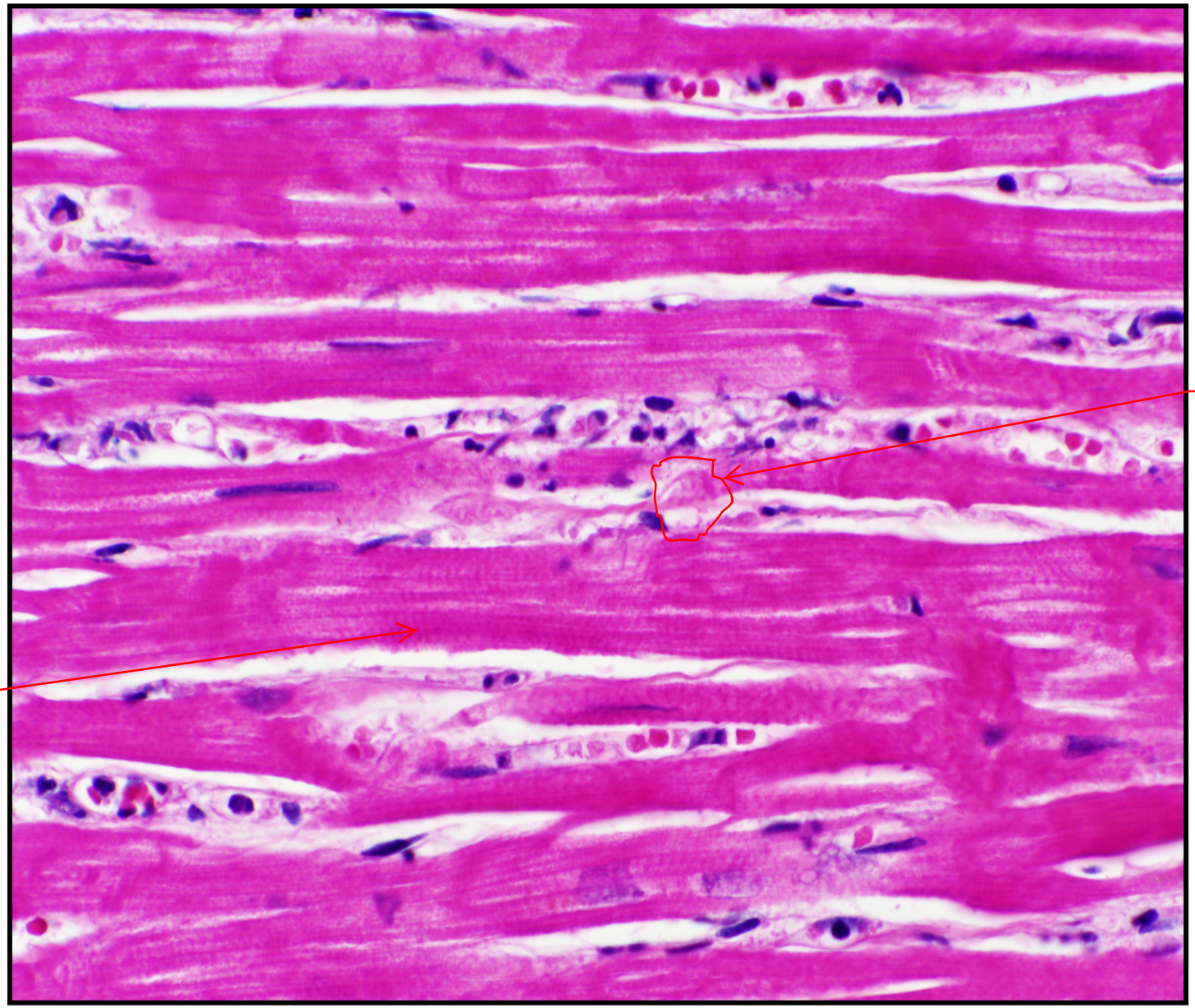
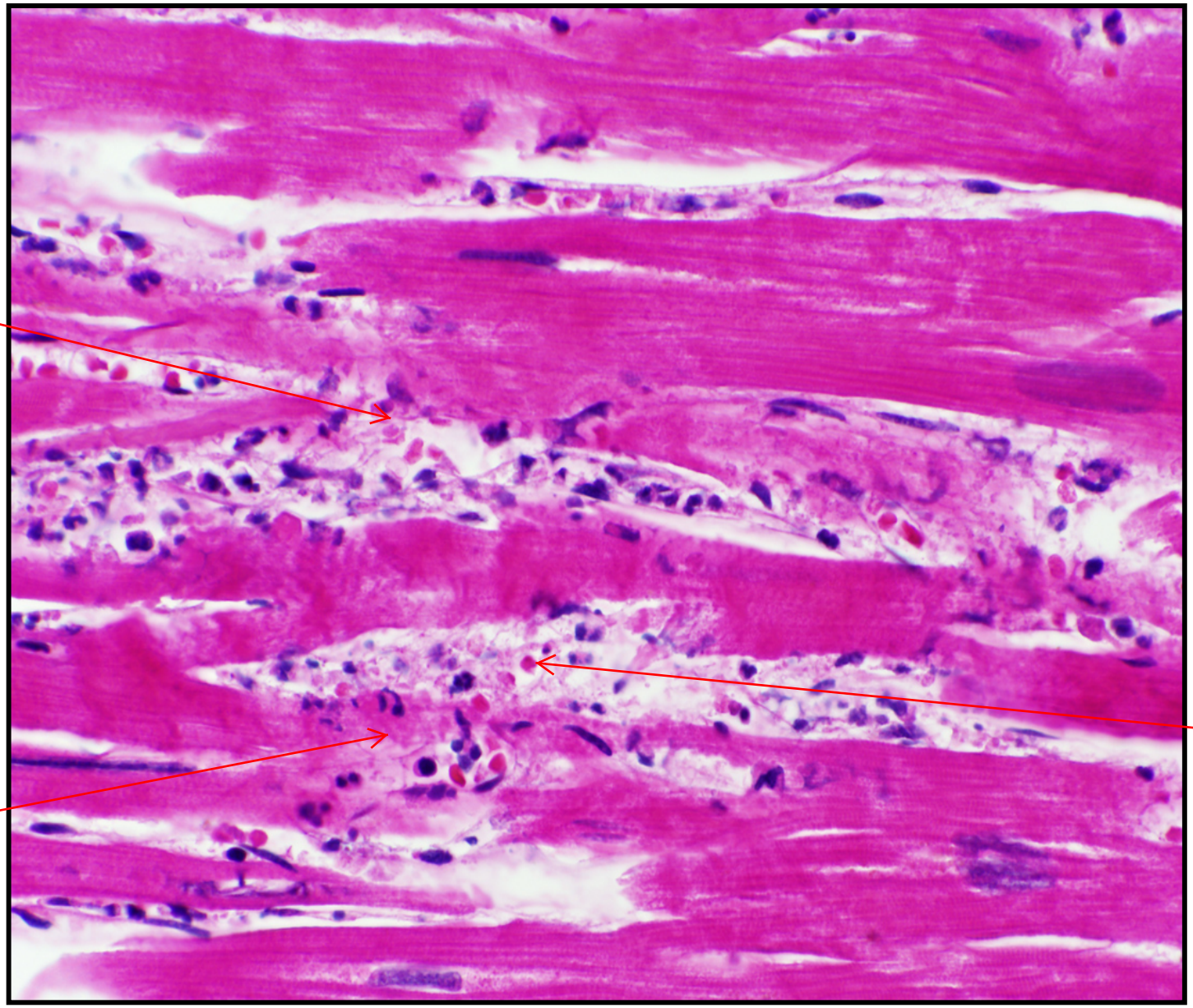
APPROVED

Case Study

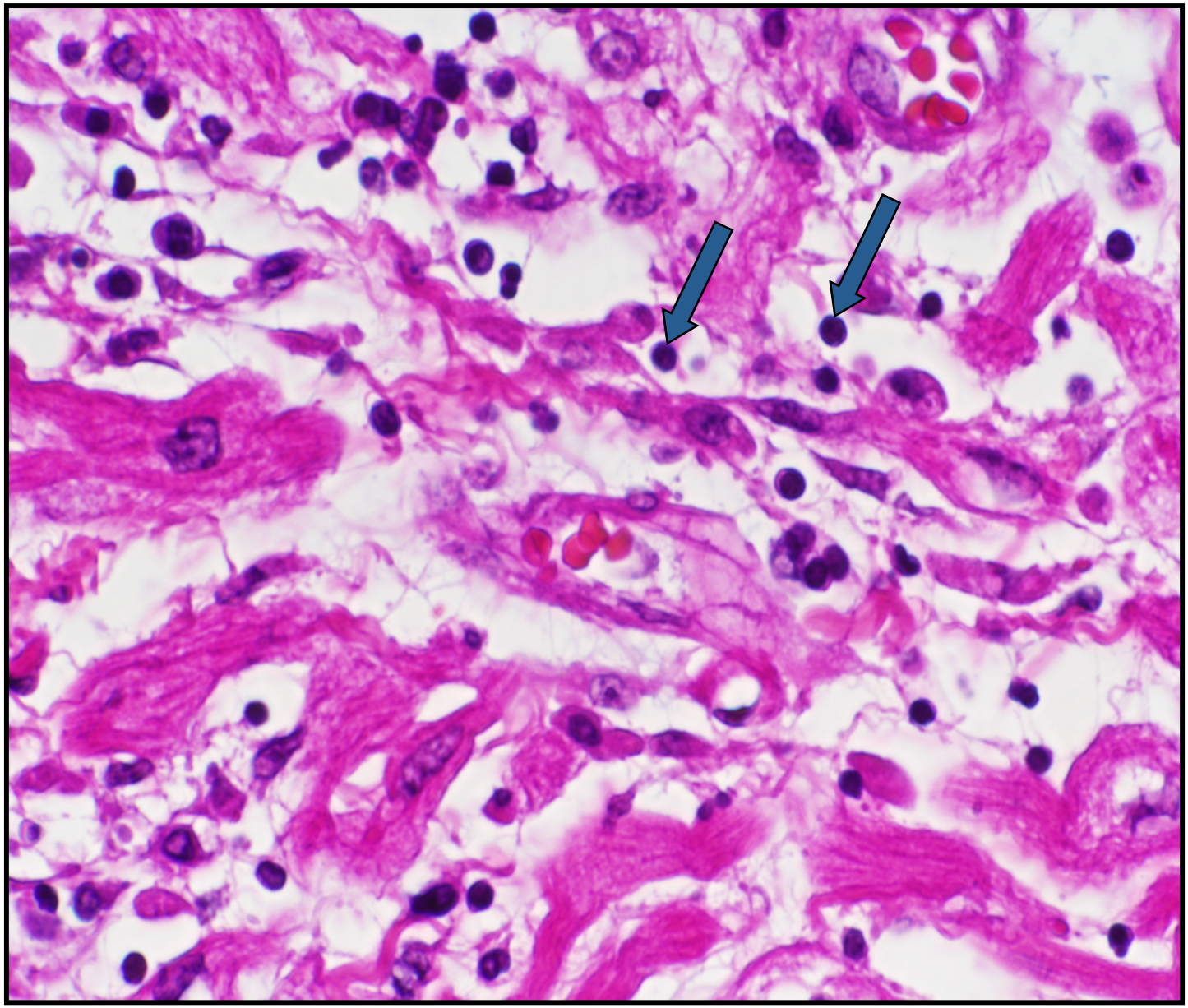
- 15-year-old young man with mild asthma
- Admitted with 5-day history of cough, myalgias, headache, and subjective fever
- 3-day history of abdominal pain, nausea, vomiting, and fever
- Developed hypotension, ventricular dysfunction, and cardiogenic shock Upon being admitted to the hospital
- Died 8 days after symptoms began


Degenerating myocyte, surrounded by inflammatory cells
normal looking myocytes

An example of myocarditis, a process inflammation of the heart muscle



The cells with the round dark nuclei are....
(identified on the next slide)



Inflammatory Cell Type?

A) Lymphocytes

Always when you see round dark nuclei!

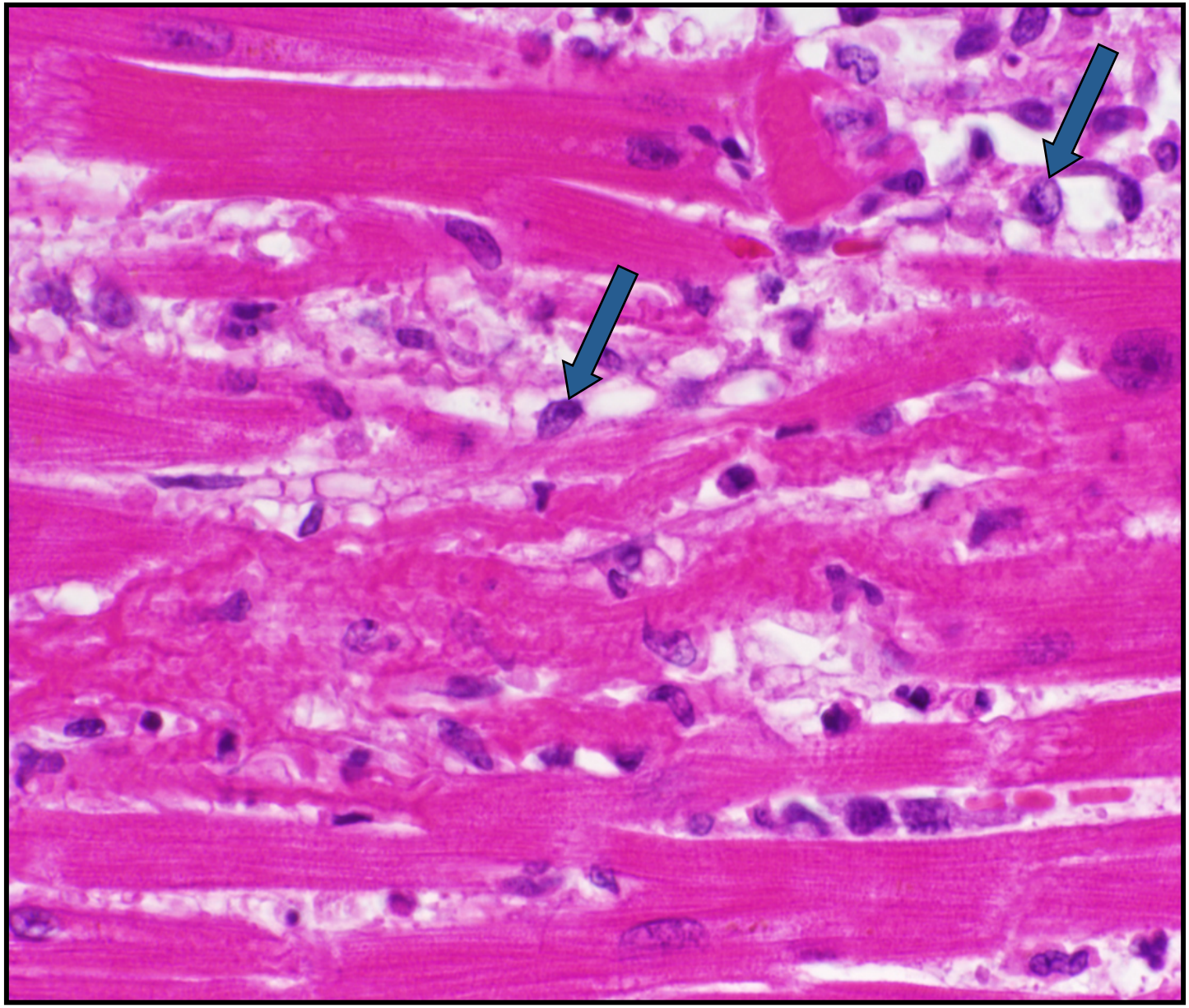
B) Eosinophils

C) Neutrophils

D) Macrophages

E) Multinucleated giant cells

Cells with a larger nuclei and more open chromatin....



Inflammatory Cell Type?

A) Lymphocytes

B) Eosinophils

C) Neutrophils

D) Macrophages

E) Multinucleated giant cells

The combination of lymphocytes and macrophages are indicative of viral myocarditis. The key is that the muscle fibers are breaking down. Heart begins to beat irregularly and arrhythmias develope

Type of Inflammatory Response?

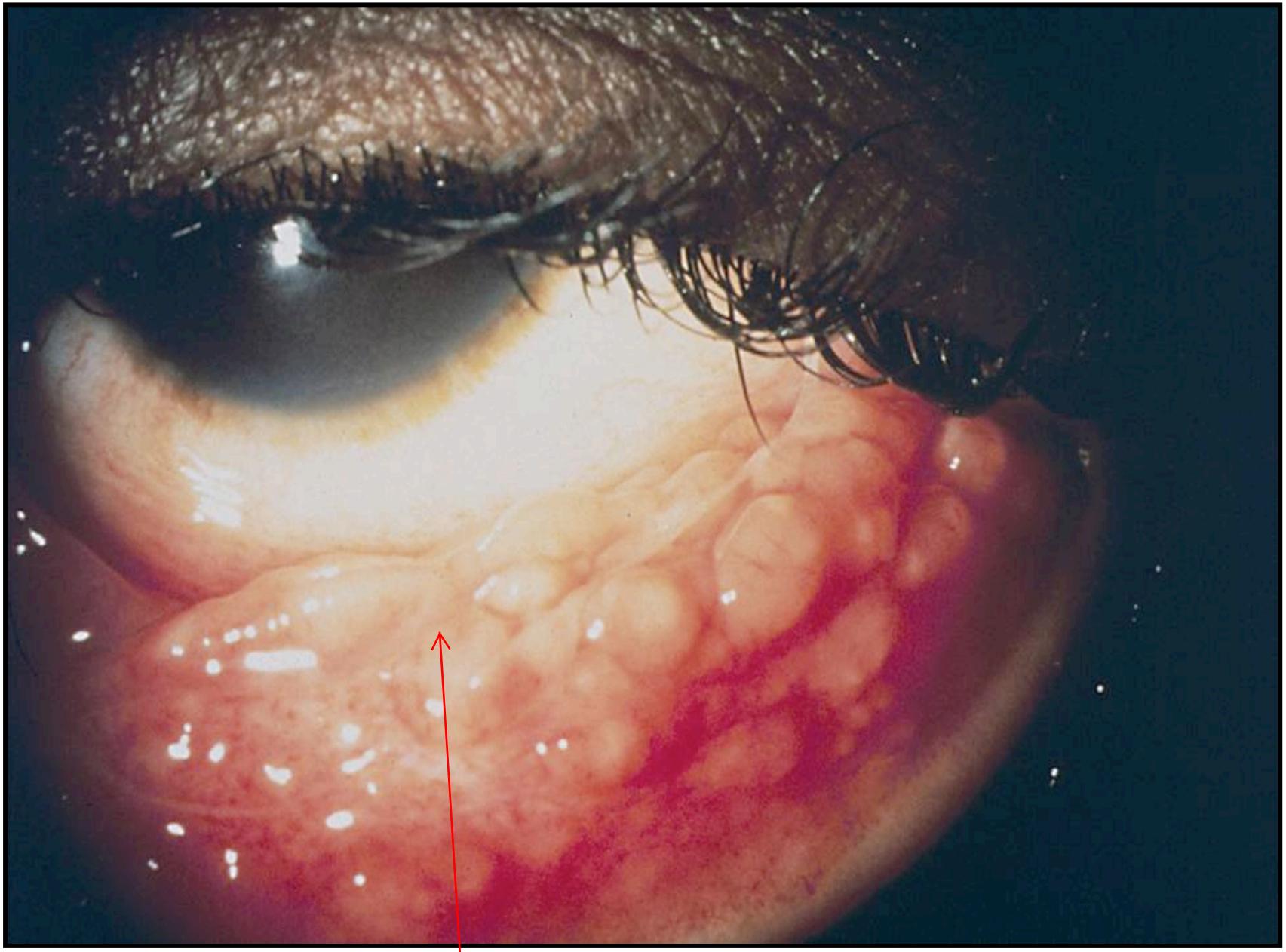
A) Acute

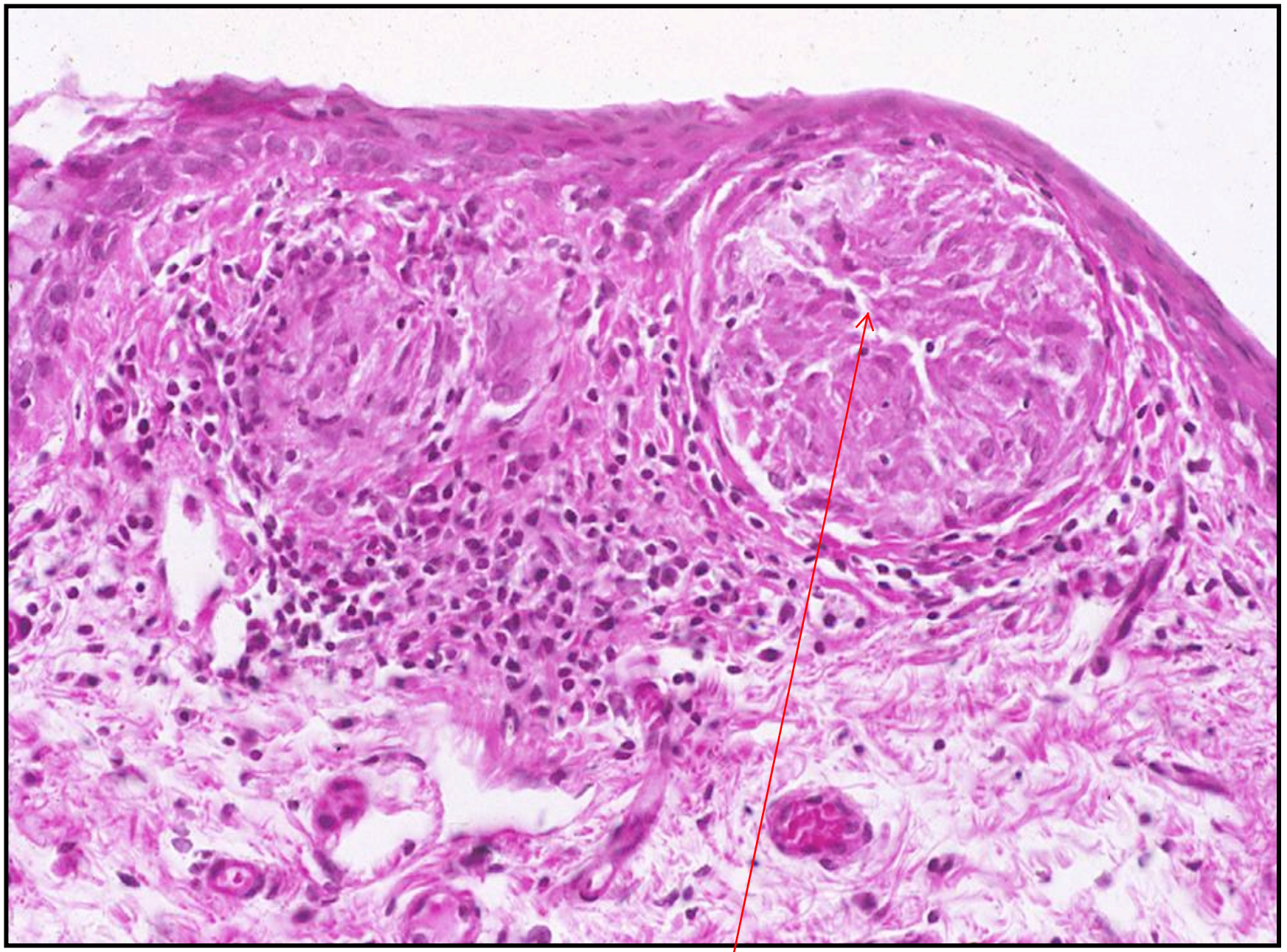
B) Chronic

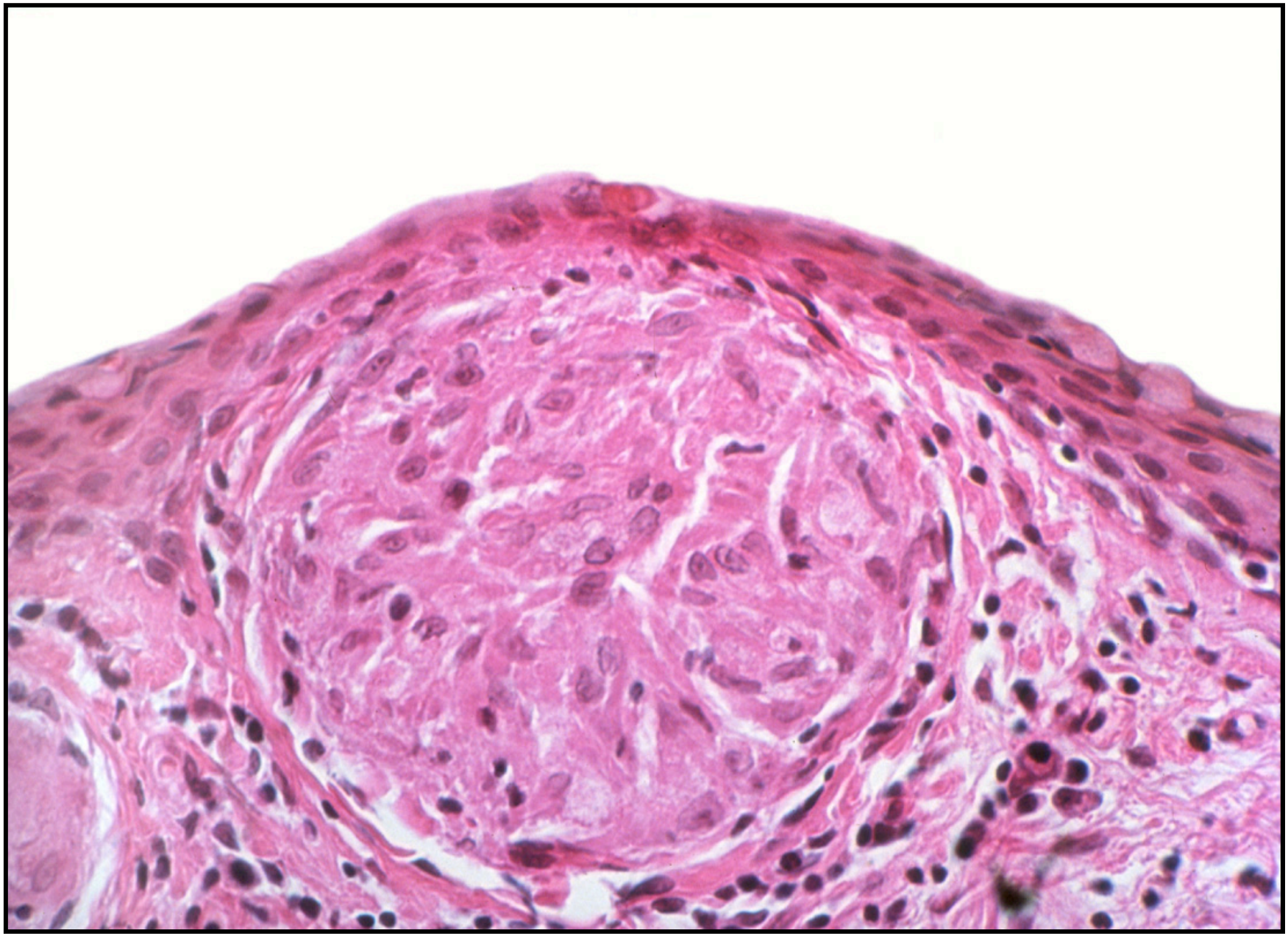
C) Granulomatous

Case Study

- 20-year-old black woman
- Follicular conjunctivitis
  Unresponsive to topical corticosteroids


Follicular
conjunctiva


Discrete aggregates of
cells..... aka granulomas!

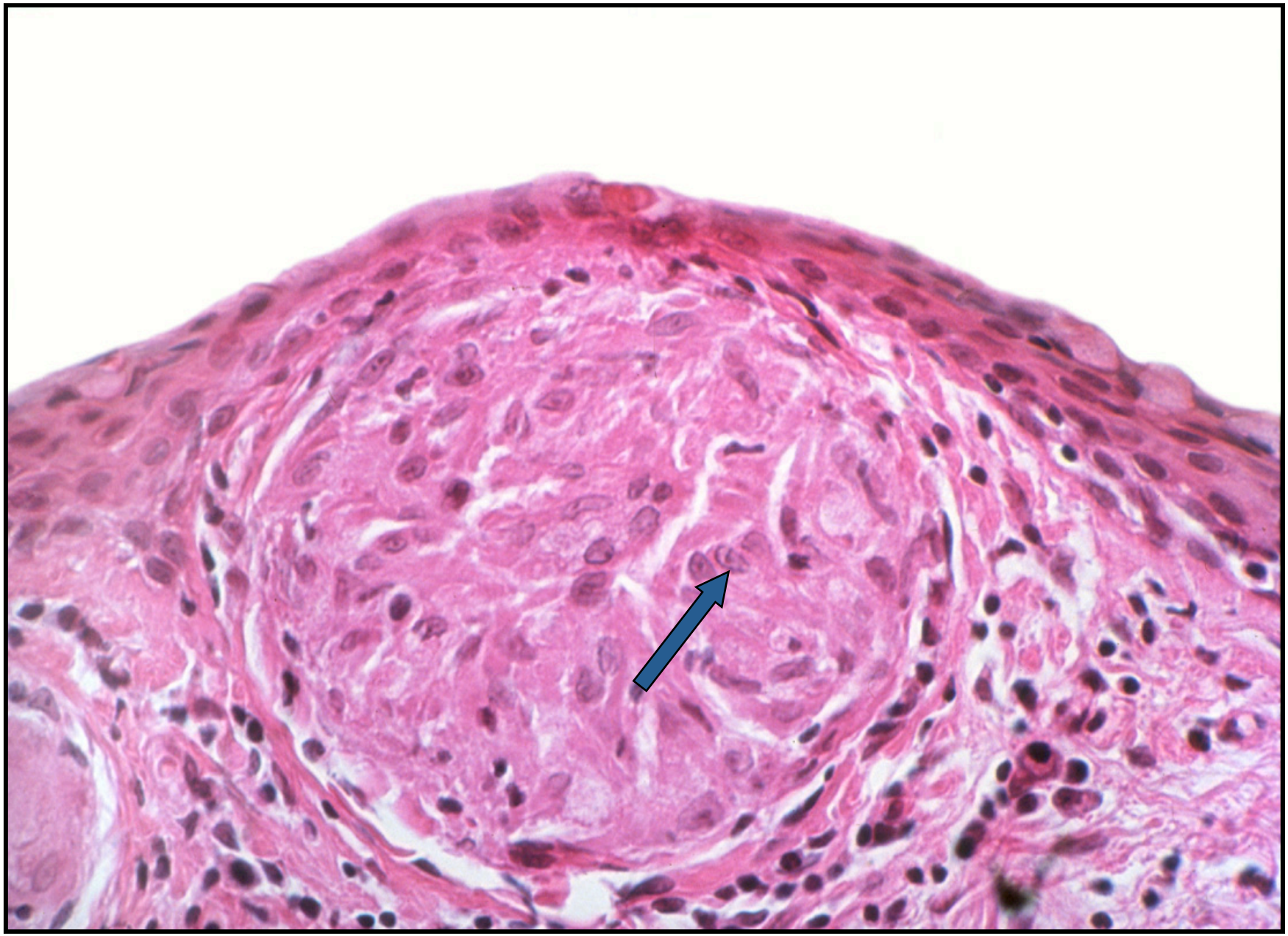


Type of Inflammatory Response?

A) Acute

B) Chronic

C) Granulomatous



Open chromatin and a lot of pink cytoplasm...

Inflammatory Cell Type?

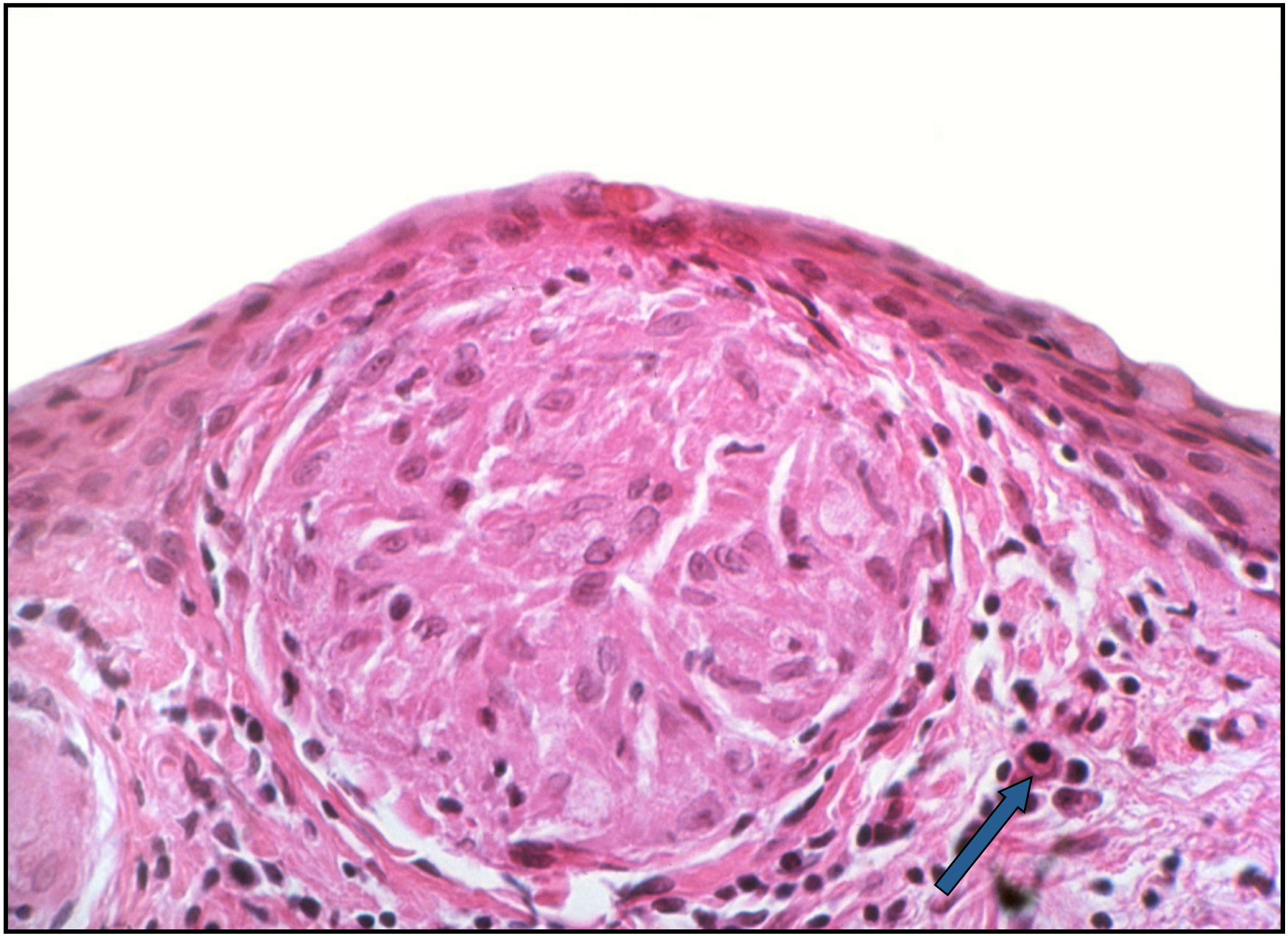
A) Lymphocyte

B) Eosinophil

C) Neutrophil

D) Epithelioid cell

E) Multinucleated giant cells



Round nucleus and a lot of cytoplasm (a modified lymphocyte). plasma cell

Inflammatory Cell Type?

A) Lymphocyte

B) Eosinophil

C) Plasma cell

D) Macrophage

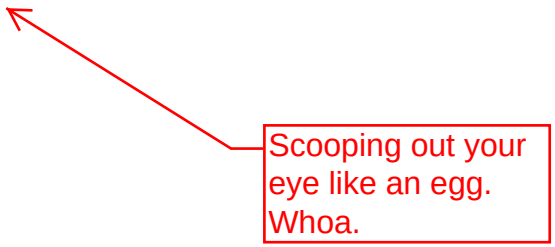
E) Neutrophil

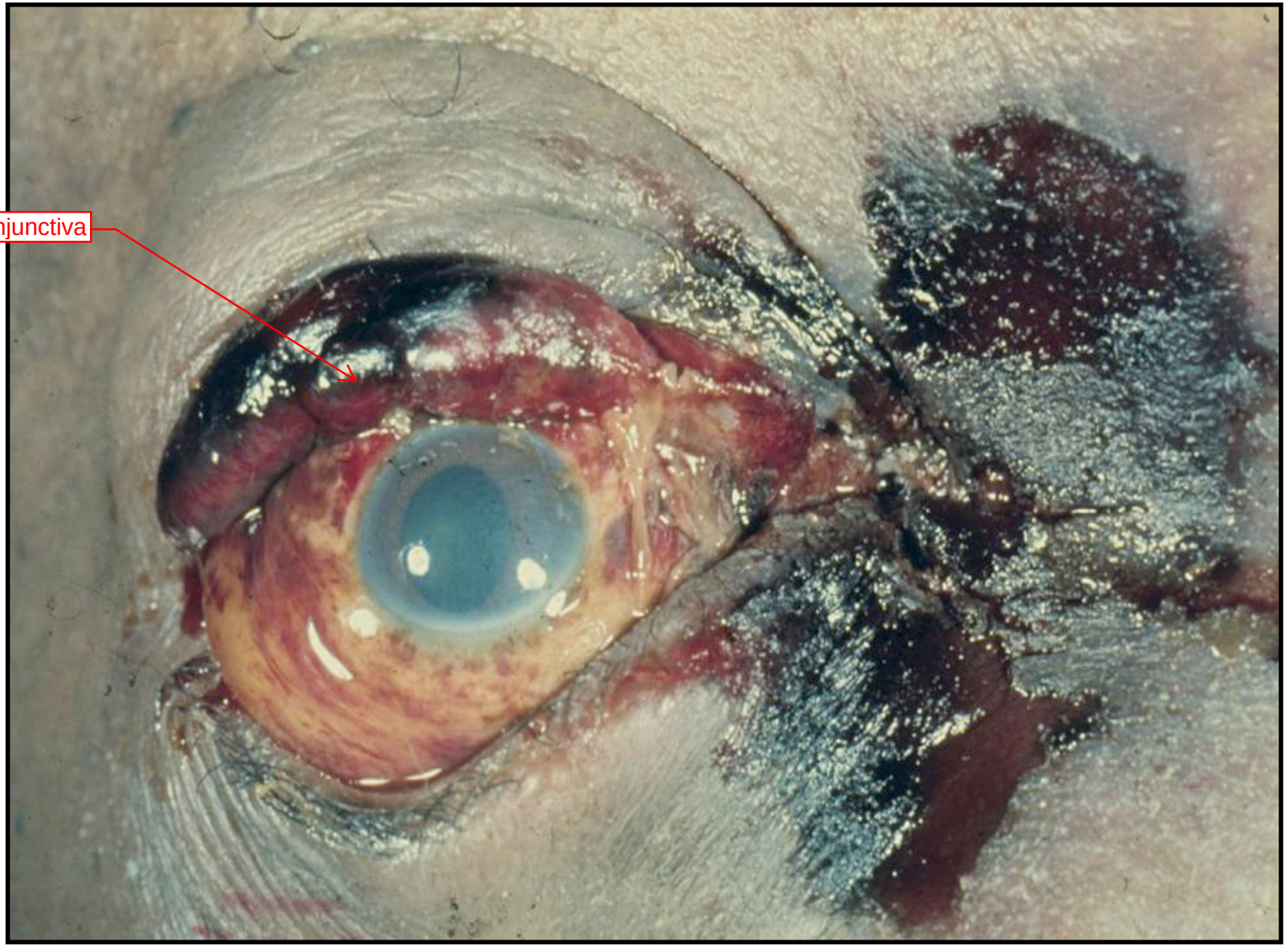
Sarcoidosis

- Noncaseating (non-necrotizing) granulomatous disease
- Affects many organs
- Unknown etiology
- Sub-acute presentation in people <30 years old; often self-limited with resolution within 2 years
- Chronic form in older people; frequent hilar adenopathy and lung involvement

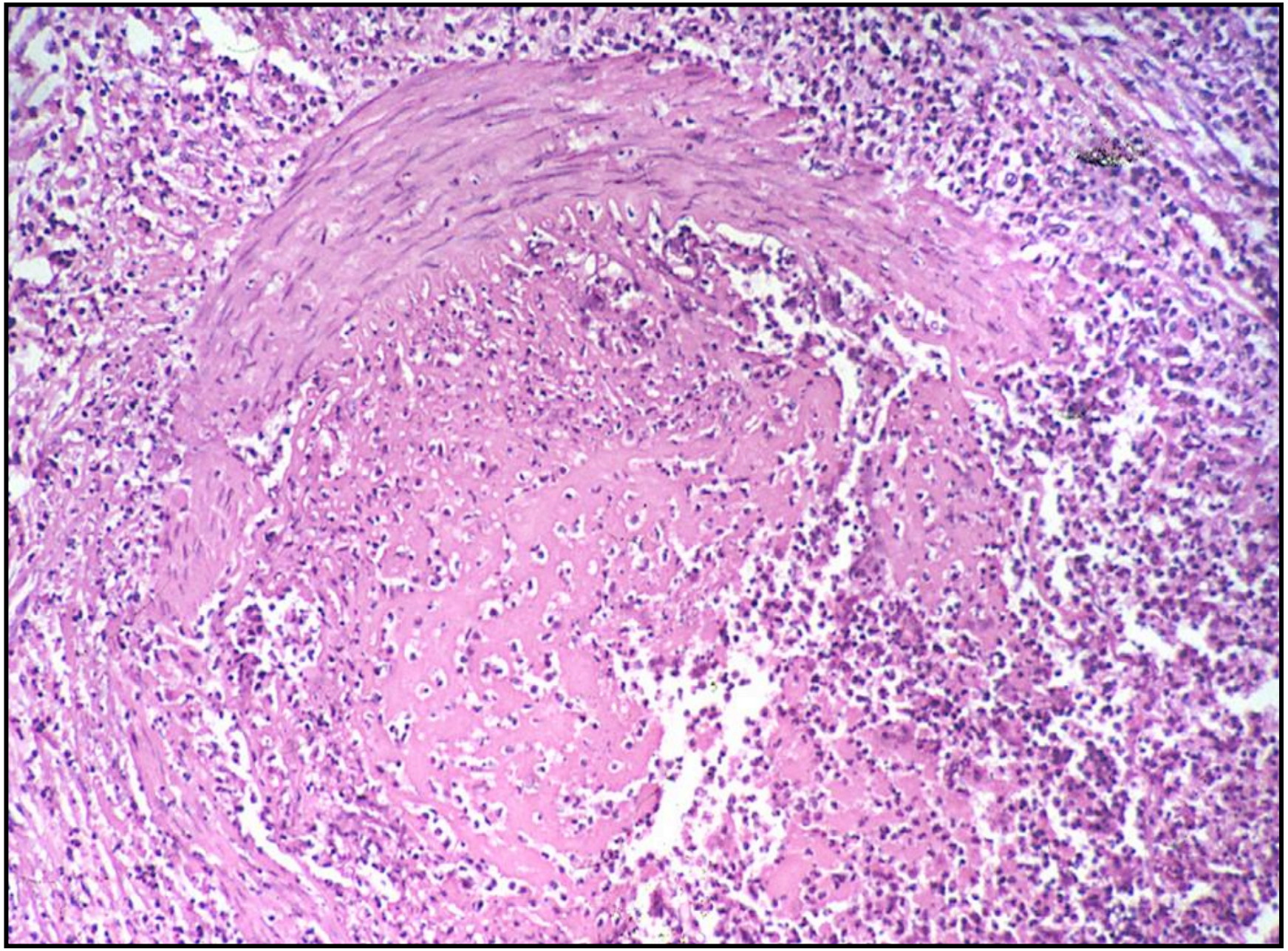
Case Study

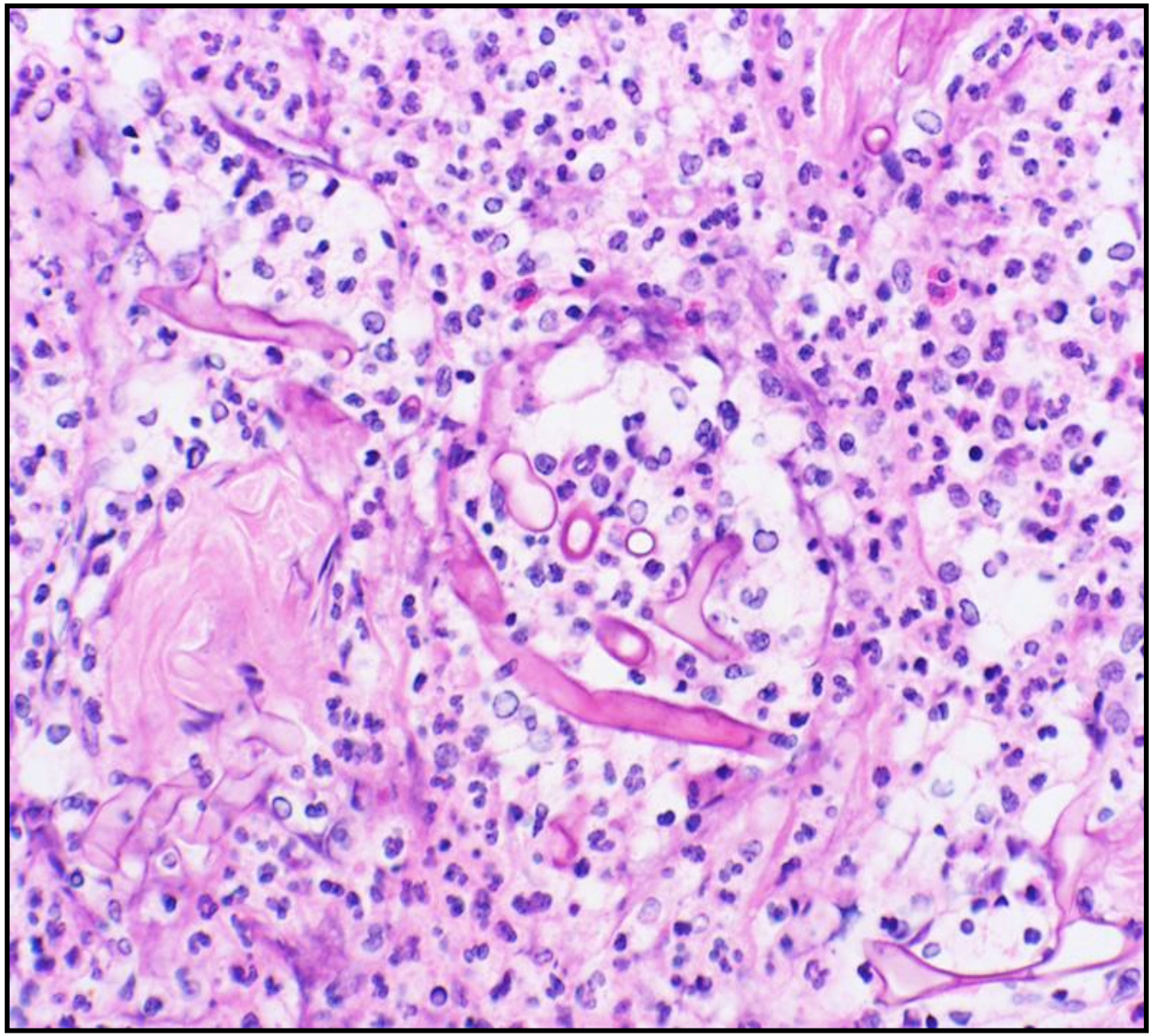
- 32-year-old black man with diabetes mellitus for 18 years
- 12/27/84 developed retro-orbital headaches and nasal stuffiness and over the next two days swelling and proptosis of the eye with complete visual loss
- Diabetic ketoacidosis on admission to hospital
- Orbital exenteration

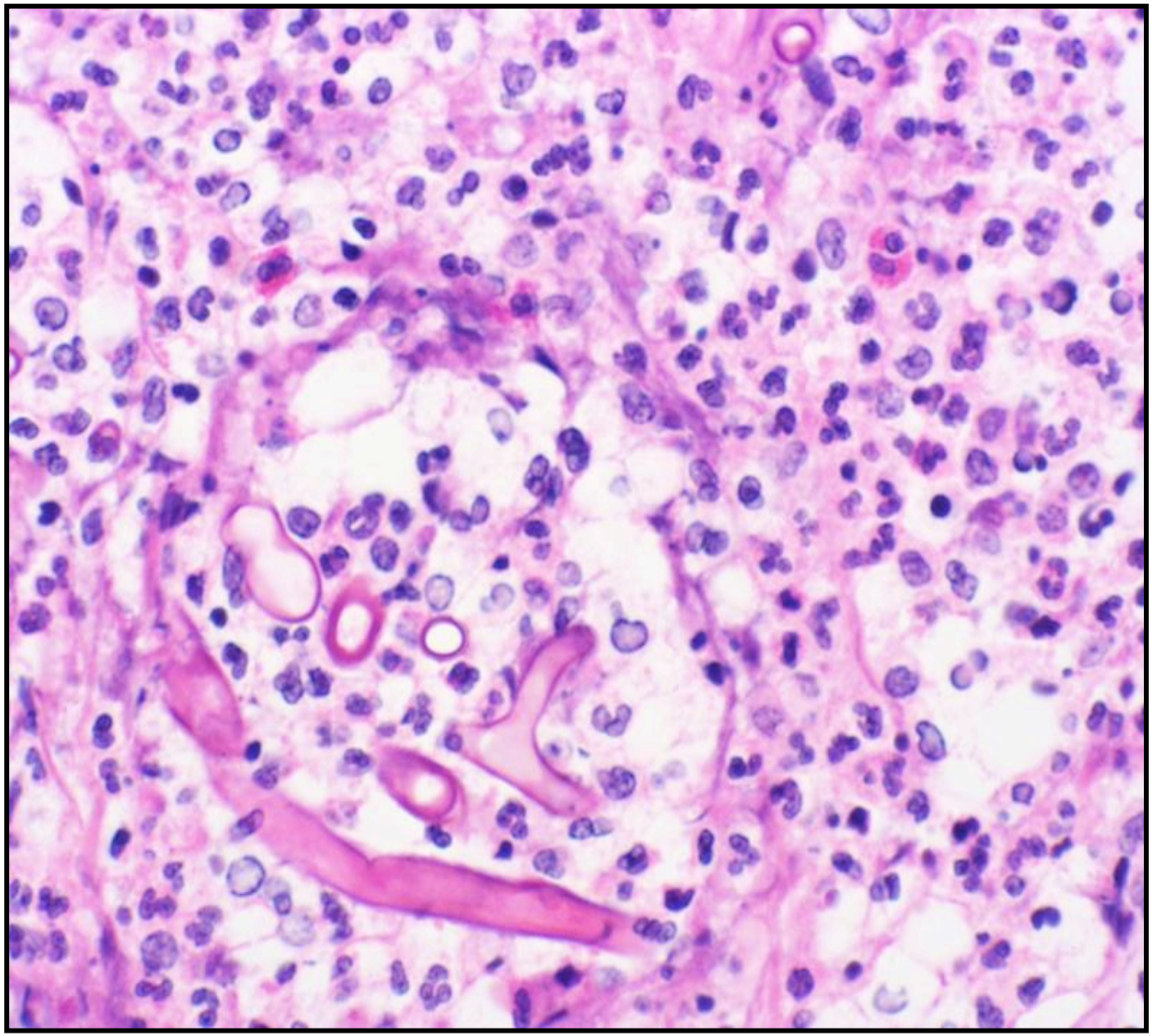



swollen conjunctiva

A blood vessel dissolved due to inflammation, angioinvasive fungus and septic thrombus Led to the necrotic tissue







Predominantly cells with irregular nuclei....

Predominant Inflammatory Cell Type?

A) Lymphocytes

B) Eosinophils

C) Neutrophils

D) Macrophages

E) Multinucleated giant cells

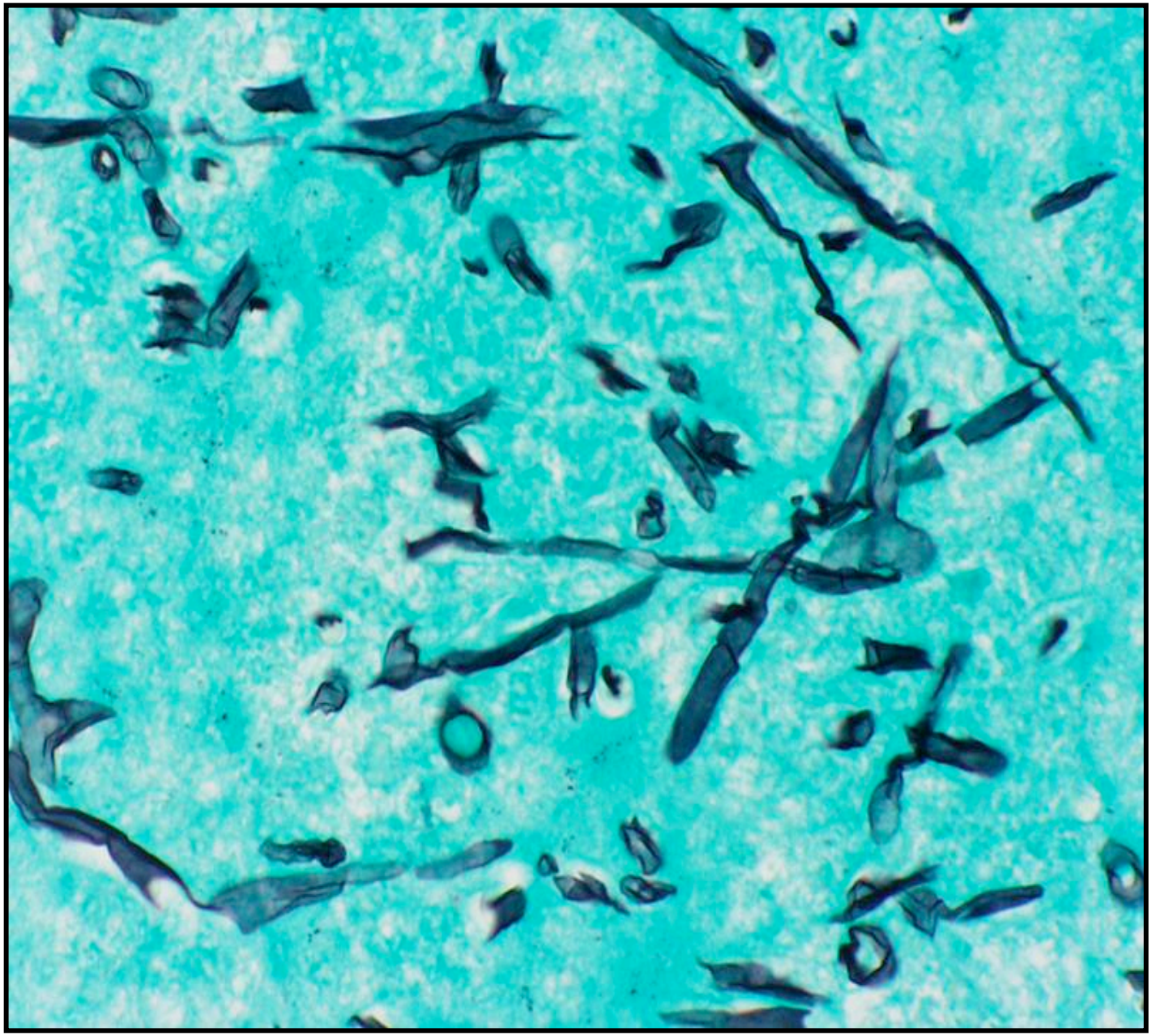
Type of Inflammatory Response?

A) Acute

B) Chronic

C) Granulomatous

Fungal infection, stain makes the fungus turn black



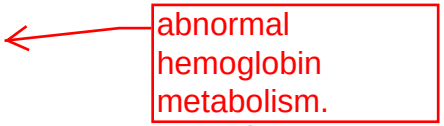
"We're in the South, people tend to mold more than up North."…….Sorry this also happens to diabetics who live in New York

Orbital Mucormycosis

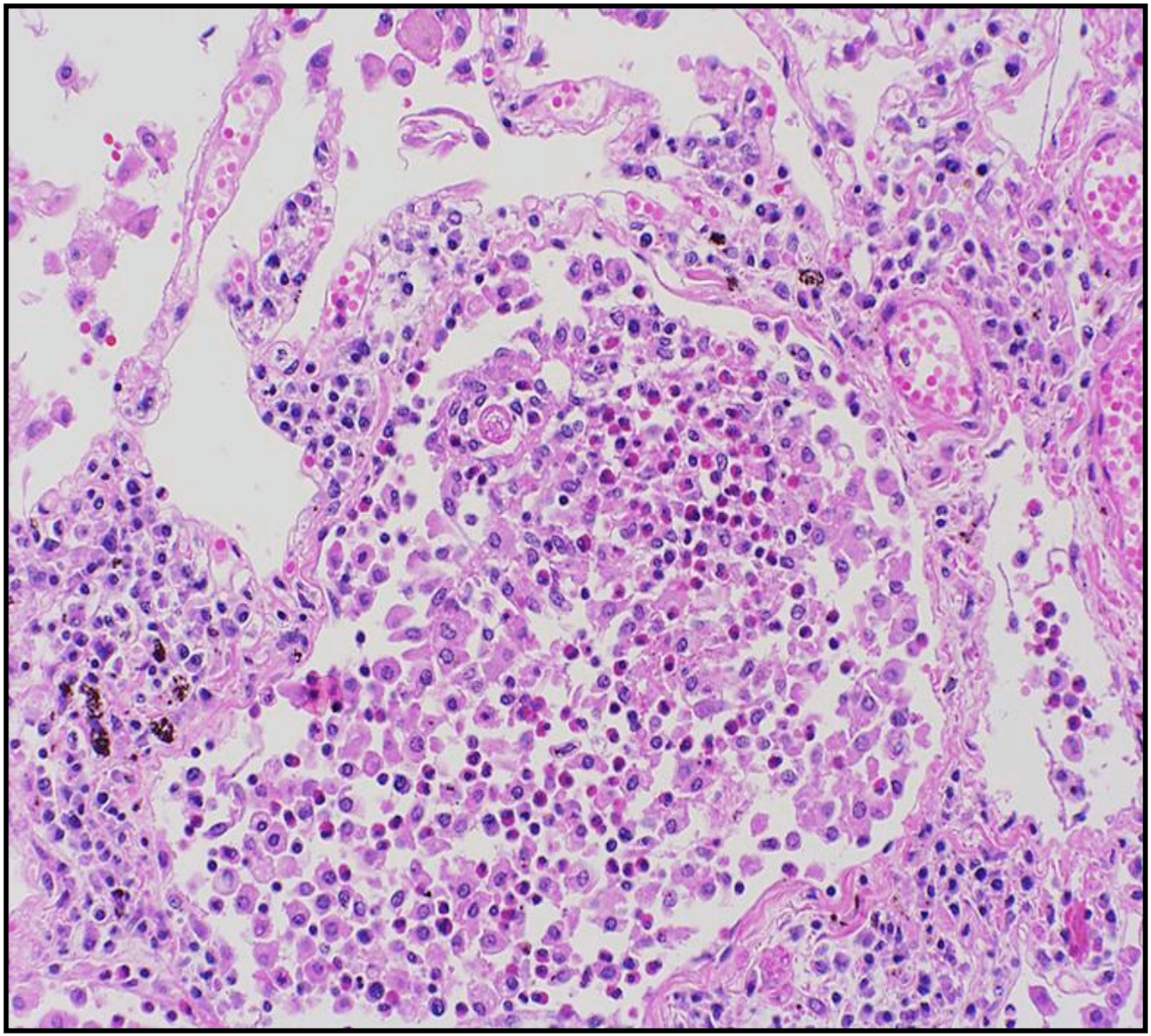
- Predisposing factors
  - Diabetic ketoacidosis
  - Leukemia

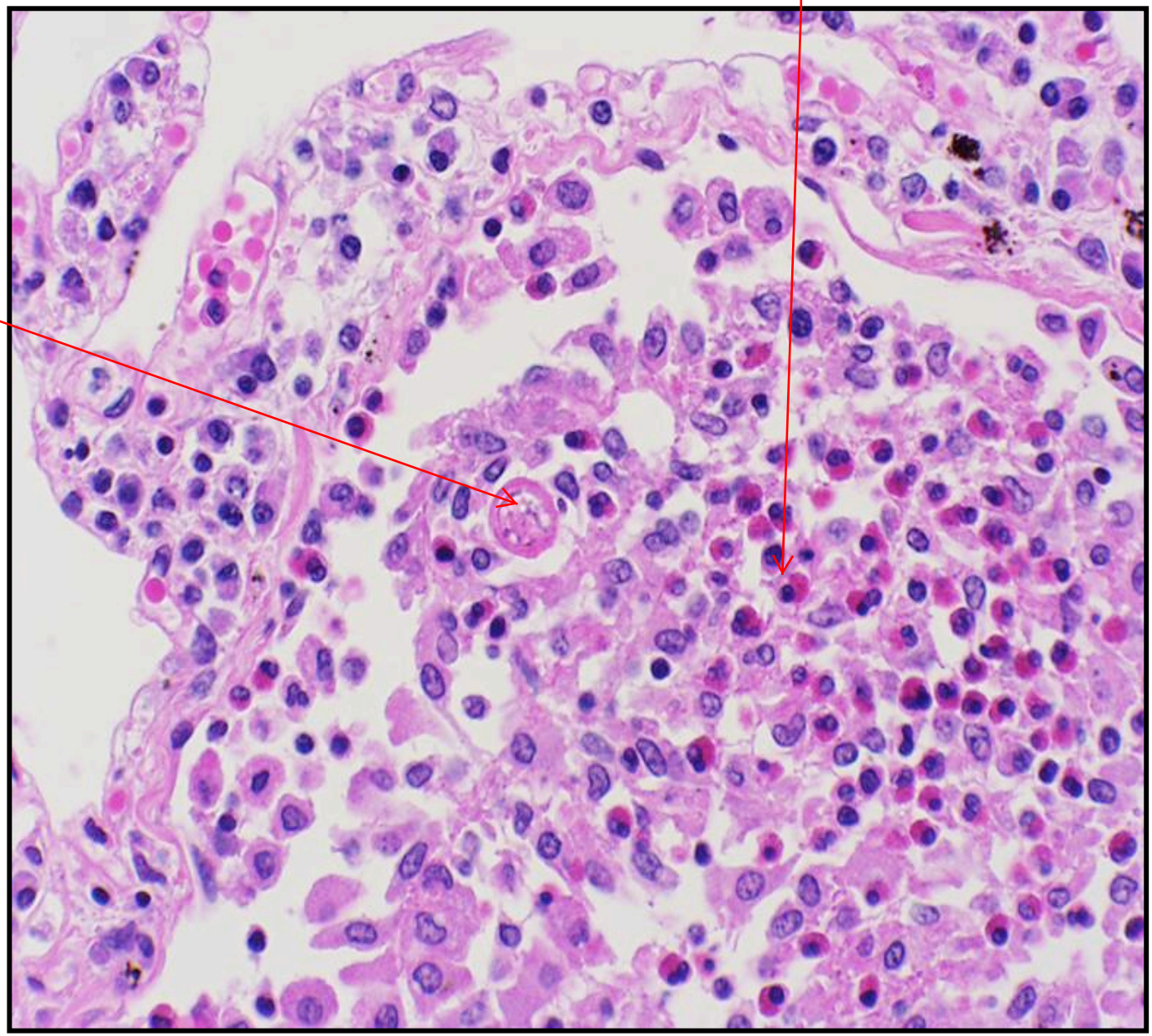
Case Study

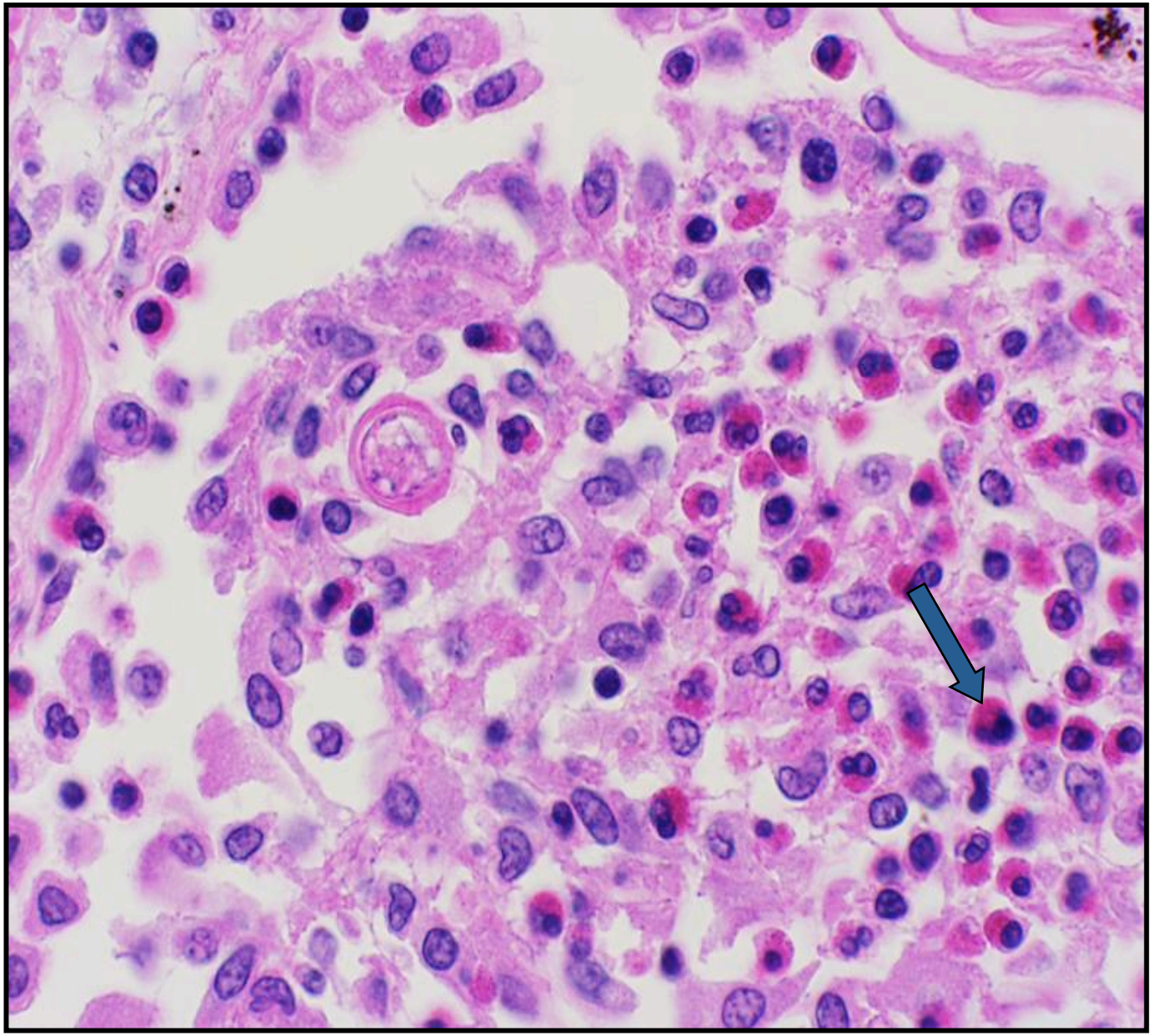
- 60-year-old man
- History of porphyria
- On 40 mg/day prednisone for several months
- Admitted to hospital for worsening mental status
- Elevated blood eosinophil count noted during admission



Section of the lung, showing pneumonia. Alveolar space is filled in.




alveolus filled with inflammation
Actually a cross section of a worm.



Inflammatory Cell Type?

A) Lymphocyte

B) Eosinophil

C) Neutrophil

D) Epithelioid cell

E) Multinucleated giant cell

Cause of the Inflammation?

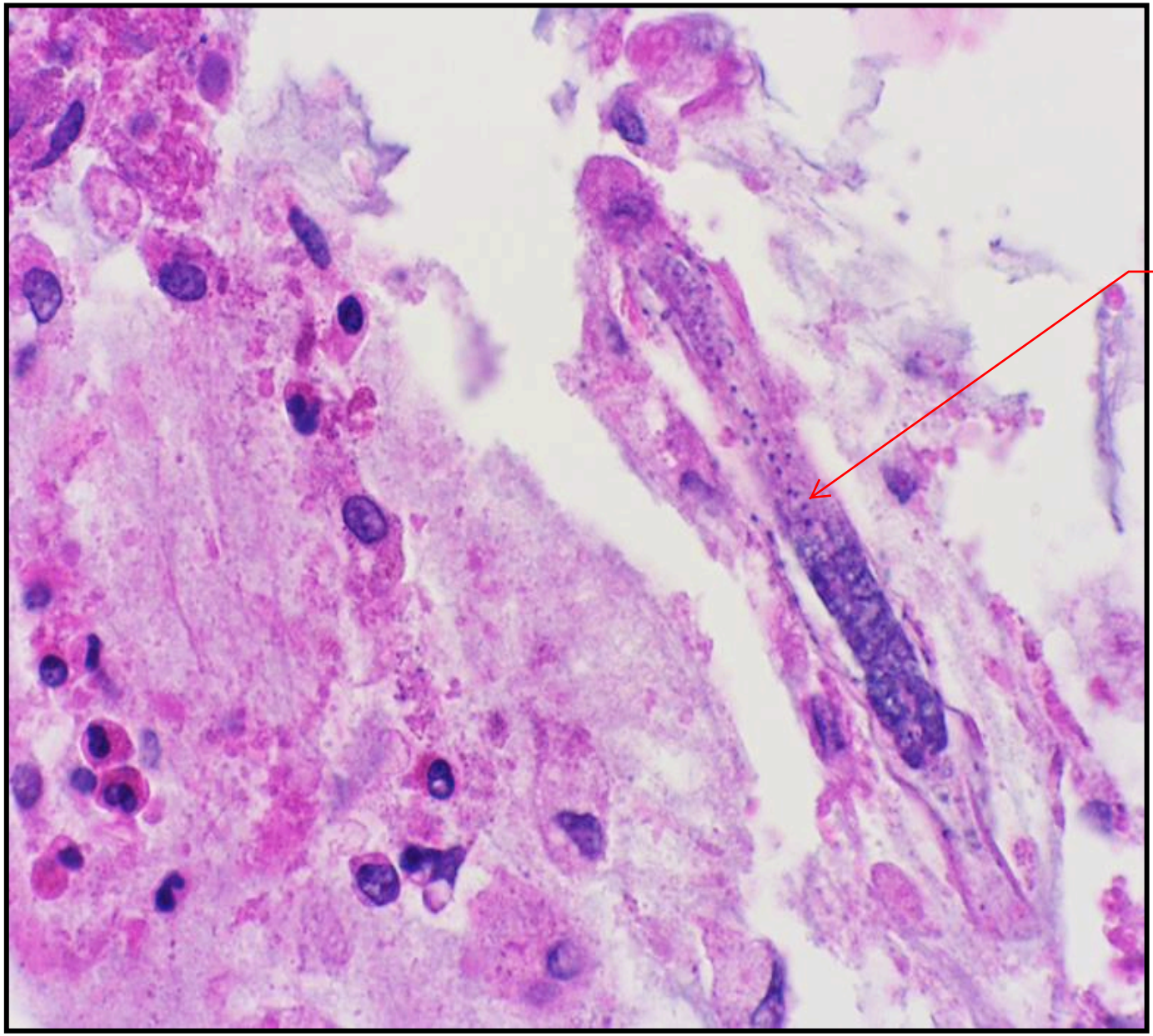
A) Parasite

B) Allergy (IgE)

C) Foreign body (suture)

D) A or B

In this case, the real answer is A. But, you'd have to recognize the parasite in the section.


larva cut
longitudinally

Strongyloides stercoralis

- Strongyloidiasis
  - Worldwide parasitic infection
  - Approximately 75 million people affected
  - Most common in areas with high temperature, high humidity, and poor hygiene
  - More common in elderly
  - Asymptomatic in about 50% of cases
- Individuals with latent or subclinical infection may develop disseminated infection if they become immunocompromised

He just read this slide....

Chemical Mediators of Inflammation

- General principles of chemical mediators
  - May be derived from plasma or cells
  - Most bind to specific receptors on target cells
  - Can stimulate release of mediators by target cells, which may amplify or ameliorate the inflammatory response
  - May act on one or a few target cells, have widespread targets, and may have differing effects depending on cell and tissue types
  - Usually short-lived
  - Most have the potential to cause harmful effects

A nice figure from Robbins.

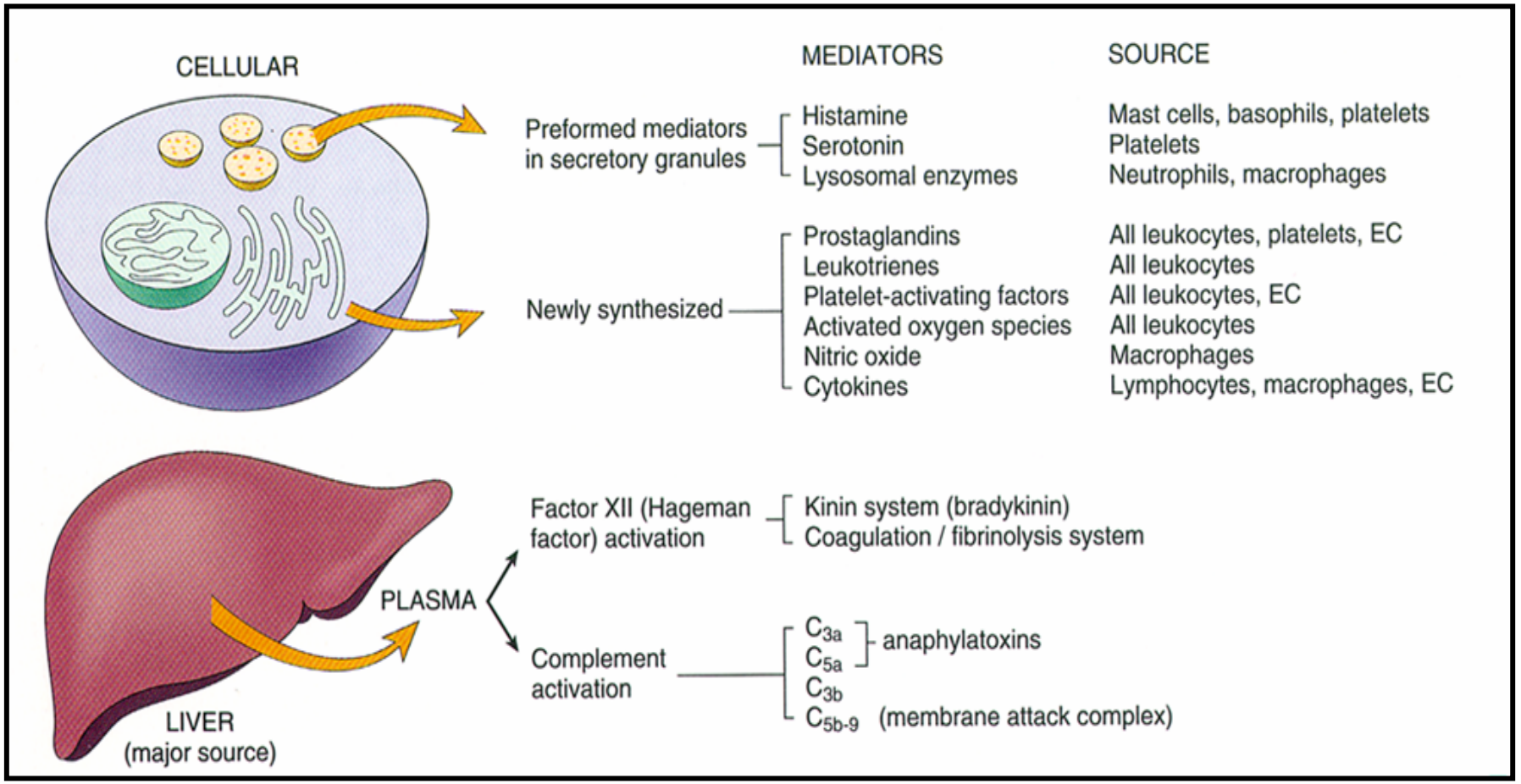


Figure 2-12 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

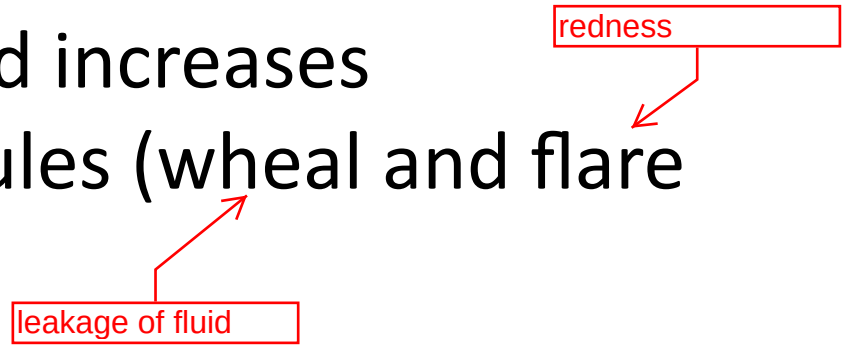
Chemical Mediators of Inflammation

- Vasoactive mediators
  - Histamine
  - Bradykinin
  - Complement (C3a, C5a)
  - Prostaglandins/ leukotrienes
  - Platelet activating factor
  - Nitric oxide
  - Neuropeptides
- Chemotactic factors
  - Complement (C5a)
  - Leukotriene (B4)
  - Platelet activating factor
  - Cytokines (IL-1, TNF)
  - Chemokines
  - Nitric oxide

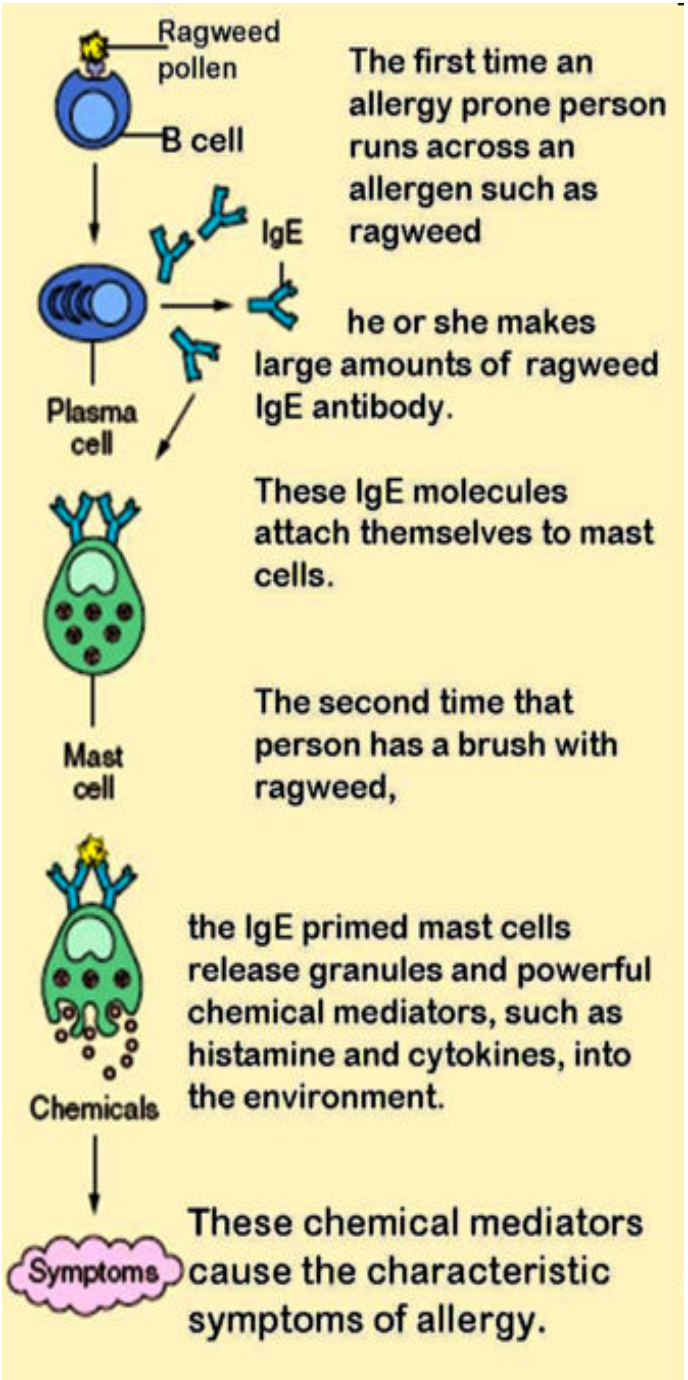
Notice complement, PAF, and NO do both.

Histamine

- Mast cells (also basophils and platelets)
- Release mechanisms
  - Binding of antigen (allergen) to IgE on mast cells releases histamine-containing granules
  - Release by nonimmune mechanisms such as cold, trauma, or other chemical mediators
  - Release by other mediators
- Dilates arterioles and increases permeability of venules (wheal and flare reaction)



A diagram of mast cell response to allergies, from Wikipedia



http://en.wikipedia.org/wiki/File:Mast_cells.jpg

Complement

- Proteins found in greatest concentration in the plasma
- Require activation
- Increase vascular permeability and cause vasodilation
  - Mainly by releasing histamine from mast cells
- Increase leukocyte adhesion, chemotaxis, and activation
- C3b attaches to bacterial wall and enhances phagocytosis by neutrophils & macrophages

Bradykinin

Another major chemotactic factor

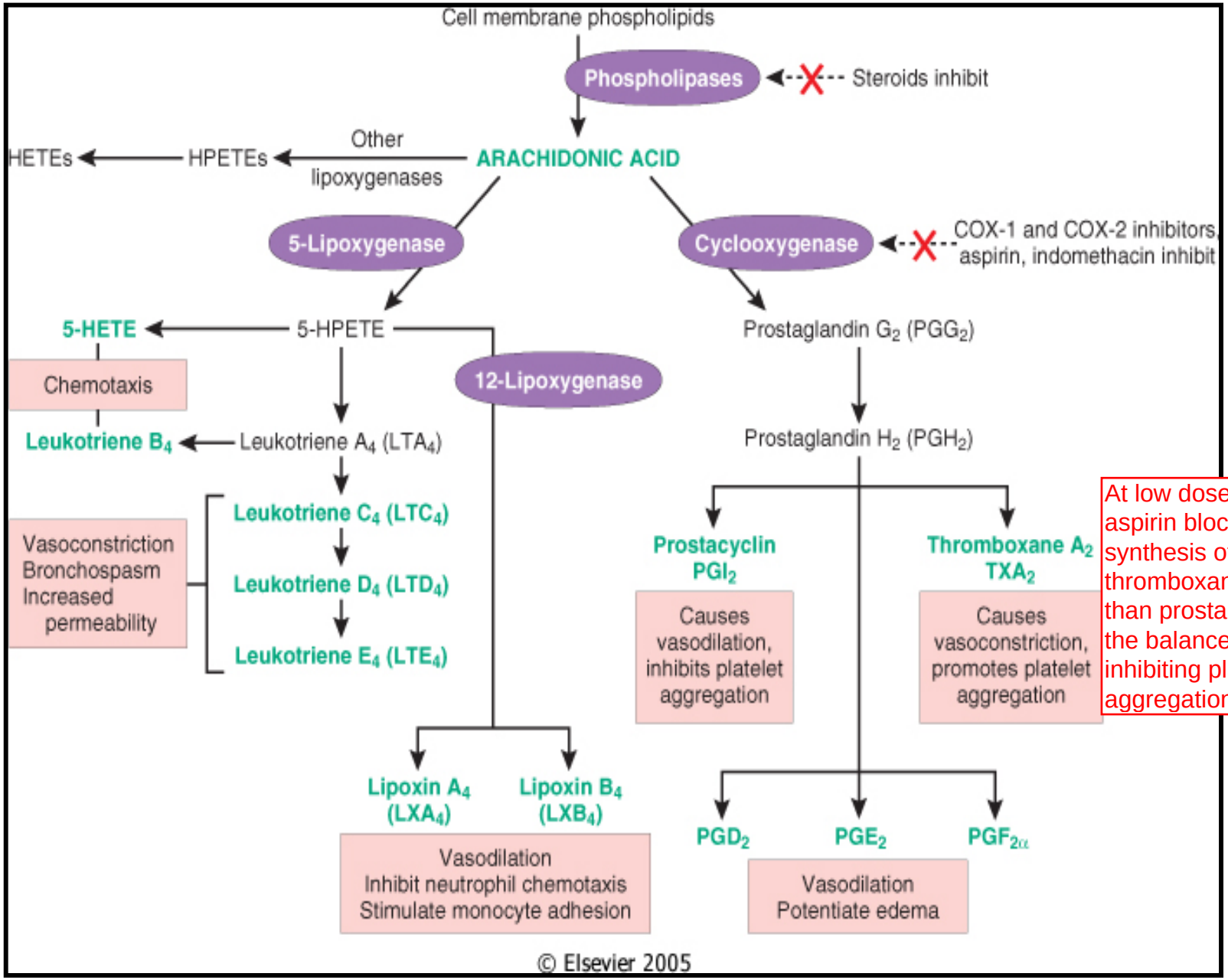
- Small peptide released from plasma precursors
- Increases vascular permeability
- Dilates blood vessels
- Causes pain
- Rapid inactivation

Have to keep synthesizing bradykinin to get the pain response because it is broken down so quickly

Arachidonic Acid Metabolites

- Prostaglandins
  - Vasodilators: prostacyclin (PGI_2), PGE_1, PGE_2, PGD_2
  - Vasoconstrictors: thromboxane A_2
  - Pain (PGE_2 makes tissue hypersensitive to bradykinin)
  - Fever (PGE_2)
  - Production blocked by steroids and nonsteroidal anti-inflammatory agents (NSAIDs)
- Leukotrienes
  - Increase vascular permeability: leukotrienes C_4, D_4, E_4
  - Vasoconstriction: leukotrienes C_4, D_4, E_4
  - Leukocyte adhesion & chemotaxis: leukotriene B_4, HETE, lipoxins
  - Production blocked by steroids but <u>not</u> conventional NSAIDs

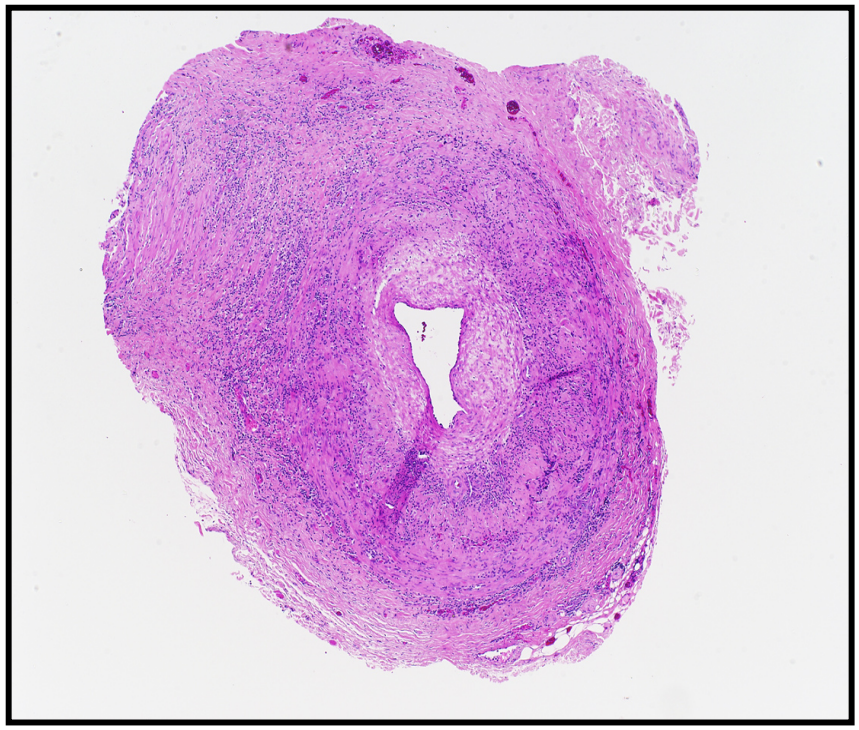
Another important figure from Robbins to get comfortable with....



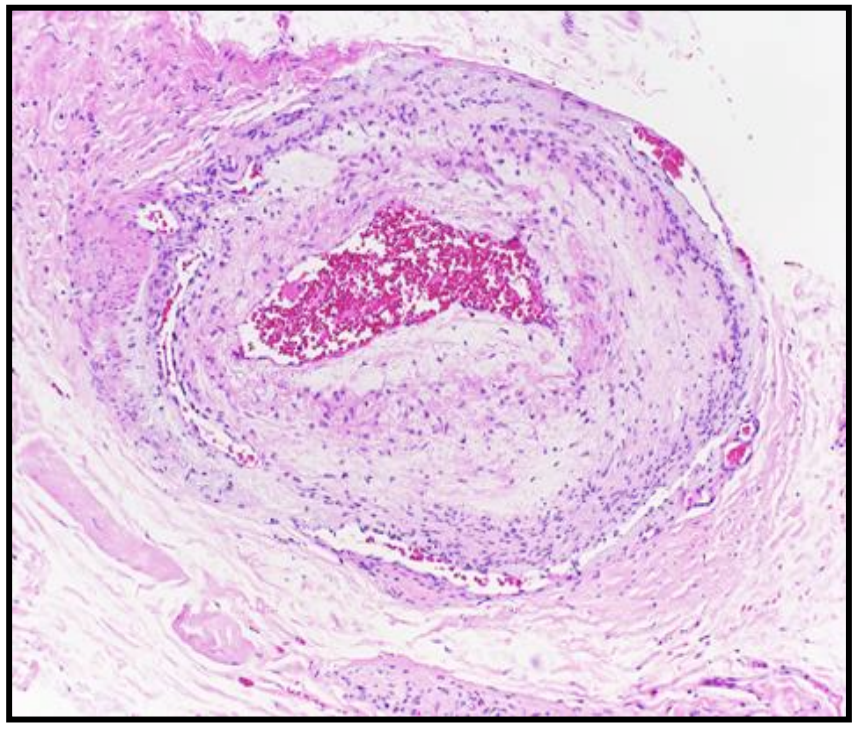
At low doses, taking aspirin blocks the synthesis of thromboxane more so than prostacyclin. Shifts the balance toward inhibiting platelet aggregation

Figure 2-16 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Steroid Effect – Temporal Arteritis



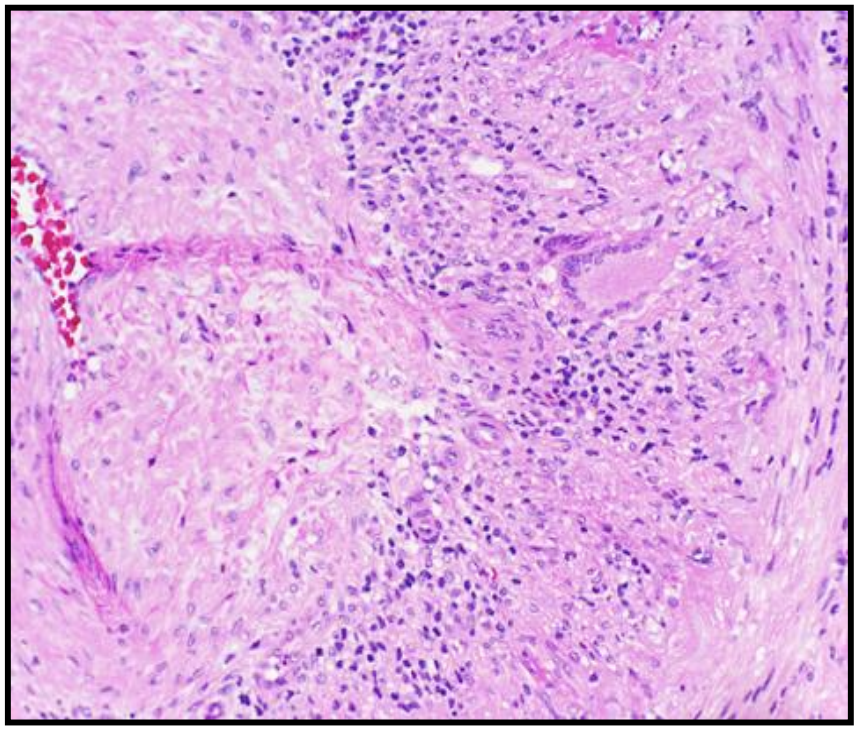
Untreated



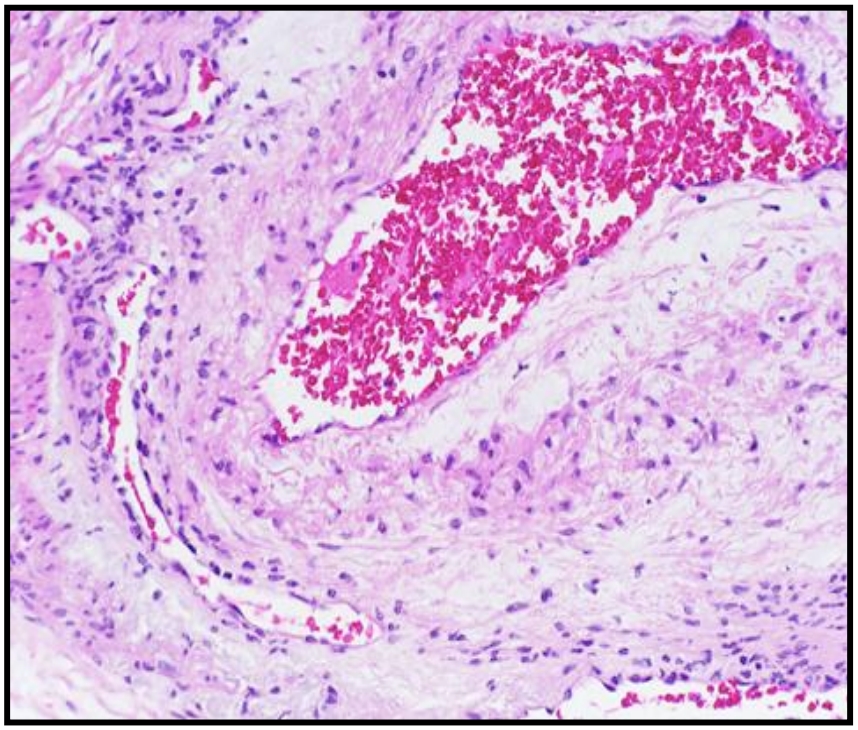
60 mg prednisone PO x 3 days

Patients will come in with headaches and problems with their vision. The blue shows the inflammatory cells. Significantly reduced in only three days

Steroid Effect – Temporal Arteritis

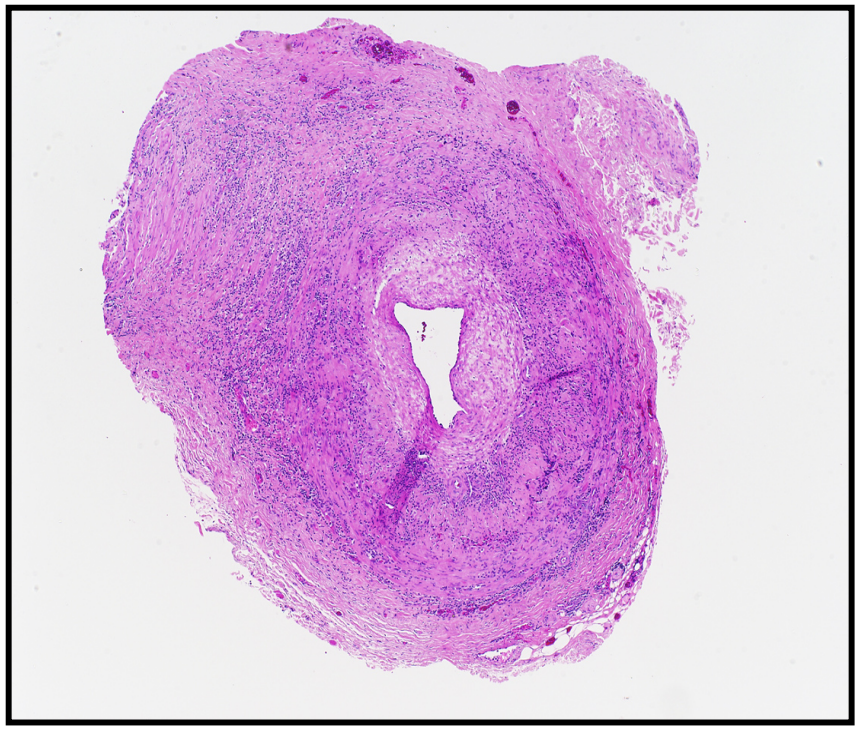


Untreated



60 mg prednisone PO x 3 days

Steroid Effect – Temporal Arteritis



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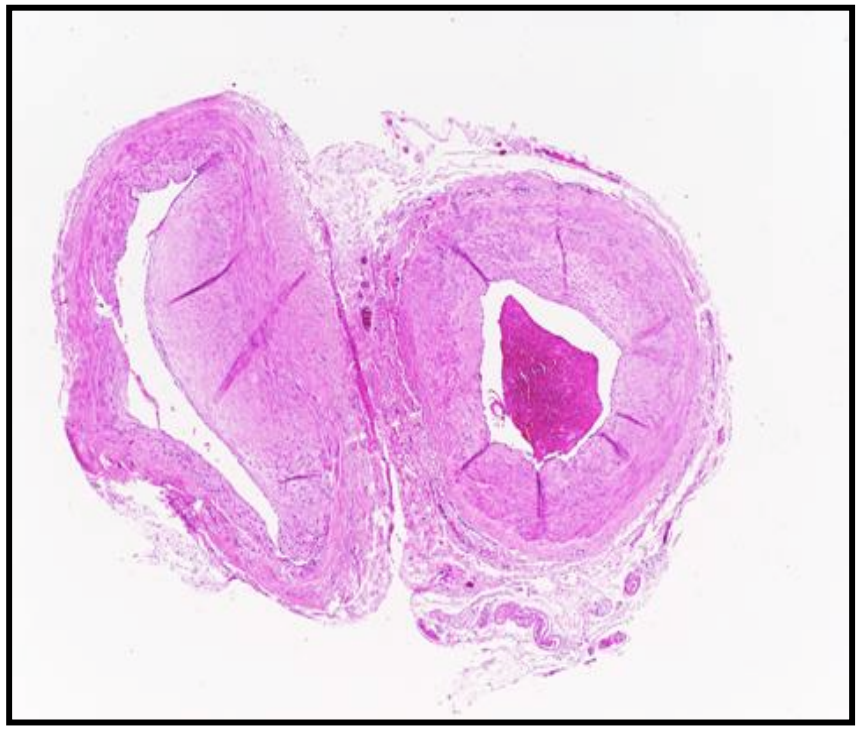
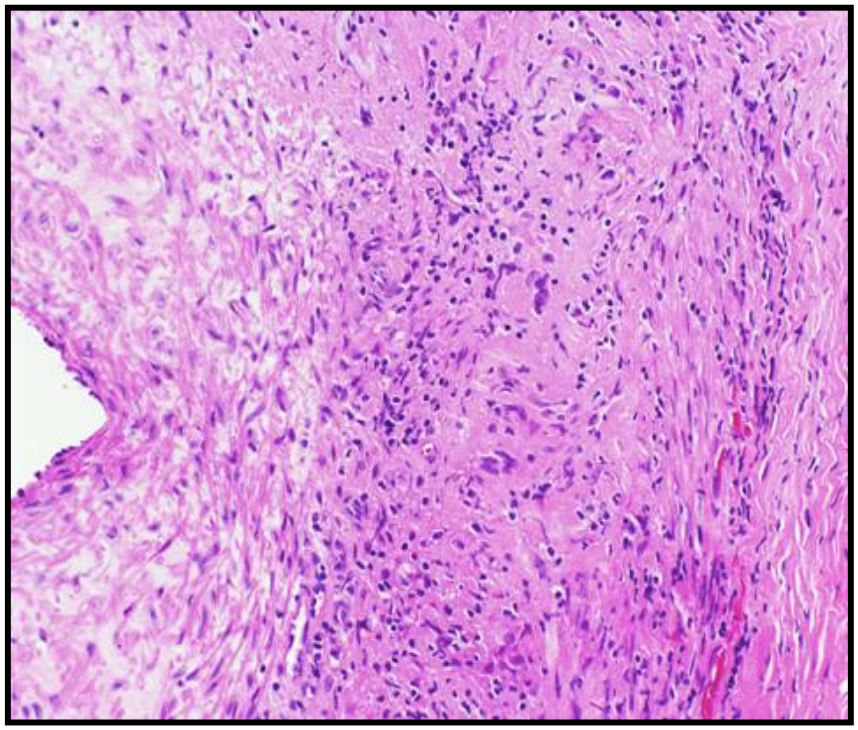


250 mg Solu-Medrol IV x 6 days

Steroids, given at the right dose, are extremely effective and quick acting anti-inflammatory agents.

Steroid Effect – Temporal Arteritis



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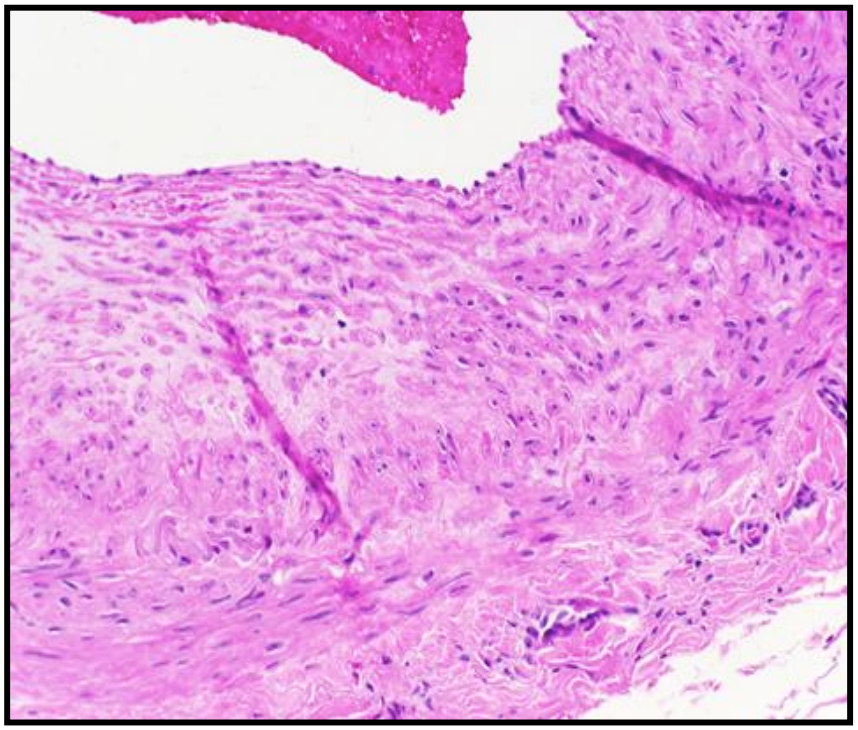


250 mg Solu-Medrol IV x 6 days

Platelet Activating Factor

- Subclass of phospholipids
- Synthesized by stimulated platelets, leukocytes, endothelium
- Inflammatory effects
  - Stimulates platelet aggregation
  - Vasoconstriction and bronchoconstriction
  - Vasodilation and increased venular permeability
  - Increased leukocyte adhesion to endothelium, chemotaxis, degranulation, and oxidative burst
  - Increases synthesis of arachidonic acid metabolites by leukocytes and other cells

Cytokines

- Proteins produced by many cell types (principally activated lymphocytes & macrophages)
- Modulate the function of other cell types
- Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are the major cytokines that mediate inflammation

Another great figure to get familiar with.

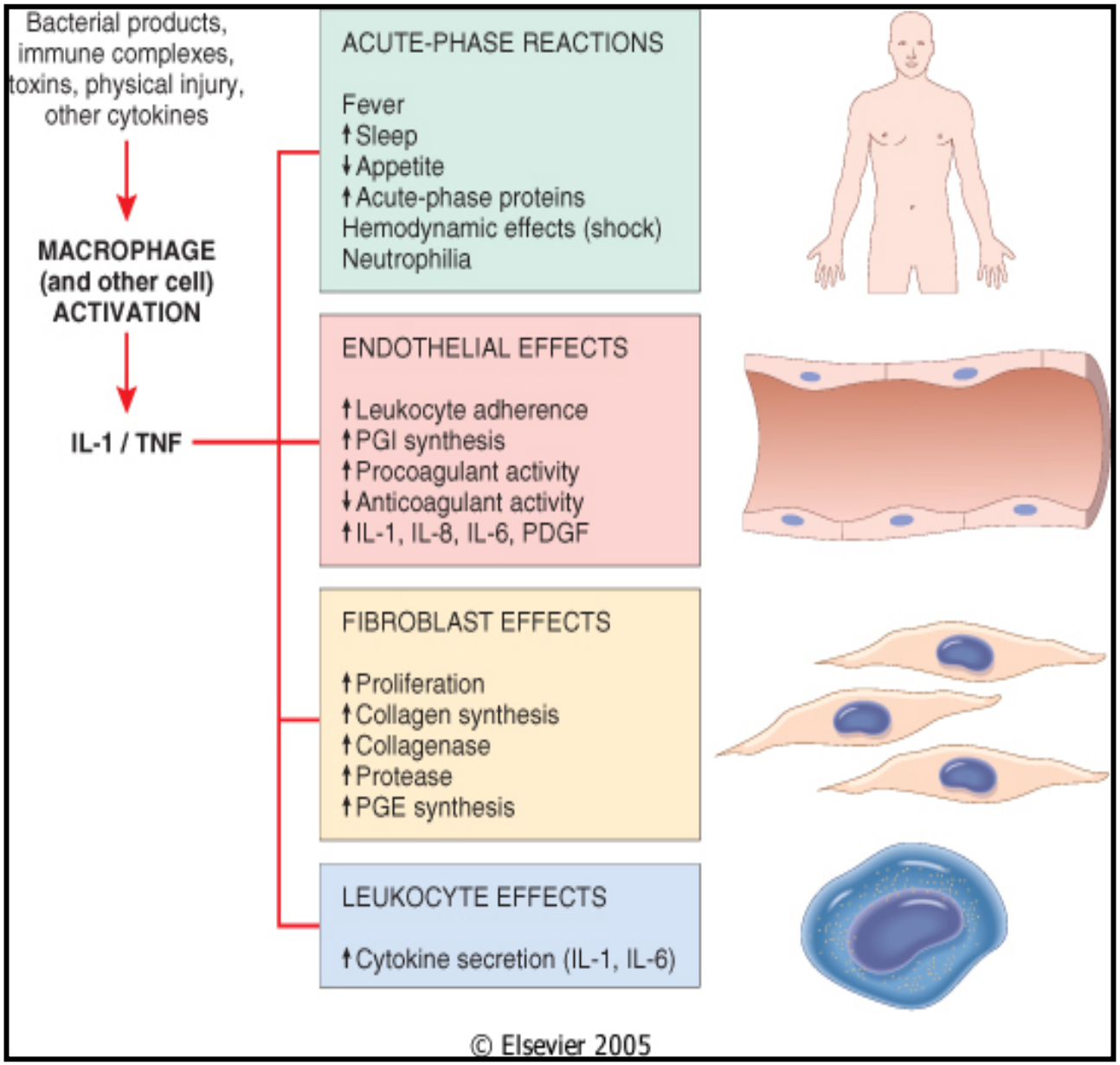


Figure 2-18 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Chemokines

- Small proteins that act primarily as chemoattractants for specific types of leukocytes (approximately 40 known)
- Stimulate leukocyte recruitment in inflammation
- Control the normal migration of cells through tissues (organogenesis and maintenance of tissue organization)
- Examples: IL-8, eotaxin, lymphotactin

NO is responsible for reducing adhesion, causing vasodilation, and inducing cytotoxicity via iNOS

Nitric Oxide

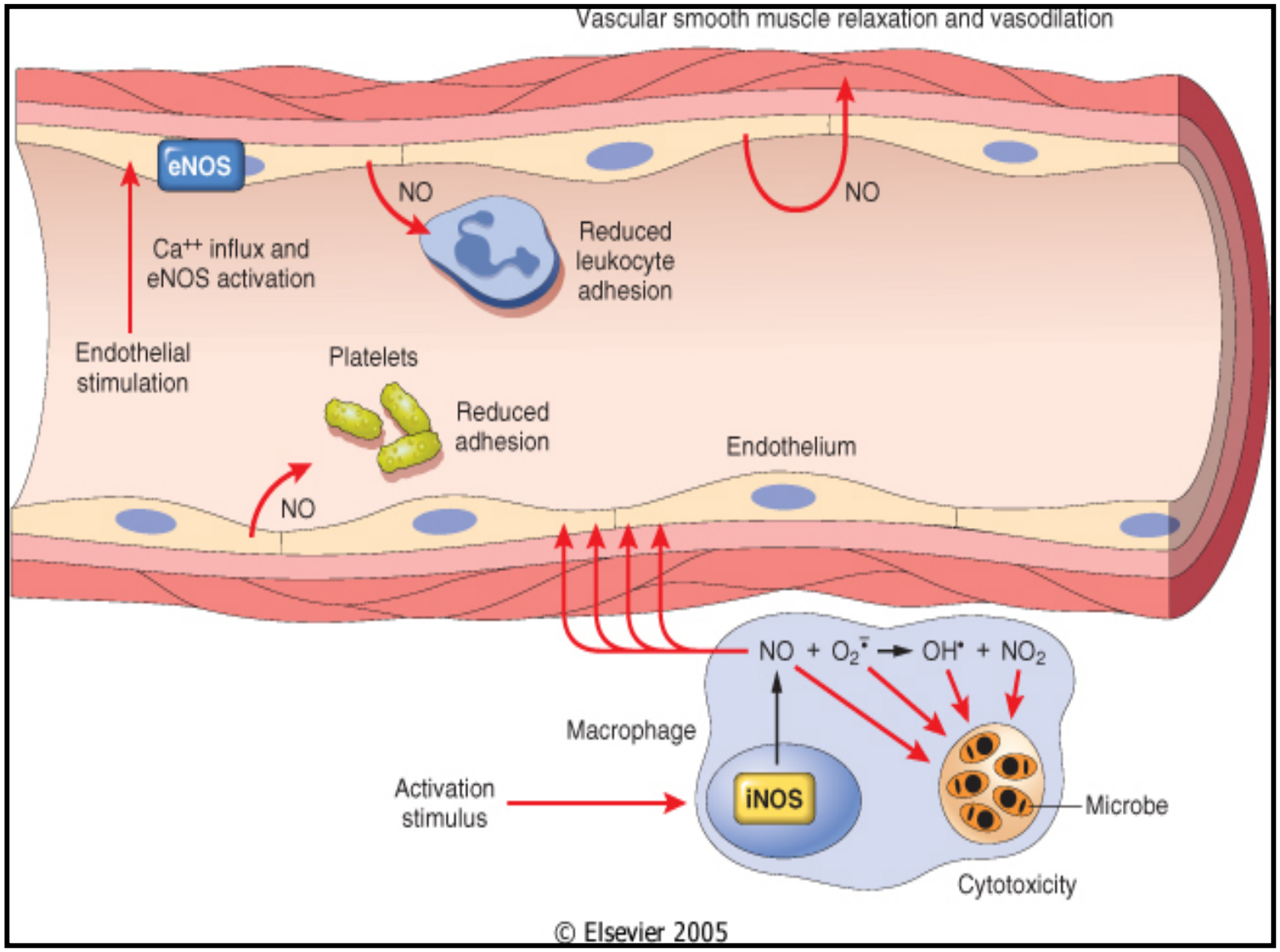


Figure 2-19 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Neuropeptides

- Substance P and neurokinin A
- Produced in central and peripheral nervous systems
  - Substance P nerve fibers prominent in lung and gastrointestinal tract
- Vasodilation (direct and through mast cell degranulation)
- Increased vascular permeability

Other Mediators

- Neutrophil granules:
  - Cationic proteins increase vascular permeability, immobilize neutrophils, chemotactic for mononuclear phagocytes
  - Neutral proteases generate other mediators and degrade tissue
- Oxygen-Derived Free Radicals:
  - Produced during phagocytosis by neutrophils ("respiratory burst")
  - Tissue damage including endothelium

Summary of Inflammatory Mediators

- Vasodilation
  - Prostaglandins
  - Nitric oxide
  - Histamine
- Increased vascular permeability
  - Histamine, serotonin
  - Complement (C3a, C5a)
  - Bradykinin
  - Leukotrienes (C_4, D_4, E_4)
  - PAF
  - Substance P

Summary of Inflammatory Mediators

- Chemotaxis, leukocyte activation
  - Complement (C5a)
  - Leukotriene B_4
  - Chemokines
  - IL-1, TNF
  - Bacterial products
- Fever
  - Interleukin-1
  - Tumor necrosis factor
  - Prostaglandins

Summary of Inflammatory Mediators

- Pain
  - Prostaglandins
  - Bradykinin
- Tissue Damage
  - Neutrophil and macrophage lysosomal enzymes
  - Oxygen metabolites
  - Nitric oxide

Pretty much read the last few slides. He says that if we know the summarized classification of all these mediators, we will be plenty aware of the mediators of inflammation. Robbins goes into far greater detail. Choose your poison.

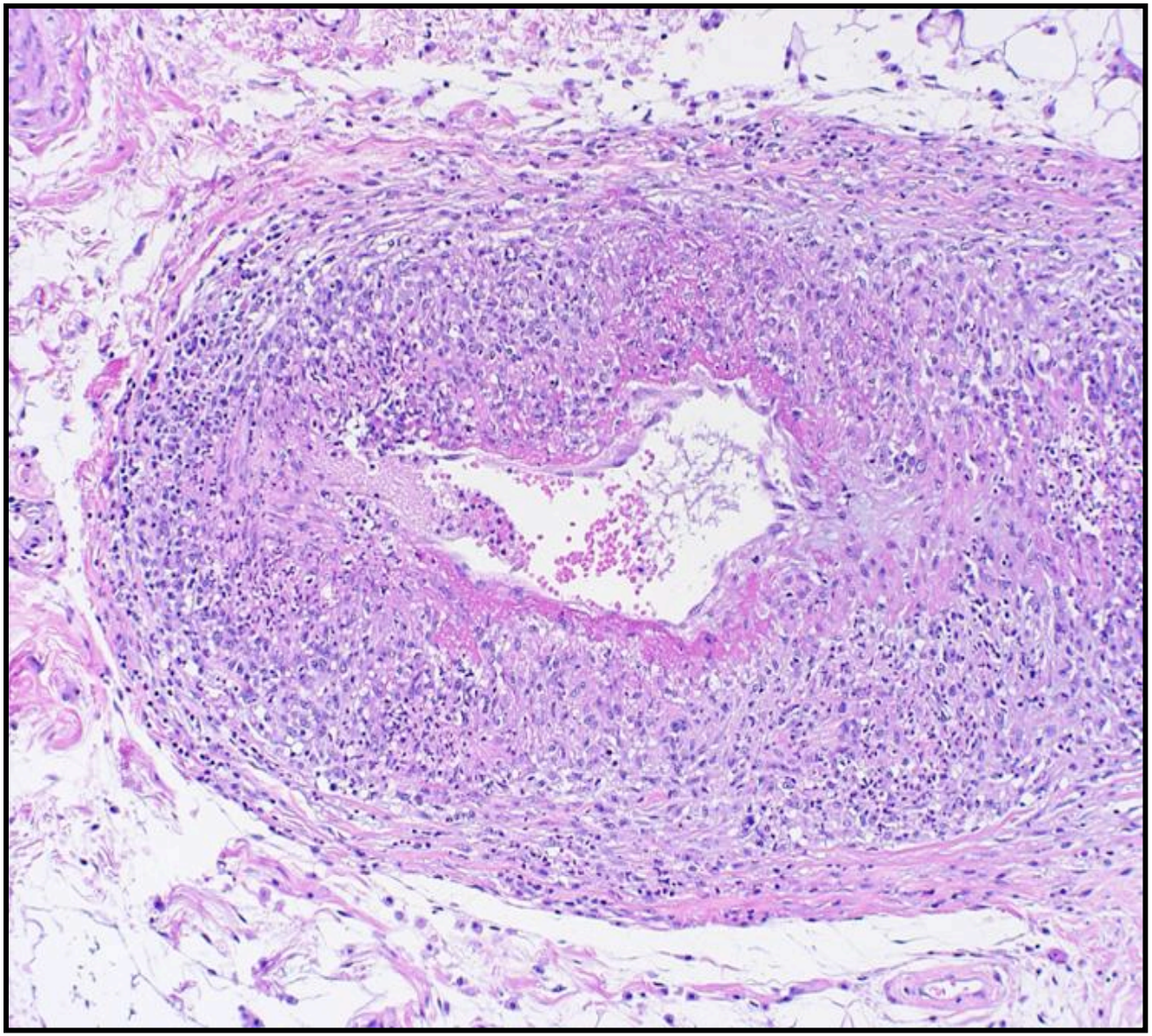
Case Study

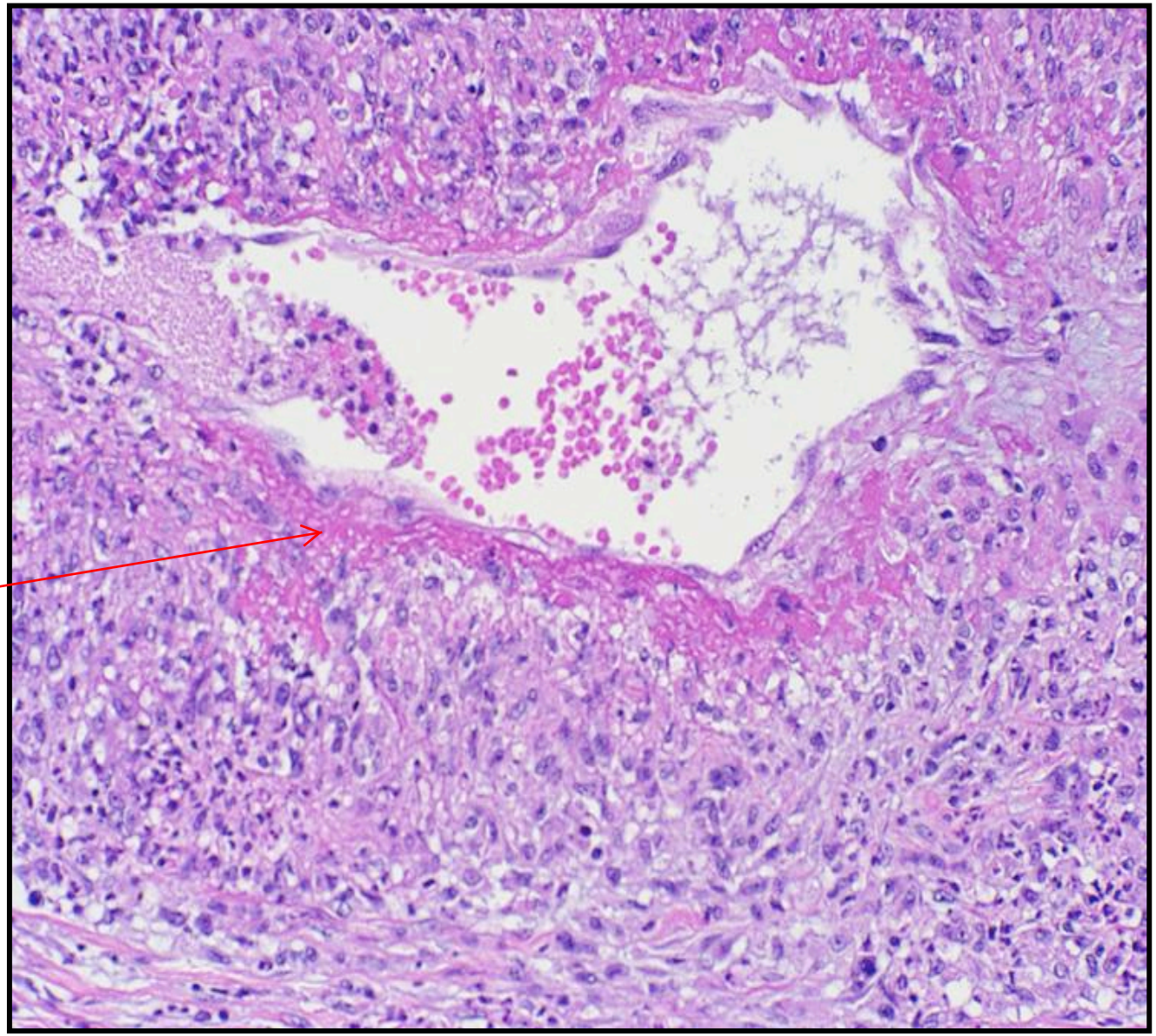
- 71-year-old retired optometrist
- May 2001: Admitted to DRH with 2-week history of nausea without vomiting
- Erosive gastritis treated with Prilosec; discharged after 2 days
- Readmitted to DRH 10 days later because of protracted nausea and 15 lb weight loss
- Five week admission complicated by acute renal failure and pulmonary hemorrhage

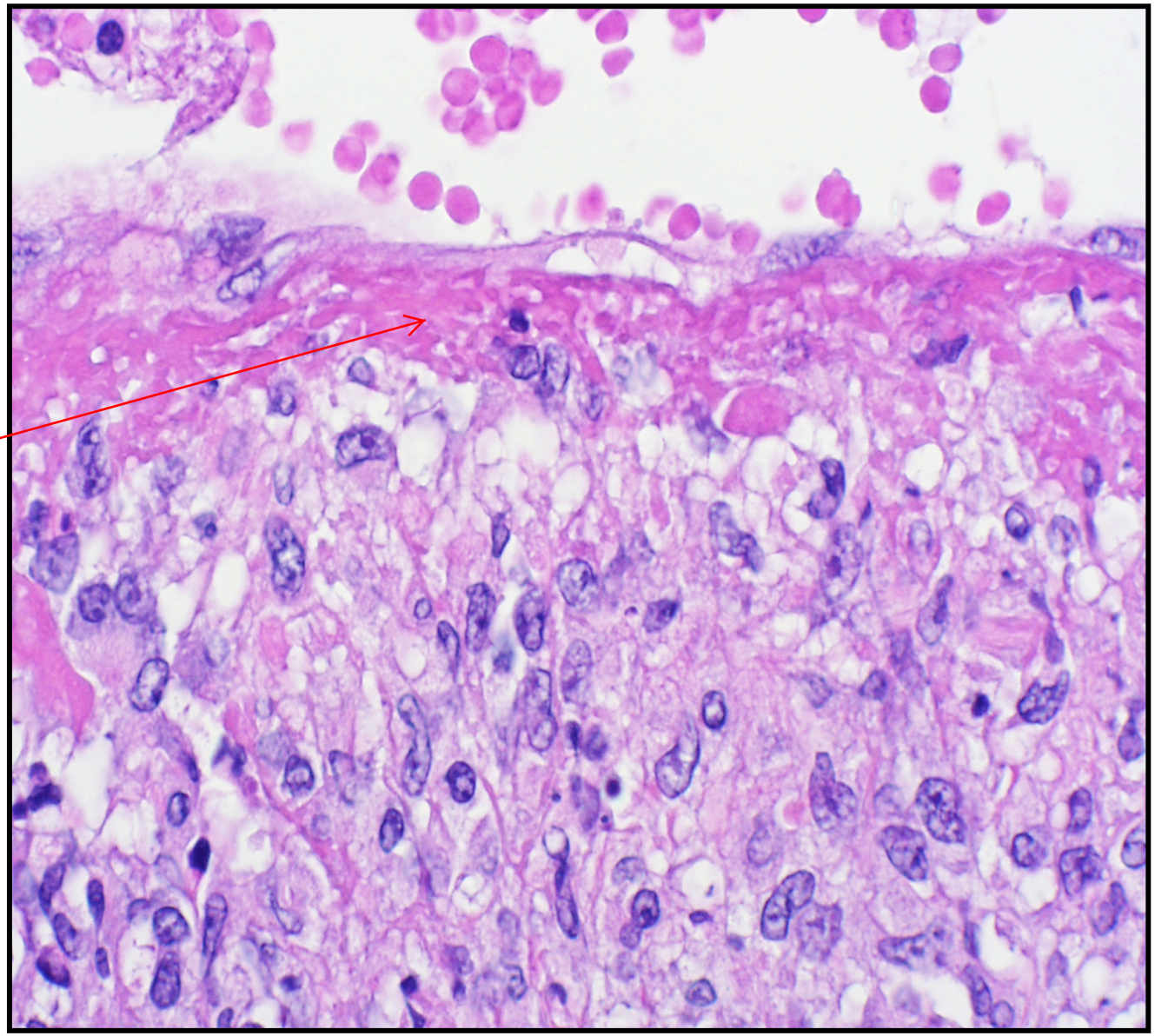
Case Study

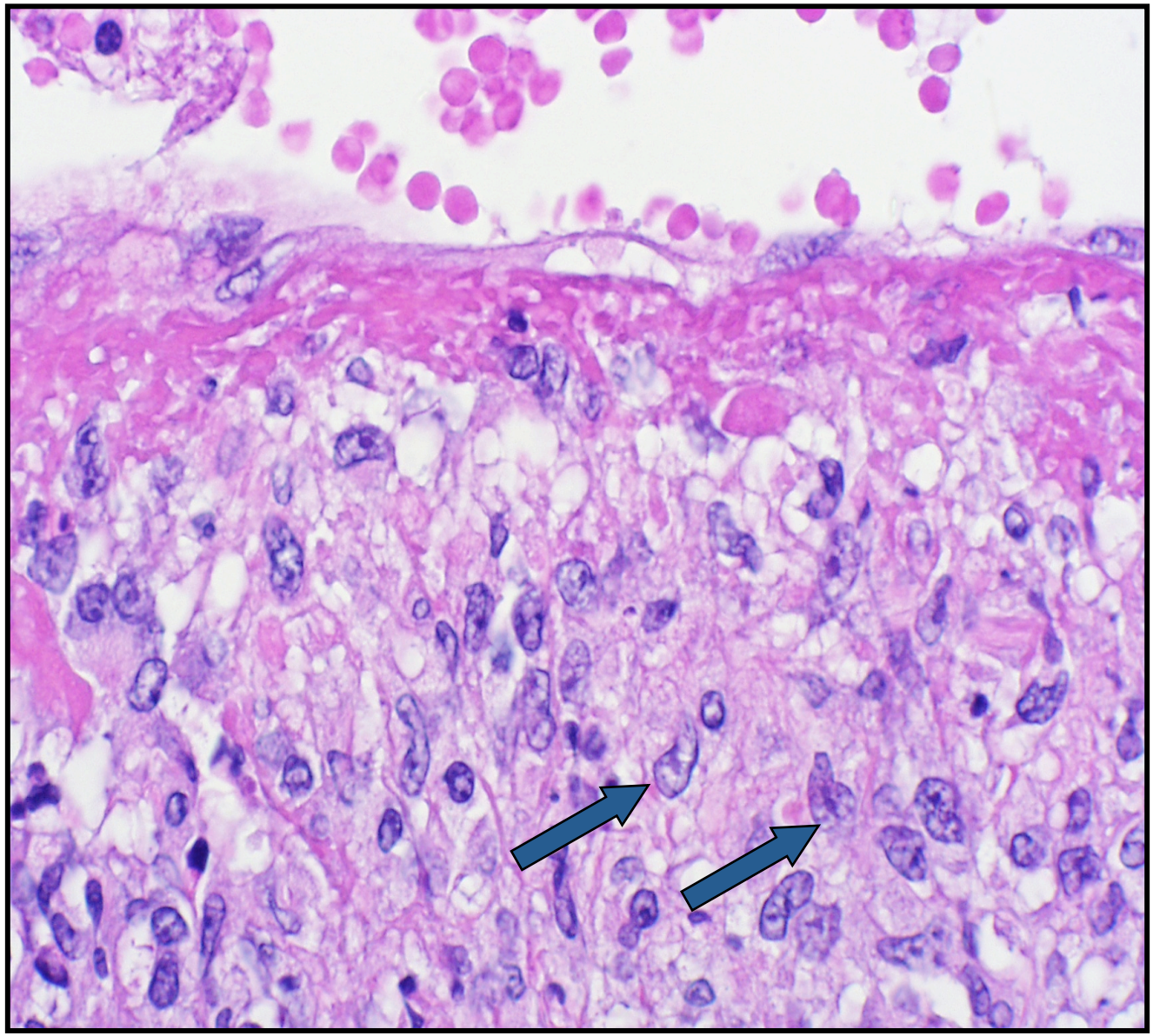
- Discharged to nursing facility
- Increasingly debilitated over next 3 months
- Admitted for 3 days and received comfort care
- Died approximately 16 months after developing first episode of nausea

Disease effected blood vessels in multiple organ systems




pink material is fibrin. Blood vessel is seen to be inflamed


Fibrinoid necrosis - you see the pink fibrin as well as necrosis of the blood vessels



Inflammatory Cell Type?

A) Lymphocyte

B) Eosinophil

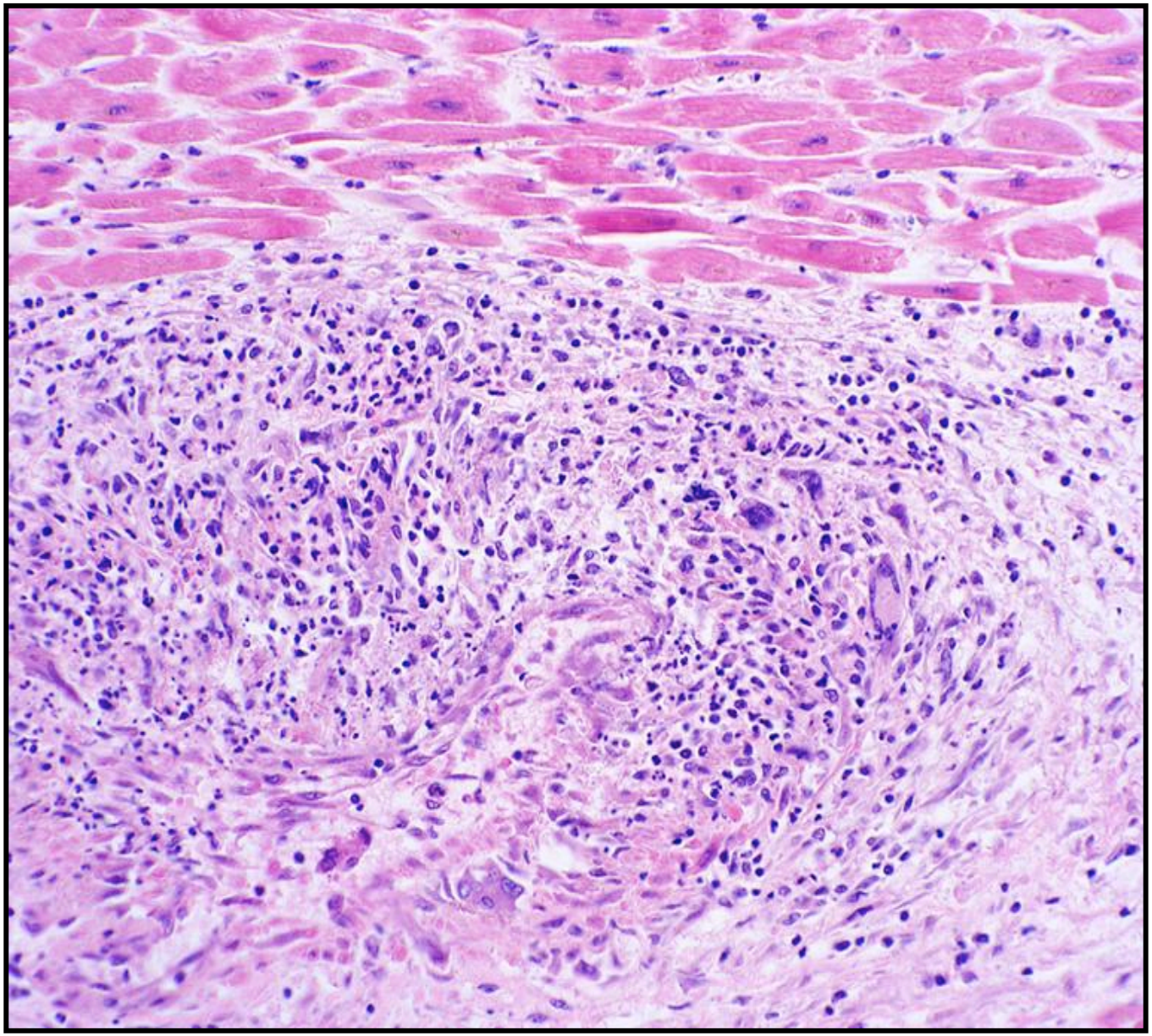
C) Neutrophil

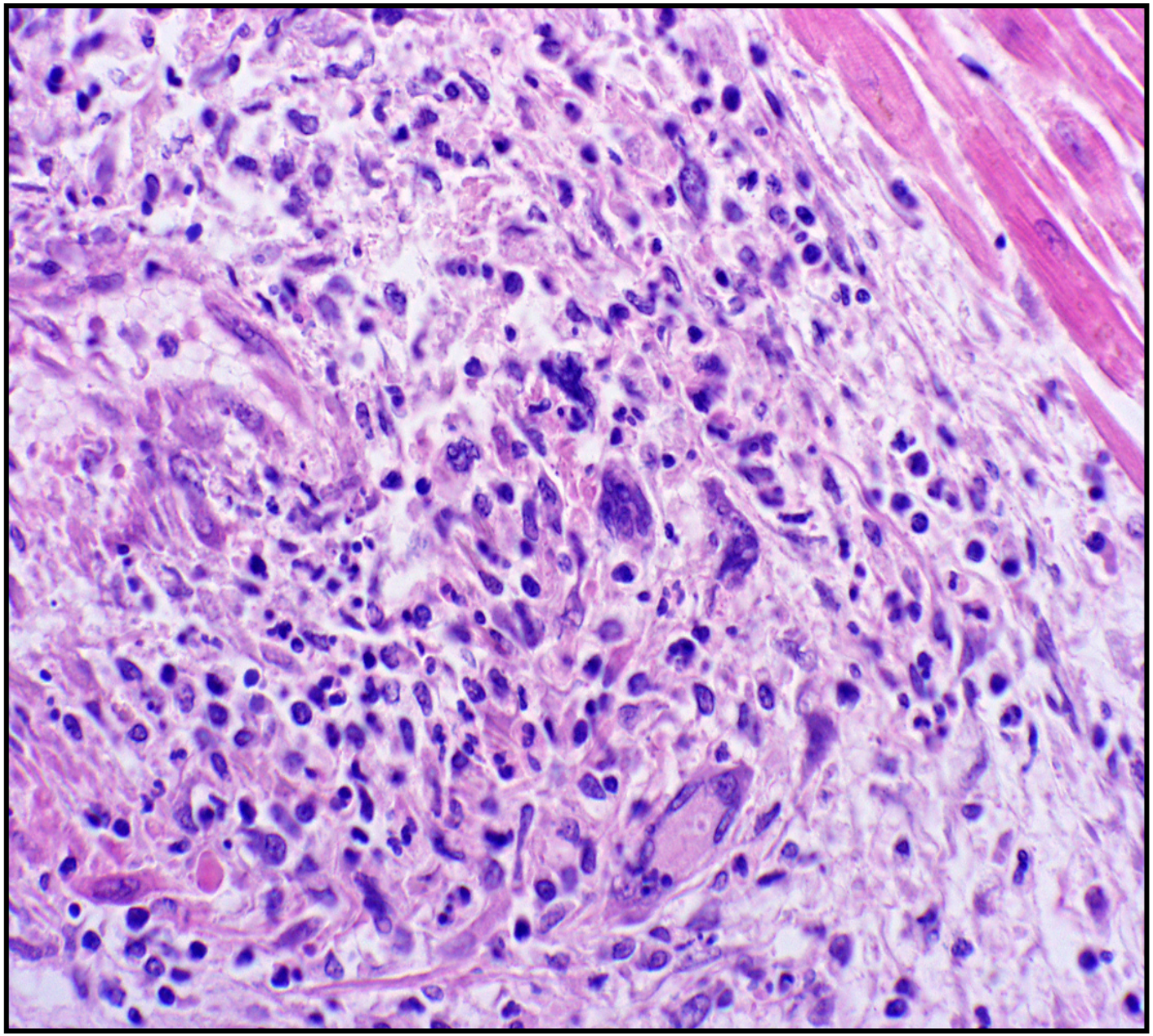
D) Epithelioid cell

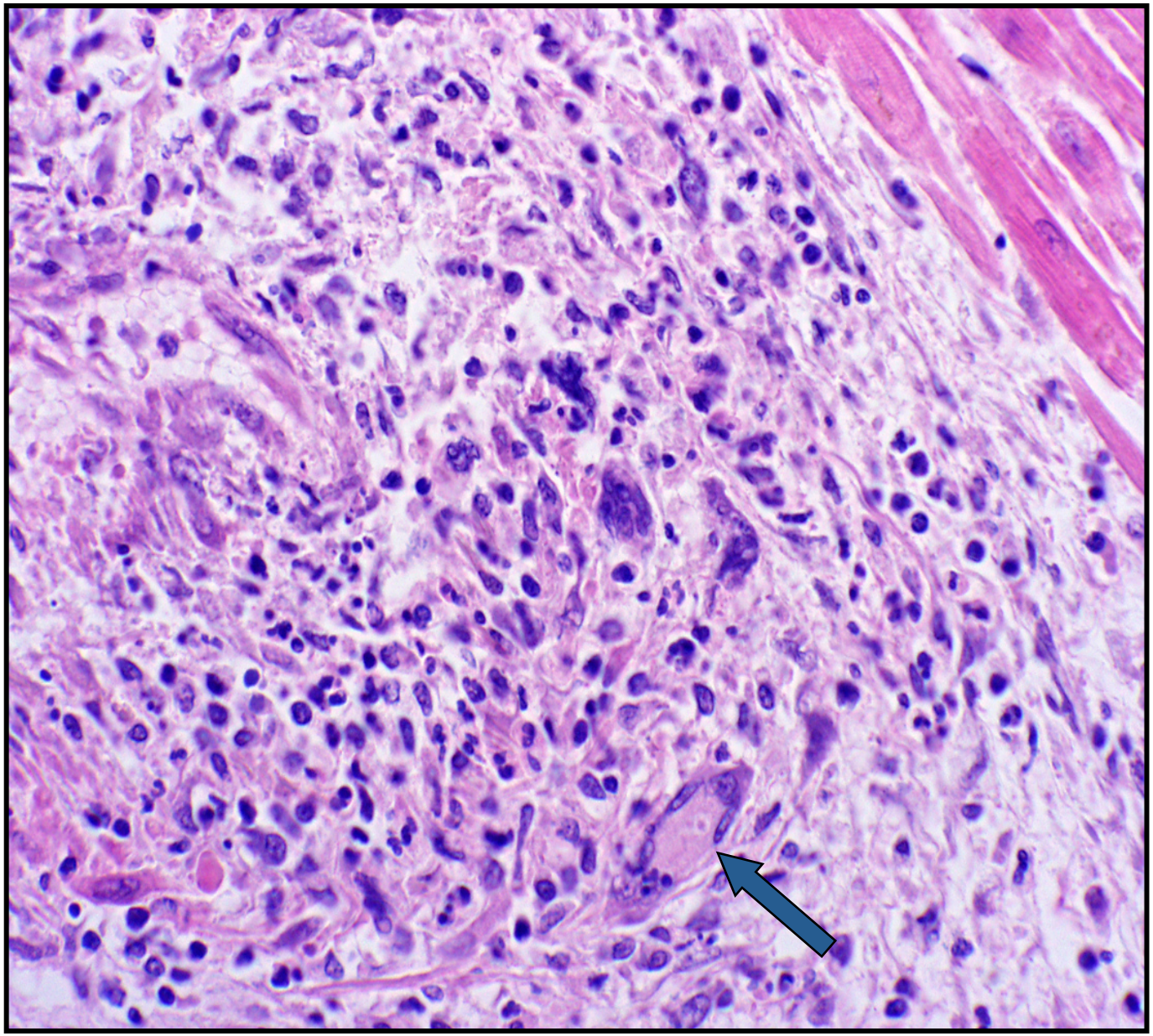
E) Multinucleated giant cells

This is a difficult classification. They look like macrophages, but they are forming a sheet. The relative lack of lymphocytes indicates a granulomatous inflammation and possibly a granuloma.

Blood vessel in the heart...







Massive and multinucleate...
hmm....

Inflammatory Cell Type?

A) Lymphocyte

B) Eosinophil

C) Neutrophil

D) Epithelioid cell

E) Multinucleated giant cell

Type of Inflammatory Response?

A) Acute

B) Chronic

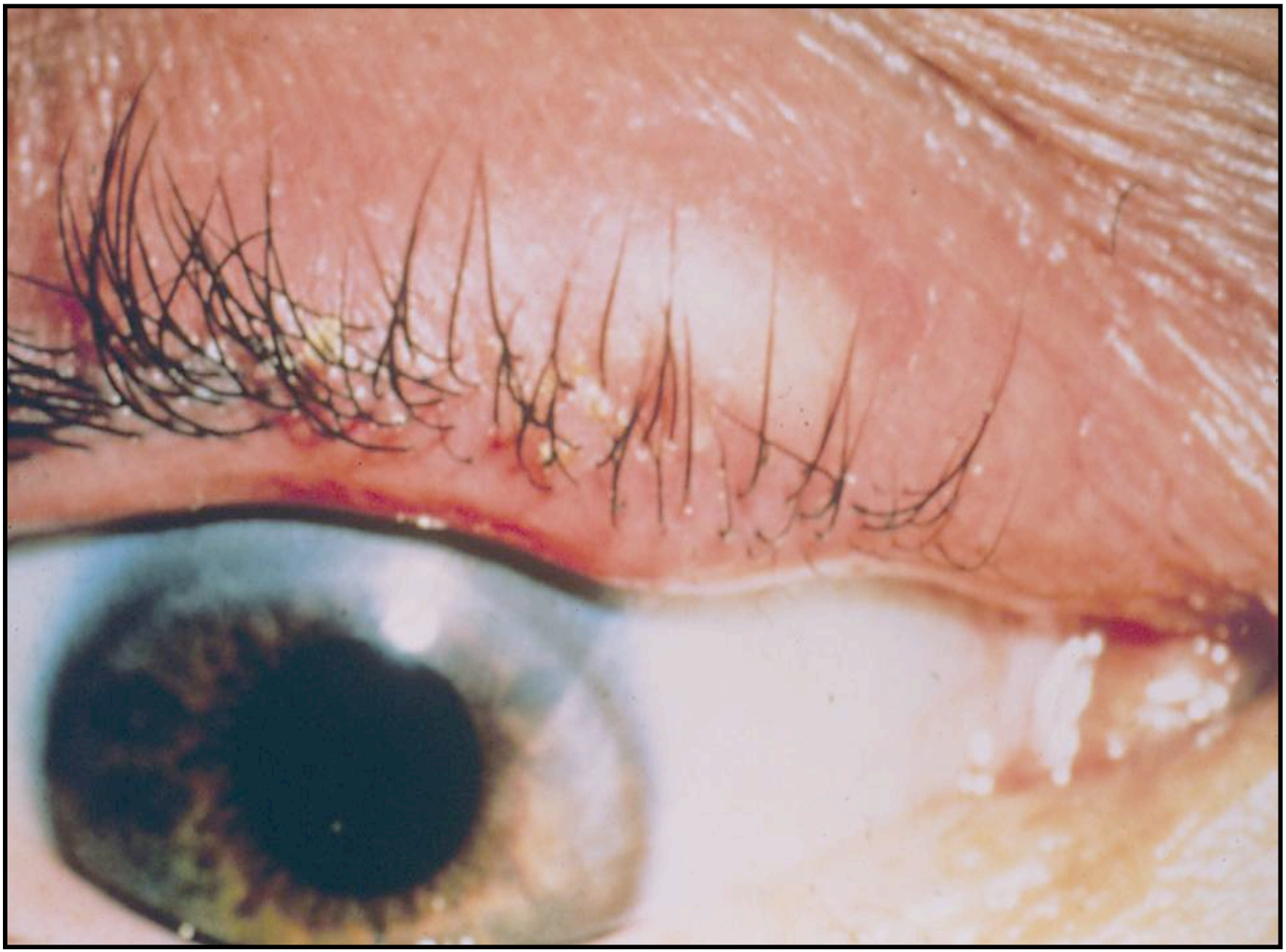
C) Granulomatous

Wegener's Granulomatosis

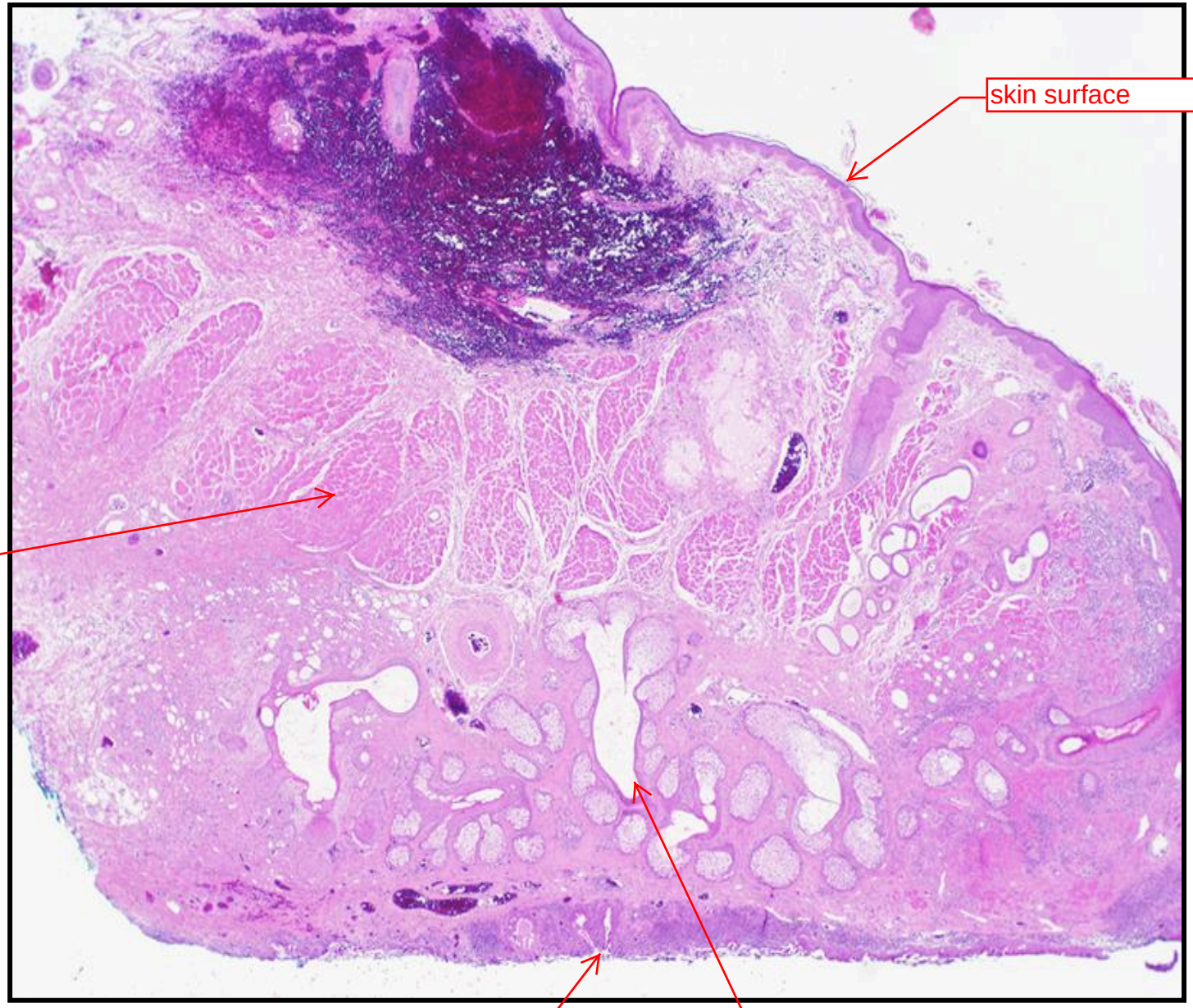
- Classical triad:
  - Necrotizing granulomatous lesions of upper and lower respiratory tract
  - Focal segmental glomerulonephritis
  - Necrotizing vasculitis of small arteries and veins
- Currently classified as an anti-neutrophil antibody (ANC) small-vessel vasculitis
- Most frequent organs:
  Upper respiratory tract, lungs, and kidneys

Case Study

- Red, tender swelling within tarsal plate of eyelid
- Not responsive to warm compresses



Full thickness eyelid.....

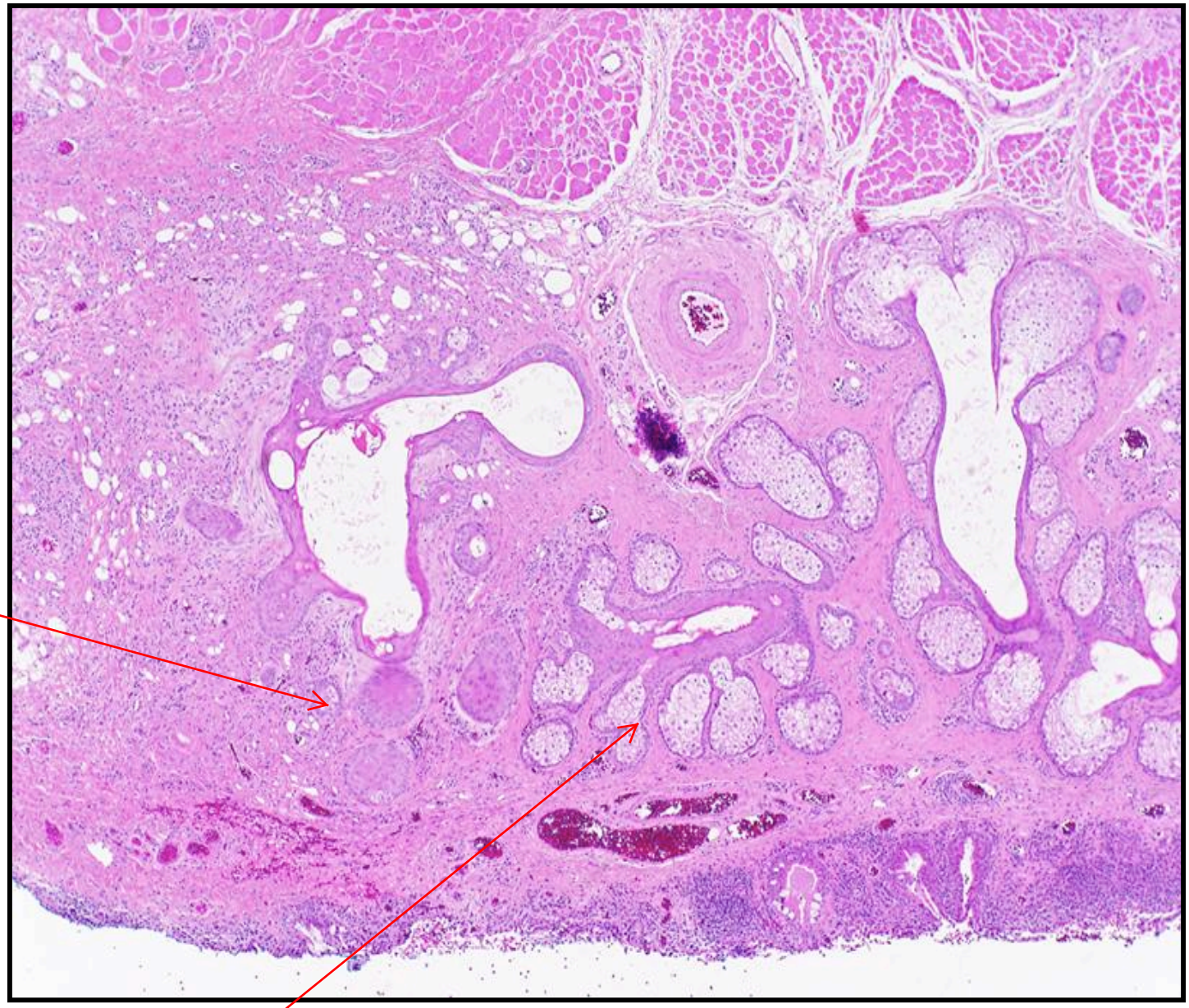


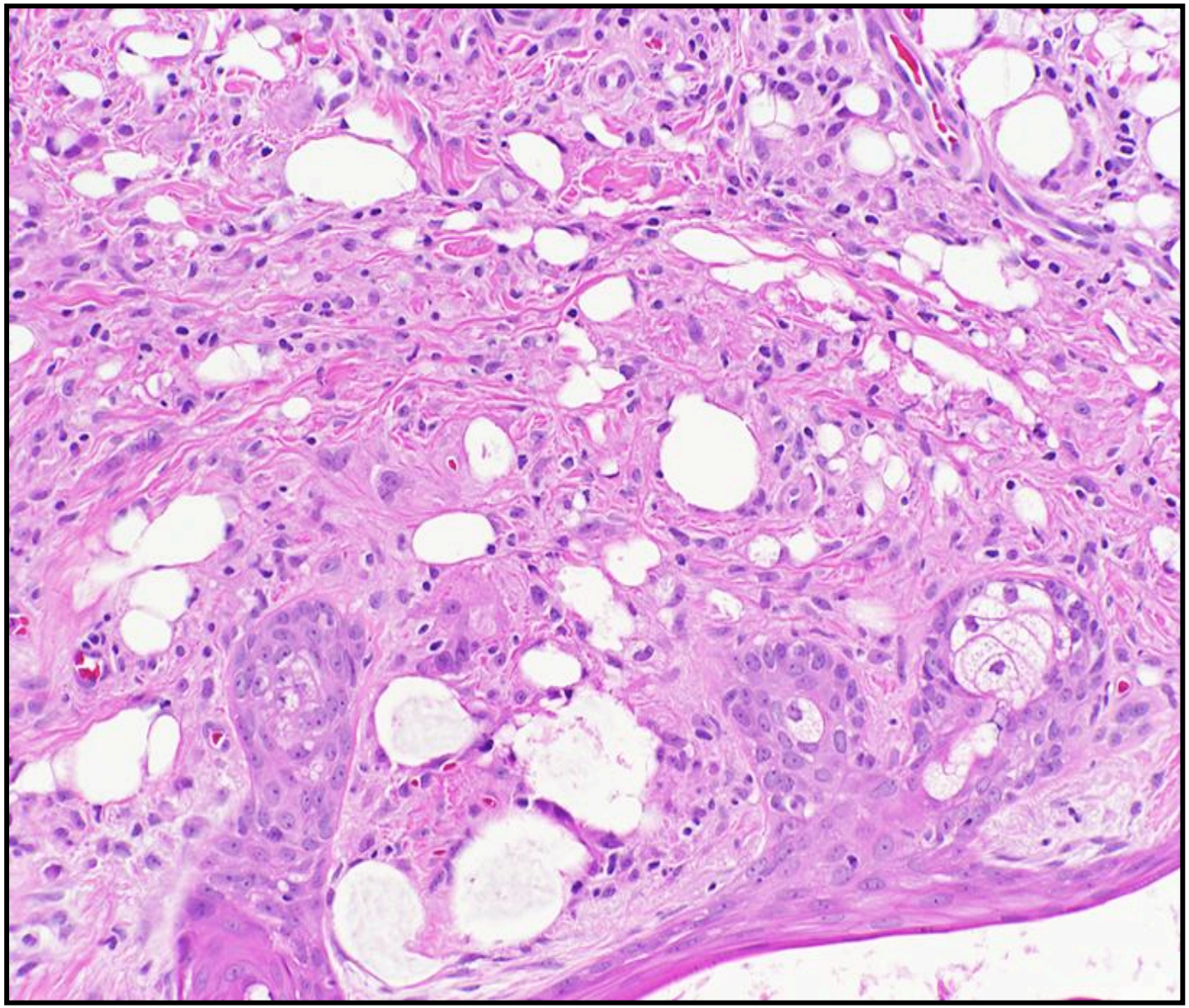
skin surface

muscle

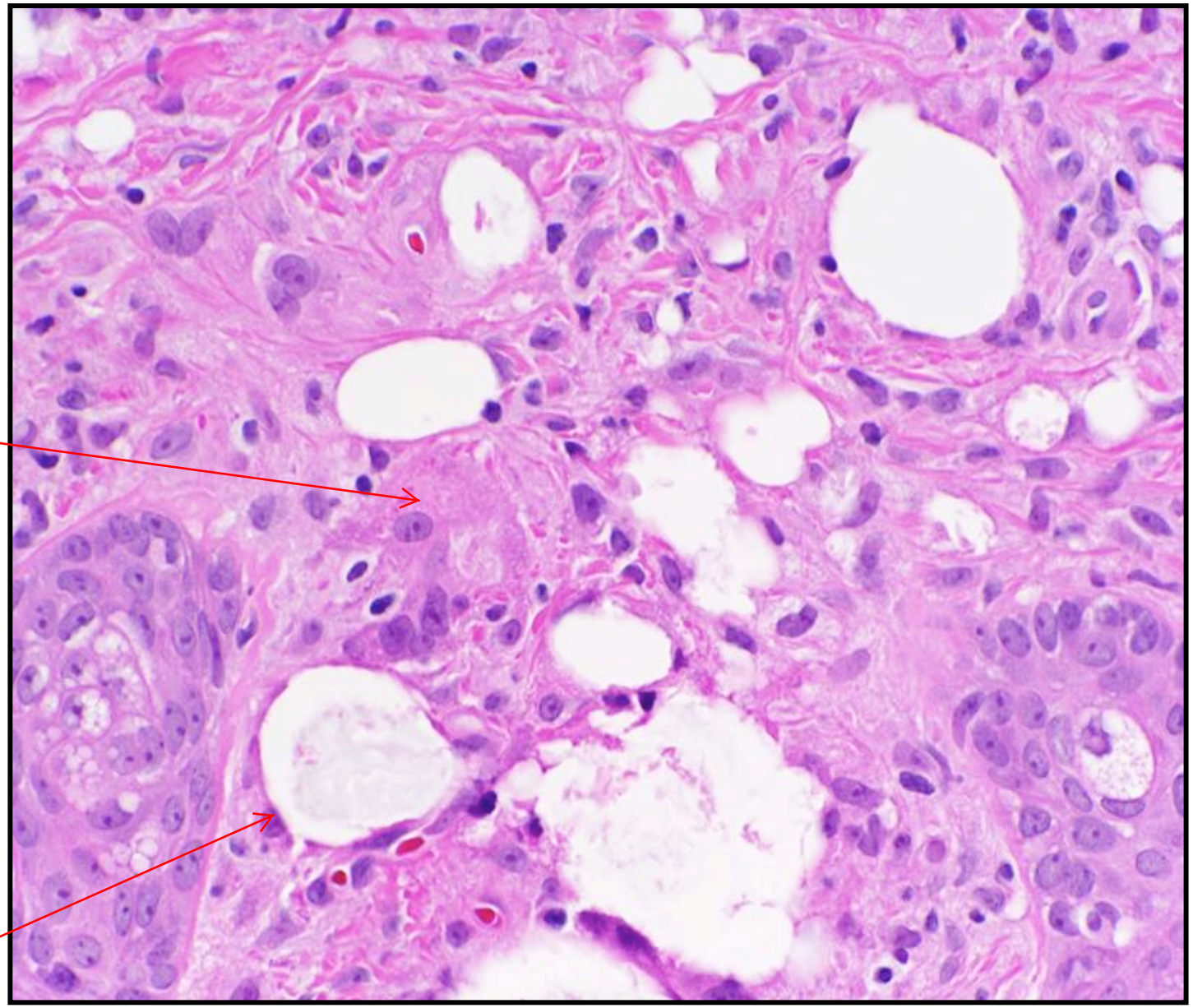
conjunctival surface

glands that produce lipids, part of tear films


area of pathology
sebaceous glands



shows vacuoles and inflammatory cells


multinucleate cell
cell surrounding lipid droplet

Type of Inflammatory Response?

A) Acute

B) Chronic

C) Granulomatous

Chalazion

- Focal inflammatory lesion of eyelid
- Results from obstruction of secretory glands
  - Meibomian glands – deep chalazion
  - Glands of Zeiss (sebaceous glands of hair follicles in the eyelids) – superficial chalazion
- Lipogranulomatous inflammation due to extravasated lipid
  - Empty vacuoles result in histological sections due to lipid dissolving during histological processing

Wound Healing

- A complex but orderly process involving many of the chemical mediators previously discussed, along with many other growth factors and cell-matrix interactions

Just read these slides

Wound Healing - Steps

- Injury induces acute inflammation
- Parenchymal cells regenerate
- Both parenchymal and connective tissue cells migrate and proliferate
- Extracellular matrix is produced
- Parenchyma and connective tissue matrix remodel
- Increase in wound strength due to collagen deposition

Wound Healing Time Course

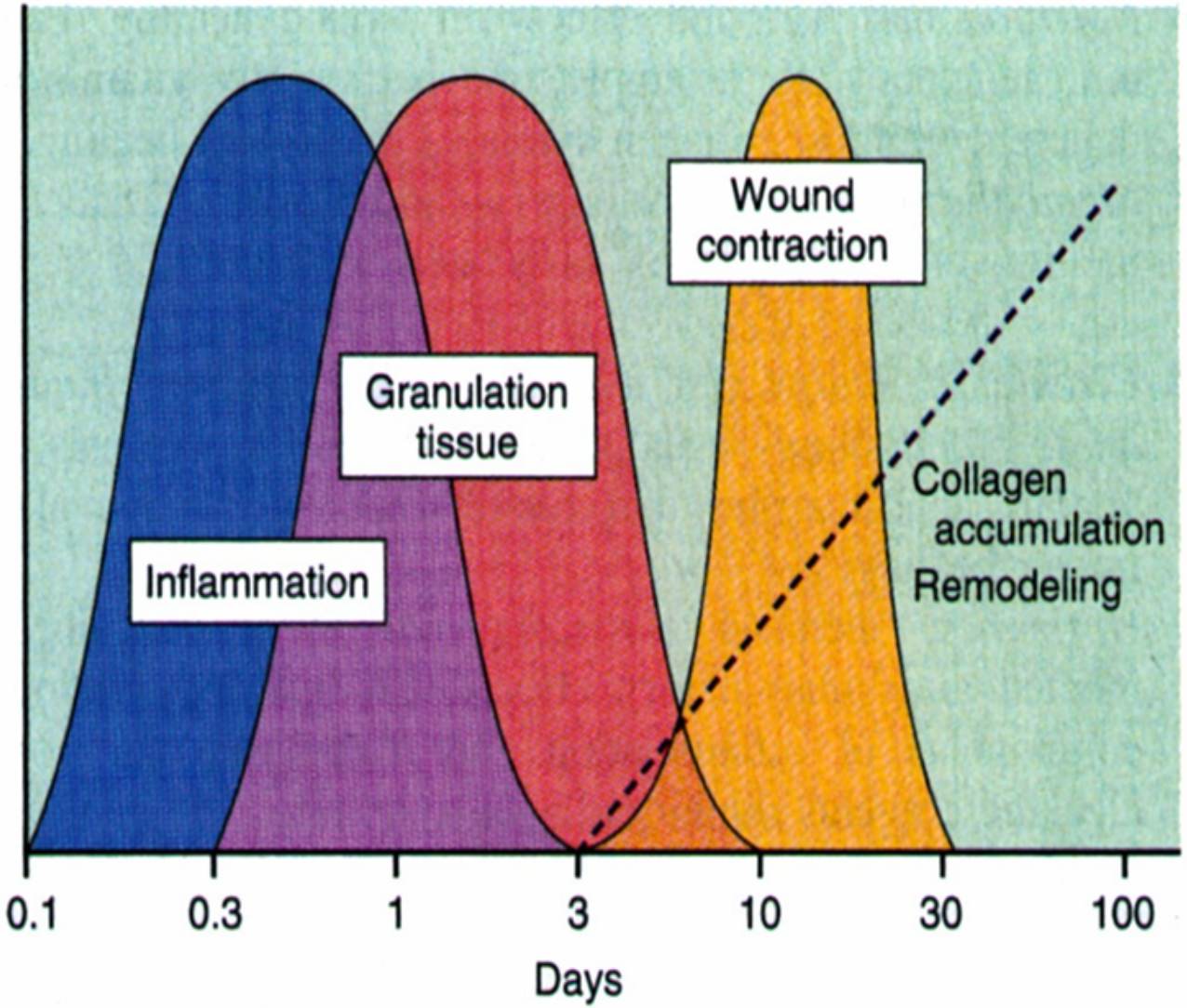
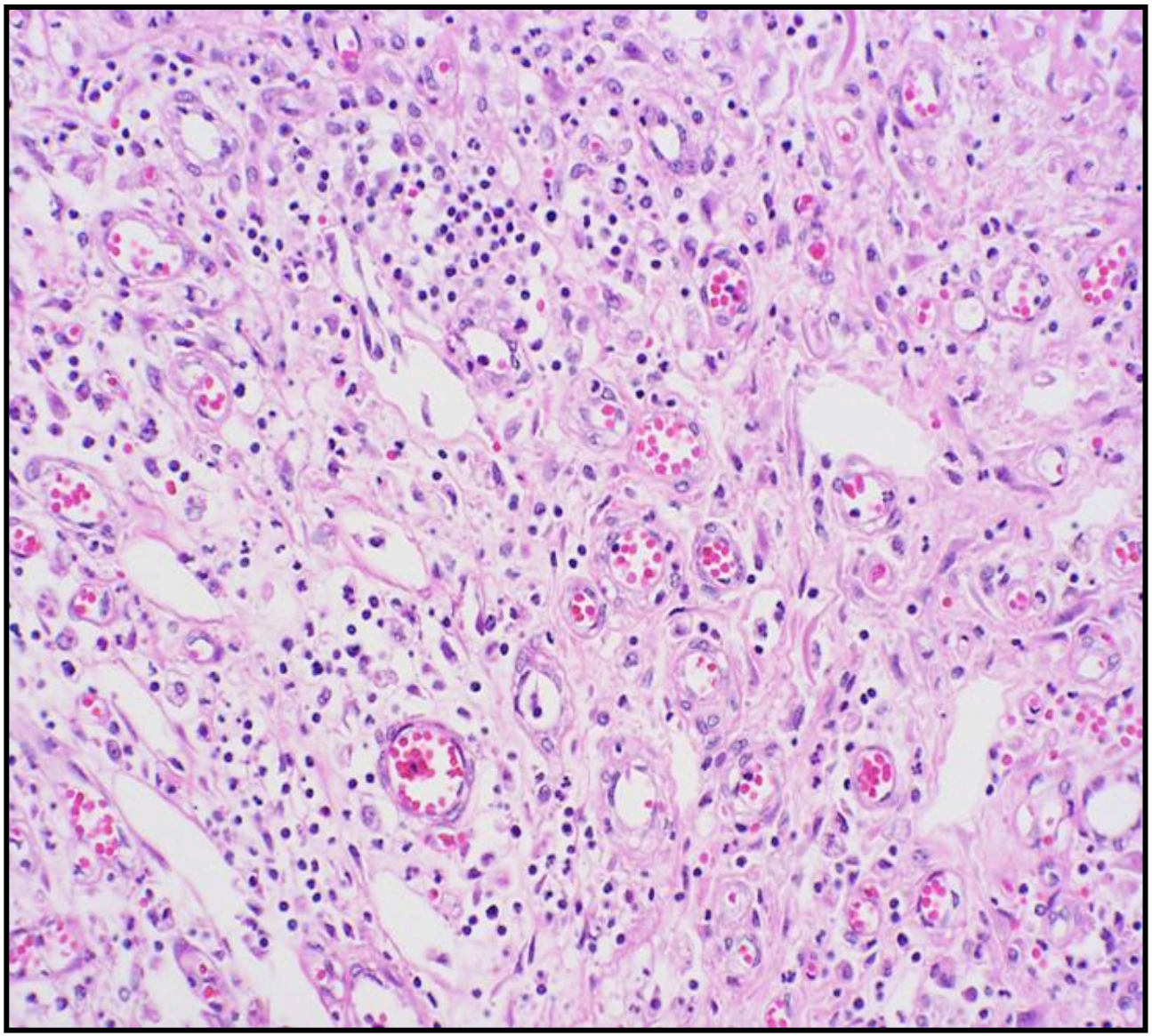


Figure 3-20 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Granulation Tissue

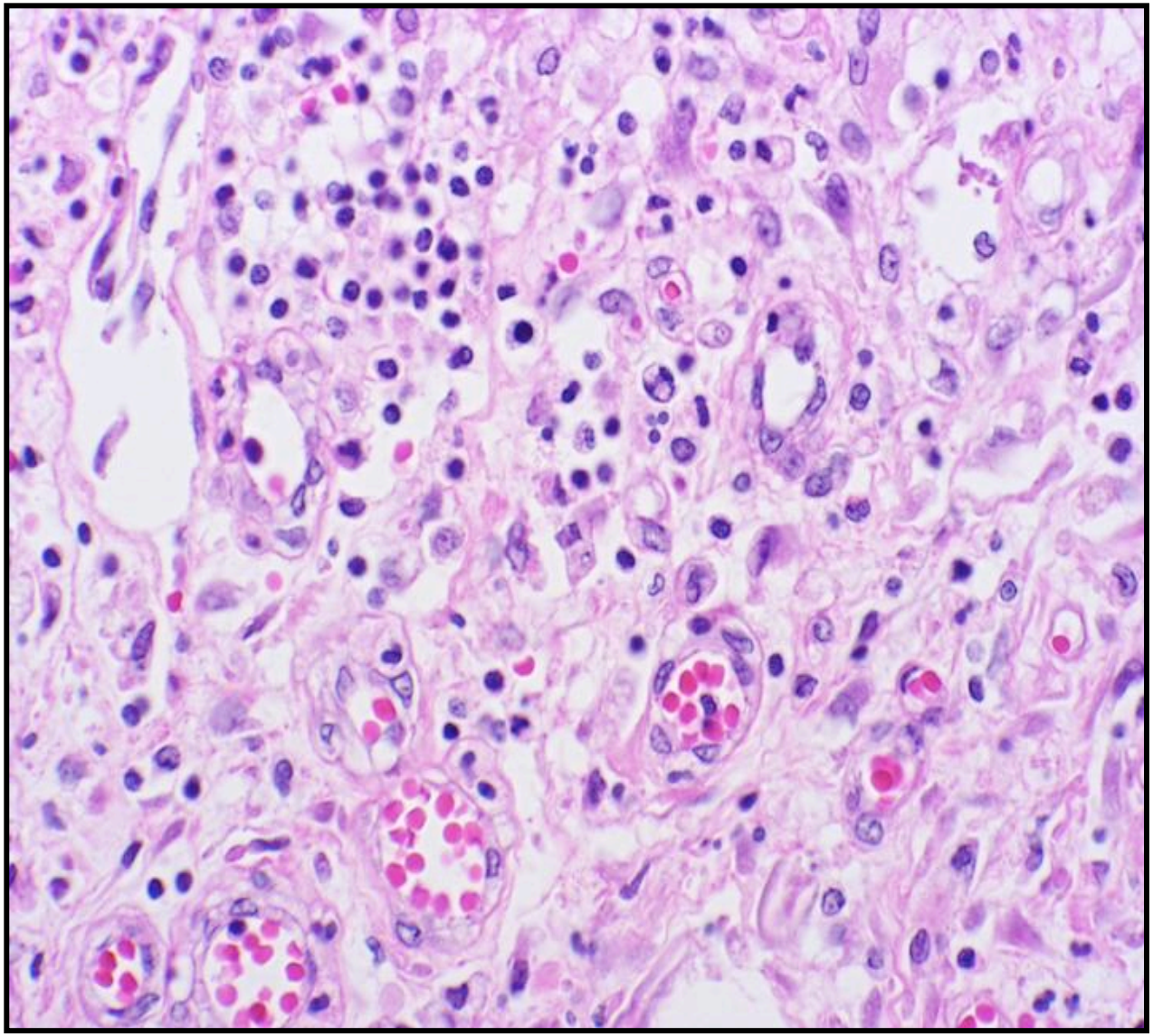
- Hallmark of healing
- Term comes from soft, pink, granular appearance when viewed from the surface of a wound
- Histology: Proliferation of small blood vessels and fibroblasts; tissue often edematous

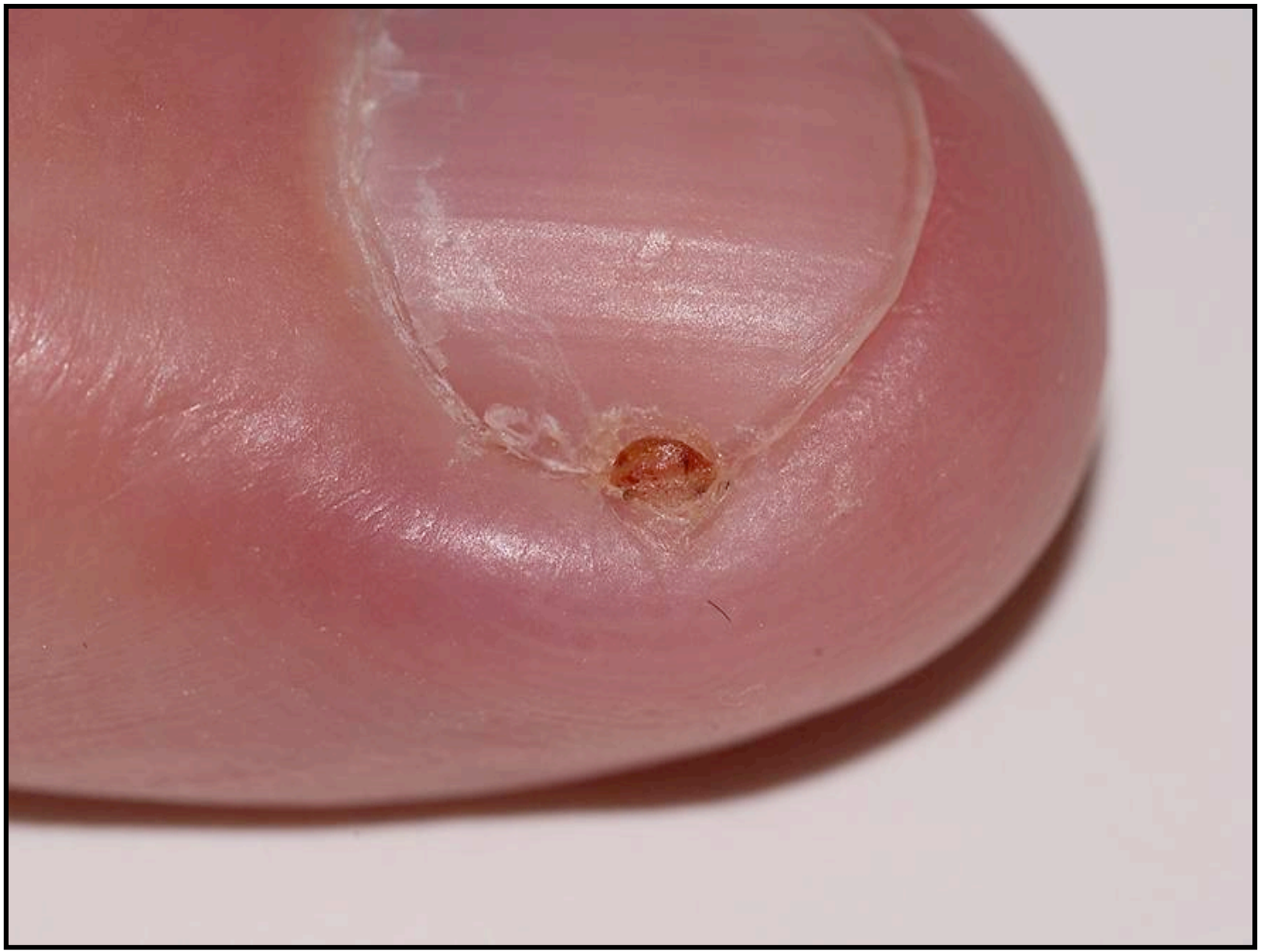
Granulation Tissue

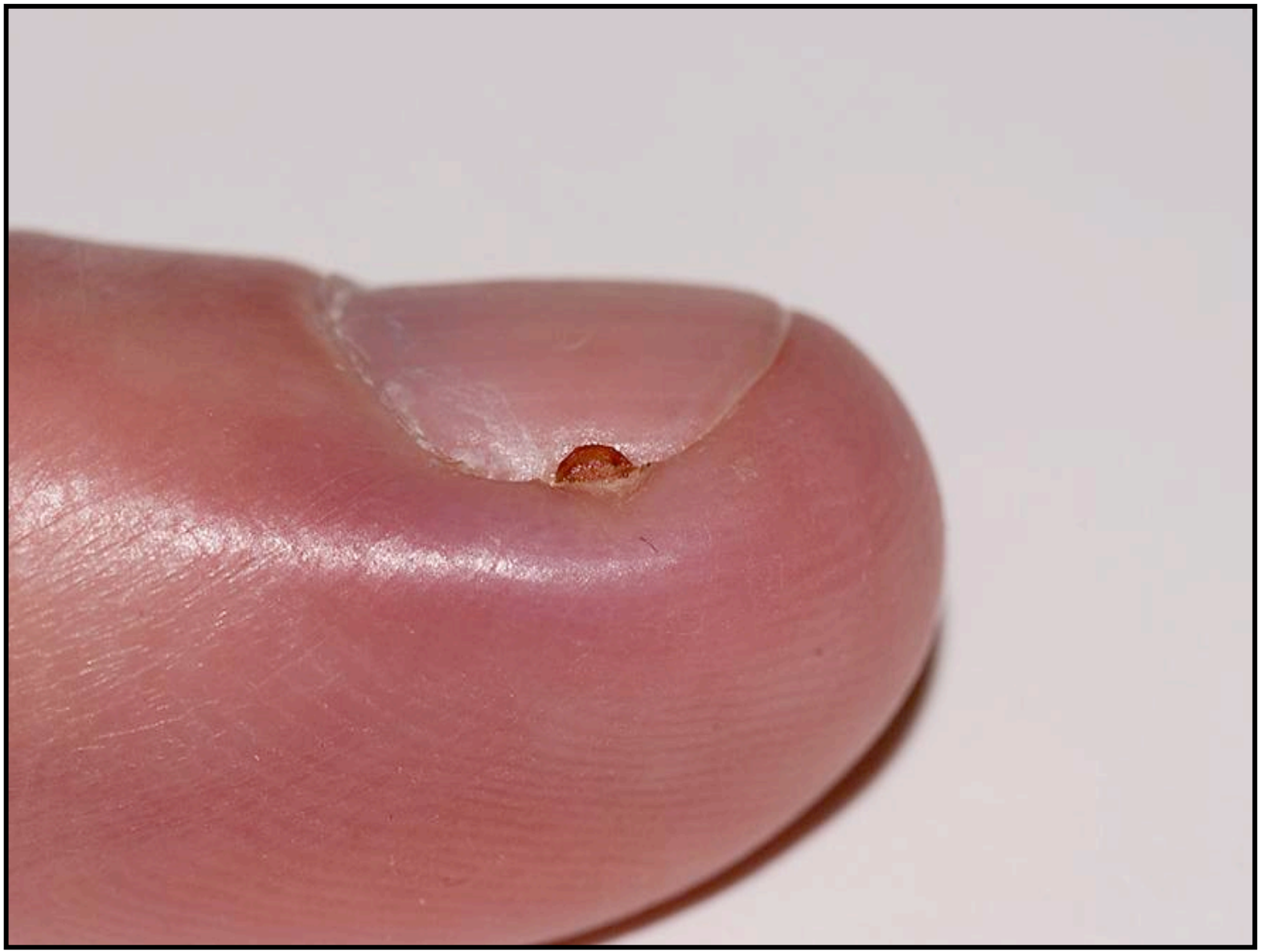


clear spaces are edema, and you have inflammation in the background

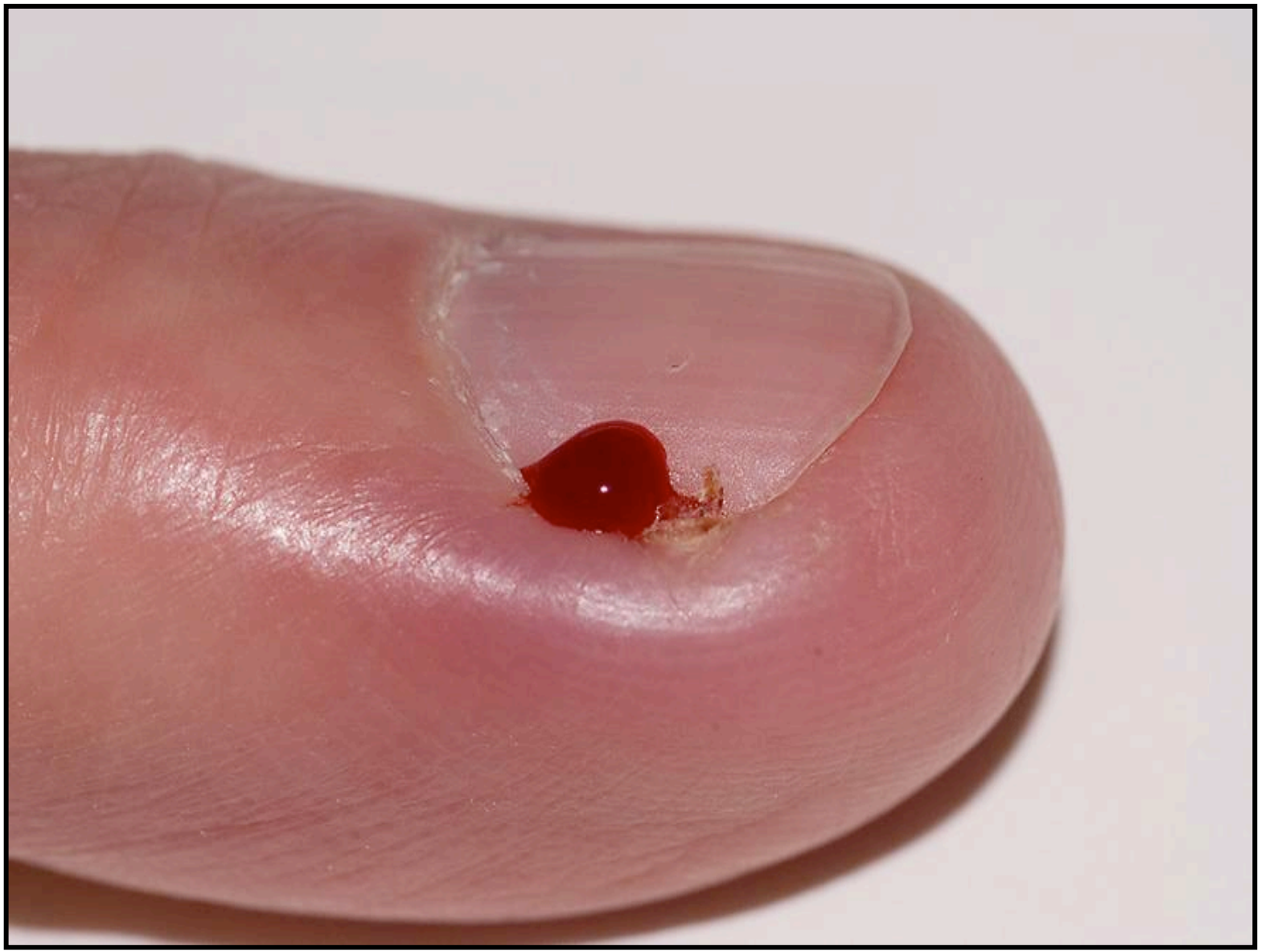
Granulation Tissue







within a second of being pricked, the blood comes out. Shows high degree of vasularization



Healing of a Skin Ulcer - 1

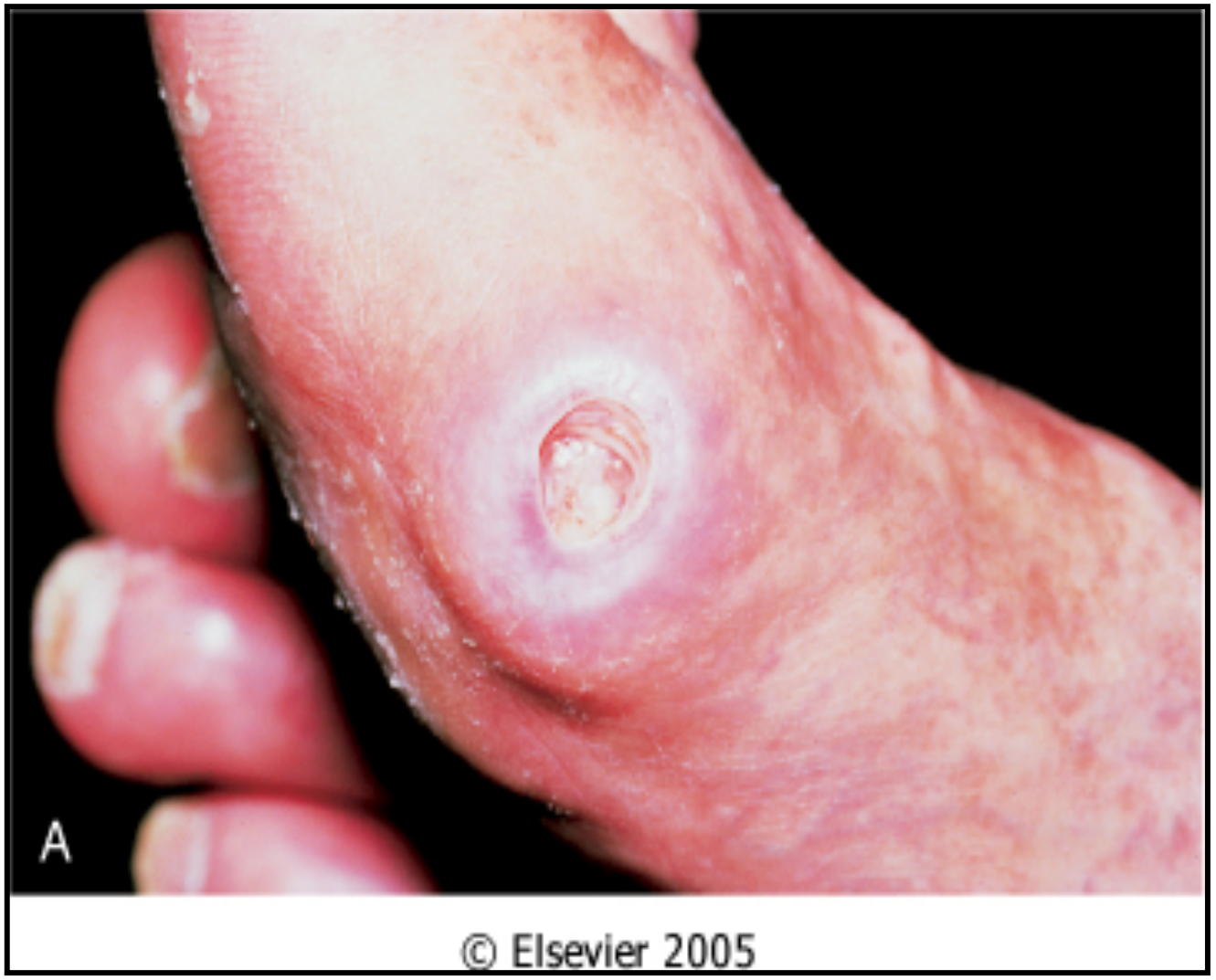
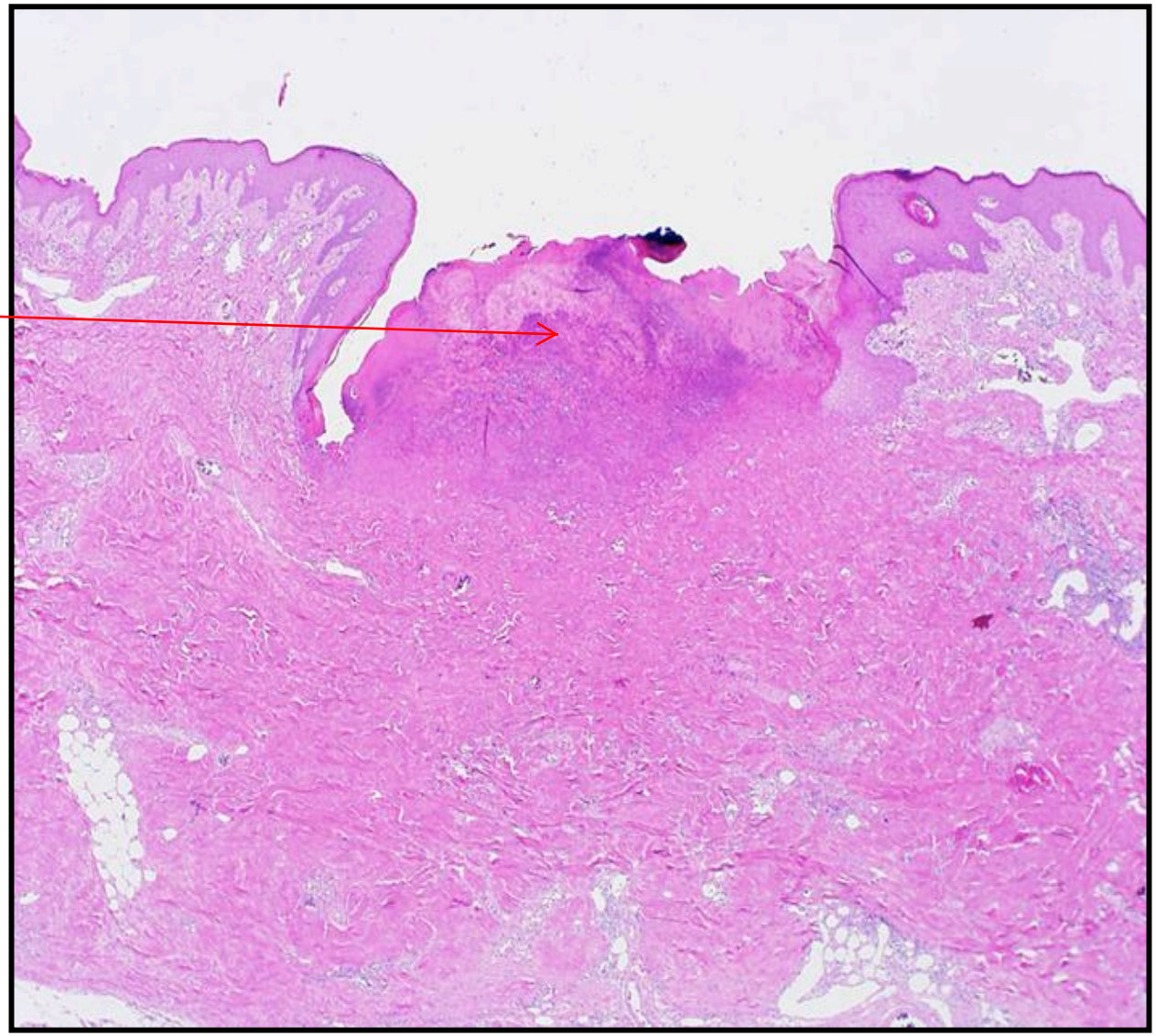


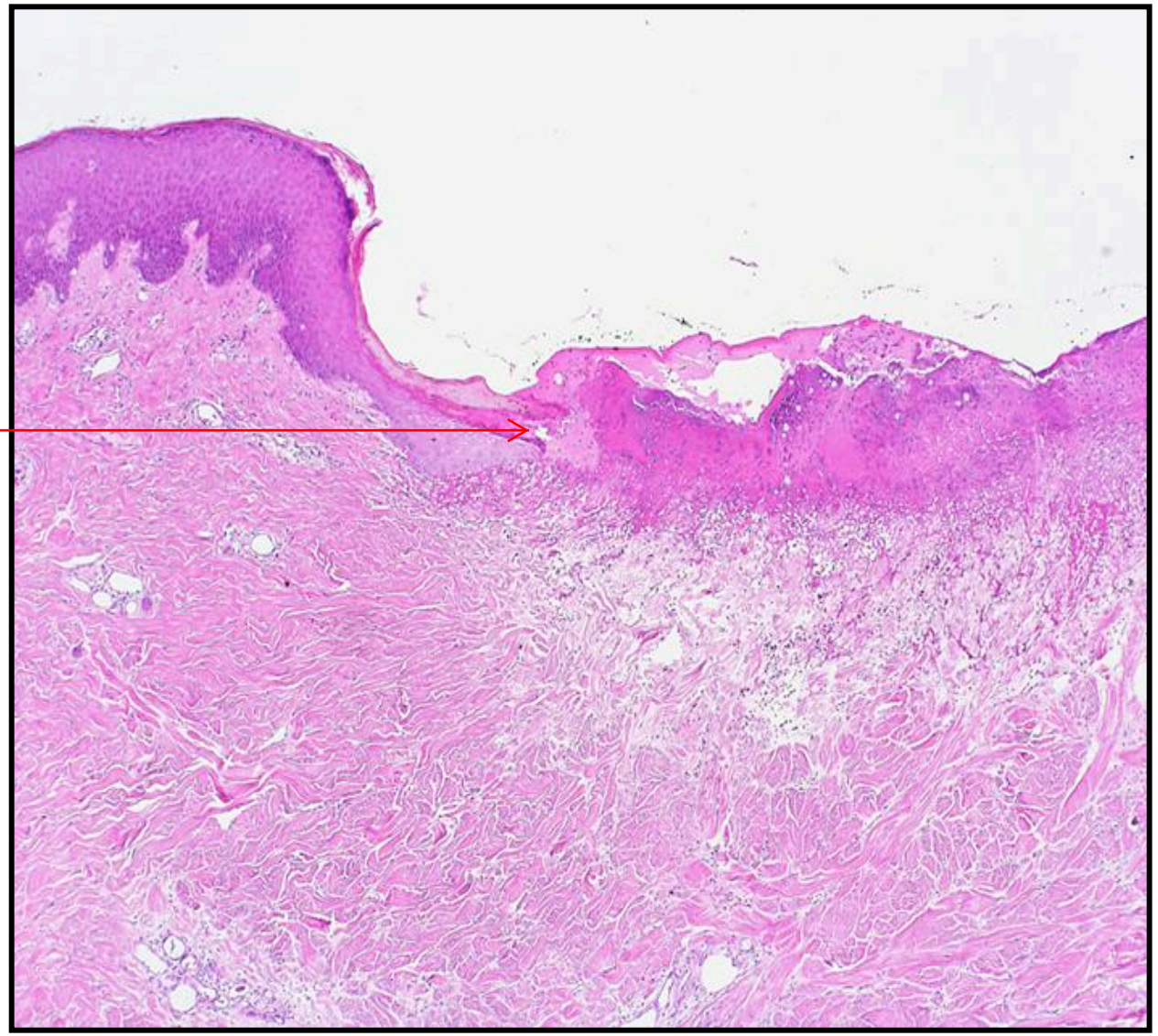
Figure 3-22 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

next few slides are pictures of skin ulcers in various stages of healing

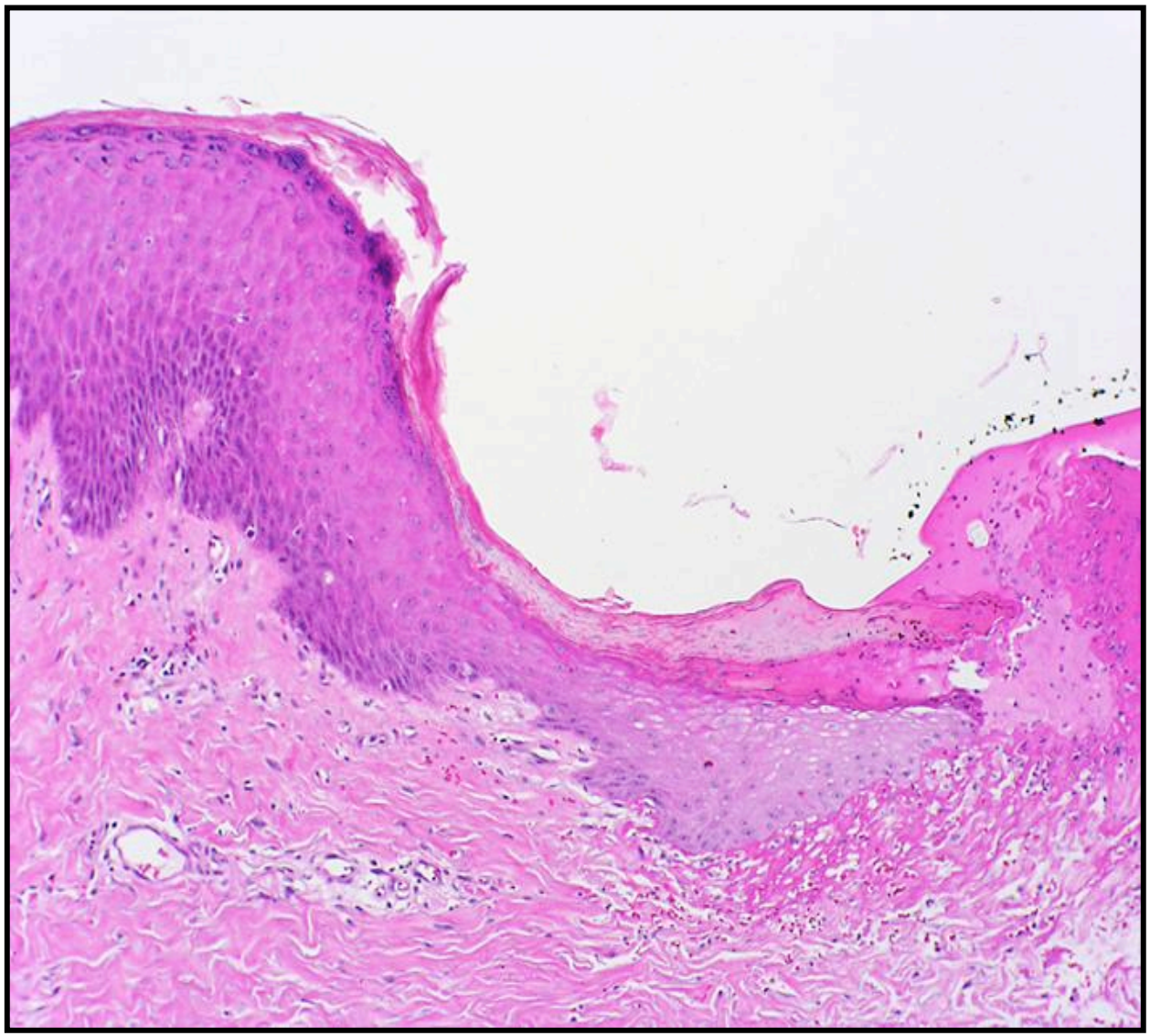
Healing of a Skin Ulcer - 2



Healing of a Skin Ulcer - 3

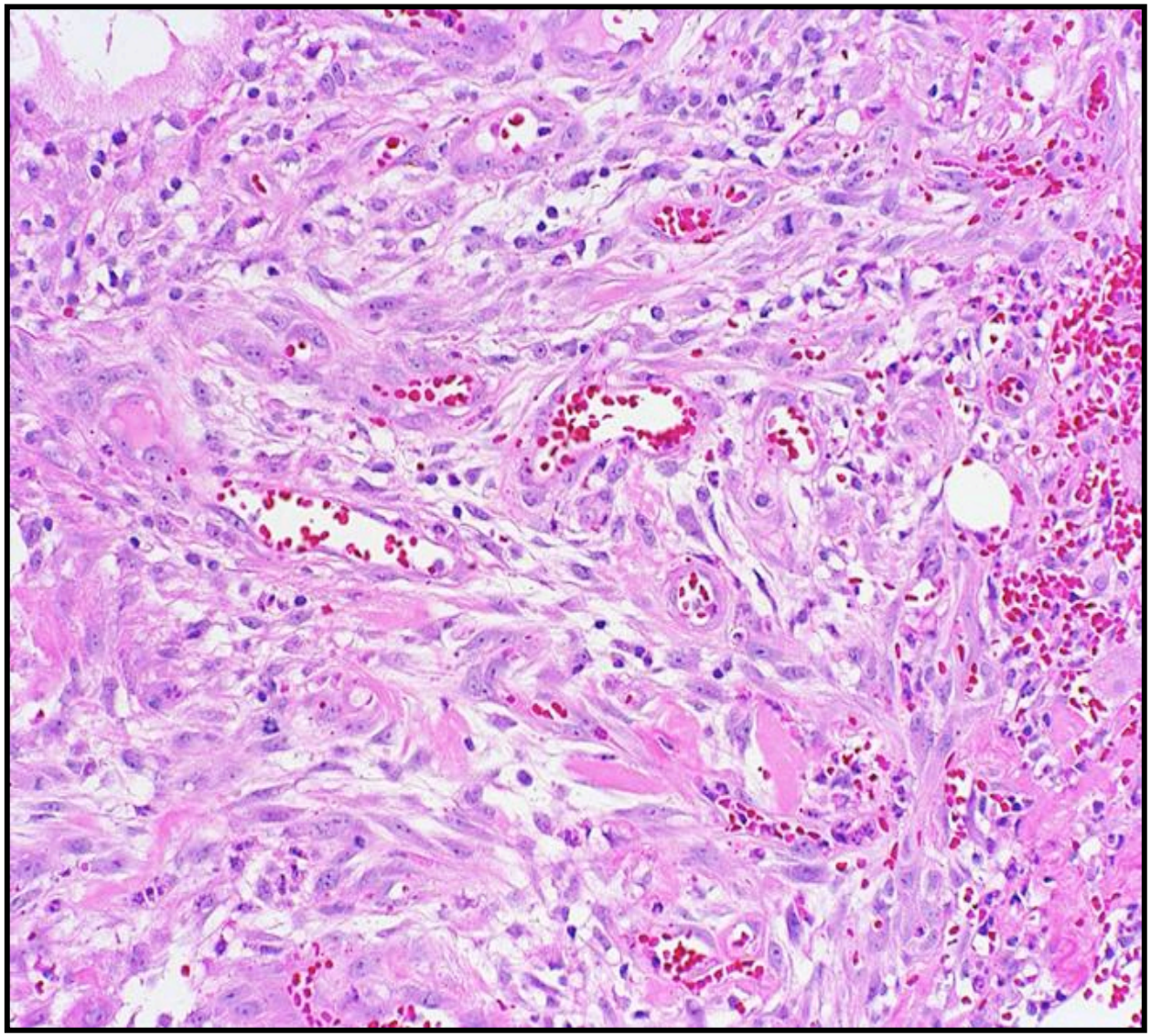


Healing of a Skin Ulcer - 4



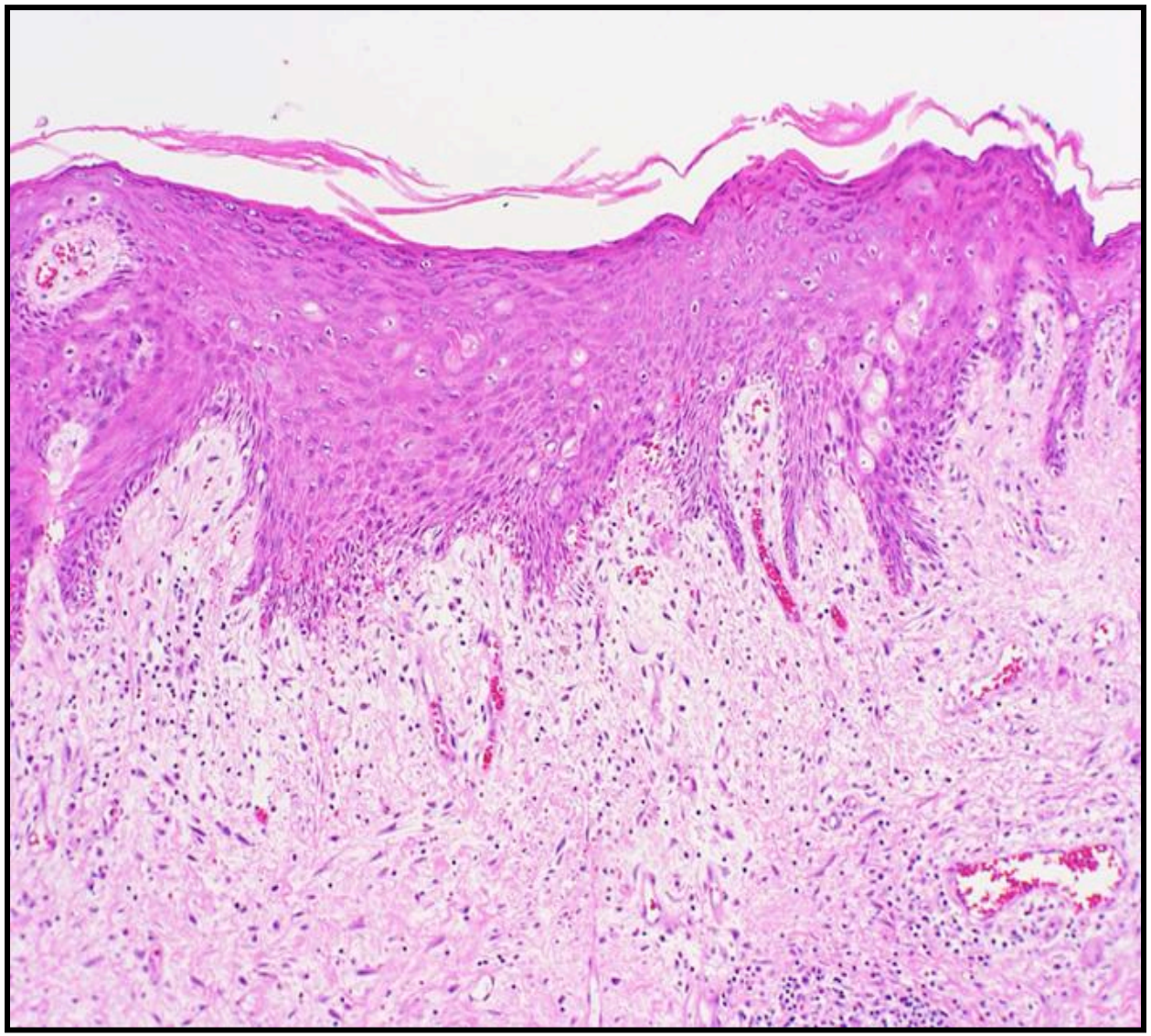
Healing of a Skin Ulcer - 5

granulation tissue forming at the base of the ulcer



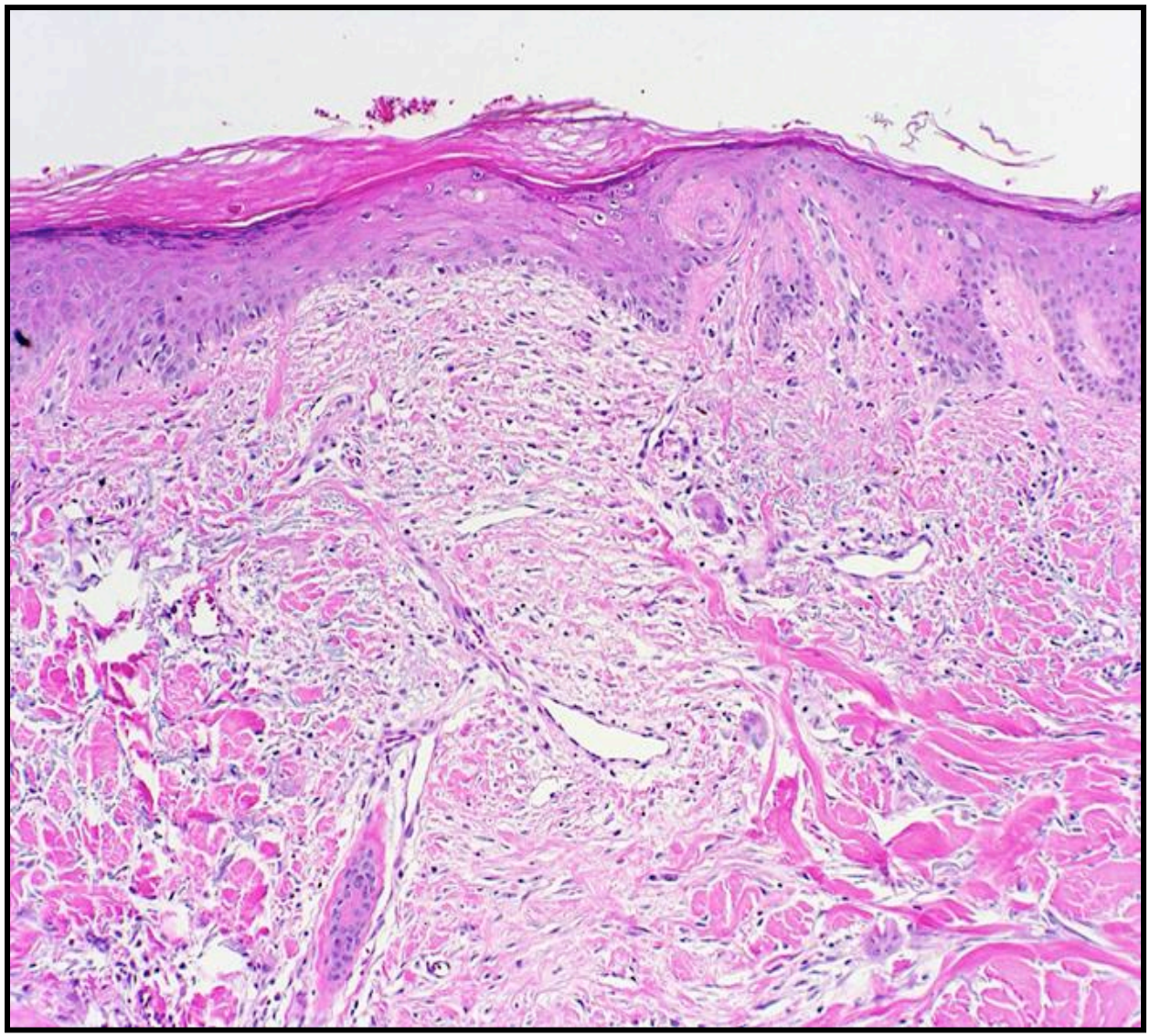
Healing of a Skin Ulcer - 6

after crawling across the surface of the ulcer, the epidermis beings to thicken and proliferate. Results in an irregular surface. Edema is still present, and blood vessels are not orderly

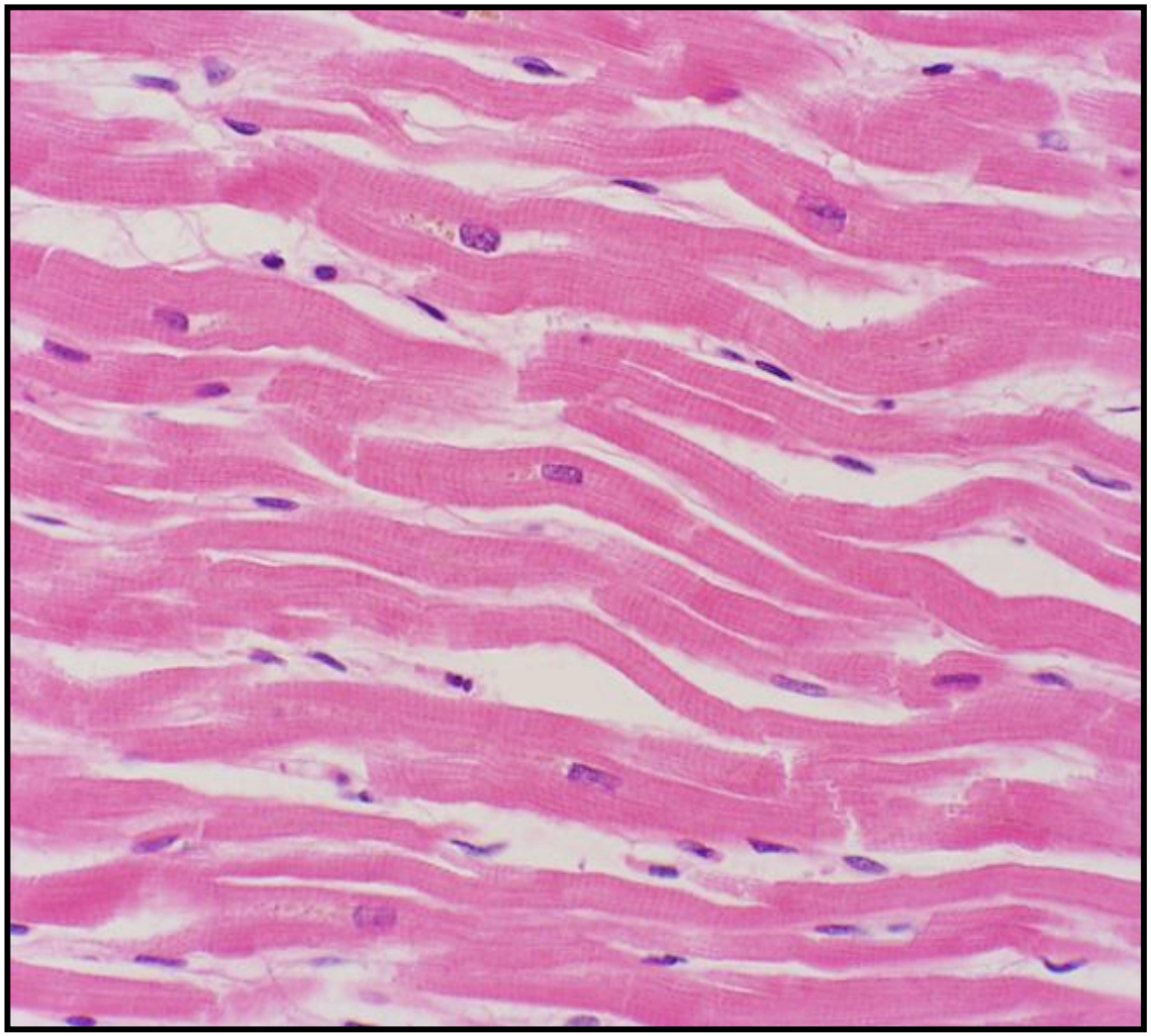


Healing of a Skin Ulcer - 7

Wound contraction then occurs in the early stage of scar formation. This wound is about a month old.

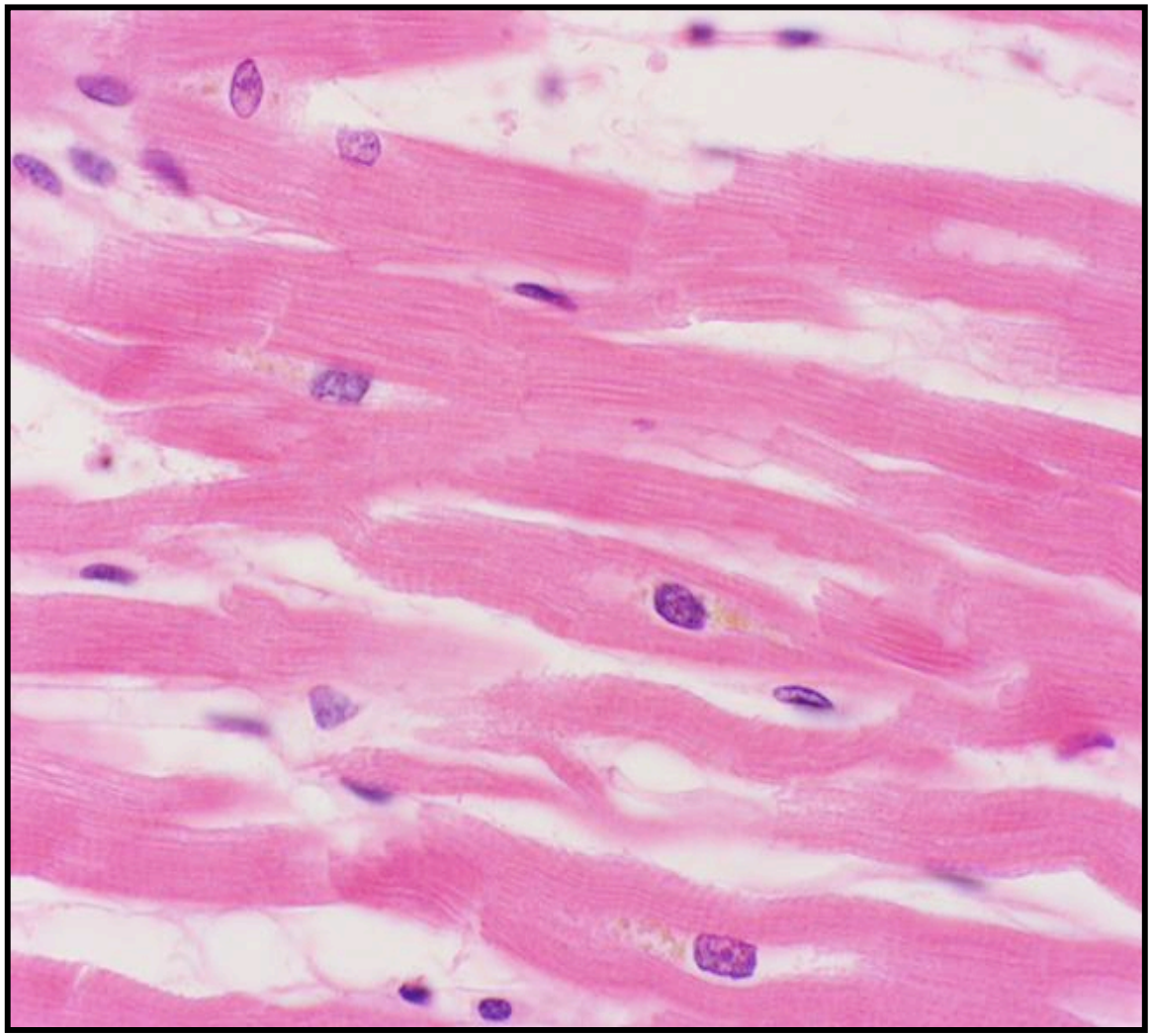


Myocardial Infarct - 1



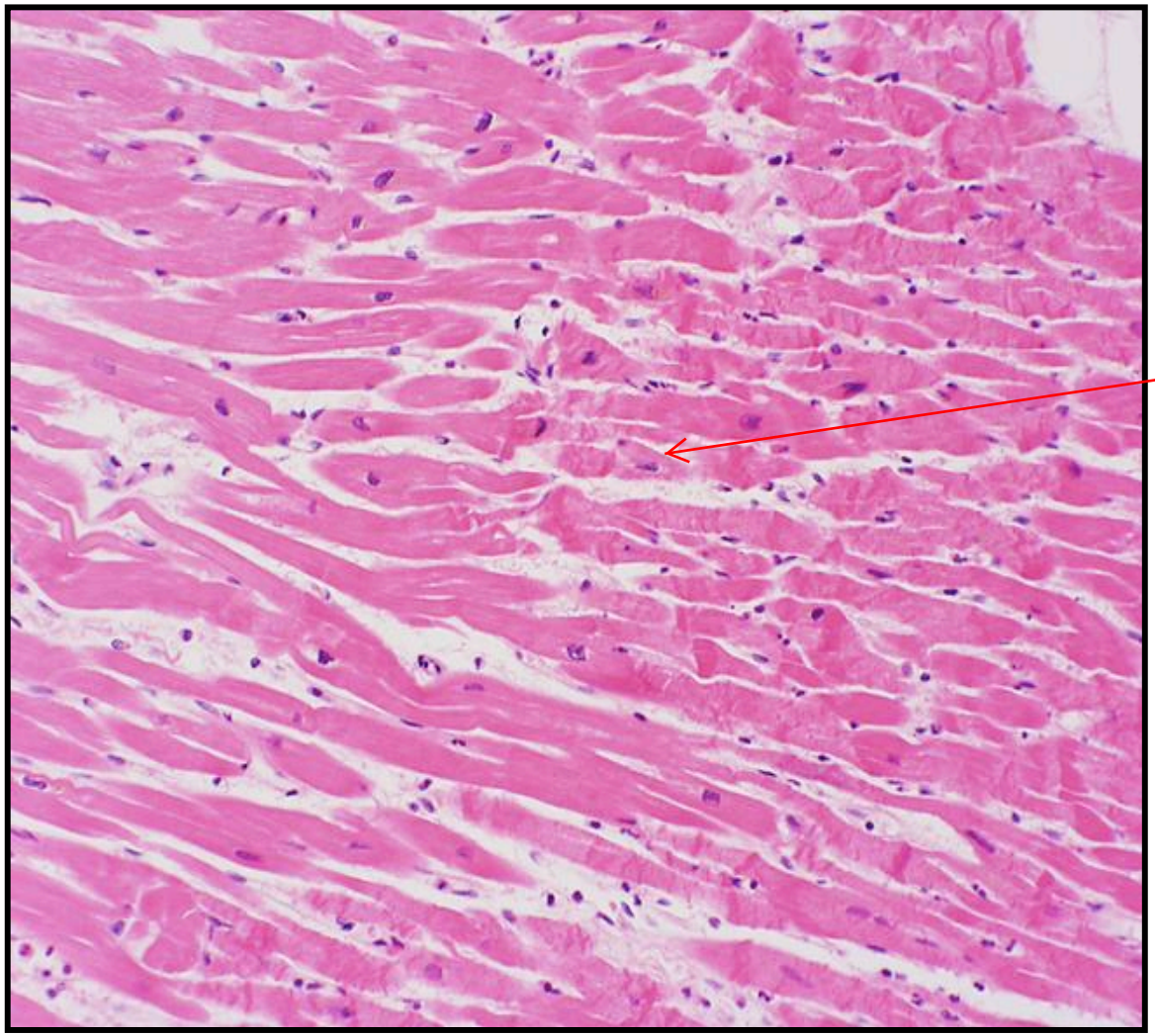
Normal heart

Myocardial Infarct - 2



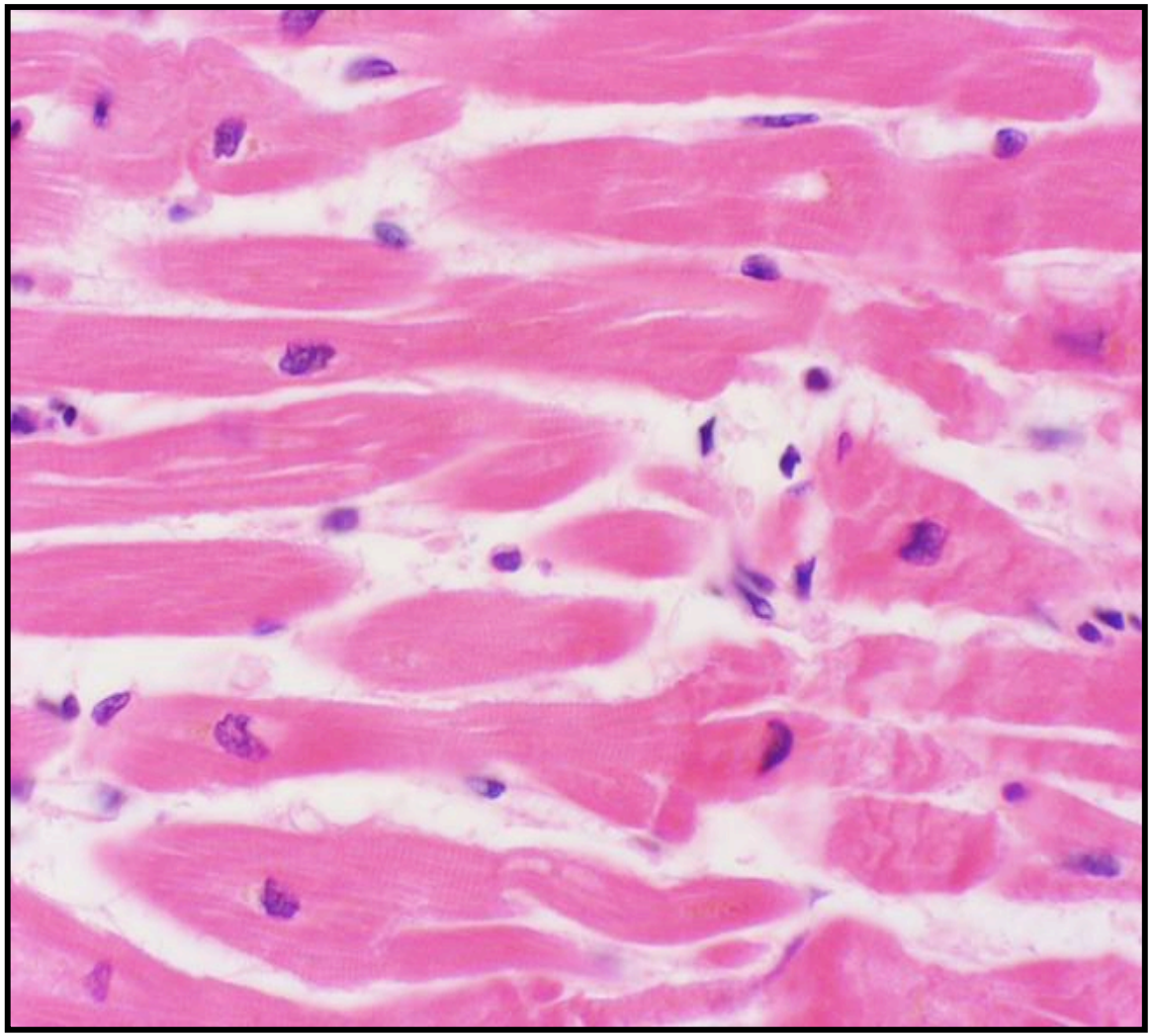
Normal heart

Myocardial Infarct - 3



Edge of acute infarct

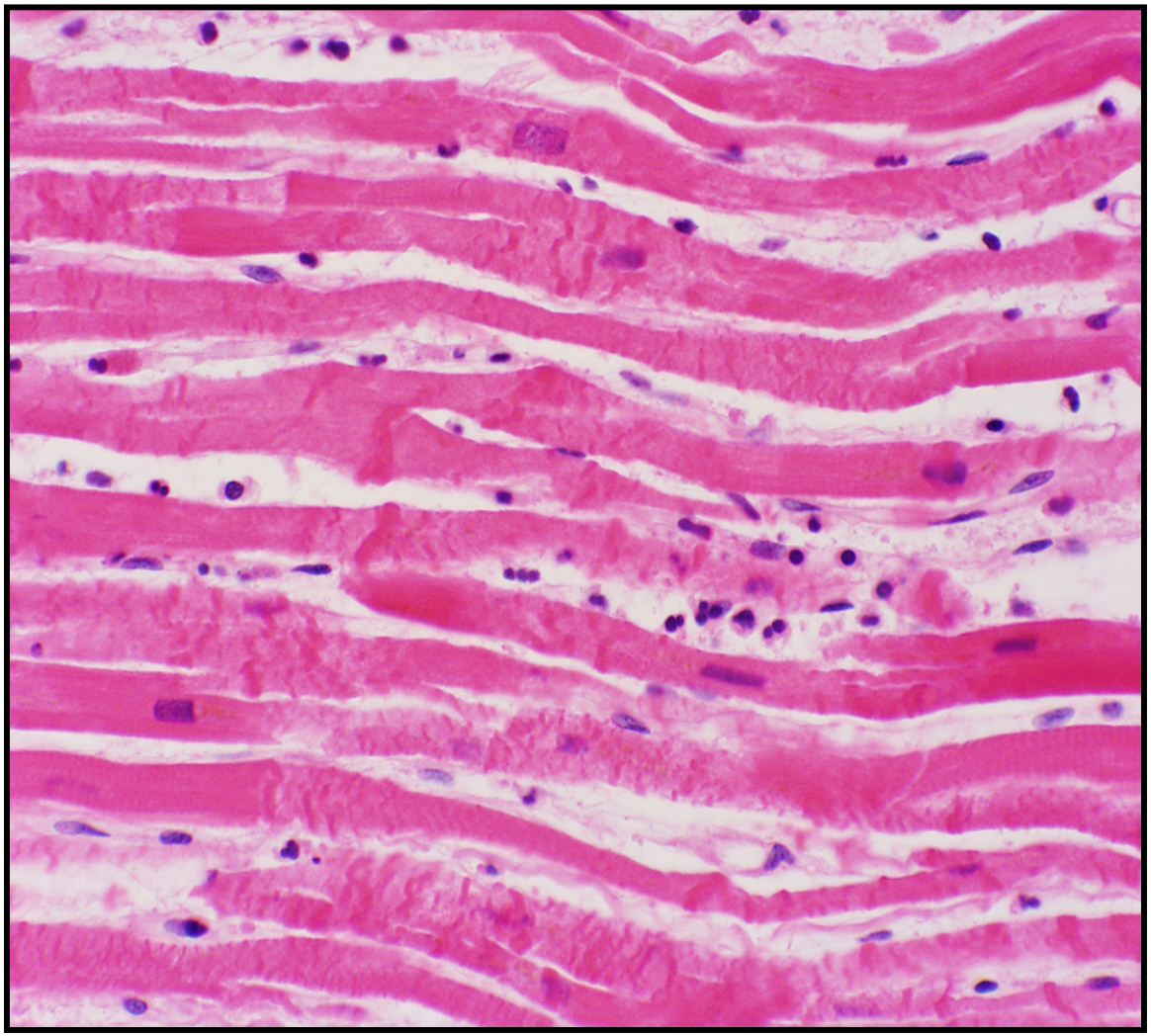
Myocardial Infarct - 4



Edge of acute infarct

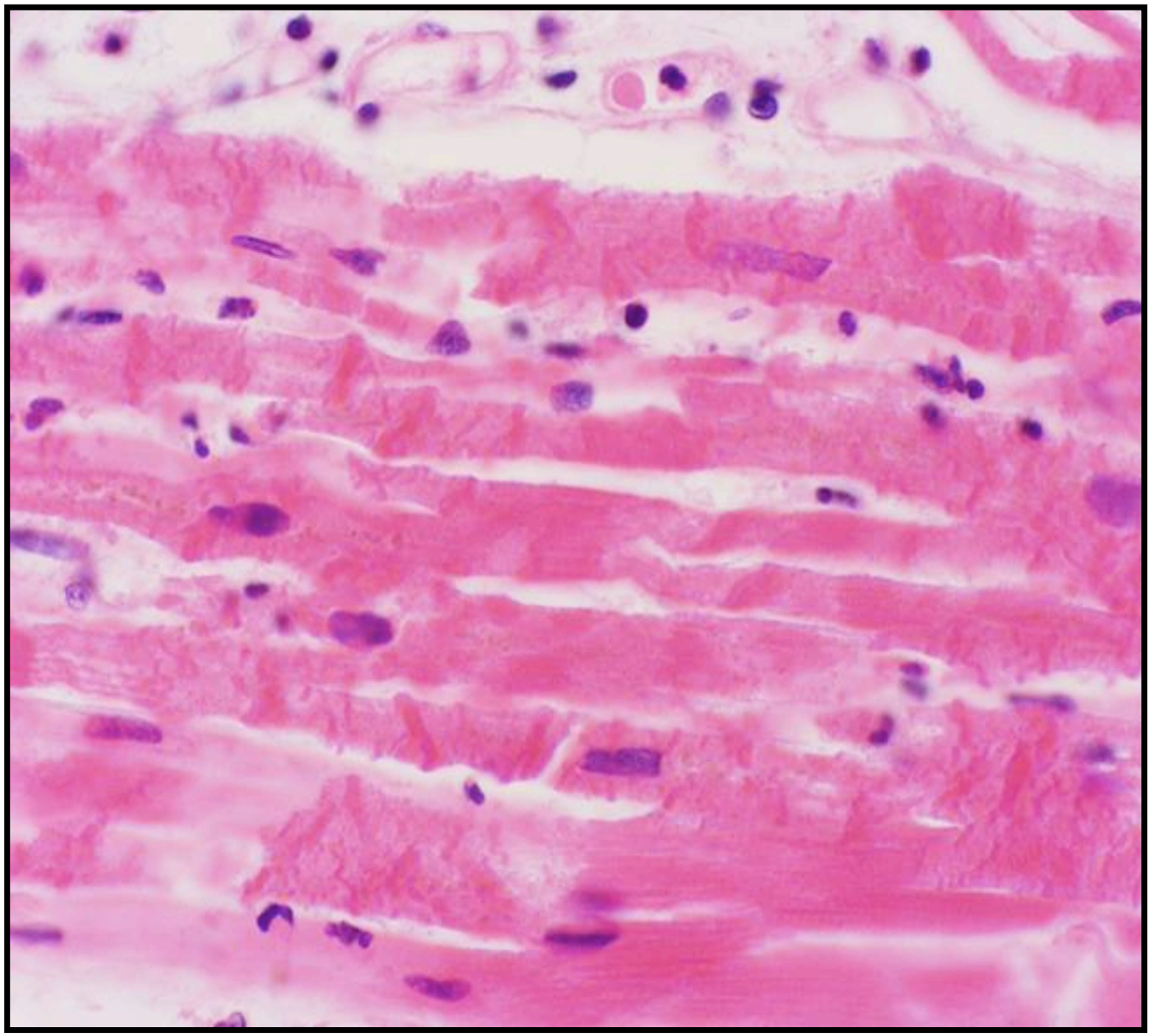
Myocardial Infarct - 5

shows the inflammatory response in myocardial infarct. Neutrophils are present.



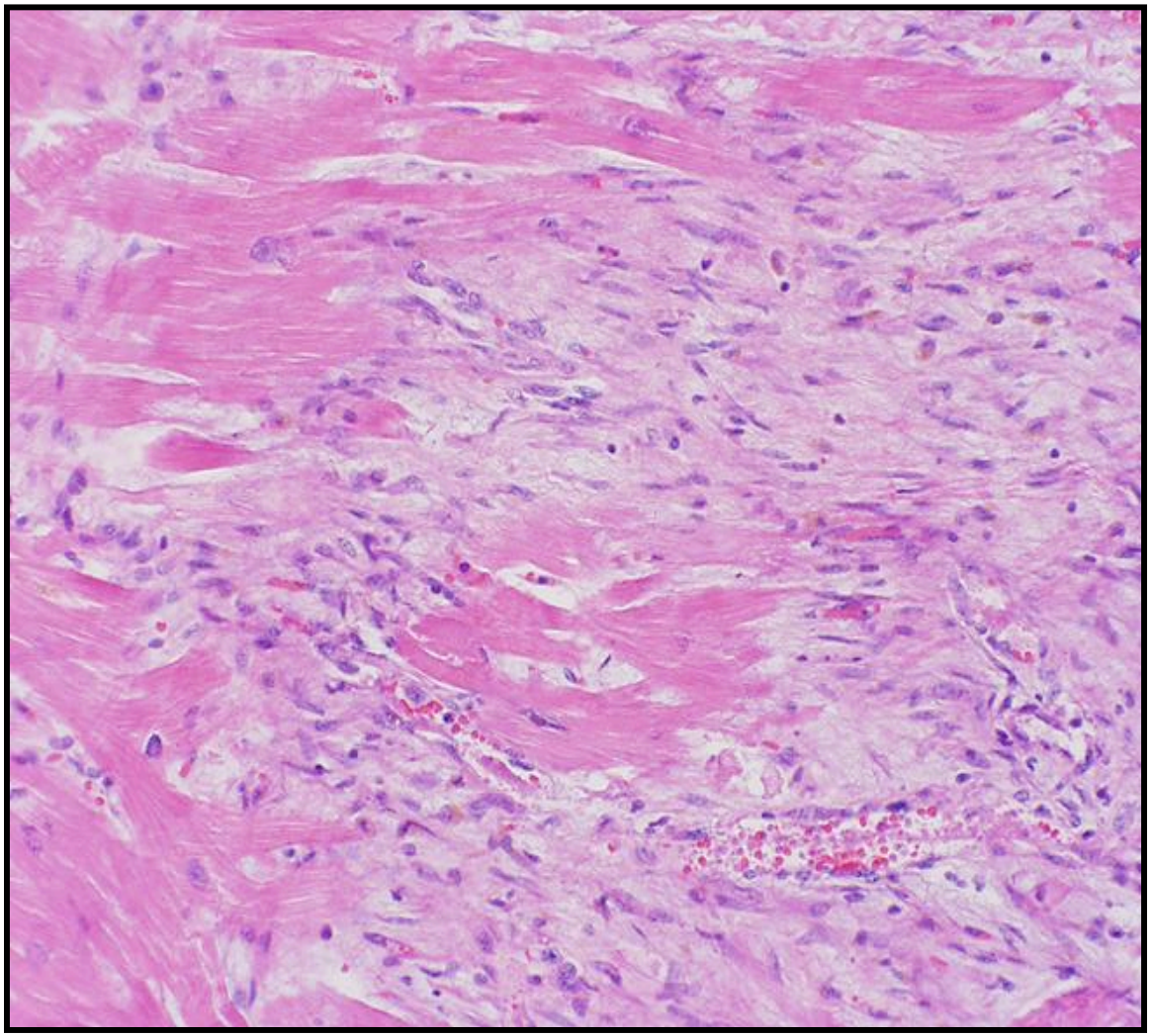
Edge of acute infarct

Myocardial Infarct - 6



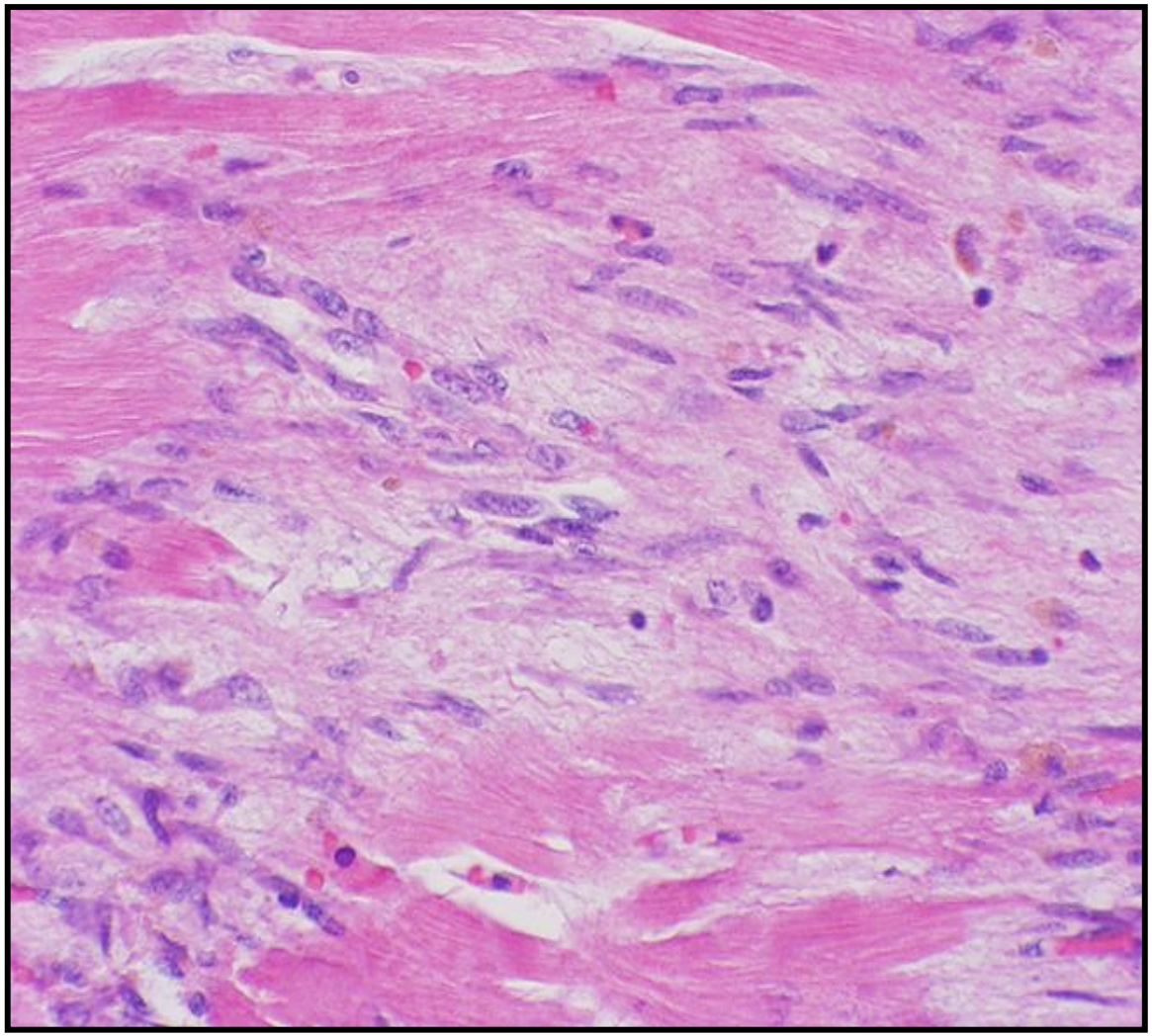
Edge of acute infarct

Myocardial Infarct - 7



Healing (remote) infarct

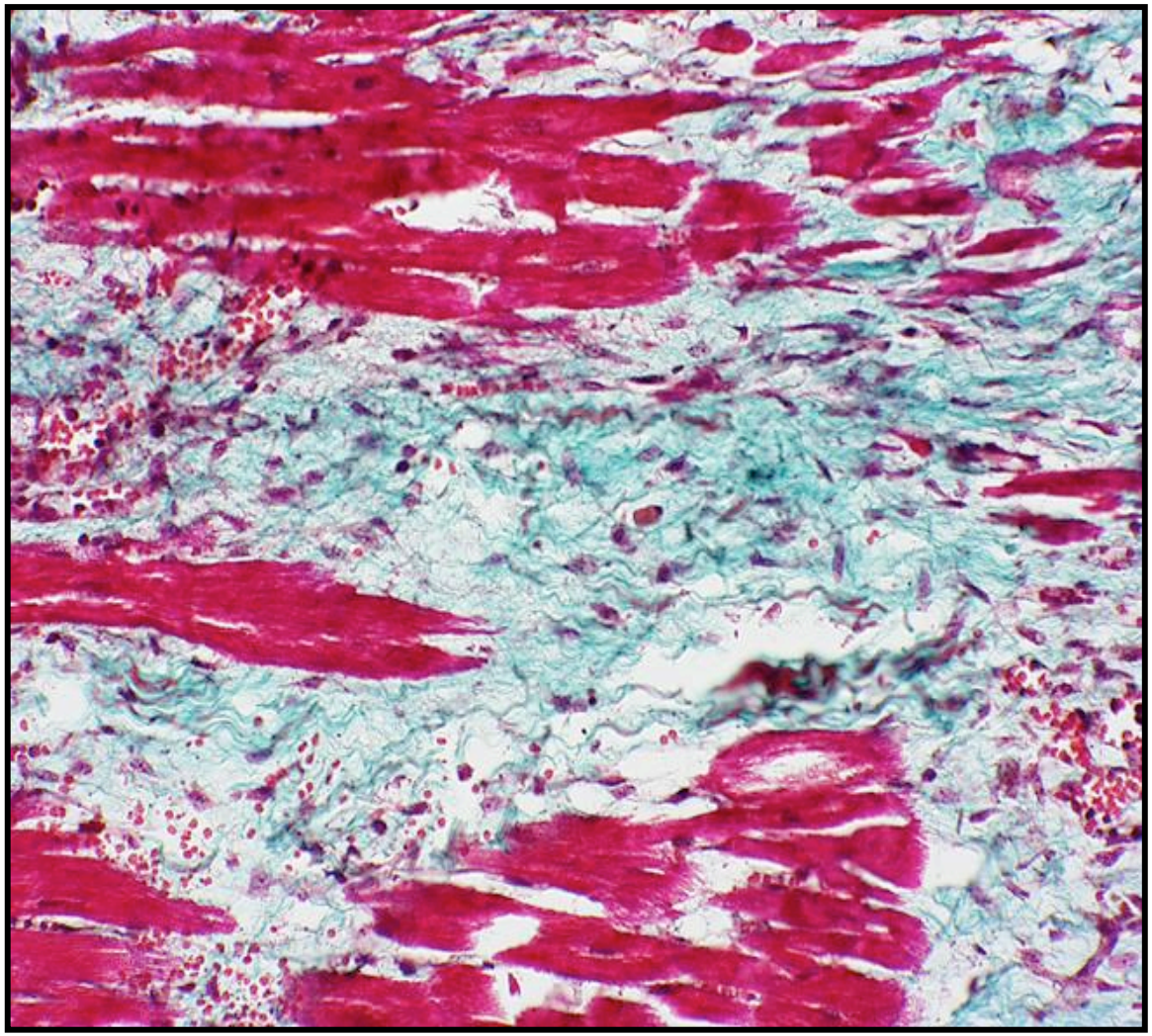
Myocardial Infarct - 8



Healing (remote) infarct

Myocardial Infarct - 9

shows scar formation

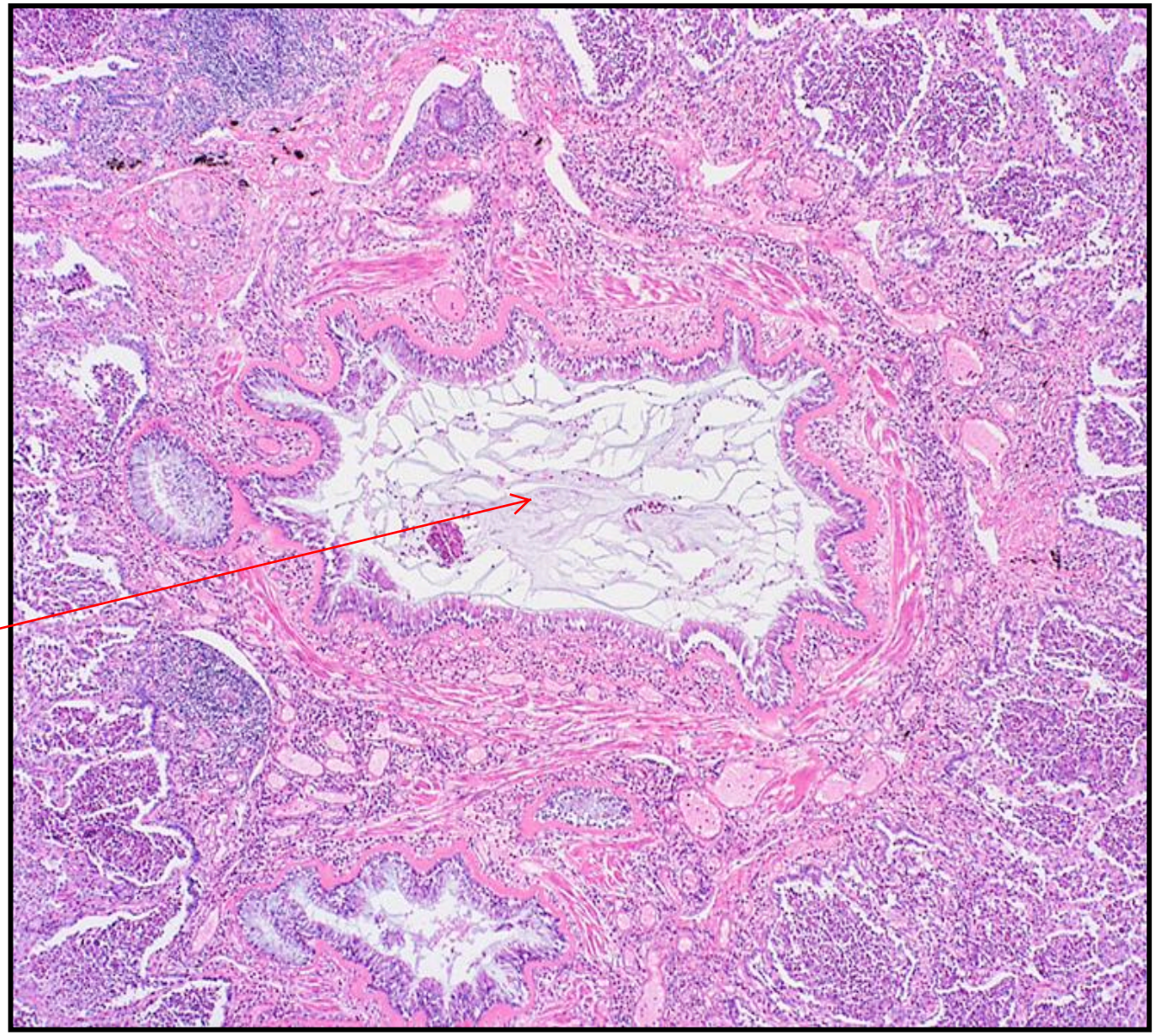


Masson trichrome stain for collagen

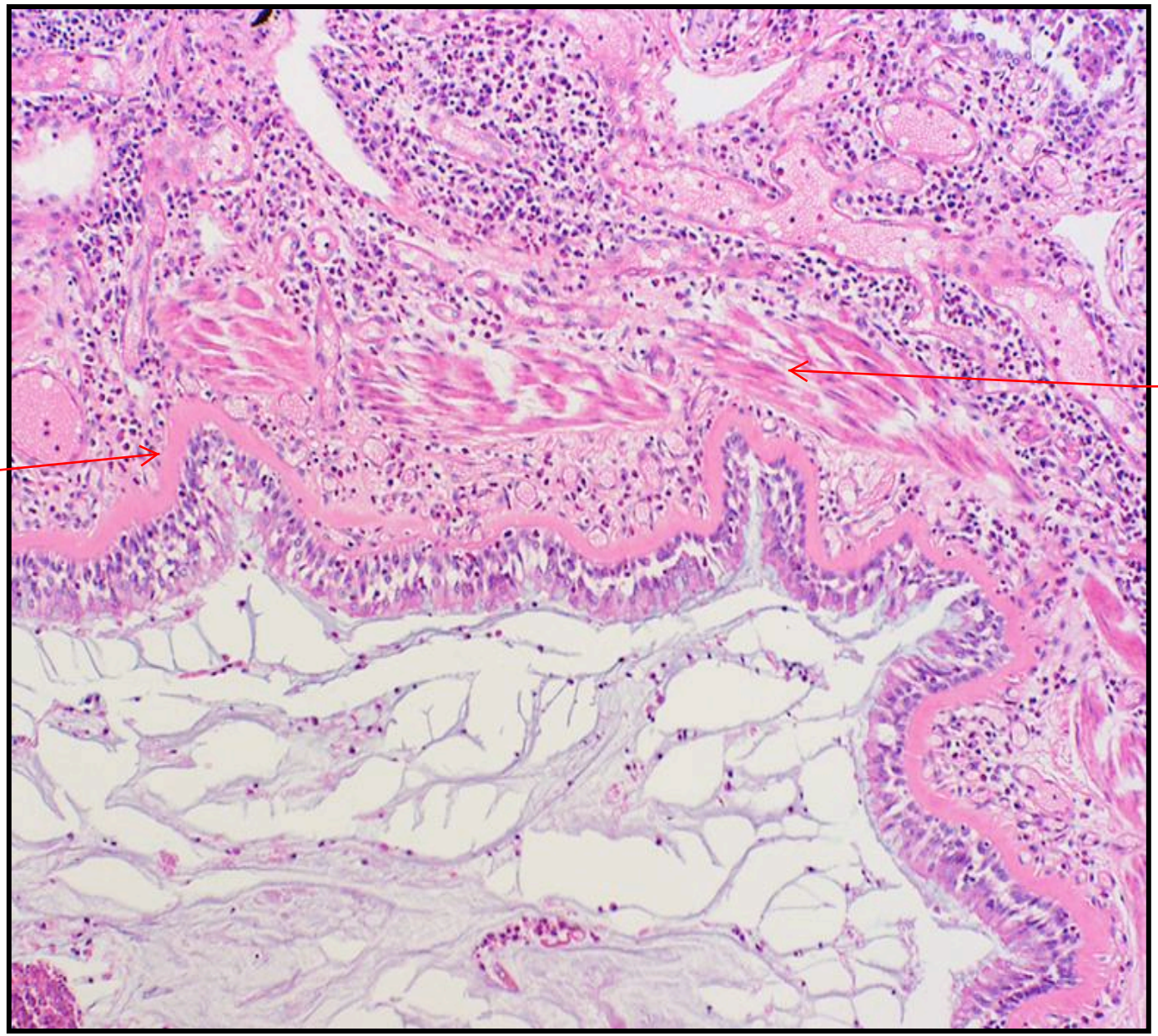
Case Study

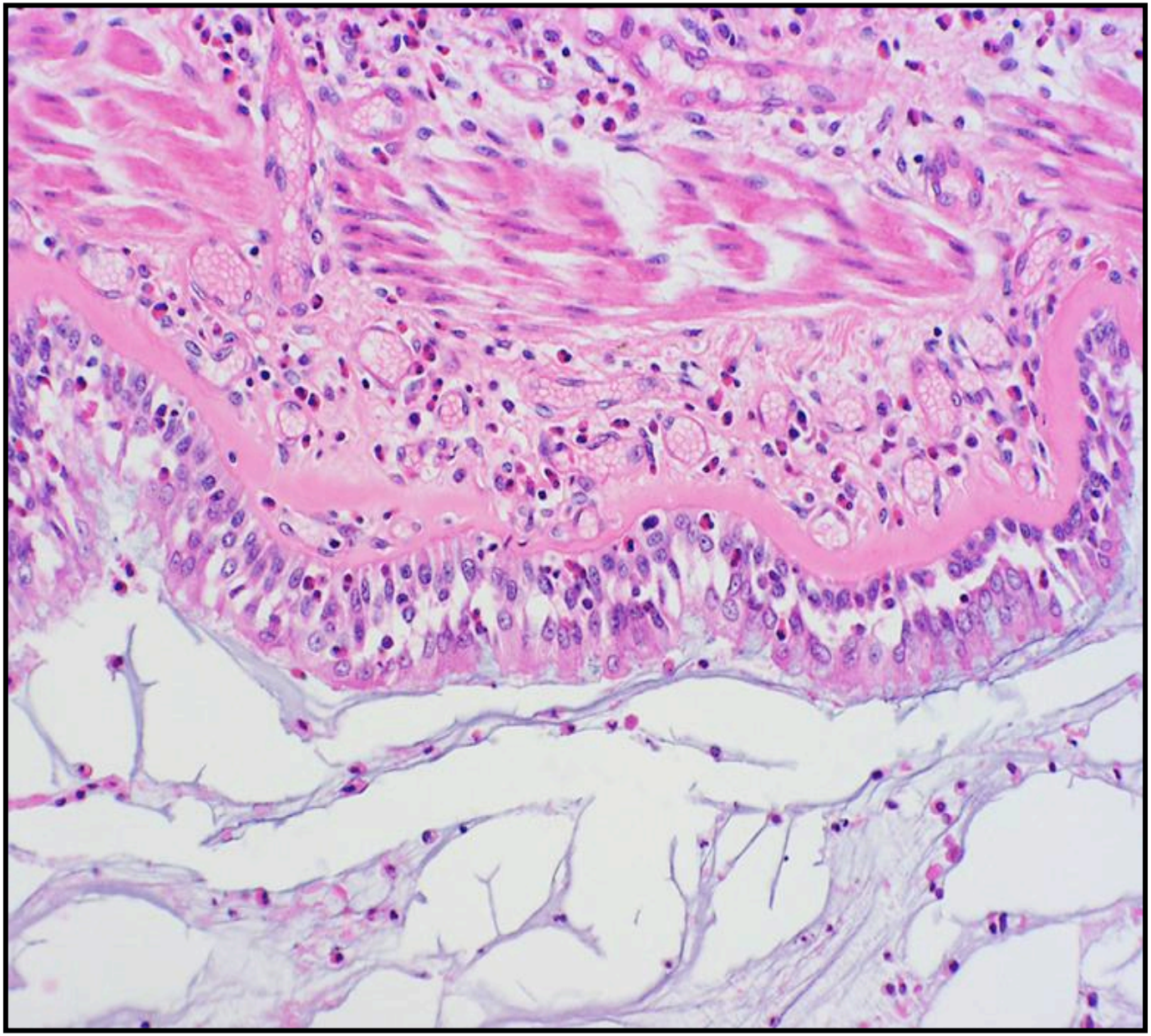
- 22-year-old black man developed severe respiratory distress
- Emergency Medical Services found the patient in cardiorespiratory arrest and could not resuscitate him

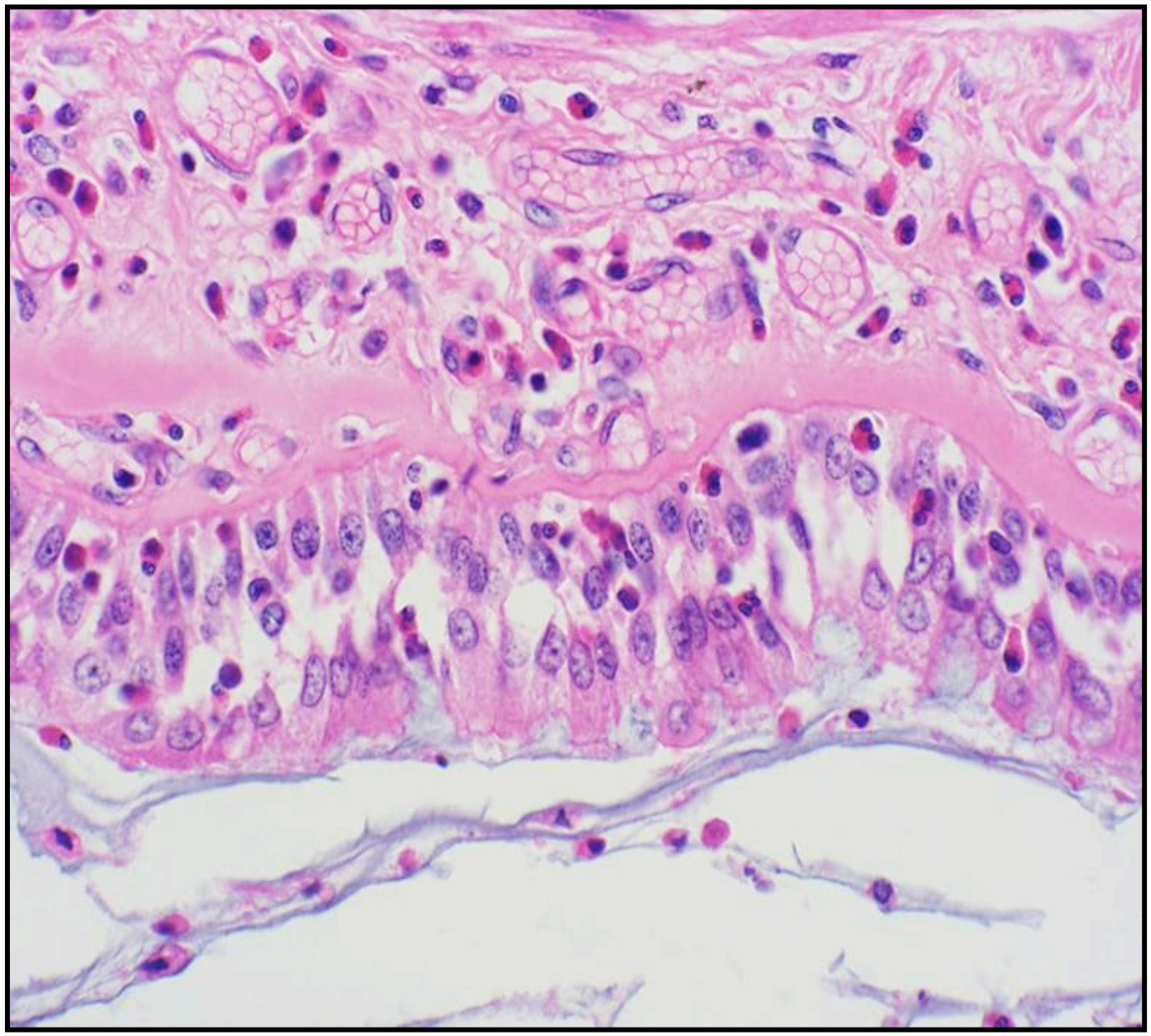
Shows one of his airways.



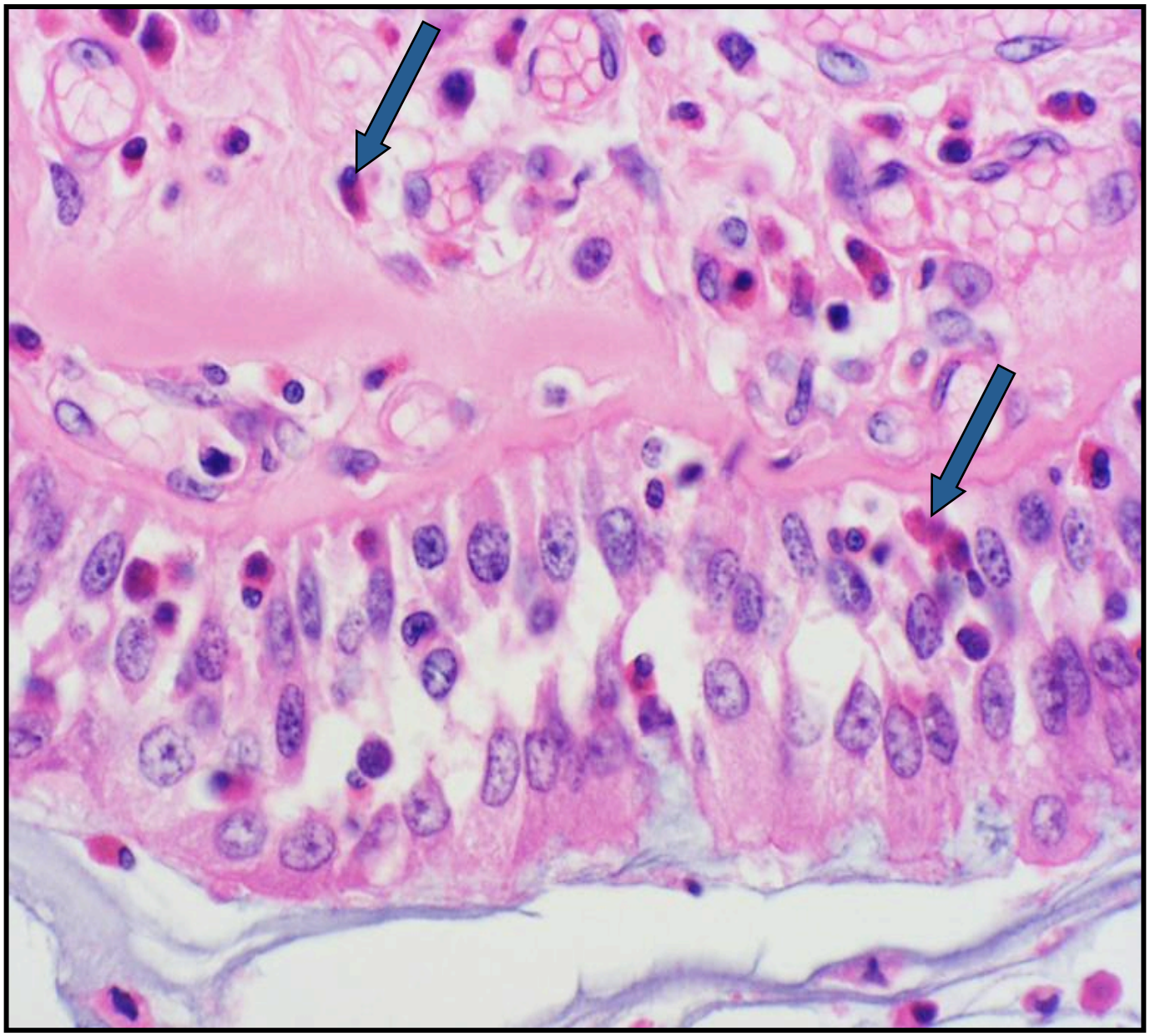
lumen with mucous inside.


basement membrane of the epithelium
smooth muscle of the bronchiole





bright pink cells are present....



Inflammatory Cell Type?

A) Lymphocytes

B) Eosinophils

C) Neutrophils

D) Macrophages

E) Multinucleated giant cells

Cause of the Inflammation?

A) Parasite

B) Allergy (IgE; asthma)

C) Bacterial pneumonia

D) Aspiration (foreign body) pneumonia

Case Study

- 47-year-old man with history of iv drug abuse
- Released from jail a few weeks prior to death; living in group home
- Three day history of headache and backache
- Found collapsed next to toilet

Cause of Death?

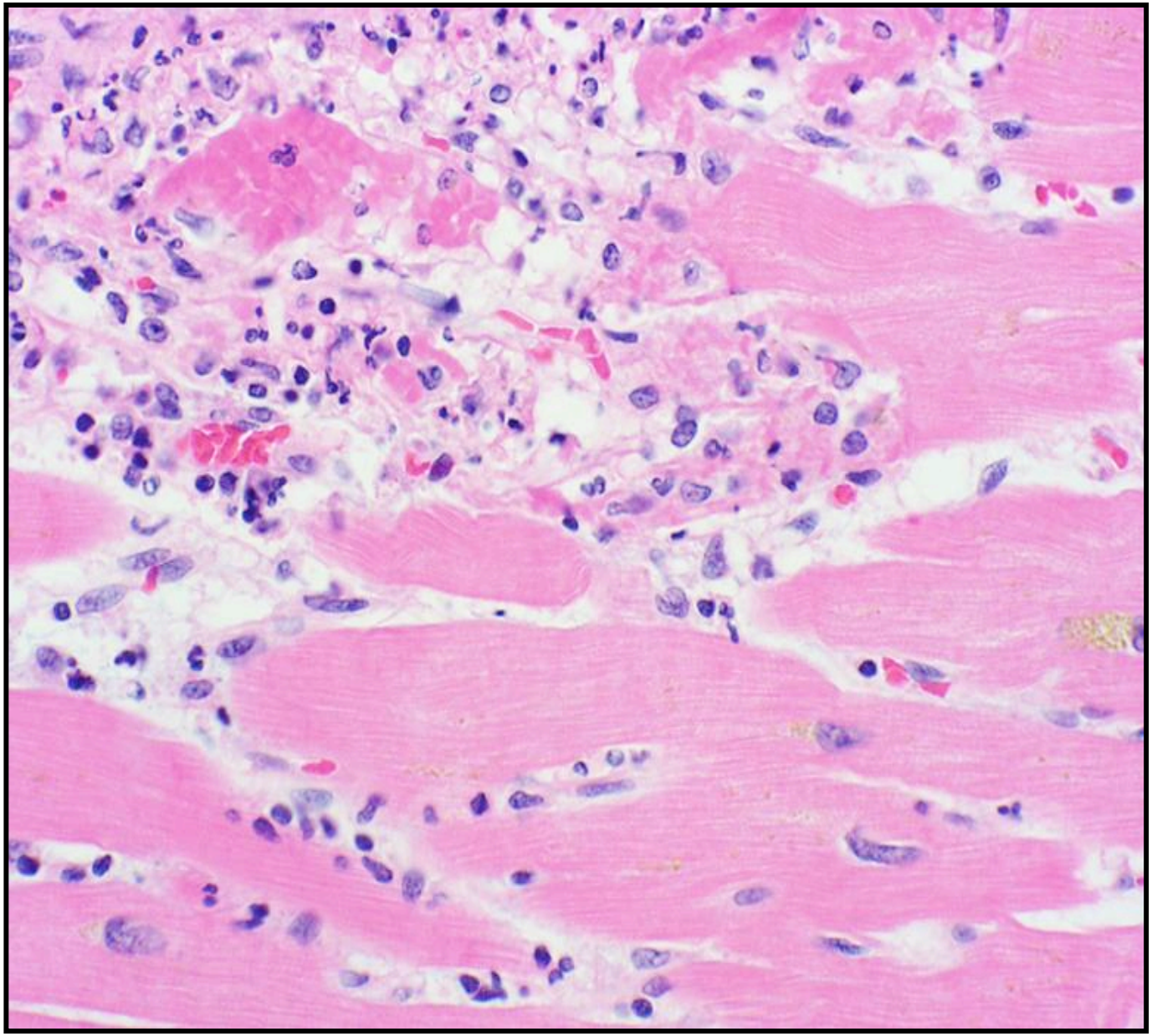
A) Accidental drug overdose

B) Homicide

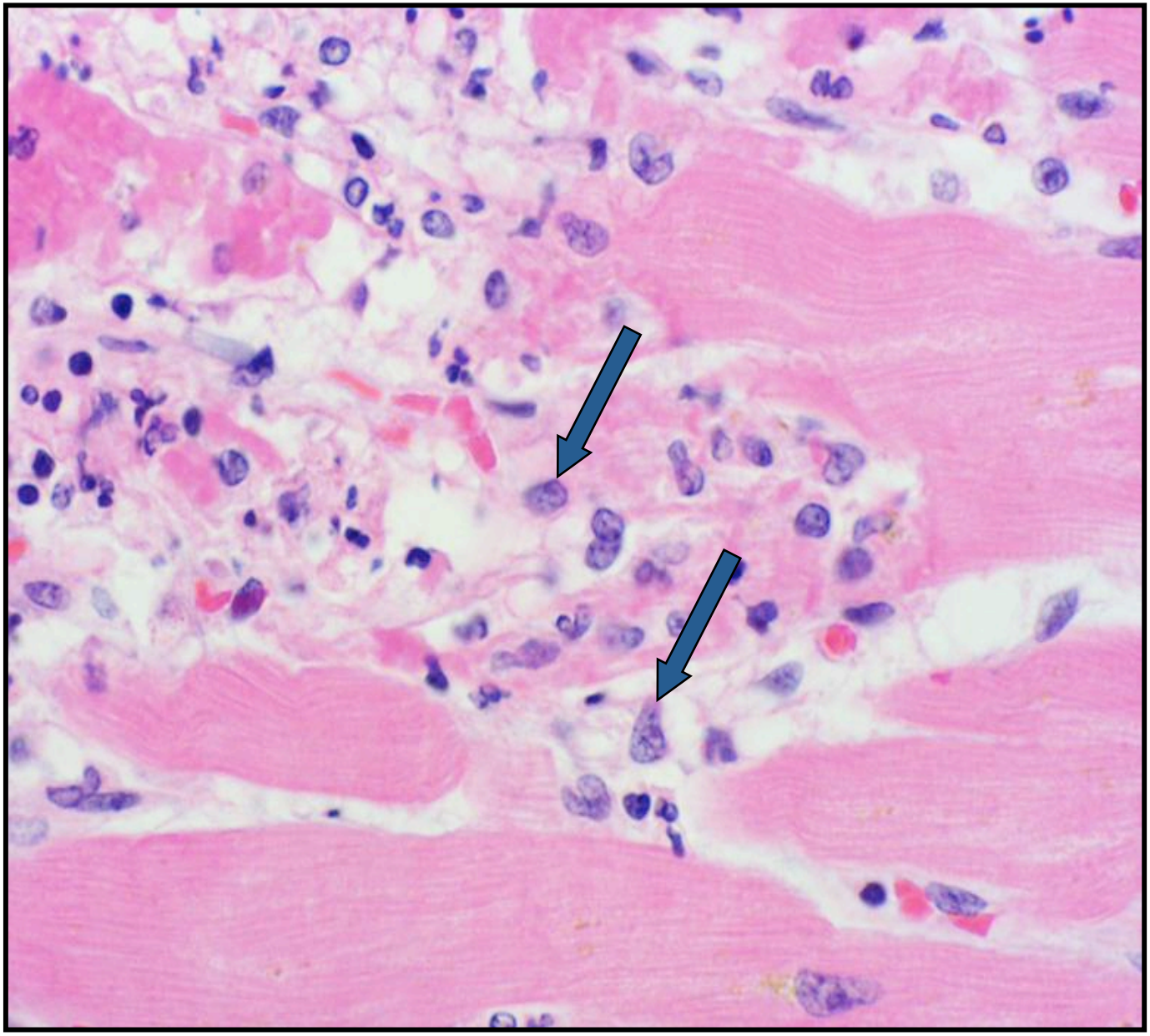
C) Suicide

D) Other

Shows his heart, with degradation of myocytes. Severe myocarditis



cells with a big cytoplasm and large nuclei



Inflammatory Cell Type?

A) Lymphocytes

B) Eosinophils

C) Neutrophils

D) Macrophages

E) Multinucleated giant cells

Toxicology

- Ethanol: None detected
- Cocaine: <0.02 mg/L
- Ecgonine methyl ester: 0.14 mg/L
  Benzoylecgonine: 1.7 mg/L
- Cocaethylene, codeine, morphine, and 6-monoacetylmorphine: None detected

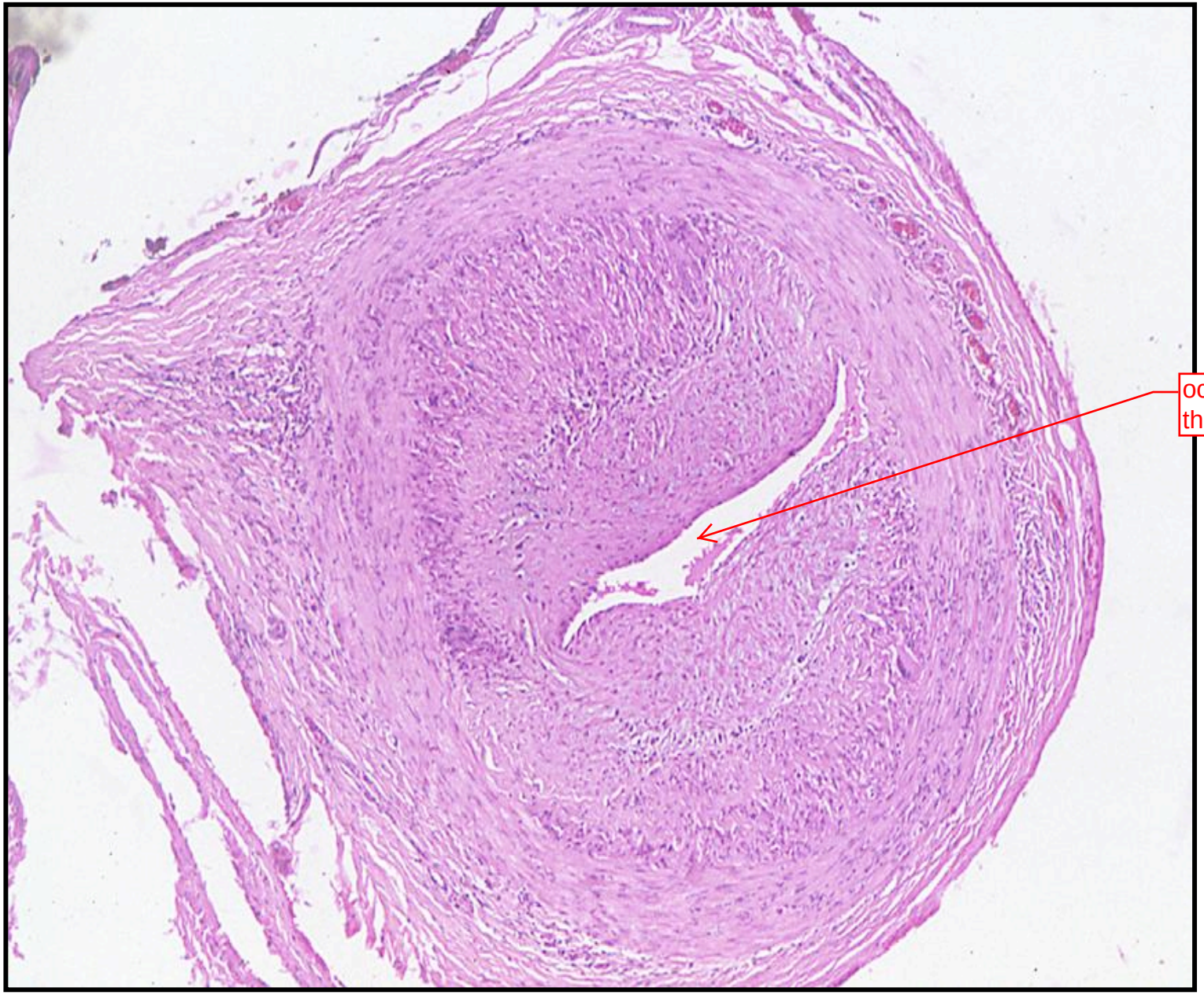
Death was actually from viral myocarditis, but the cocaine use could/may have contributed.

Case Study

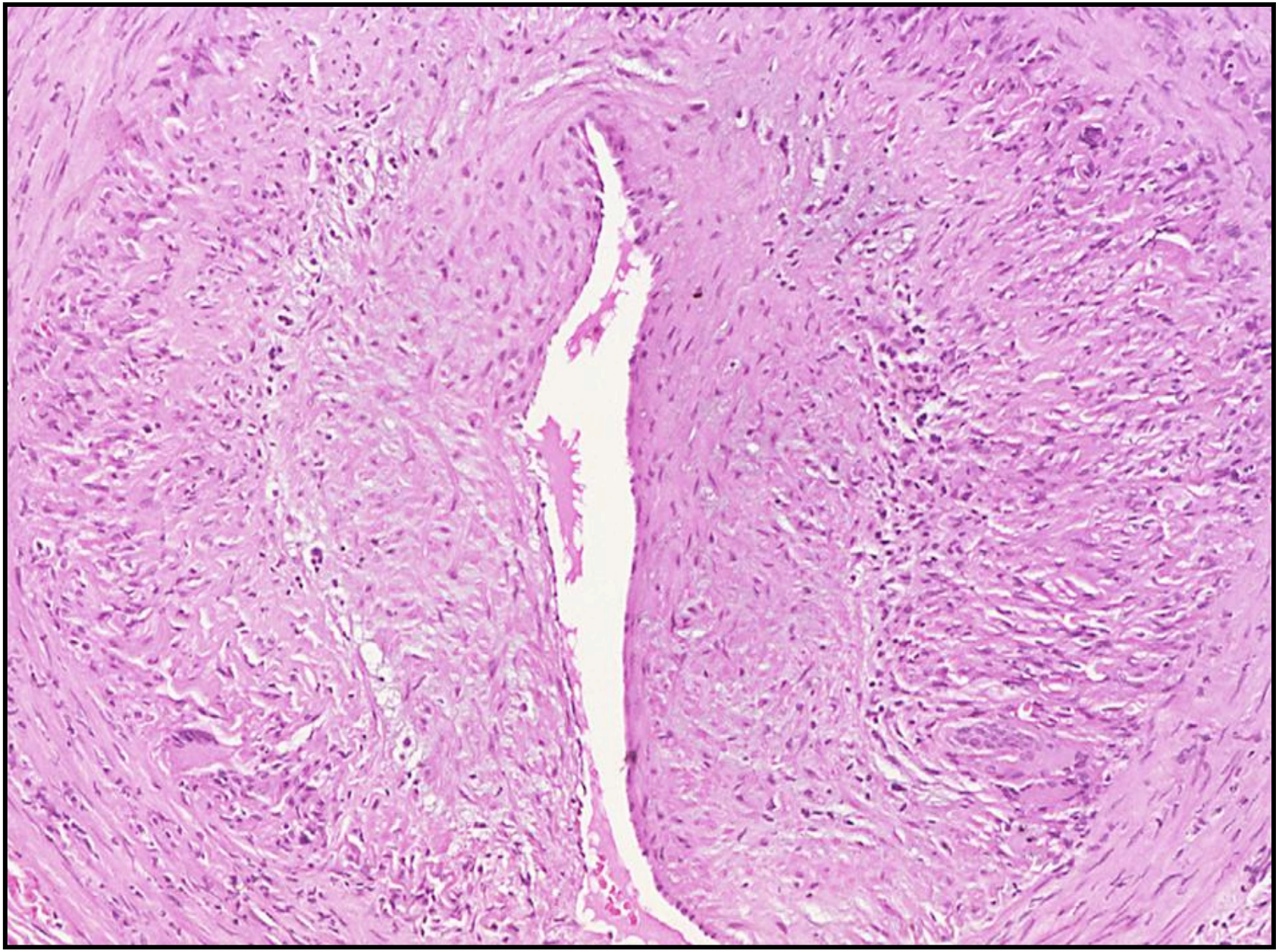
- 68-year-old woman with bitemporal headache, arthralgias, and ESR = 96 (normal <15)
- Decreasing visual acuity with pale optic discs
- Temporal artery biopsy performed

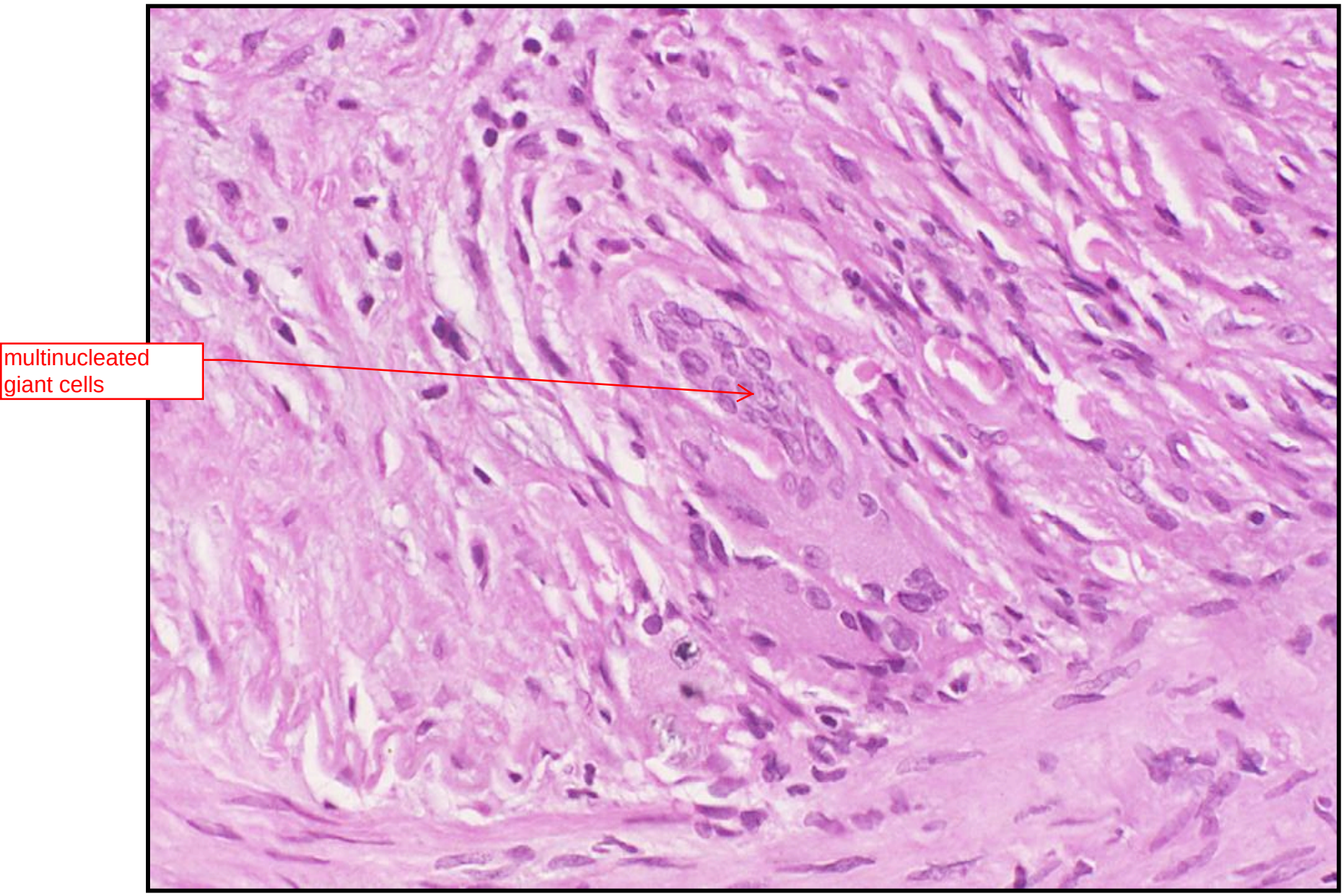
ESR is a sedimentation rate. How long it takes for blood cells to settle out.

actue phae reactions cause this to be elevated


occluded lumen of
the blood vessel

inflammation surrounding the vessel....




multinucleated
giant cells

Type of Inflammatory Response?

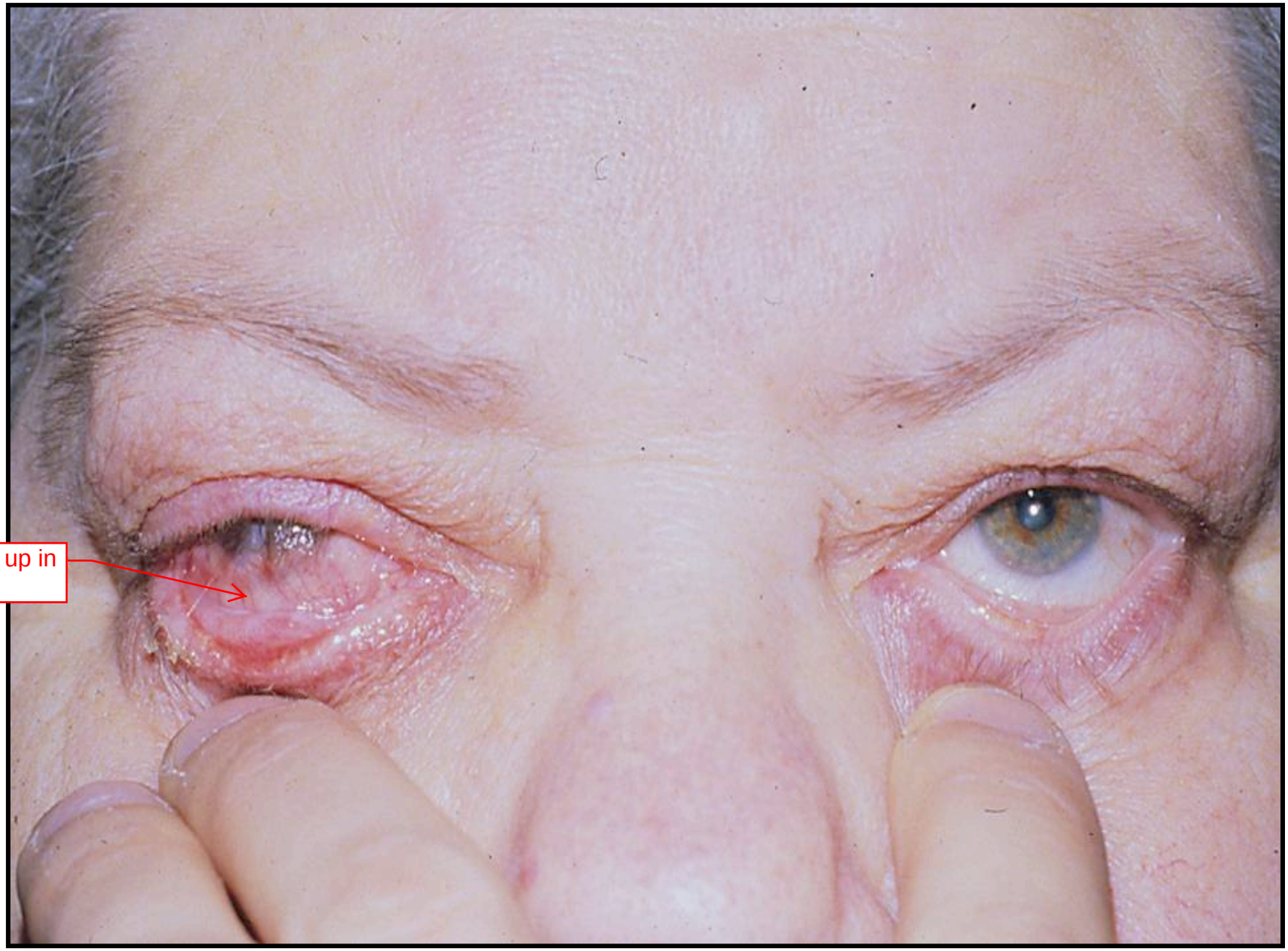
A) Acute

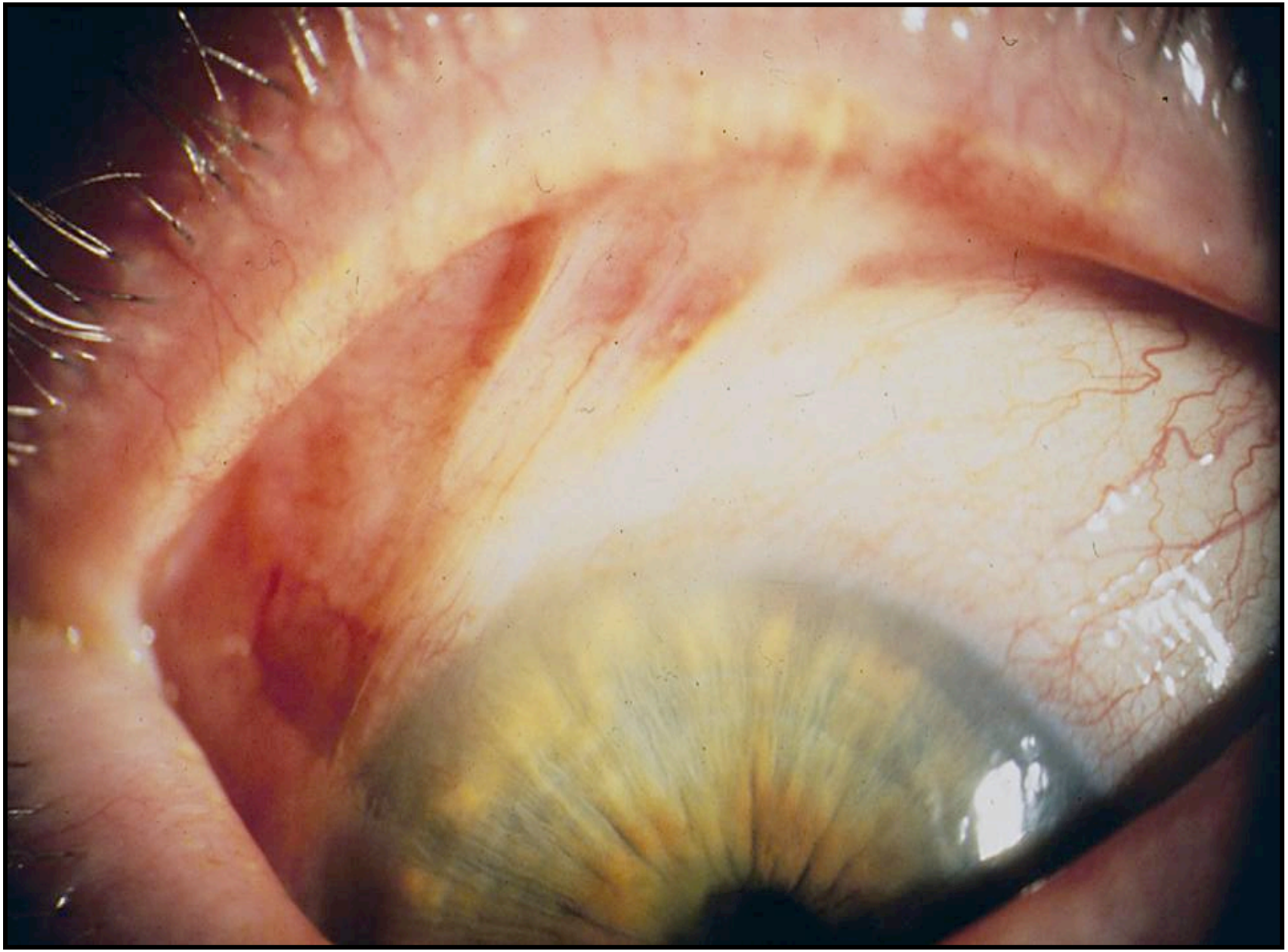
B) Chronic

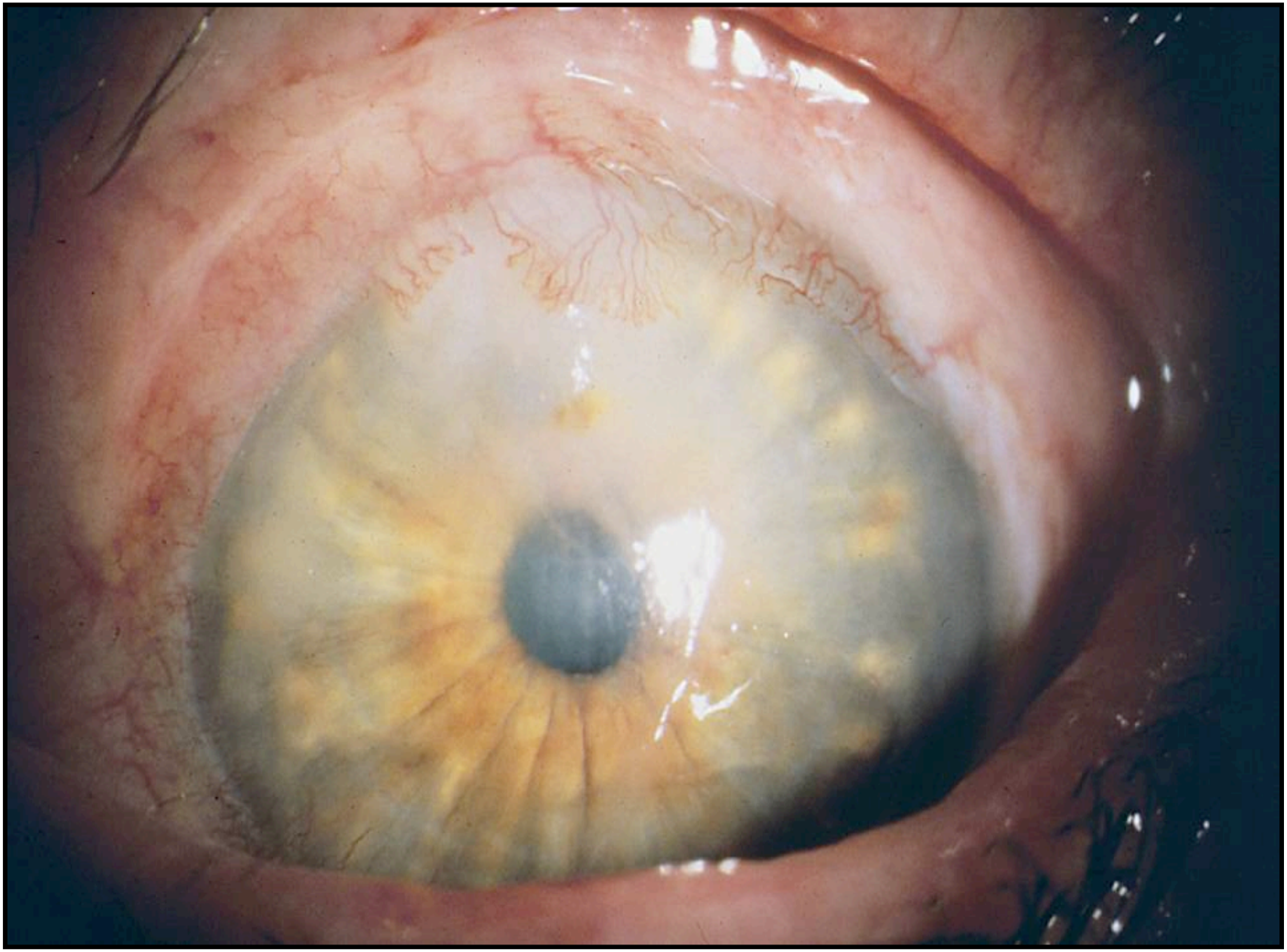
C) Granulomatous

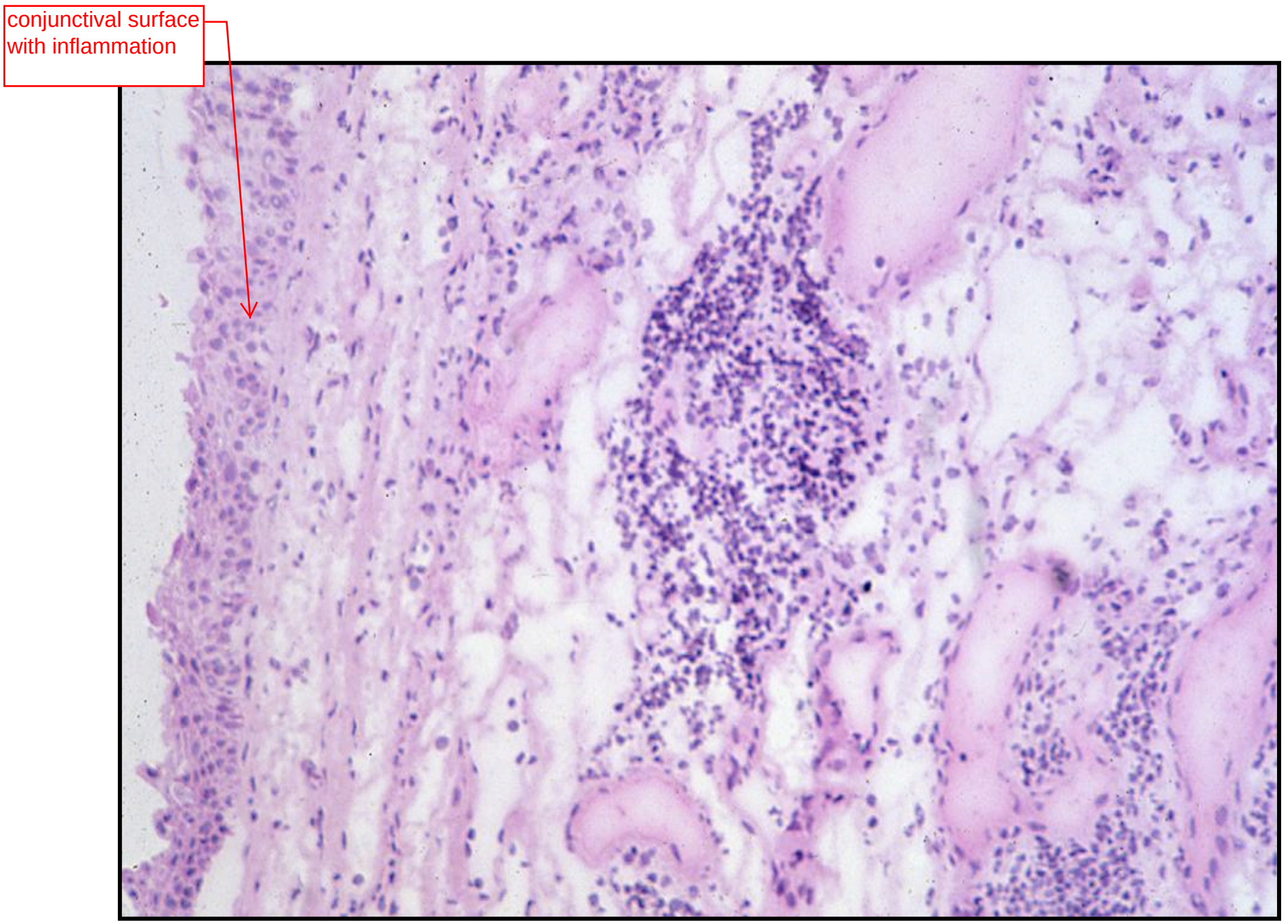
Case Study

- 67-year-old white woman with recurrent blisters in the mouth and conjunctiva
- Conjunctival scarring (symblepharon = adhesion of eyelid to eyeball)


scar tissue all up in ya eye.






conjunctival surface
with inflammation

Shows the immune process of debilitating scarring.

Cicatricial Pemphigoid

- An example of immune-mediated inflammation leading to debilitating scarring

Case Study

- 63-year-old woman with a blood alcohol level in the 190s fell and smashed her eyeglasses into her face
- Three months later she developed fullness under her right eyelid
- Incision and drainage led to no improvement so she underwent attempted excisional biopsy