

Challenging General Internal Medicine Cases

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We have nothing to disclose regarding conflicts of interest

Objectives: Present common clinical scenarios, their appropriate work-up, and their pathologic appearances

BRIGHAM HEALTH



BRIGHAM AND WOMEN'S
Department of Medicine



HARVARD
MEDICAL SCHOOL

Postgraduate
Medical Education

Case 1

49F presenting with 1 month of fatigue, peripheral edema, and flu-like symptoms; she is found to have low central venous pressures

Case 1

Basic Labs:

- HCT 35 (35-46)
- BUN 28 (7-30)
- Creatinine 1.4 (≤ 1.2)
- Albumin 2.8 (3.5-5.5)
- Globulin 3.6 (1.3-4.1)

Case 1

Additional Lab Work-Up:

- Cholesterol 440 (< 200)
- Urinalysis: 4+ protein/benign sediment
- CCr 90% predicted
- Urine protein 3.5 gm/24 hrs
- Anti-PLA₂R1 titer is normal

Nephrotic Syndrome

Defined by the constellation of:

- Heavy proteinuria ($>3.5\text{g}/24\text{h}$)
- Hypoalbuminemia ($<3\text{g}/\text{dl}$)
- Peripheral Edema

*** Also common are hyperlipidemia and both arterial and venous thromboses**

Nephrotic Syndrome

Etiologies Differ by Age:

Children:

Minimal change	60%
Focal and segmental glomerulosclerosis (FSGS)	10%
Proliferative GN (nephritic syndrome)	10%
Membranoproliferative GN	10%
Membranous GN	5%

Nephrotic Syndrome

Etiologies Differ by Age:

Adults:

Diabetes, SLE, amyloid, etc.	40%
Membranous GN	20%
Proliferative GN (nephritic syndrome)	15%
FSGS	10%
Minimal Change	10%
Membranoproliferative GN	5%

Nephrotic Syndrome

Membranous GN:

Majority of cases previously diagnosed as “idiopathic” are now known to have specific immune complex deposition:

- 70-80% are due to auto-antibodies directed against PLA₂ receptor 1 (phospholipase A₂ receptor 1)
- auto-antibodies to THSD-7A (thrombospondin type I-domain containing 7A) and NELL-1 (neural epidermal growth factor-like 1) are associated with secondary malignancies

Presence of specific autoantibodies in the serum are diagnostic and predict treatment response, disease activity, and outcome

Nephrotic Syndrome

Minimal Change Disease:

Steroid responsive

**Secondary to lymphoma and
leukemia**

Nephrotic Syndrome

Focal and Segmental Glomerulosclerosis

Primary vs. Secondary

Secondary causes:

- HIV, CMV, HCV
- Drugs: heroin, interferon, bisphosphonates, anabolic steroids
- Severe obesity

Nephrotic Syndrome

Numerous Secondary Causes:

Infectious:

Bacterial – Endocarditis

Viral - Hepatitis B + C, HIV

Protozoal – Malaria

Helminths

Nephrotic Syndrome

Numerous Secondary Causes:

Neoplastic:

Carcinoma – Prostate, Lung, Breast

Lymphoma

Leukemia

Multiple Myeloma

Nephrotic Syndrome

Numerous Secondary Causes:

Toxin:

Heroin

NSAIDs

Gold, Mercury

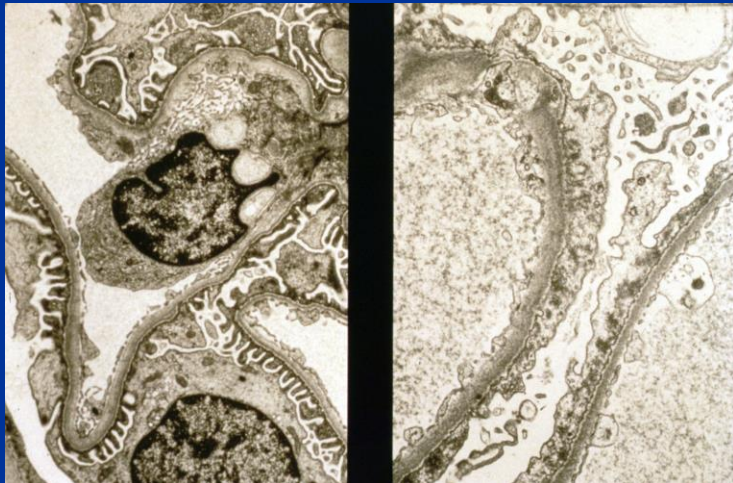
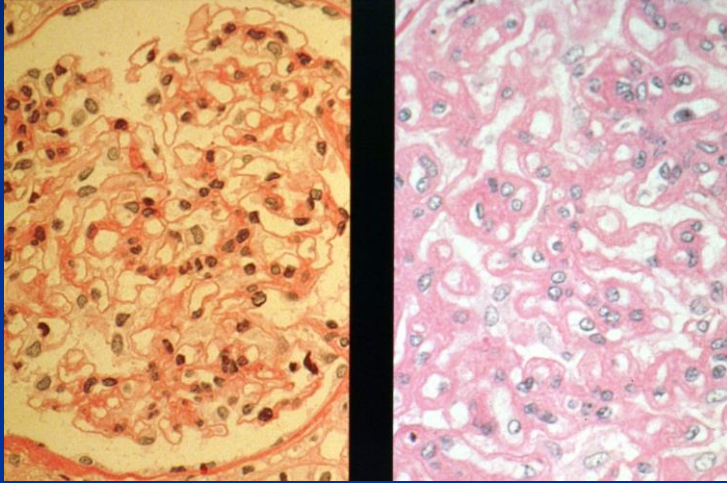
Miscellaneous:

Pre-eclampsia

Sickle cell disease

Renovascular

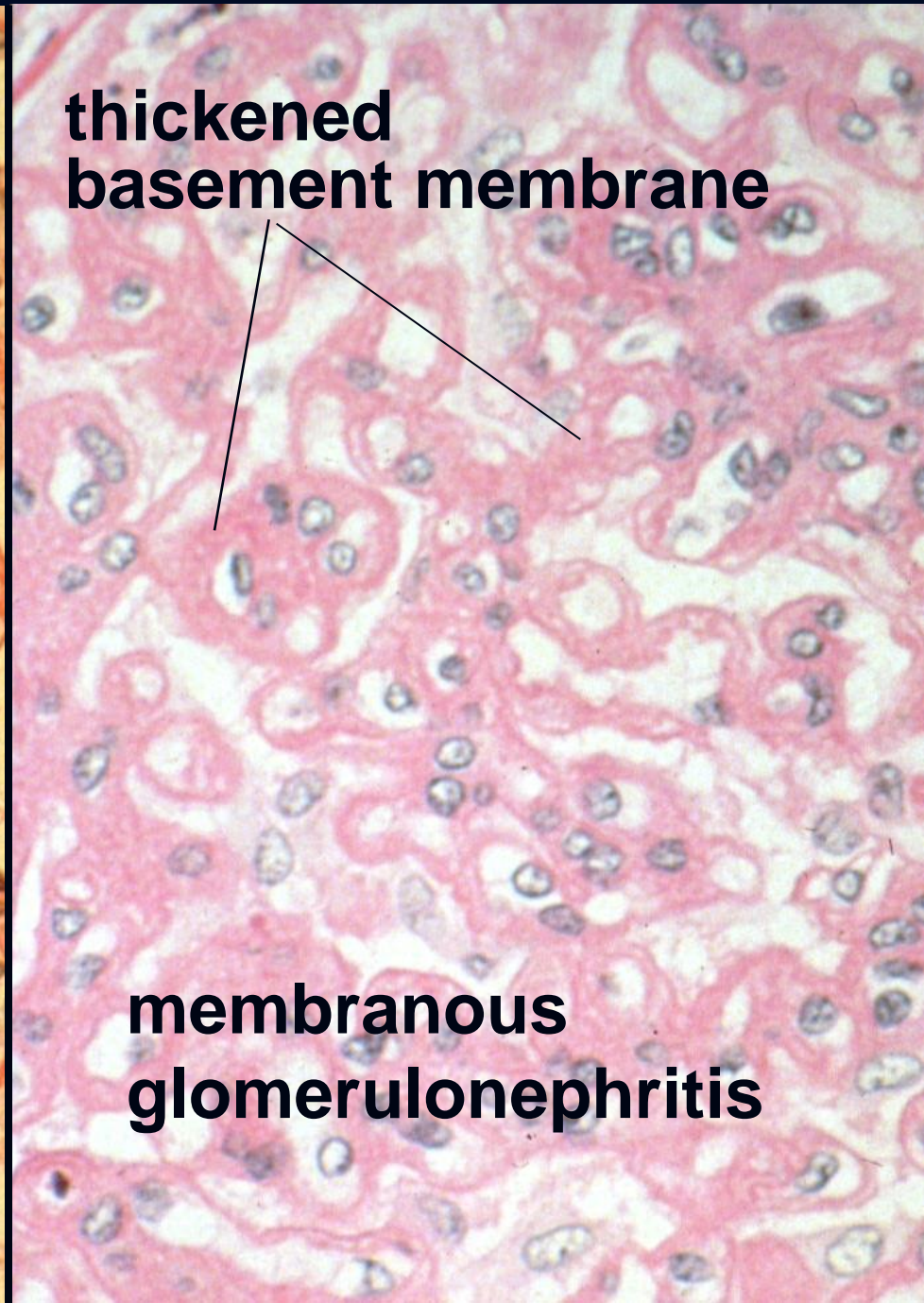
What to look for: proteinuria



- glomerulus
- cellularity of glomerulus
- basement membrane
- cellular architecture (based on EM)
- immunofluorescence

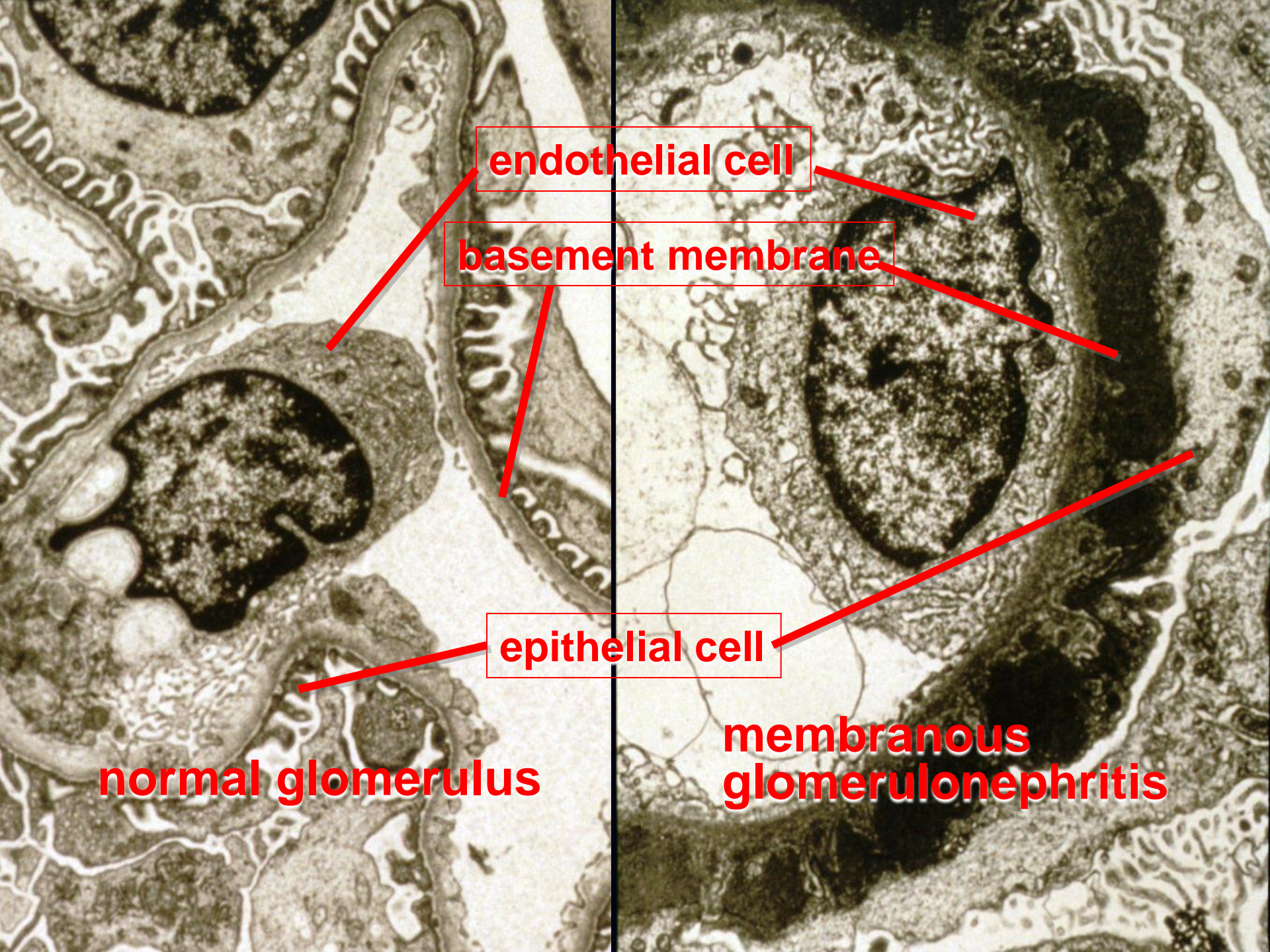


normal glomerulus



**thickened
basement membrane**

**membranous
glomerulonephritis**



endothelial cell

basement membrane

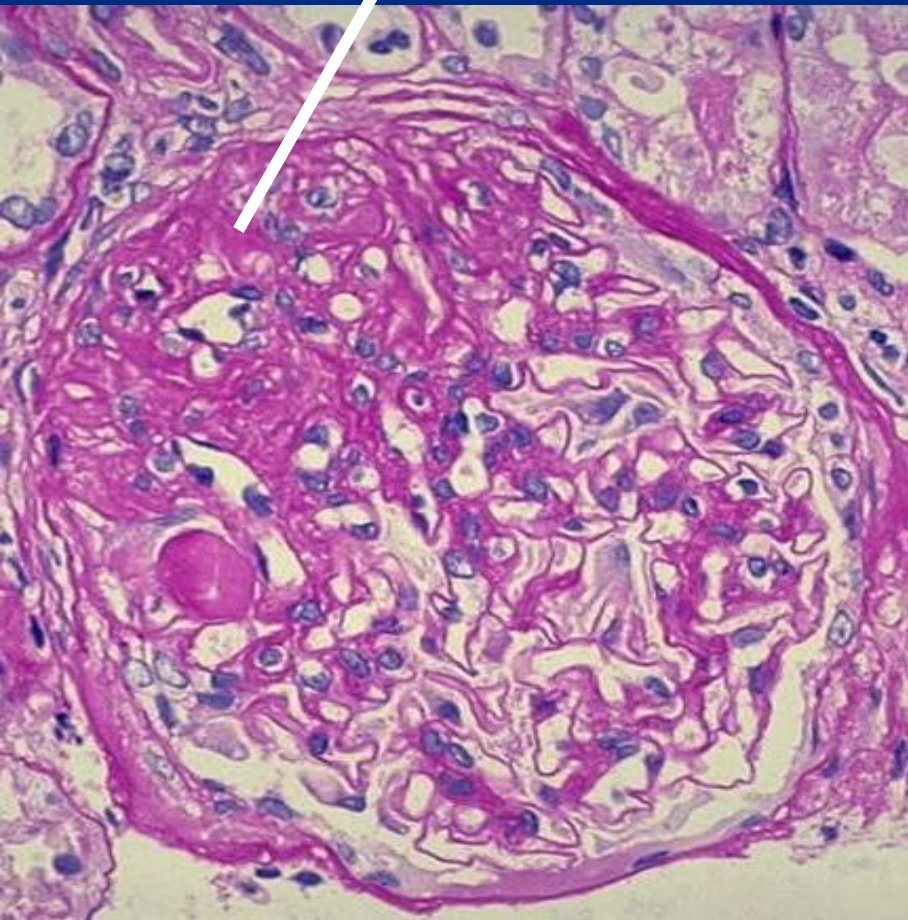
epithelial cell

normal glomerulus

**membranous
glomerulonephritis**



**focal and segmental
glomerulosclerosis
(FSGS)**

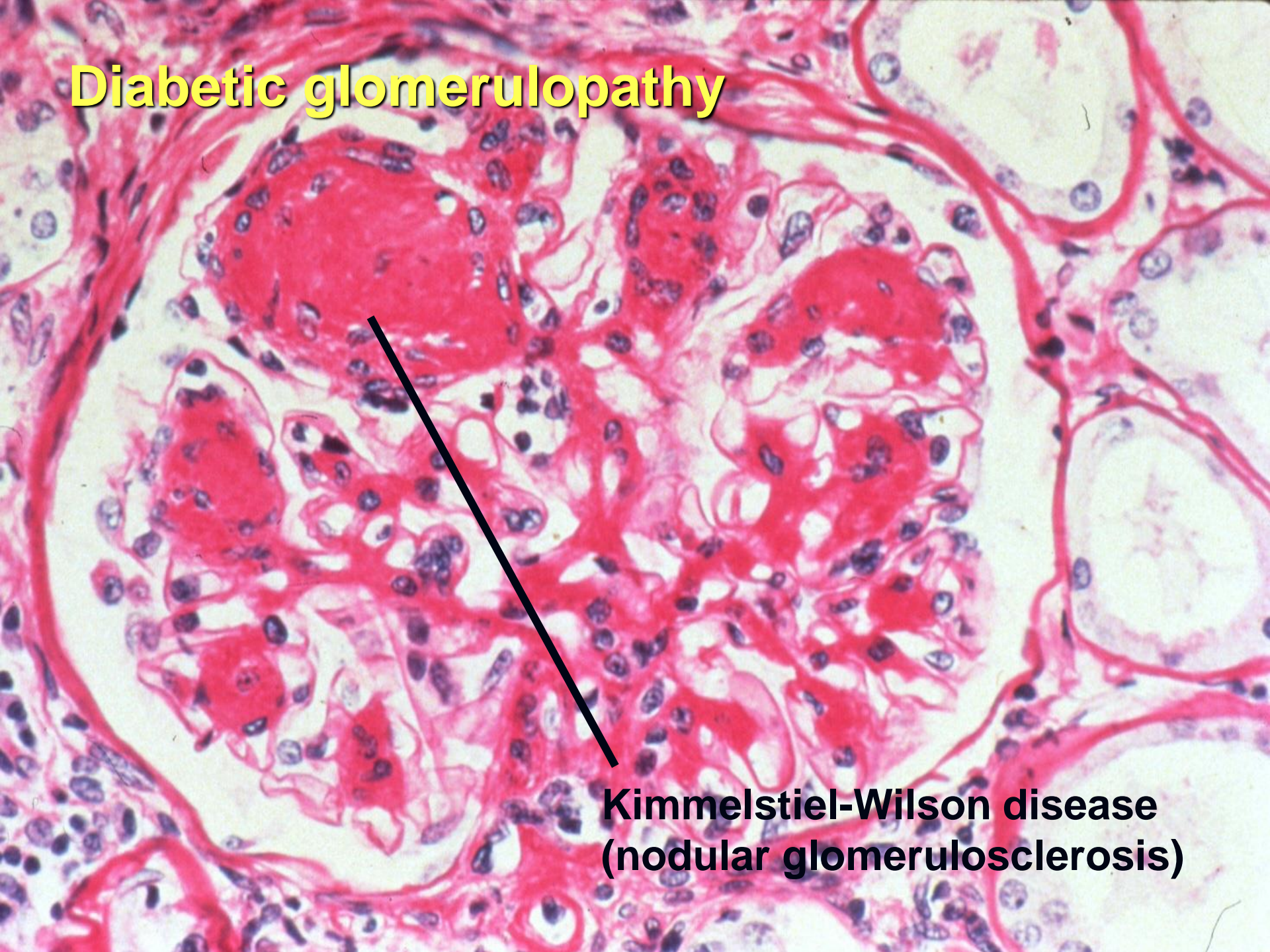


Courtesy of Dr. Astrid Weins



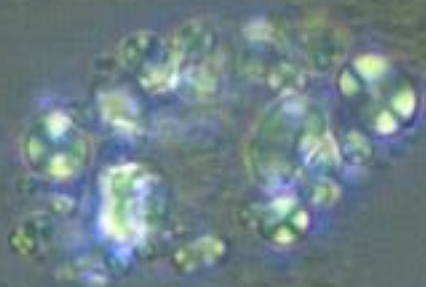
**intraepithelial
tubuloreticular body
(HIV or heroin)**

Diabetic glomerulopathy

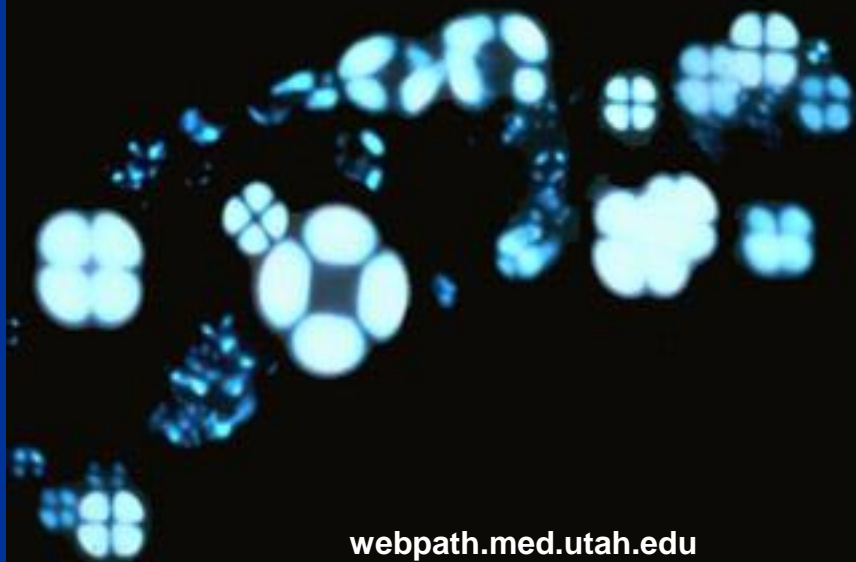


**Kimmelstiel-Wilson disease
(nodular glomerulosclerosis)**

oval fat bodies



“Maltese cross” (polarized light)



webpath.med.utah.edu

waxy cast

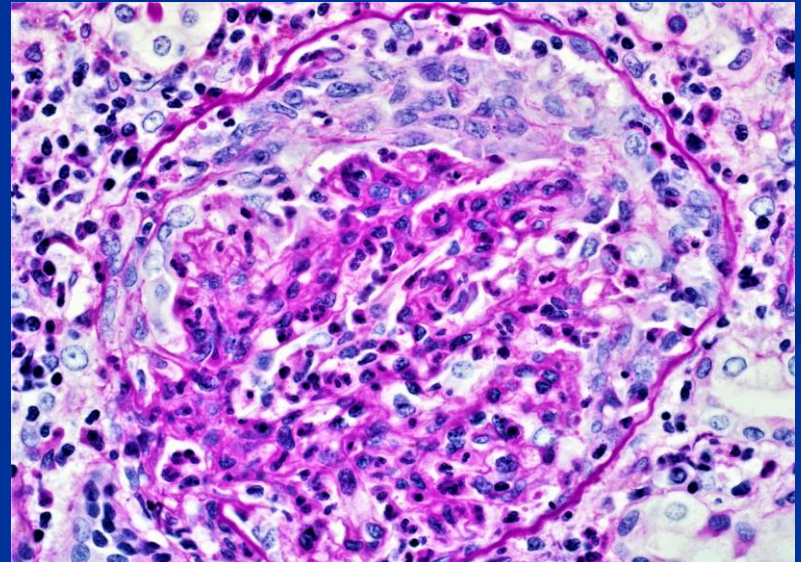
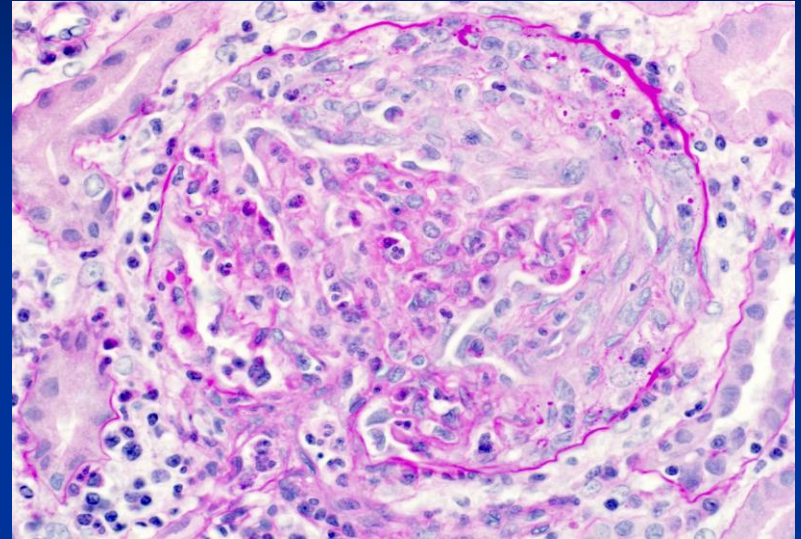
(protein and degenerated epithelial cells)



x.com/JoseTesser/status/

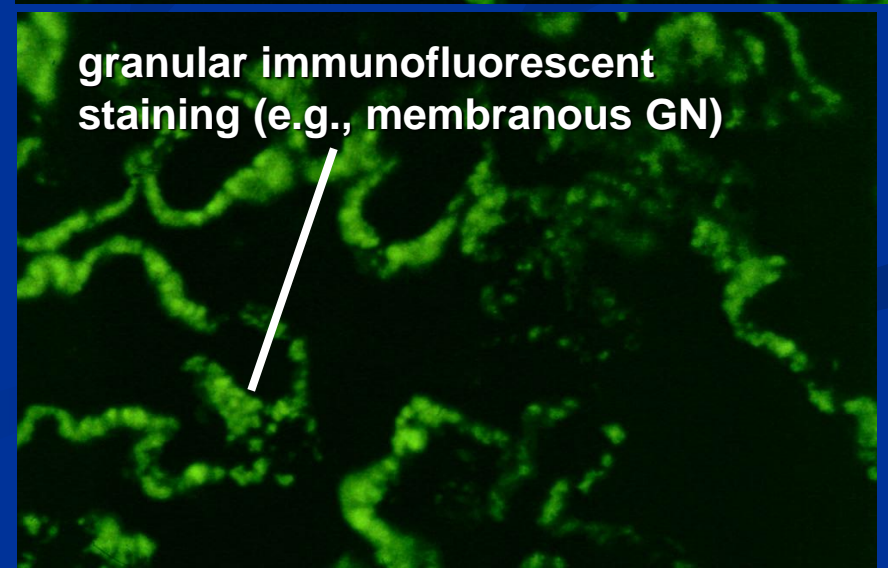
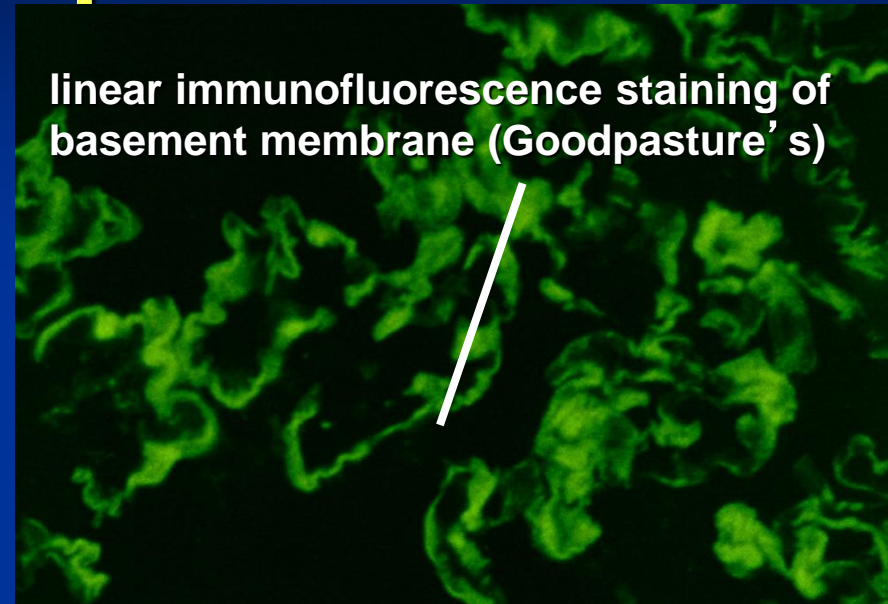
Crescentic (proliferative) glomerulonephritis

- Nephritic syndrome (HTN, hematuria, proteinuria)



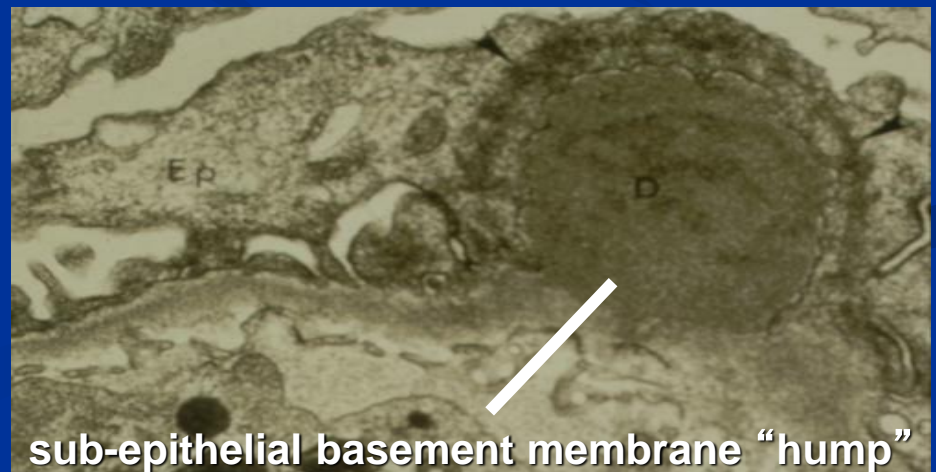
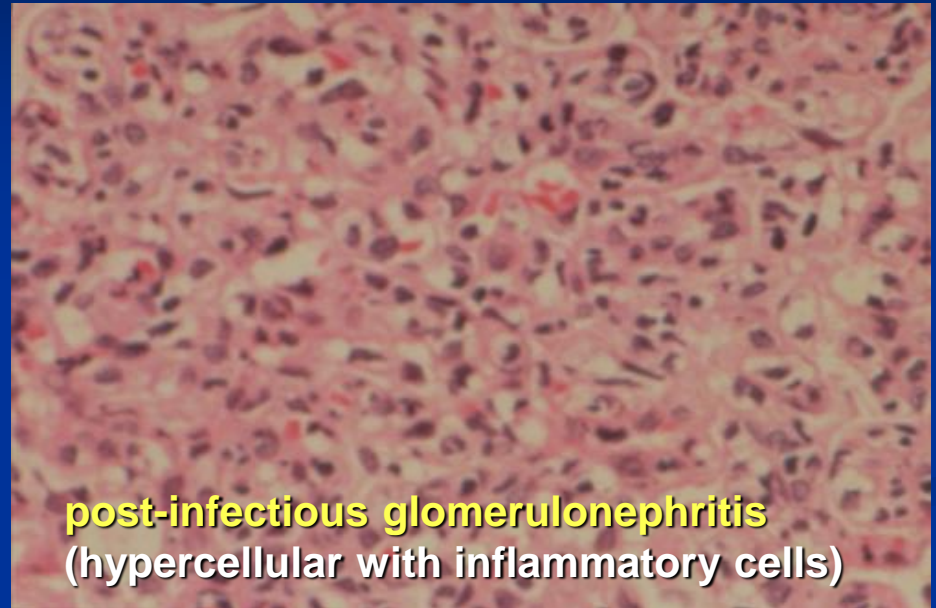
Crescentic (proliferative) glomerulonephritis

- **Nephritic syndrome** (HTN, hematuria, proteinuria)
- **Autoimmune-systemic disease**
 - Goodpasture's
 - Vasculitis (e.g., GPA, HSP, SLE, PAN)



Crescentic (proliferative) glomerulonephritis

- Nephritic syndrome (HTN, hematuria, proteinuria)
- Autoimmune-systemic disease
 - Goodpasture's
 - Vasculitis (e.g., GPA, HSP, SLE, PAN)
- Post-infectious
- Idiopathic



Case 2

34M with a h/o of obesity (BMI 39), alcohol use (~4 beers per week), and occasional acetaminophen use presenting with 3-4 months of fatigue.

Case 2

Basic Labs:

- AST 255 (≤ 42)
- ALT 200 (≤ 48)
- Alkaline phosphatase 155 (20-125)
- TBILI 0.8 (≤ 1.3) / DBILI 0.6 (≤ 0.4)
- INR 1.0
- Albumin 3.0 (3.5-5.5)

Transaminitis

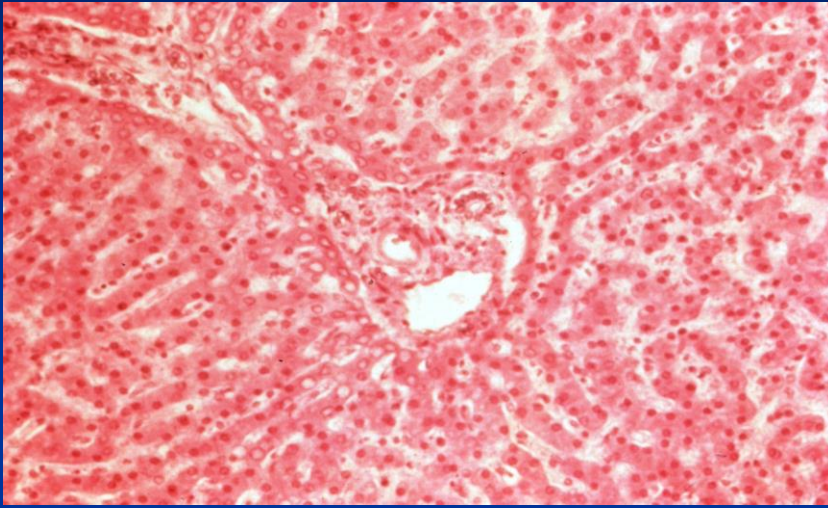
- Poor correlation between transaminitis and the extent of hepatic damage
- AST/ALT ratio can guide your differential diagnosis

Transaminitis

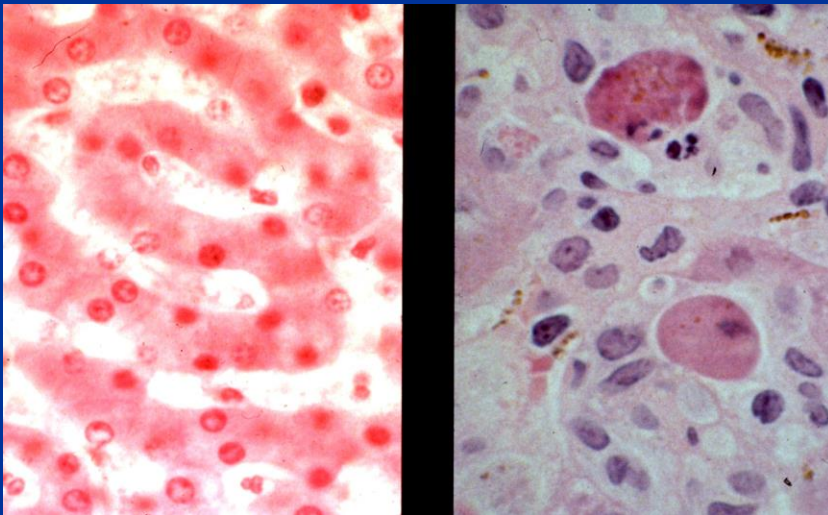
Recommended Work-up:

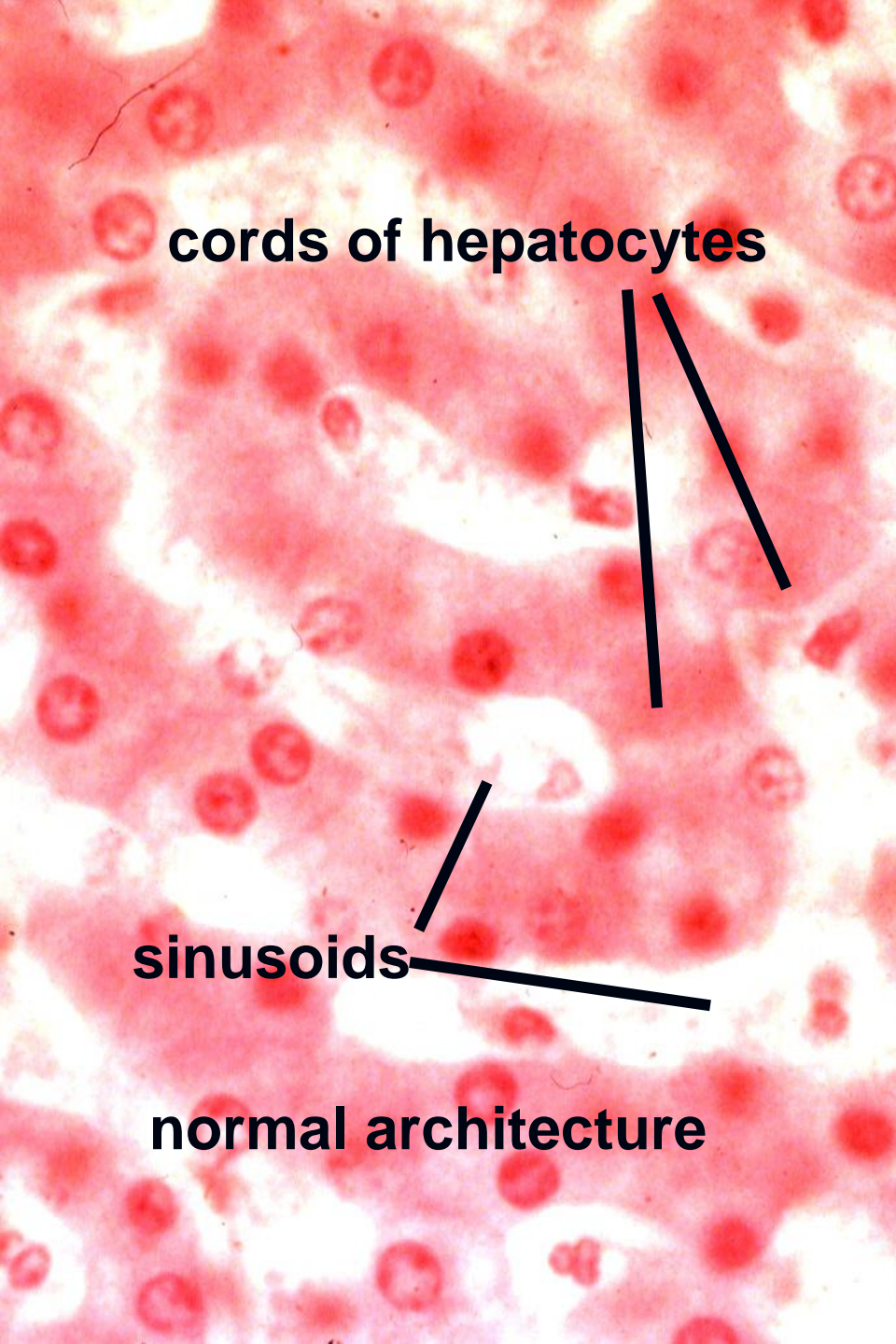
- Hepatitis serologies
- ANA, ASMA, ALKM-1
- Toxin levels
- Fe/TIBC, Ferritin
- Ceruloplasmin
- α -1-anti-trypsin
- Abdominal US

What to look for: elevated transaminases



- liver architecture
- portal inflammation
- hepatocyte necrosis
- inclusions

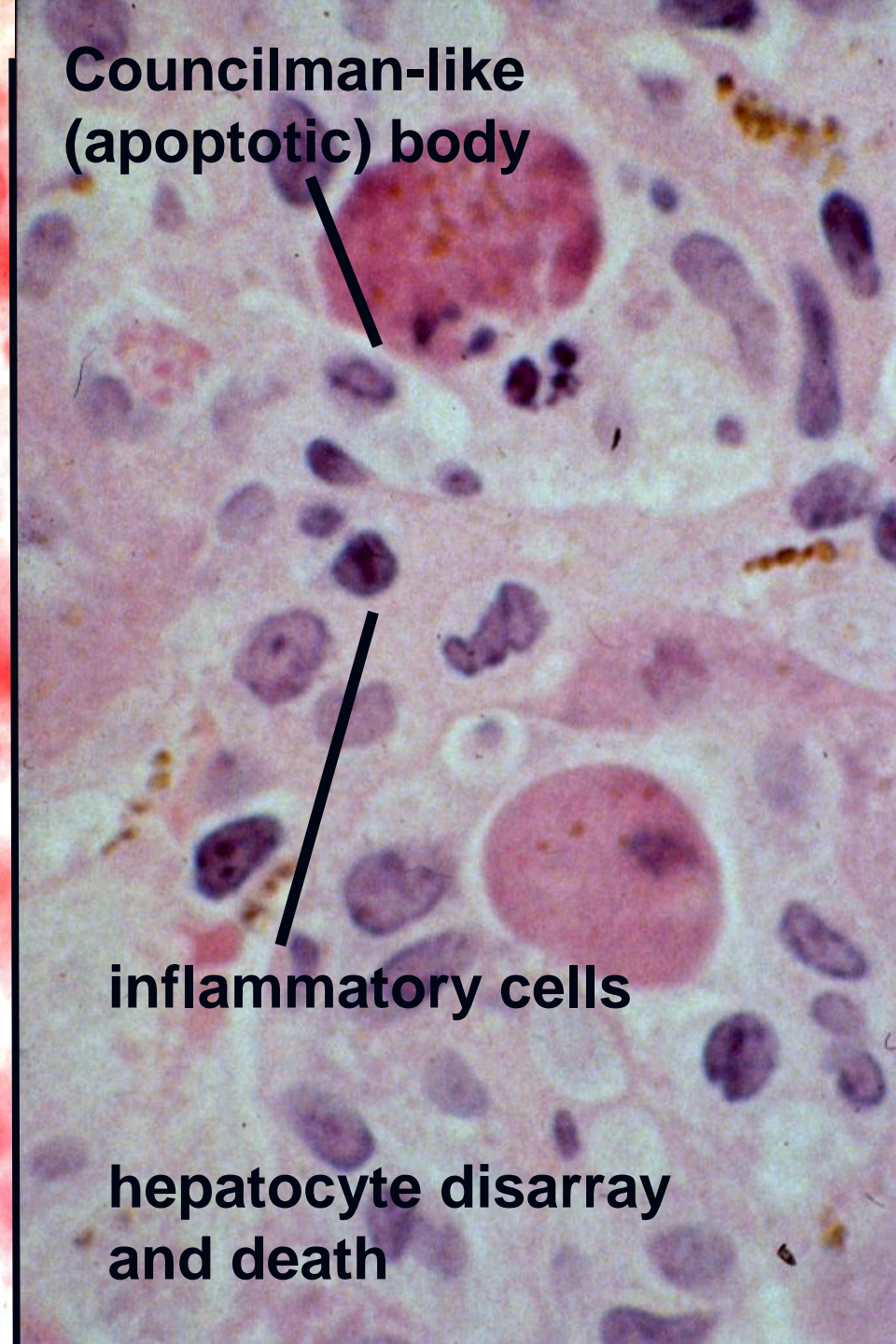




cords of hepatocytes

sinusoids

normal architecture



**Councilman-like
(apoptotic) body**

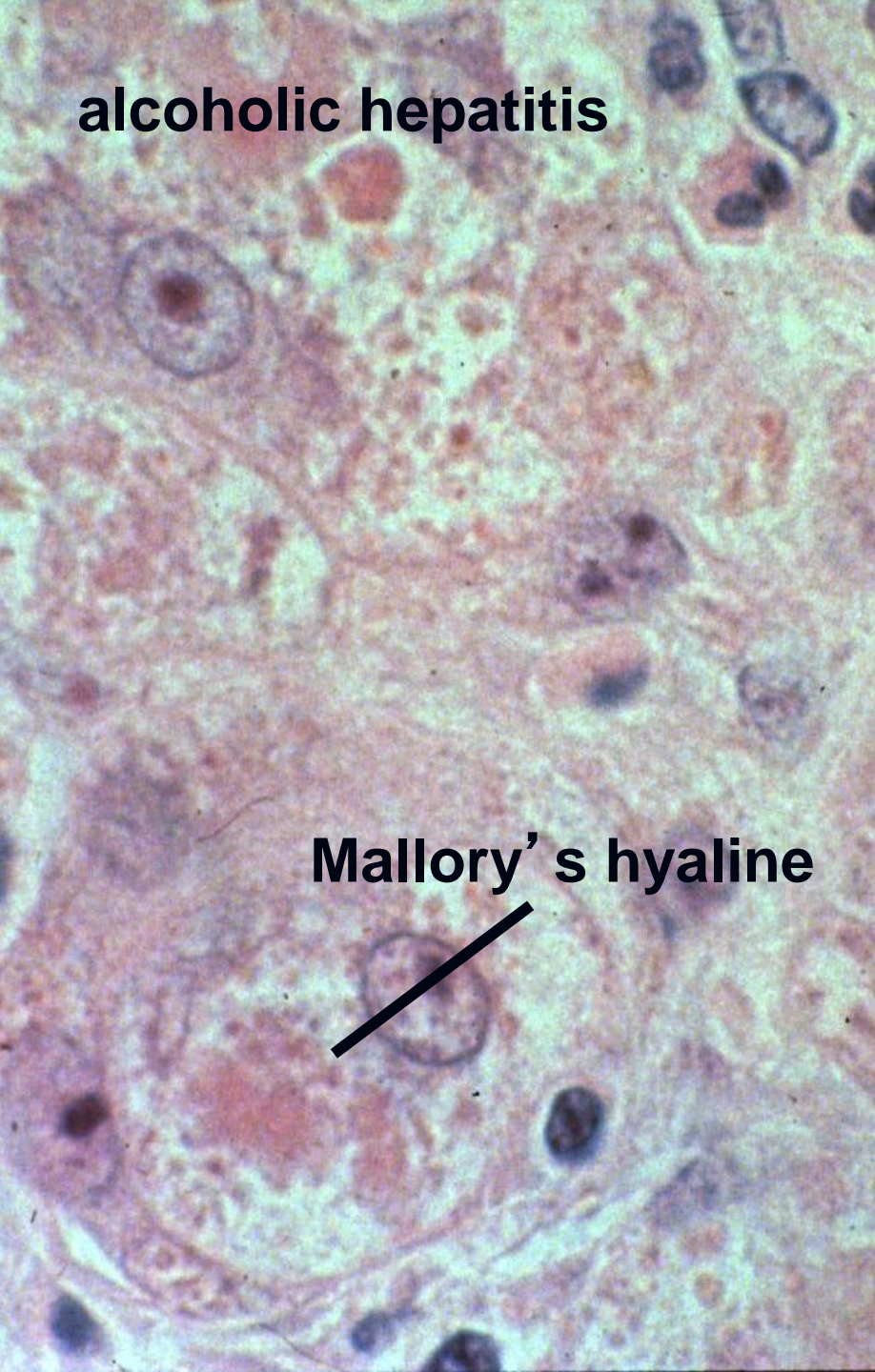
inflammatory cells

**hepatocyte disarray
and death**

Acute hepatitis

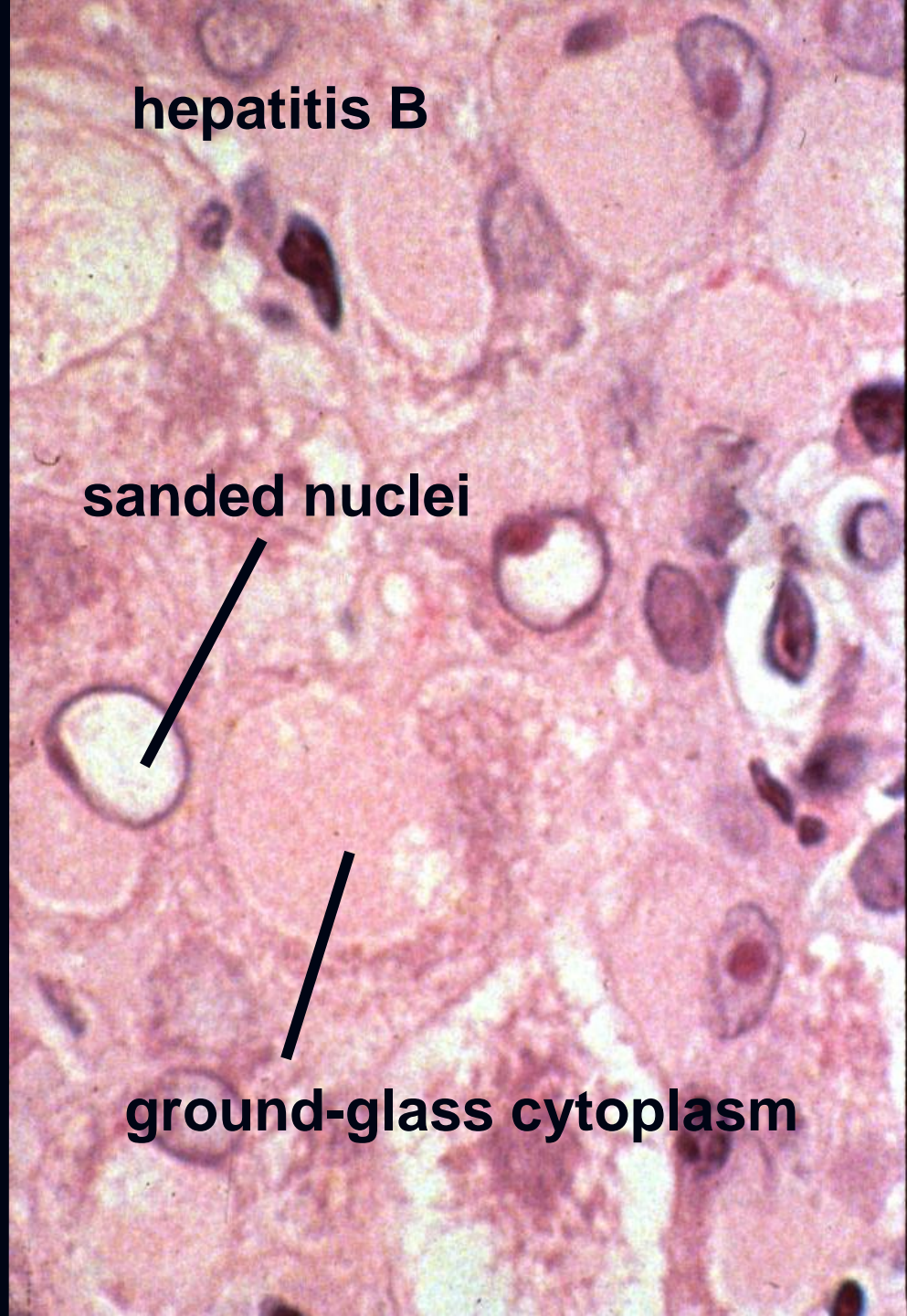
- **Toxic**
- **Ischemic**
- **Infectious**
- **Auto-immune**

alcoholic hepatitis



Mallory's hyaline

hepatitis B



sanded nuclei

ground-glass cytoplasm

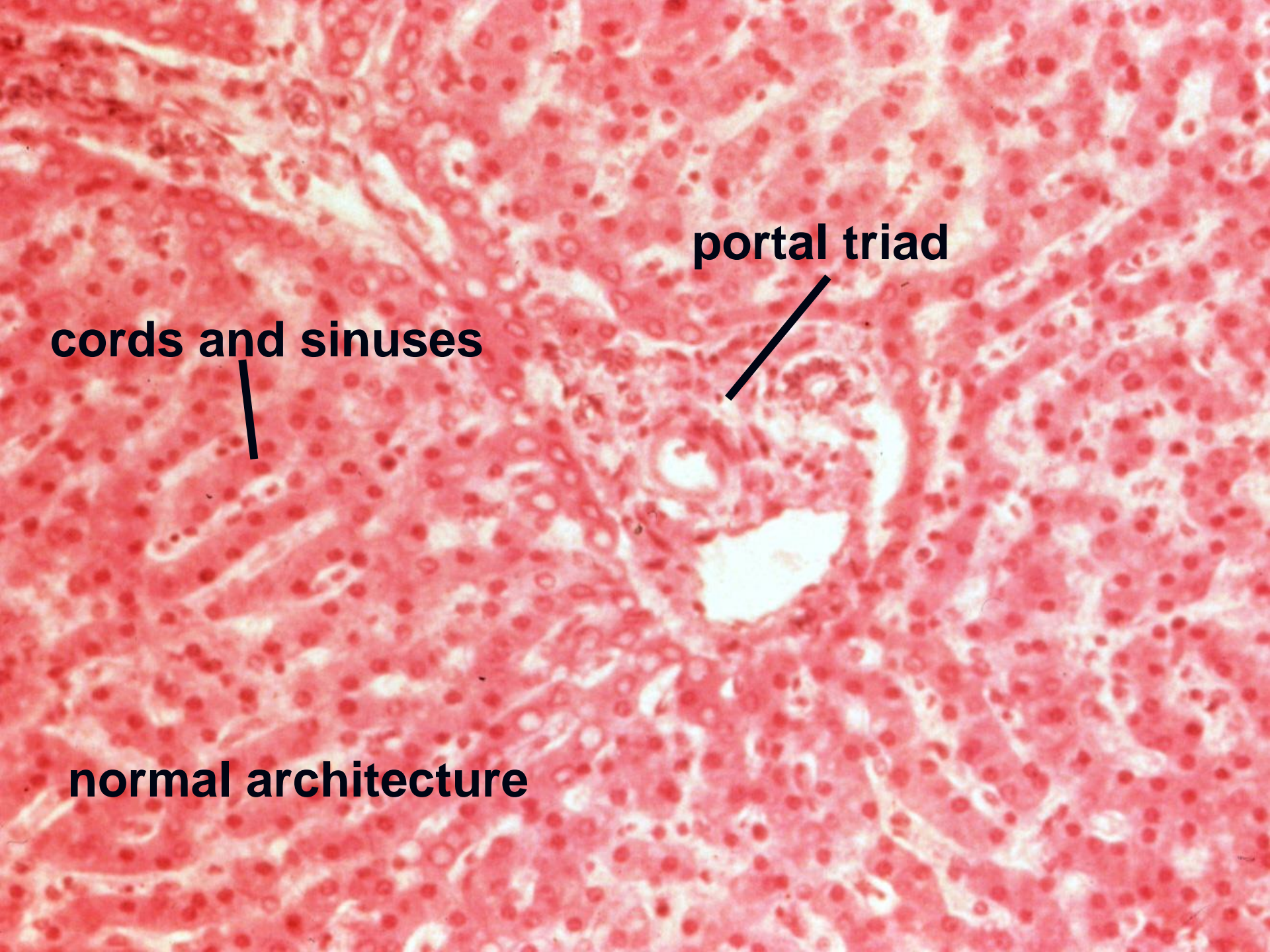
Non-alcoholic steatohepatitis (NASH)

inflammation

hepatocyte death

steatosis

20-30% of obese individuals



cords and sinuses

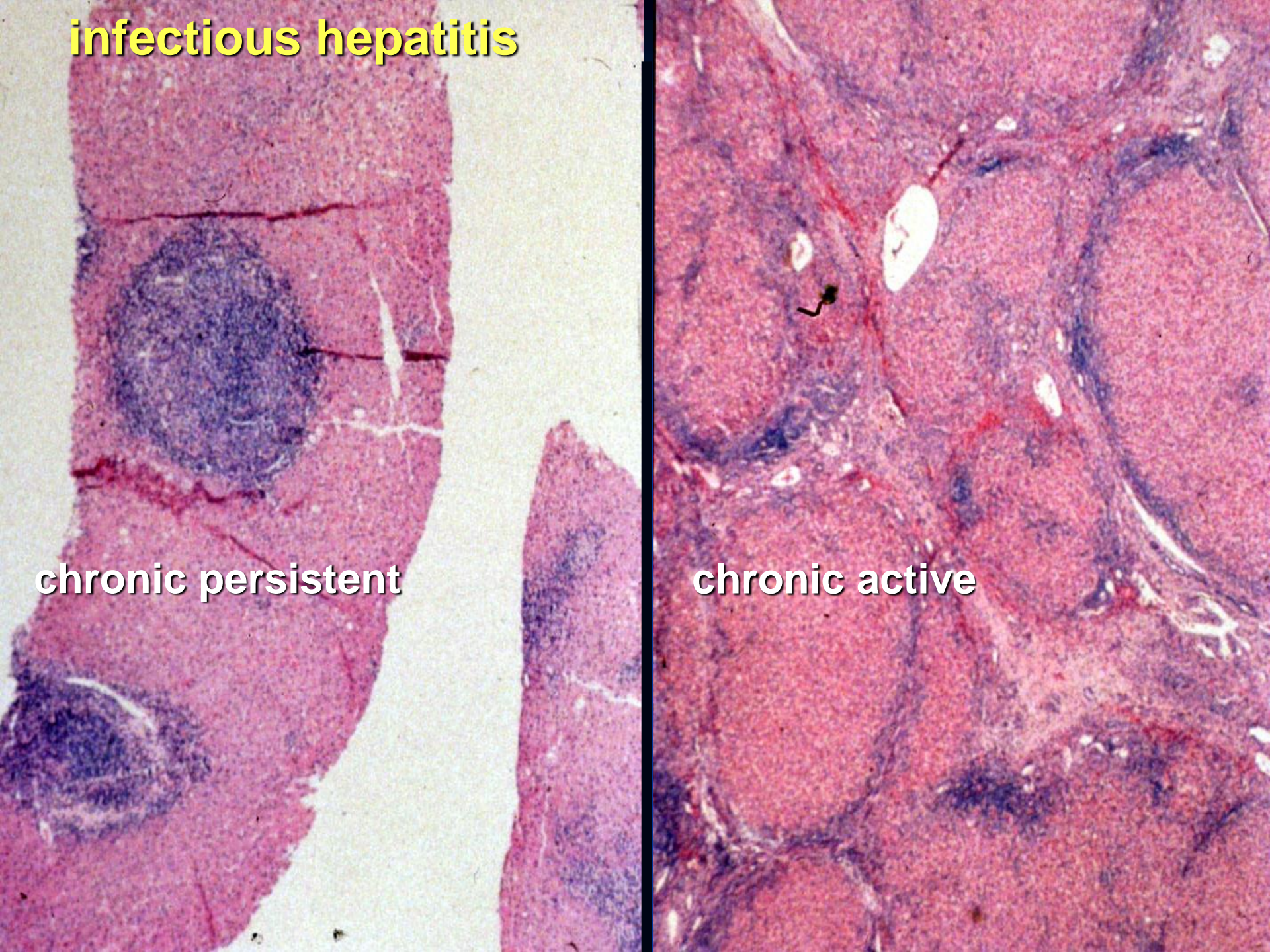
portal triad

normal architecture

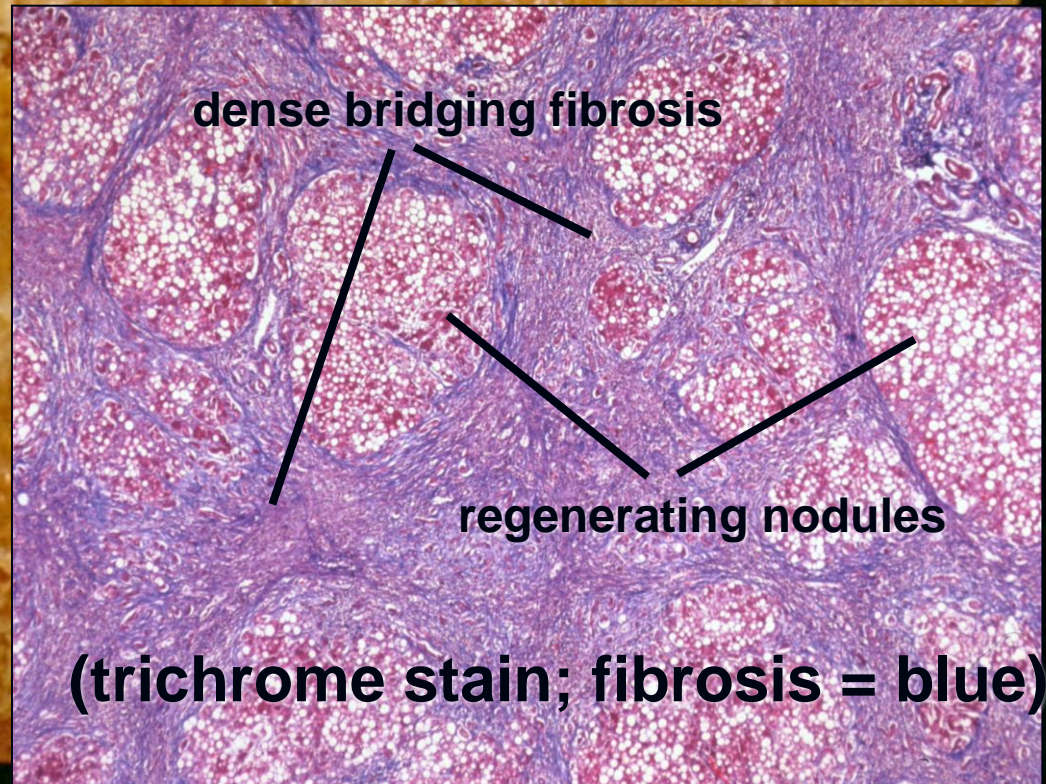
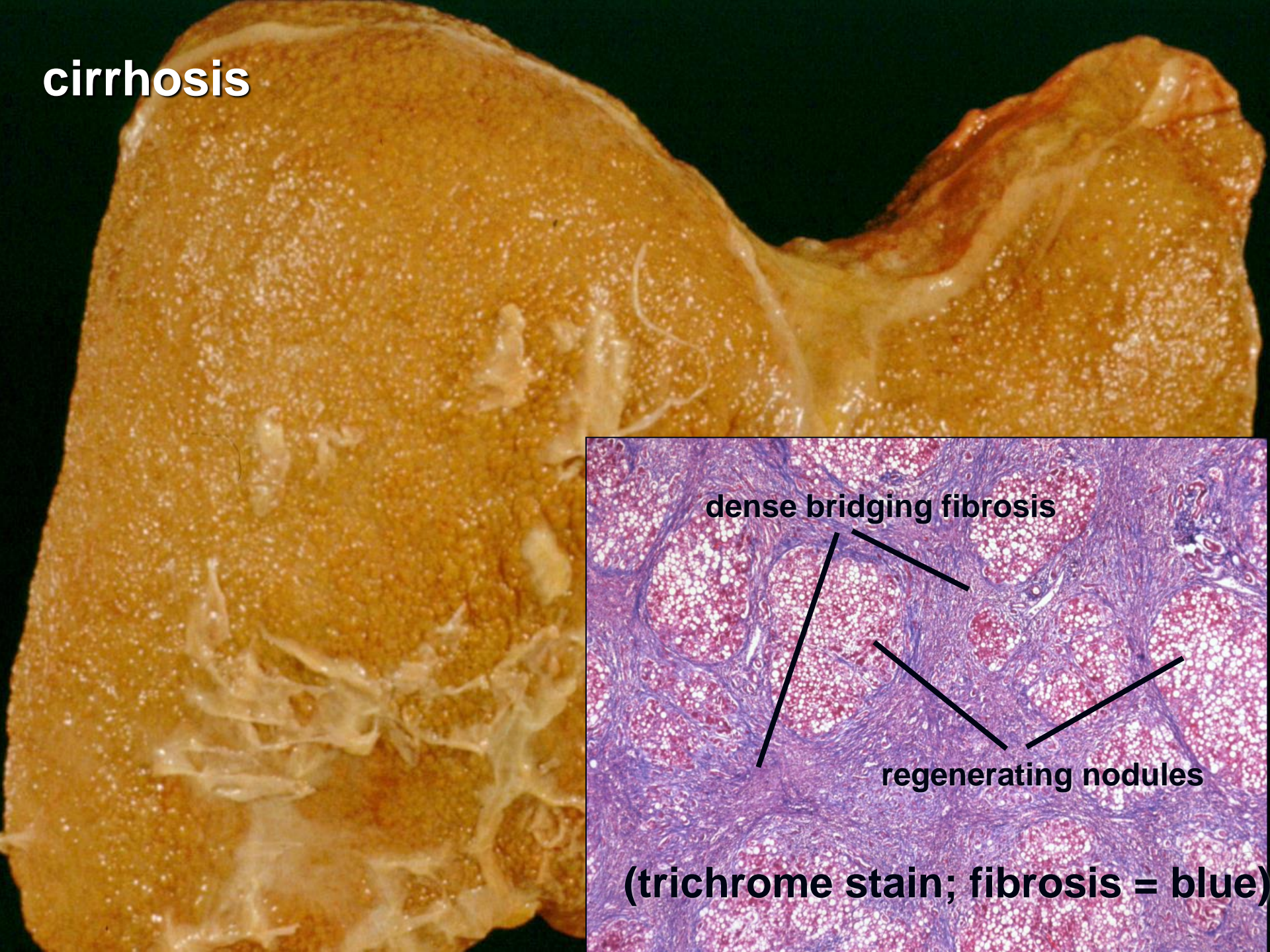
infectious hepatitis

chronic persistent

chronic active



cirrhosis



dense bridging fibrosis

regenerating nodules

(trichrome stain; fibrosis = blue)

Cirrhosis

- Hepatitis C
- Non-alcoholic fatty liver disease
- Alcoholic liver disease
- Hepatitis B +/- Hepatitis D
- Miscellaneous
(Wilson's, hemochromatosis, α -1-
anti-trypsin deficiency, autoimmune,
PBC, PSC, VOD, etc.)

Case 3

**45M presenting with 1 month
of fragile blisters.**

Blisters

Pemphigus Vulgaris:

Clinical finding: Superficial dermis ruptures spontaneously (Nikolsky)

Location: Skin, mucous membranes

**Histological Finding: IgG
Intercellular Space**

Blisters

Bullous Pemphigoid:

Clinical finding: Intact superficial dermis

Location: Spares mucous membranes

**Histological Finding: IgG Linear
Dermal-Epidermal Junction**

Blisters

Dermatitis Herpetiformis (associated with gluten sensitivity):

Clinical finding: Pruritis

Location: Symmetric and includes back, knees, elbows

Circulating anti-transglutaminase antibodies suggests gluten sensitivity

Histological Finding: IgA Granular Dermal-Epidermal Junction

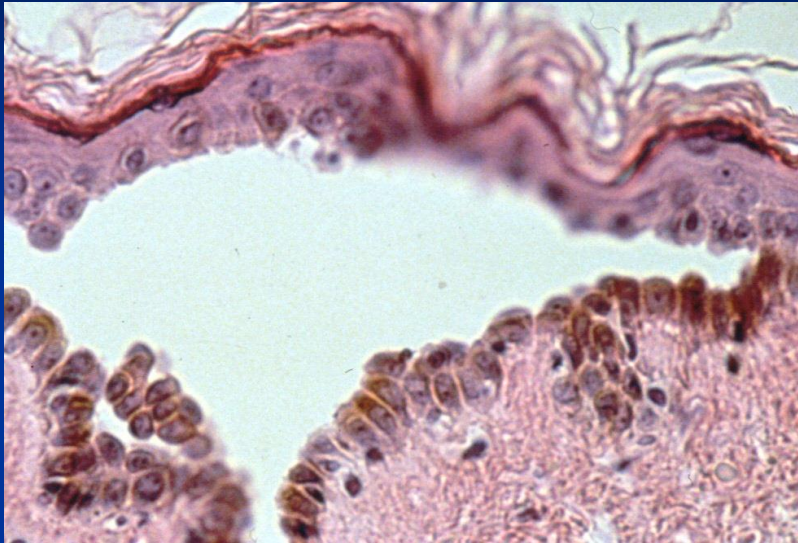
Blister

Lupus:

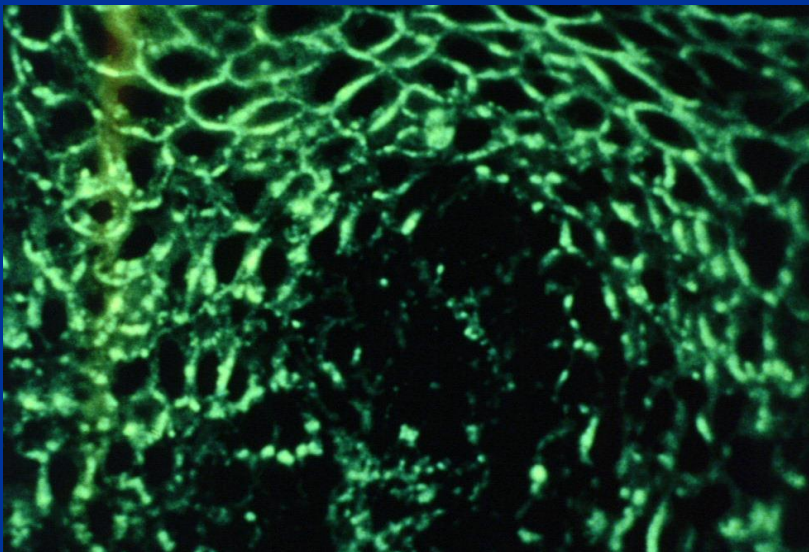
Location: Sun exposed sites

**Histological Finding: IgG and IgM
Granular Dermal-Epidermal
Junction**

What to look for: blisters

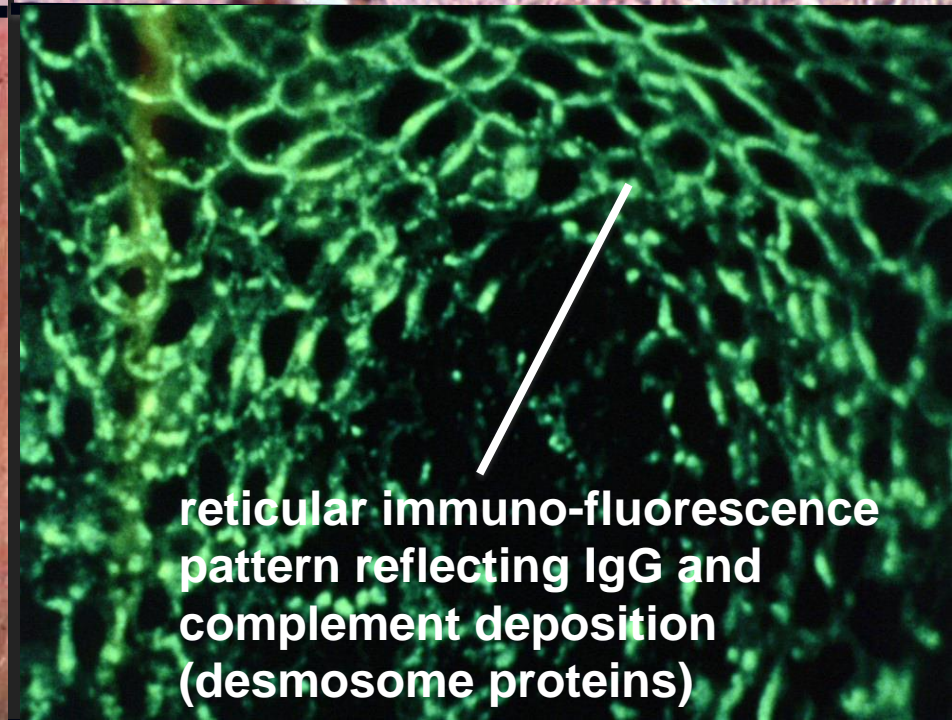
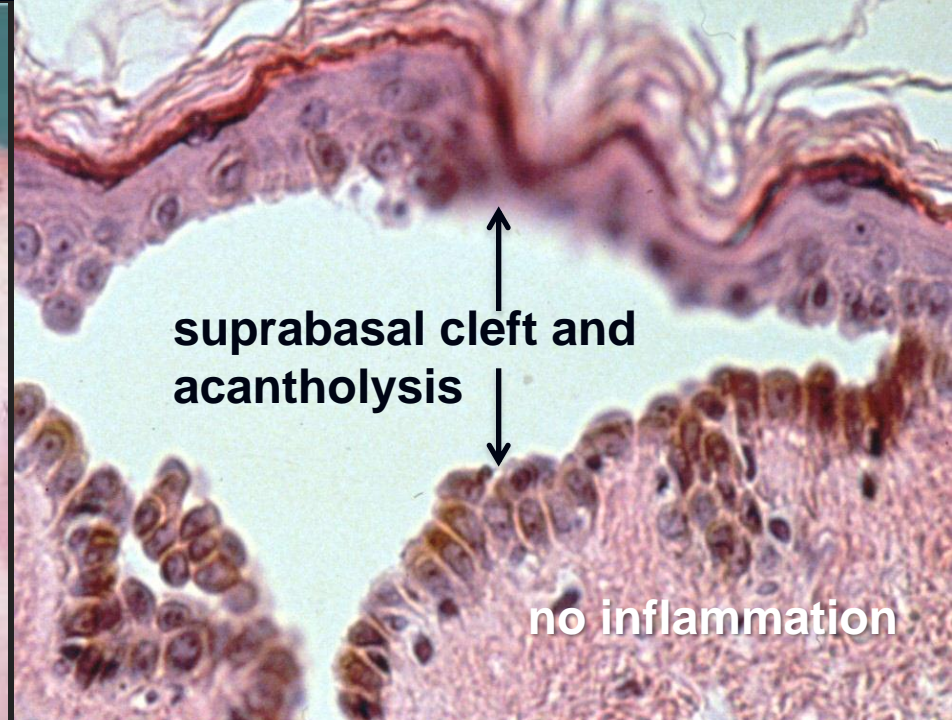


- location of cleft
- inflammation
- immuno-
fluorescence
pattern

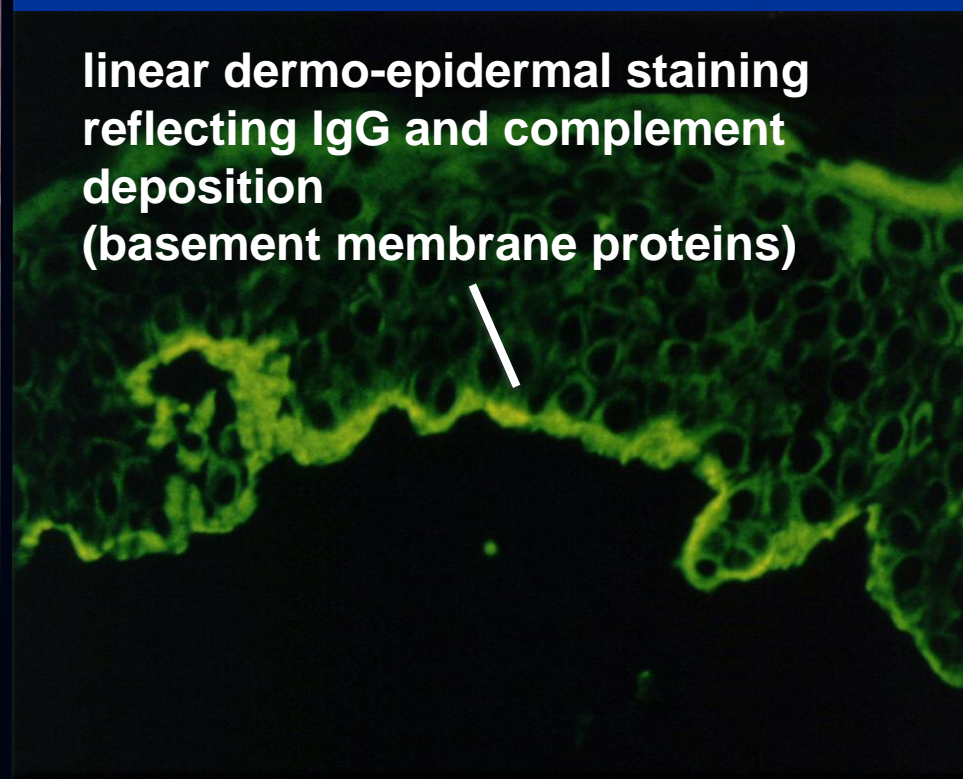
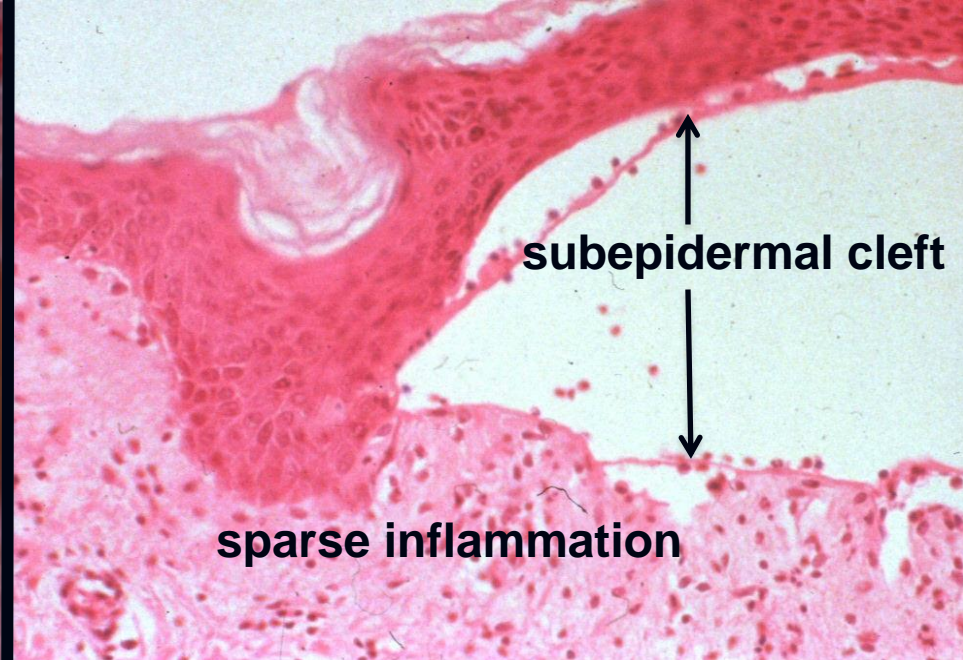


pemphigus vulgaris

www.dermis.net

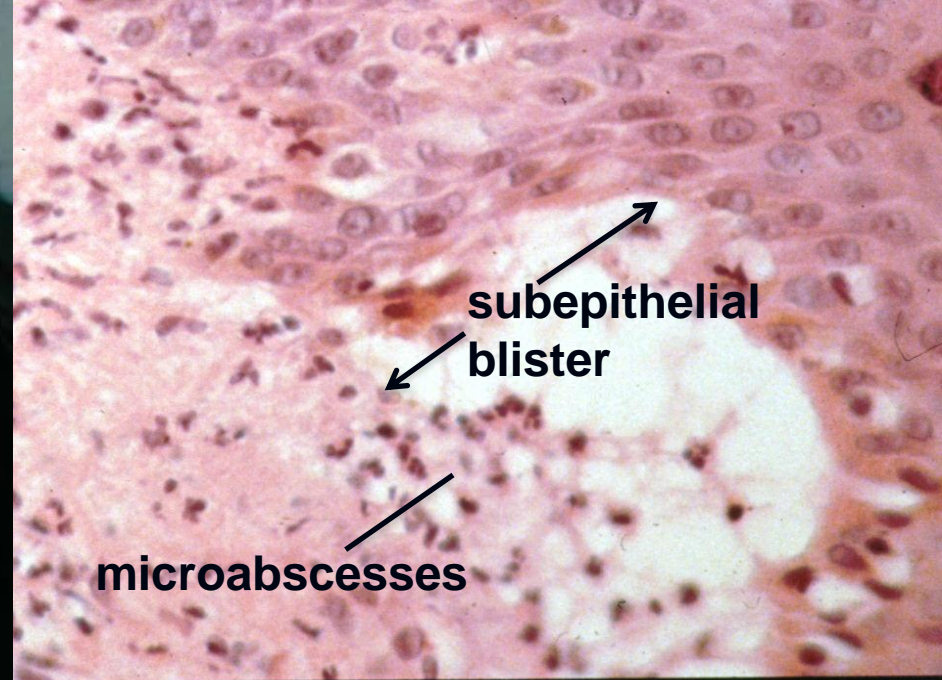


bullous pemphigoid

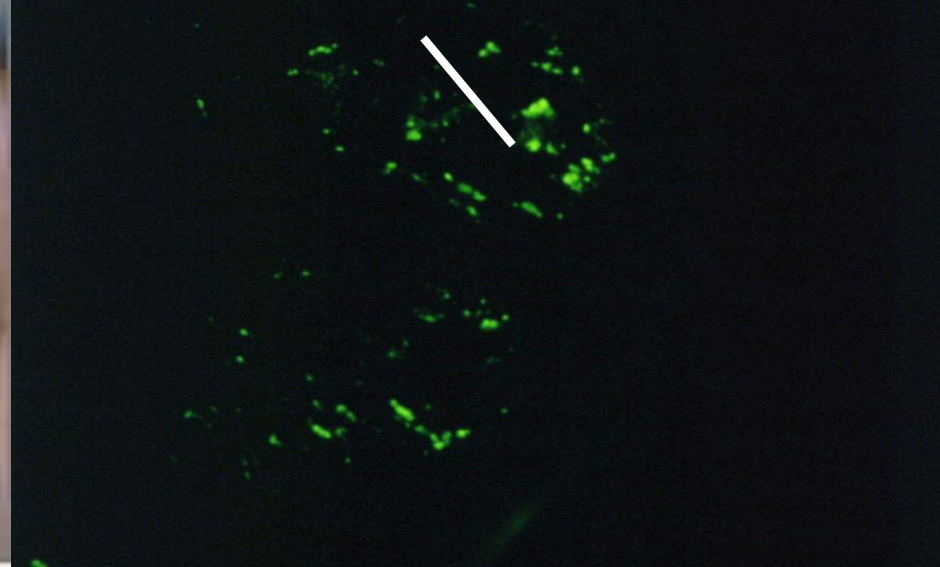


dermatitis herpetiformis

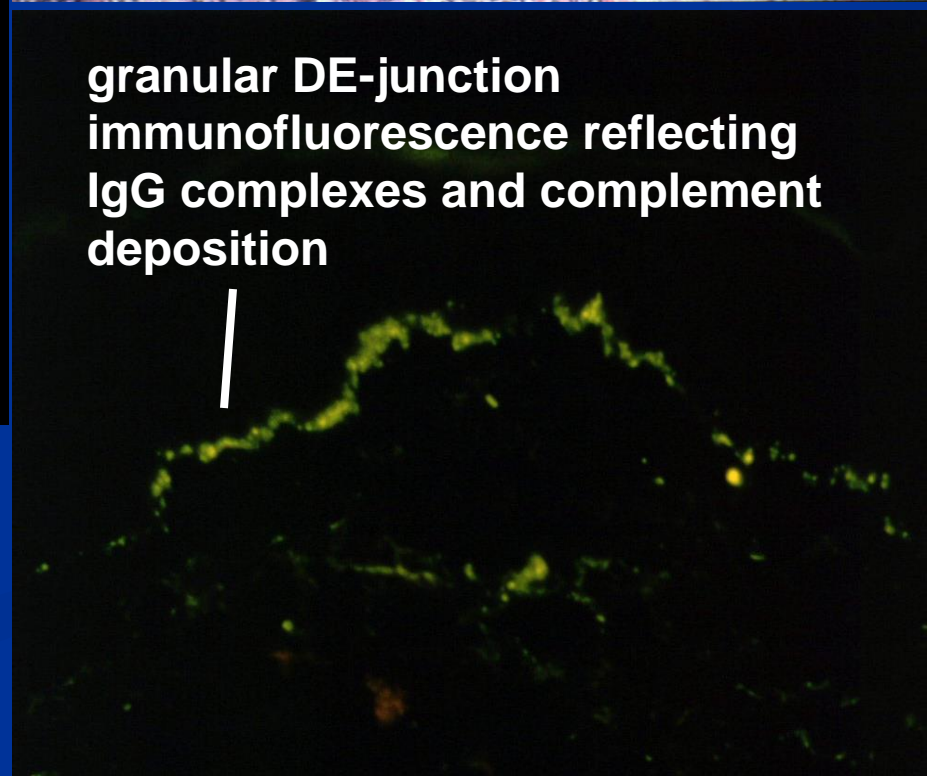
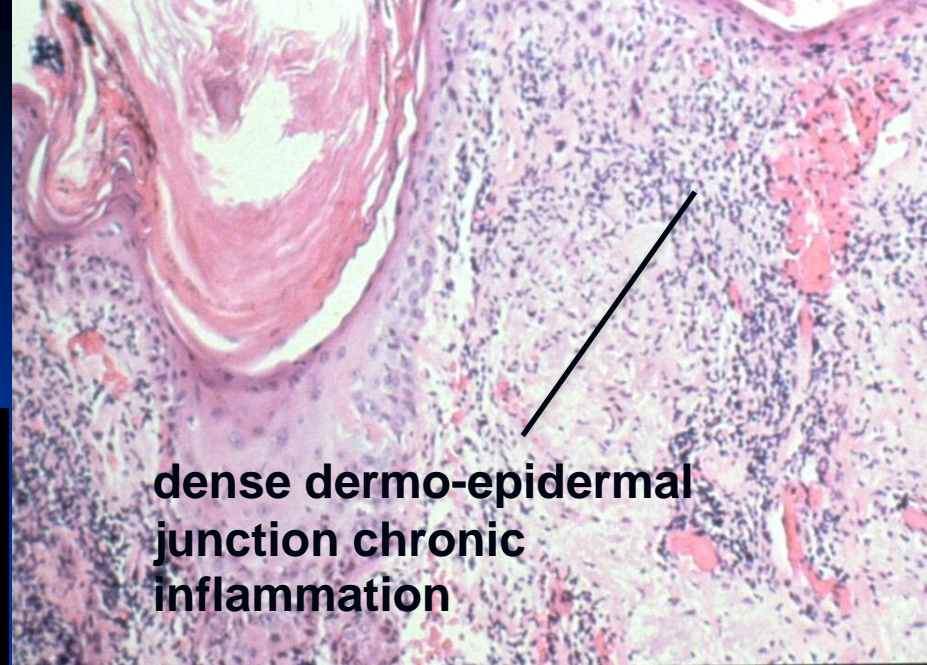
glutenfree.ca



granular immunofluorescence
reflecting IgA complexes and
complement deposition



systemic lupus erythematosus (not classically blistering)



Case 4

29F volunteers to give blood and is found to have a HCT of 24 (41-50).

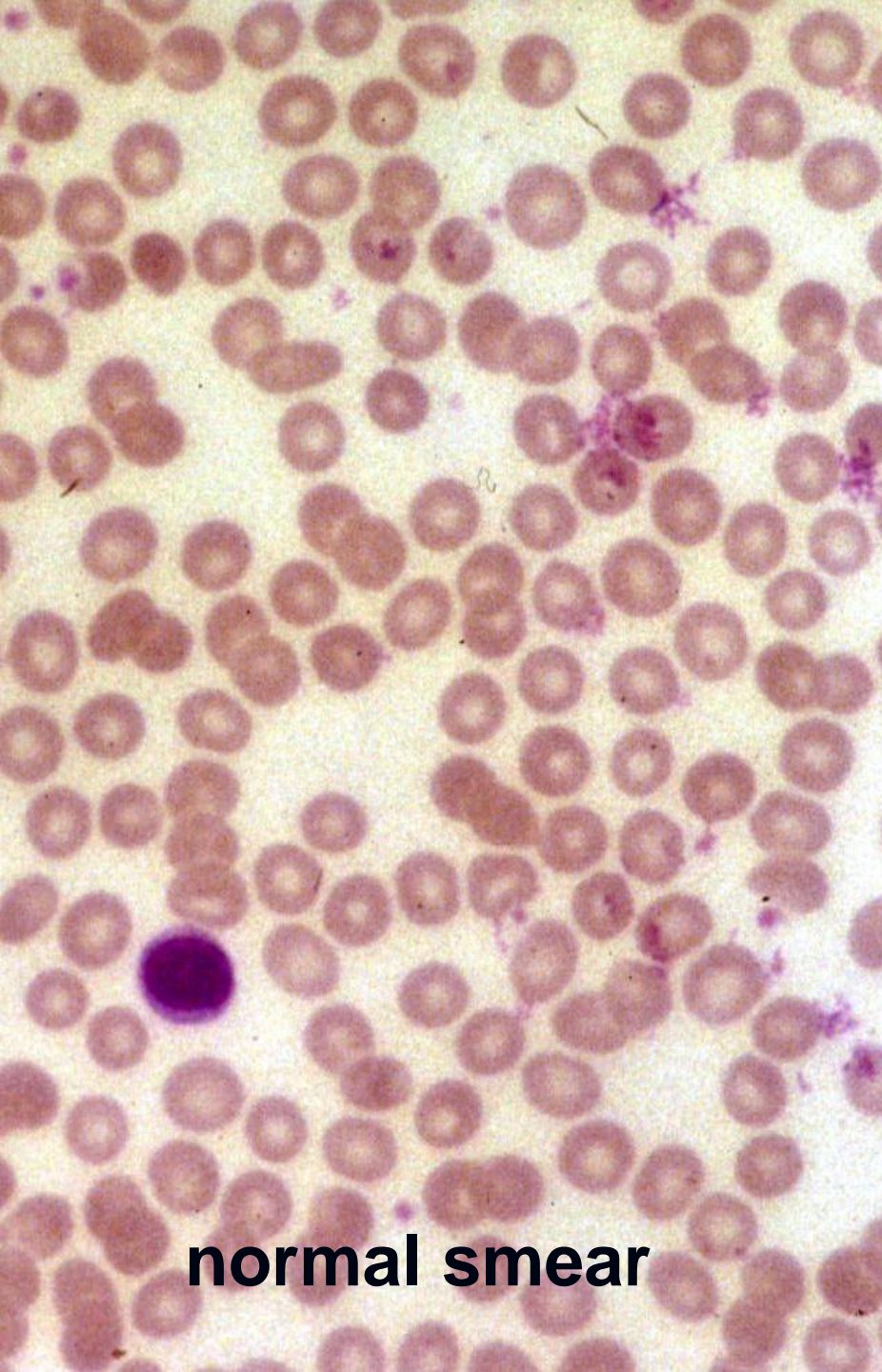
No history of abnormal menses or blood donation.

You order a peripheral smear, stool guaiac, and serum iron/TIBC:

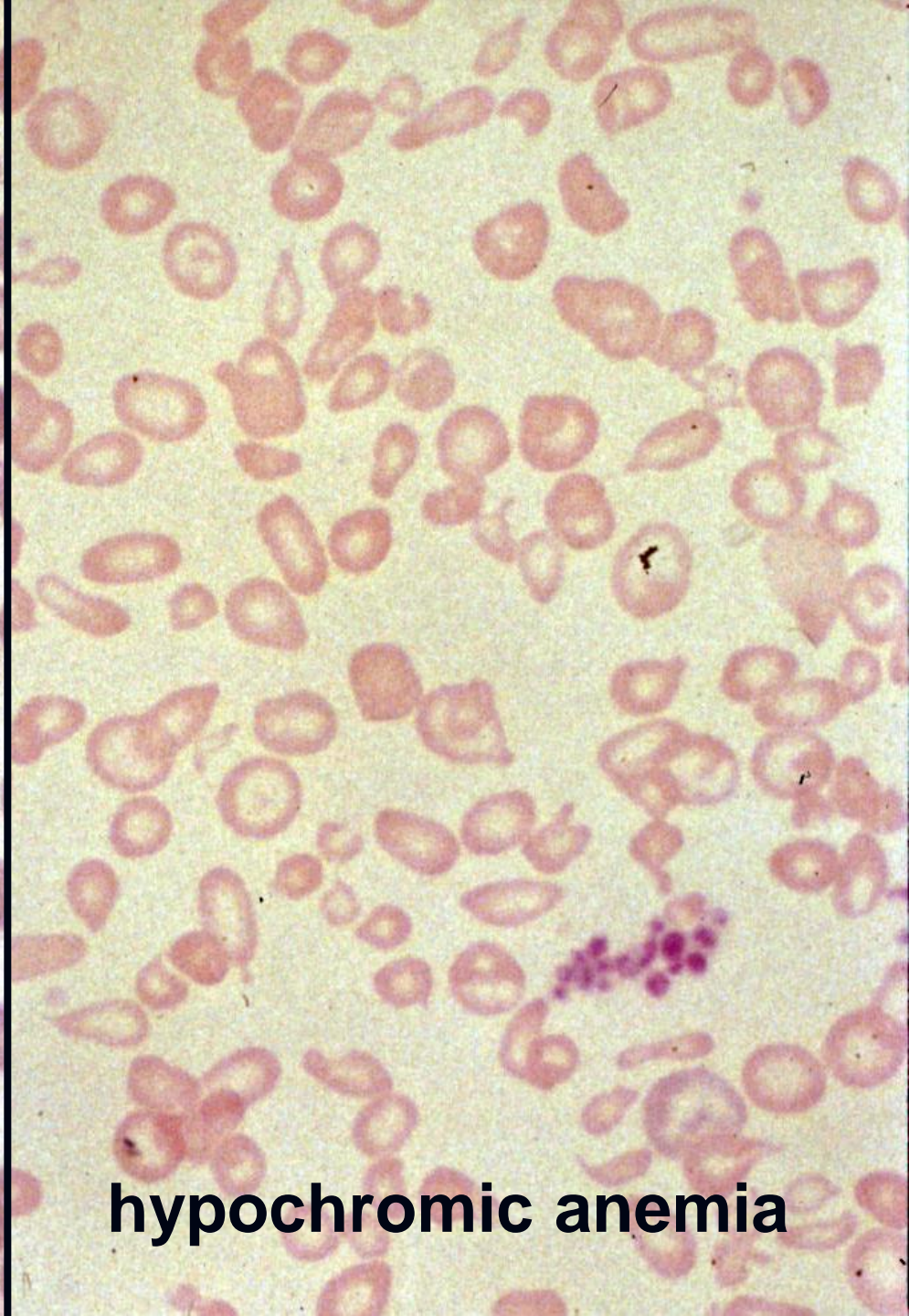
What to look for: peripheral smear



- RBC size, shape, central pallor
- WBC number, granularity, nuclear segmentation
- platelet number, size
- anemia:
hypochromic, megaloblastic, or hemolytic



normal smear



hypochromic anemia

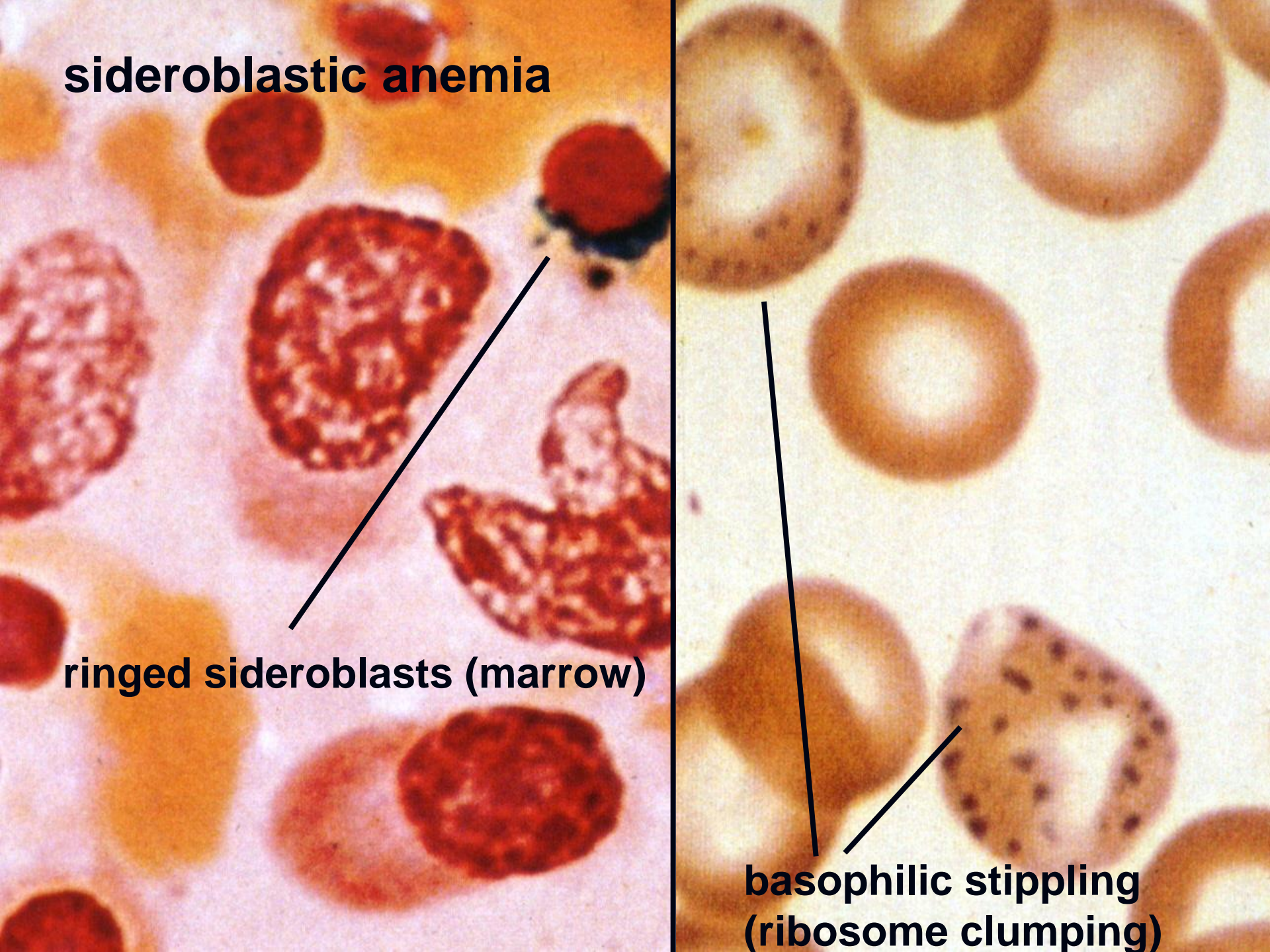
Hypochromic anemia

- **Iron deficiency**
 - Blood loss
 - Malabsorption
 - Increased requirement
- **Impaired heme synthesis (sideroblastic)**
 - Hereditary, idiopathic, toxins (lead, alcohol)

sideroblastic anemia

ringed sideroblasts (marrow)

**basophilic stippling
(ribosome clumping)**



Hypochromic anemia, cont' d

- **Altered iron mobilization**
 - Anemia of chronic inflammation
 - Increased hepcidin levels
- **Impaired globin synthesis**
 - α - and β -thalassemia

β -thalassemia

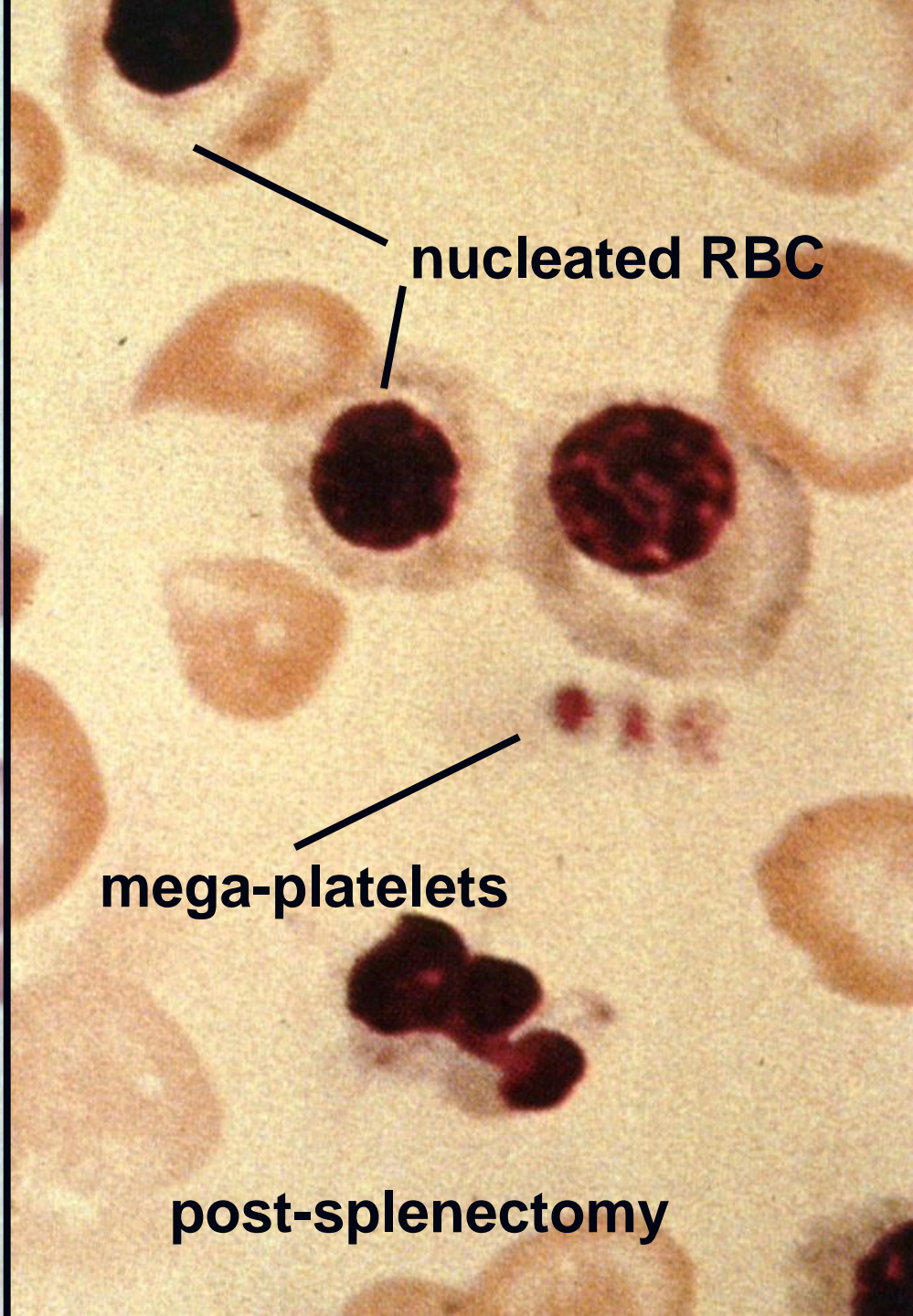
pre-splenectomy

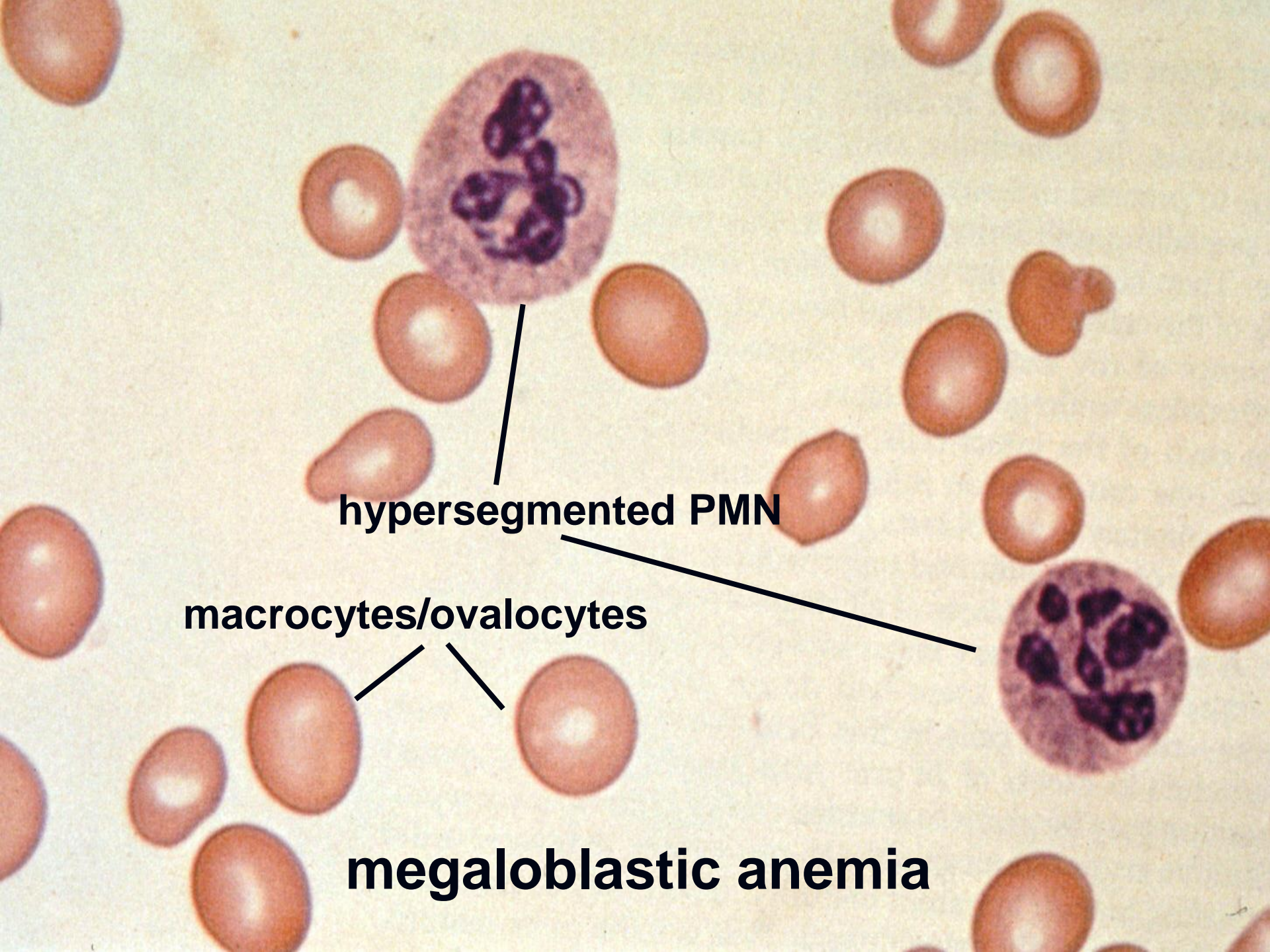


nucleated RBC

mega-platelets

post-splenectomy





hypersegmented PMN

macrocytes/ovalocytes

megaloblastic anemia

hemolytic anemia

schistocytes

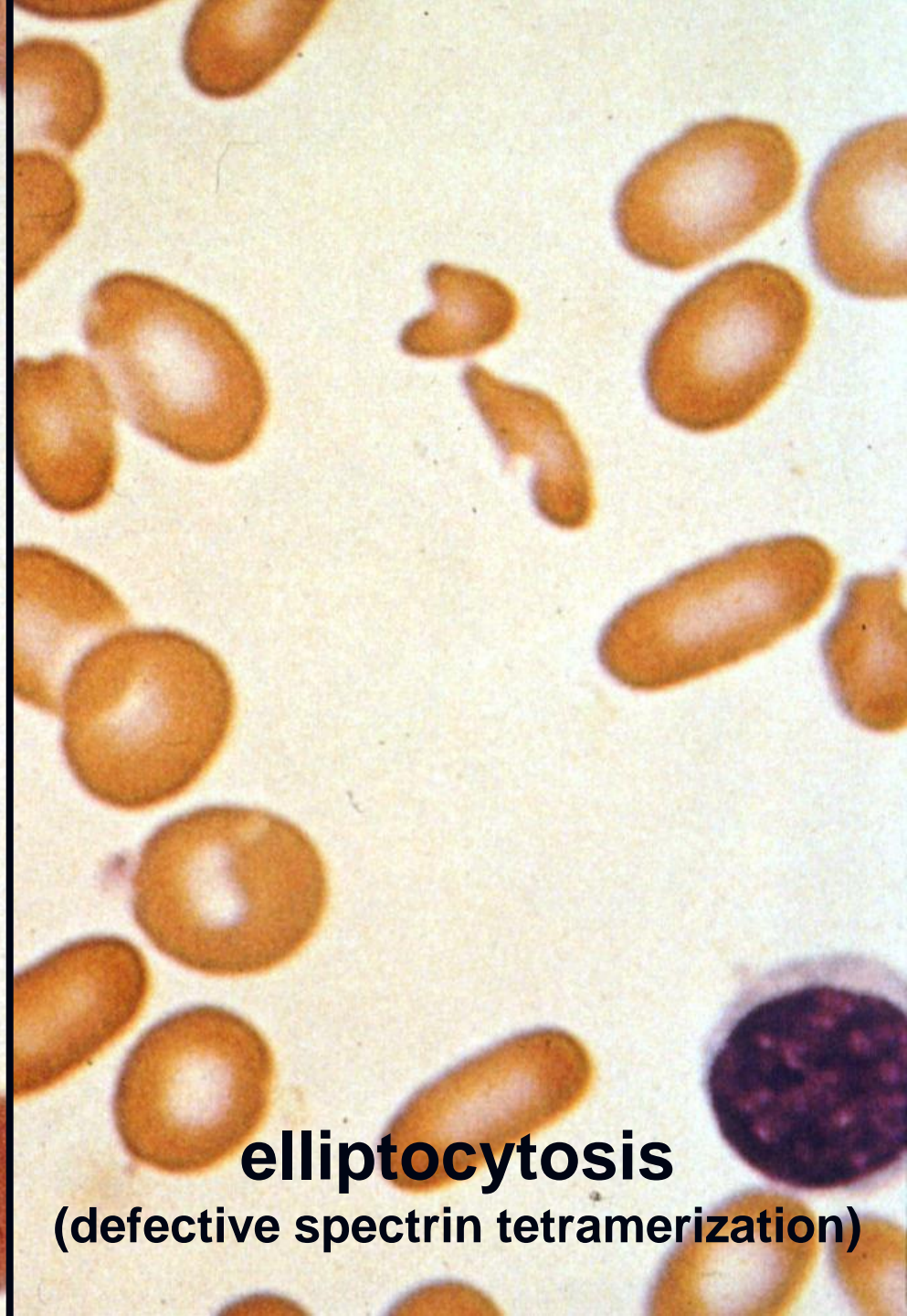
mechanical

TTP or DIC

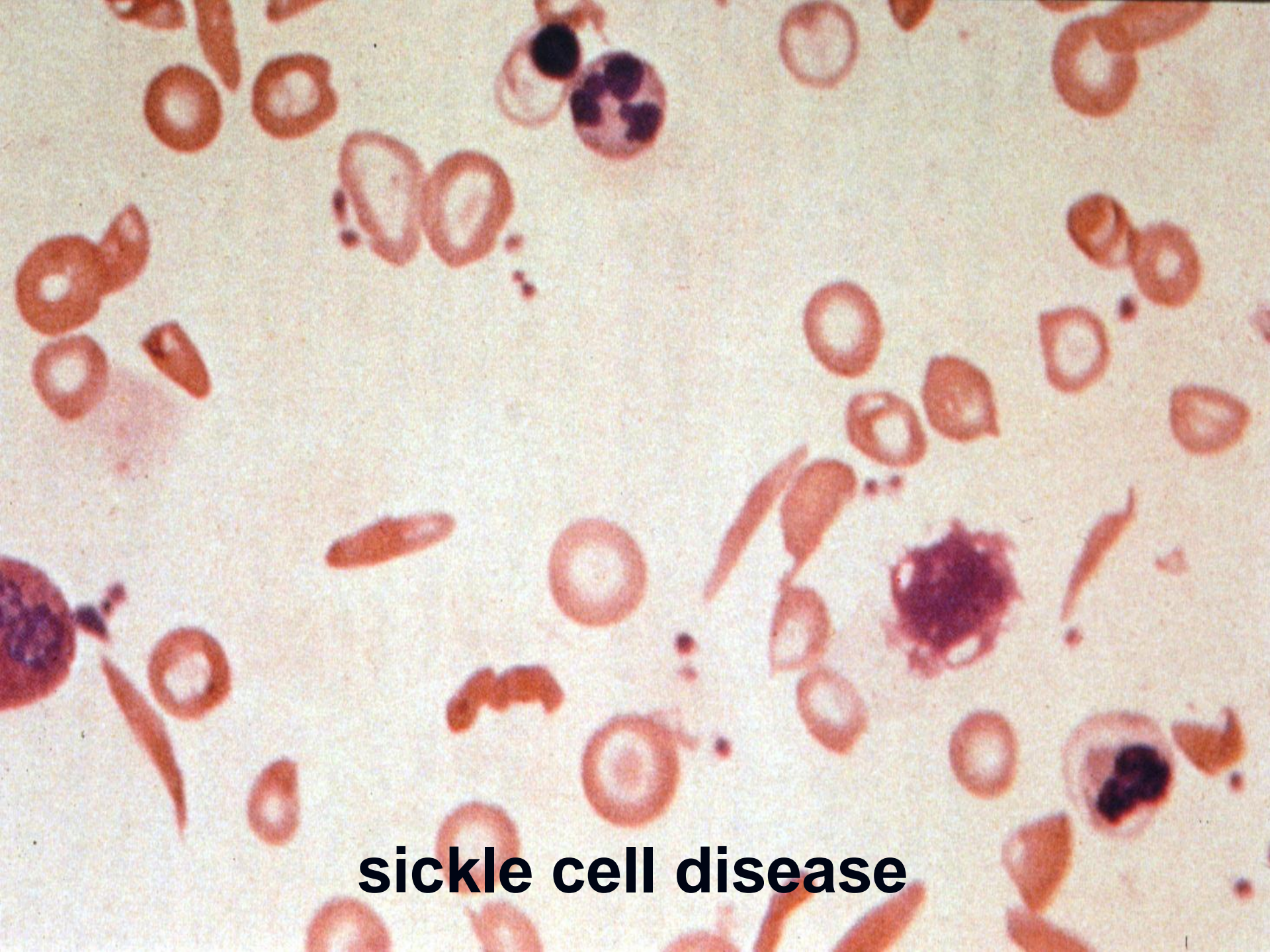
schistocytes



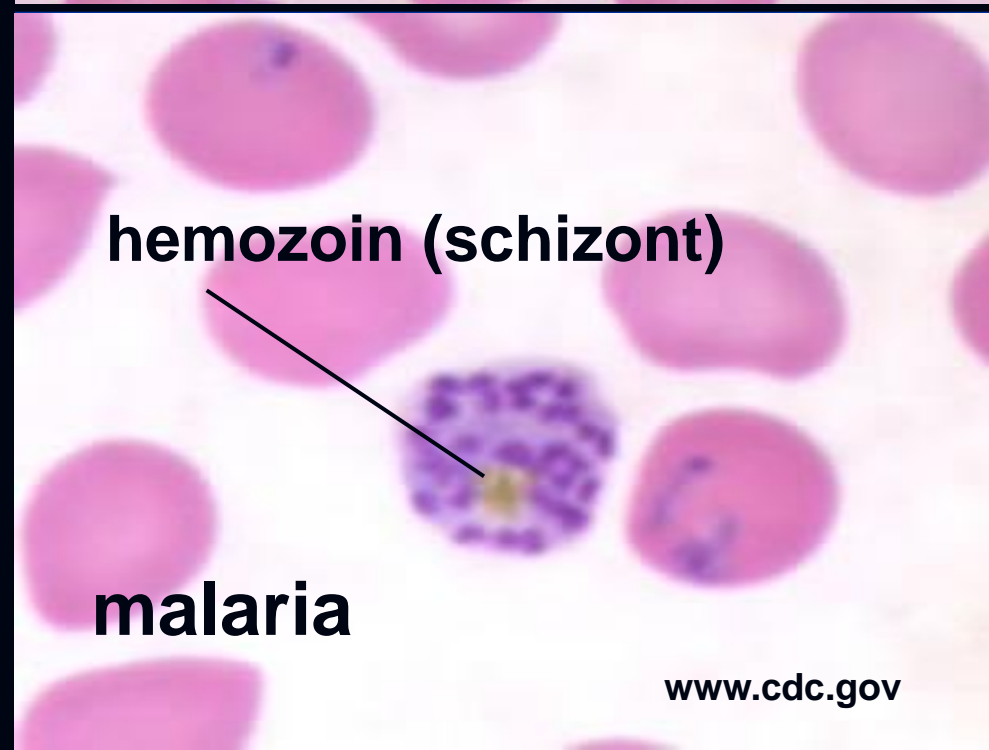
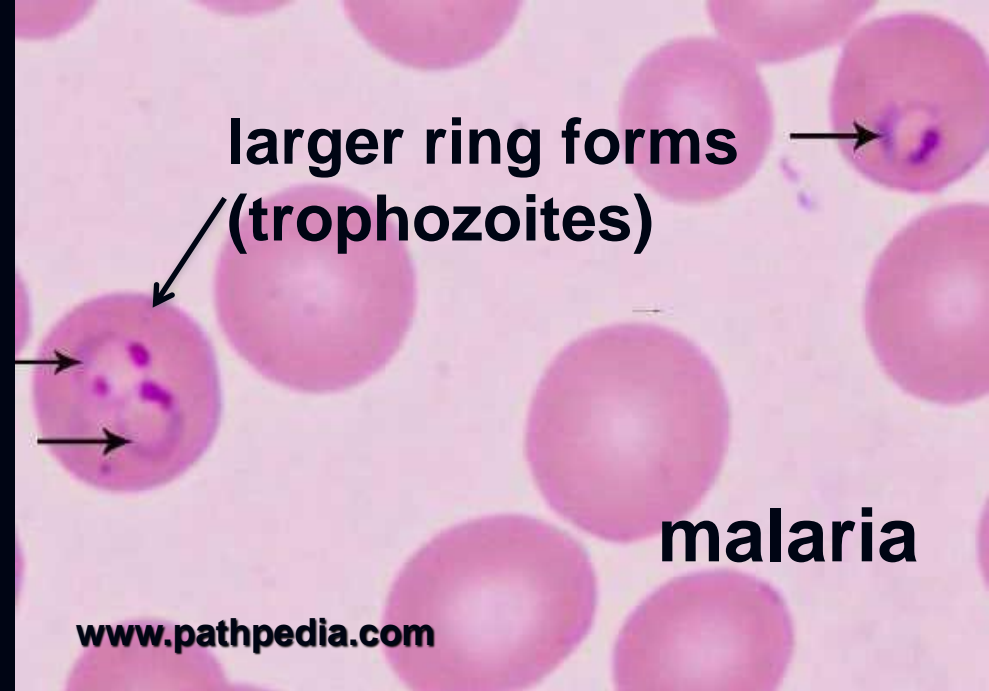
spherocytosis
(insufficient spectrin)



elliptocytosis
(defective spectrin tetramerization)

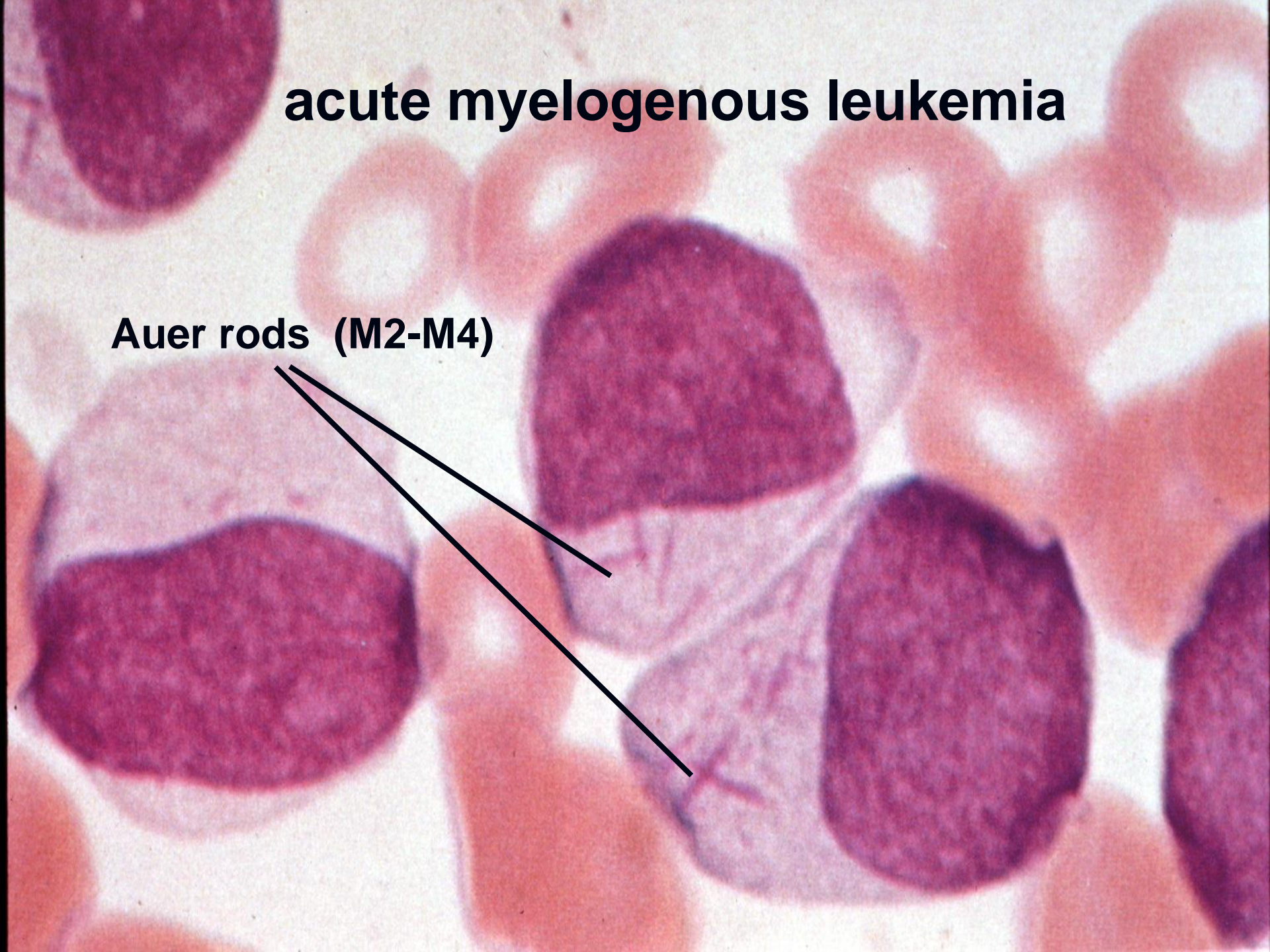


sickle cell disease



acute myelogenous leukemia

Auer rods (M2-M4)



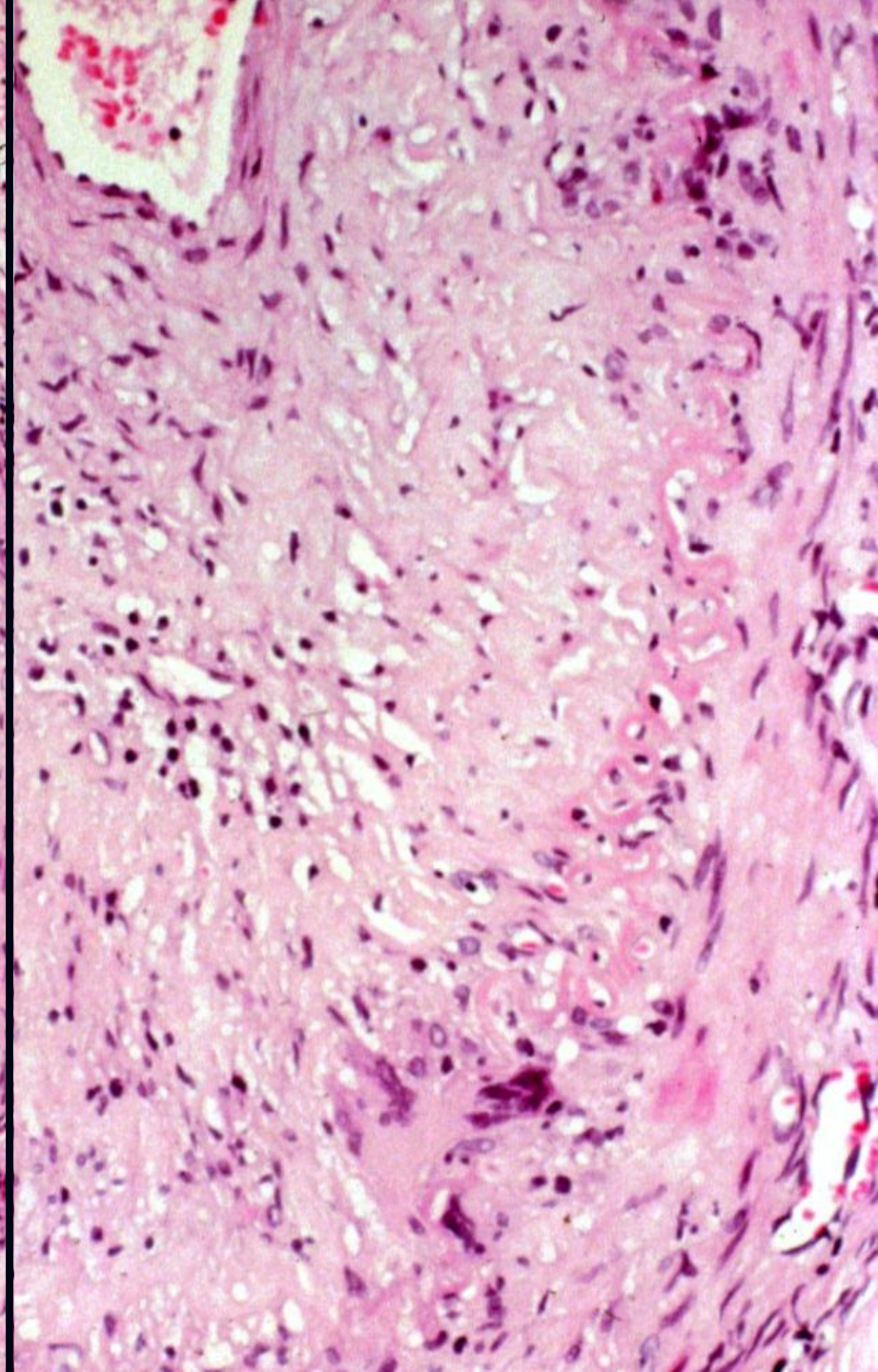
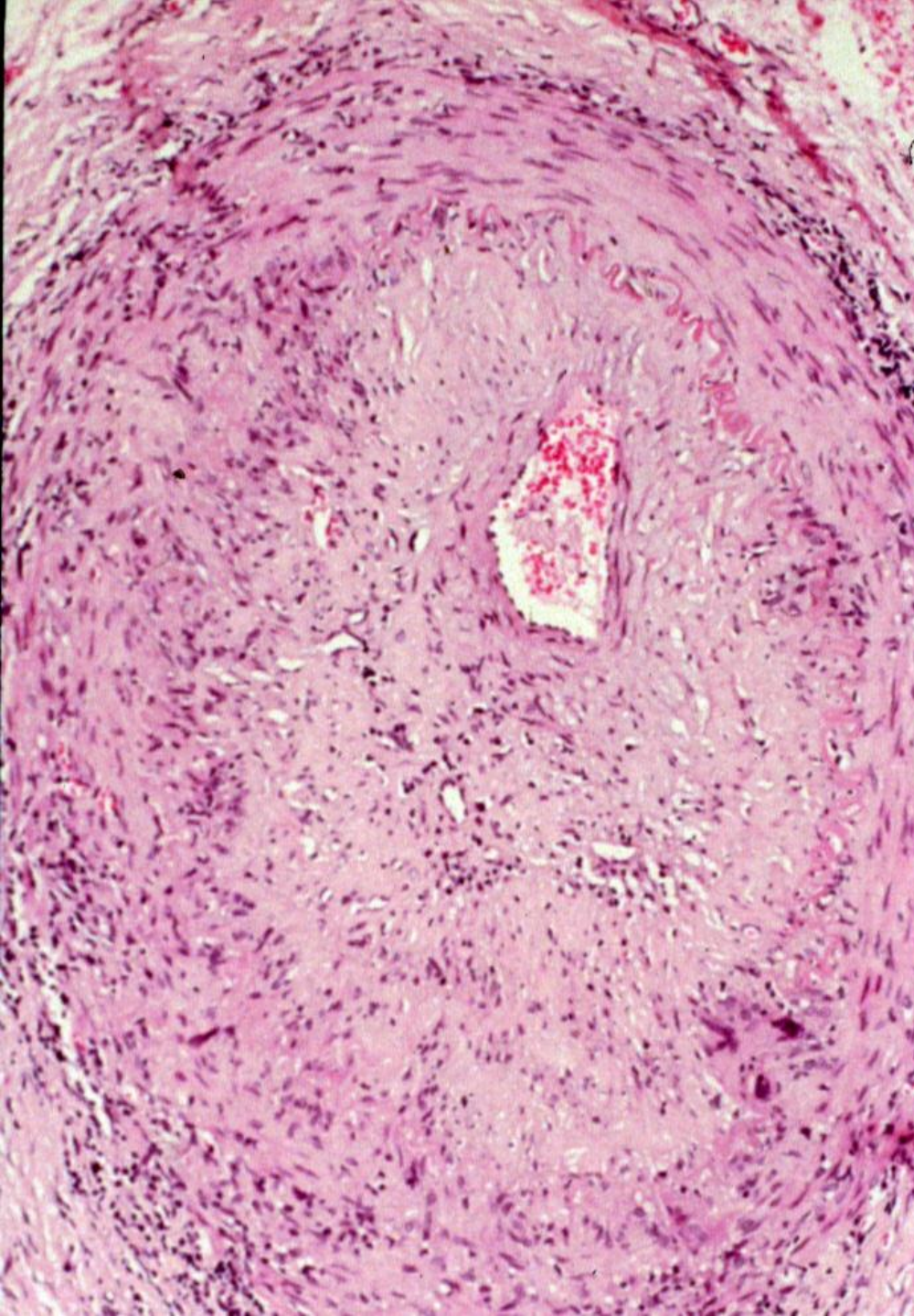
Summary: Take-Home Points

- History and physical exam suggest a differential (of course)
- Laboratory tests can refine the list (absolutely)
- Directed biopsy or smear is often definitive (yes!)
- Form follows (dys)function
- Pathologists can be fun

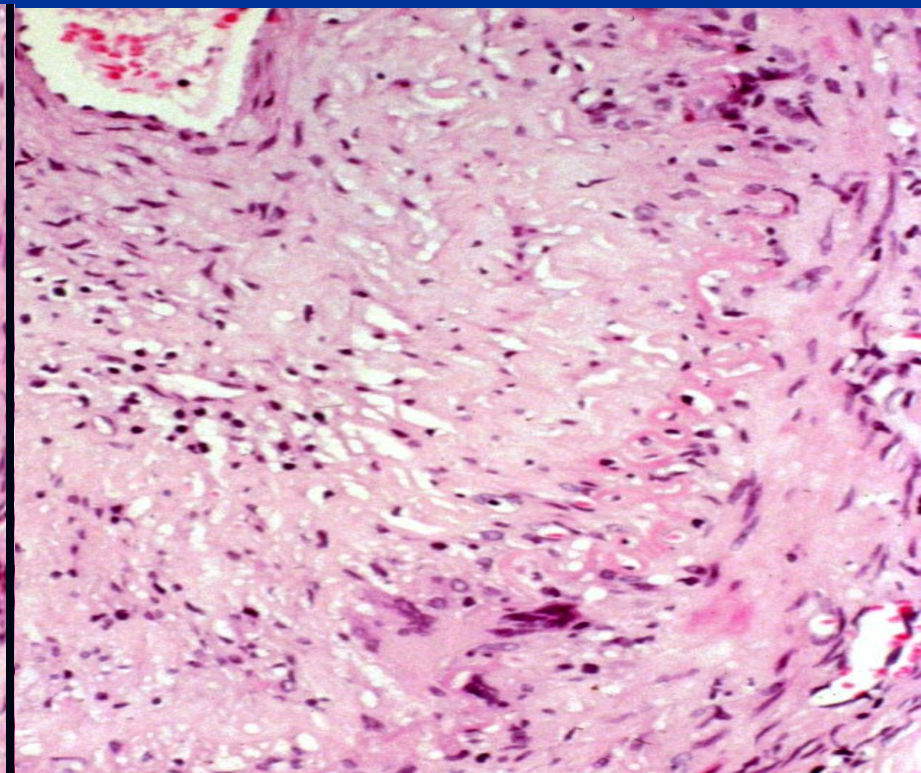
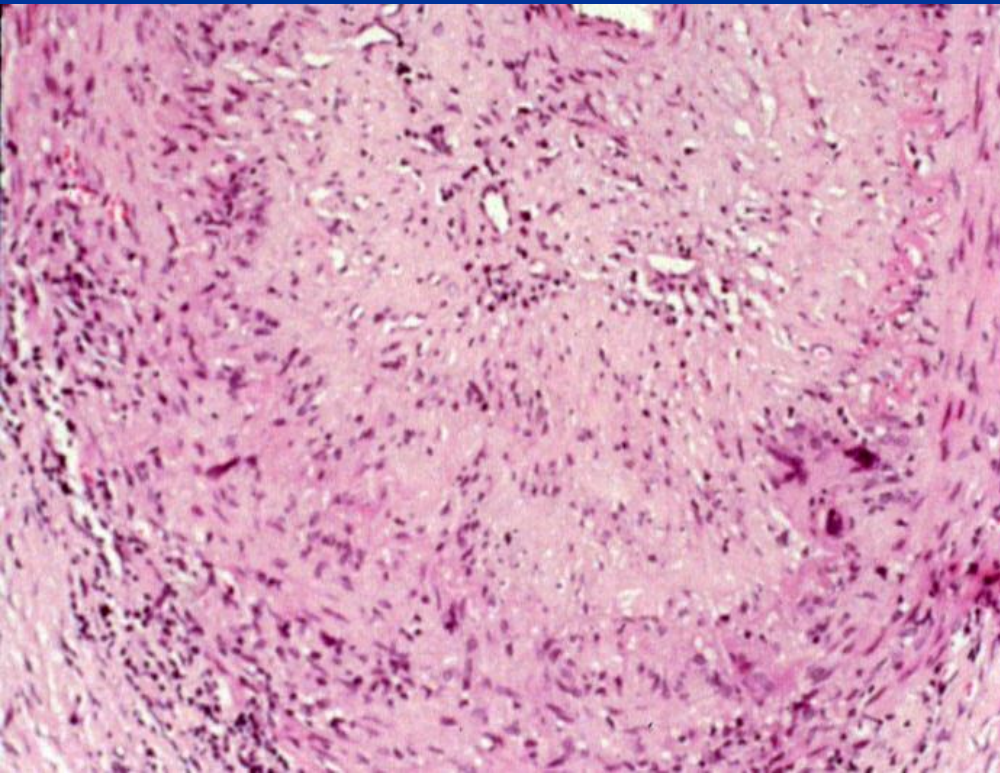
Board Style Practice Question

**79 y.o. woman with 6-month
h/o headache, episodic
diplopia, and fatigue.**

A biopsy is performed.

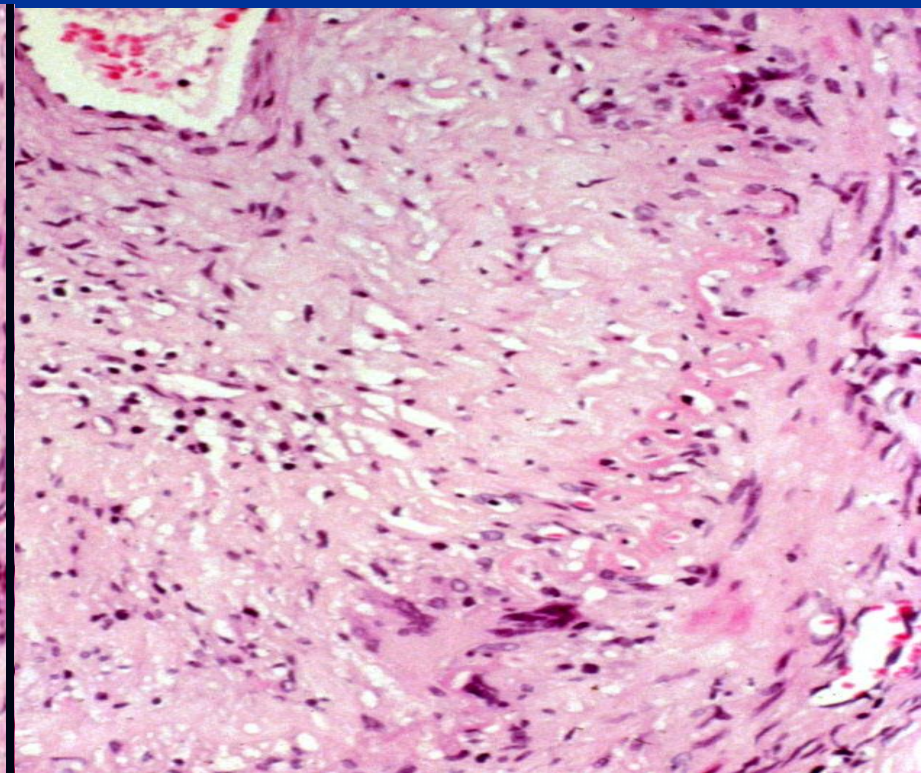
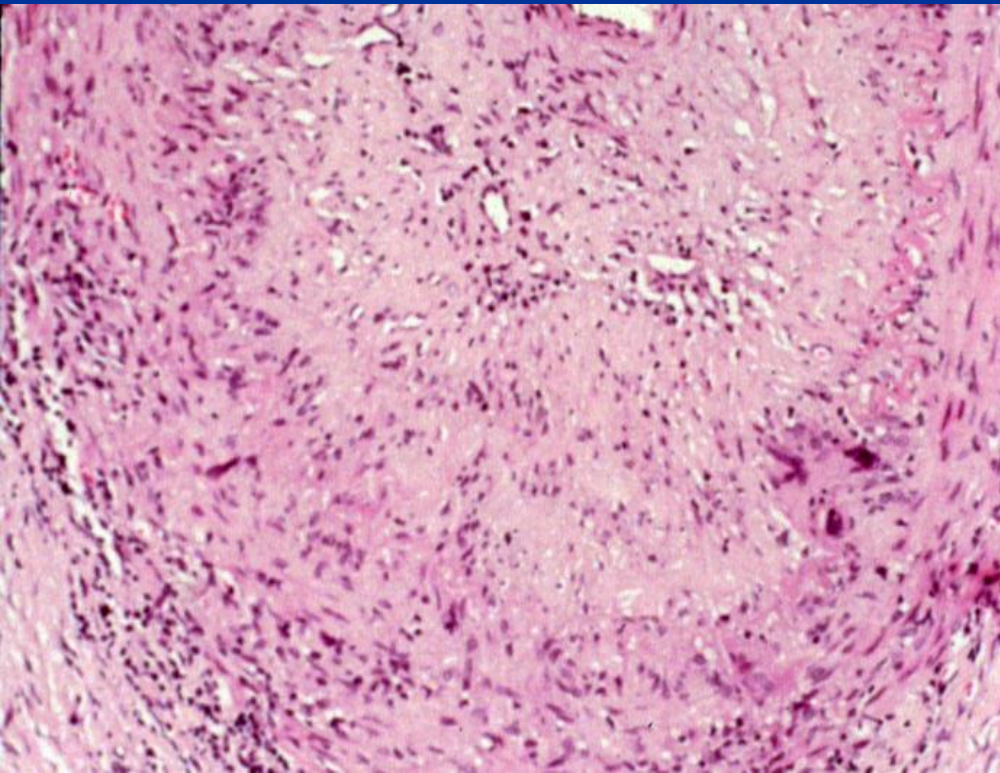


- A. amyloidosis**
- B. Hashimoto's thyroiditis**
- C. temporal arteritis**
- D. Churg-Strauss syndrome**
- E. rheumatoid arthritis**



C. temporal (giant cell) arteritis

- intimal hyperplasia
- internal elastic lamina disruption
- medial attenuation
- adventitial fibrosis
- medial inflammation +/- giant cells
- can be focal; inflammation rapidly changed by rx

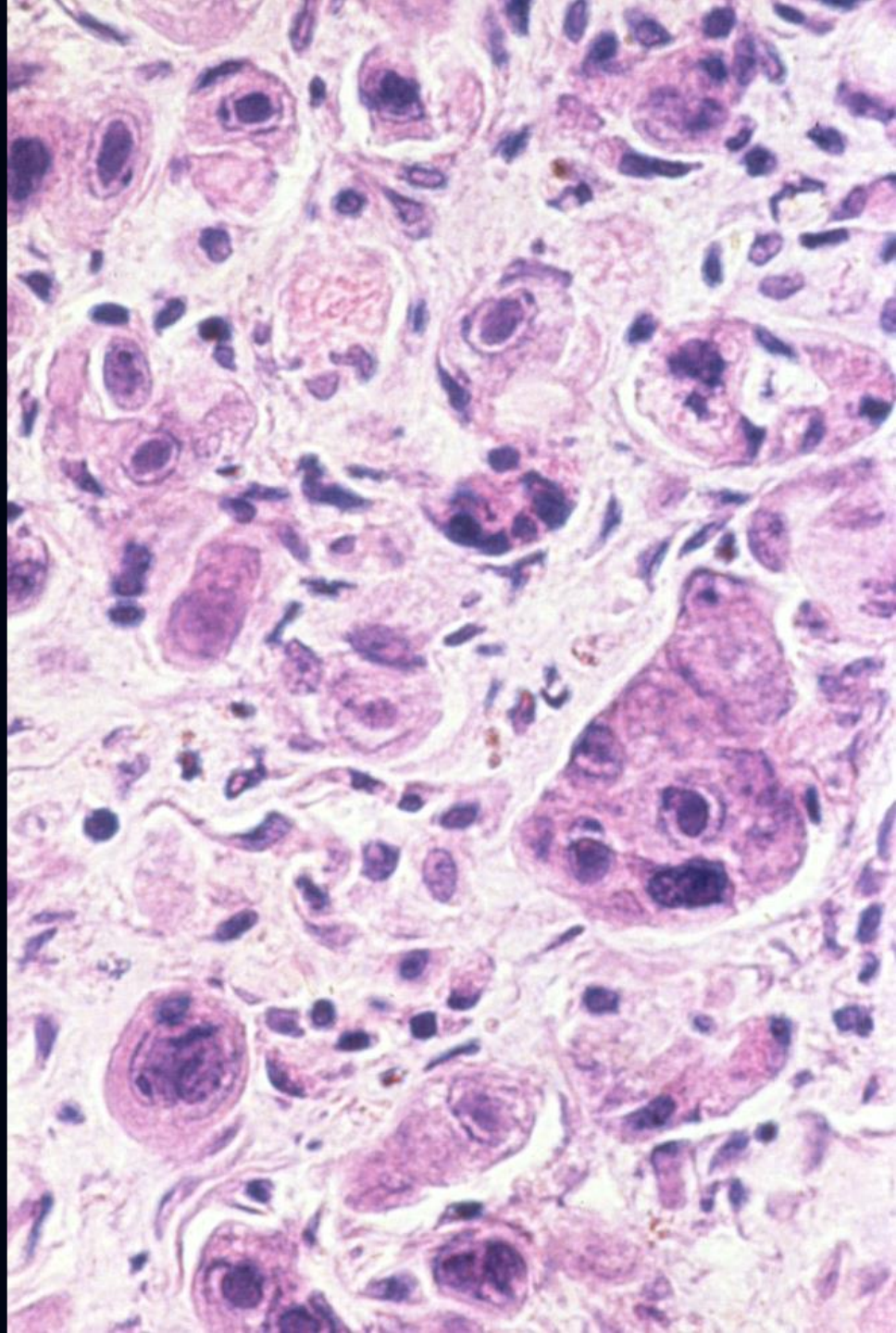
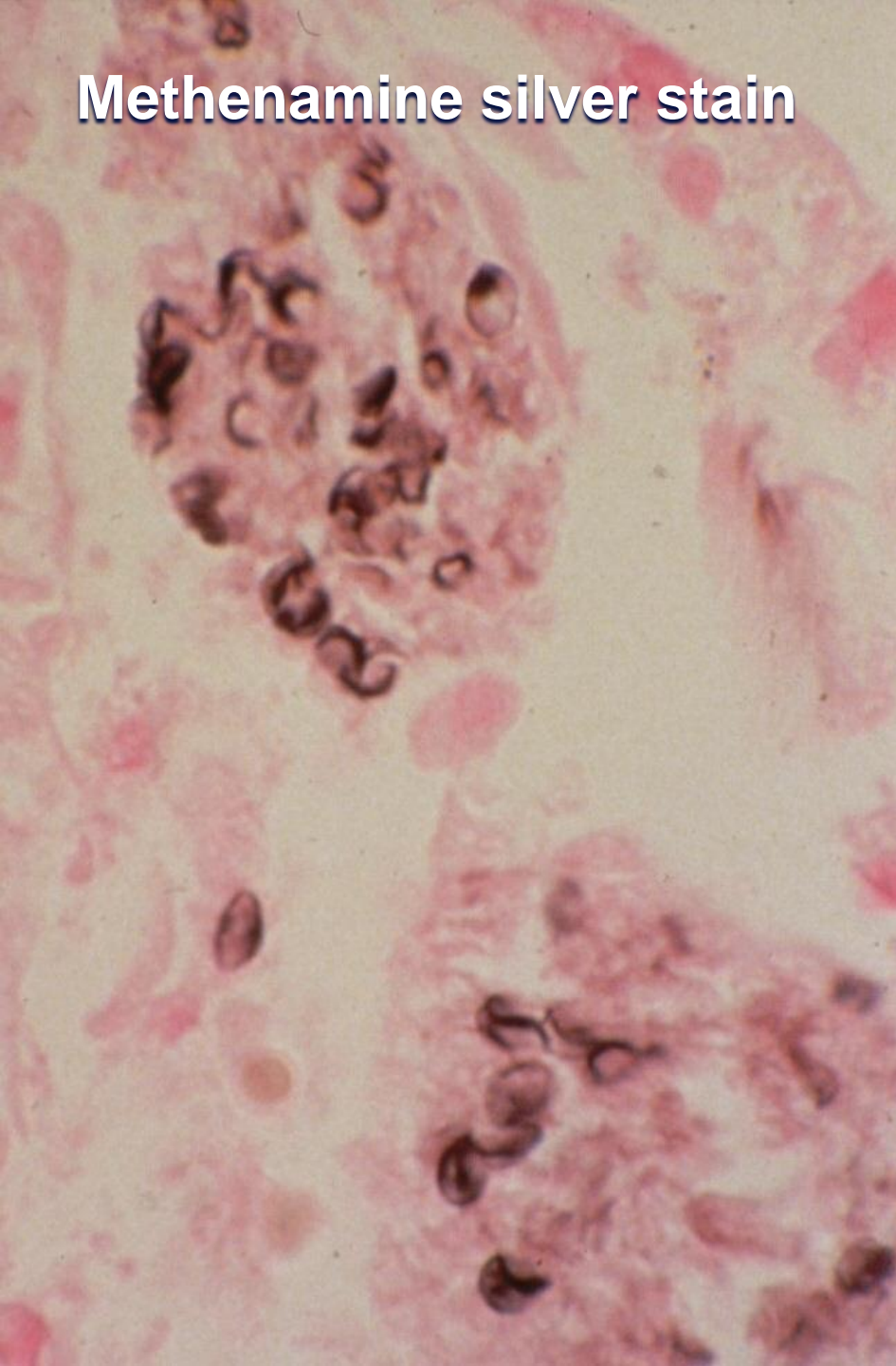


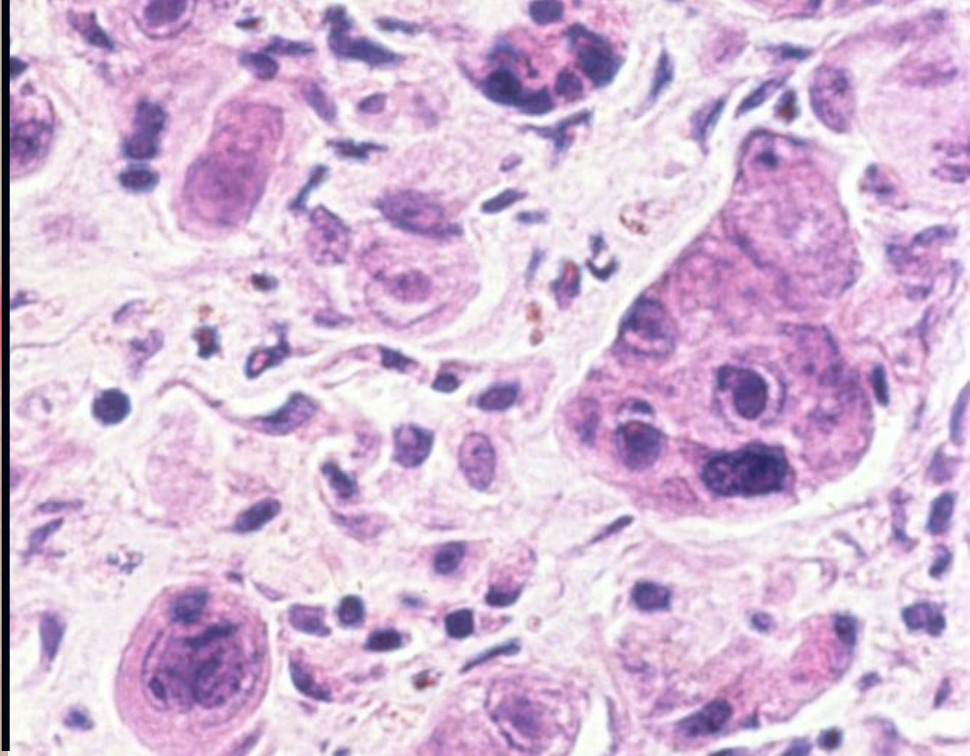
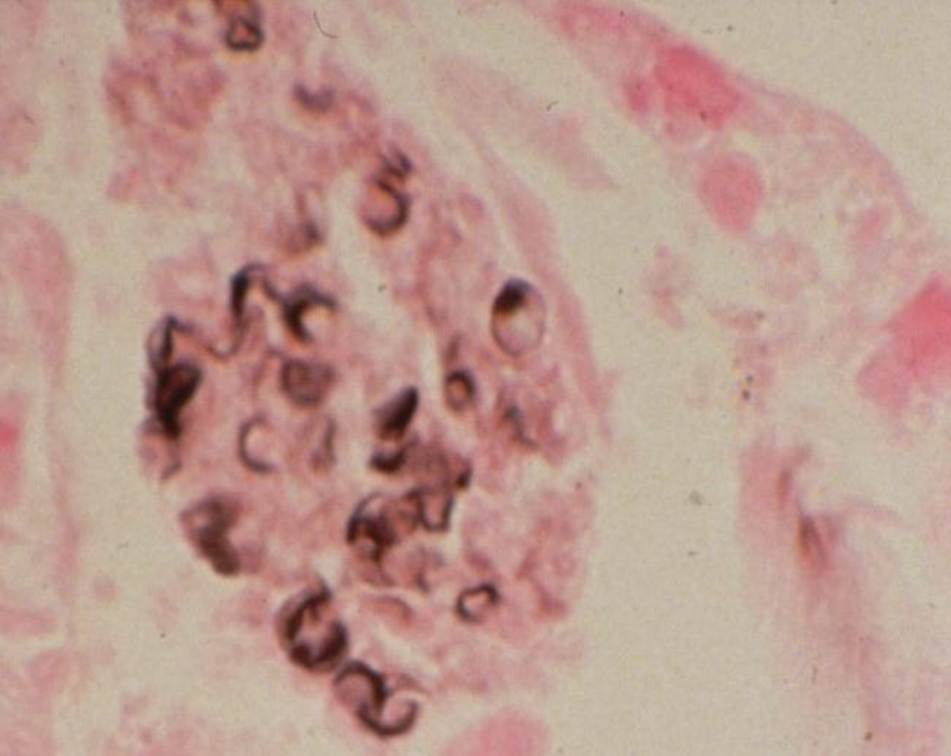
Board Style Practice Question

36 y.o. man with 5 year h/o HIV infection; frequently misses medications. Now with progressive dyspnea and lung opacifications.

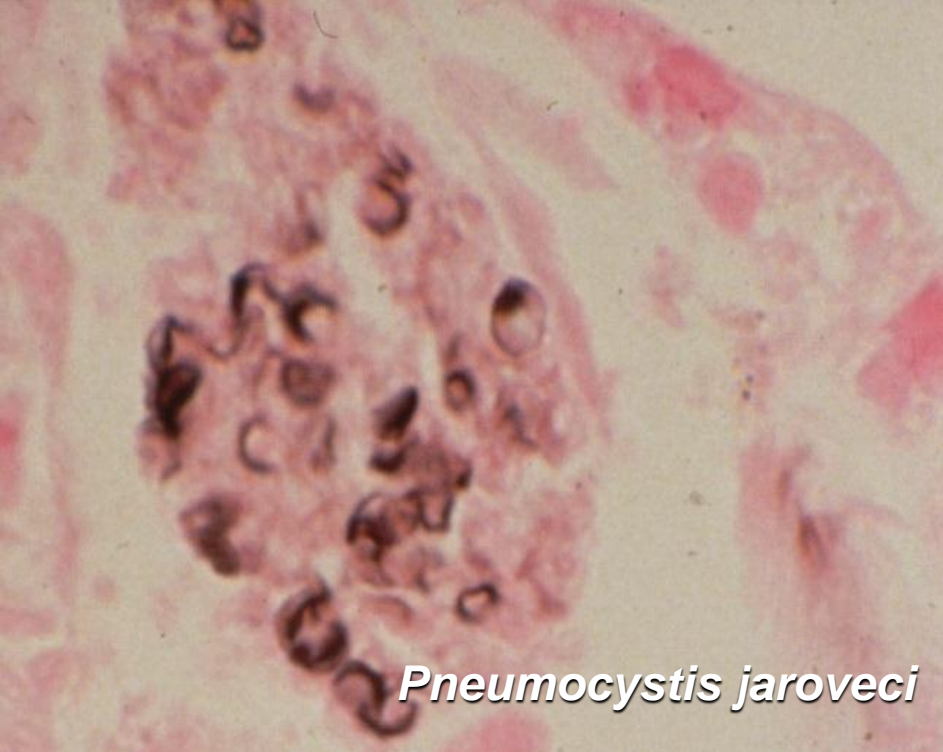
A biopsy is performed.

Methenamine silver stain

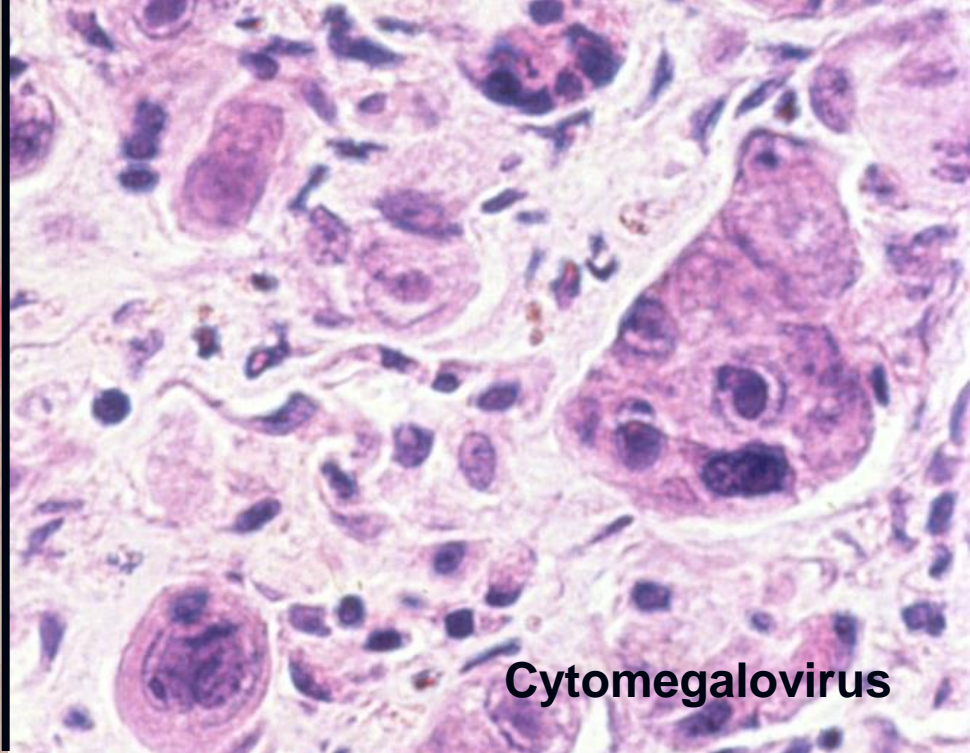




- A. *Pneumocystis jirovecii* pneumonia
- B. respiratory syncytial virus
- C. hypersensitivity pneumonitis
- D. sarcoidosis
- E. cytomegalovirus



Pneumocystis jirovecii



Cytomegalovirus

A. *Pneumocystis jirovecii* pneumonia

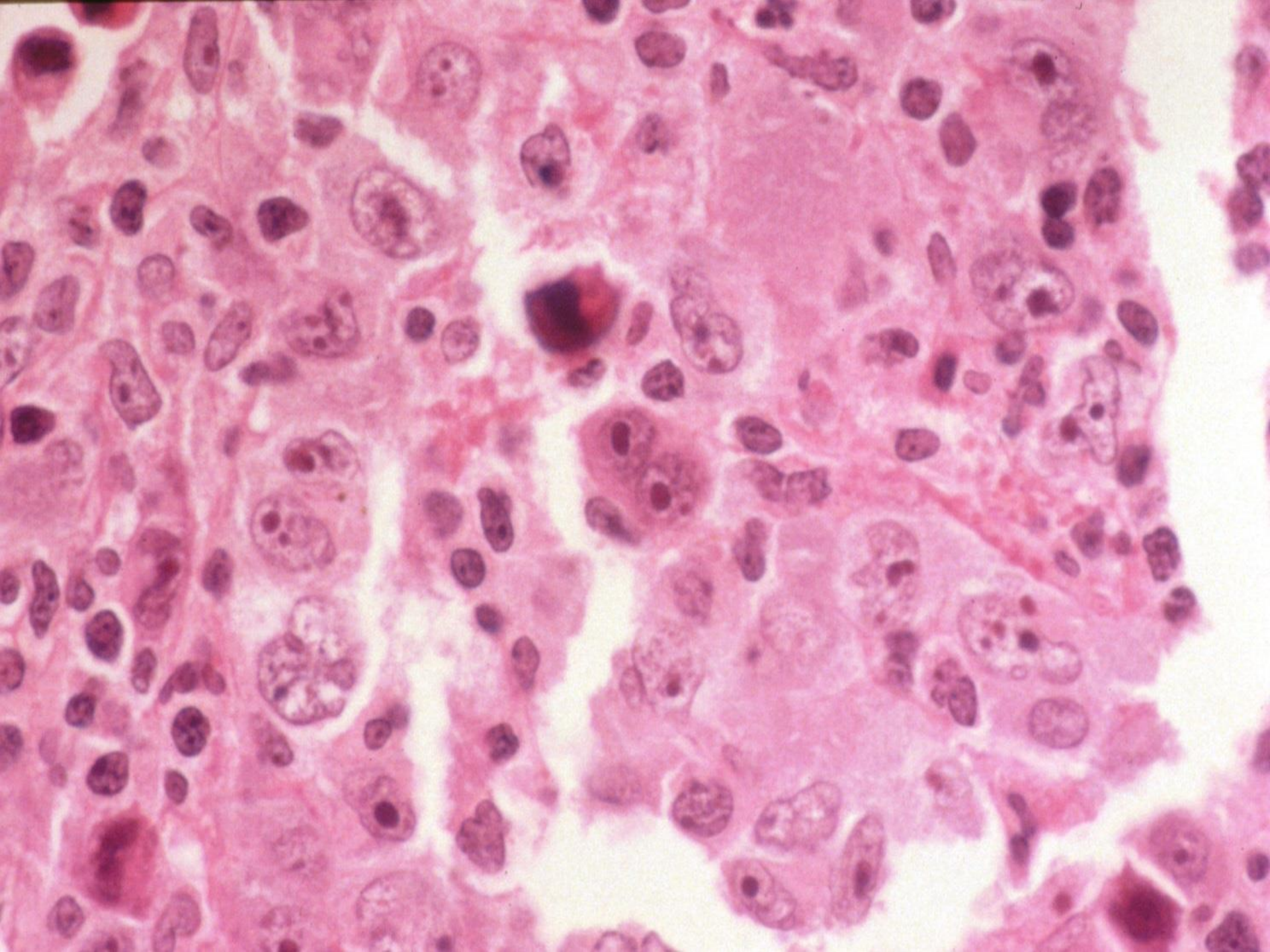
E. Cytomegalovirus

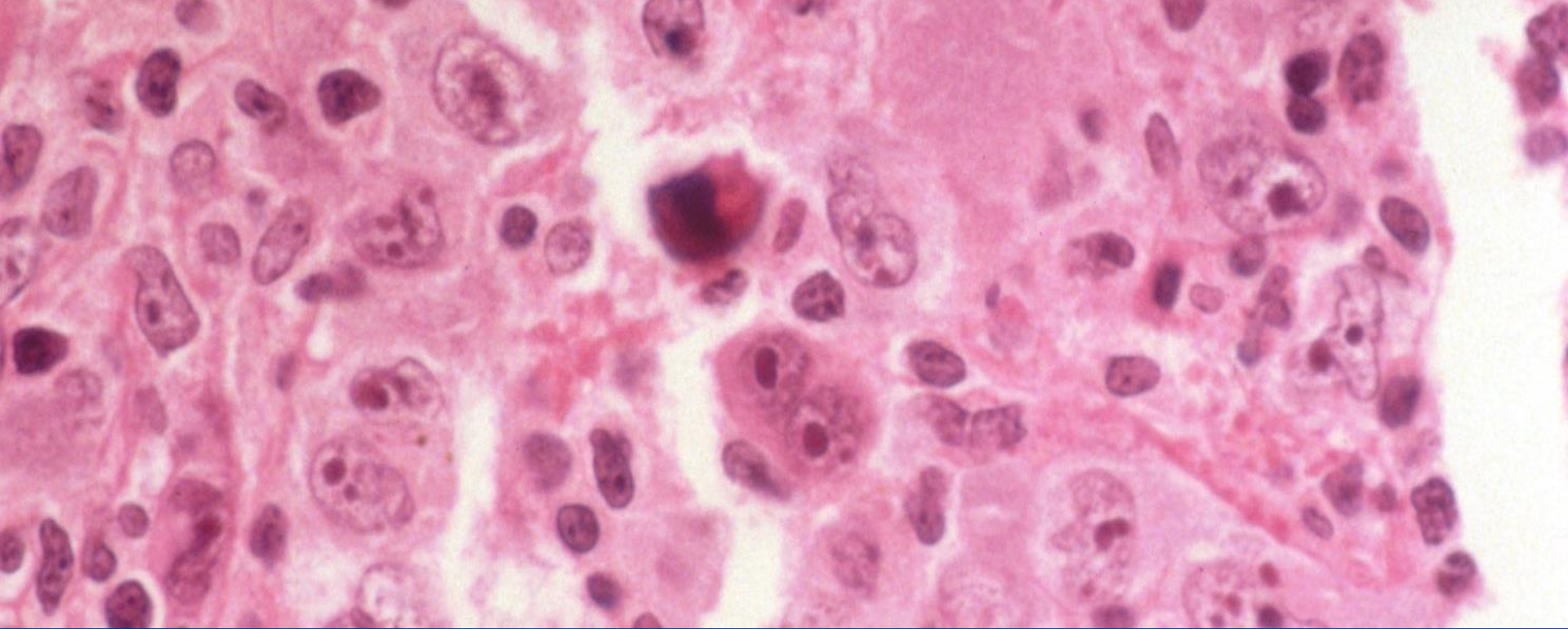
- opportunistic infections
- can be coincident
- *Pneumocystis* cysts can persist after active infection
- *Pneumocystis* commonly dx' d by immunofluorescence
- CMV may represent primary infxn or reactivation

Board Style Practice Question

**25 y.o. woman with a single
supraclavicular lymph node.**

A biopsy is performed.





- A. non-Hodgkins lymphoma**
- B. Hodgkins lymphoma**
- C. metastatic ovarian carcinoma**
- D. tuberculosis**
- E. reactive lymphadenopathy**



Reed-Sternberg cell

B. Hodgkins lymphoma

- pathognomonic Reed-Sternberg cells (with variant forms)
- variably present dependent on type of Hodgkins (mixed cellularity has most)
- nodular sclerosing Hodgkins has best prognosis
- neoplasm of germinal center B cells
- most cells in the lesions are reactive

Challenging General Internal Medicine Cases

**Dr. Marshall A. Wolf and
Dr. Richard N. Mitchell**

**We *still* have nothing to disclose
regarding conflicts of interest**

Challenging General Internal Medicine Cases

Suggested reference:
***Robbins and Cotran Pathologic
Basis of Disease, 10th Edition***
Saunders/Elsevier, 2021