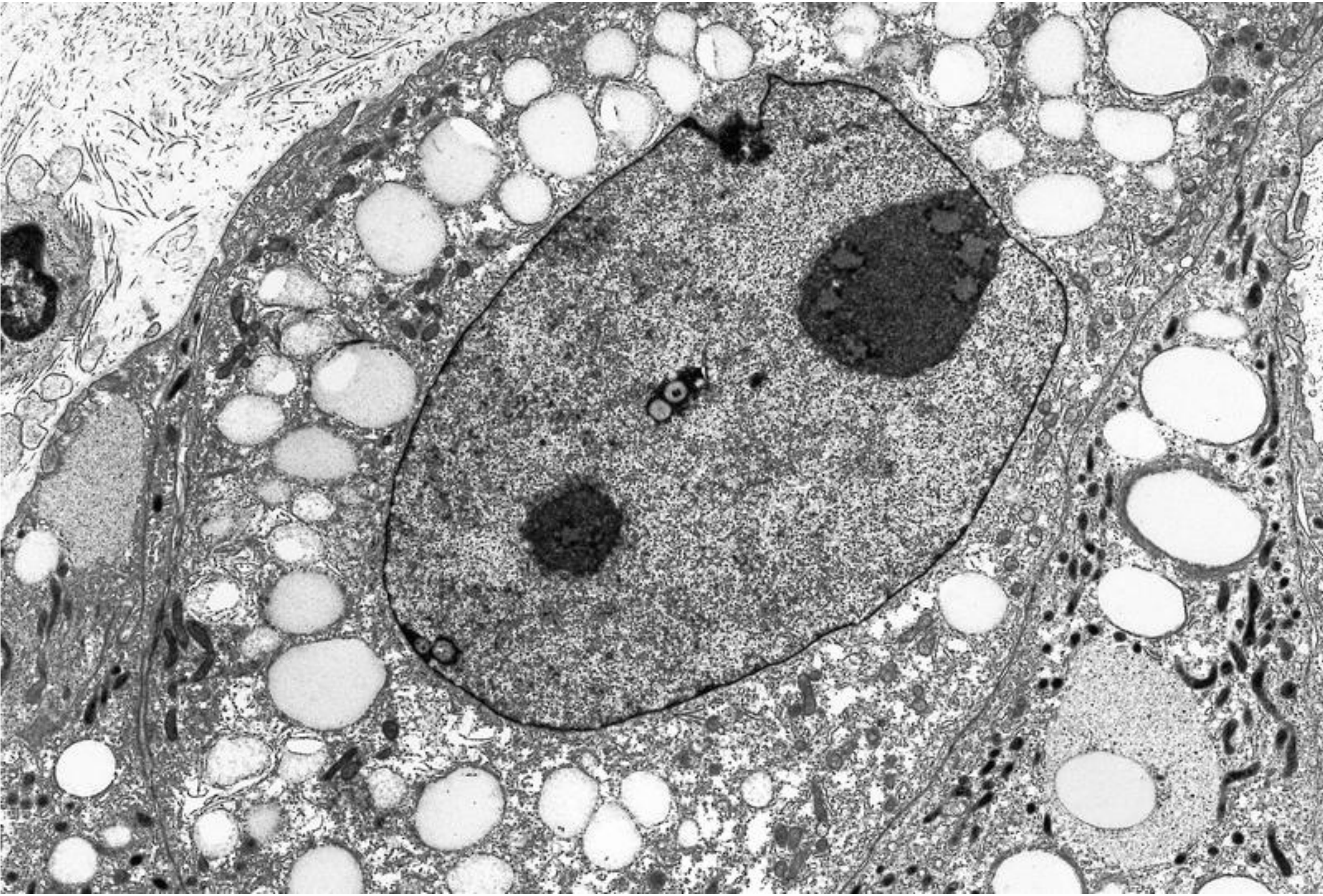


27:46

27:55 Example of a necrotic area in clear RCC



28:13 Electron microscopy showing lysosome, fat globules, glycogen, etc



28:28

Conventional (clear-cell) RCC (CCRCC):

Molecular pathology

3p = hypermutable region rich in tumor suppressor genes,
deletions seen in about 80% of CCRCC

- *VHL* (3p25)
  Specific CCRCC association (next 2 slides)
- *FHIT* (3p14.2)
  Nucleotide hydrolase inactivated in many cancers incl. familial CCRCC with t(3;8)
- *RASSF1A* (3p21)

it has the most consistent cytogenetics of all the RCC - usually they will have a deletion or abnormality in genes located in the short arms of chromosome 3:(3p)
It turns out the 3p has a lot of suppressor tumor genes among then, VHL gene - von hippel -lindal tumor suppressor gene.

29:09

von Hippel-Lindau (VHL) tumor suppressor gene (3p25)

- Germline mutation → familial CCRCC

always have mutation on VHL gene

- Inactivation in ~60% sporadic CCRCC
  - Deletion, mutation or hypermethylation
- Reintroduction of wild-type VHL into CCRCC cell lines suppresses tumorigenicity in vivo

Thus conventional or clear RCC is caused by mutations on the genes of the 3P arm, specially affecting the von Hippel-Lindau (VHL) tumor suppressor gene

30:08

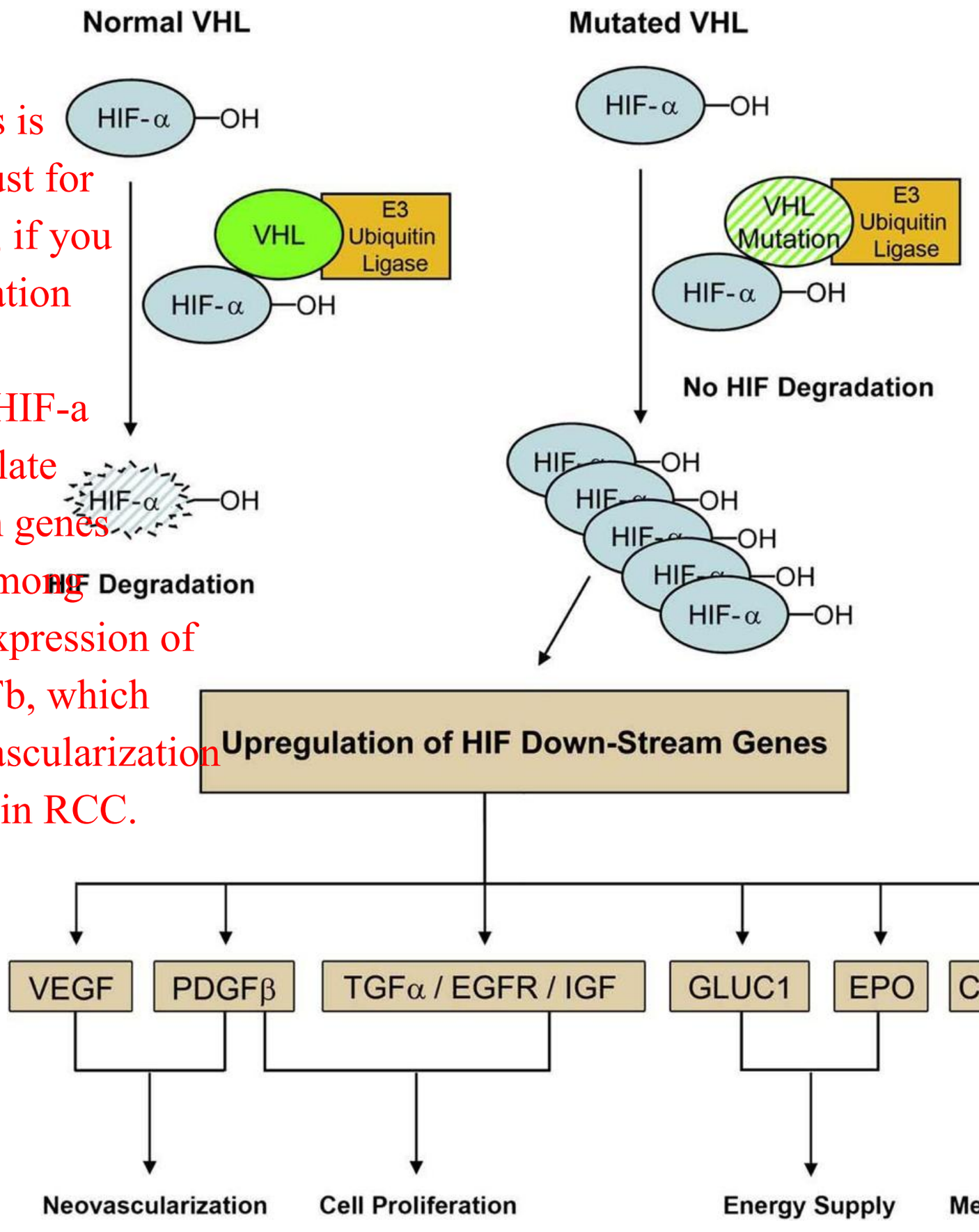
VHL gene product (pVHL)

VHL products has regulatory function in several regulatory pathways. Upregulation of this genes can affect these pathways. He showed a cartoon in the next page but said we are not responsible to know that. Also he did not talk about anything else in this slide. Move on :)

- 213 AA soluble protein, not closely related to any other known proteins
- Specifically binds to components of multiple regulatory pathways
  - Incativation of VHL results in mTOR up-regulation
  - Forms a complex with E3 ubiquitin ligase that normally degrades HIF-⟨

30:42

He again said this is not testable but just for your information, if you have a VHL mutation this will lead to accumulation of HIF-a - that will upregulate HIF down-stream genes. They will lead, among other things, to expression of VEGF and PDGFb, which will lead to neovascularization usually observed in RCC.



31:54

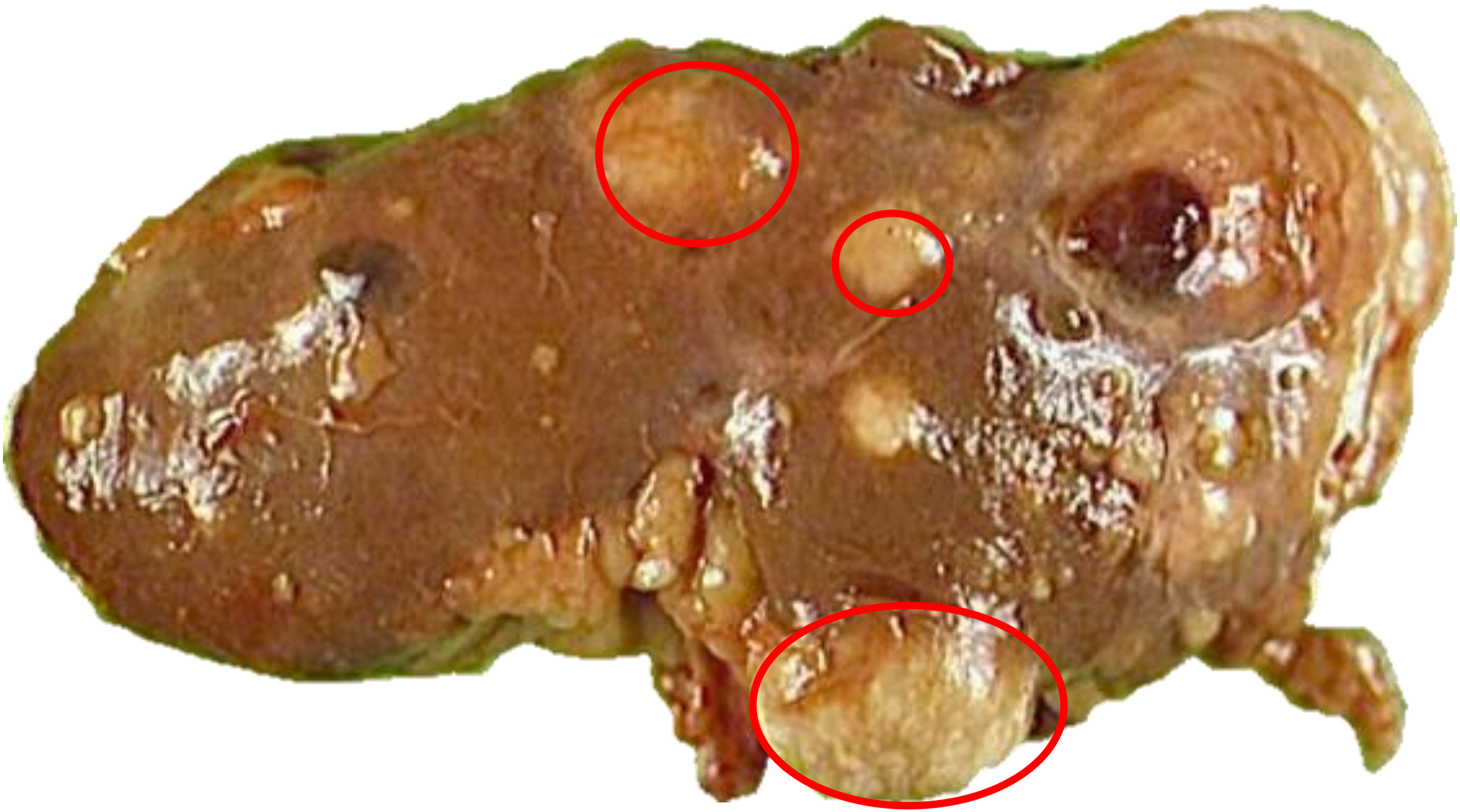
Papillary RCC

- Second-most common type (15%)
- Appearance different from CCRC
  - —Peripheral cortex
  - —Often multifocal
  - —Can be very large, yet circumscribed
  - —Usually low stage
- Better prognosis than CCRCC
- Acquired cystic disease associated

it is macroscopically and radiologically distinct from CCRC

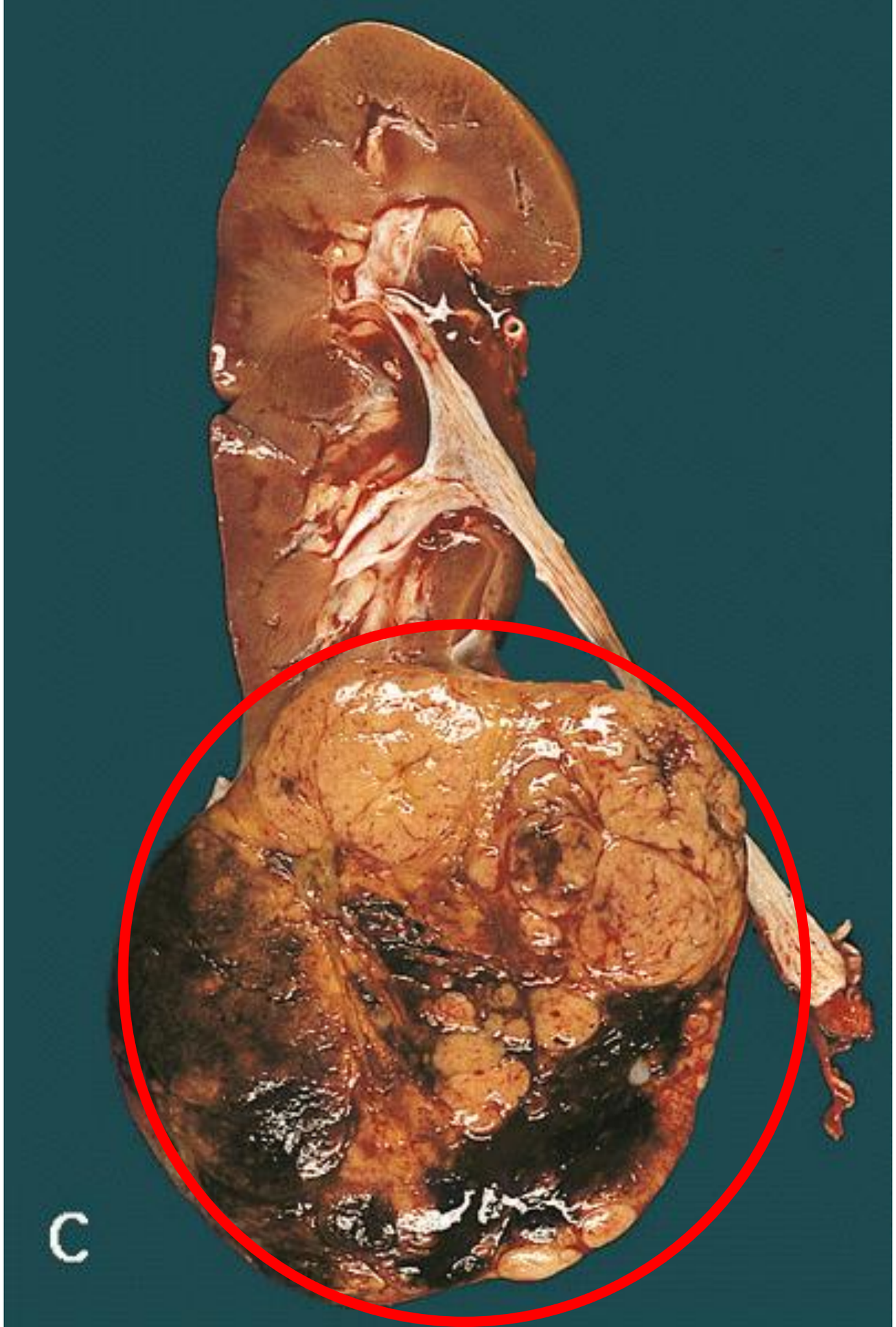
the better prognosis is due to its low stage

33:00 The characteristic of the second most common RCC after CCRC it the multifocal appearance. Beautiful example of a PAPILLARY RCC.



33:19

Example of an unifocal papillary RCC but quite large



33:04

Different from CCRC that is usually glandular or solid, this one is papillary.

33:37

they usually have foamy macrophages that contains mucous substances and fat that they englobe

34:00

“Renal cell adenoma”

In the past there was this questions about if the tumors in the kidney go from adenoma to carcinoma.

- Historically, small tumors discovered incidentally (e.g. at autopsy)
- However, even small, localized RCC can metastasize
- Term is currently reserved for papillary subtype RCC ≤0.5 cm

Basically in the past, small renal cell carcinoma were considered adenoma. Currently this view is no longer accepted since even small, localized RCC can metastasize. The only exception is the small renal cell papillary carcinoma that is still named "adenoma" when its size is less than 0.5cm.

35:27

example of small papillary renal cell carcinoma (less than .5cm) that could be called renal cell adenoma

35:46

Papillary RCC (PRCC):

Molecular pathology

the molecular mechanisms is not well characterized as for CCRCC

- Various trisomies (7, 17) and -Y common in sporadic cases

but it seems to include various trisomies in chromosome 7, 17 and deletion of Y chromossome.

- *MET* proto-oncogene (7q31)

there is also some familial cases in this case in chromossome 7

  - Many familial and some sporadic cases
  - Mutations in tyrosine kinase domain of pMET → constitutive activation
  - Trisomy 7 common in sporadic cases, can selectively amplify mutant *MET*

36:04

Less-common RCC subtypes

we do not need to know them. It is important if you decided to become a pathologist.

- Chromophobe cell type
  - Very distinctive cytology
  - Genetics not yet understood
- Collecting duct type
  - Arises near medulla
  - Very poor prognosis
- Sarcomatoid RCC
  - Not really a separate type
  - High grade, de-differentiated form of (usu.) CCRCC
  - Very poor prognosis

37:49 When staging RCC it is EXTREMELY important to know these parameters:

a) located in the kidney only: distinction between stage I or II is size.

RCC Staging

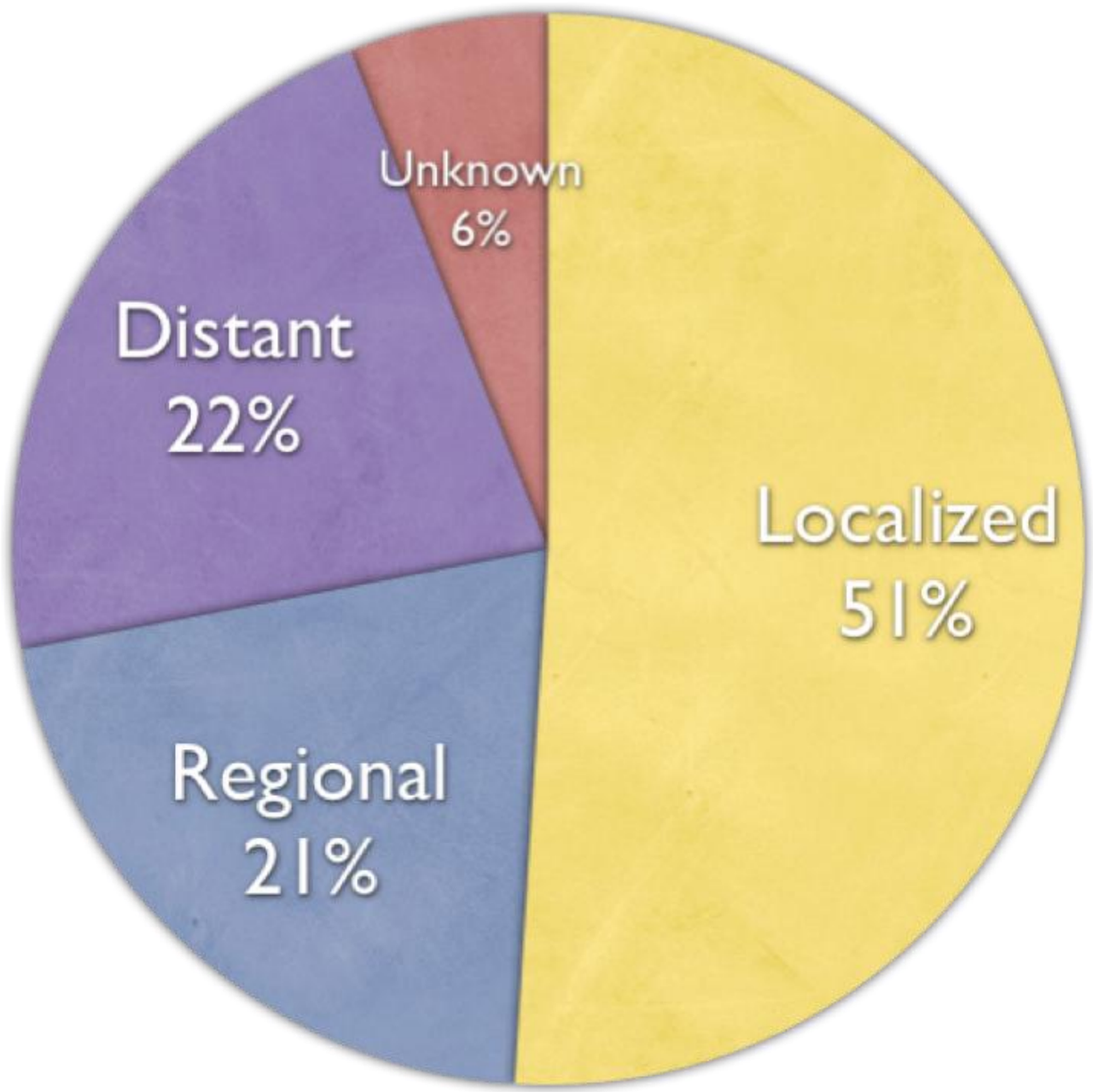
- Stage I: Localized to kidney, <7 cm
- Stage II: Localized to kidney, <10 cm
- Stage III: Compartmental invasion and/or nodal metastasis (including vena cava)
- Stage IV: Extracompartmenal invasion (adrenal, retroperitoneum) and/or distant metastasis

b) stage III means outside the kidney but within the retroperitoneal compartment of the kidney. Kidney is surrounded by fat: if tumor is outside the kidney but inside this fat (not reach the retroperitoneum yet) it is stage 3. Also vena cava.

THIS SLIDE IS IMPORTANT!!!

39:06 This indicates RCC at time of diagnose. Pretty self-explanatory.

RCC Stage Distribution

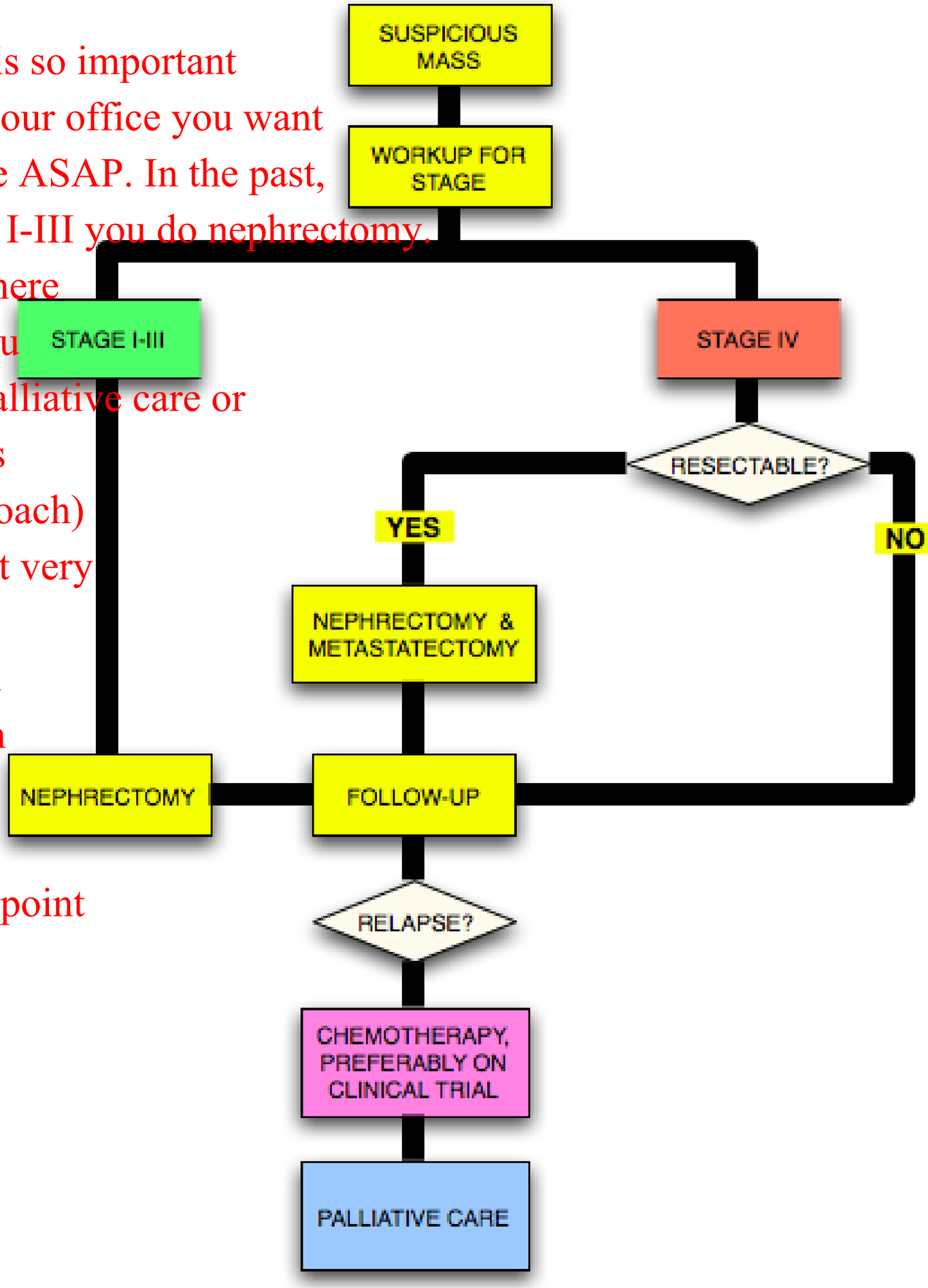


39:18

RCC survival (1988-2002)

I believe this is also another important graph but again the data is not showing here. Yellow line (in the top) showed the survival rate of people with localized RCC. In 10 years, approximately 80% of the people survive. However if you look at the purple line (botton one), representing people with metastasis, only 25% will survive WITHIN A YEAR!! Pretty scary!

39:45 Because stage is so important
if someone come to your office you want to determine the stage ASAP. In the past,
If the RCC was stage I-III you do nephrectomy.
If there was relapse there was nothing much you could offer besides palliative care or eventually chemo (as an experimental approach) because chemo wasn't very effective.
If it was stage IV you might have the option to remove the tumorn or not.
The prognosis at this point was bad anyway.



41:13 In the last 5- 10 years some options start to become available.

Emerging treatment options

- **Kidney-sparing surgery** for small tumors this is an option
  - Partial nephrectomy
  - Cryosurgery, HIFU, radiofrequency ablation
- **Chemotherapy** this is improving.
  - Kinase inhibitors (sunitinib, sorafenib) can increase your life for a couple months
    - Doubles progression-free survival in Stage IV RCC
  - mTOR inhibitor (temsirolimus) have become routine
  - Cytokines (IFNα, IL-2)
  - Antiangiogenic (bevacizumab/avastin) people are still trying to use this one

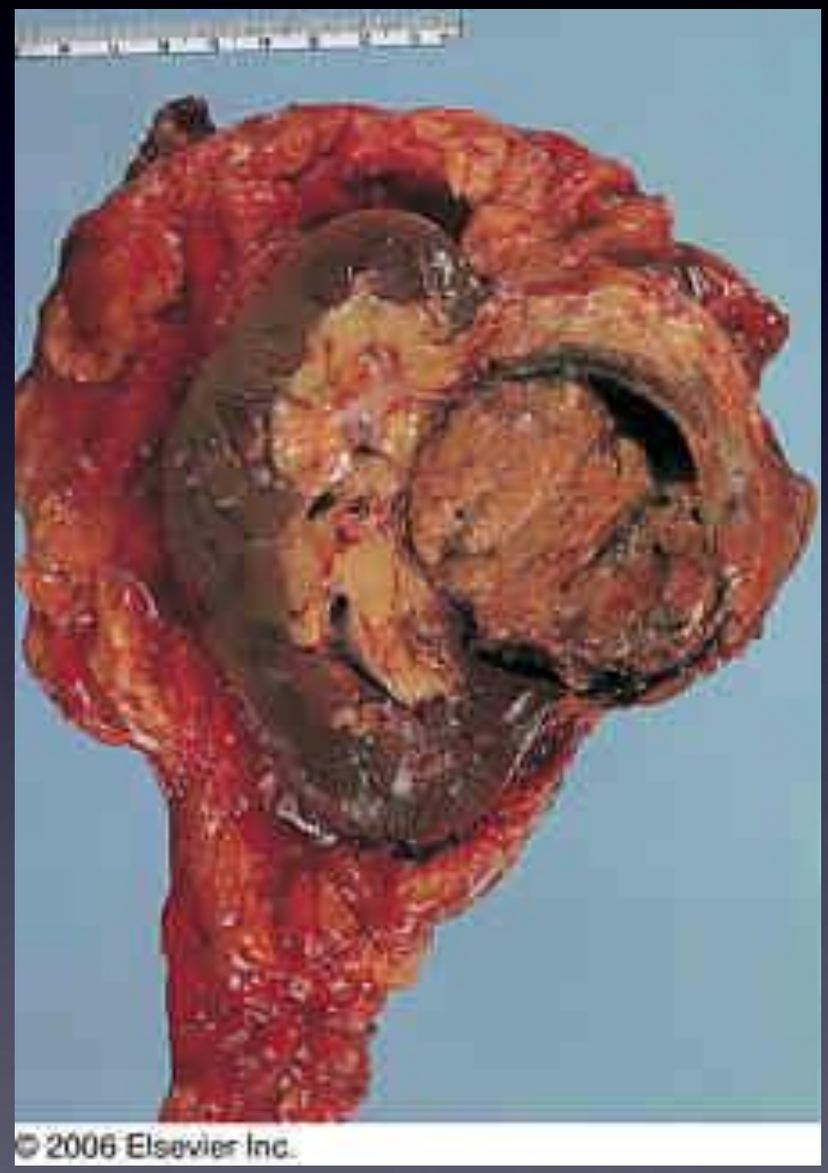
Chemotherapy increases the survival to months, maybe a year on average. It is not great but better than nothing.

43:11

Renal medullary carcinoma

It an interesting tumor that usually is not classified in the group of RCC

- "Seventh sickle nephropathy"
- Almost exclusively in patients with sickle cell disease/trait
- Males > females
- Age ~20



Renal Medullary carcinoma: It happens in young people, with sickle cell disease/ trait. It is very high grade tumor and usually fatal.

44:00

Nephroblastoma (Wilms' Tumor)

important tumor, specially if you are going to do pediatrics.

- Recapitulates structures of embryonic kidney
- #1 renal cancer of childhood
- #3 solid cancer of childhood
  - 6% of childhood cancer
  - About 500 U.S. cases/year
  - >90% of pediatric renal tumors
- Males~females, average age ~3 years
  - Rare before 6 mos or after 10 yrs

44:58

Nephroblastoma

Clinical

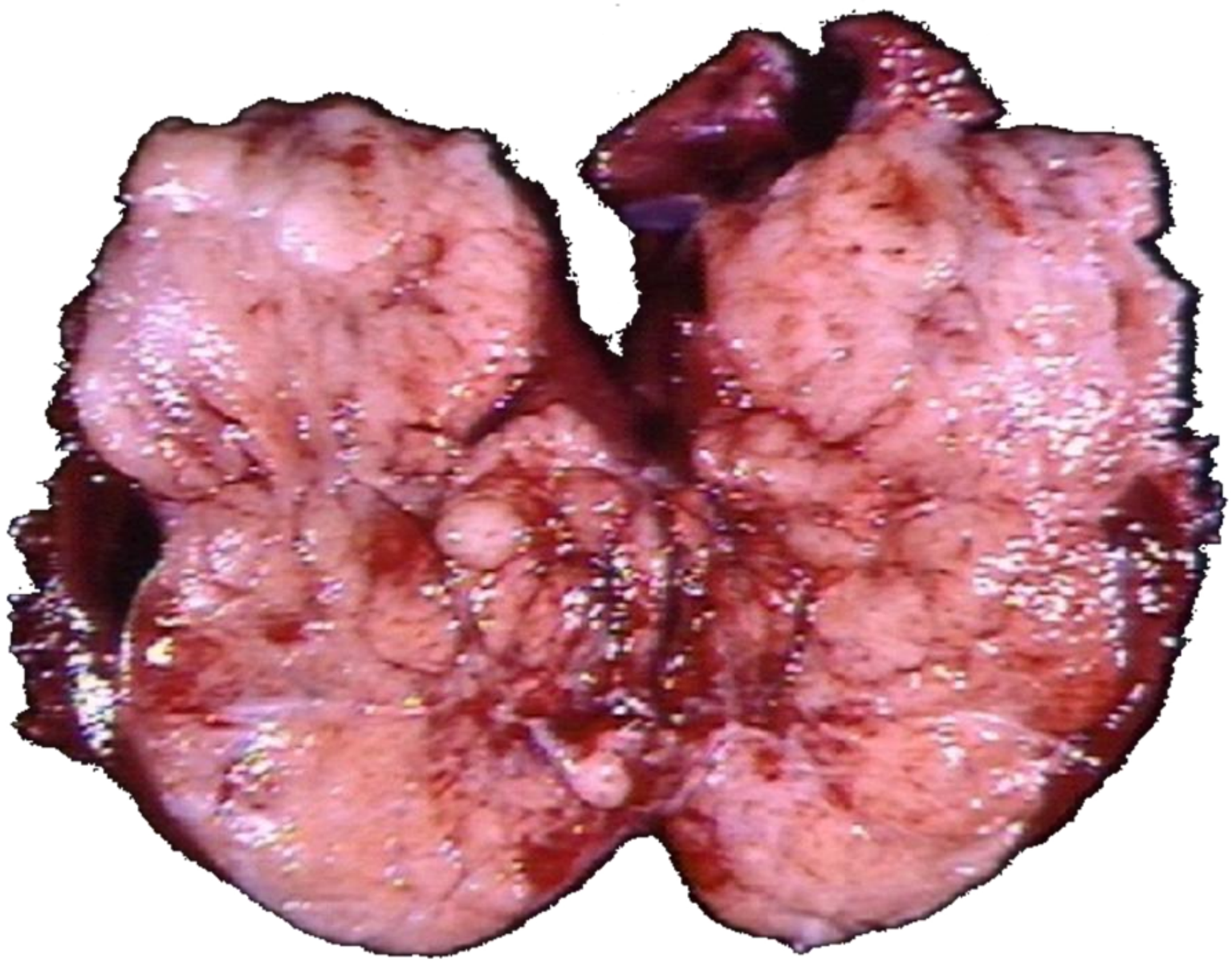
- 85% abdominal mass
- 40% pain
- 60% hypertension
- 5% coexisting urogenital anomalies
- 5% bilateral

Nephroblastoma : common cause of renal cancer in child. Average age 3 years old. Child usually will present with abdominal mass and hypertension.

45:37

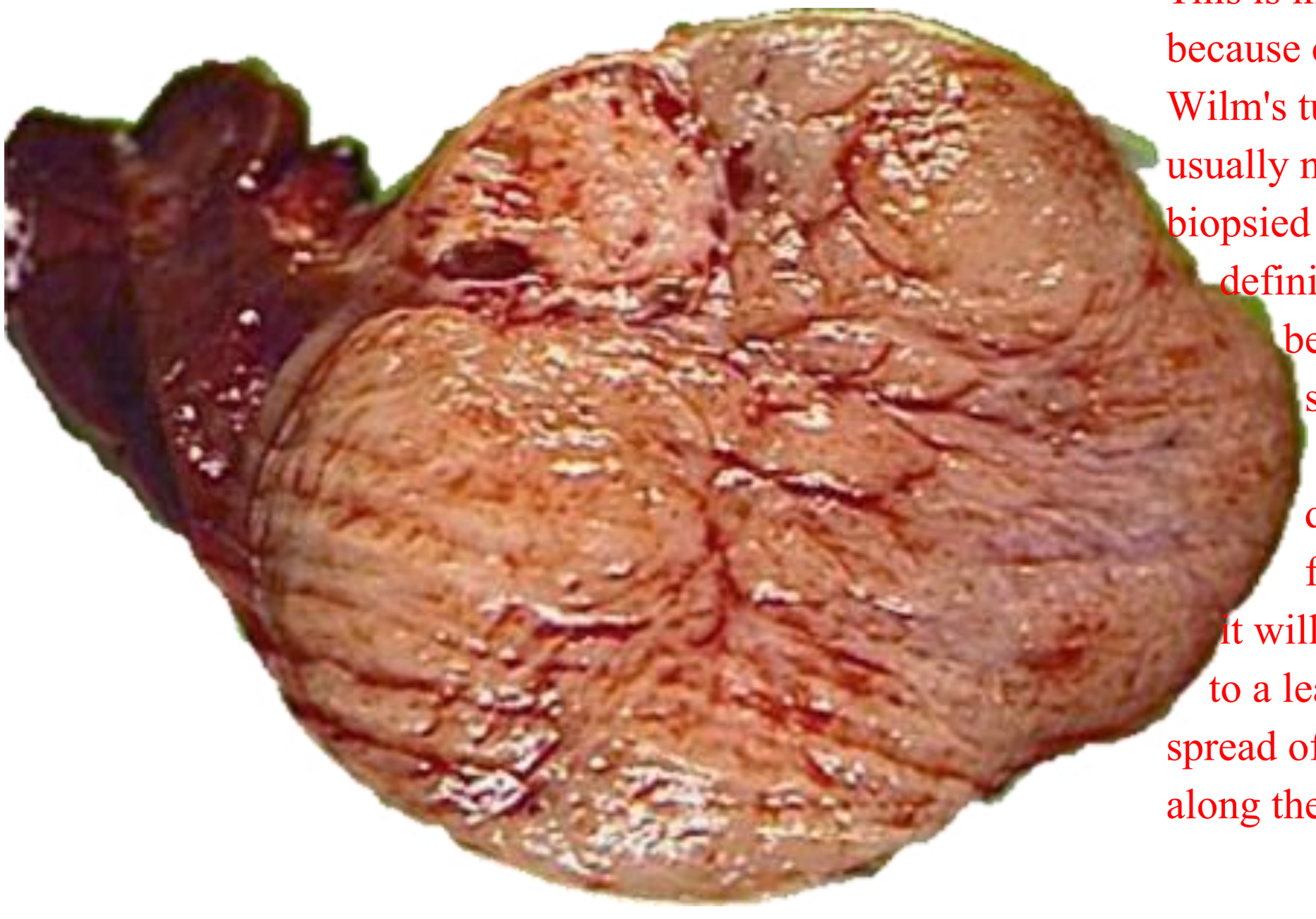
Fleshy, friable mass replacing entire kidney

when you cut through it it is like cutting through a "custard".



45:50

Soft, friable texture easily dislodged during sectioning



This is important because children with Wilm's tumor are usually not biopsied prior to definitive resection because if you stick a needle inside it, due to its friability, it will lead to a leakage and spread of the tumor along the needle track.

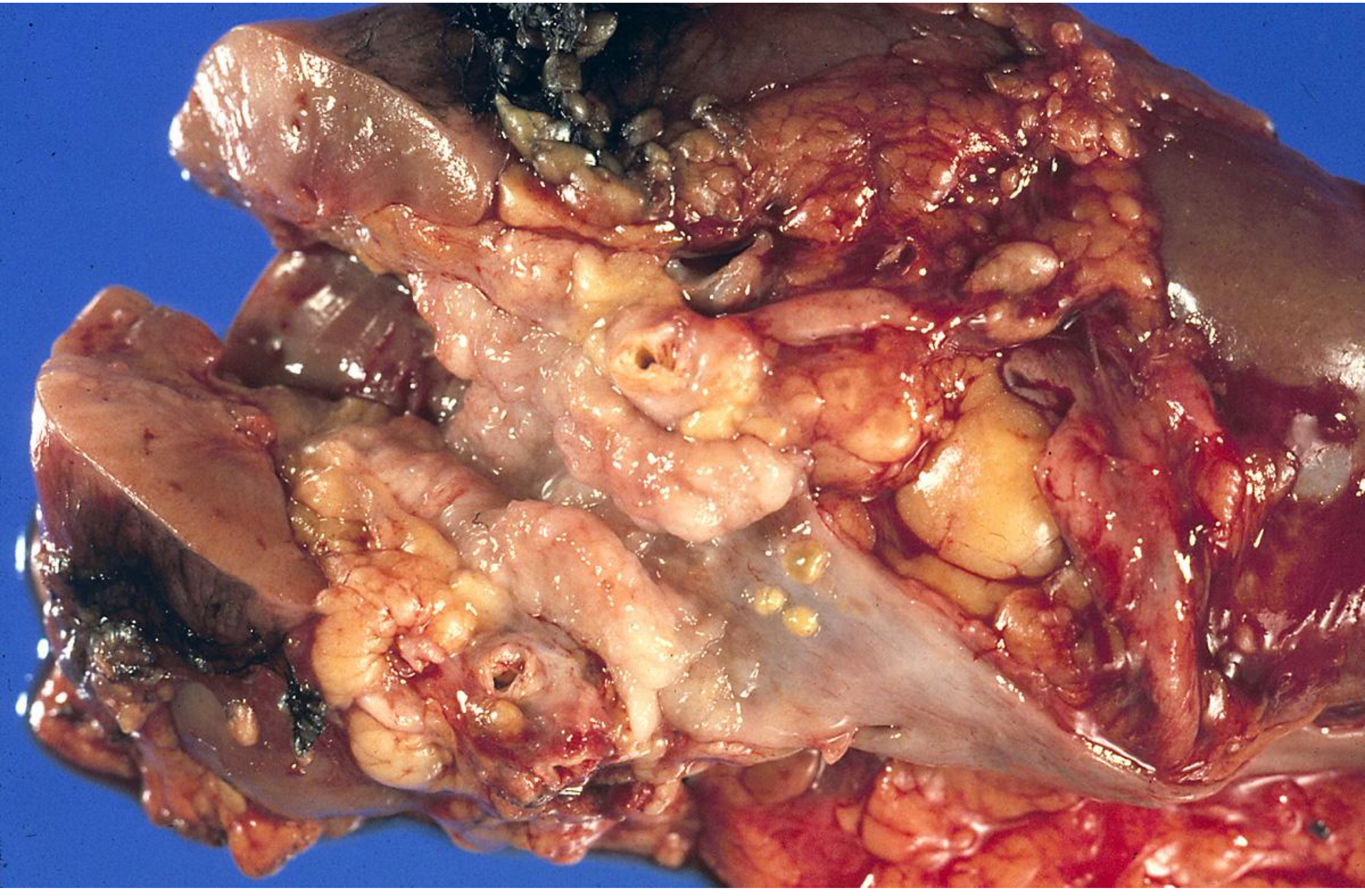
46:31

Components of nephroblastoma

It is a triphasic tumor. It recapitulates structures that occurs during embrionic devolopment of the kidney . The components of the tumor are below:

- Blastema
- Epithelium
- Stroma

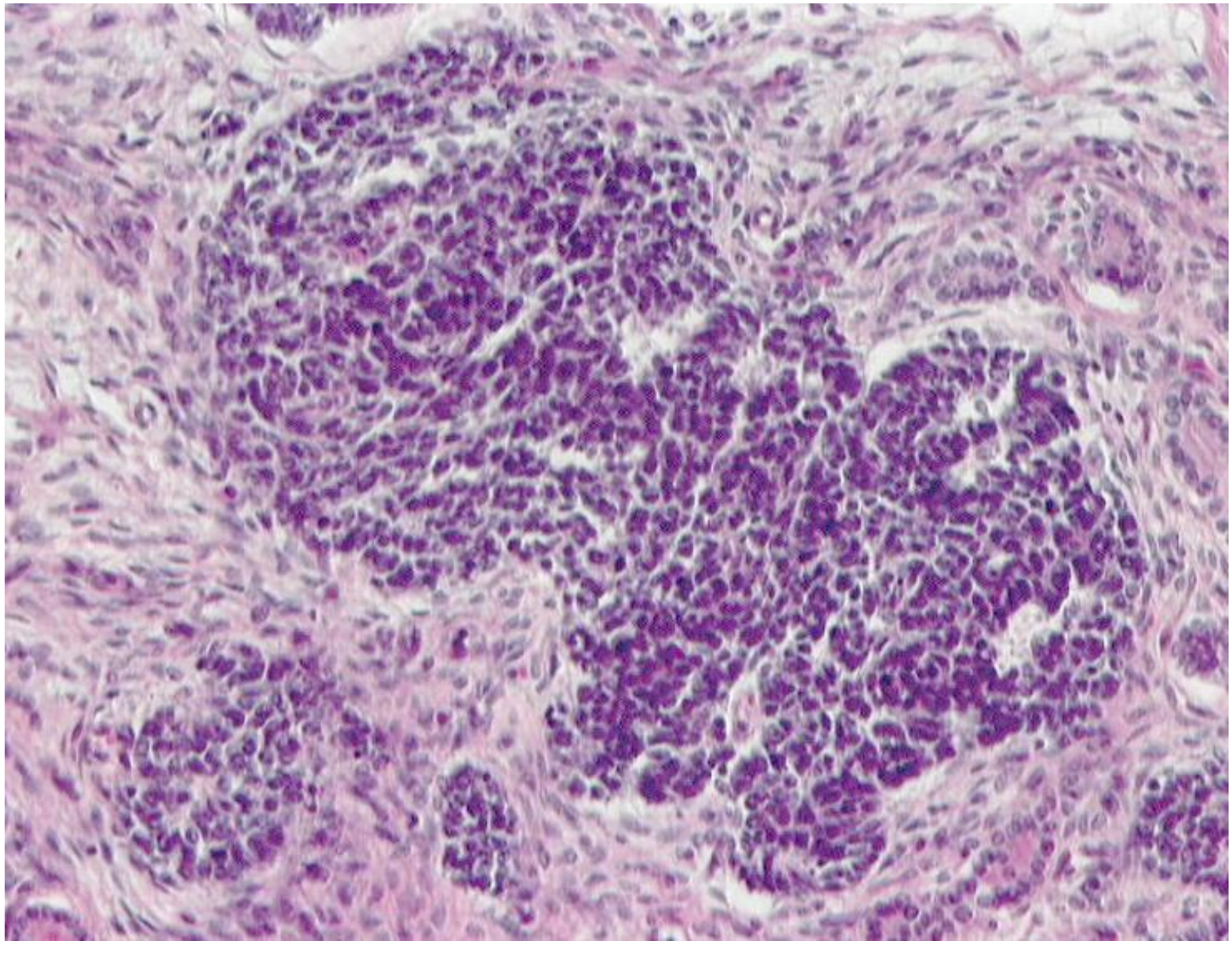
46:40 Wilm's tumor just as renal cell carcinoma tends to invade the renal vein.



46:56

Blastema

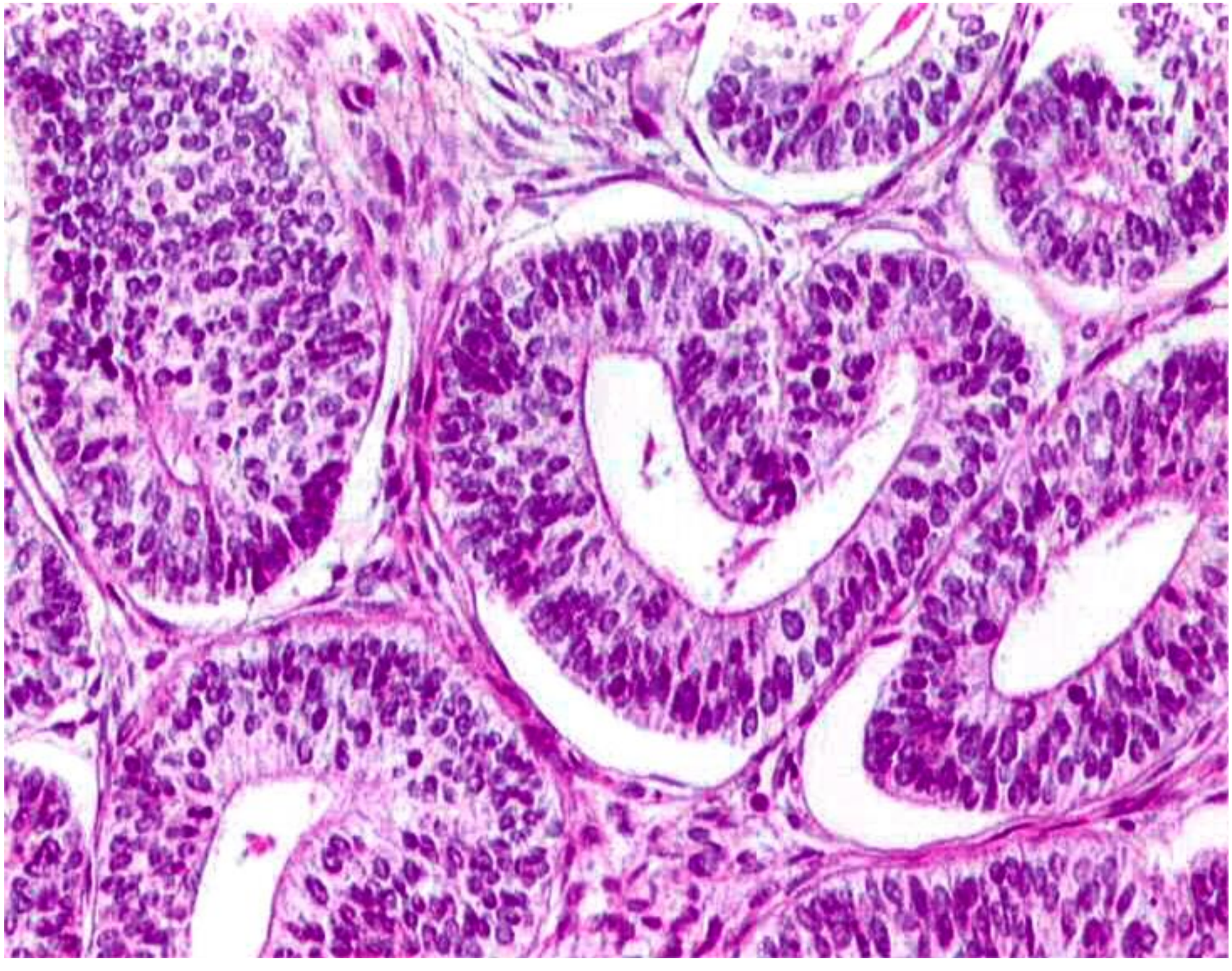
One of the components of wilm's tumor: a bunch of undifferentiated blue cells



47:02

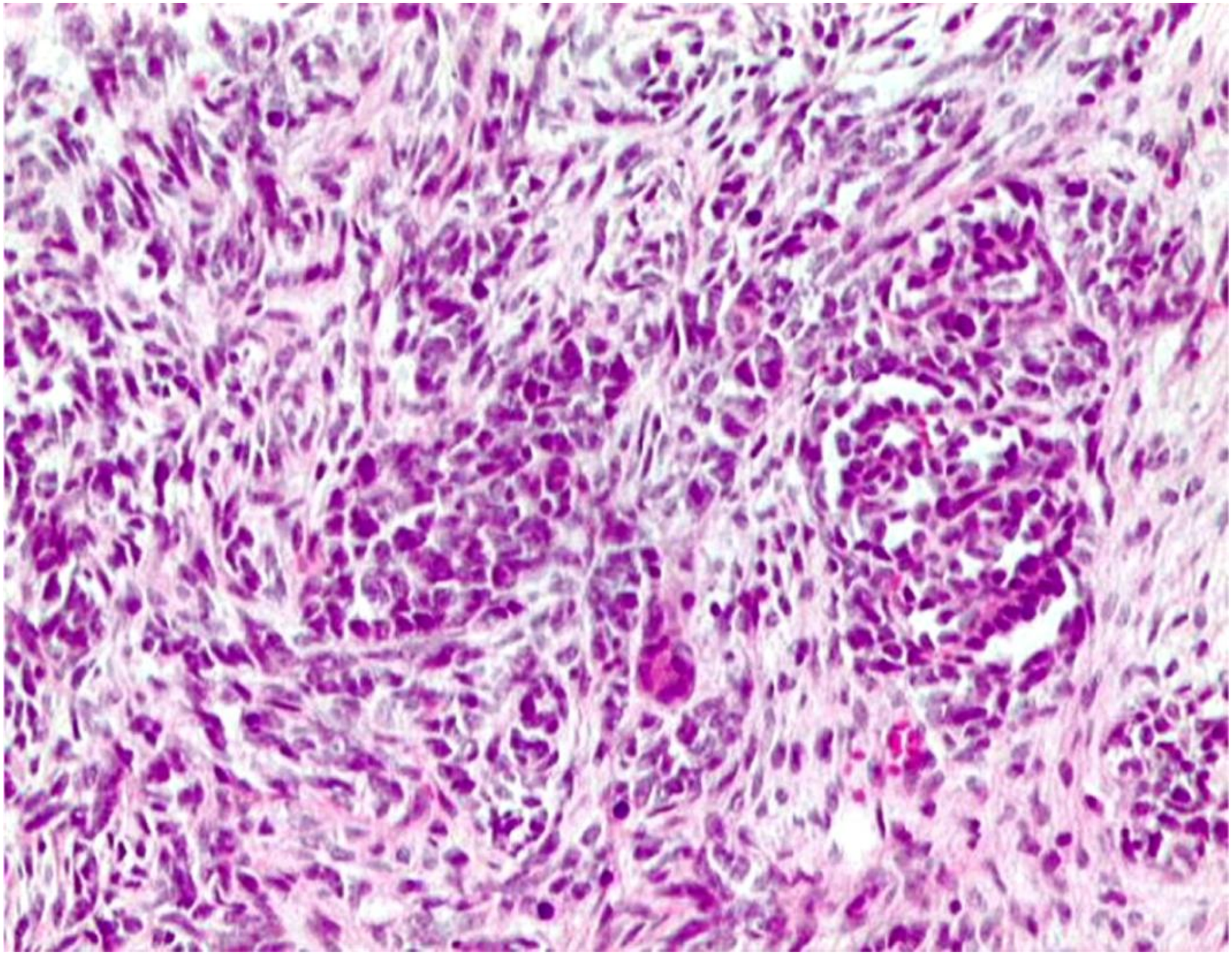
Epithelium

intermixed with blastema, you can observe "epithelium" it looks like renal tubule but it is kind of messy!

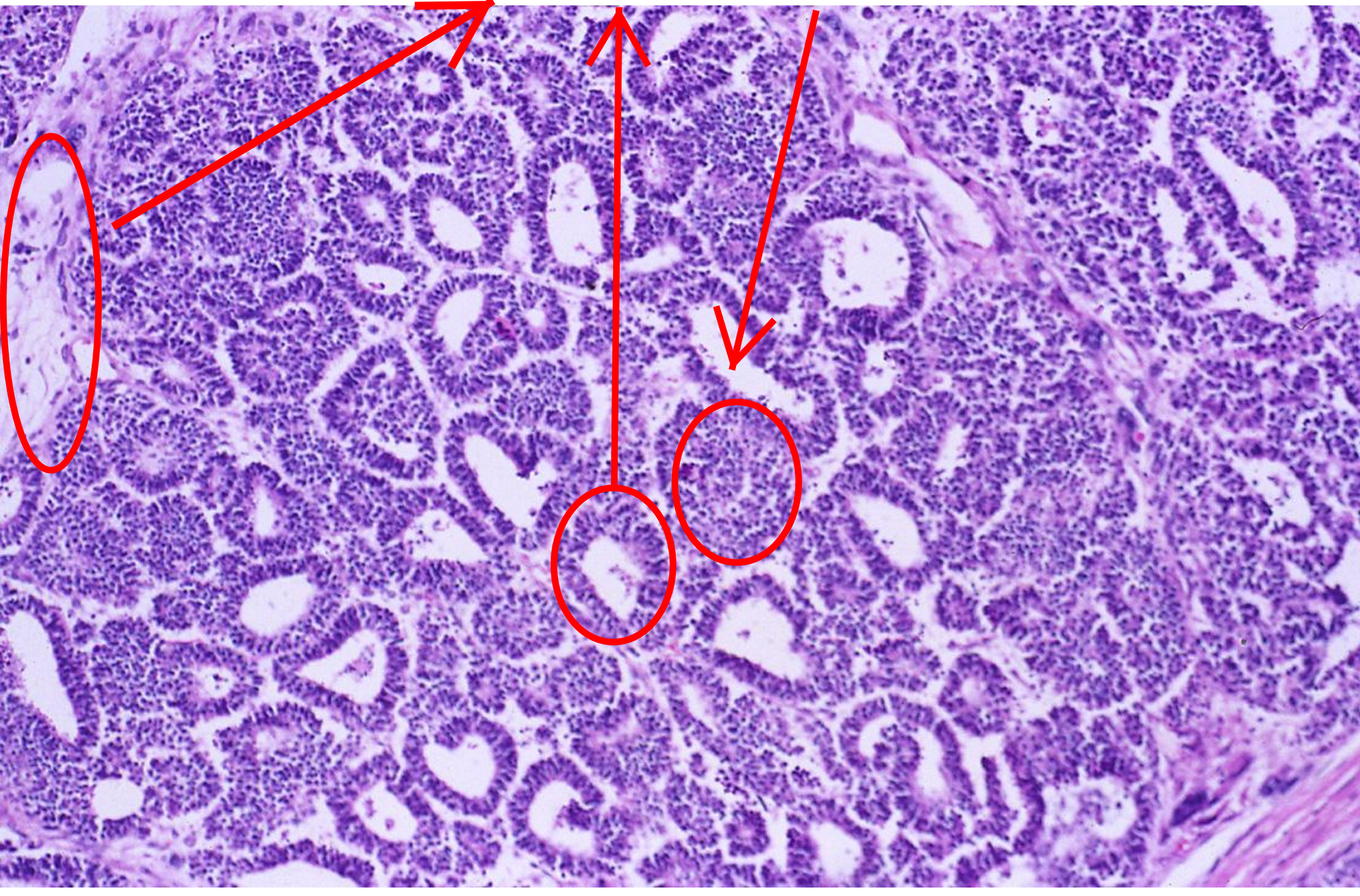


47:22 it is the last component of wilm's tumor. It looks like fibroblast, it can have muscle cells in it, and cartilage. In summary: Wilm's tumor is a triphasic tumor.

Stroma



47:37 Low power view showing: stroma, epithelium and blastema



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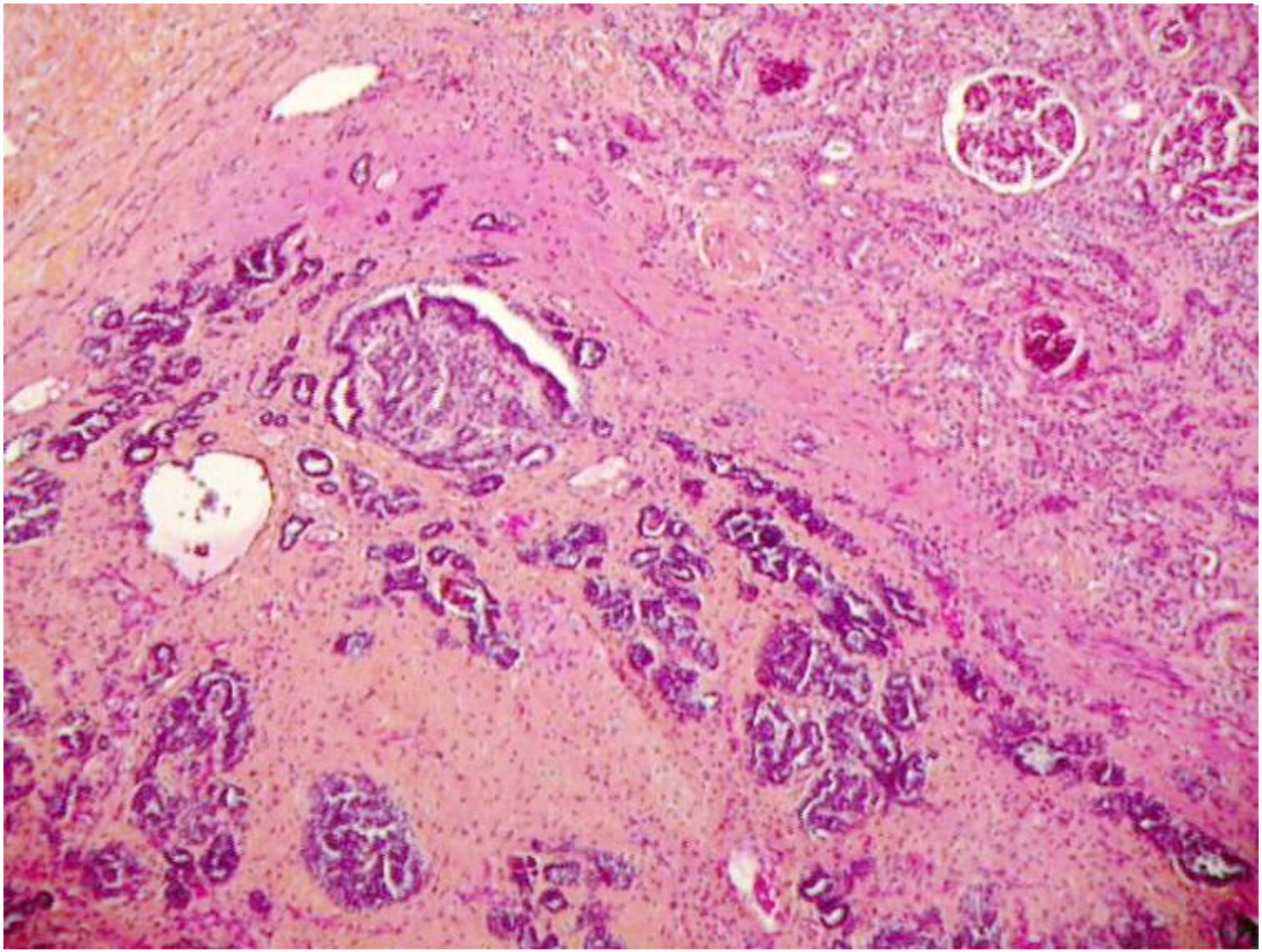
Nephrogenic rests (formerly “nodular blastema)

- Abnormally persistent foci of embryonal kidney, probably precursor to nephroblastoma

skipped

Intralobar nephrogenic rest



47:58

Nephroblastoma Cytogenetics

genetics well worked out.

- WT1 Tumor Suppressor Gene (11p13)
  - LOH in one-third of NB loss of heterozygocity in 1/3 in this tumor
  - DNA-binding protein
  - Normally extremely tissue- and developmentally-restricted expression
  - Transcriptional regulation usually it is turns down after the kidney develops. In this tumor it is still on
- WT2 Tumor Suppressor Gene (11p15)
  - Beckwith-Weidemann Syndrome
- WT3 (16q)
  - Poor prognosis

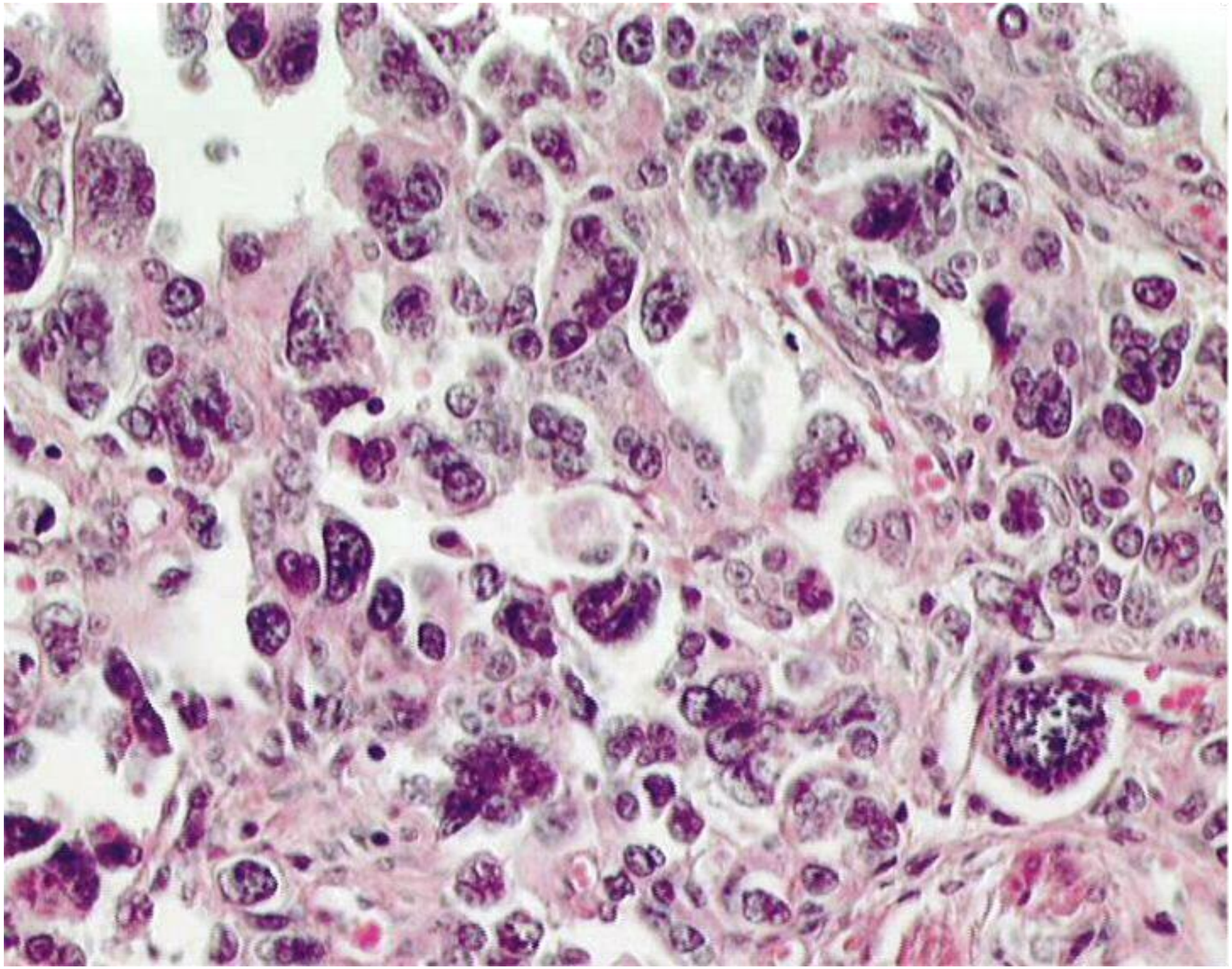
48:56 Options of treatment for these kids? It will depend on grading again. If you can, first of all, try to remove it as much as you can. Occasionally these kids resection followed by chemo. What will determine the clinical approach will depend on the grading (if favorable or unfavorable) and the age of pt.

Nephroblastoma grading

- "Favorable histology" (95%)
  - Without anaplasia
  - Focal anaplasia
- "Unfavorable histology" (5%)
  - Diffuse anaplasia

49:45 If the anaplasia is too difuse...we have a problem!

Anaplasia



49:50 Pretty self-explanatory

Nephroblastoma staging

- Stage I — Limited to kidney, completely excised
- Stage II — Extends beyond kidney, but completely excised
- Stage III — Residual tumor confined to abdomen
- Stage IV — Distant (hematogenous) metastasis
- Stage V — Bilateral renal involvement at diagnosis

49:55

Important prognostic factors

- Age at detection (older = worse)
- Stage
- Unfavorable histology

50:18

Typical therapy

- Favorable, Stage I-II or Unfavorable, Stage I
  - – Light chemo and surgery
- Favorable, Stage III-IV or Unfavorable, Stage II-IV
  - – Chemo, radiation, surgery

Treatment options will depend on the stage. VERY IMPORTANT ! Because if you treat a child with radiation in their flank region, you can damage the spinal cord and the child can develop scoliosis. So make sure you are treating for a reason.

51:01 The good news is that even with high stage and unfavorable histology the survival is still good! God bless! THE END !

NB treatment outcome

Stage	Histology	Survival
I-III	Favorable	>95%
IV	Favorable	90%
II-IV	Unfavorable	82%

I. Classify the non-neoplastic diseases of the kidney as tubulointersitial, vascular, or hereditary/metabolic
    a. Tubulointersitial
        i. Acute tubular necrosis
            1. Ischemic type
            2. Toxic type
        ii. Acute interstitial nephritis
    b. Vascular disease
        i. Hypertensive nephropathy
            1. Ordinary type
            2. Malignant hypertension
    c. Hereditary/metabolic
        i. Renal cystic disease (to be covered in a later lecture)
            1. Adult polycystic kidney disease
                a. Autosomal dominant
            2. Dialysis-associated cystic disease
                a. Acquired
            3. Pediatric cystic diseases & others
                a. Autosomal recessive
        ii. Diabetic nephropathy (He did not specifically discuss this etiology in class. Our textbook classifies this under "glomerular lesions associated with systemic diseases")

II. What he actually did in lecture: classification according to clinical presentation
    a. Non-progressive **acute** renal injury
        i. Acute tubular necrosis
            1. Ischemic type
            2. Toxic type
        ii. Acute interstitial nephritis
    b. Progressive to **chronic** renal failure (ERSD)
        i. Renovascular disease
            1. Diabetic nephropathy
            2. Hypertensive nephropathy
                a. Ordinary type
                b. Malignant hypertension

III. Recognize and describe the pathology of non-neoplastic kidney diseases:
    a. Acute tubular necrosis:
        i. Occurs in the most susceptible tubules
            1. Proximal tubule
            2. Ascending loop of Henle
        ii. Gross pathology
            1. Pale, edematous, swollen
        iii. Histology

1. Ischemic
    a. Patchy damage
    b. Loss of tubular epithelium
    c. Tubular dilation
    d. Cellular casts
    e. Little or no inflammation
2. Toxic
    a. Contiguous damage
    b. Tubular dilatation
    c. Some toxins result in crystal formation in the tubules
    d. Cast formation

b. Acute interstitial nephritis
    i. Inflammation between the tubules (in the intersitium)
        1. Eosinophils
        2. T cells
    ii. Edema

c. Diabetic nephropathy:
    i. Gross organ
        1. Pox marks covering the renal capsule
    ii. Histology
        1. Glomerulosclerosis
            a. Nodular lesion (Kimmelstiel-Wilson lesions)
            b. Diffuse mesangial expansion
            c. Exudative lesions
        2. Arterial damage
            a. Hyalinosis of small arteries
            b. Accelerated atherosclerosis
        3. Tubulointersitial changes
            a. Tubular dropout
            b. Intersitial fibrosis
            c. Papillary necrosis

d. Hypertensive nephrosclerosis
    i. Ordinary type
        1. Gross pathology
            a. Pox marks covering the renal capsule
            b. Additional larger fibrotic lesions due to involvement of larger arteries and arteiroles
        2. Histology
            a. Medial thickening and intimal fibrosis of medium and large-sized arteries
            b. Arteriolar thickening and hyalinosis
            c. Global glomerulosclerosis

d. Tubulointersitial fibrosis

ii. Malignant hypertension
1. Gross pathology
a. Small hemorrhages in the parenchyma due to arteriolar ectasias
2. Histology
a. Fibrinoid necrosis
b. Proliferative endarteritis
c. Onion-skin myointimal proliferation
d. Arteriolar ectasias

iii. End stage kidney: end result of chronic renal disease
1. Gross pathology
a. Shrunken kidney
b. Thinned cortex
c. Fat fills in the hilum
d. Cystic change

IV. Explain the pathogenesis and describe the typical clinical course of non-neoplastic kidney disease

a. Acute tubular necrosis
i. Causes:
1. Ischemic:
a. Hypotension, blood loss, MI, obstetric complications, sepsis, surgery
2. Toxic:
a. Drugs (aminoglycosides, amphotericin B, cytotoxic drugs, cyclosporine), radio contrast media, mylglobinuria, ethylene glycol, heavy metals, organic solvents

ii. Clinical course
1. Initiation phase: rapid decline of GFR (over hours)
2. Maintenance phase: low GFR (5-10 days)
3. Recovery phase: Sudden recovery of GFR and profuse diuresis (several days)
4. Late recovery: In patients without pre-existing disease there can be complete recovery (may take weeks to months). In patients with background disease, long-term survival varies.

b. Acute interstitial nephritis
i. T-cell mediated hypersensitivity reaction
1. Associated mainly with antibiotics and NSAIDS
2. The drug can haptenize to endogenous TBM or interstitial component
3. The drug can form immune complexes and deposit in the intersitium
4. Release of fibrogenic cytokines can cause irreversible fibrosis

ii. Clinical course
1. Delay between drug exposure and renal failure ~10 days

2. Arthralgia, fever, skin rash, and hematuria are common

c. Diabetic nephropathy
    i. Occurs in both IDDM and NIDDM
    ii. Pathogenesis
        1. Not well understood
        2. Advanced glycosylation end products and cytokine pathway activation are both implicated
    iii. Clinical course:
        1. Stage I: compensatory increase in GFR
        2. Stage II: GFR returns to normal
        3. Stage III: A gradual decline in GFR
        4. Stage IV-V: A more rapid decline in GFR over 5-25 years

d. Hypertensive nephrosclerosis
    i. Ordinary type
        1. Clinical:
            a. Long term systolic hypertension which is both a cause and effect of the renal disease
            b. Risk factors are the same as for hypertension in general
        2. Pathogenesis
            a. Very poorly understood: due to both elevated intrarenal BP and glomerular ischemia
    ii. Malignant hypertension
        1. Clinical
            a. Acute onset of SBP >160 with acute end-organ damage
            b. May occur with or without chronic hypertension
        2. Additional effects due to arteriolar damage
            a. Retinopathy
            b. Encephalopathy
        3. Mechanical effects of malignant hypertension
            a. Aortic dissection
            b. CHF
            c. Pulmonary edema
            d. Hemorrhagic stroke

Renal Diseases

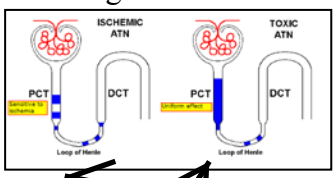
Overview of Kidney Diseases:

1. We can divide non-neoplastic kidney diseases into tubulointerstitial and vascular
2. **Tubulointerstitial**:
    a. Infectious = ascending infections, pyelonephritis
    b. Allergic or toxic
    c. Acute tubular necrosis
3. **Vascular**:
    a. Arterial/arteriolar
    b. Glomerular disease

Acute Tubular Necrosis:

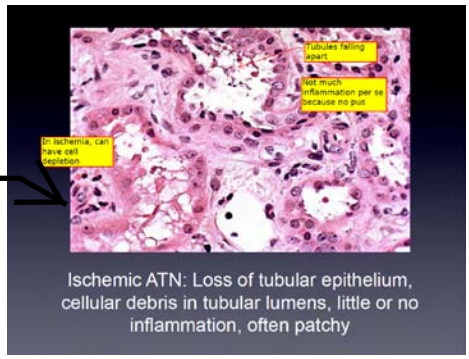
1. Presents as **acute renal failure**
2. Most common cause of acute renal failure, 50% survival
3. **Acute signs**:
    a. Decreased GFR
    b. Increased BUN and creatinine
4. Over 1-2 weeks, will get decreased urine production
5. After tubular epithelium regenerates, get diuresis and BUN/Cr go down
6. **Caused by either toxic or ischemic insult** to kidney
7. **PCT especially susceptible**:
    a. Toxic = uniform attack
    b. Ischemic = more sporadic
8. Causes of **ischemic** injury:
    a. Hypotension from any cause
    b. Blood loss, prerenal state, MI
    c. Obstetric, sepsis, surgery
9. Causes of **toxic** injury:
    a. Aminoglycosides, ampho B, cisplatin
    b. Radiographic contrast, myoglobinuria

Treatment for ATN:
- remove offending agent
- supportive (volume, hyperkalemia, loop diuretics)
- dialysis

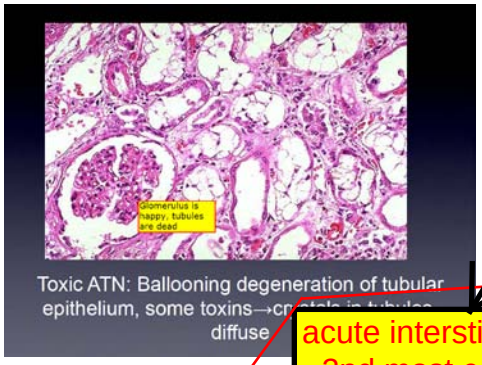


ischemic effect can be patchy, whereas toxic effect is uniform

extent of tubular injury correlates poorly with renal impairment (patchiness, medullary damage more important, etc.)



Ischemic ATN: Loss of tubular epithelium, cellular debris in tubular lumens, little or no inflammation, often patchy



Toxic ATN: Ballooning degeneration of tubular epithelium, some toxins→cr... diffuse

inTErstitial - T cells and eosinophil
- causes hematuria, rash, arthalgia

acute interstitial nephritis
- 2nd most common cause of ARF
- eosinophil-rich inflammation
- >75% drug-induced (antibiotics, NSAIDs, furosemide)
- usually 10 days b/t exposure and ARF
- usually have hematuria
- treatment: remove drug + steroids

Renovascular Disease:

1. Most common cause of **end stage renal disease** (ESRD)

- AIN caused by the formation of neo-antigens with tubulo BM, causing cell-mediated resopnse
- sometimes fibrosis is **irreversible**

2. **Diabetes (#1) and hypertension (#2)** are major causes
3. Other causes are glomerulonephritis and cystic kidney disease
4. These patients can't survive without dialysis or transplant
5. **Transplantation** = best treatment for ESRD, highest survival
6. Survival for hemodialysis isn't determined by initial cause of ESRD
7. **Diabetic nephropathy**:
    a. Persistent albuminuria, decrease in GFR, HTN
    b. Untreated mortality is 100%
    c. IDDM 30%, NIDDM 15%
    d. Takes around 20 years of uncontrolled diabetes to get ESRD
    e. *Gross*: get acne of the kidney, each mark represents dead glomerulus
    f. Cause of diabetic nephropathy not entirely understood, probably relates to hyperfiltration (because protein in urine), glycosylation, cytokines
8. **Diabetic nephropathy** continued:
    a. *Glomerulosclerosis*:
        i. Hallmark component of diabetic nephropathy
        ii. Kimmelstiel-Wilson nodular lesions
        iii. Diffuse mesangial expansion
        iv. Exudative lesions (adhesions between glomerulus and bowman's capsule)
    b. *Arterial damage*:
        i. Hyalinosis of small arteries
        ii. Accelerated atherosclerosis
    c. *Tubulointerstitial changes*:
        i. When glomerulus dies, related tubules die
        ii. Tubular dropout, interstitial fibrosis, papillary necrosis
9. **Hypertension** renovascular disease:
    a. HTN is both a **cause and effect** of renal disease
    b. *Gross*: see large craters which are infarcts from arcuate artery infarction
    c. Hypertensive nephrosclerosis see medial thickening and intimal fibrosis of larger arteries, see arteriolar thickening and hyalinosis, etc.
    d. **Malignant hypertension** = hypertensive crisis, BP >160 with end-organ damage, most cases are renovascular, now can treat quite well
    e. Pathology of malignant hypertension:
        i. Arteriolar damage:
            1. Fibrinoid necrosis and proliferative intima/media
            2. See "onionskin" intima proliferation
            3. See sausage-string arteriolar ecstasias
        ii. Nephropathy, retinopathy, encephalopathy
    f. Examples given, shrunken kidney

Cystic Kidney Disease:

1. Fourth-leading cause of ESRD
2. Approximately 90% of cases are **autosomal dominant**
3. **Hereditary mechanisms**:
    a. Infant = juvenile nephronophtisis or glomerulocystic kidney
    b. Adult = VHL/TS, medullary sponge, or glomerulocystic

because these are no longer the main causes of ESRD, the population is "graying" since ESRD patients now tend to be older as more ESRD is caused by DB and high BP

insulin-dependent and non-insulin dependent

entire unit dies (tubules, etc.)

not just acne like in diabetic nephropathy b/c whole groups of units die

sudden increase in hypertension, leading to functionally incompetent arterioles

this makes it different from diabetic nephropathy

"blow-outs"

malignant hypertension affects other organs with many small arterioles, too

adult polycystic kidney disease

adult PCKD is most important

Cystic disease we talked about:
1. APKD (adult hereditary)
2. Acquired cystic renal disease (adult non-hereditary)
3. IPKD (infant hereditary)
4. Multicystic dysplasia (infant non-hereditary)

4. **Non-hereditary mechanisms**:
    a. Infant = multicystic dysplastic kidney
    b. Adult = dialysis-associated cystic disease
5. **Adult polycystic kidney disease**:
    a. Most common genetic disease
    b. Frequency 1:750
    c. 100% penetrance by age 80, most present in 30's to 40's
    d. Early symptoms = flank pain, hematuria, infection
    e. Complications = HTN, nephrolithiasis, perinephric abscess
    f. Would remove the kidney (other diseases typically leave kidney in place)
    g. **PKD1 and PKD2** = polycystin gene for ion channels
6. **Infantile polycystic kidney disease**:
    a. Autosomal recessive
    b. Multi-organ manifestations (liver cysts, pulmonary hypoplasia)
    c. Most die in utero or early infancy
7. **Multicystic renal dysplasia**:
    a. Non-hereditary, may occur as component of multiple malformation syndrome
    b. Obstructive ureteral anomaly 90%
8. **Acquired cystic renal disease**:
    a. Found in chronically non-functioning dialysis patients (takes many years)
    b. Increased risk of RCC

25% = no hx, so new mutation

widely variable expressivity

kidney stones!

also renalmegaly

also renal cell carcinoma

mutations in these genes lead to APKD

didn't really focus on any of these

adult, non-hereditary

APKD associated with:
- hypertension
- kidney stones
- nephric abscesses
- RCC

Go on...

Benign:
- Angiomyolipoma
- Renal oncocytoma
Malignant:
- Renal cell carcinoma
- Renal medullary carcinoma
- Nephroblastoma

Kidney Neoplasms

lots of blood vessels, fat, and smooth muscle cells

Angiomyolipoma:

1. **Benign** tumor (larger will be symptomatic but smaller probably incidental)
2. Consists of **abnormal blood vessels, proliferating smooth muscle, and fat**
3. **Females** more than males, **middle aged**, and **2%** of renal tumors
4. Strong correlation with **tuberous sclerosis** (25%)
5. Very vascular tumor, lights up on contrast CT scans
6. Differential diagnosis is RCC
7. Treatment:
    a. Symptomatic = nephrectomy
    b. Asymptomatic = embolization

contains perivascular epitheliod cell (PEC) type

Complications:
- hemorrhage
- renal failure

angiomyolipoma - lots of cell types, associated with tuberous sclerosis
oncocytoma - mahogany (red!) colored, central stellate scar

Renal Oncocytoma:

1. **Benign** neoplasm of "**oncocytes**"
2. **Males** more than females, **older** adults, and **3%** of nephrectomies
3. Usually asymptomatic, found using imaging accidently
4. Buzzwords:
    a. **Mahogany colored** cortical mass
    b. **Central stellate** scar
5. Typically circumscribed
6. **Mahogany** = deep red colored because oncocytes are full of **mitochondria** (cyt c)
7. *Histology*: clusters of oncocytes, which appear as big balloon-like cells, very **red**

circumscribed

Renal Cell Carcinoma:

1. **Malignant**, most common renal tumor
2. **Males** more than females, median age **55 years**, **3%** of adult malignancies
3. This is the *most important*, it is more common than the benign ones
4. **Risk factors**:
    a. Tobacco
    b. Cystic kidney disease (also with acquired cystic on renal dialysis)
    c. Von Hippel-Lindau syndrome
5. **Majority asymptomatic**
6. Triad of symptoms = **hematuria, flank pain, flank mass**
7. Paraneoplastic syndrome = liver dysfunction, **hypercalcemia**, erythrocytosis
8. Mortality data has not changed much since 1970s
9. Characteristic feature = **renal vein full of tumor**, RCC crawls out of renal vein
10. RCC staging:
    a. T1 = localized under 7 cm, T2 = over 7 cm, T3 = extended, T4 = wide extensions
    b. N = nodes, M = metastasis

RCC: think BIG, PAINFUL, BLOODY mass. or asymptomatic.

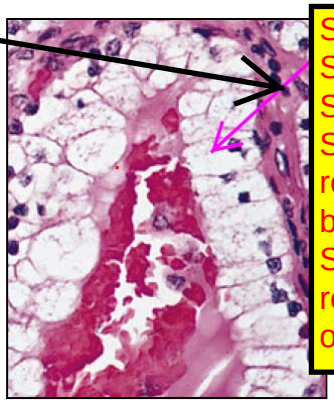
mutation in tumor suppressor gene

can go up vena cava to right atrium

RCC Subtypes:

1. **Conventional "clear cell" RCC**:
    a. Most common subtype (70%)
    b. Often has deletion on chromosome 3p

all pretty similar in terms of prognosis and treatment

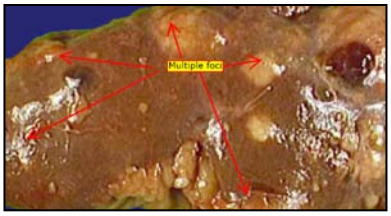


Staging:
SI: kidney, <7
SII: kidney, <10
SIII: inside retroperitoneum, but outside kidney
SIV: reaches retroperitoneum or goes beyond

contains many tumor suppressor genes, including VHL

c. Rounded cortical mass, yellow (necrosis) or red (hemorrhage) or white (calcification), odd surfaces
d. **Clear cells** = have **lipid and glycogen** — clear = conventional
e. Prominent capillary network
f. Frequently hemorrhage and necrosis — due to large number of leaky capillaries
g. Genetics: remember that **3p** is the hot spot for genes related to the tumor

2. **Papillary RCC**:
   a. Second most common (15%)
   b. Found in the **peripheral cortex**
   c. Often **multi-focal**
   d. Can be large, yet circumscribed
   e. Associated with **acquired cystic disease**
   f. Better prognosis than clear cell RCC
   g. Called "papillary" because on histology look like cauliflower frawns — as opposed to looking glandular or solid like CCRCC
   h. Genetics: remember **MET trisomy 7**



due to low stage of most tumors

3. **Sarcomatoid RCC**:
   a. High grade, super aggressive

Treatment for Kidney Cancers:

1. **Kidney-sparing surgery** = partial nephrectomy
2. **Chemotherapy**:
   a. Kinase inhibitors = sunitinib, sorafenib
   b. mTOR inhibitor = temsirolimus
3. RCC stage typically presents as localized (51%), so kidney-sparing possible
4. Survival is based on if it is localized or not

Renal Medullary Carcinoma: — very high grade, usually fatal

1. Almost exclusively in patients with **sickle cell anemia**
2. **Males** more than females, **20 years** old
3. Note, this occurs in medulla not cortex (like RCCs)

Nephroblastoma:

1. Also called **Wilms' tumor** — important to know well if pediatrician
2. Mainly in childhood
3. Very prevalent: **#1 renal cancer of children**, #3 solid cancer overall
4. **Males** more than females, average age **3 years**
5. Clinical presentation = 85% **abdominal mass**, 40% pain, 60% HTN
6. Gross: see fleshy, friable mass replacing entire kidney (consistency of pudding) — or custard...
7. Disintegrates easily, should diagnose with images and not biopsy because of rupture
8. Composed of three parts:
   a. **Blastema** = embryonic progenitor cells, look undifferentiated
   b. **Epithelium** = look like developing nephrons
   c. **Stroma** = look like immature stroma
9. Showed "classic" picture = half epithelial structures, half blastema, some stroma
10. **Nephrogenic rests** = risk factor for Wilms' tumor, persistent foci of embryonal kidney, should involute and go away — but don't, possibly becoming precursors to nephroblastoma

can also invade renal vein, like RCC

Prognostic factors:
- age at detection (older = worse)
- stage
- unfavorable histology (degree of anaplasia)

11. Genetics: **WT1 and WT2** are tumor suppressor genes on chromosome 11
12. Staging:
    a. Stage 1 = limited to kidney, stage 2 = extends beyond kidney but can excise
    b. Stage 3 = residual tumor confined to abdomen, stage 4 = distant metastasis
    c. Stage 5 = bilateral renal involvement
13. Therapy = light chemo/surgery for stages 1-2 or chemo/radiation/surgery for stages 3-4
14. **Very high survival rate** (over 95% for stages 1-3)

still over 80% for unfavorable II-IV

only radiation for more severe cases, other costs outweigh benefits