

Challenging General Internal Medicine Cases

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We have no relevant financial relationships with ineligible companies

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

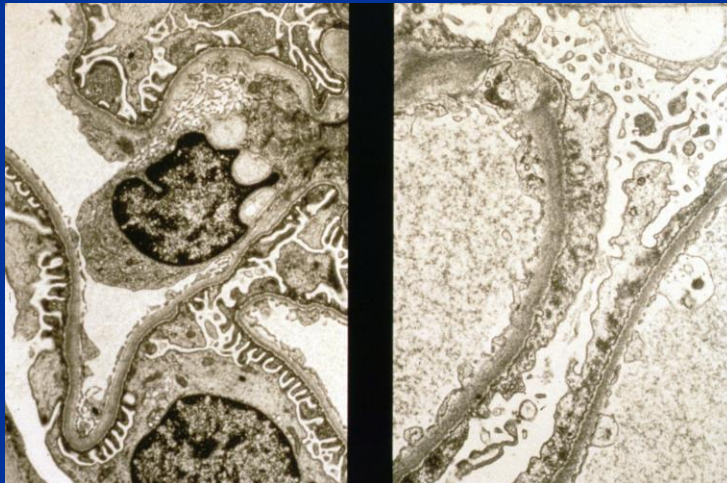
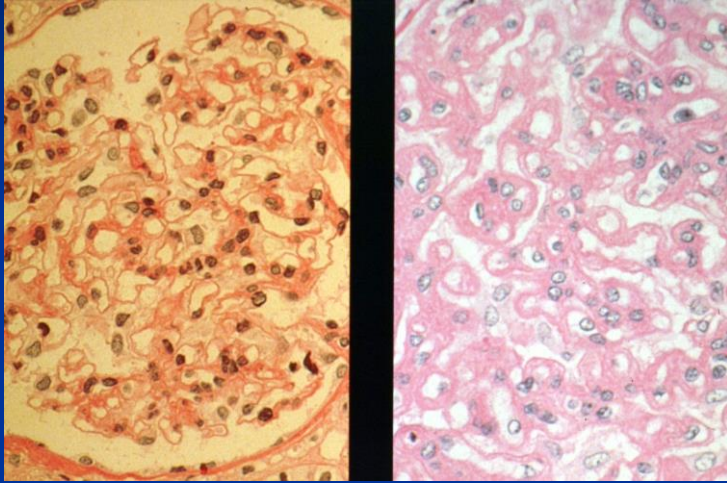
Miscellaneous:

Pre-eclampsia

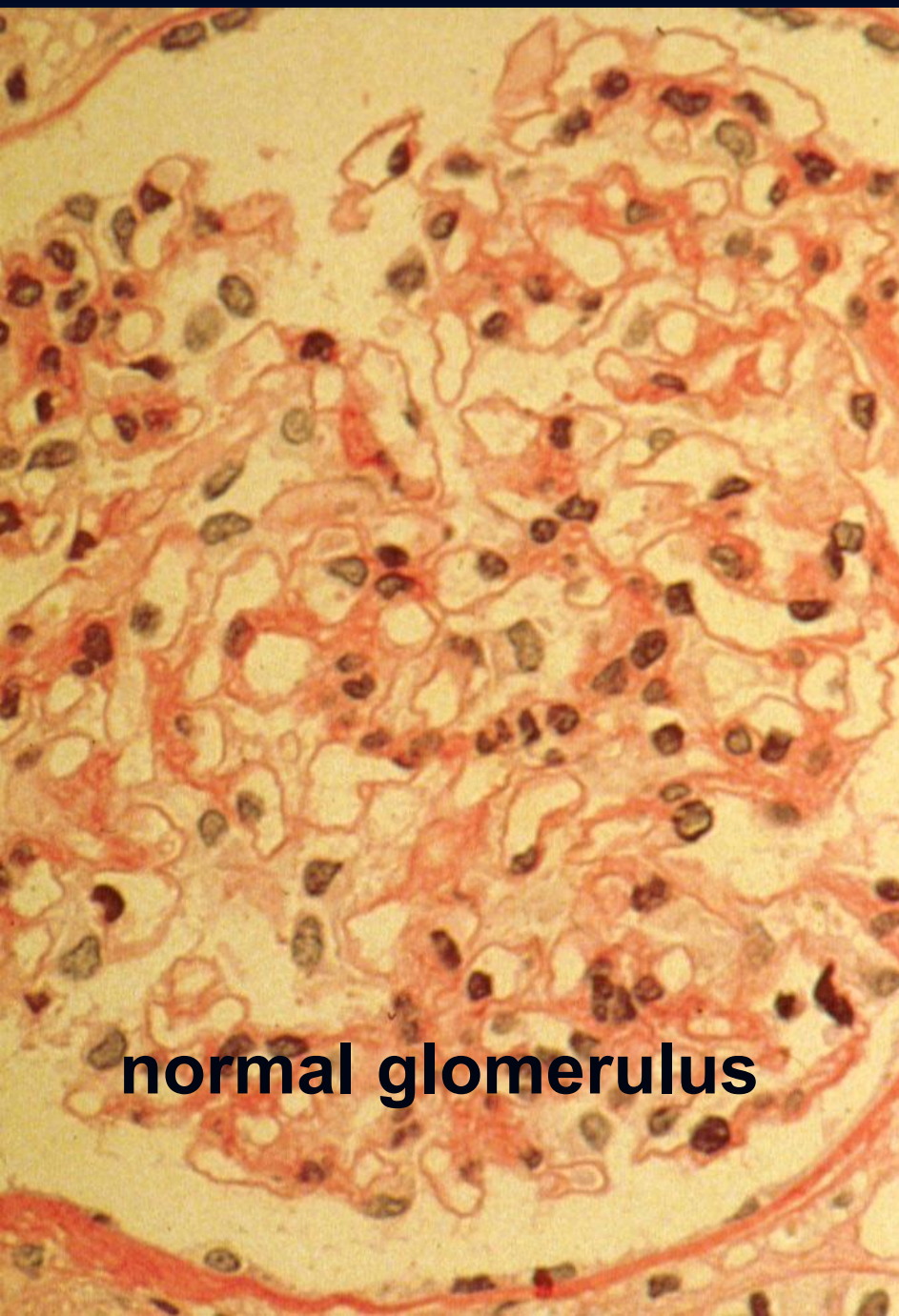
Sickle cell disease

Renovascular

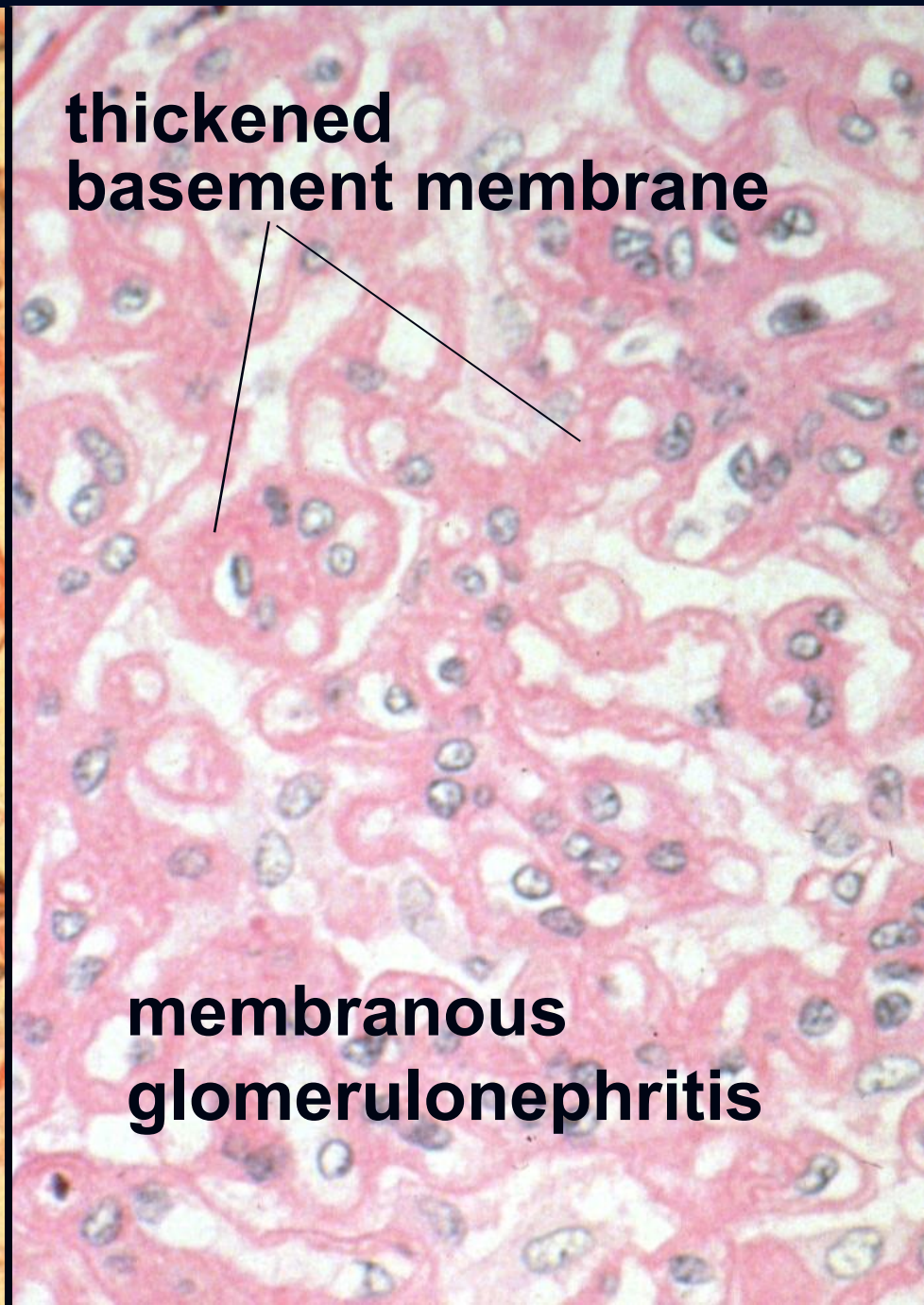
What to look for: proteinuria



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

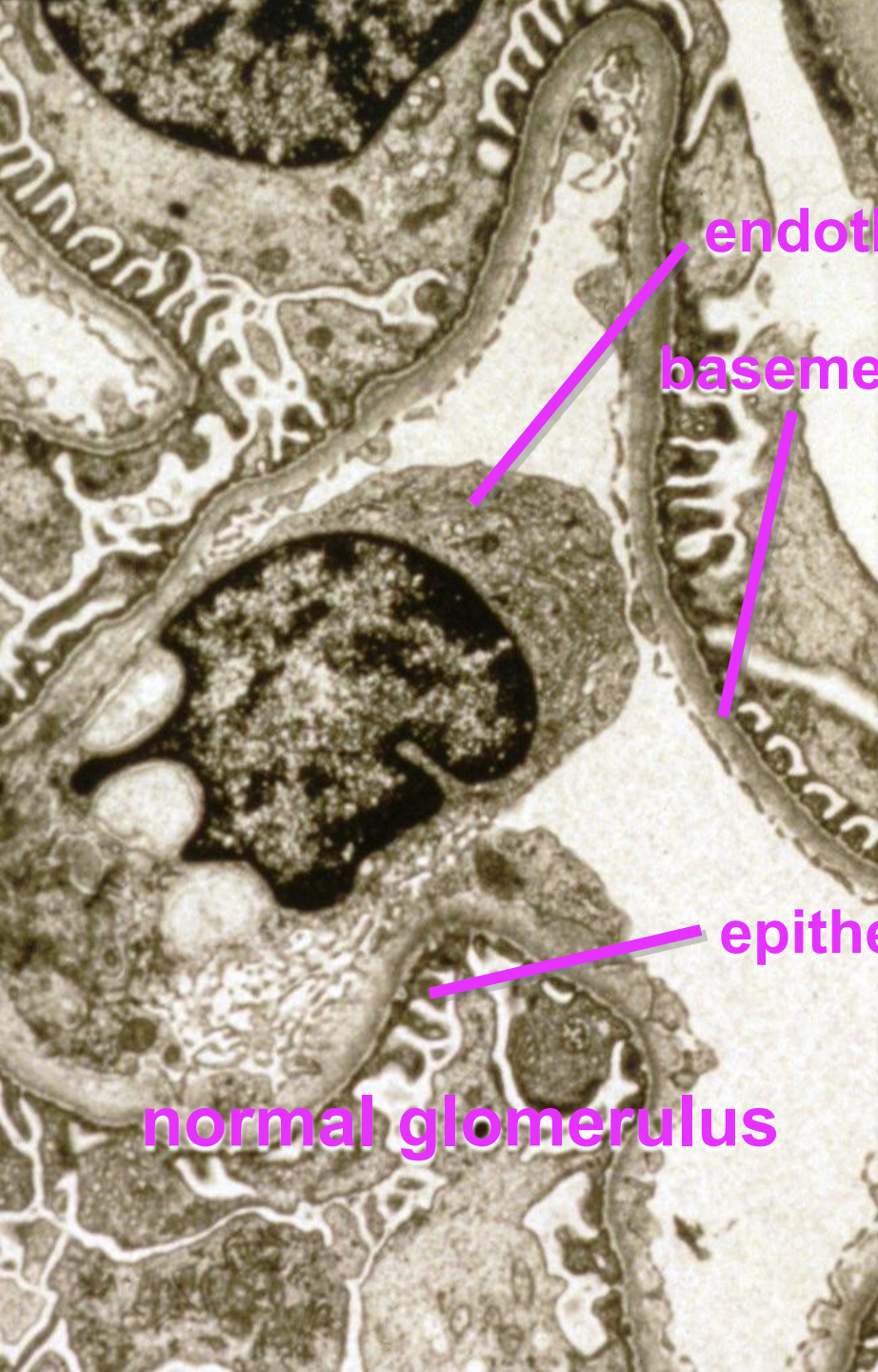


normal glomerulus



**thickened
basement membrane**

**membranous
glomerulonephritis**

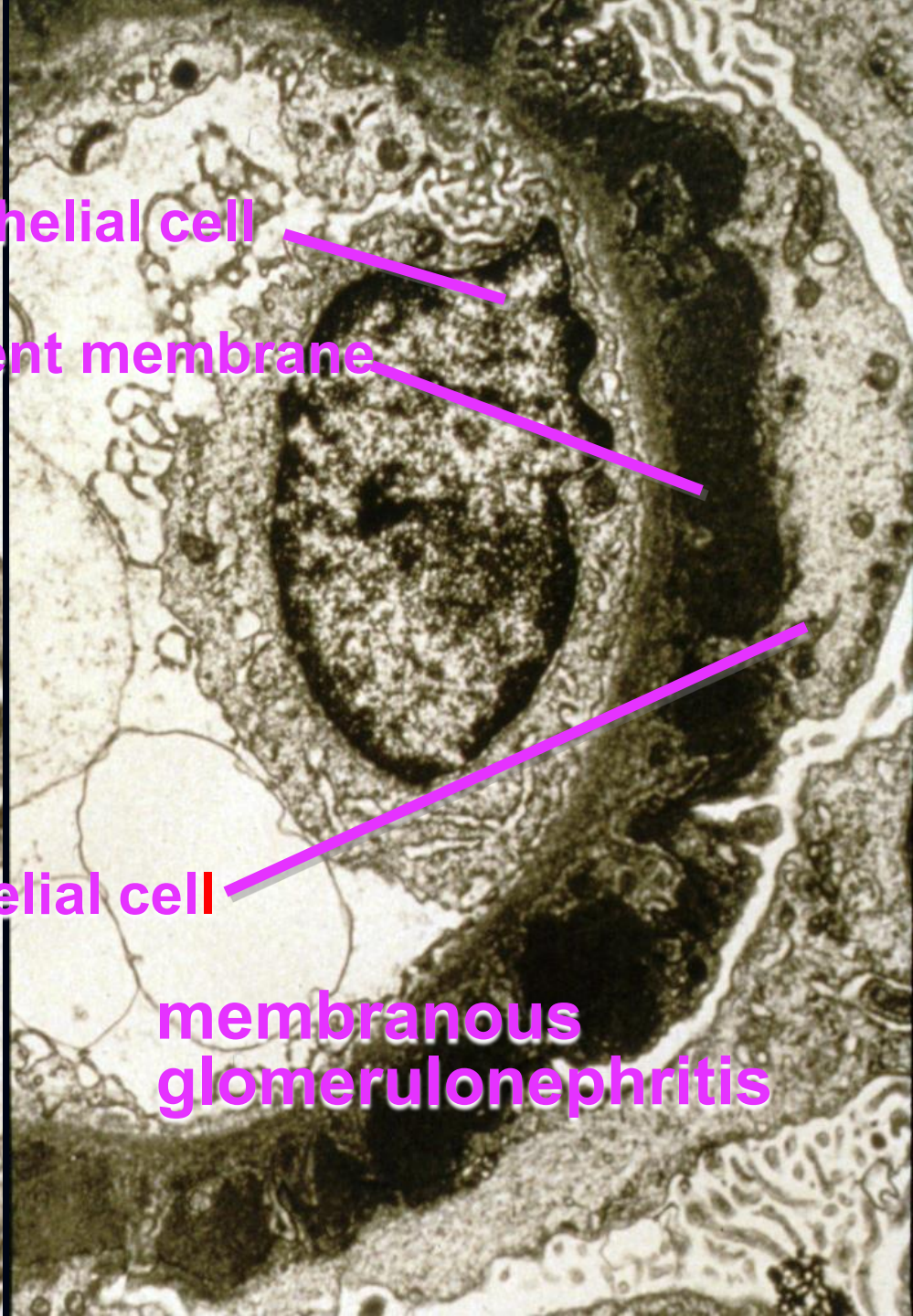


endothelial cell

basement membrane

epithelial cell

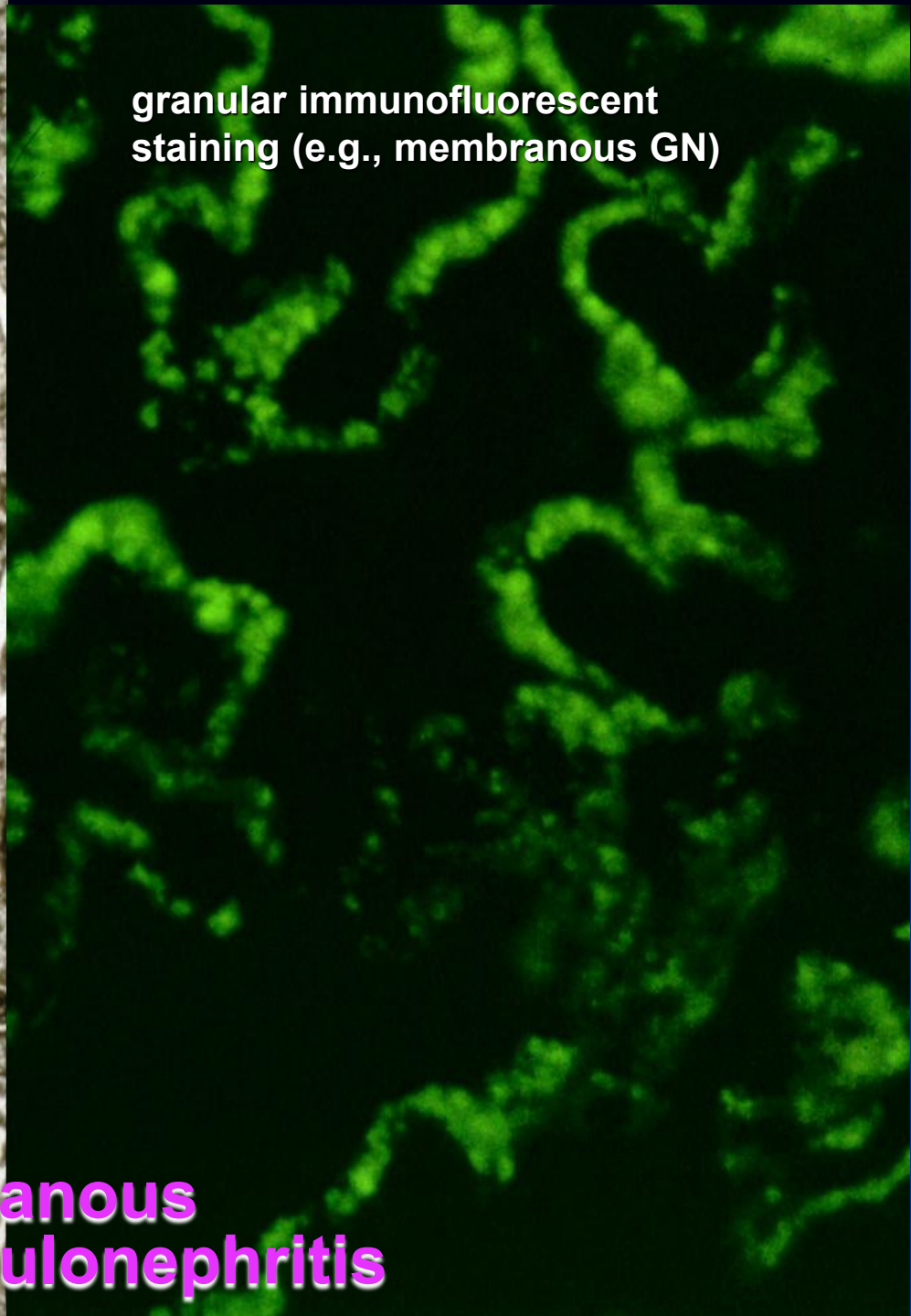
normal glomerulus



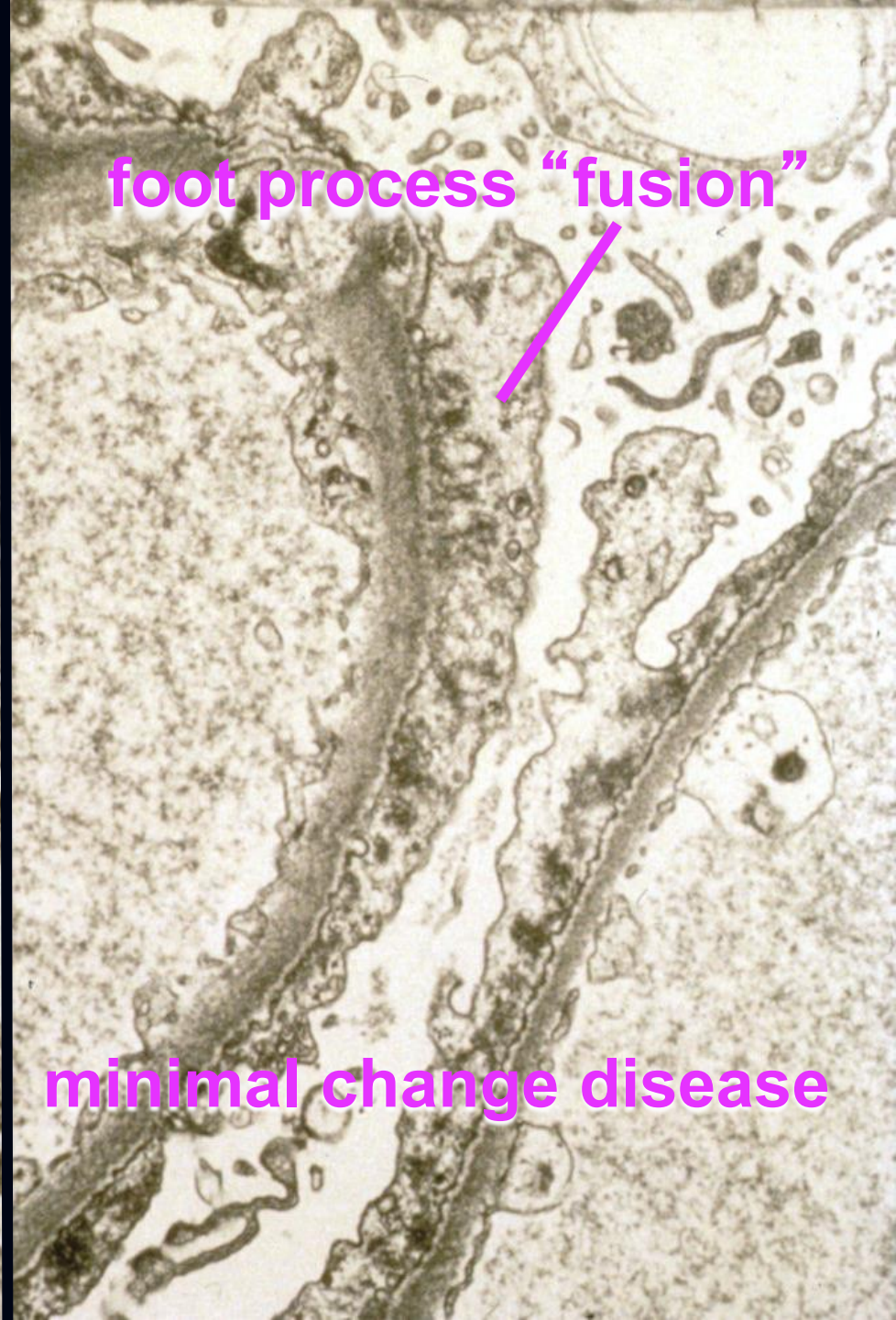
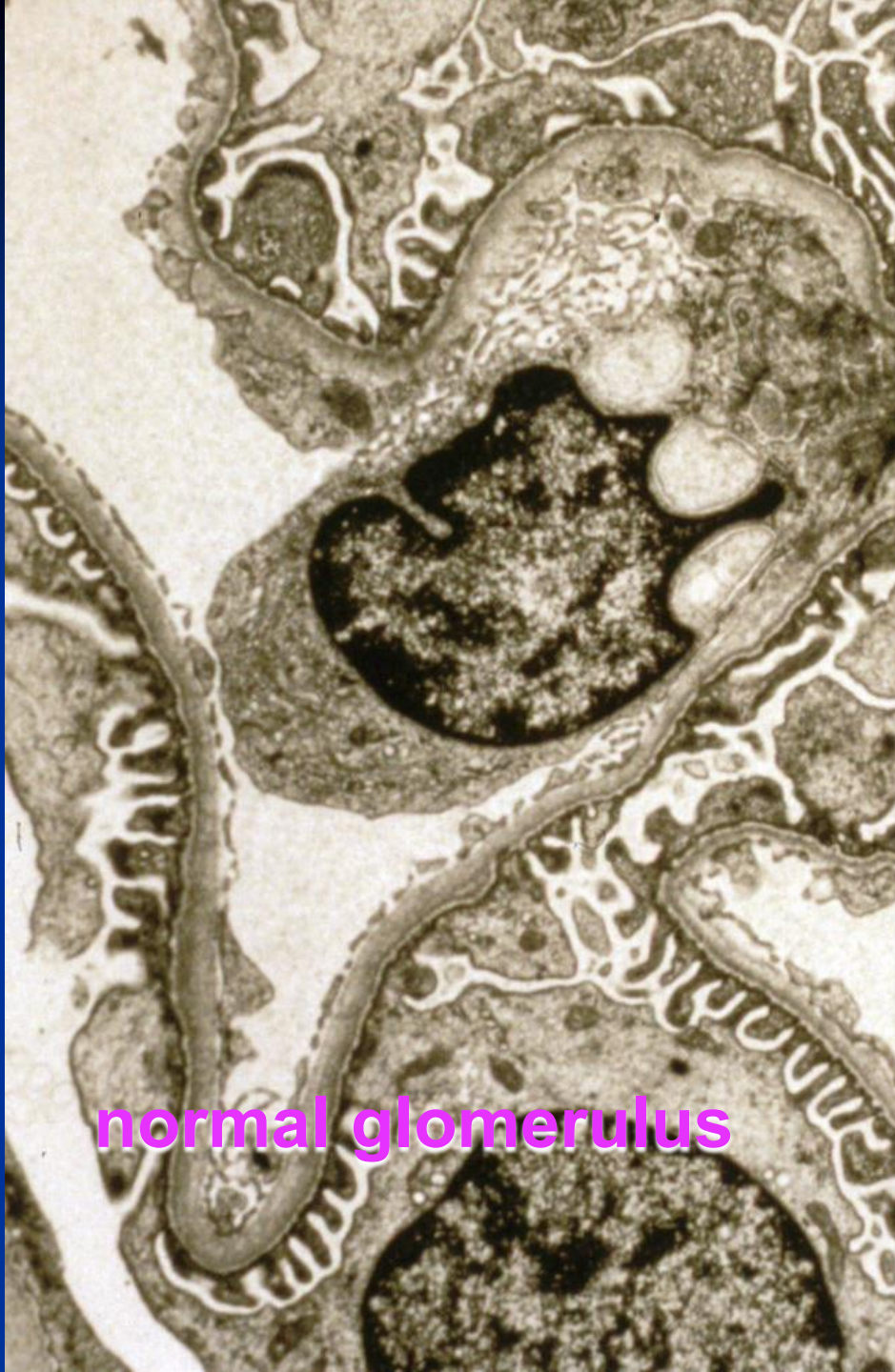
membranous
glomerulonephritis



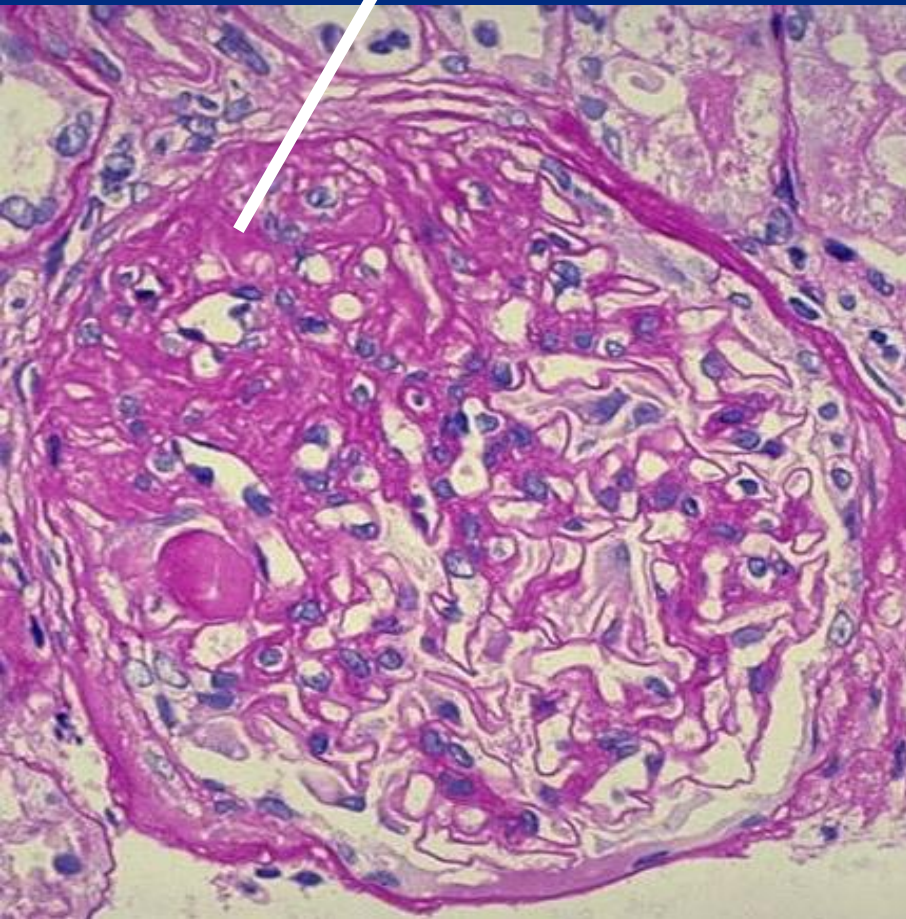
granular immunofluorescent
staining (e.g., membranous GN)



membranous
glomerulonephritis



**focal and segmental
glomerulosclerosis
(FSGS)**

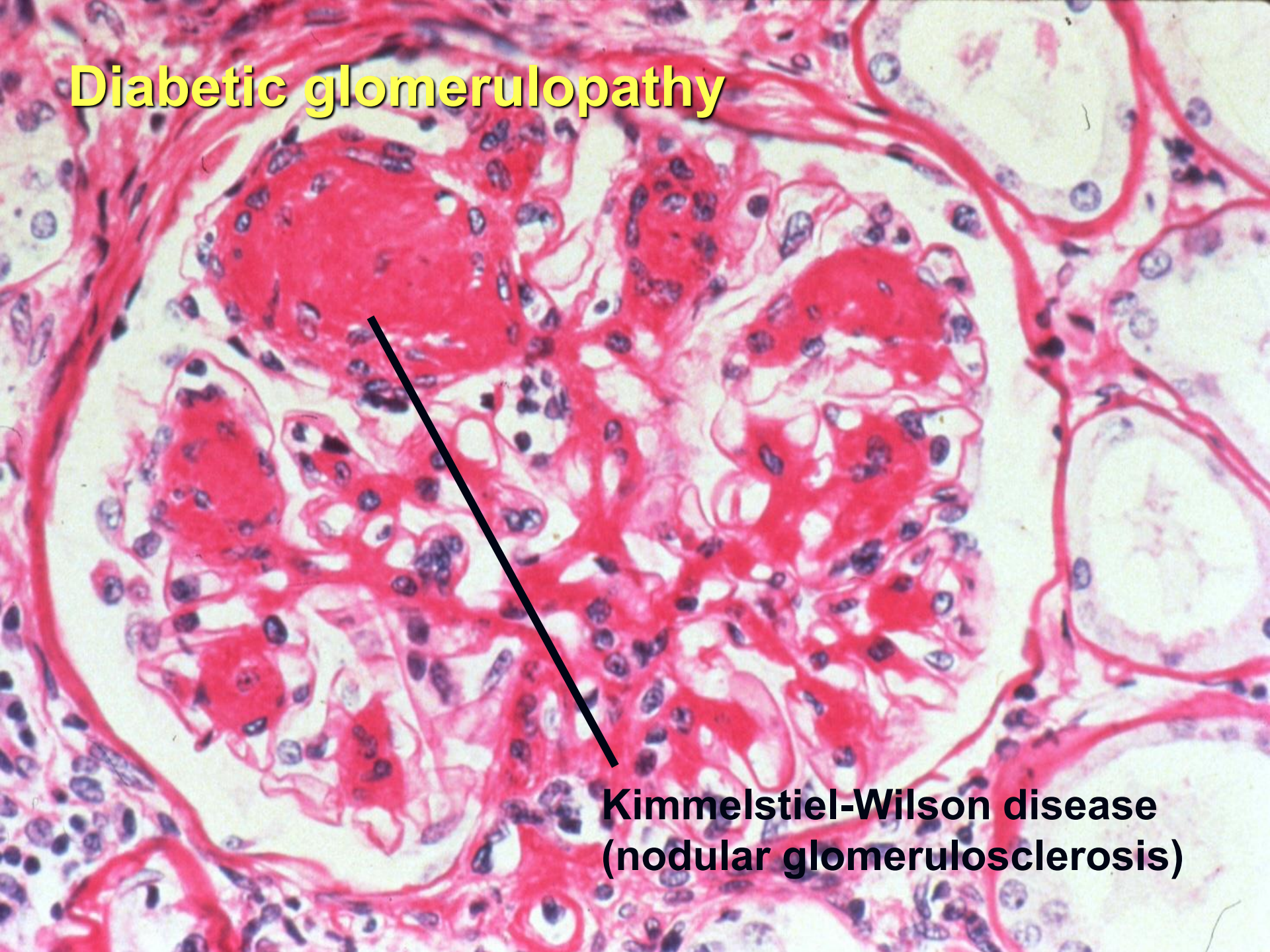


Courtesy of Dr. Astrid Weins



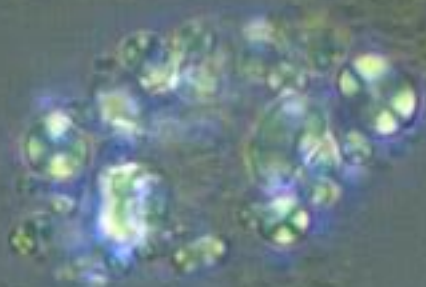
**intraepithelial
tubuloreticular body
(HIV or heroin)**

Diabetic glomerulopathy

A light micrograph of a renal glomerulus stained with hematoxylin and eosin (H&E). The glomerulus is characterized by several prominent, dense, pink-staining nodules of hyaline material, which are the Kimmelstiel-Wilson nodules. These nodules are located within the glomerular tuft, surrounded by the glomerular capillary loops. The surrounding tissue shows some cellular infiltration and structural changes consistent with diabetic glomerulopathy.

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

oval fat bodies



“Maltese cross” (polarized light)



webpath.med.utah.edu

waxy cast

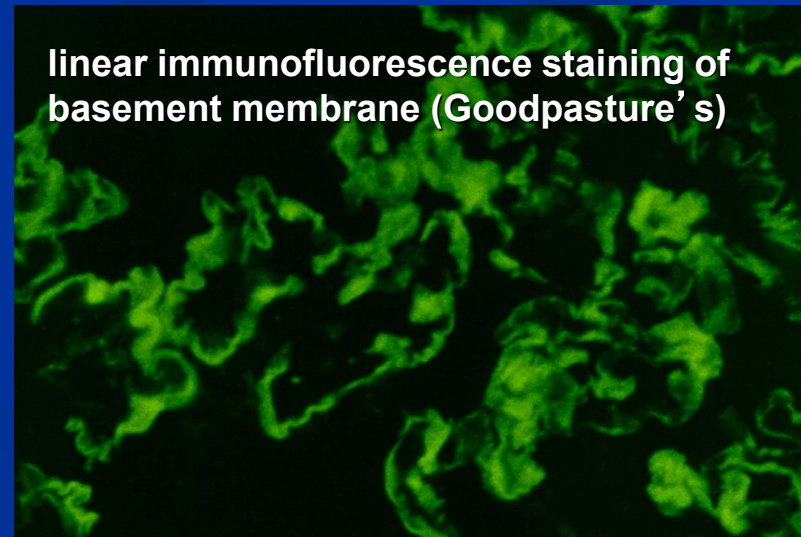
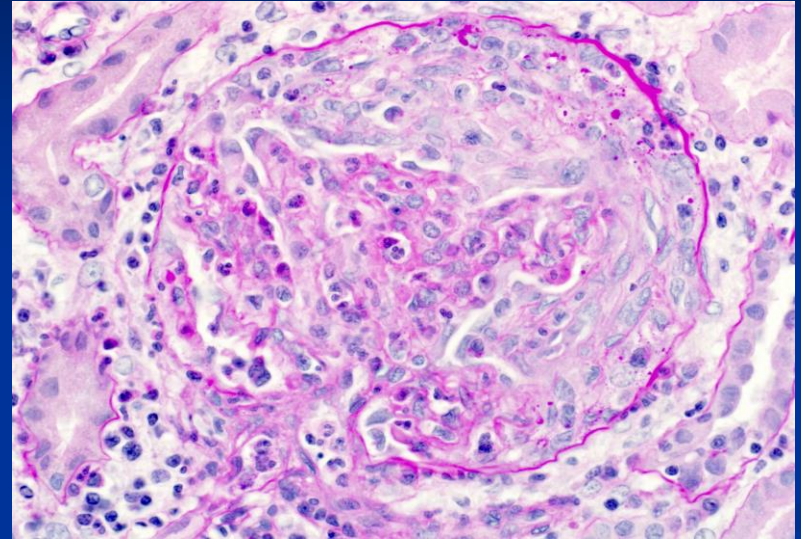
(protein and degenerated epithelial cells)



x.com/JoseTesser/status/

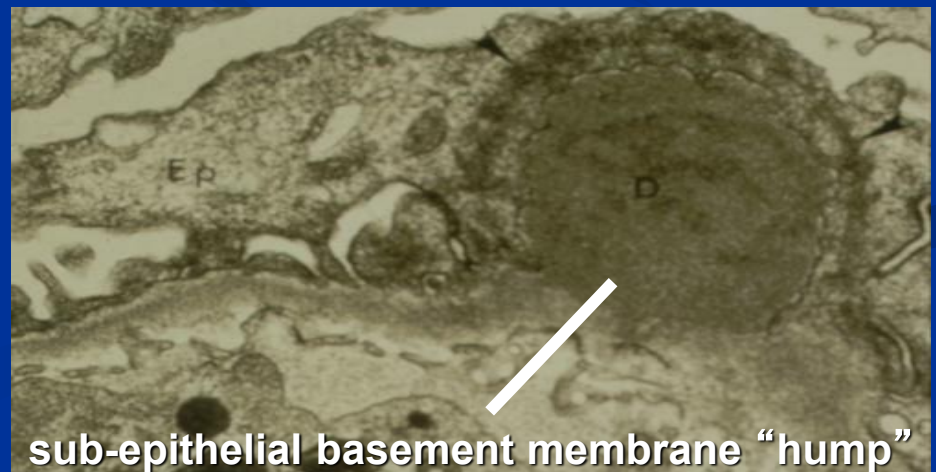
Crescentic (proliferative) glomerulonephritis

- Nephritic syndrome (HTN, hematuria, proteinuria)
- 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

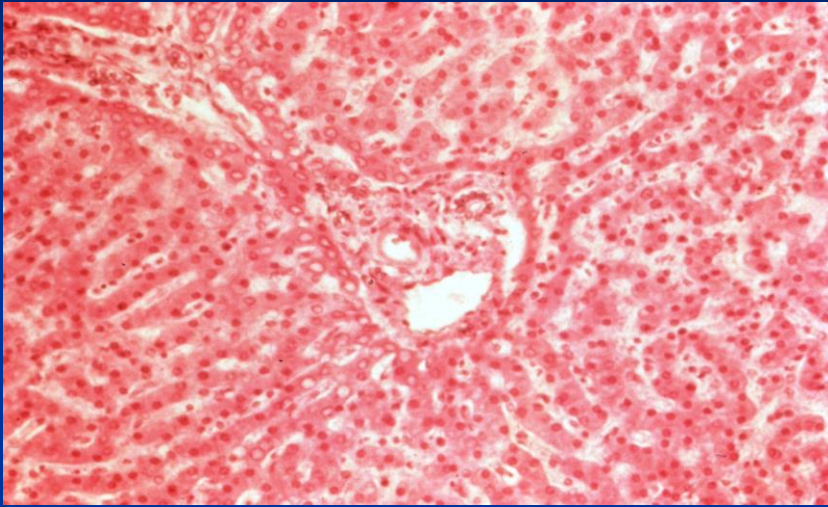
- Poor correlation between transaminitis and the extent of hepatic damage
- AST/ALT ratio can guide your differential diagnosis

Transaminitis

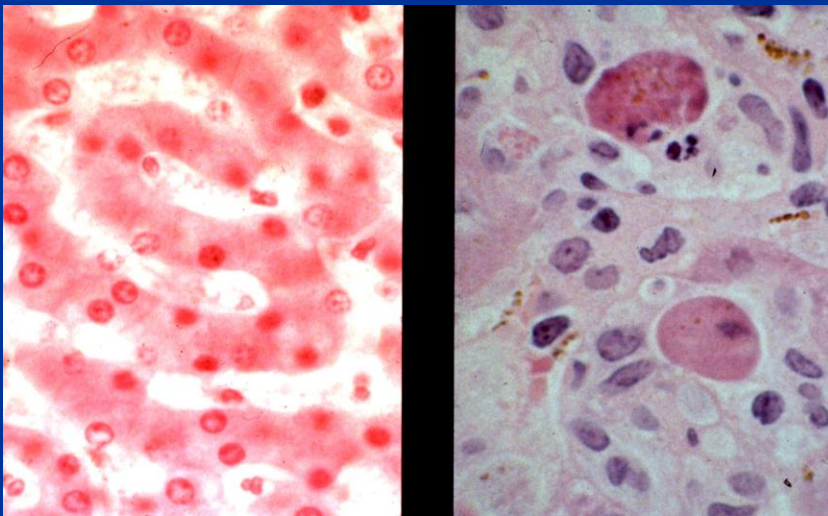
Recommended Work-up:

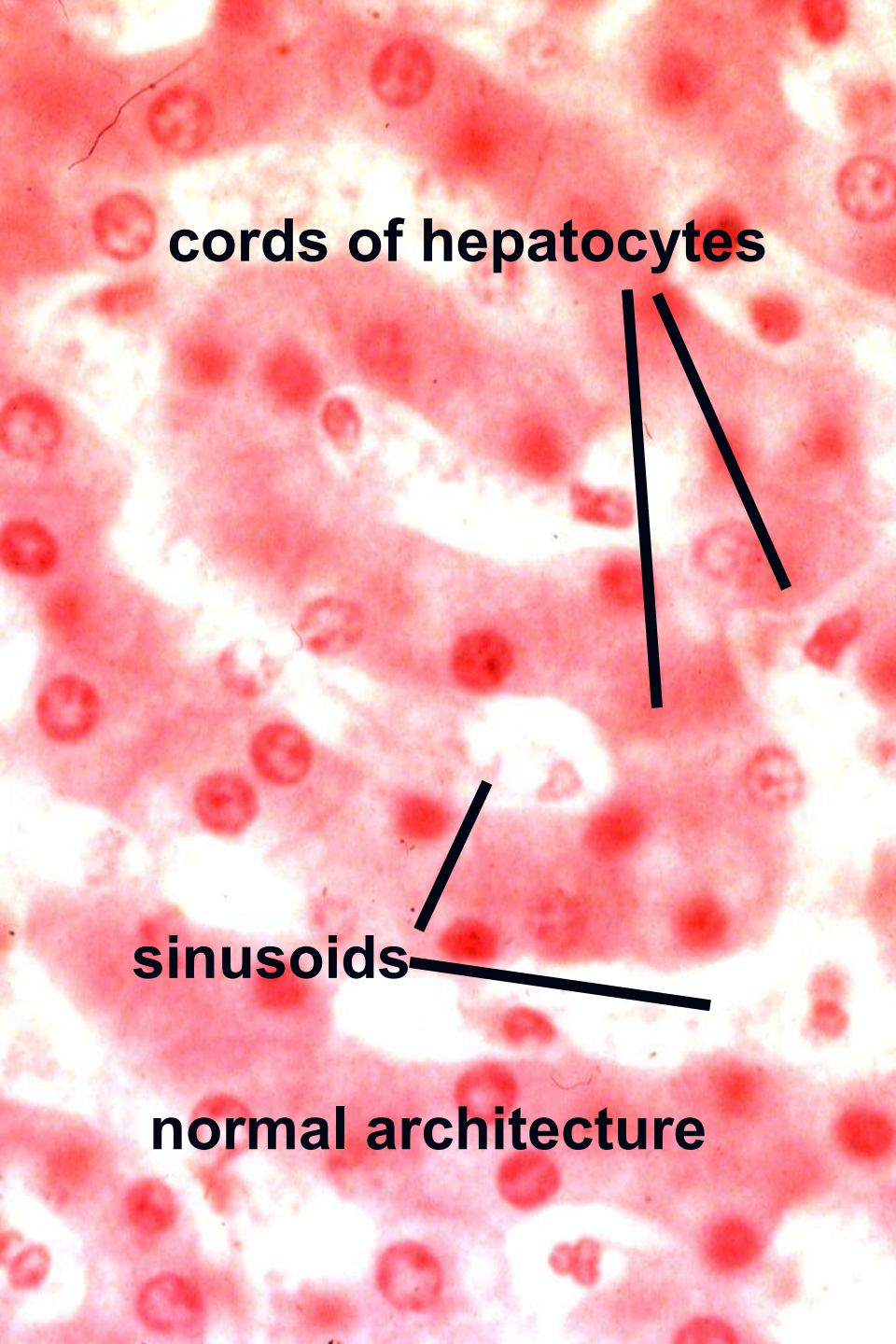
- Hepatitis serologies
- ANA, ASMA, ALKM-1
- Toxin levels
- Fe/TIBC, Ferritin
- Ceruloplasmin
- α -1-anti-trypsin
- Abdominal US

What to look for: elevated transaminases



- liver architecture
- portal inflammation
- hepatocyte necrosis
- inclusions

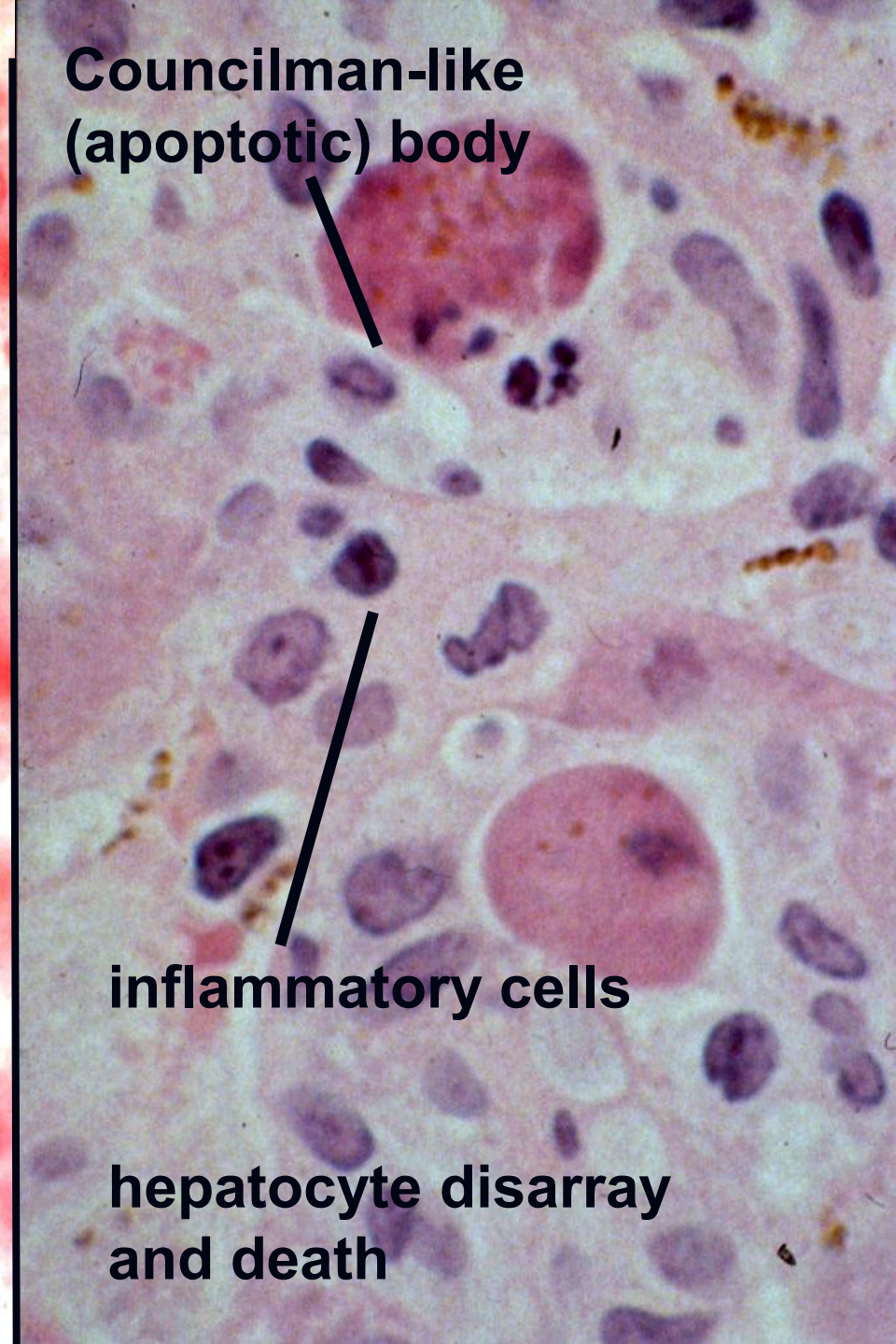




cords of hepatocytes

sinusoids

normal architecture



**Councilman-like
(apoptotic) body**

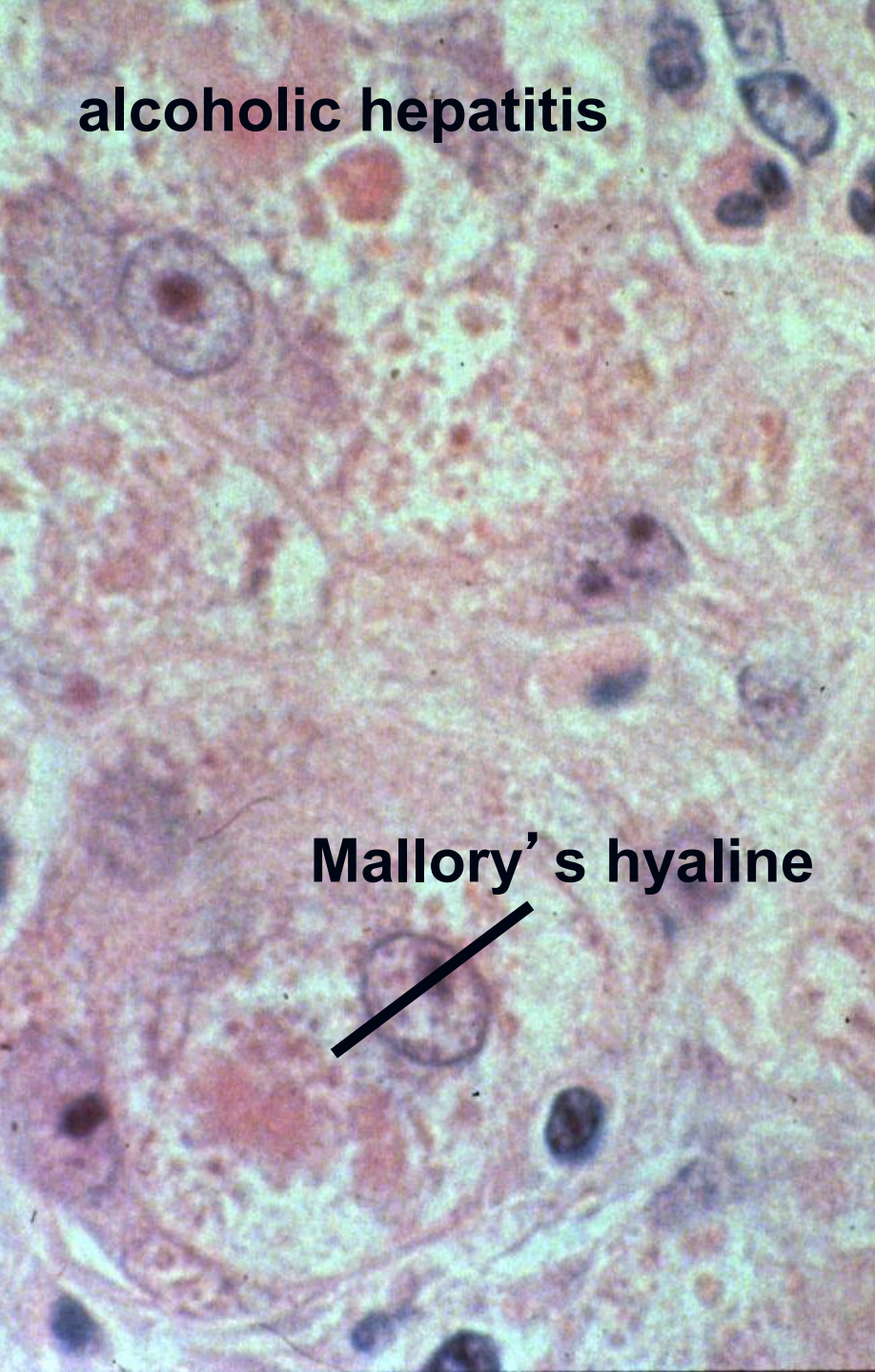
inflammatory cells

**hepatocyte disarray
and death**

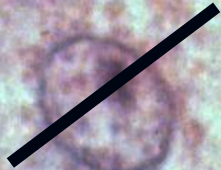
Acute hepatitis

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

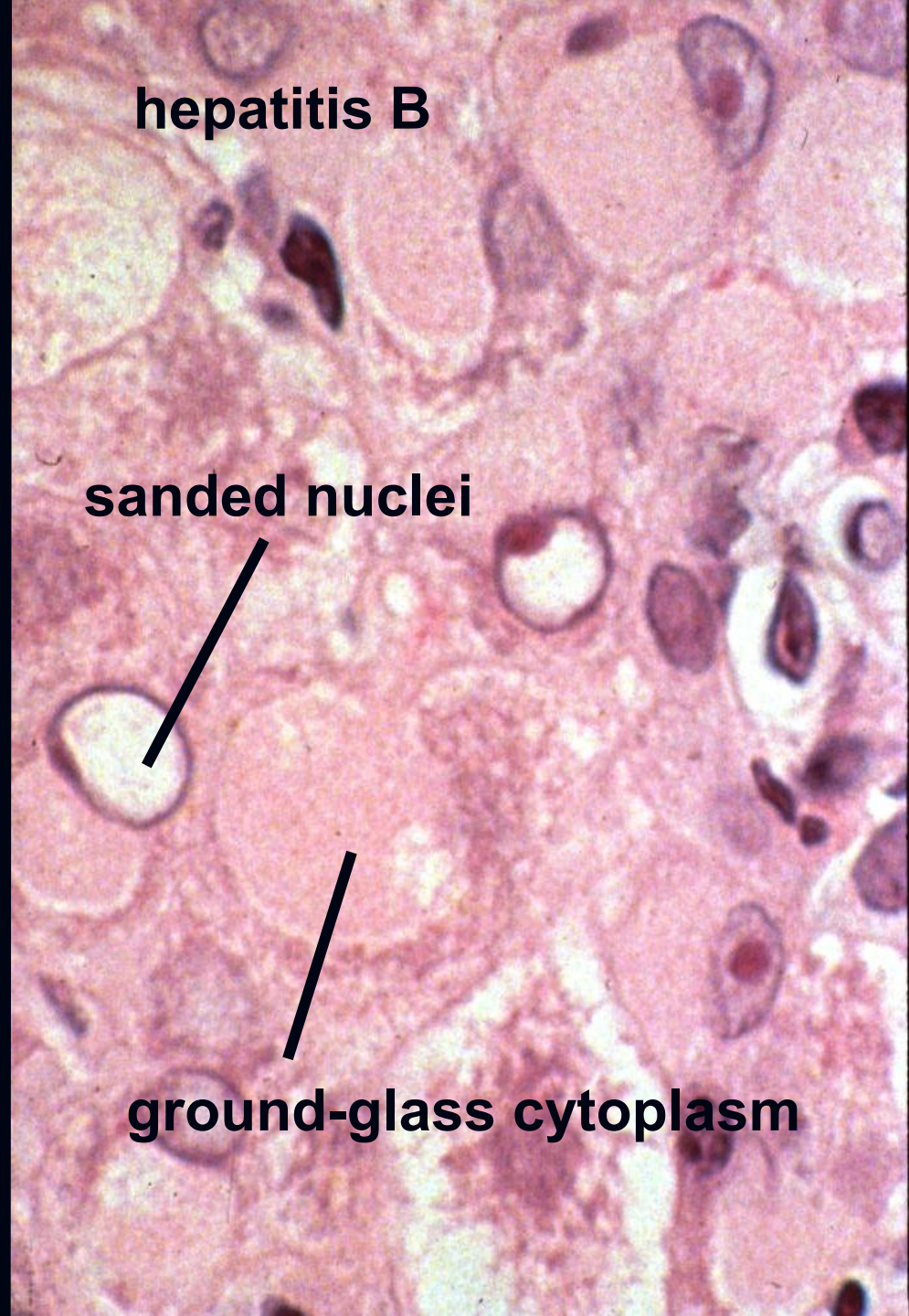
alcoholic hepatitis



Mallory's hyaline



hepatitis B



sanded nuclei



ground-glass cytoplasm



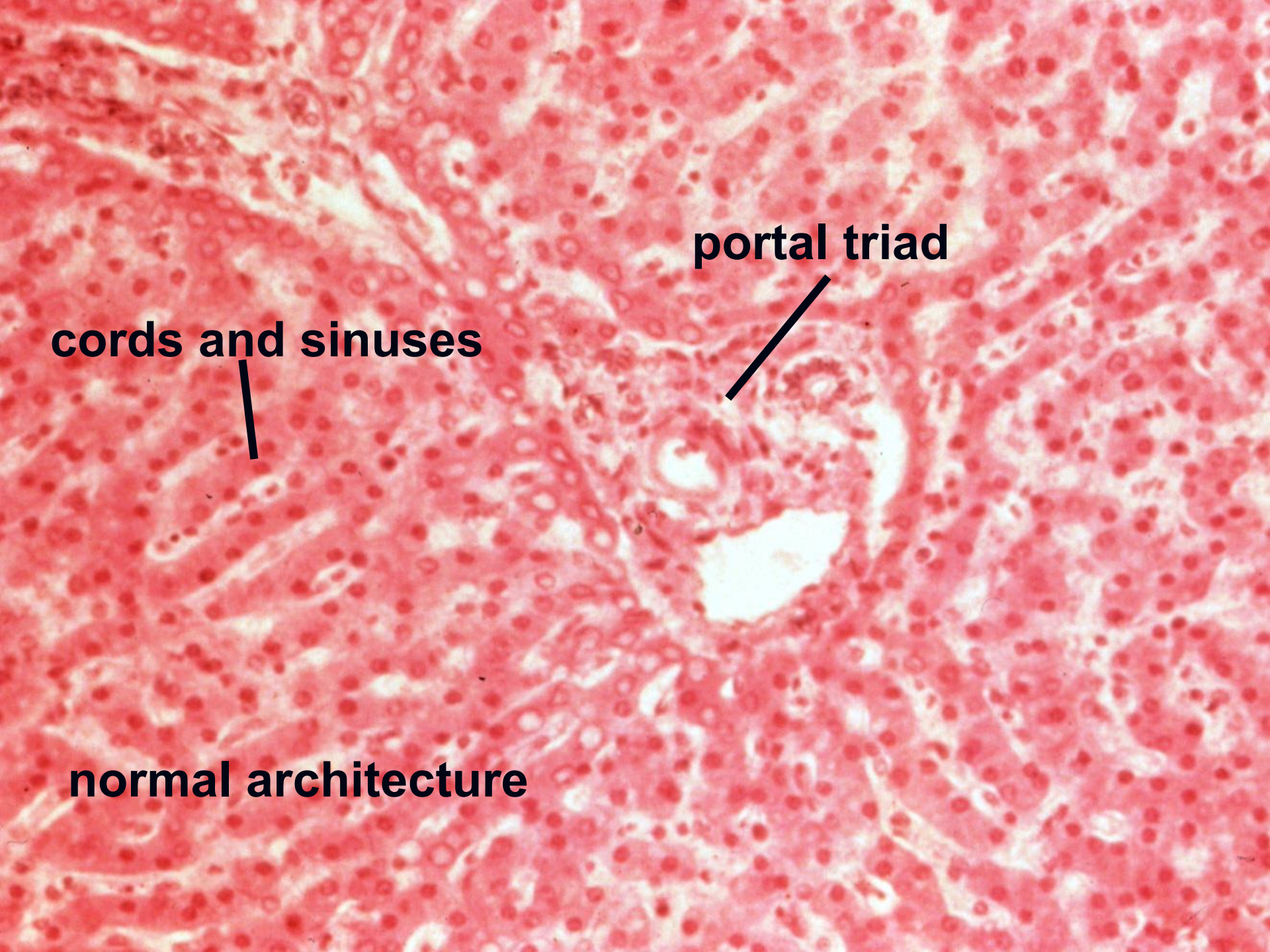
Metabolic dysfunction-associated steatohepatitis (MASH)

inflammation

hepatocyte death

steatosis

20-30% of obese individuals

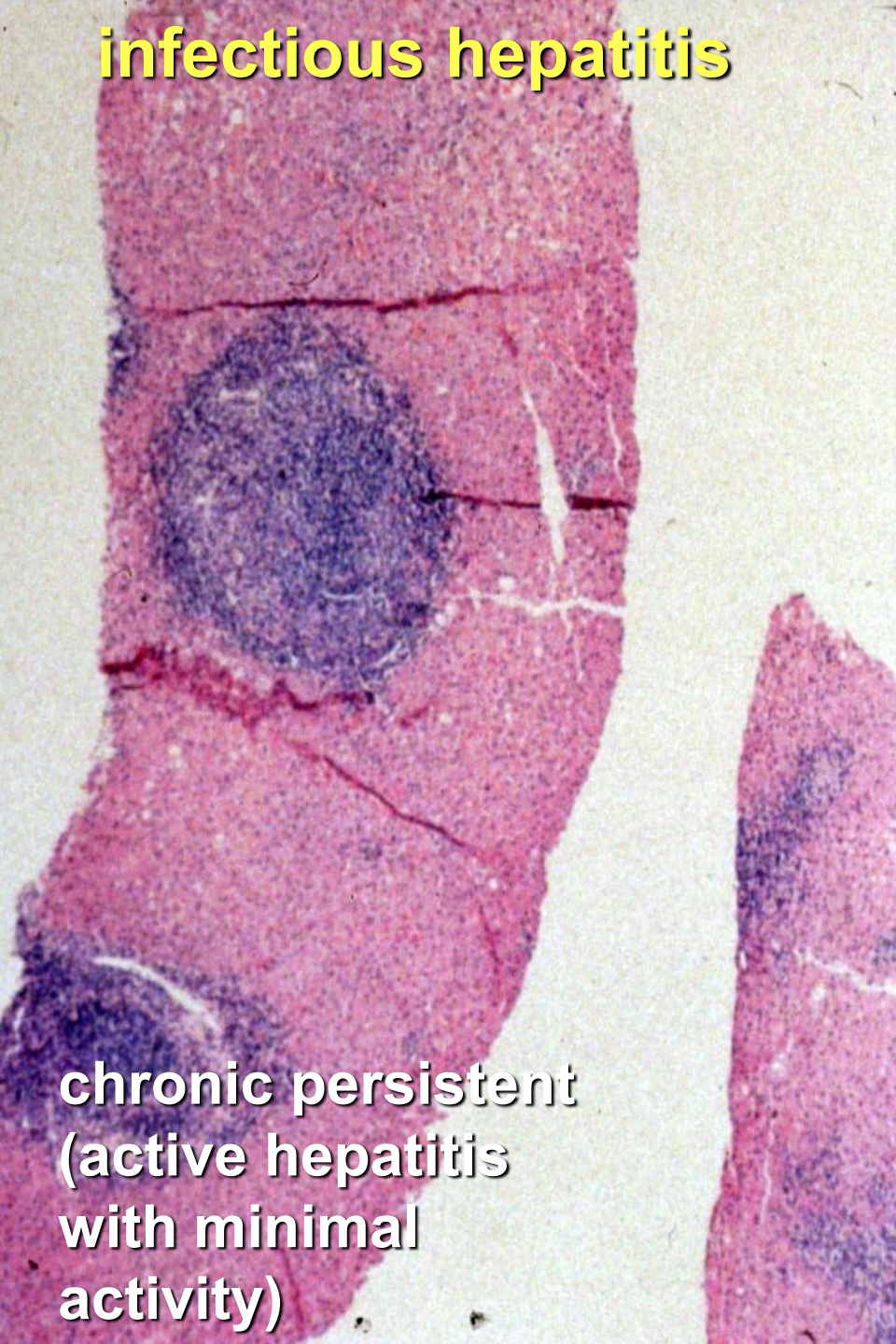


cords and sinuses

portal triad

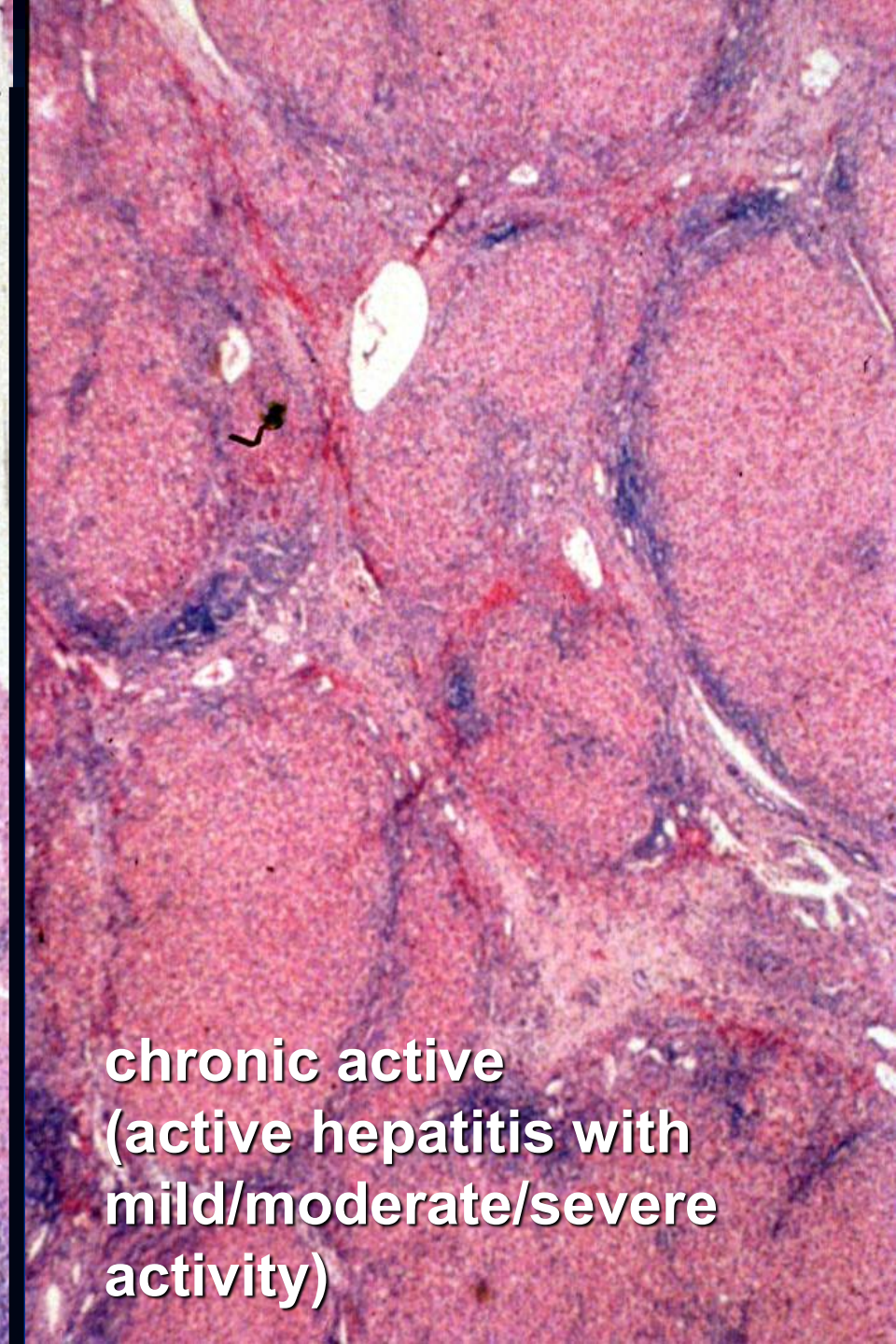
normal architecture

infectious hepatitis



chronic persistent
(active hepatitis
with minimal
activity)

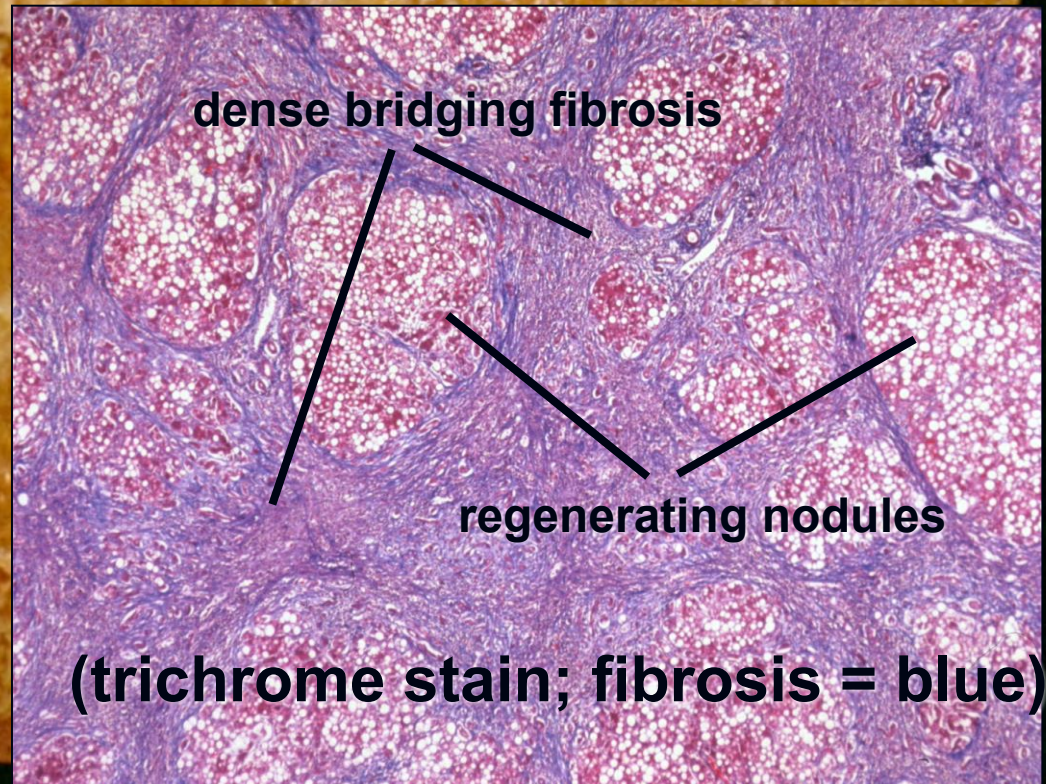
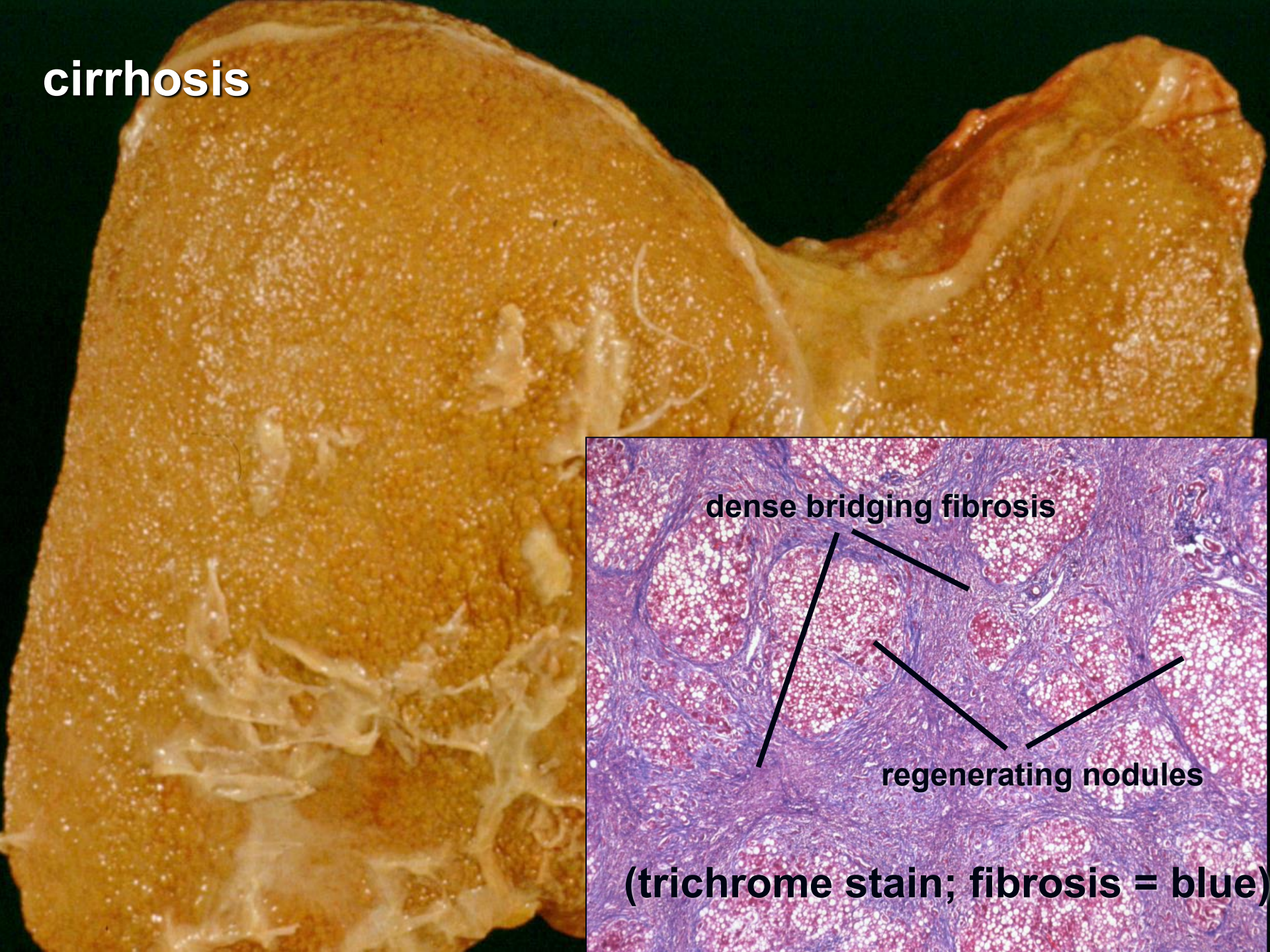
This image shows a low-power microscopic view of liver tissue stained with hematoxylin and eosin (H&E). A large, dark, circular area of dense cellular infiltration is visible, representing a portal tract. The surrounding liver parenchyma appears relatively normal, with some minor inflammation and architectural changes consistent with chronic persistent hepatitis.



chronic active
(active hepatitis with
mild/moderate/severe
activity)

This image shows a higher magnification view of liver tissue. It displays more extensive and disorganized inflammatory cell infiltration within the portal tracts and extending into the surrounding liver parenchyma. There is evidence of hepatocyte damage, including ballooning and necrosis, which is characteristic of chronic active hepatitis.

cirrhosis



dense bridging fibrosis

regenerating nodules

(trichrome stain; fibrosis = blue)

Cirrhosis

- Alcoholic liver disease
- Metabolic dysfunction-associated steatotic liver disease (MASLD)
- Hepatitis C
- 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

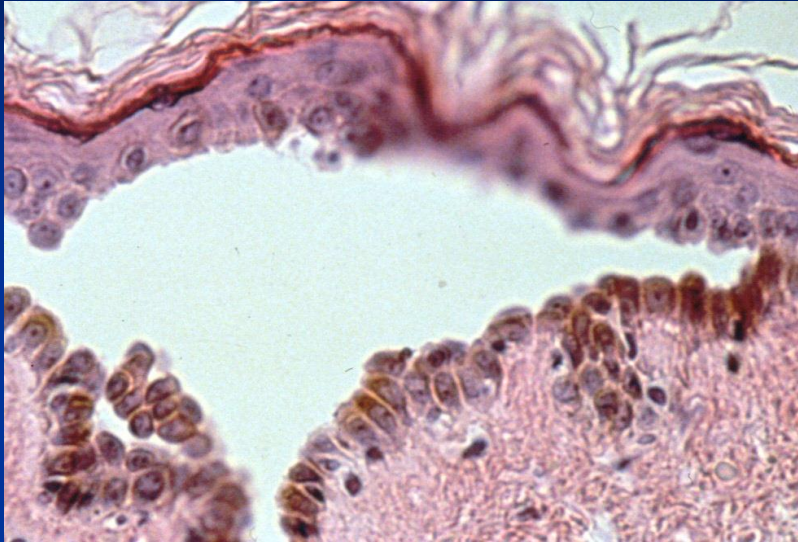
Blister

Lupus:

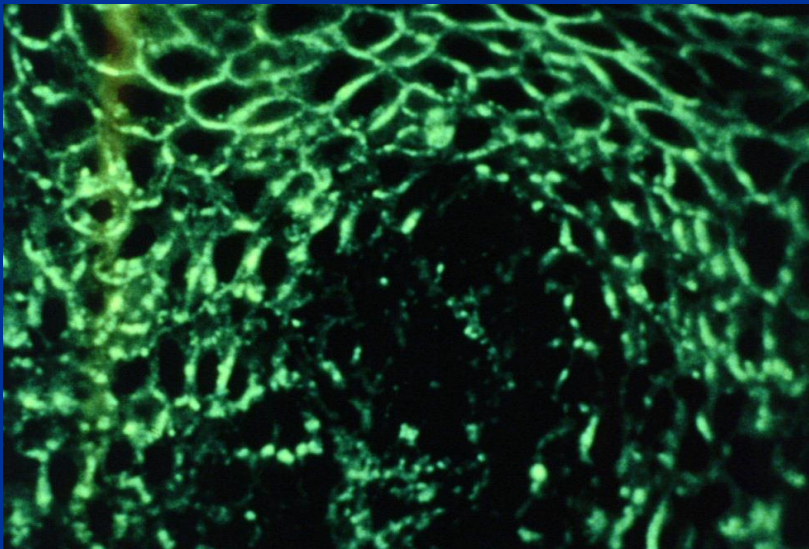
Location: Sun exposed sites

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

What to look for: blisters

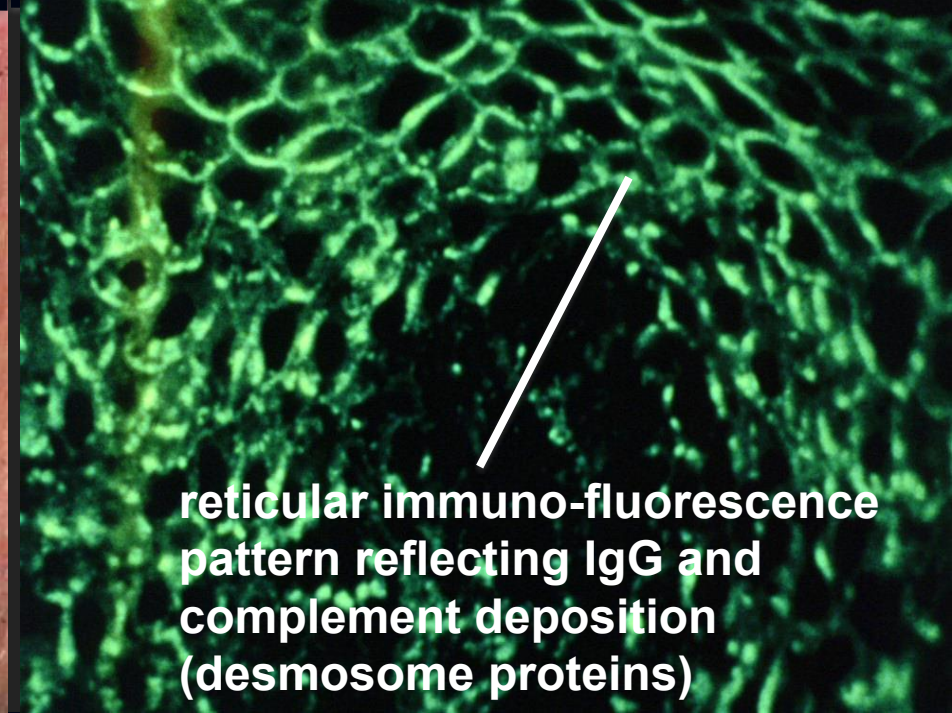
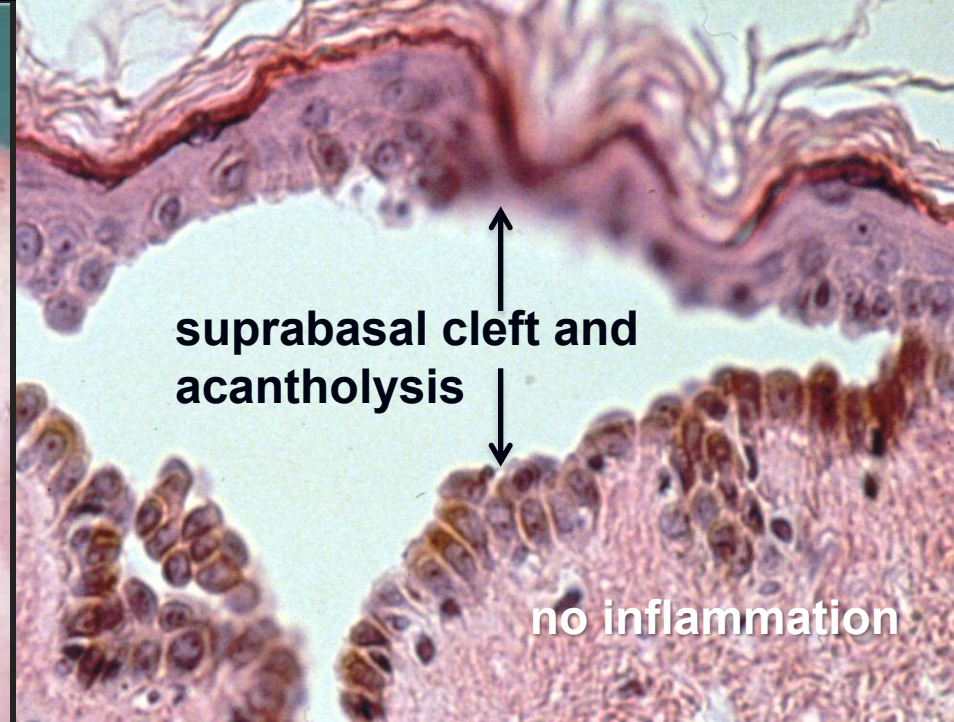


- location of cleft
- inflammation
- immuno-
fluorescence
pattern

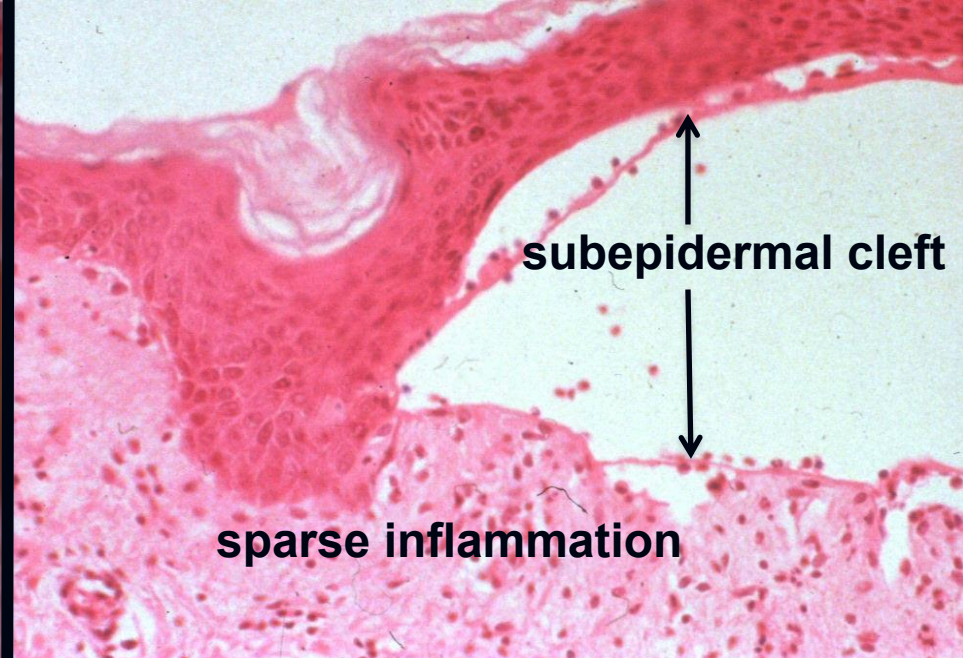


pemphigus vulgaris

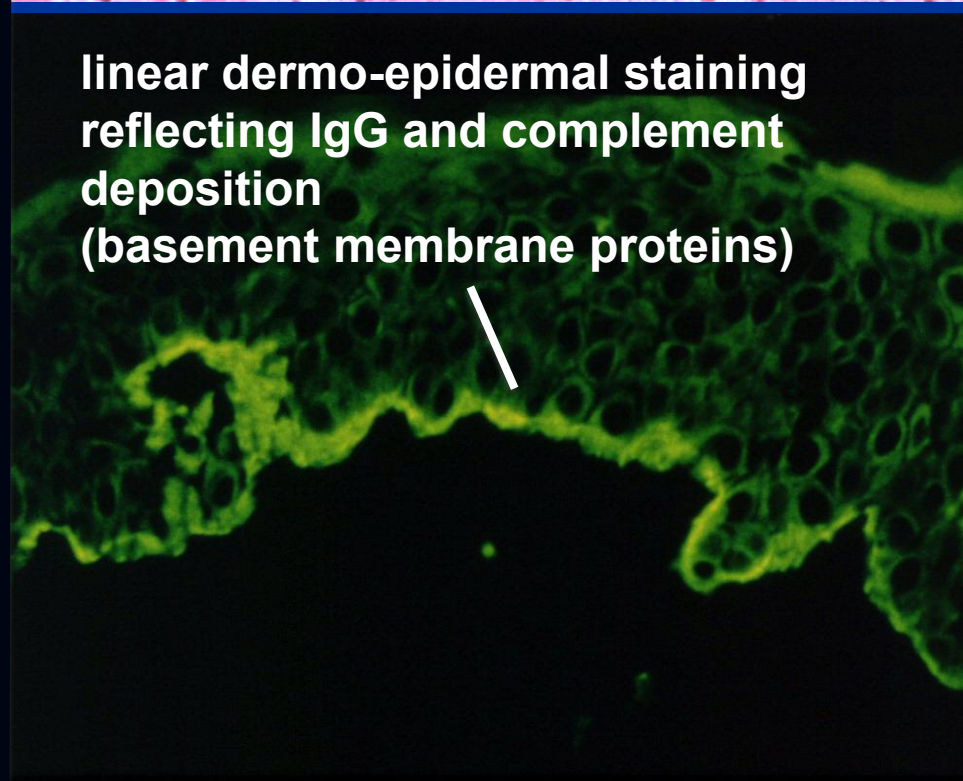
www.dermis.net



bullous pemphigoid

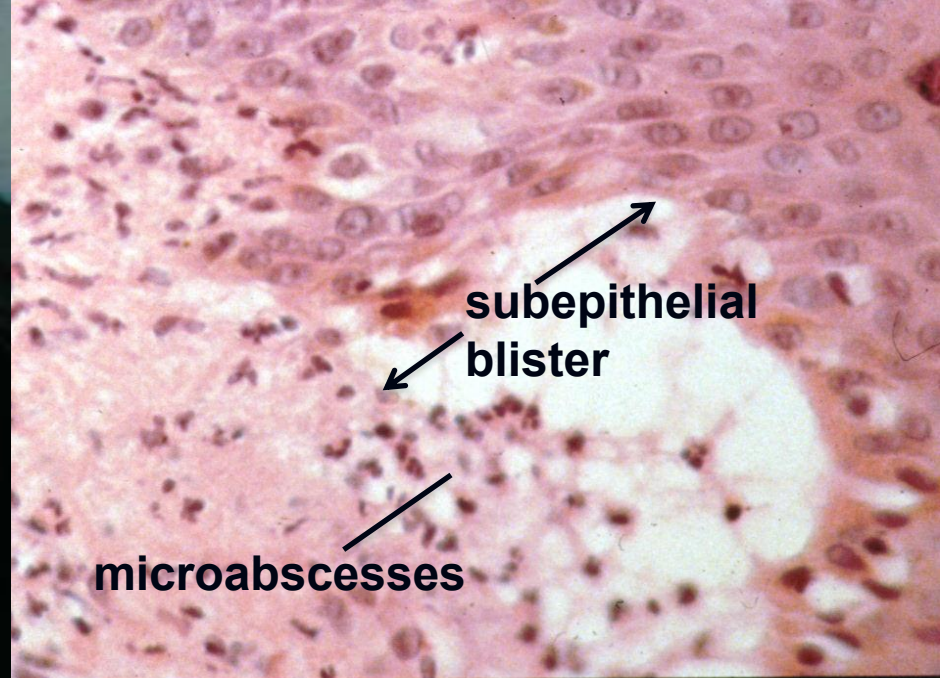


linear dermo-epidermal staining
reflecting IgG and complement
deposition
(basement membrane proteins)

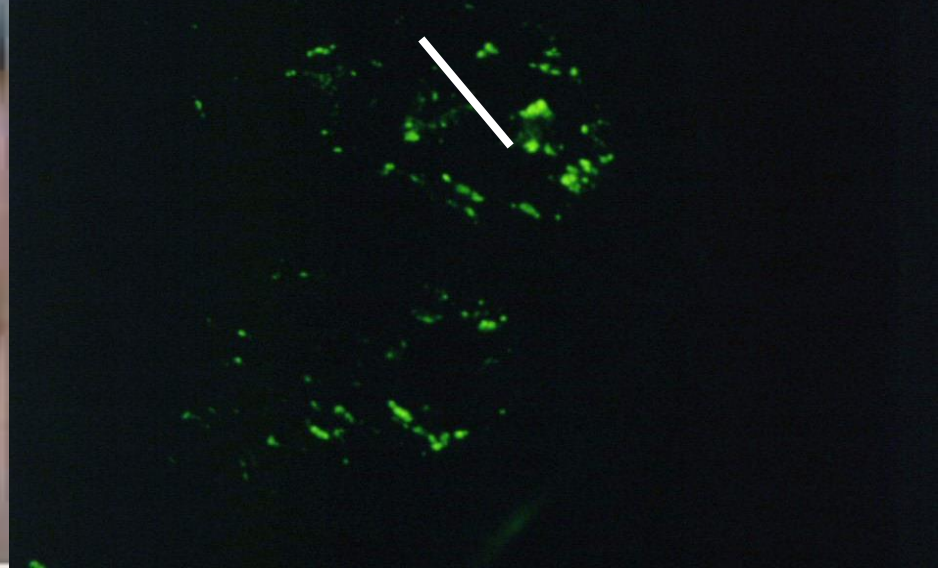


dermatitis herpetiformis

glutenfree.ca

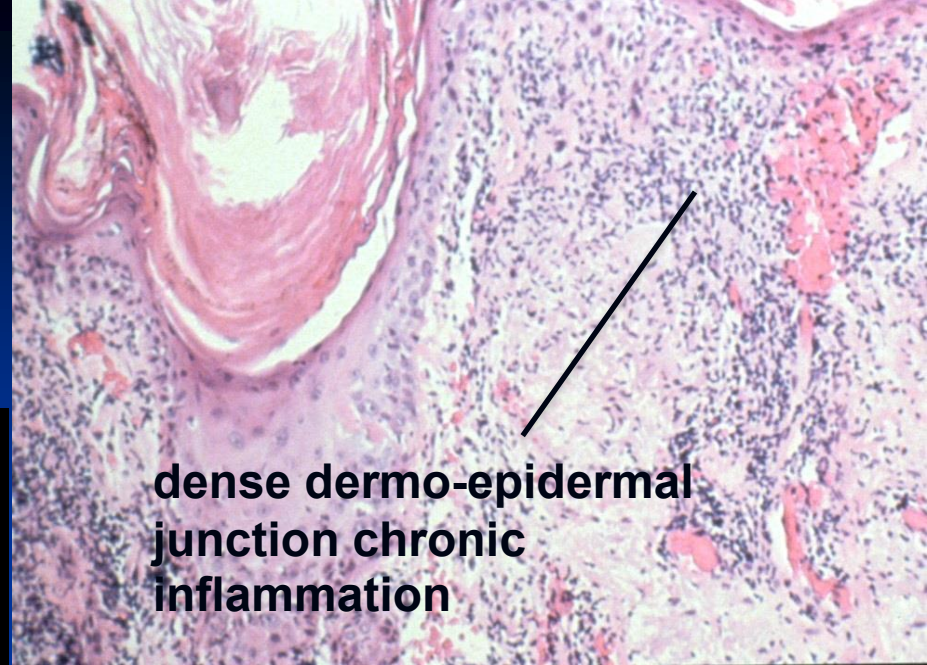


granular immunofluorescence
reflecting IgA complexes and
complement deposition

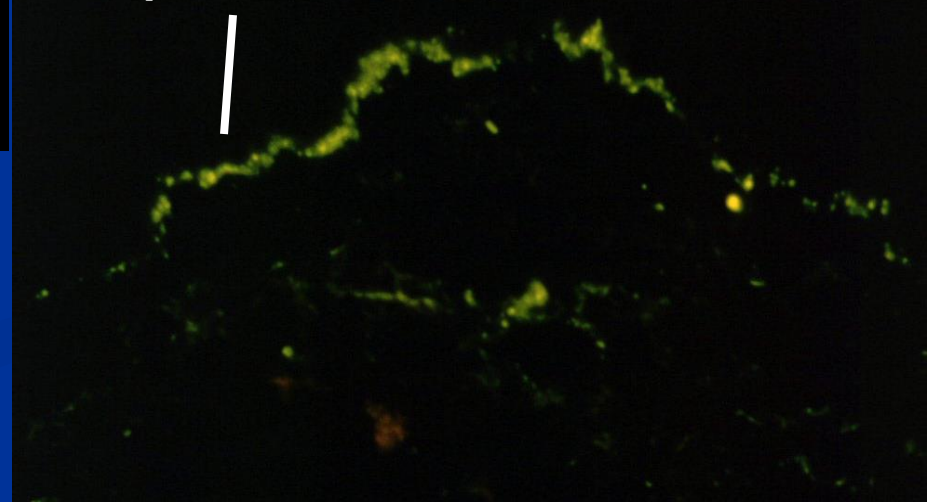


systemic lupus erythematosus

(not classically blistering)



granular DE-junction
immunofluorescence reflecting
IgG complexes and complement
deposition



Case 4

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

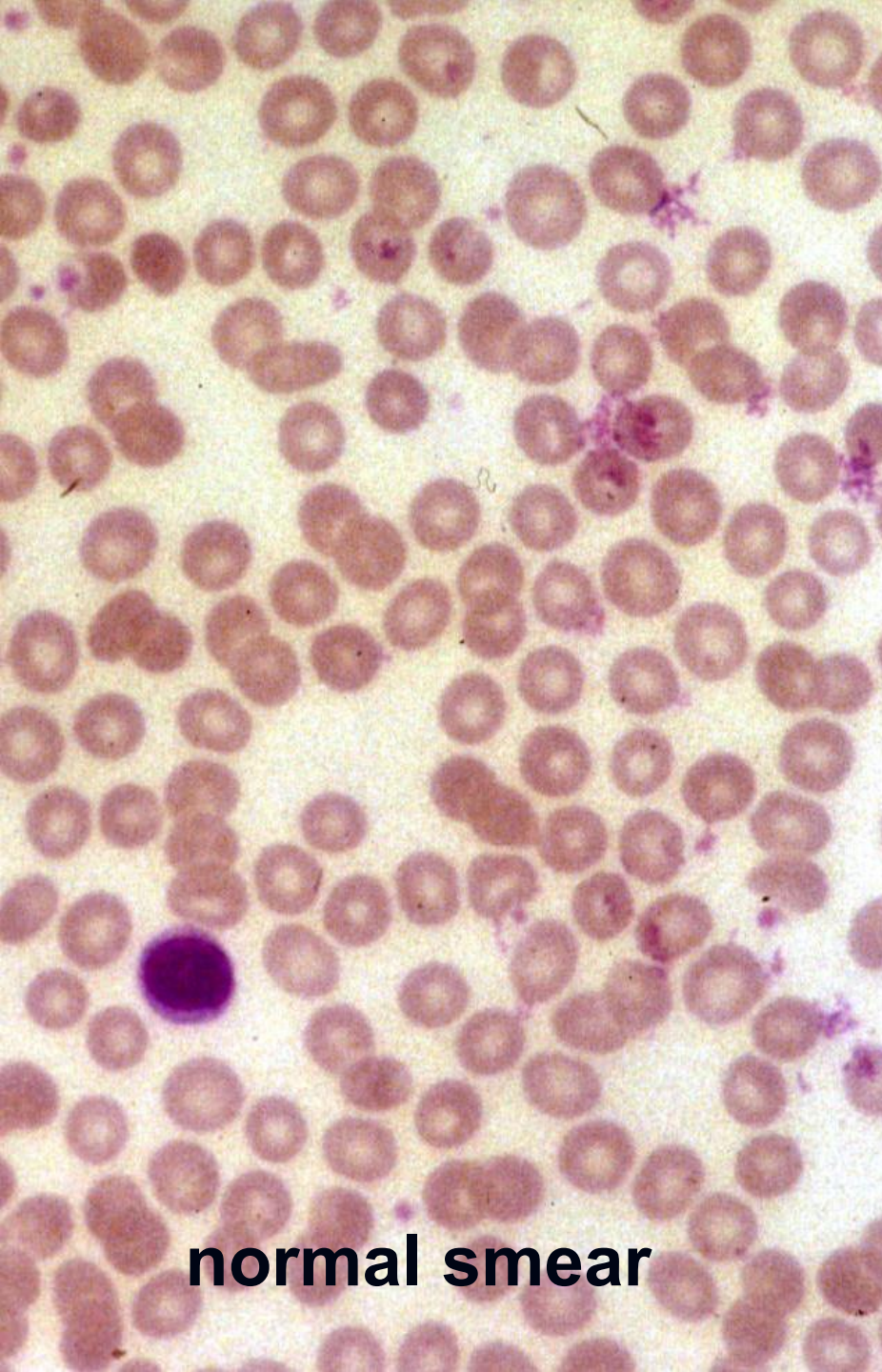
No history of abnormal menses or blood donation.

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

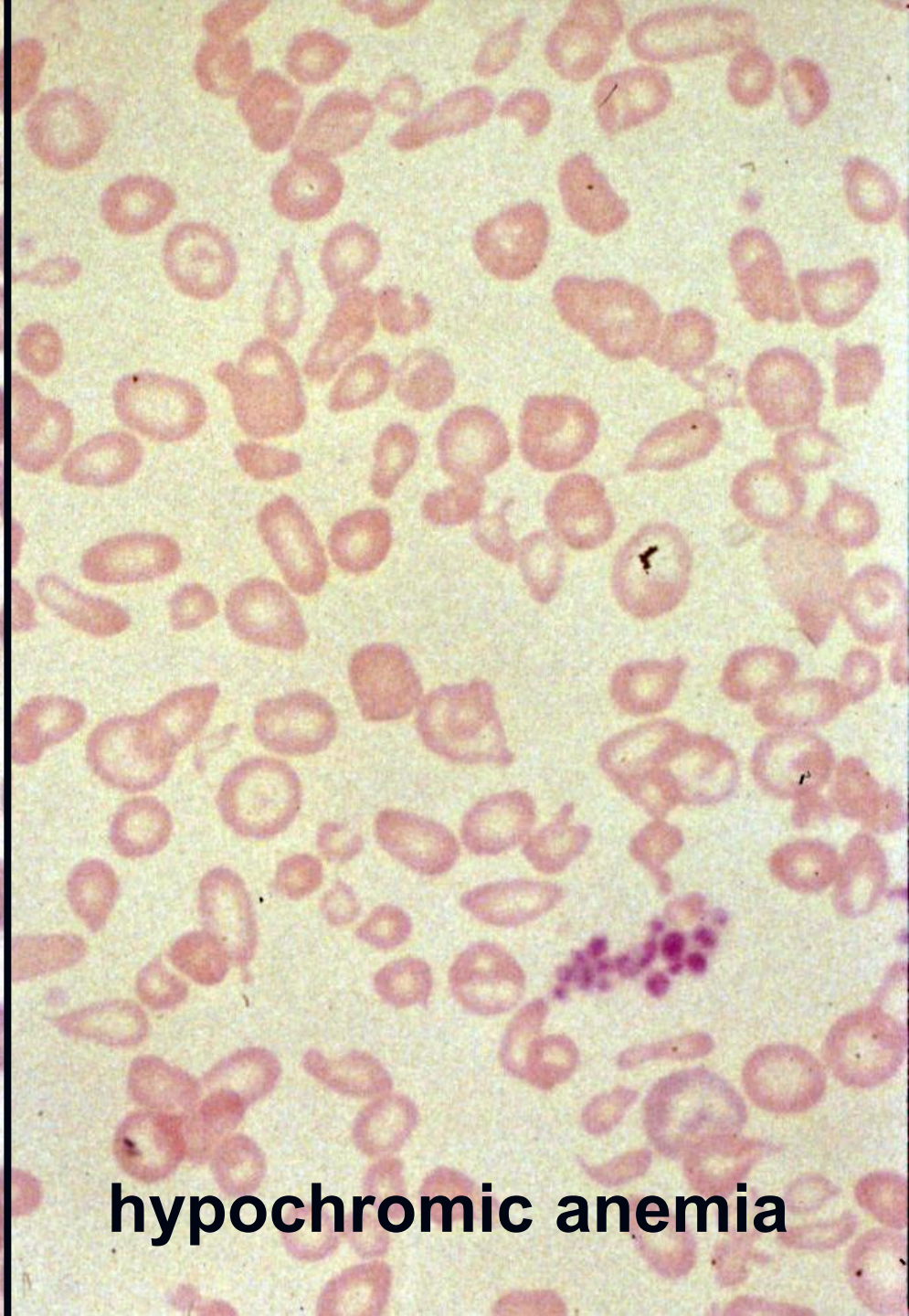
What to look for: peripheral smear



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



normal smear



hypochromic anemia

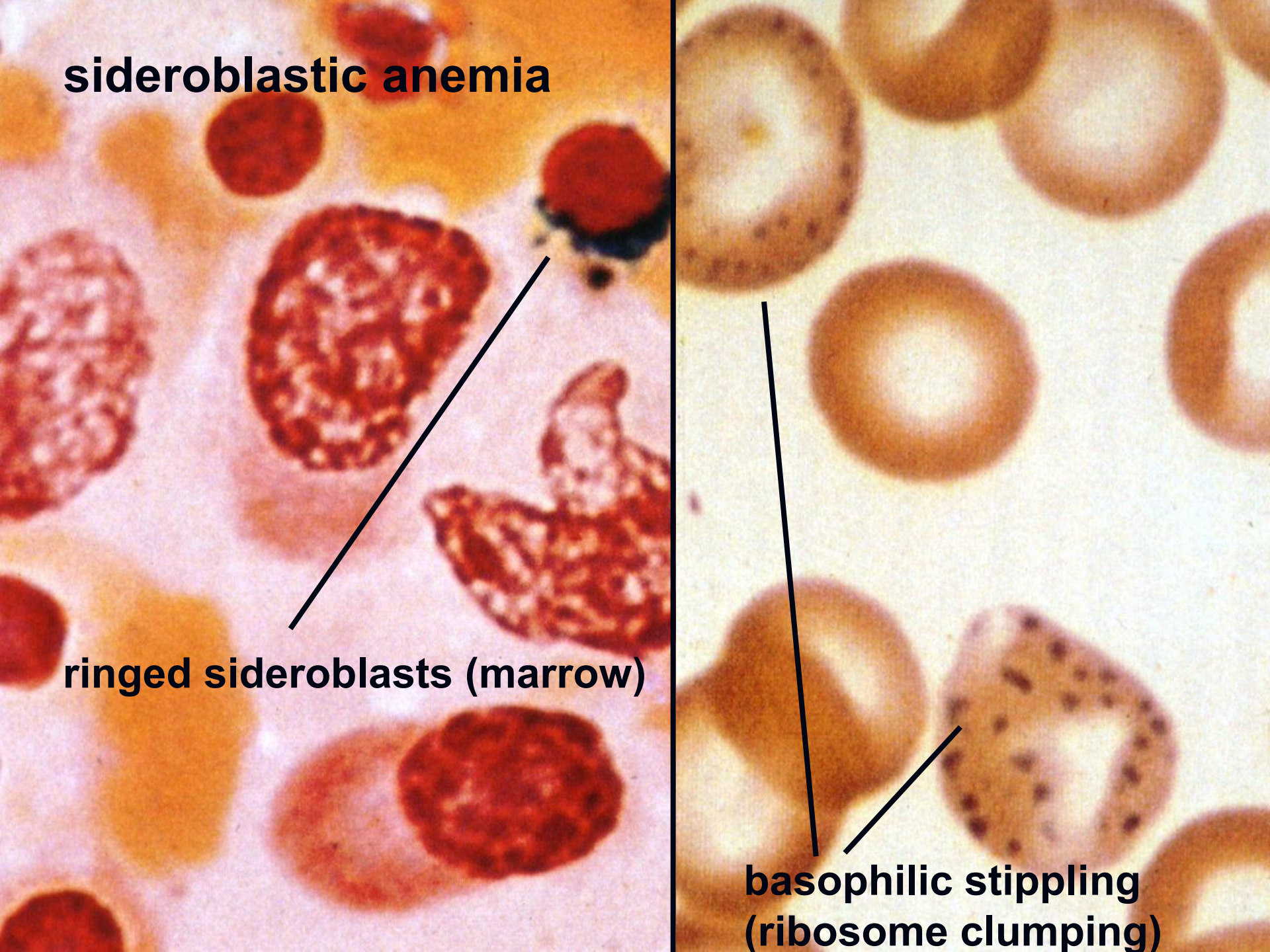
Hypochromic anemia

- **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

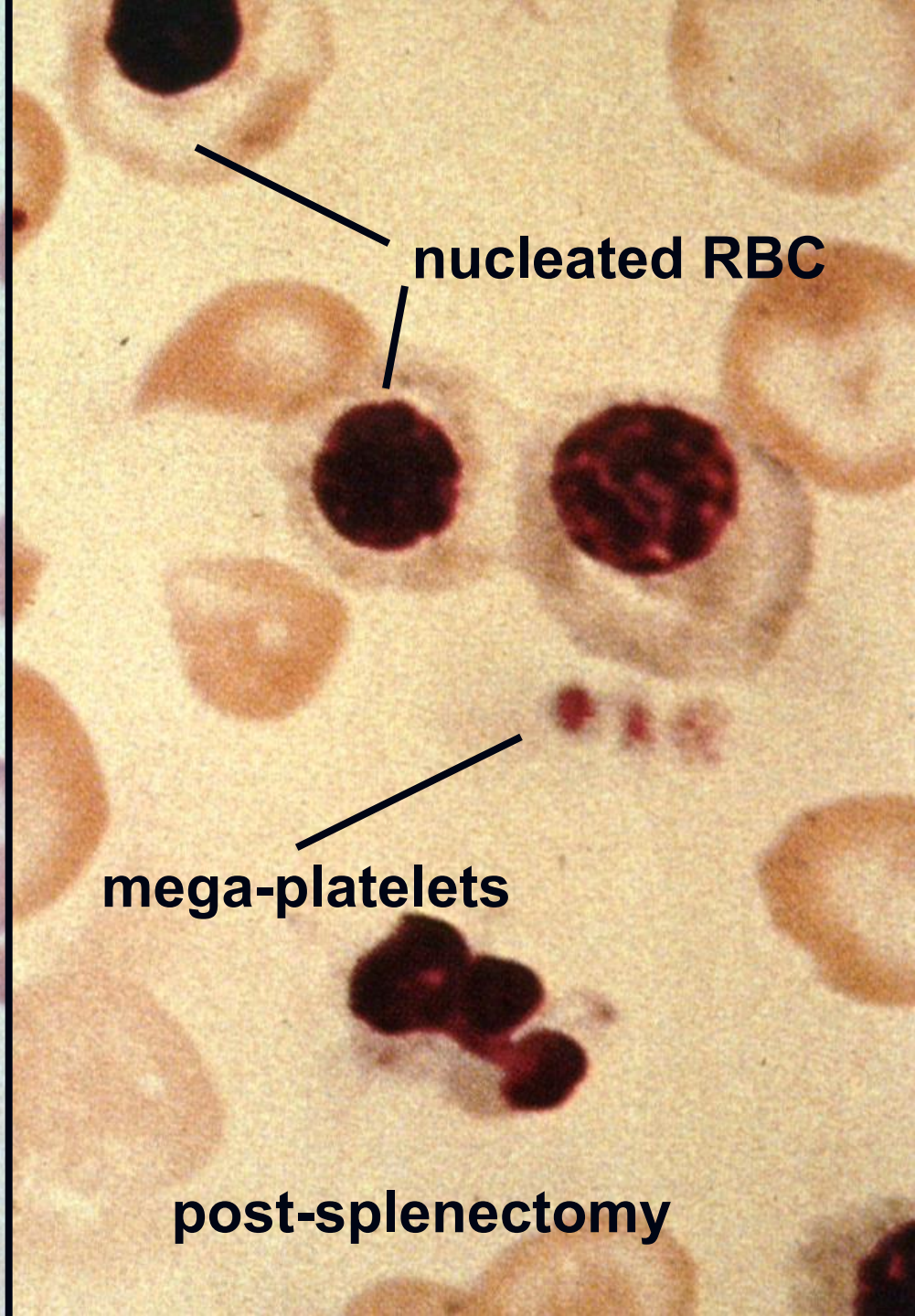
pre-splenectomy

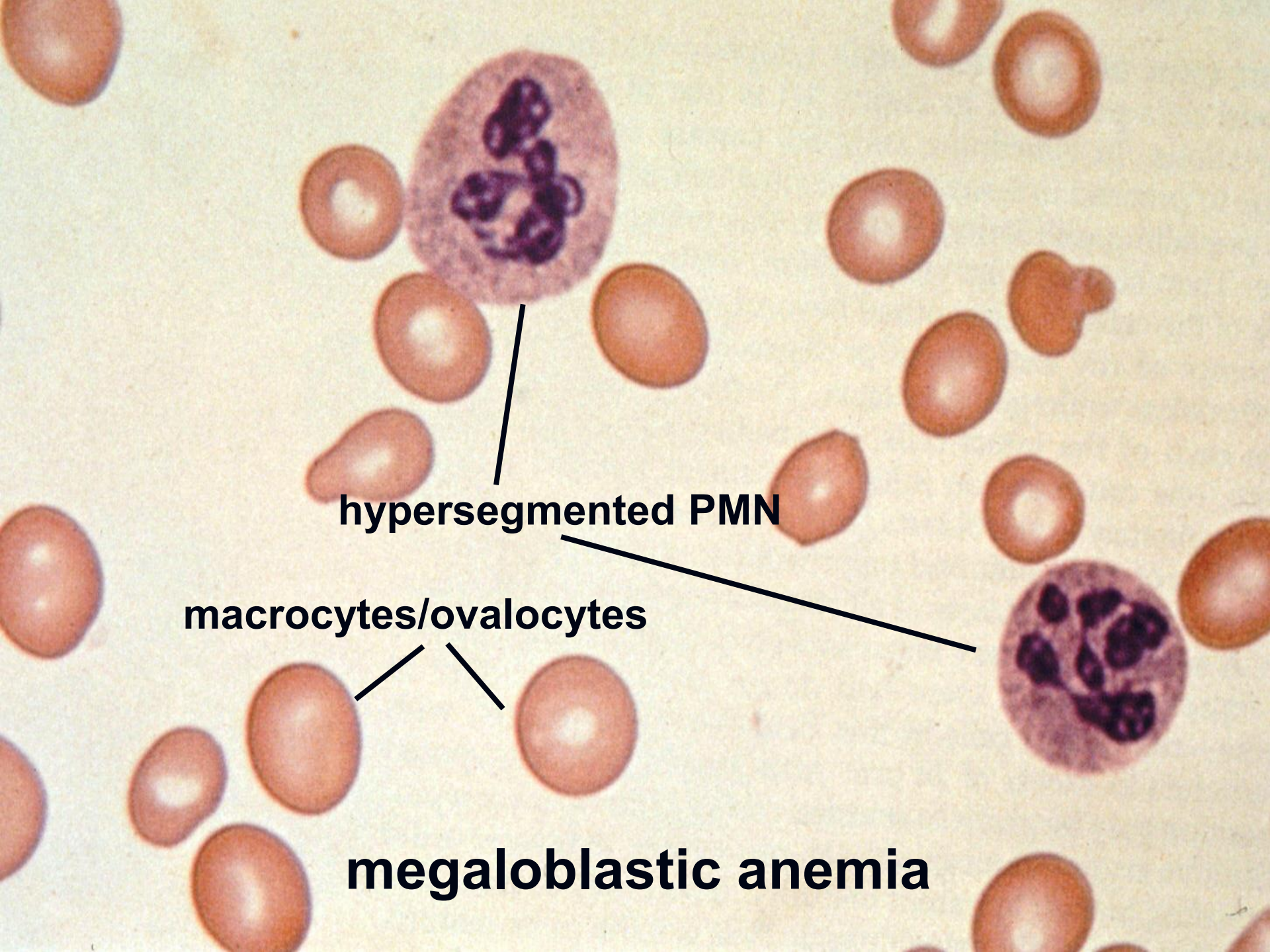


nucleated RBC

mega-platelets

post-splenectomy





hypersegmented PMN

macrocytes/ovalocytes

megaloblastic anemia

hemolytic anemia

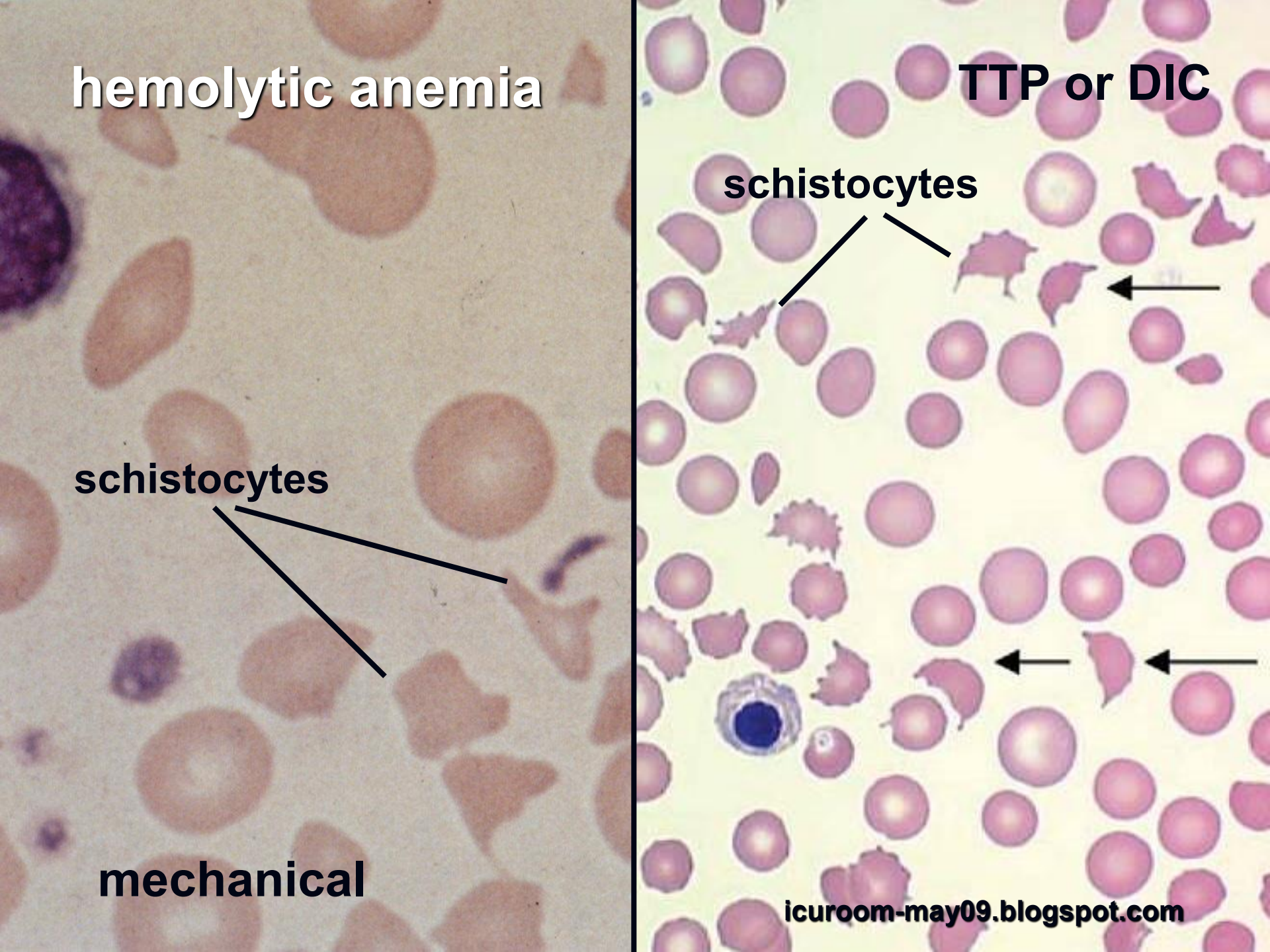
schistocytes

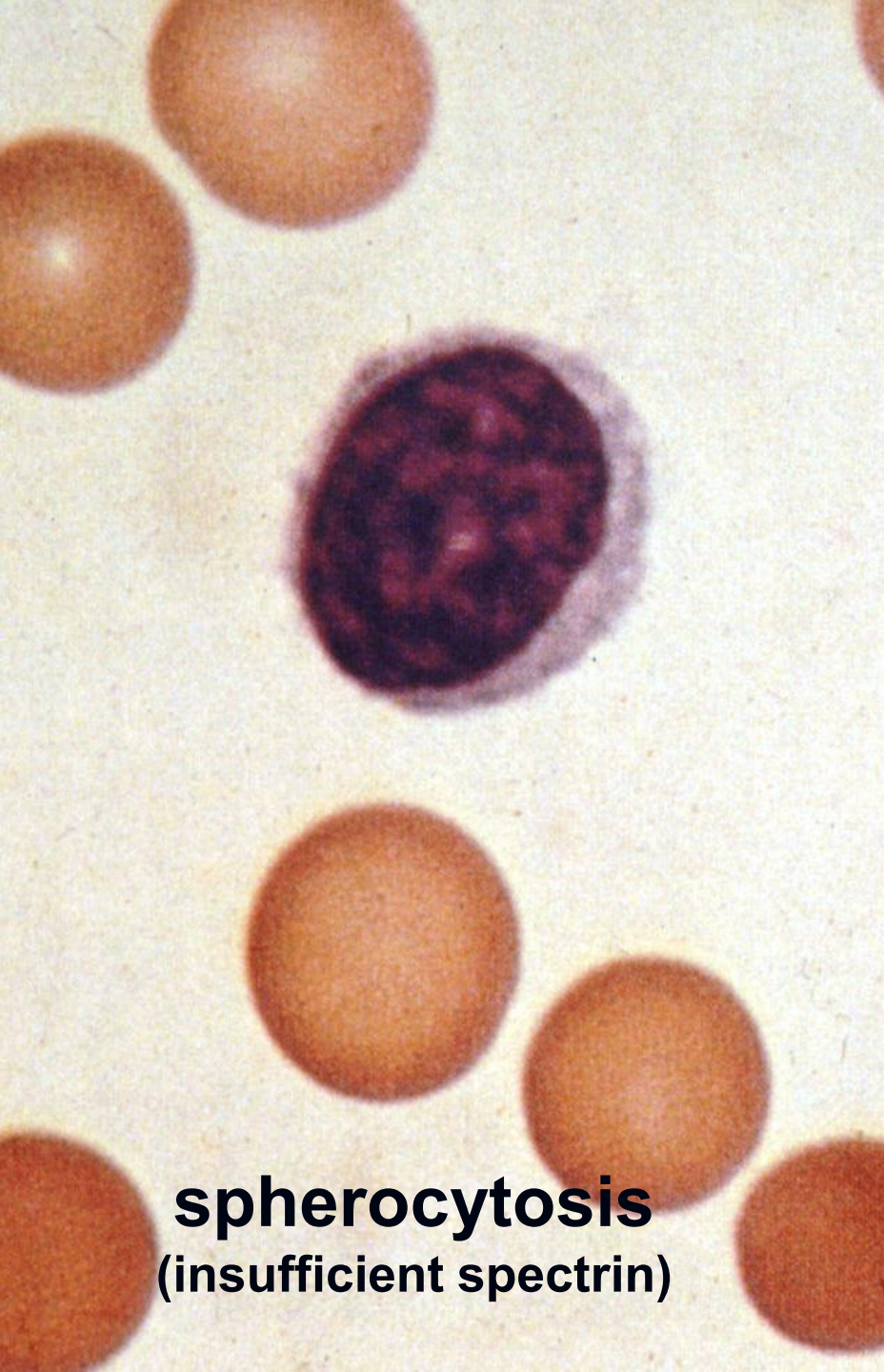
mechanical

TTP or DIC

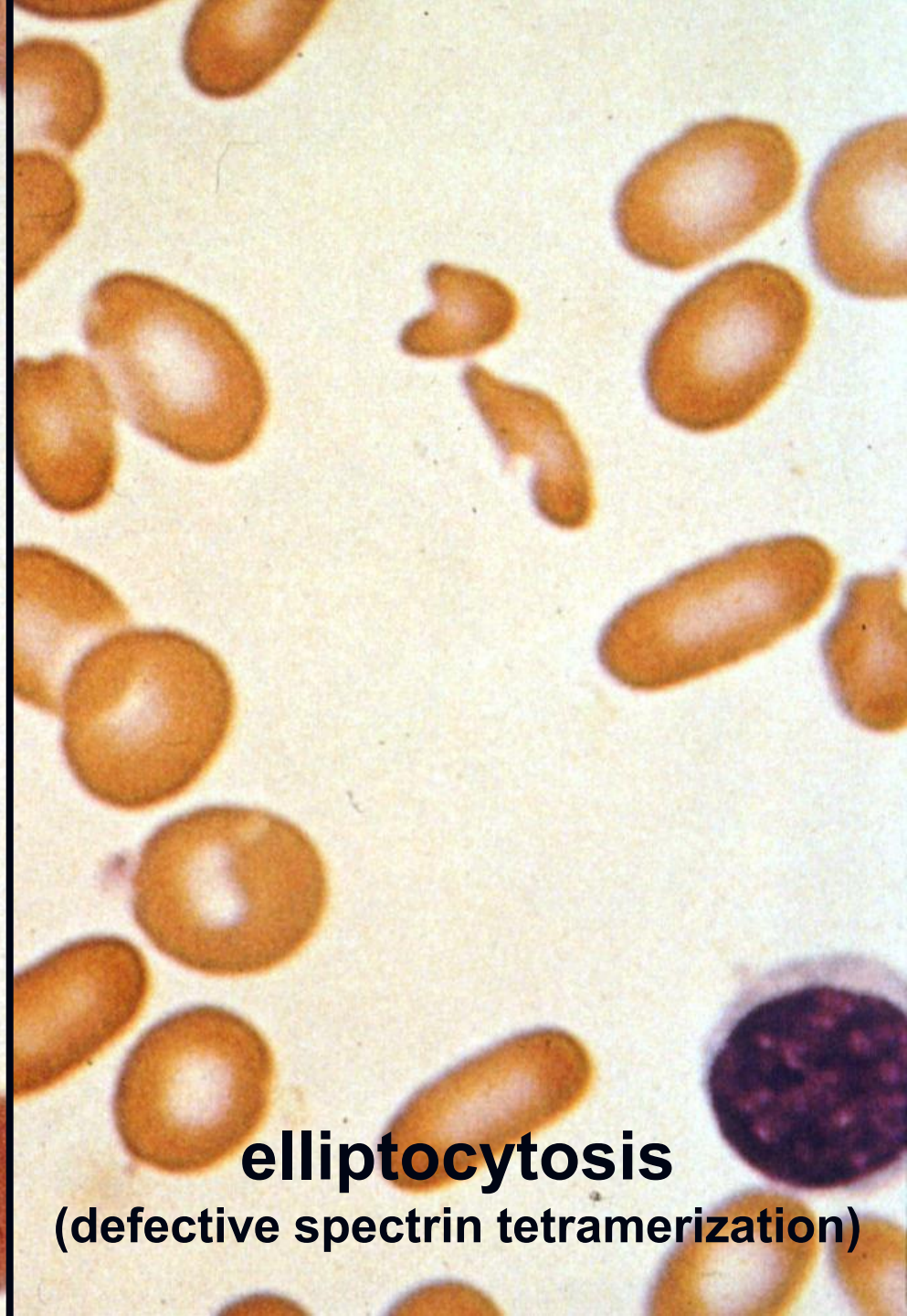
schistocytes

icuroom-may09.blogspot.com

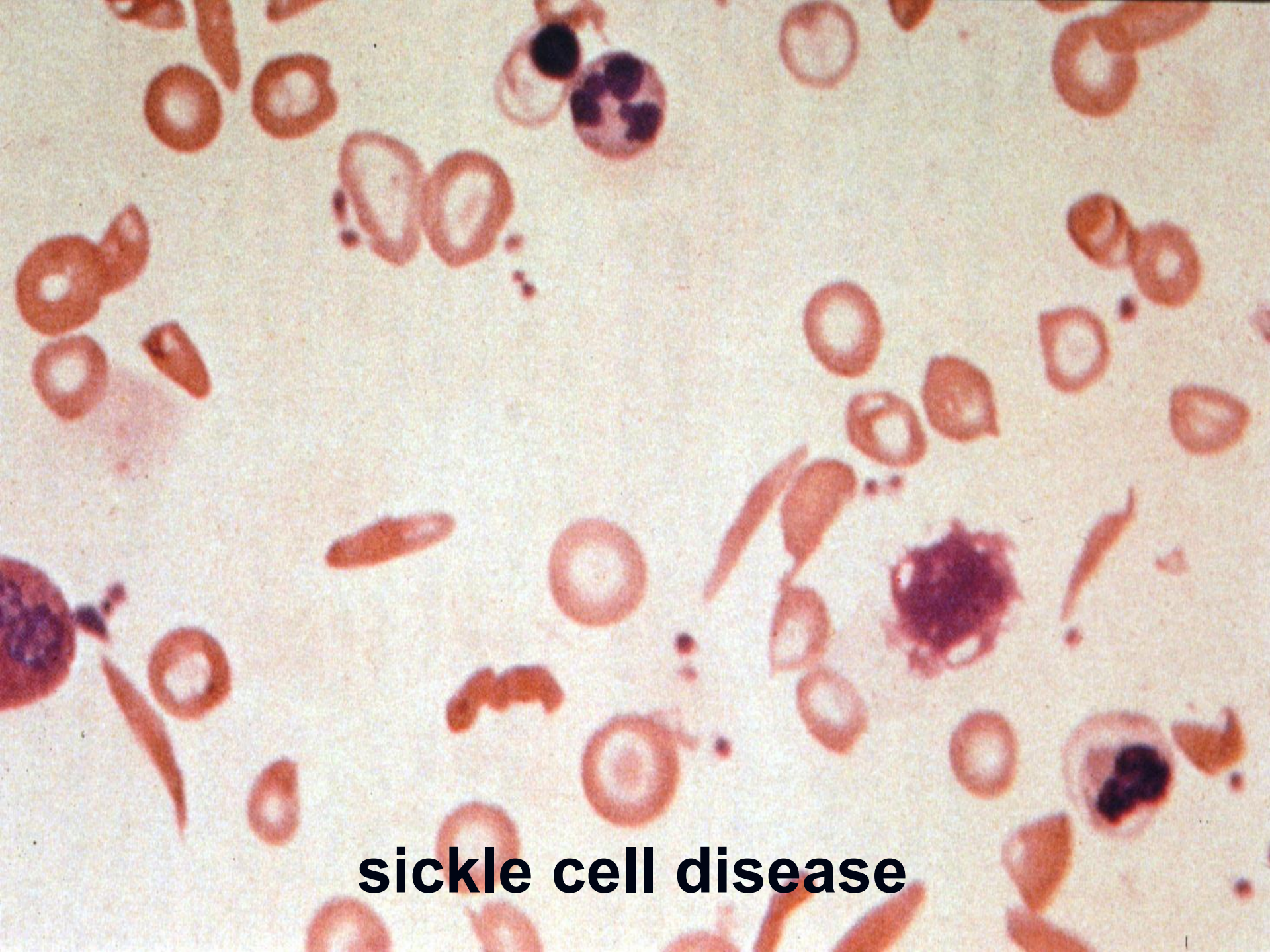




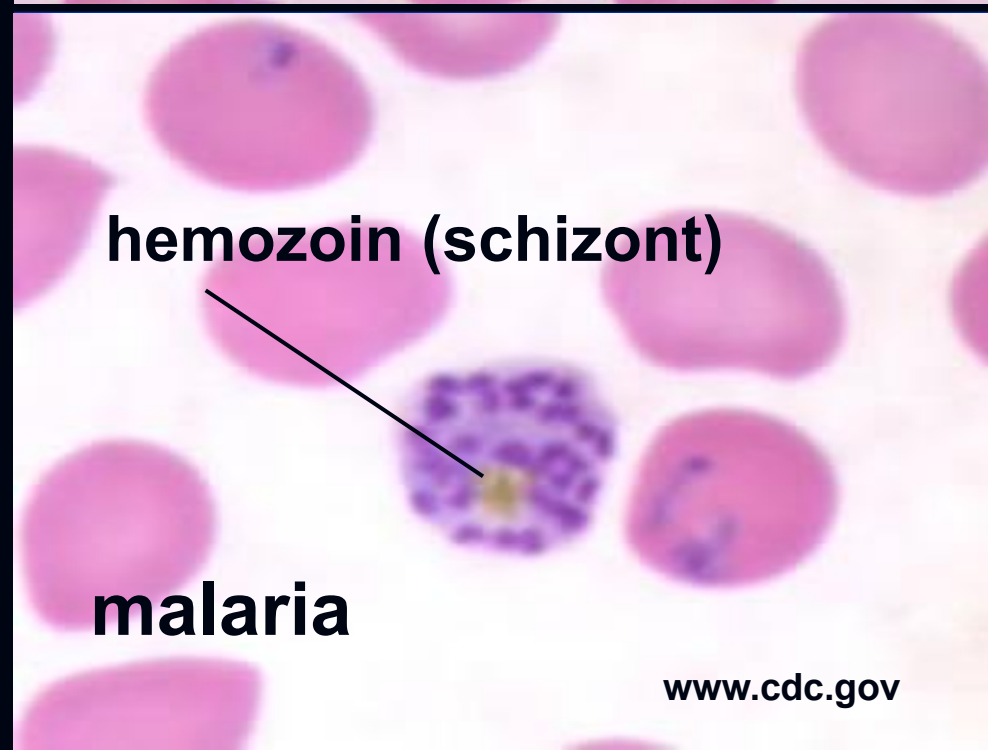
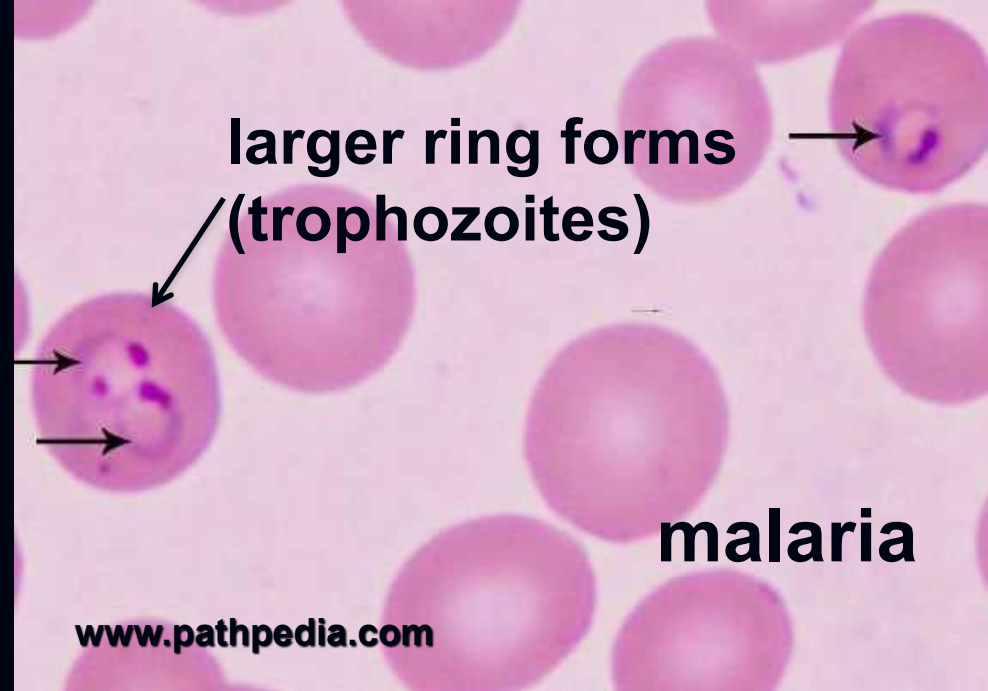
spherocytosis
(insufficient spectrin)



elliptocytosis
(defective spectrin tetramerization)

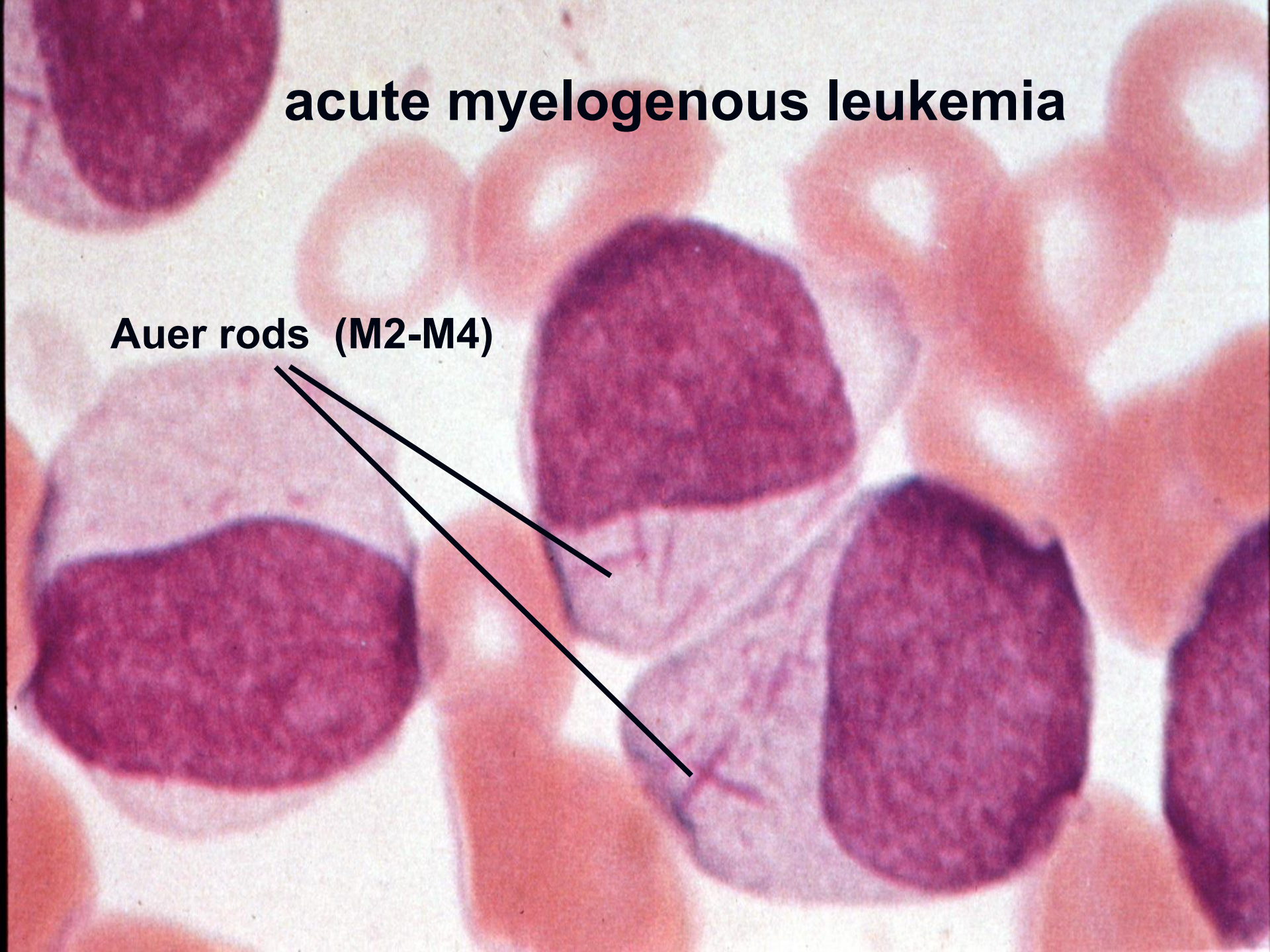


sickle cell disease



acute myelogenous leukemia

Auer rods (M2-M4)



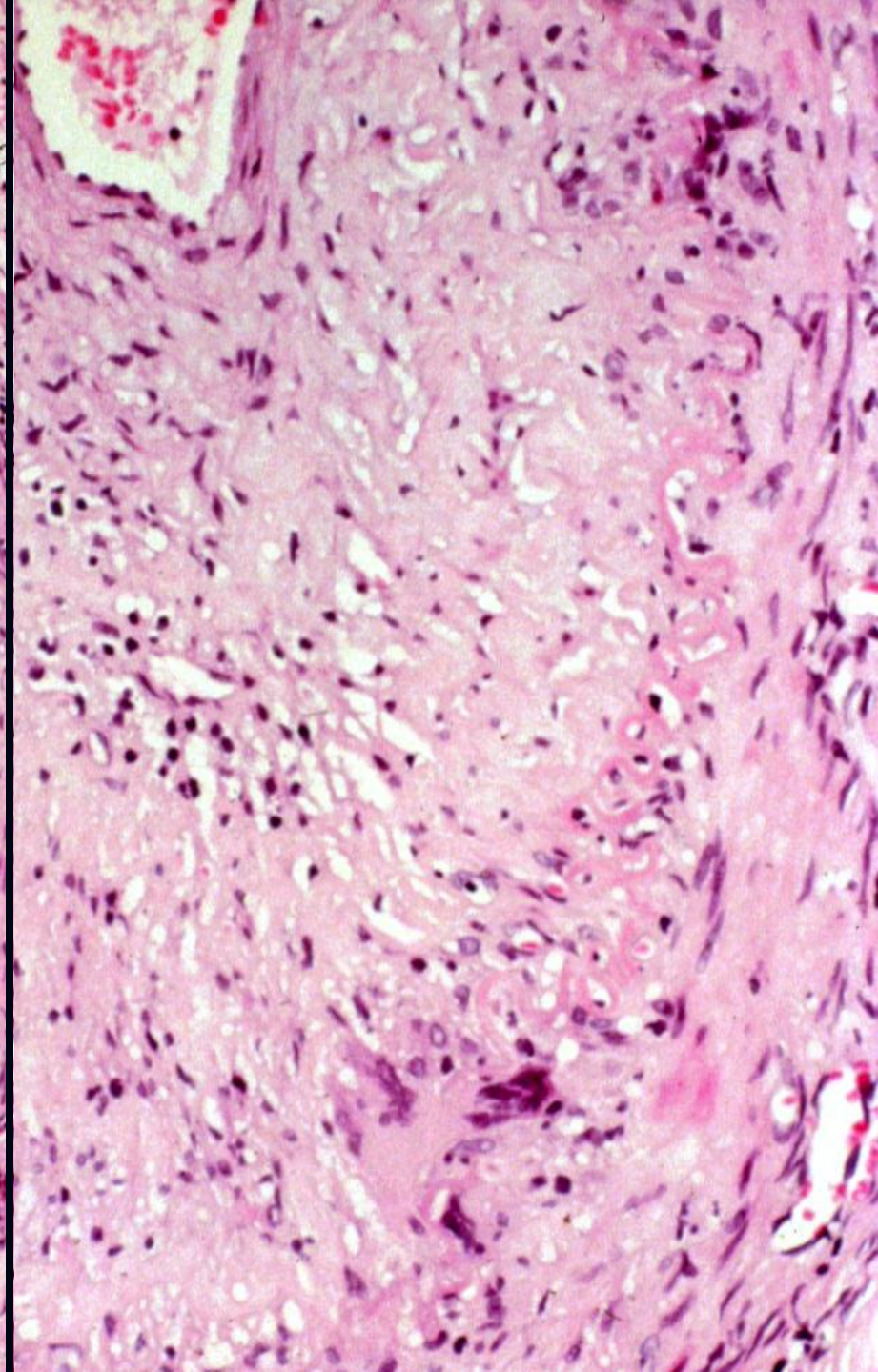
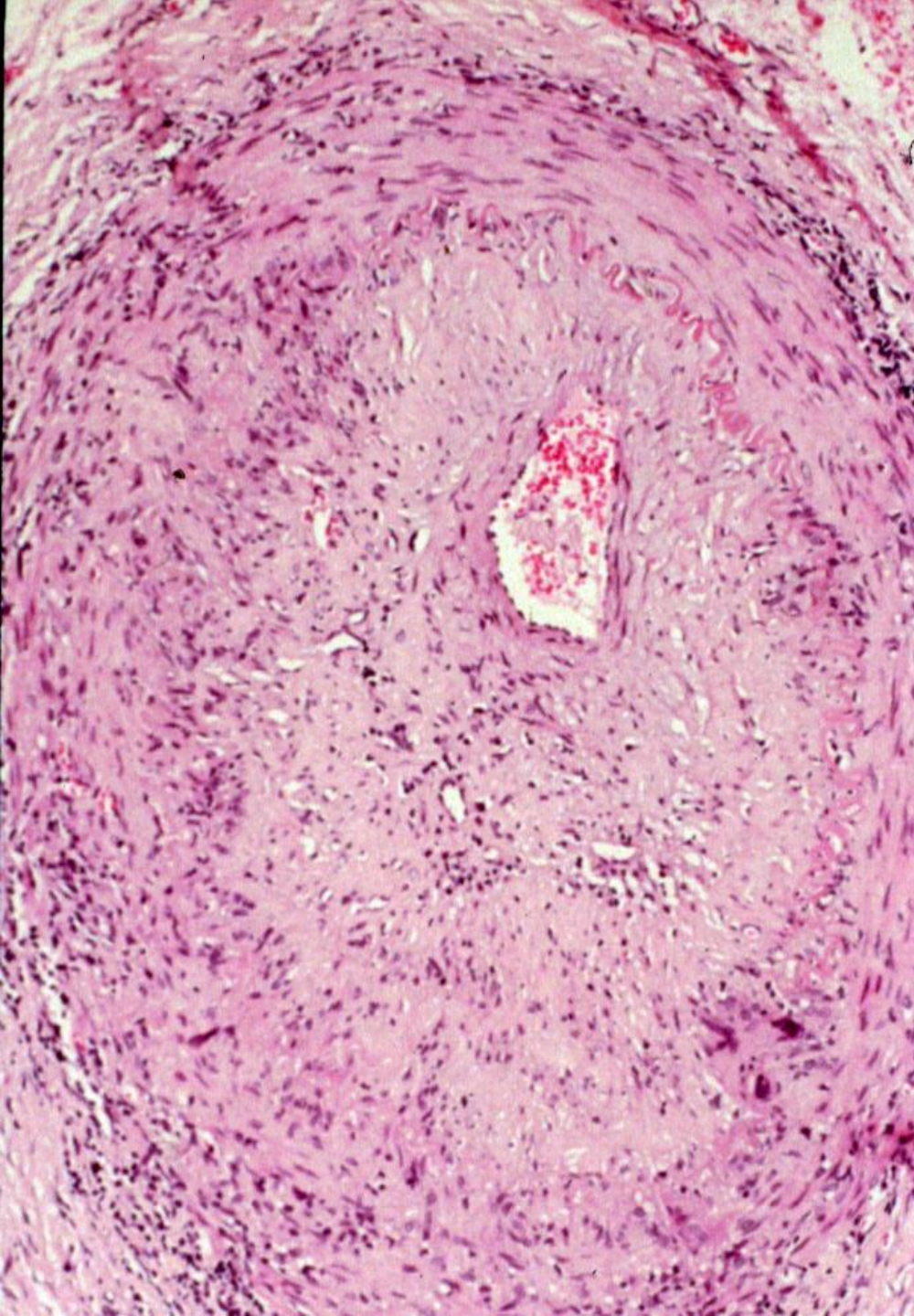
Summary: Take-Home Points

- 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

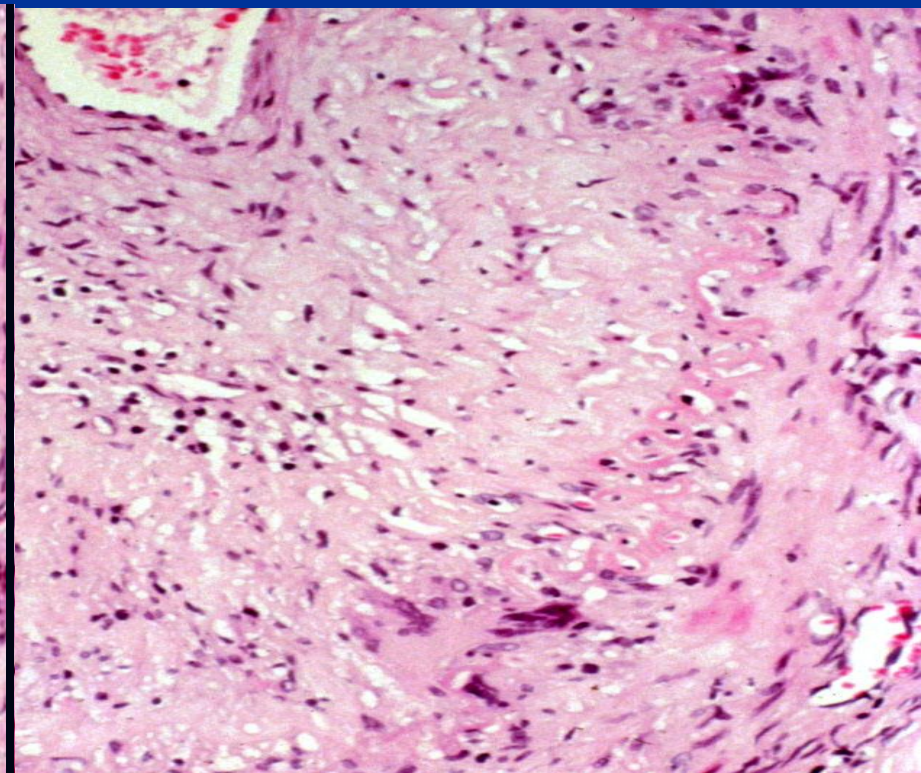
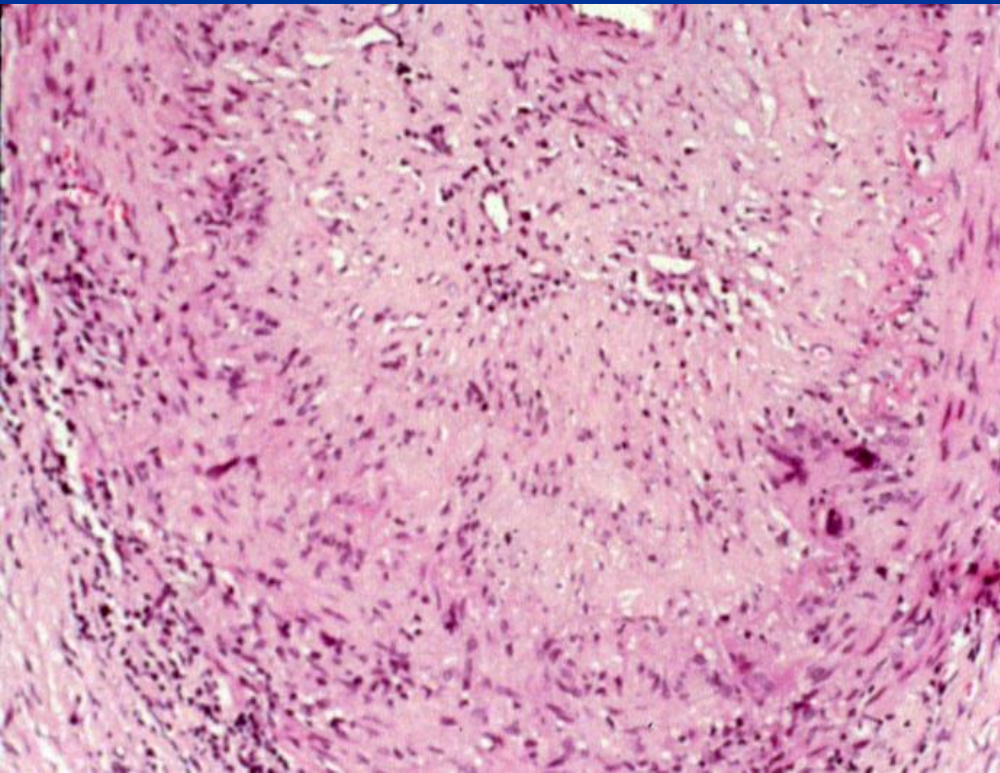
Board Style Practice Question

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

A biopsy is performed.

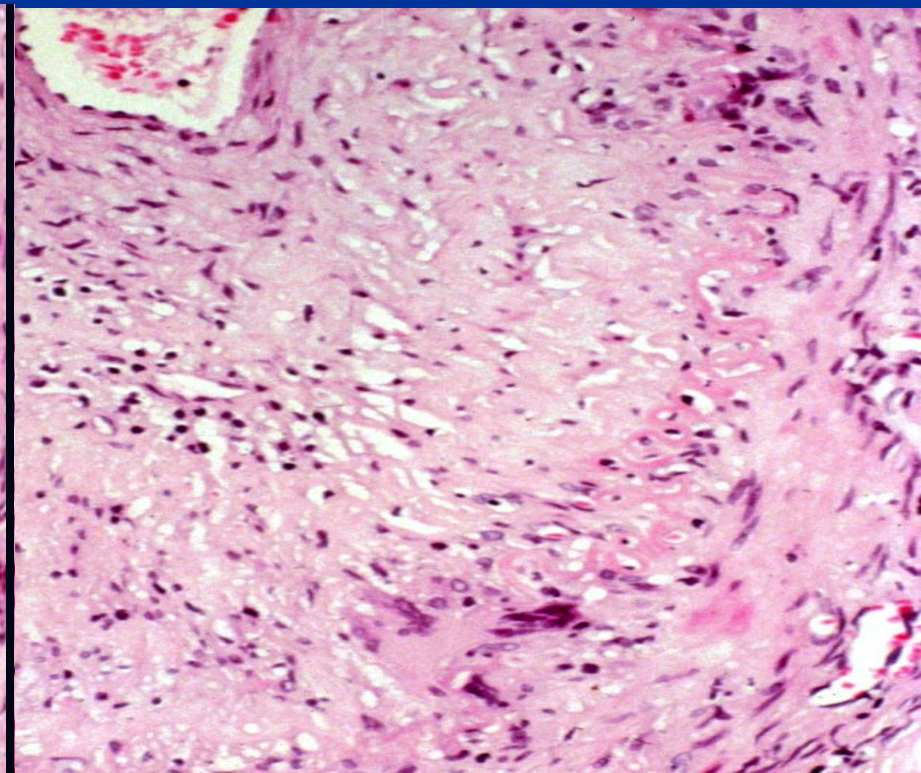
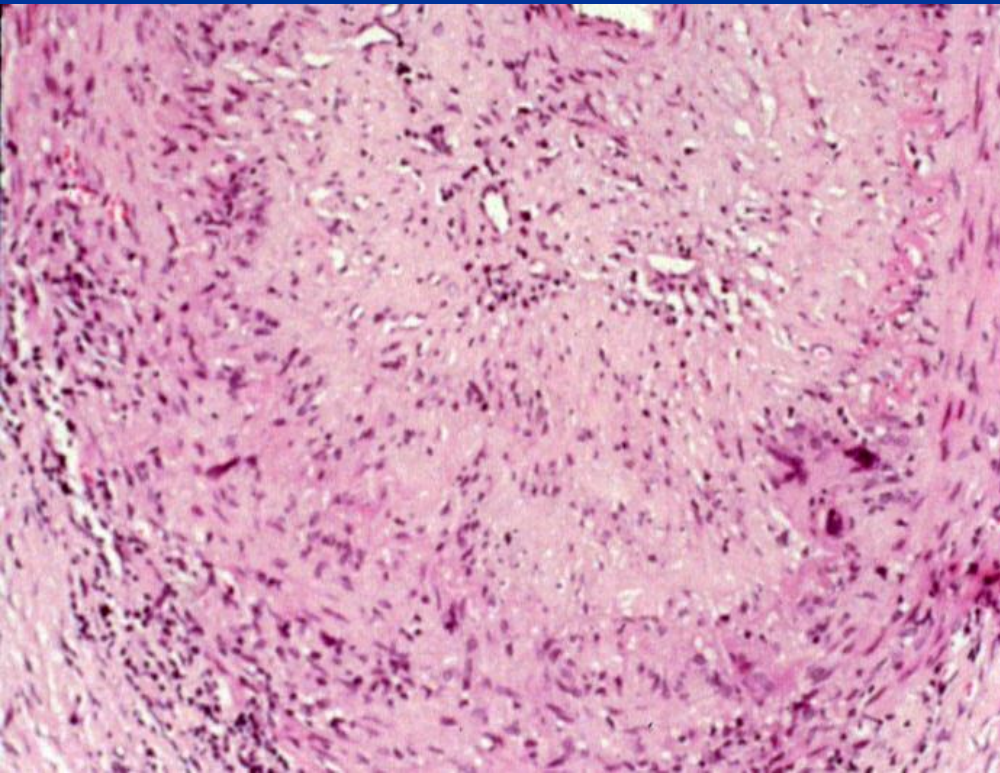


- A. amyloidosis**
- B. Hashimoto's thyroiditis**
- C. temporal arteritis**
- D. Churg-Strauss syndrome**
- E. rheumatoid arthritis**



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

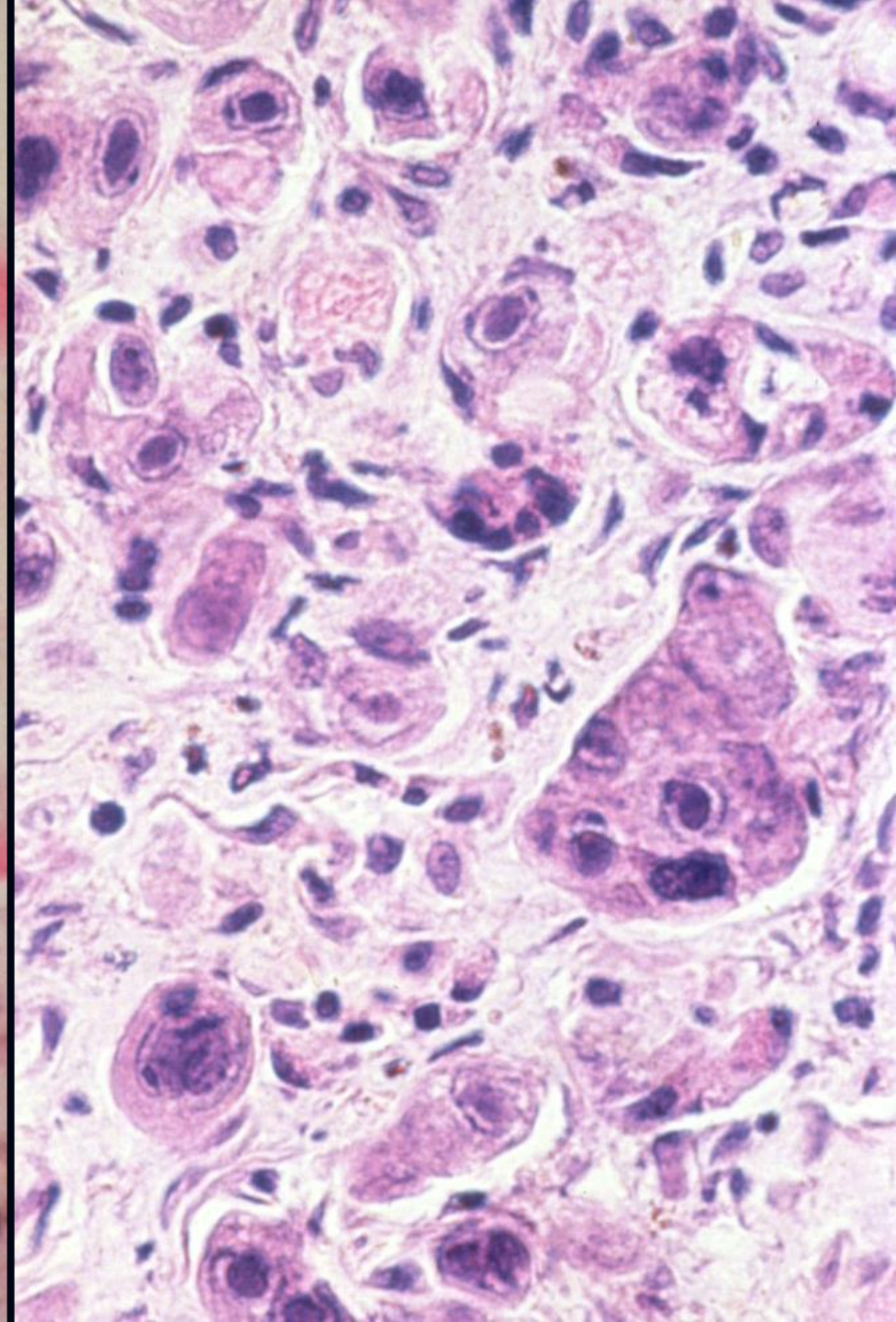
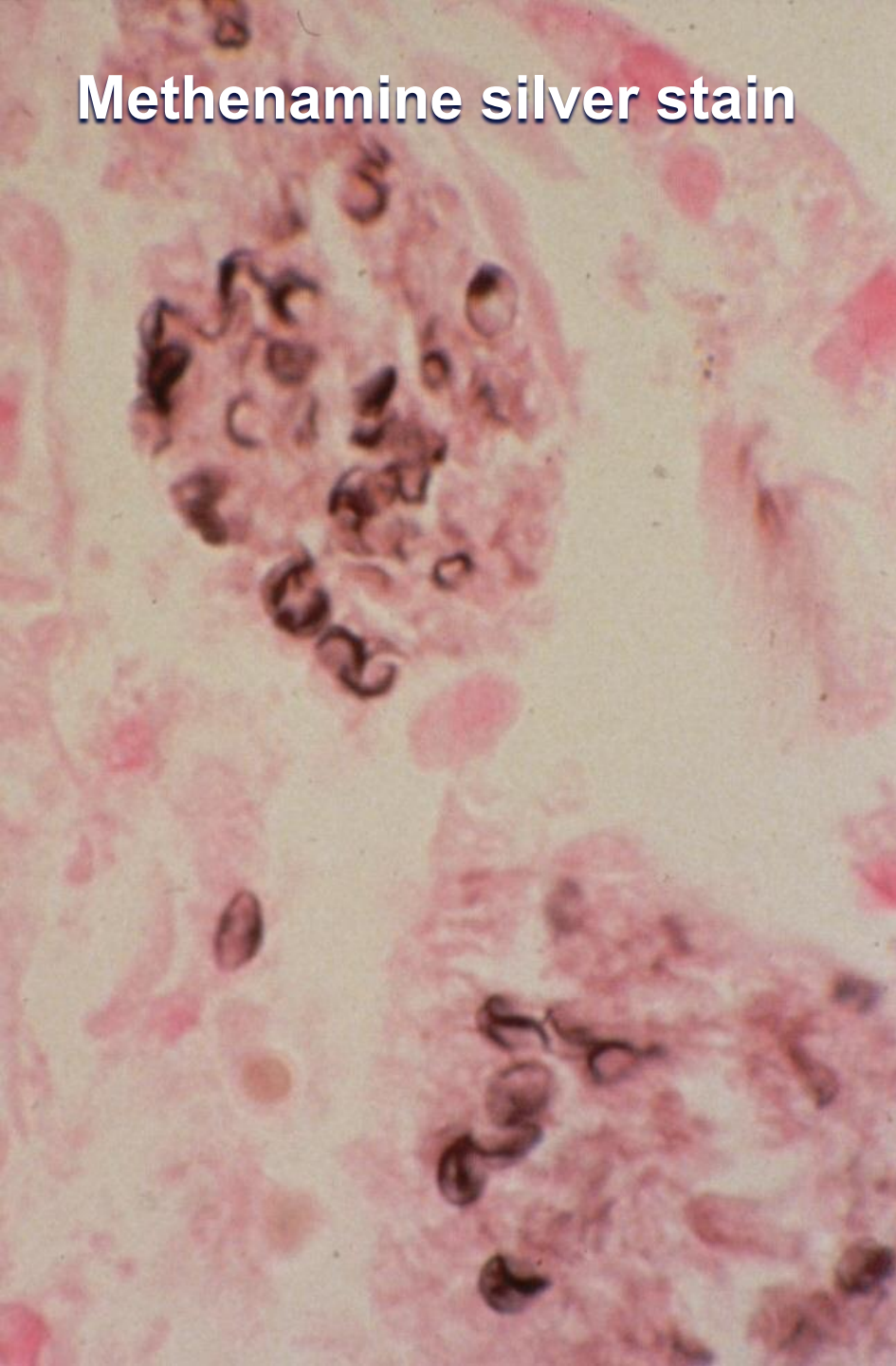


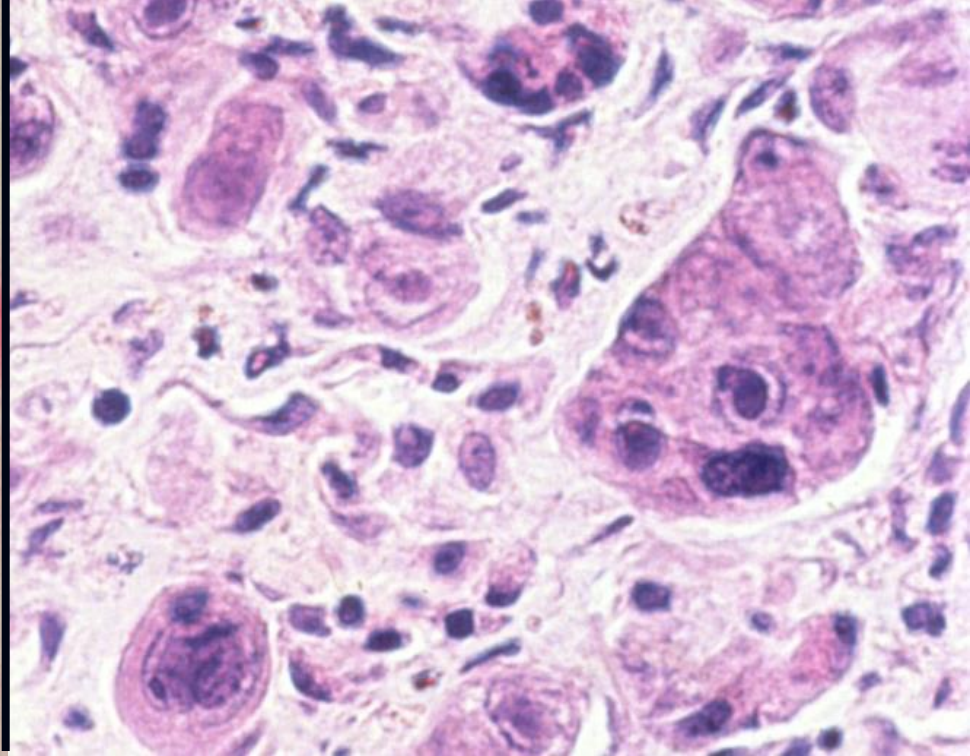
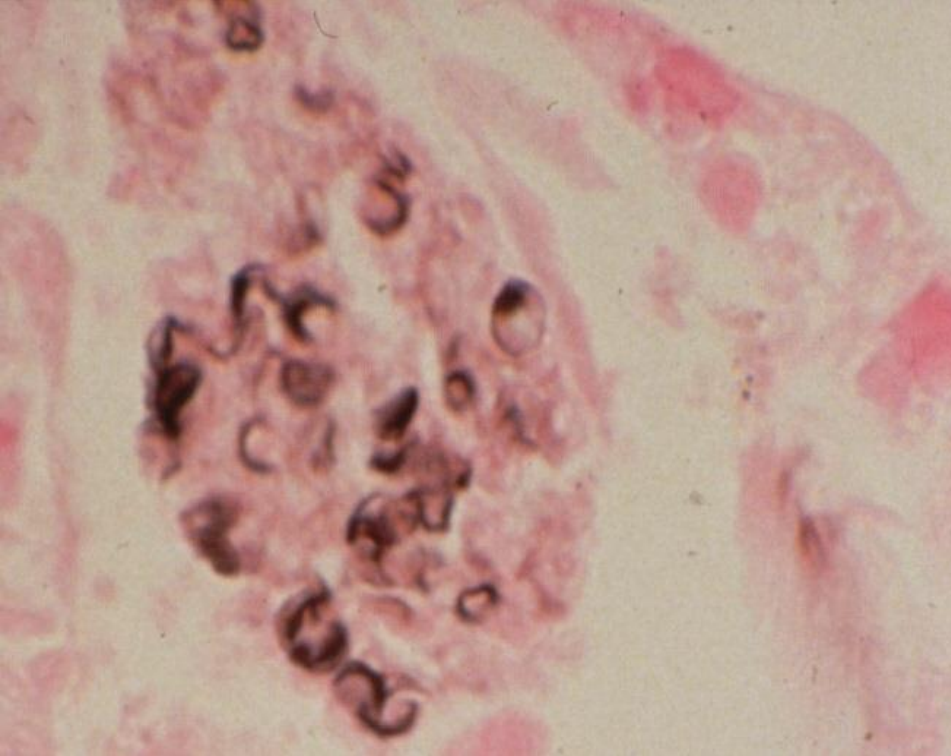
Board Style Practice Question

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

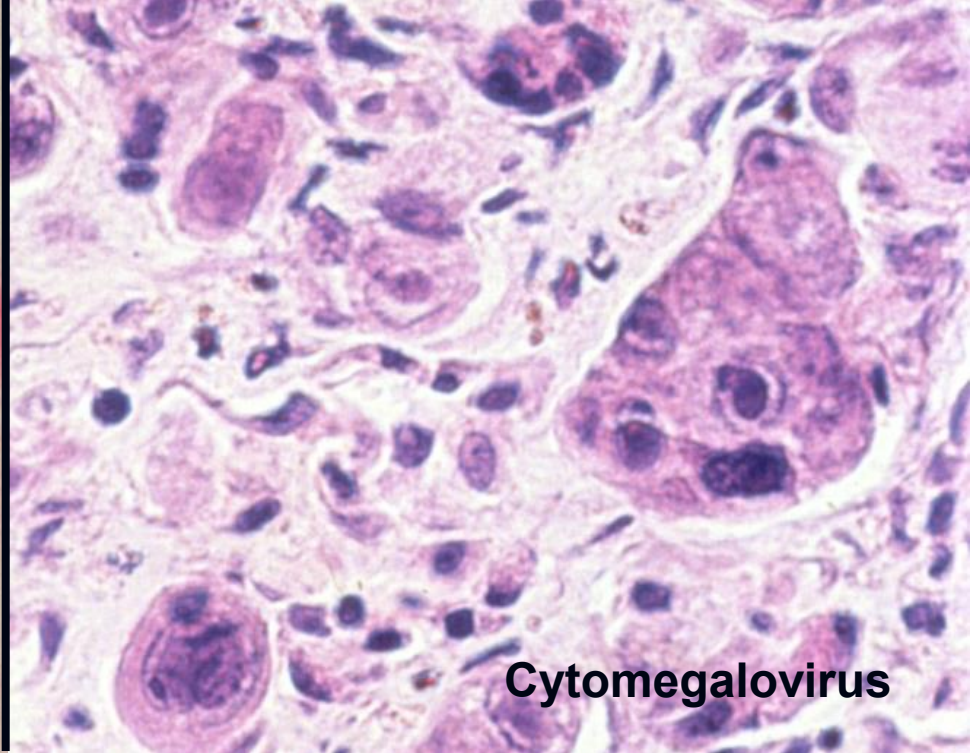




- A. *Pneumocystis jirovecii* pneumonia**
- B. respiratory syncytial virus**
- C. hypersensitivity pneumonitis**
- D. sarcoidosis**
- E. cytomegalovirus**



Pneumocystis jirovecii



Cytomegalovirus

A. *Pneumocystis jirovecii* pneumonia

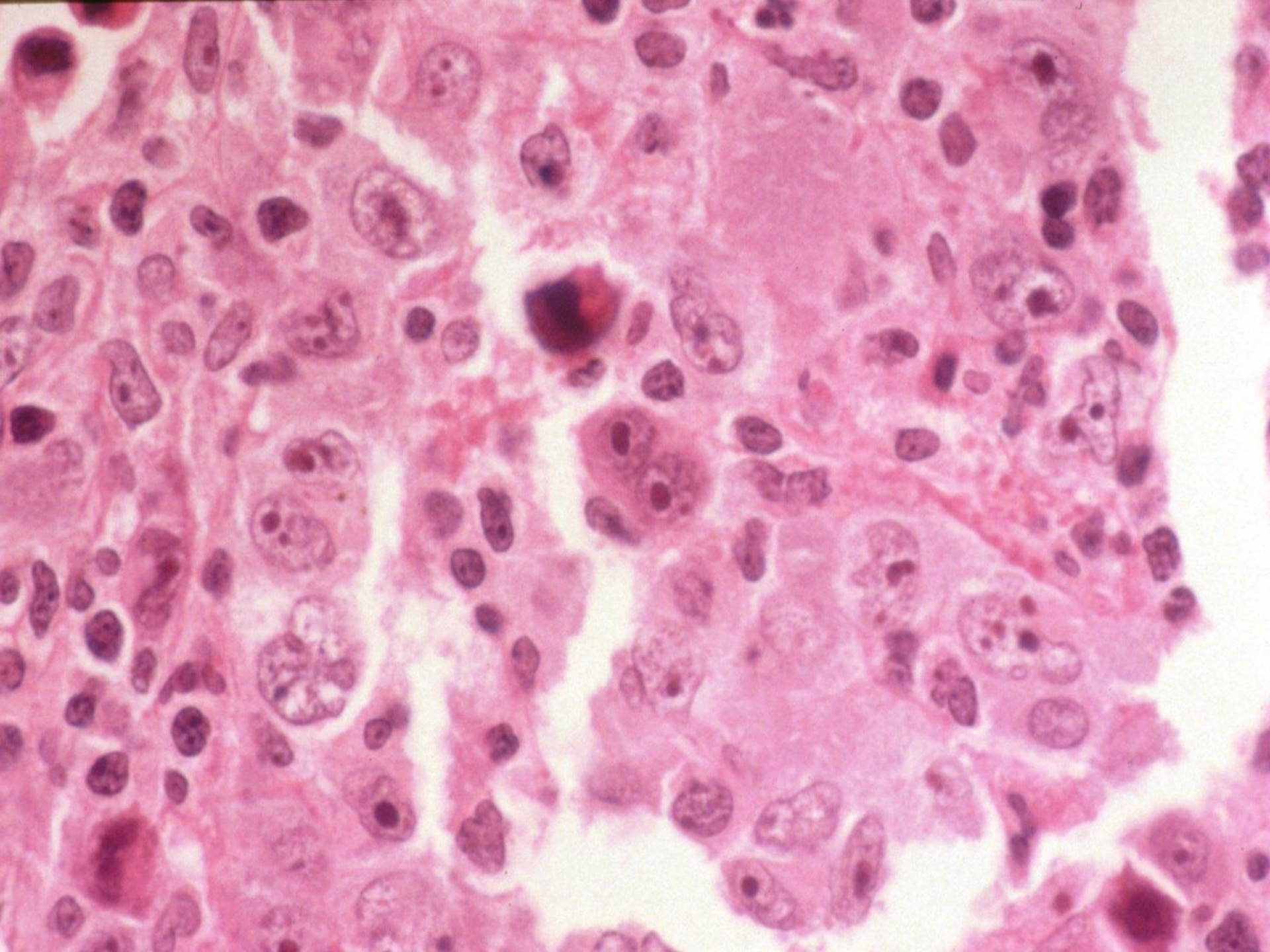
E. Cytomegalovirus

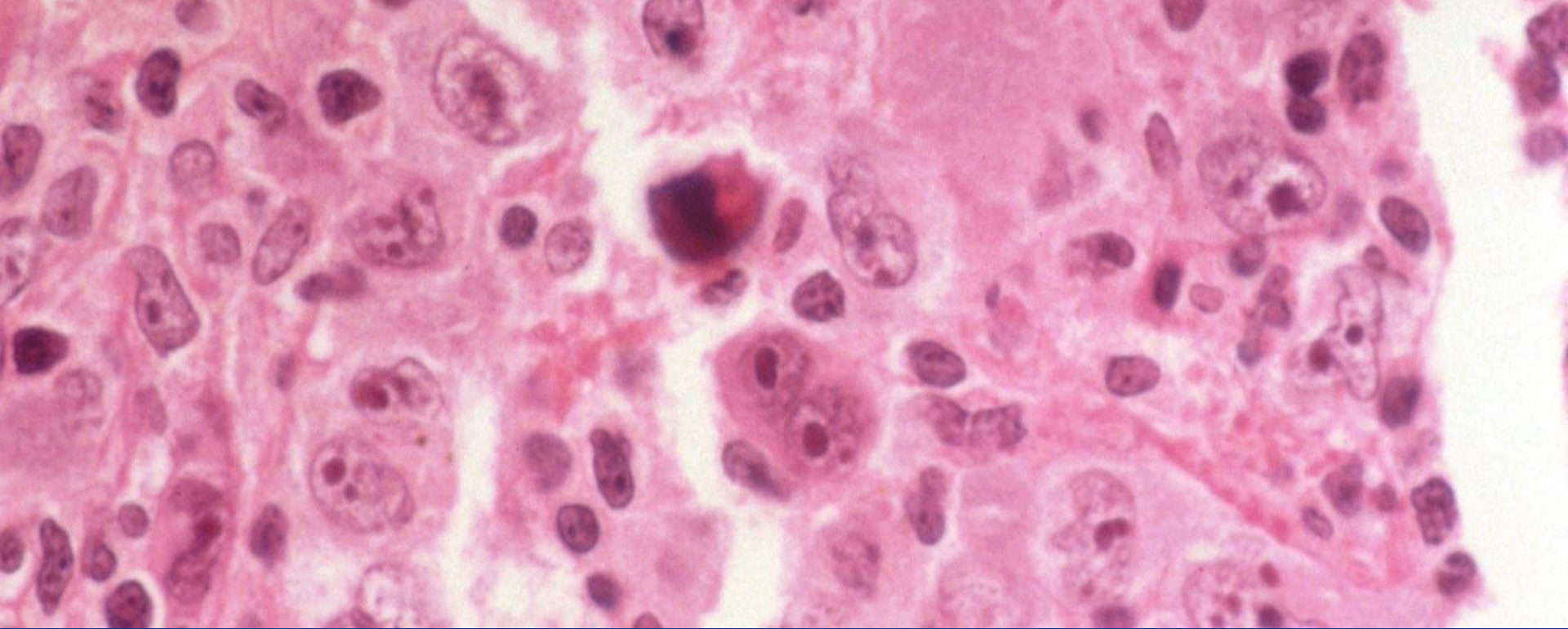
- opportunistic infections
- can be coincident
- *Pneumocystis* cysts can persist after active infection
- *Pneumocystis* commonly dx' d by immunofluorescence
- CMV may represent primary infxn or reactivation

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