Immune-Mediated Diseases

i.e. let's talk about a small subset auto-immune diseases.

In a Nutshell

His general style was to have relatively sparse slides but to cover everything on them. Thus, all the bullet points on all of the slides (unless otherwise noted) are probably fair game IMO.

Too much material to cover in one lecture, so he's just going to go through the key example diseases highlighted below. He's counting on your reading to fill in the gaps.

Objectives

Describe the epidemiology, clinical presentation, pathogenesis and pathologic changes of autoimmune diseases, including lupus erythematosis, rheumatoid arthritis, vasculitis, temporal arteritis and Wegener's granulomatosis

Hah!

Witch doctor waiting rooms

Immune system has access to many organ systems so there usually is involvement of multiple tissues in these diseases.

Systemic Lupus Erythematosus

He read all points on this slide.

Systemic lupus erythematosus: clinical features

Pleural surfaces and the lining of the peritineal cavity

- Febrile, multisystem inflammatory disease
- Variably affects wide range of organs and tissues, especially skin, kidneys, serosal surfaces, joints, heart
- Clinical course highly variable, often with multiple exacerbations and remissions
- Especially prevalent in young women, black Americans
- Prevalence: up to 1 to 2,500 persons "not common" but "not rare"

He read this slide.

Systemic lupus erythematosus: pathogenesis

Autoantibodies develop against a variety of antigens:

- **Nucleoproteins / nucleic acids**
  - **DNA**
  - **histones**
  - **nonhistone RNA-binding proteins**
- **Blood cells**
  - **erythrocytes**
  - **platelets**
  - **lymphocytes** and other leukocytes.
- **Phospholipids (e.g., “lupus anticoagulant”)**

recall the misnomer, it's only an anticoagulant in vitro, it's a pro-coagulant in vivo.

He read this slide too (with some additions). The main point is that the antibodies bind to antigens either in the blood or directly on cells and then trigger inflammation and cytotoxicity.

Systemic lupus erythematosus: pathogenesis

2 different routes of pathogenesis

Soluble antigens

Antigen-antibody immune complexes form in the blood.

Particularly lodge in blood vessels (kidney is a great place)

Complexes deposit in numerous sites, initiate complement cascade, and trigger inflammation

Type III Hypersensitivity

Non-Soluble Antigens

Antibody bound to cells leads to lysis via complement-mediated cytotoxicity or ADCC

Antibody-Dependent Cell-mediated Cytotoxicity

Type II Hypersensitivity

Brief intro to the 4 different types of hypersensitivity:
1) Anaphylaxtic reaction (like allergies), IgE-mediated (and then Mast Cells)
2) Antibody-mediated (IgG and IgM).
3) Immune-complex mediated (antibody and antigen meet in the fluid and THEN deposit)
4) "Delayed-Type" or "Cell-mediated". T-Cells hitting antigens and then causing a cascade.

Systemic lupus erythematosus: pathogenesis

Possible causes of autoantibody production

We just don't know.

Intrinsic B cell defect

Some people's B-cells might be inherently hypersensitive to being activated

Excessive helper T cell activity

Deficient suppressor T cell activity

Another possibility: you get infected with a microbe whose antigens look like your own tissue. E.g. bacterial dsDNA might be antigenic and cause autoimmunity against your own dsDNA. This theory is speculative at this point.

TABLE 6–5. THE 1982 REVISED CRITERIA FOR THE CLASSIFICATION OF SLE*

1. Butterfly rash
2. Discoid lupus
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
   a. Pleuritis: rub heard by a physician or pleural effusion, *or*
   b. Pericarditis: documented by EKG or rub, or evidence of pericardial effusion
7. Renal disorder
   a. Persistent proteinuria > 0.5 gm/dl/day
   b. Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder
   a. Seizures: in the absence of offending drugs or known metabolic derangements
   b. Psychosis in the absence of offending drugs
9. Hematopoetic disorder
   a. Hemolytic anemia: with reticulocytosis *or*
   b. Leukopenia: 4000 cells/μl on two or more occasions *or*
   c. Lymphopenia: 1500 cells/μl on two or more occasions *or*
   d. Thrombocytopenia: 100,000/μl in the absence of offending drugs
10. Immunologic disorder
    a. Positive LE cell preparation *or*
    b. Anti-DNA: presence of antibody to untreated DNA in abnormal titer *or*
    c. Anti-Sm: presence of antibody to Sm nuclear antigen *or*
    d. False-positive STS known to be positive for at least six months and confirmed by TPI or FTA tests
11. Antinuclear antibody. An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

This is usually positive (~10% don't though).

This slide demonstrates that the diagnosis of lupus hasn't changed much over time.

-

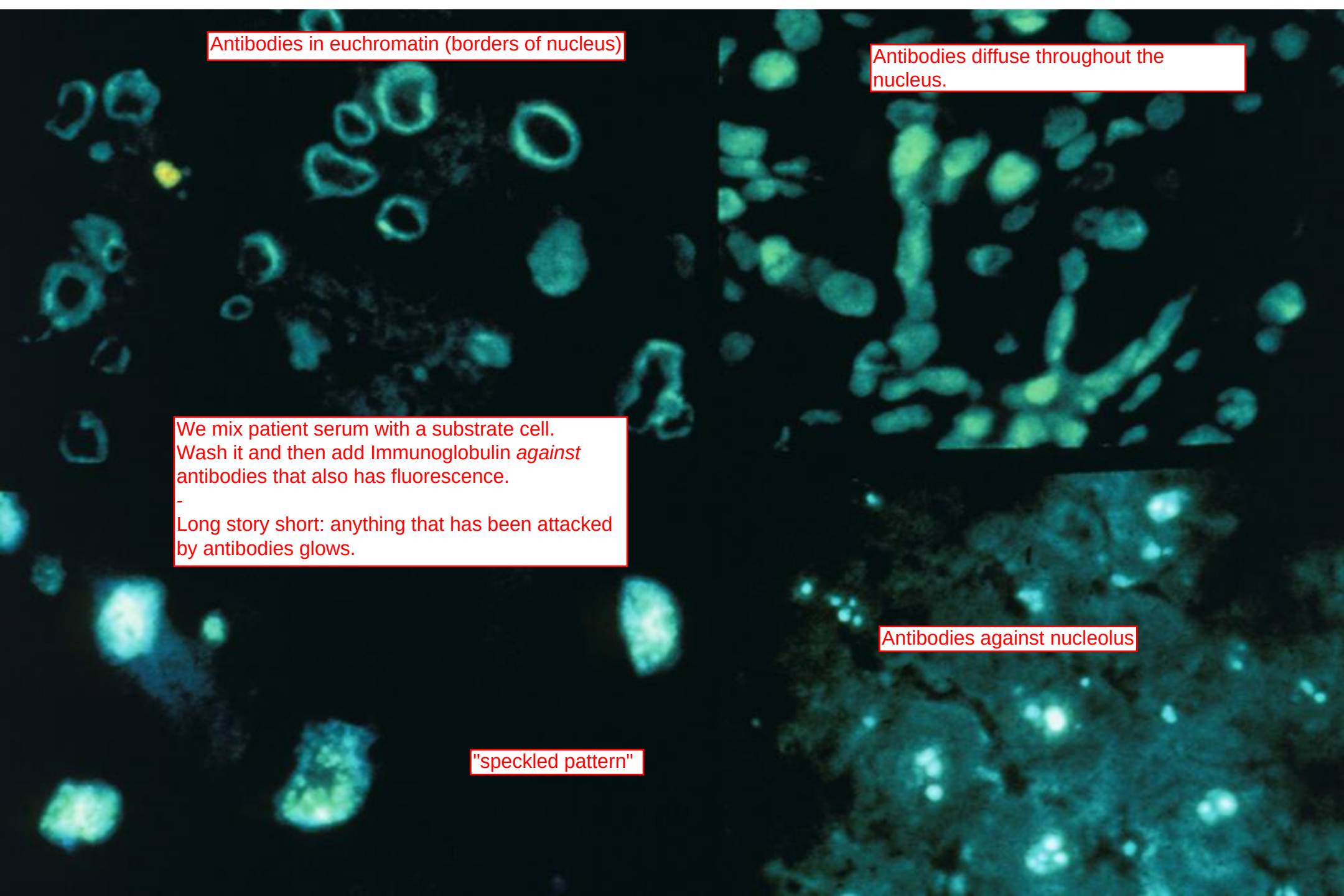
Back in 1982 this was the criterion for diagnosis. It's not that much different now adays, we still use all of these now.

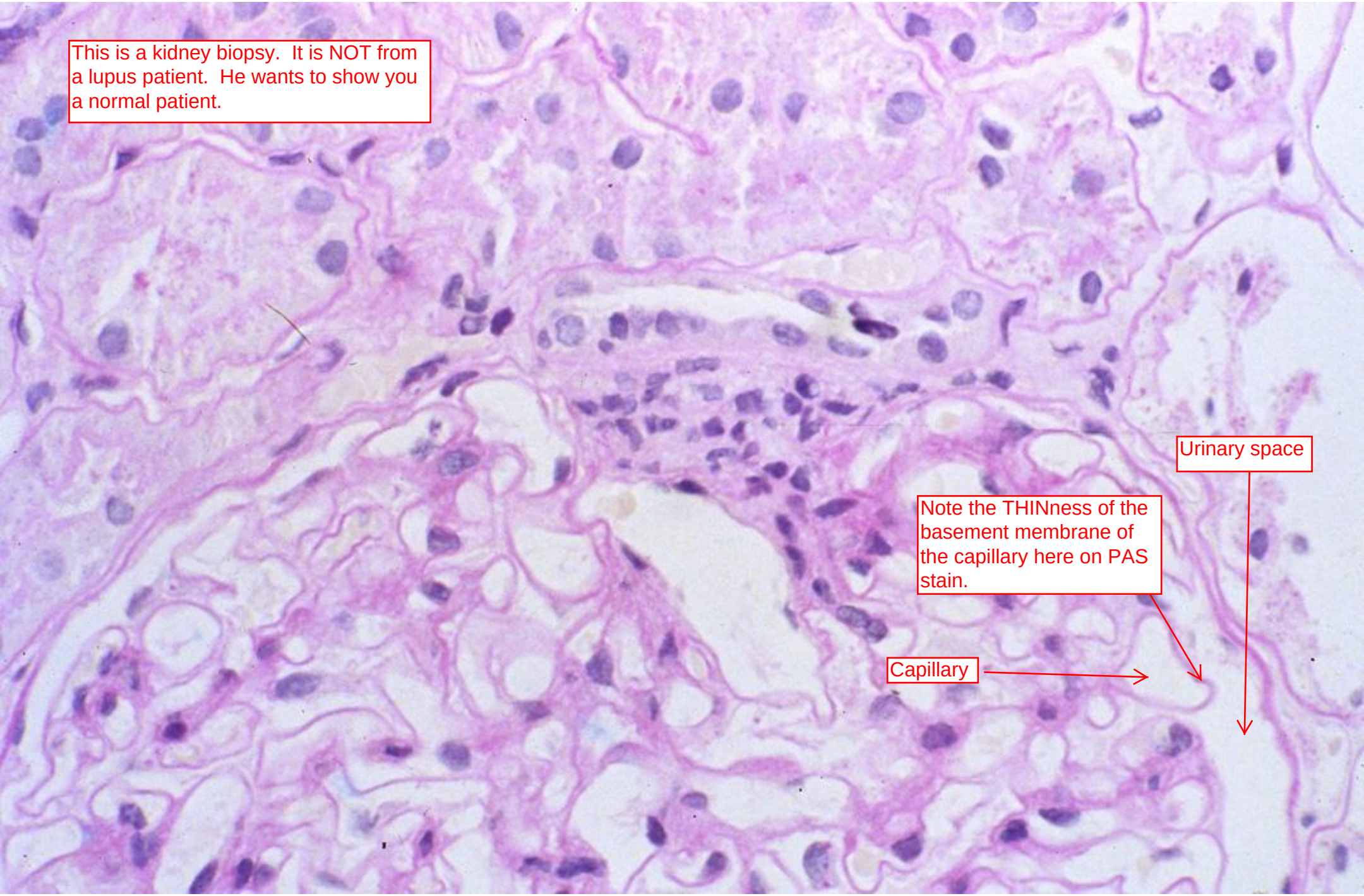
-

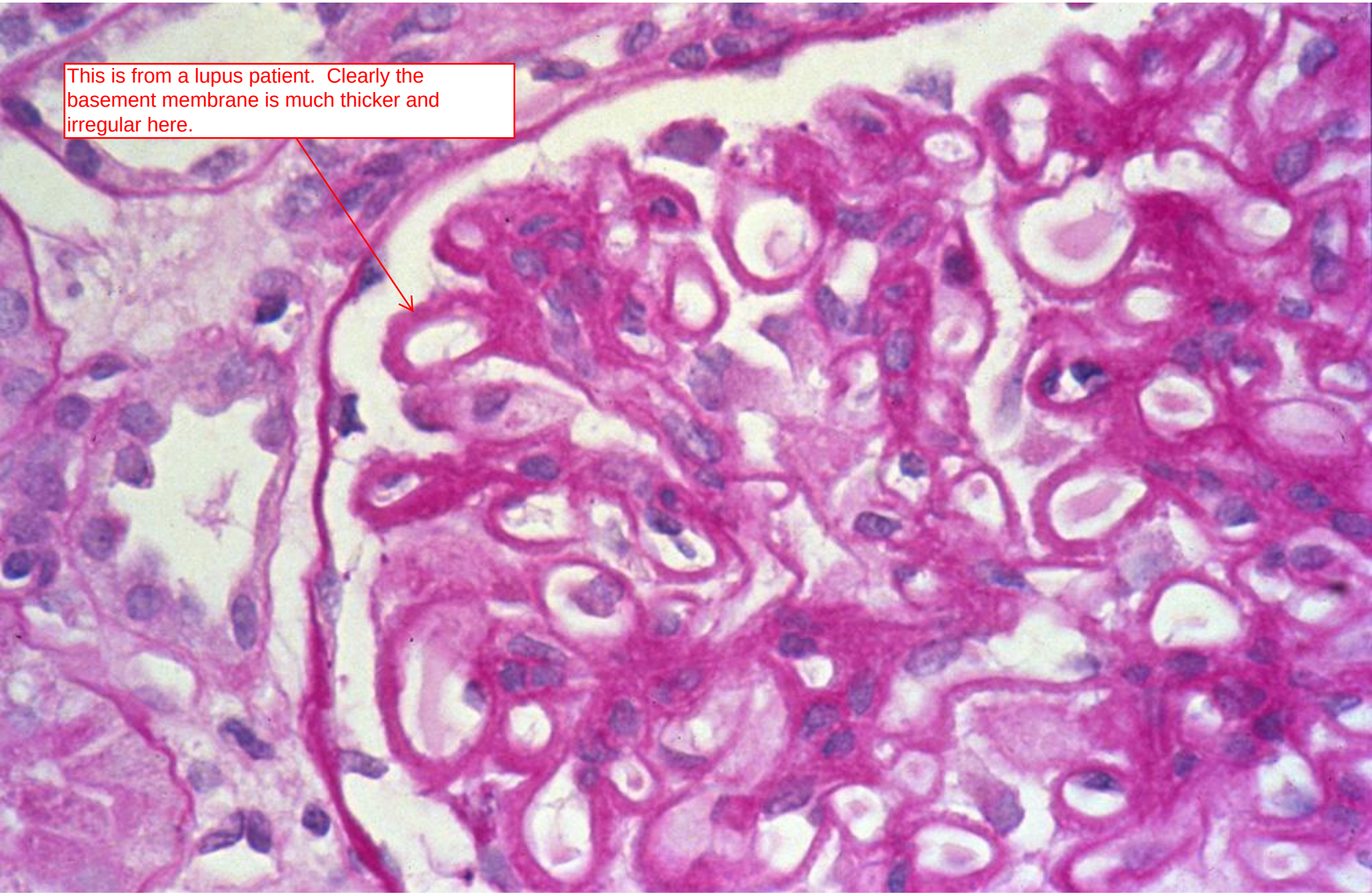
For the diagnosis of lupus, you have to have 4 of 11 (disease symptoms are very disparate and thus hard to diagnosis some times).

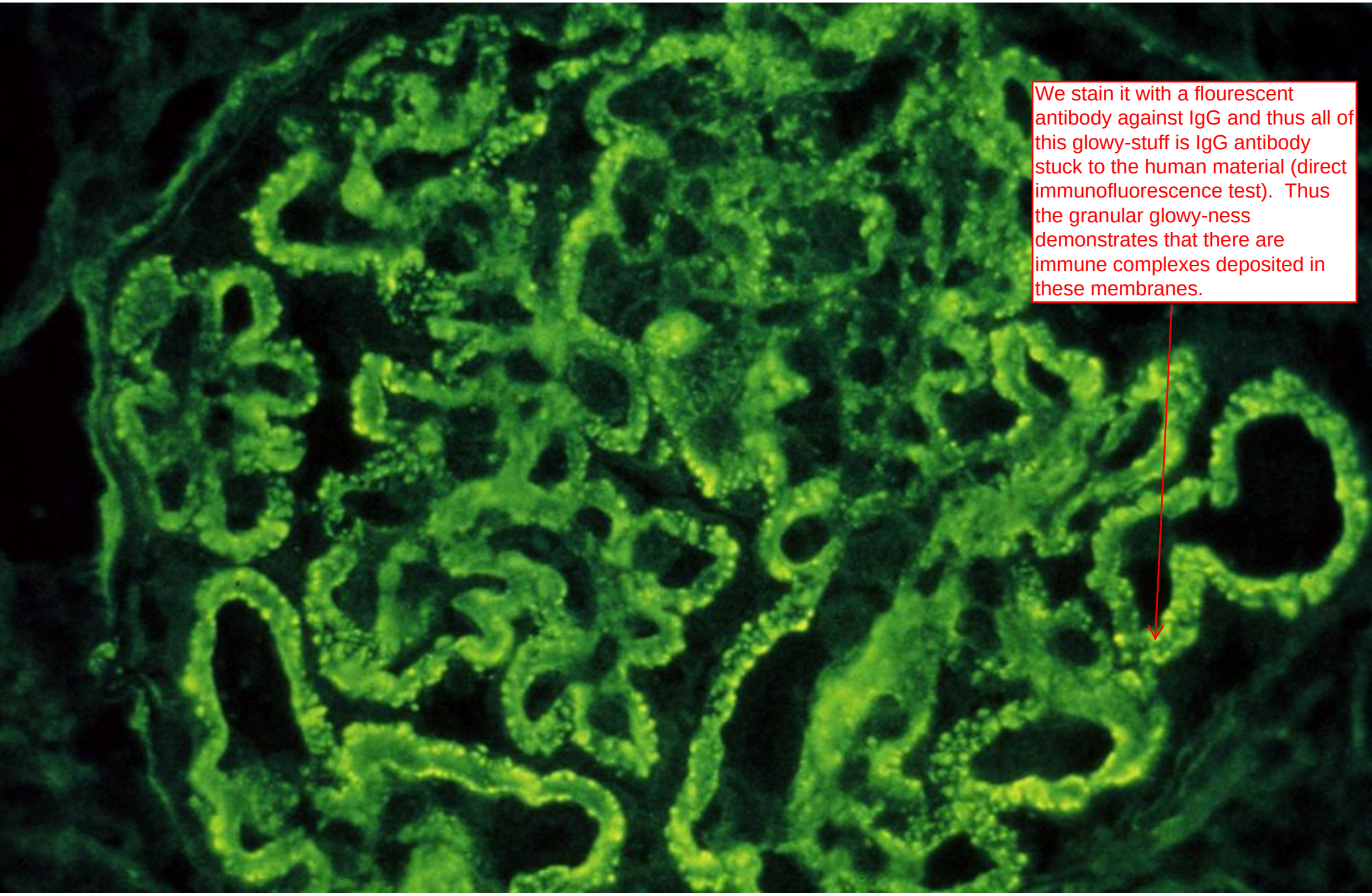
-

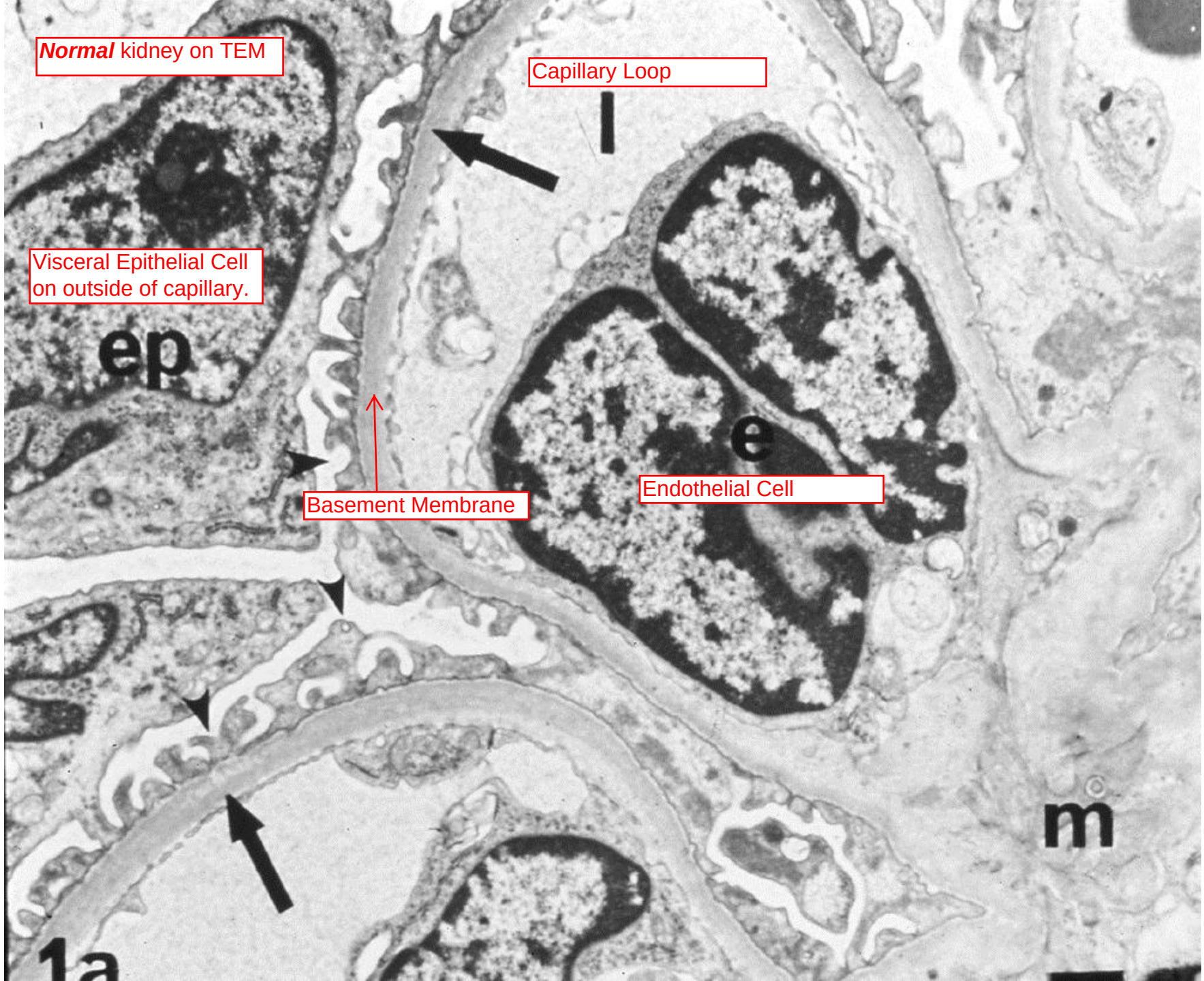
He read all of the major bullet points (but didn't do the subdetails within the headings).

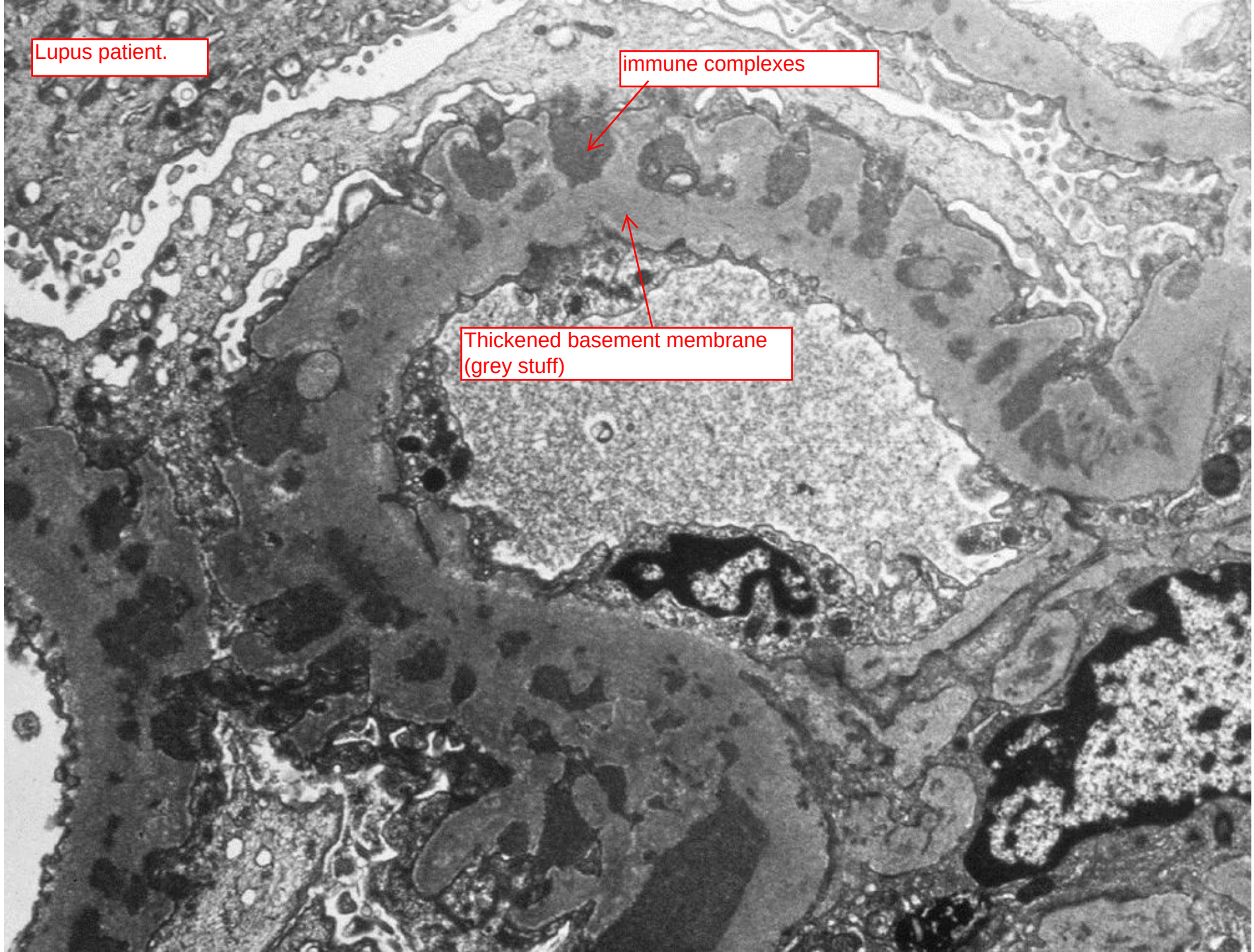

Antibodies in euchromatin (borders of nucleus)
Antibodies diffuse throughout the nucleus.
We mix patient serum with a substrate cell.
Wash it and then add Immunoglobulin *against* antibodies that also has fluorescence.
-
Long story short: anything that has been attacked by antibodies glows.
Antibodies against nucleolus
"speckled pattern"


This is a kidney biopsy. It is NOT from a lupus patient. He wants to show you a normal patient.
Urinary space
Note the THINness of the basement membrane of the capillary here on PAS stain.
Capillary


This is from a lupus patient. Clearly the basement membrane is much thicker and irregular here.


We stain it with a flourescent antibody against IgG and thus all of this glowy-stuff is IgG antibody stuck to the human material (direct immunofluorescence test). Thus the granular glowy-ness demonstrates that there are immune complexes deposited in these membranes.


Normal kidney on TEM
Capillary Loop
Visceral Epithelial Cell
on outside of capillary.
ep
e
Endothelial Cell
Basement Membrane
m
1a


Lupus patient.
immune complexes
Thickened basement membrane
(grey stuff)

Next disease.

Rheumatoid Arthritis

He read this slide.

Rheumatoid arthritis: clinical features

- **Systemic, chronic inflammatory disease**
- **Principally affects joints: severe, deforming, symmetric polyarthritis**
- **May involve other organs and tissues (e.g., skin, heart, blood vessels, muscles, lungs)**
- **Onset generally in 3rd or 4th decade**
- **Especially prevalent in women**
- **Prevalence: approximately 1% of population**

has waxing and waning of its course.

"poly" means affects multiple joints. symmetric means both sides of the body (as opposed to something like an infectious arthritis).

Very common.

Rheumatoid arthritis: pathogenesis

hypothesized

Activation of CD4+ T cells, possibly by arthritogenic infectious agent

which leads to

Lymphokine production

which lead to

Why do we need anti-antibodies? It's a way for the body to downregulate an immune response if the infectious agent has already been dealt with.

Rheumatoid arthritis: pathogenesis

Activation of macrophages and other inflammatory cells, with subsequent tissue destruction

and

Activation of B cells, including some producing autoantibodies (e.g., IgG anti-IgG, or rheumatoid factor); immune complex formation

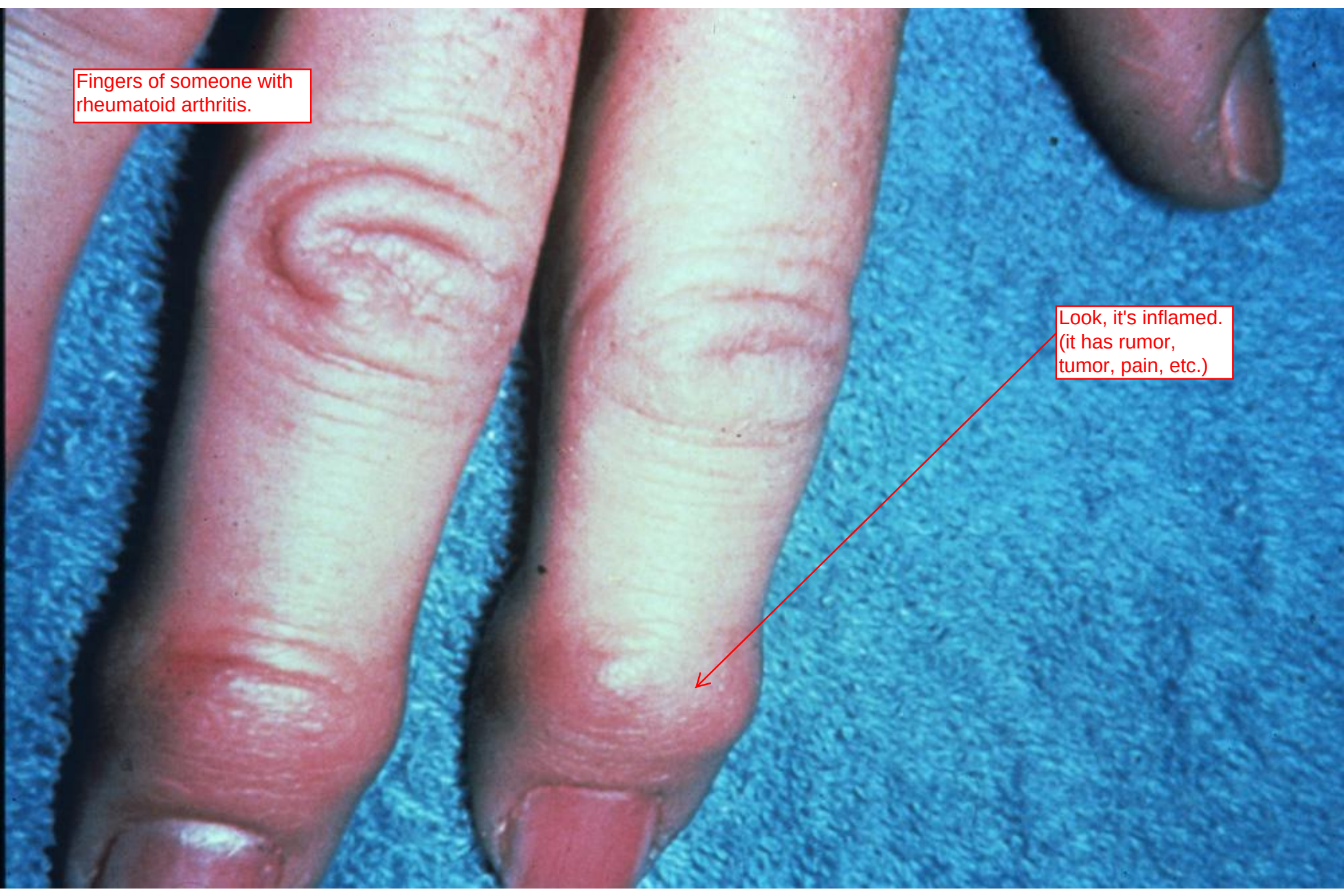
rheumatoid factor is an Ig that reacts with OTHER Igs (the constant portions). These IgG-Anti-IgG-complexes and form these immune complexes that deposit.

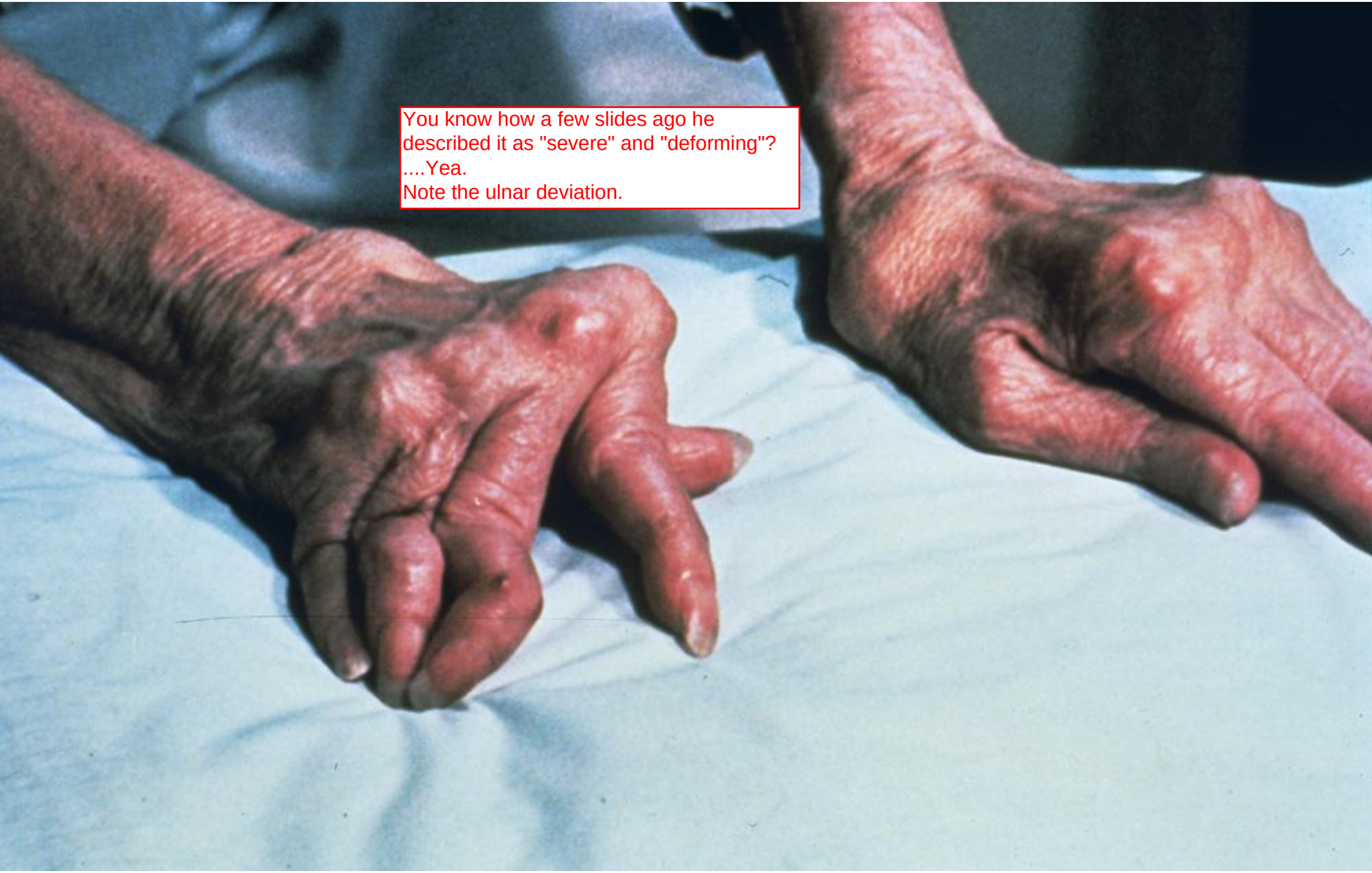
Type IV hypersensitivity

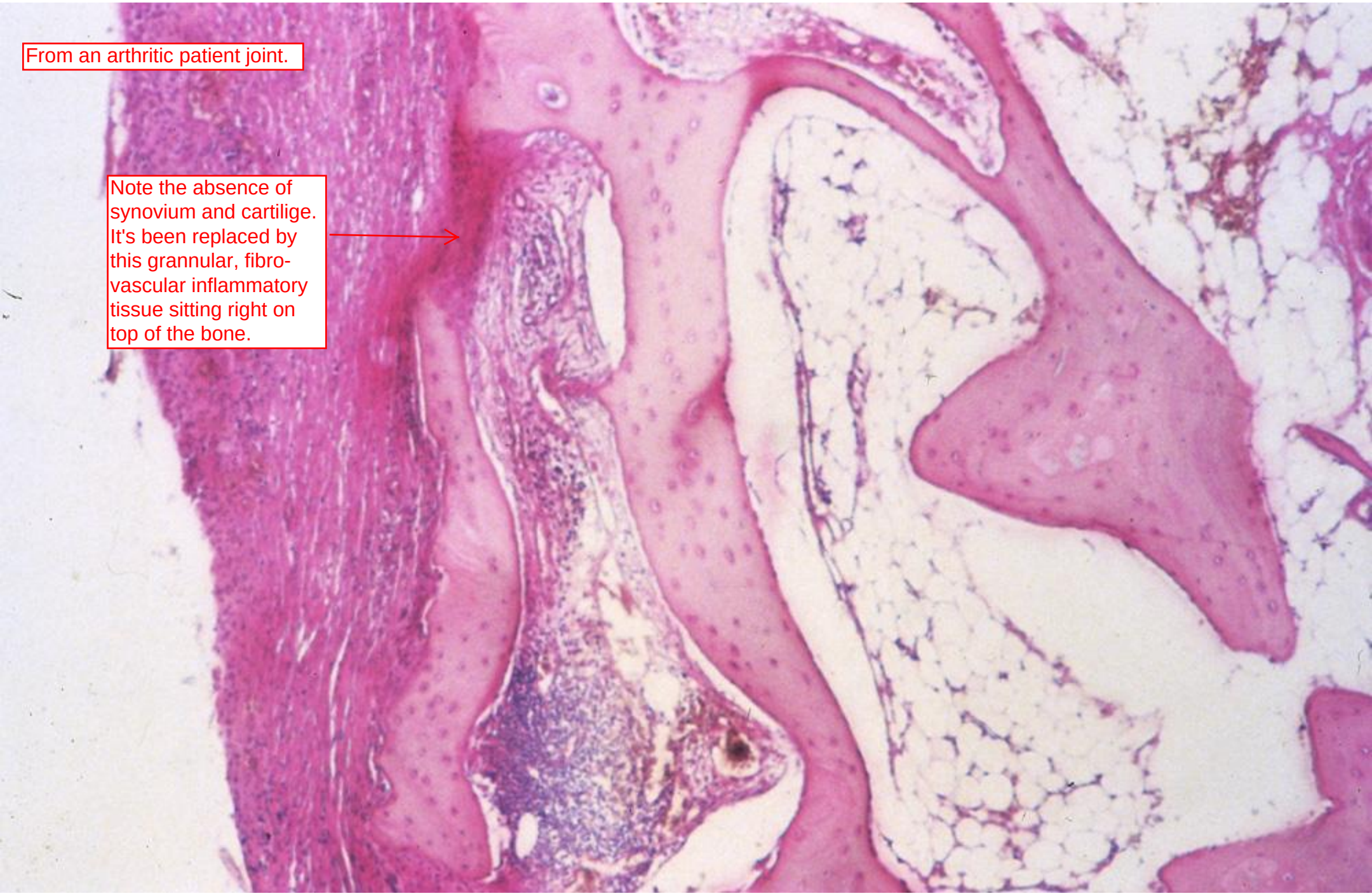
This one is more important for pathogenesis.

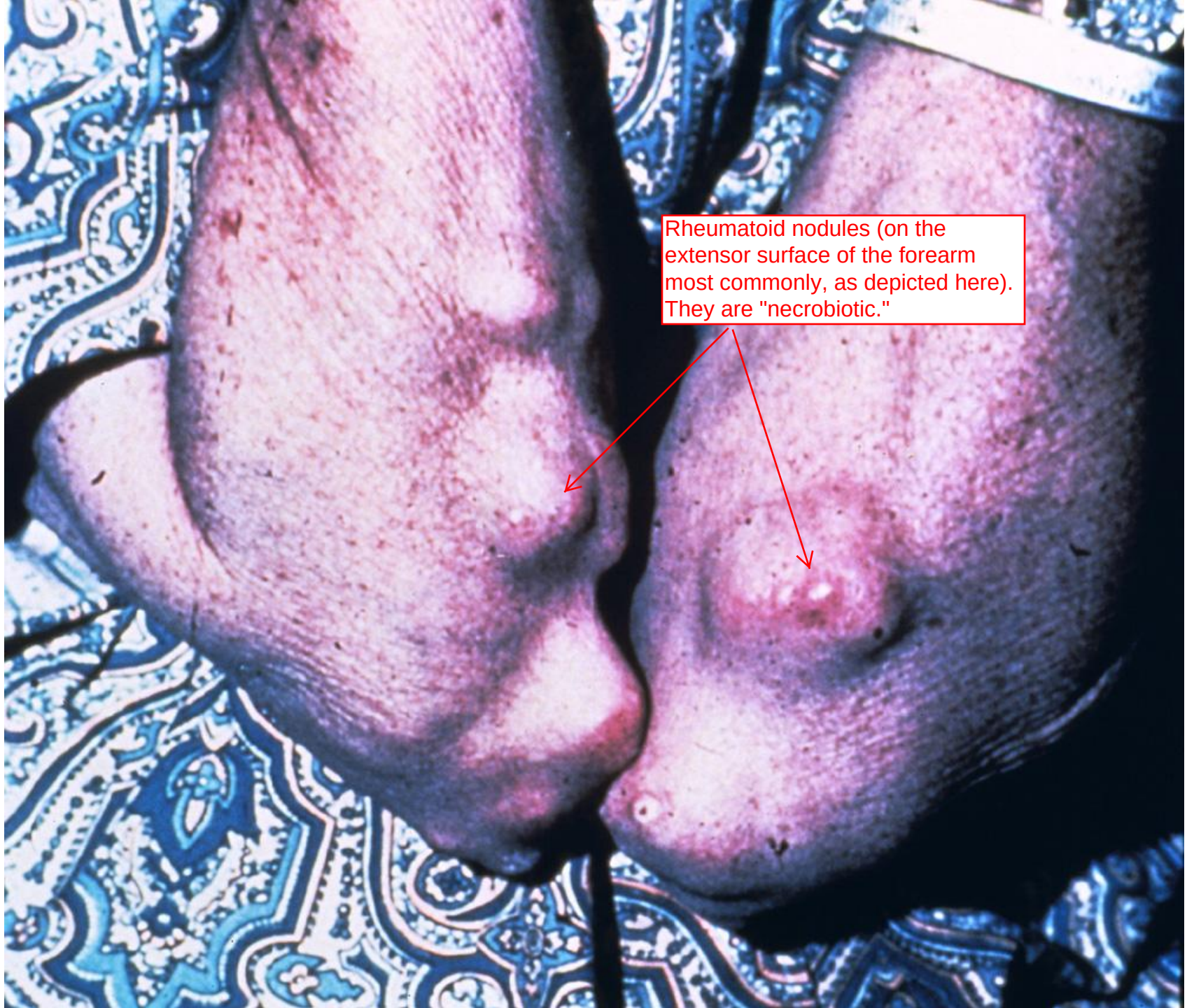
Type III hypersensitivity

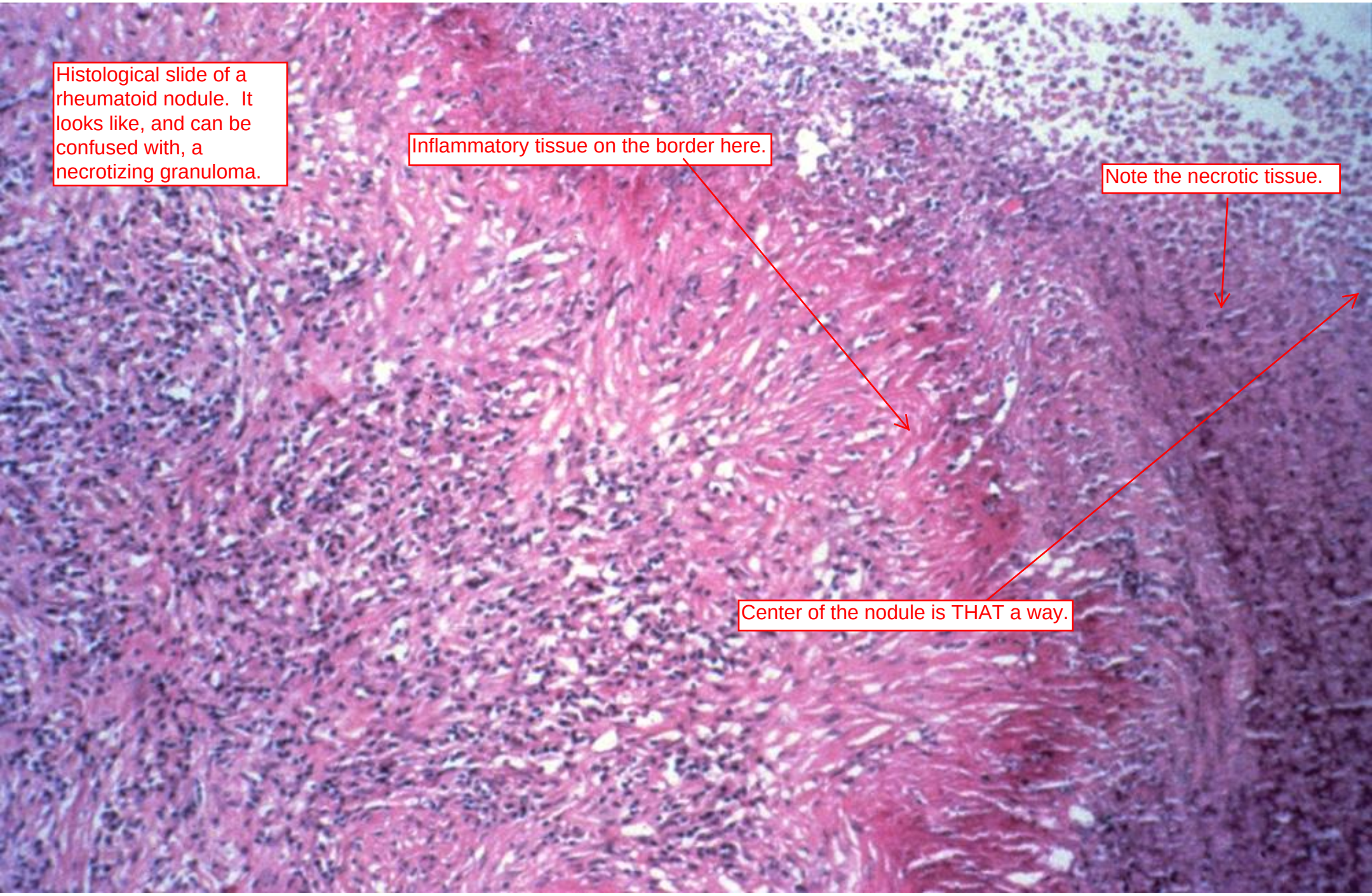
This one is important because we can detect it in the lab for diagnosis.


Fingers of someone with rheumatoid arthritis.
Look, it's inflamed. (it has rumor, tumor, pain, etc.)


You know how a few slides ago he described it as "severe" and "deforming"?
....Yea.
Note the ulnar deviation.

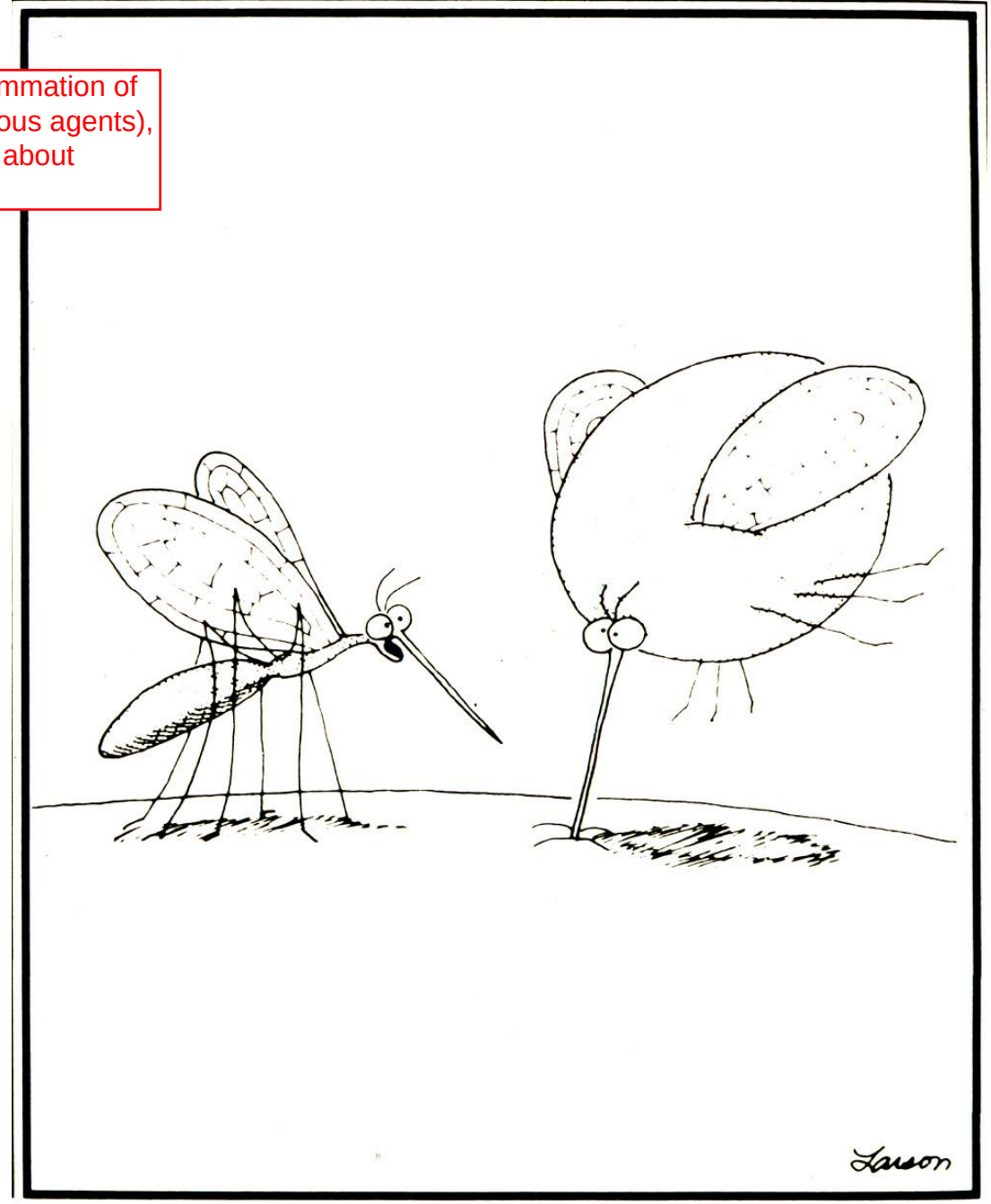

From an arthritic patient joint.
Note the absence of synovium and cartilige. It's been replaced by this grannular, fibro-vascular inflammatory tissue sitting right on top of the bone.


Rheumatoid nodules (on the extensor surface of the forearm most commonly, as depicted here). They are "necrobiotic."


Histological slide of a rheumatoid nodule. It looks like, and can be confused with, a necrotizing granuloma.
Inflammatory tissue on the border here.
Note the necrotic tissue.
Center of the nodule is THAT a way.

Vasculitis

Lots of things can cause inflammation of the blood vessels (e.g. infectious agents), today we're only going to talk about immune-mediated ones.

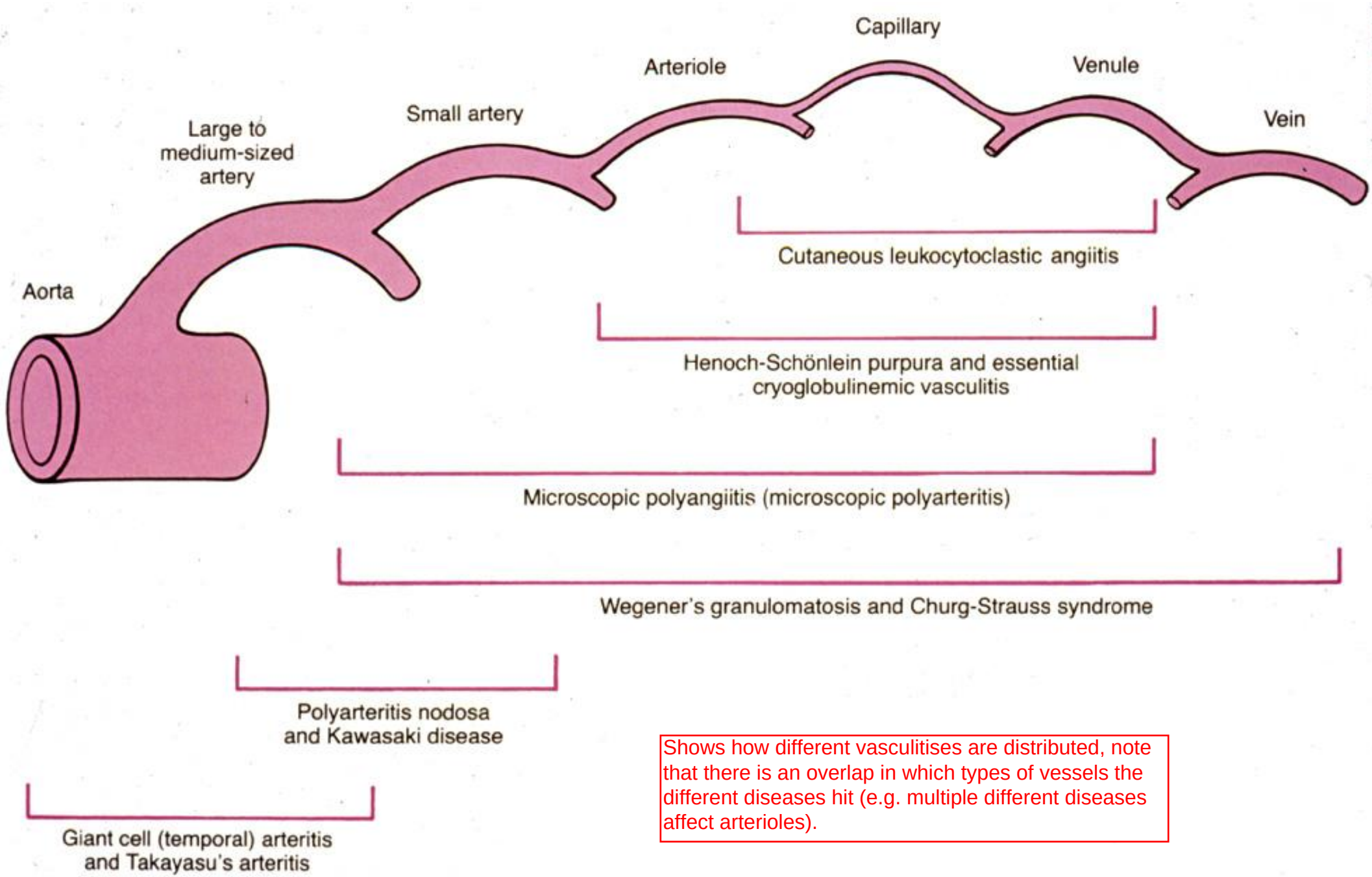


"Pull out, Betty! Pull out! . . . You've hit an artery!"

TABLE 10–2. MAJOR VASCULITIS SYNDROMES

Syndrome	Vessels Involved	Distribution of Vascular Involvement	Principal Morphologic Features
Hypersensitivity (leukocytoclastic) vasculitis	Venules, capillaries, arterioles small vessels	Widespread, but particularly skin	Necrosis and neutrophilic infiltration of venules with leukocytoclasis
Polyarteritis nodosa	Medium-sized and small arteries	GI tract, liver, kidney, pancreas, muscles, other sites	Panmural acute necrotizing arteritis with fibrinoid necrosis, neutrophil and eosinophil infiltration, and extension into adventitia
Wegener's granulomatosis	Small to medium-sized arteries	Upper and lower respiratory tracts; occasionally eye, skin, heart	Acute and chronic (sometimes granulomatous) angiitis with prominent eosinophils and occasional giant cells in association with extravascular granulomas
Churg-Strauss allergic angiitis and granulomatosis	Medium-sized and small arteries and veins	Systemic, with pulmonary involvement in many cases	Same as for Wegener's with more eosinophils
Temporal (cranial) arteritis	Elastic tissue–rich major arteries big vessels	Head, including ocular and intracranial vessels; uncommonly systemic	Chronic mononuclear inflammatory infiltration, mostly in inner half of the media, with giant cells and granuloma formation
Kawasaki's arteritis	Small and medium-sized arteries	Skin, ocular and oral mucosa, coronary arteries, but may	Acute and chronic infiltration, mainly with lymphocytes and macrophages, and with endothelial cell necrosis and immunoglobulin deposition
Thromboangiitis obliterans (Buerger's disease)			Acute and chronic inflammatory infiltration of arteries and veins, often with giant cells, granulomas, intravascular thrombi containing microabscesses, and later perivascular fibrosis trapping nerve trunks

Not going to talk about all of them today, just the circled ones.
Note that there are 3 different ways we can classify these vasculitises (the headings up top):
1) Which type of vessels are hit (big / small / arteries / veins?)
2) Distribution of the vessels hit: (which organs affected?)
3) Histological / morphological features: (necrosis? giant cells? chronic vs acute inflammation?)



Shows how different vasculitises are distributed, note that there is an overlap in which types of vessels the different diseases hit (e.g. multiple different diseases affect arterioles).

The first type of vasculitis we will talk about today. It's not so much one disease as a type of pathogenesis that fits multiple diseases (each with a different clinical presentation)

Hypersensitivity (leukocytoclastic) vasculitis

These all look very similar under the microscope but have different clinical presentations.

Henoch-Schönlein purpura ← involves kidneys, will hear more about later.

Serum sickness ← Used to happen when we treated people with animal serum.

Connective tissue diseases
(e.g., systemic lupus erythematosus)

Mixed cryoglobulinemia

Chronic active hepatitis B

Lymphoproliferative disorders

Reactions to drugs, pathogens → Important: "By far the most common type of hypersensitivity vasculitis"

Hypersensitivity vasculitis

Vessels involved

Small vessels involved. Will often involve the skin (because there are so many capillaries there).

Venules

Capillaries

Arterioles

Skin lesions are by far the most common presentation of hypersensitivity vasculitis

Hypersensitivity vasculitis: clinical features

little red bumps that you can feel, the bumps caused by bleeds (they're filled with blood). Picture appears a few slides from now.

Skin lesions (palpable purpura, macules, vesicles, necrosis, ulceration)

Vascular lesions in other organs (lungs, brain, kidneys, gastrointestinal tract) with variable manifestations (e.g., glomerulonephritis, infarcts)

Hypersensitivity vasculitis: pathogenesis

"exogenous antigen" e.g. a drug.
"autoantigen" like in lupus.

1. Antibody response to exogenous antigen or autoantigen

Which leads to.

2. Immune complex formation

Which leads to.

3. Deposition of immune complexes in vessels (especially venules)

Which leads to.

Hypersensitivity vasculitis: pathogenesis

4. Complement fixation; generation of chemotactic fragments (e.g., C5a)

which leads to.

5. Attraction of inflammatory cells (especially neutrophils); tissue destruction

Repeat of last slide, just note that it's a type 3 hypersensitivity reaction.

Hypersensitivity vasculitis: pathogenesis

4. Complement fixation; generation of chemotactic fragments (e.g., C5a)

5. Attraction of inflammatory cells (especially neutrophils); tissue destruction

Type III hypersensitivity

He read this slide.

Hypersensitivity vasculitis: histology

Infiltration of vessel walls by neutrophils, neutrophil degeneration (leukocytoclasis), vessel wall necrosis ← in severe cases.

Which leads to the term "leukocytoclastic vasculitis" as a synonym for hypersensitivity vasculitis.

Immune complex deposition

Immunoglobulin components may vary:

Henoch-Schönlein purpura: IgA

Systemic lupus erythematosus: mixed

Thus, you can use different fluorescent anti-antibodies to differentiate between the different types of hypersensitivity vasculitises (vasculitii?)

Cartoon demonstrated what's on the previous slides. Just to recap: We have immune-complexation in the blood, it deposits in the small vessels, induces inflammation and cell destruction, and possibly eventually rupture (in the venule).

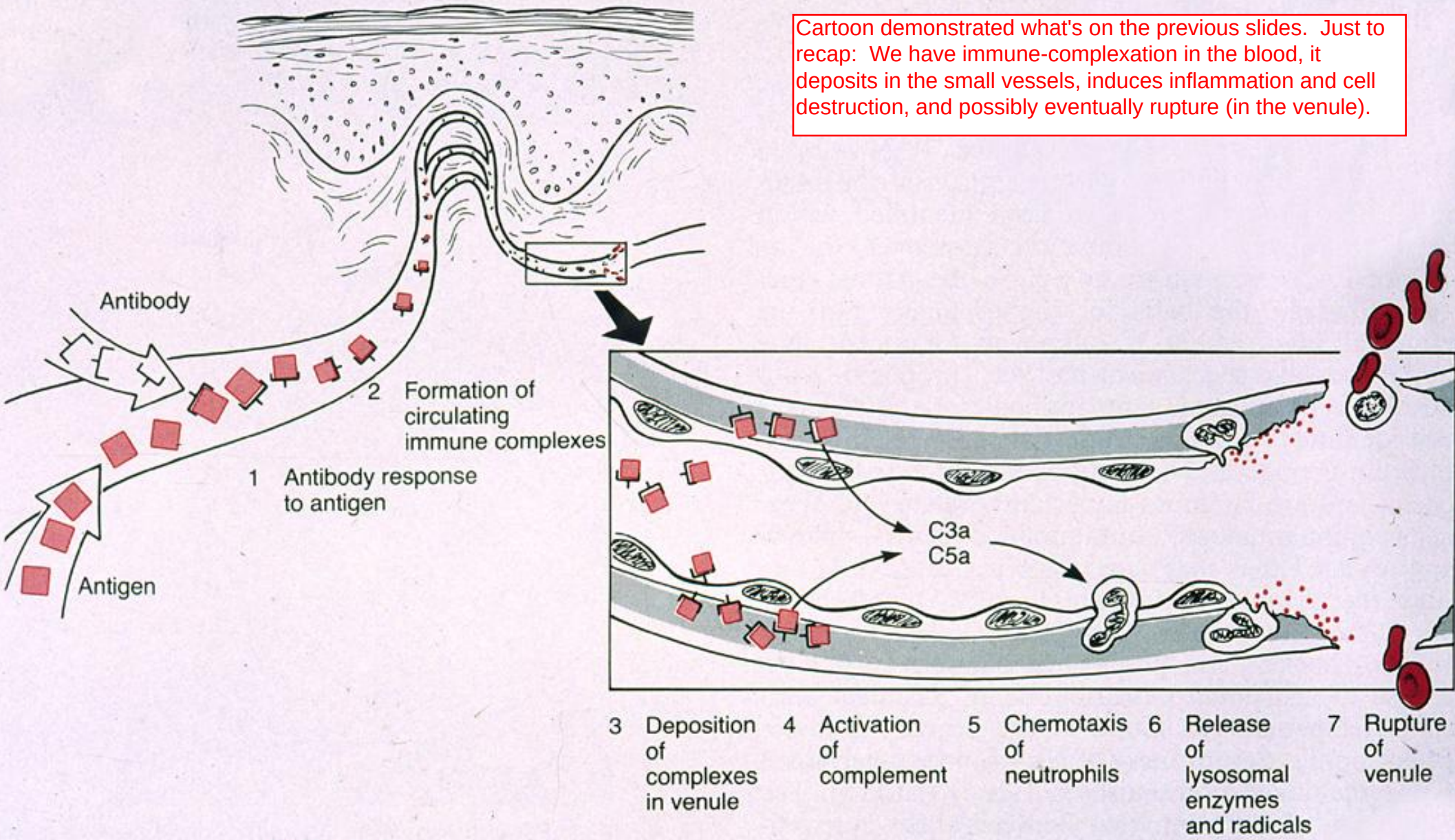
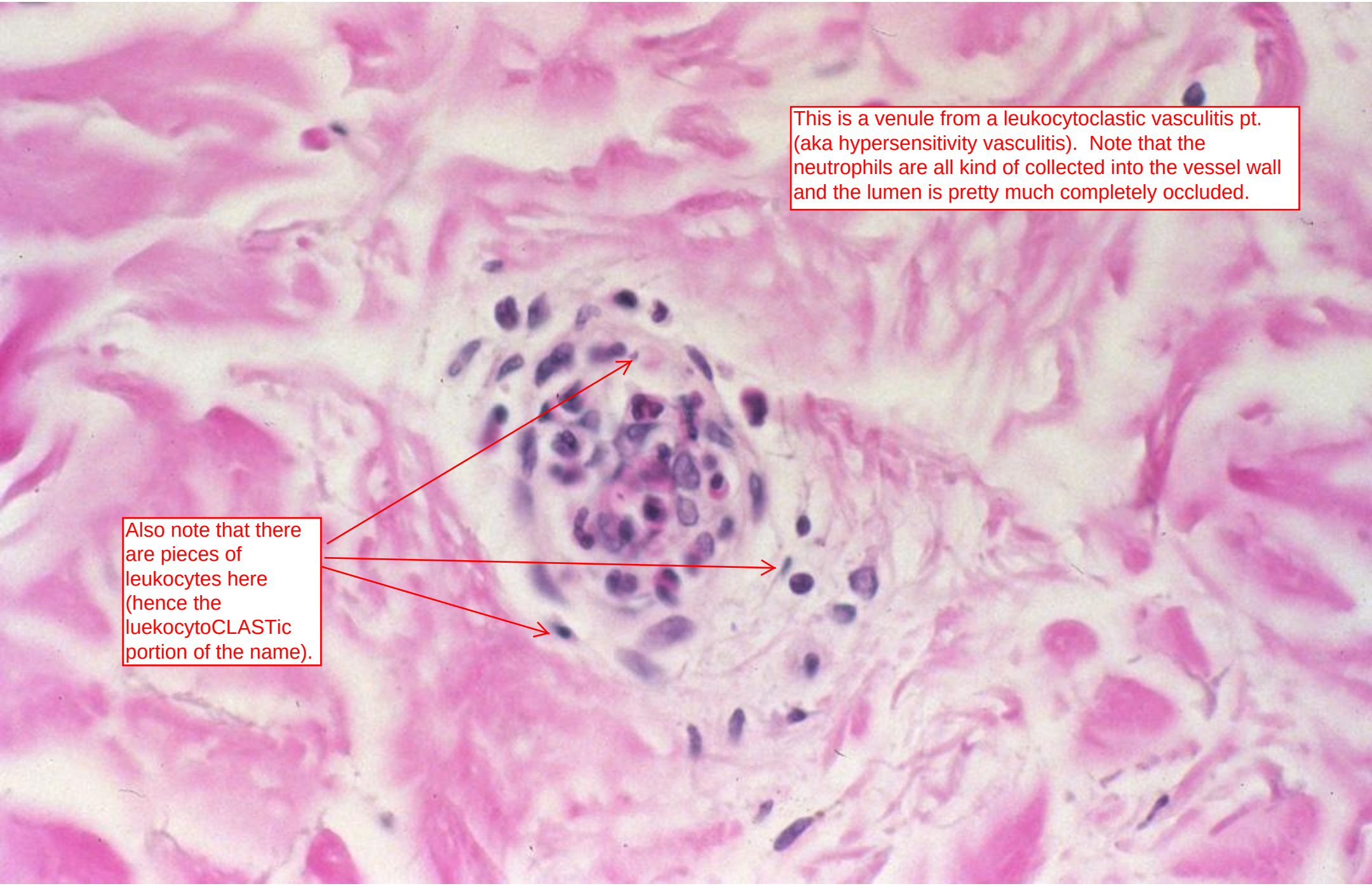
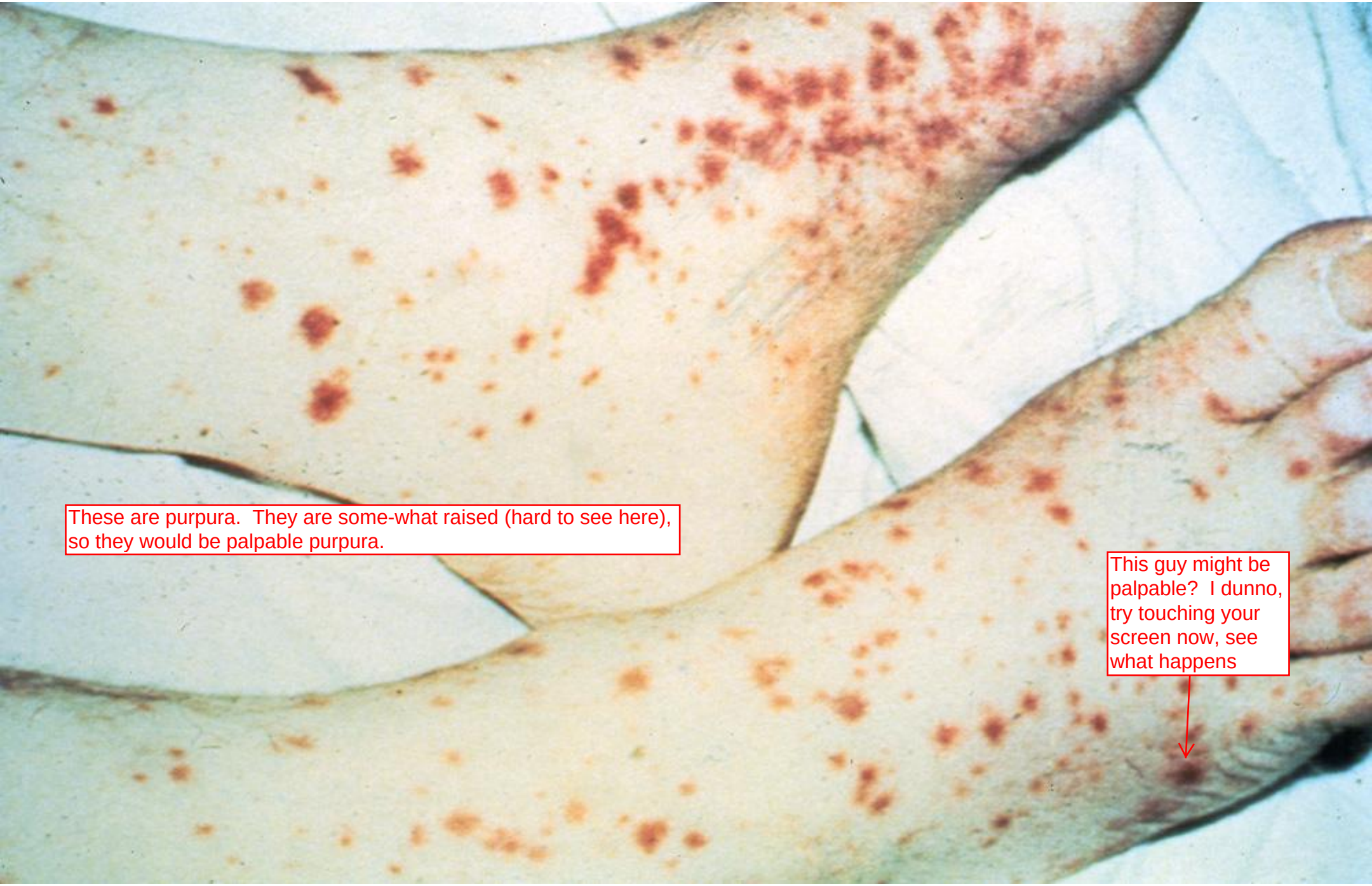
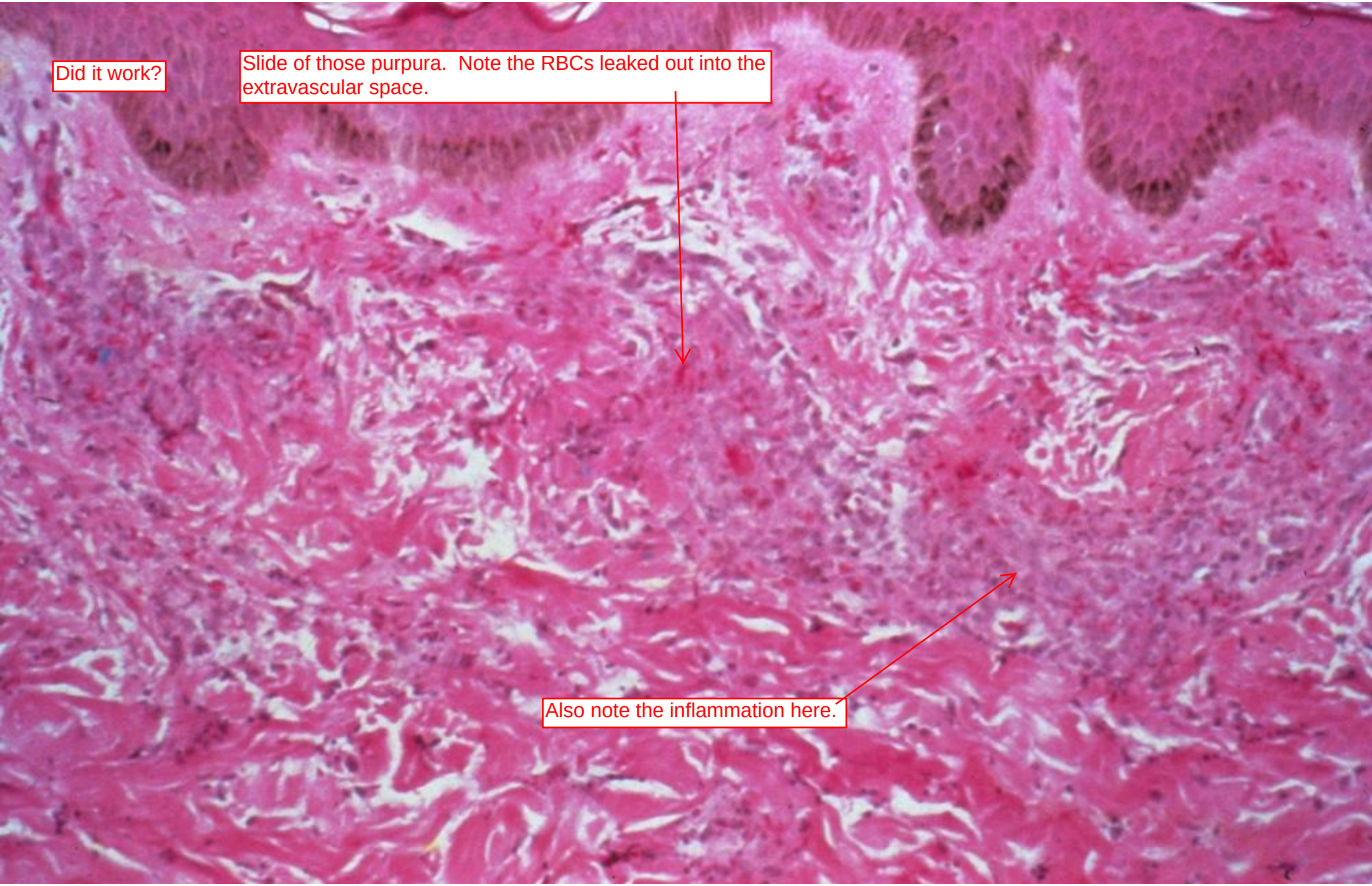
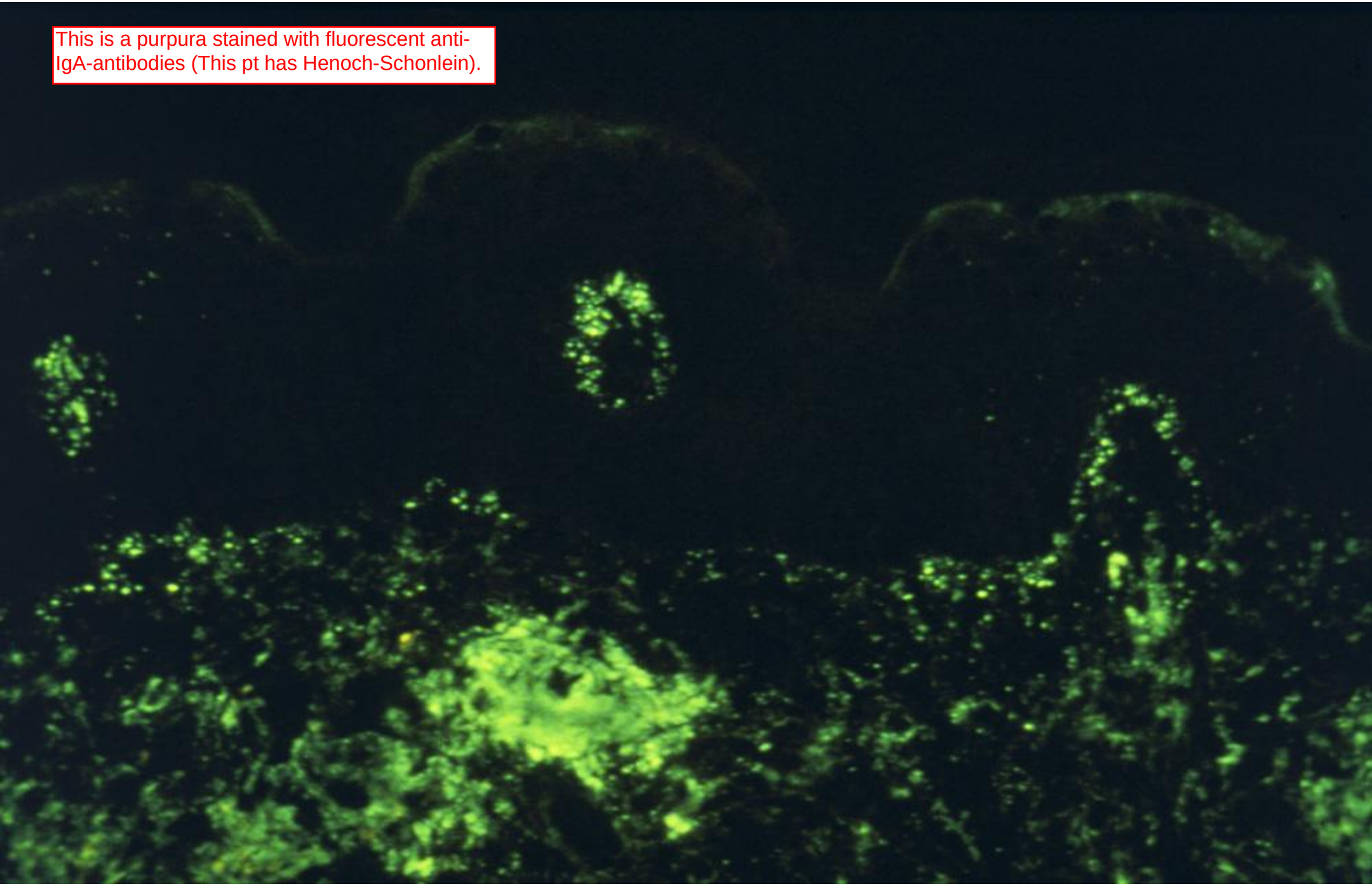


Figure 10–7. A schematic representation of the pathogenesis of hypersensitivity venulitis.


This is a venule from a leukocytoclastic vasculitis pt. (aka hypersensitivity vasculitis). Note that the neutrophils are all kind of collected into the vessel wall and the lumen is pretty much completely occluded.
Also note that there are pieces of leukocytes here (hence the luekocytoCLASTic portion of the name).


These are purpura. They are some-what raised (hard to see here), so they would be palpable purpura.
This guy might be palpable? I dunno, try touching your screen now, see what happens


Did it work?
Slide of those purpura. Note the RBCs leaked out into the extravascular space.
Also note the inflammation here.


This is a purpura stained with fluorescent anti-IgA-antibodies (This pt has Henoch-Schonlein).

Okay, second vasculitis we're talking about. This is at the other end of the spectrum, targets LARGE vessels.

Temporal arteritis

other names:

(giant cell arteritis; cranial arteritis)

He read this slide.

Temporal arteritis

Vessels involved

Elastic tissue-rich major arteries

involvement here can lead to blindness.

(branches of carotid artery, including temporal and ophthalmic arteries; less frequently, aorta and other arteries; heart and lungs generally spared)

not necessarily true of other vasculitises

He read this slide.

Temporal arteritis: clinical features

- Severe headache or facial pain, often unilateral and most intense along temporal artery
- Visual disturbances (diplopia, blindness)

if opthalmic arteries involved, blindness can be permanent if not treated rapidly.

- Constitutional symptoms (fever, fatigue, weight loss)
- Associated in approximately half of cases with polymyalgia rheumatica (syndrome of pain and muscle stiffness)

particularly associated with older patients.

- Most common in older adults
- Male:female ratio 1:2 or 1:3

He read this slide.

Temporal arteritis: pathogenesis

Unknown; may involve type IV hypersensitivity to antigens associated with elastic tissue or smooth muscle

Familial clustering of cases and predilection for white patients suggests genetic component

He read this slide.

Temporal arteritis: histology

Two histologic patterns:

1. **Granulomatous inflammation with multinucleate giants cells, centered on internal elastic lamina, which is often disrupted**
2. **Mononuclear inflammatory infiltrate without giant cells, occasionally with fibrinoid necrosis**

Can either be 1 or 2. #1 is the more traditional / textbook example but you can see #2.

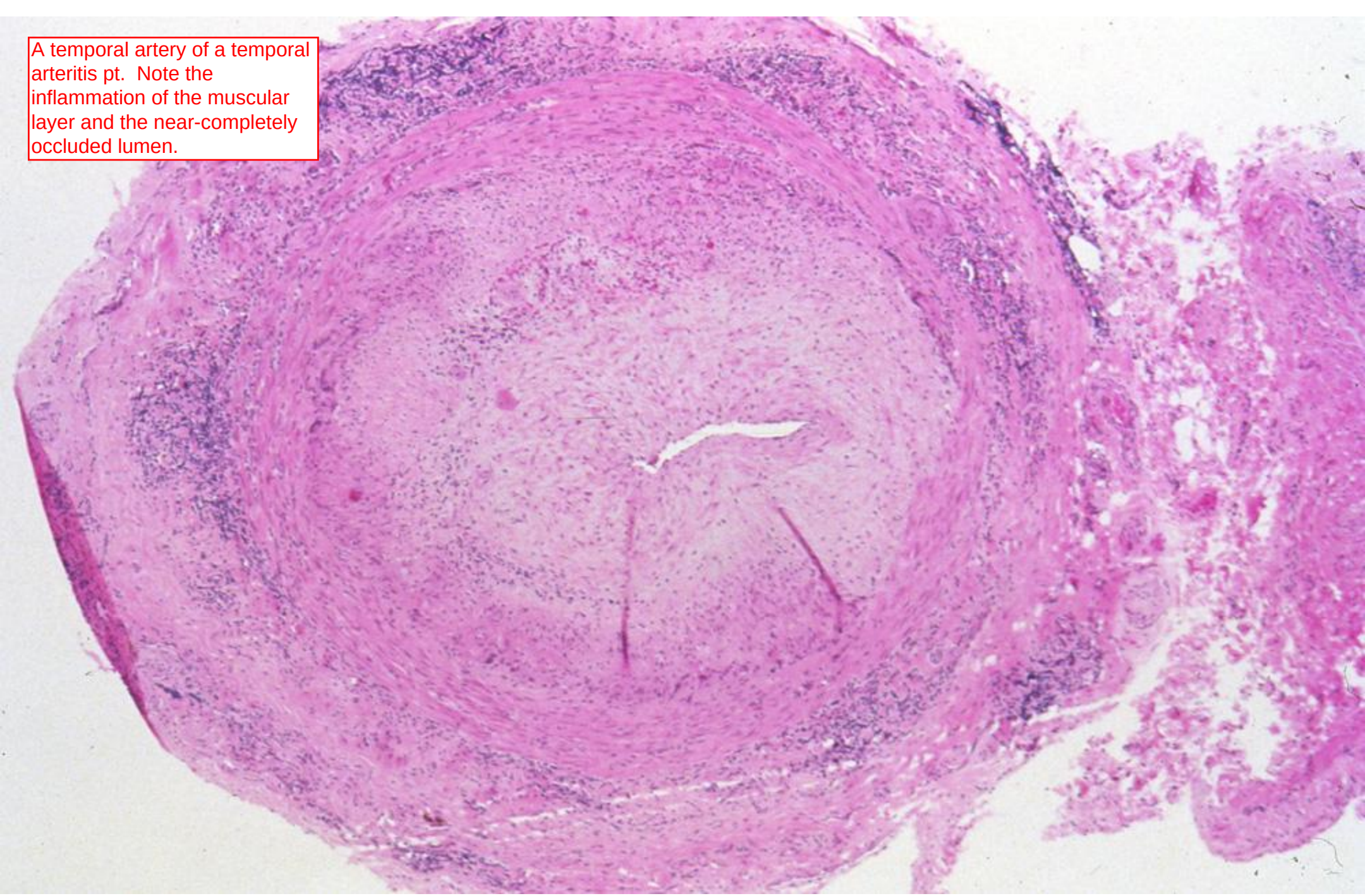
Vascular lumen often obliterated or thrombosed

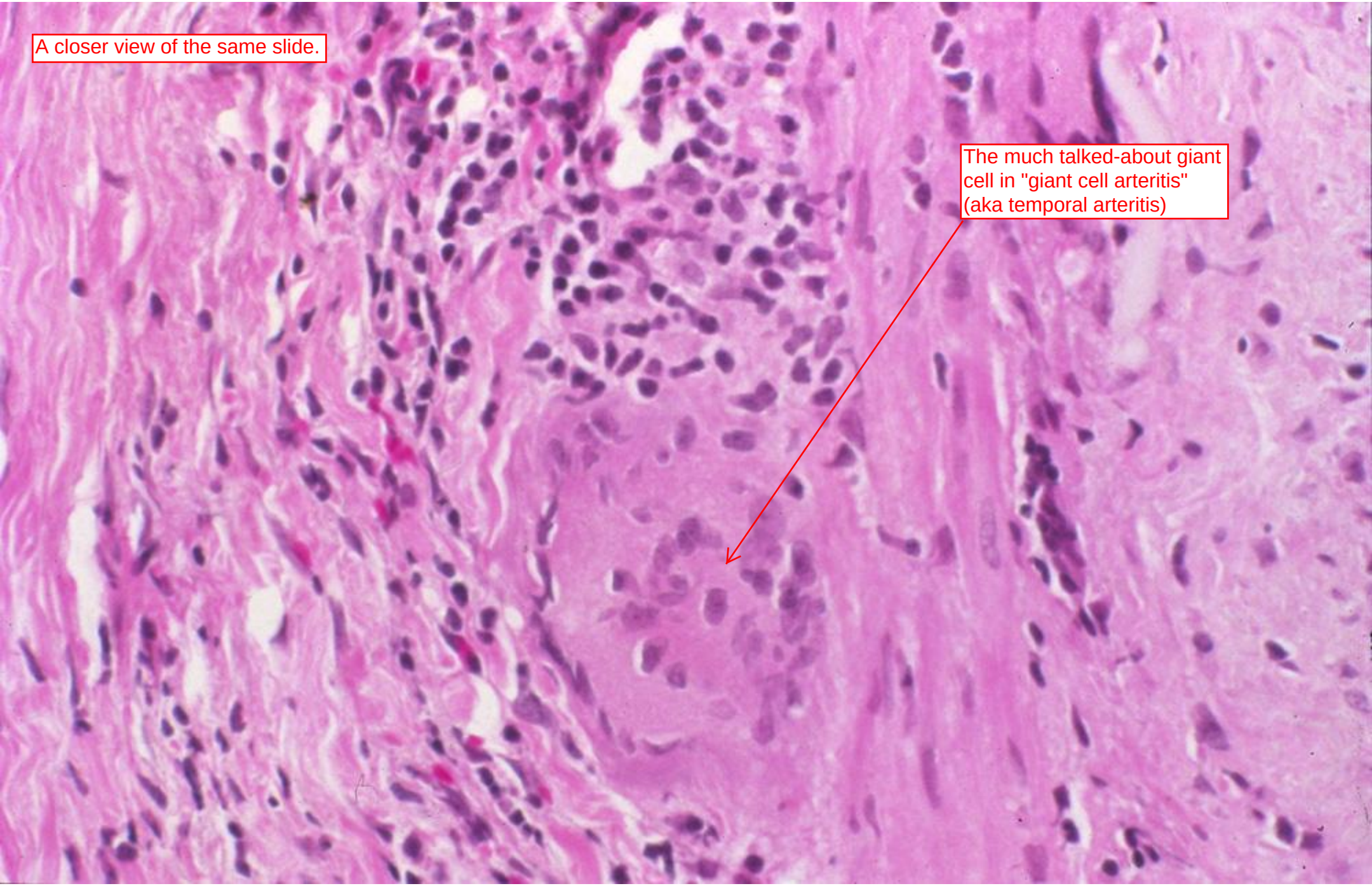
In healing phase, vessel may be largely replaced with fibrous tissue

Only select portions ALONG the artery are affected. Thus you need to take a lot of slices along the artery when you're looking at slides (and look at all of them).

Luckily you don't really need your temporal artery.

Segmental lesions alternating with unaffected areas may produce "nodular" morphology


A temporal artery of a temporal arteritis pt. Note the inflammation of the muscular layer and the near-completely occluded lumen.


A closer view of the same slide.
The much talked-about giant cell in "giant cell arteritis" (aka temporal arteritis)

Note: these are TWO DIFFERENT things, but they are similar in many ways.

Wegener's granulomatosis and Microscopic polyangiitis

Vessels involved

The "baby bear" vasculitises (it effects medium-sized vessels, those that are juuuuuuuust the right size).

Venules, capillaries, arterioles

Small to medium sized arteries

They are fairly UNcommon diseases.

He read off this slide.

Wegener's granulomatosis: clinical features

It's a type of "pulmonary-renal syndrome."

- Upper respiratory inflammation (e.g., sinusitis, often severe, with bloody nasal discharge)
- Pulmonary symptoms (cough, hemoptysis, shortness of breath)
- Renal manifestations (hematuria, rapidly progressive renal failure)
- Lesions involving other organs (eyes, skin, occasionally heart)
- Most common in middle aged adults
- Males more commonly affected

He read off this slide.

Microscopic polyangiitis: clinical features

- Variable, can involve different organ systems
- Isolated renal disease with hematuria, renal insufficiency is a common presentation

Different kidney presentation and doesn't involve the pulmonary system like Wegener's.

The two diseases are different clinically but have common pathogenic processes.

Pathogenesis

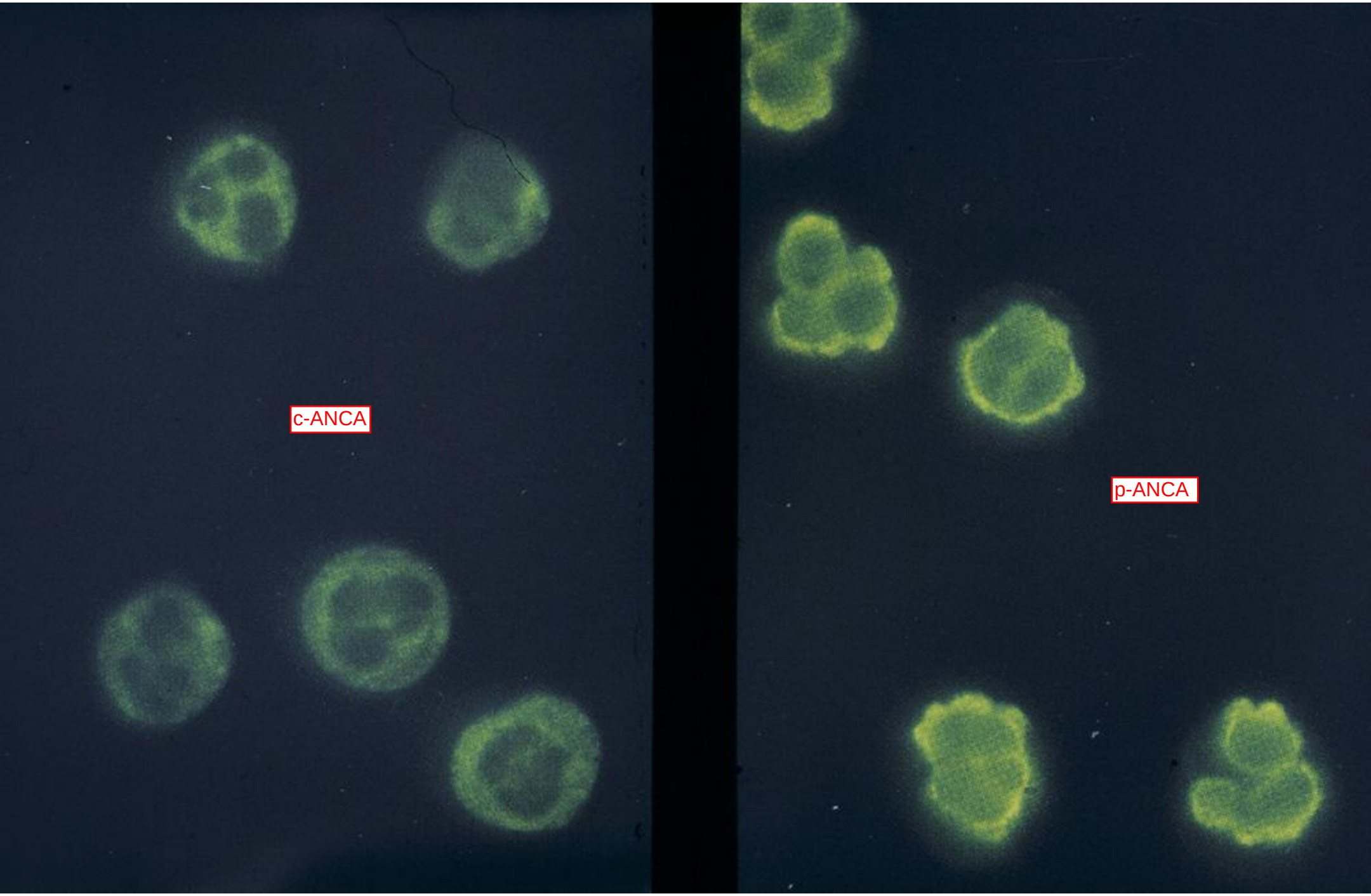
Generation of autoantibodies to neutrophils (anti-neutrophil cytoplasmic antibodies, or ANCA), neutrophil activation, tissue damage

Didn't cover mechanism here.

Patients with Wegener's granulomatosis often have "cytoplasmic" ANCA (c-ANCA) (anti-proteinase 3)

Patients with microscopic polyangiitis often have "perinuclear" ANCA (p-ANCA) (anti-myeloperoxidase)

Note that ANCAs target things INSIDE the cytoplasm of the neutrophils.


c-ANCA
p-ANCA

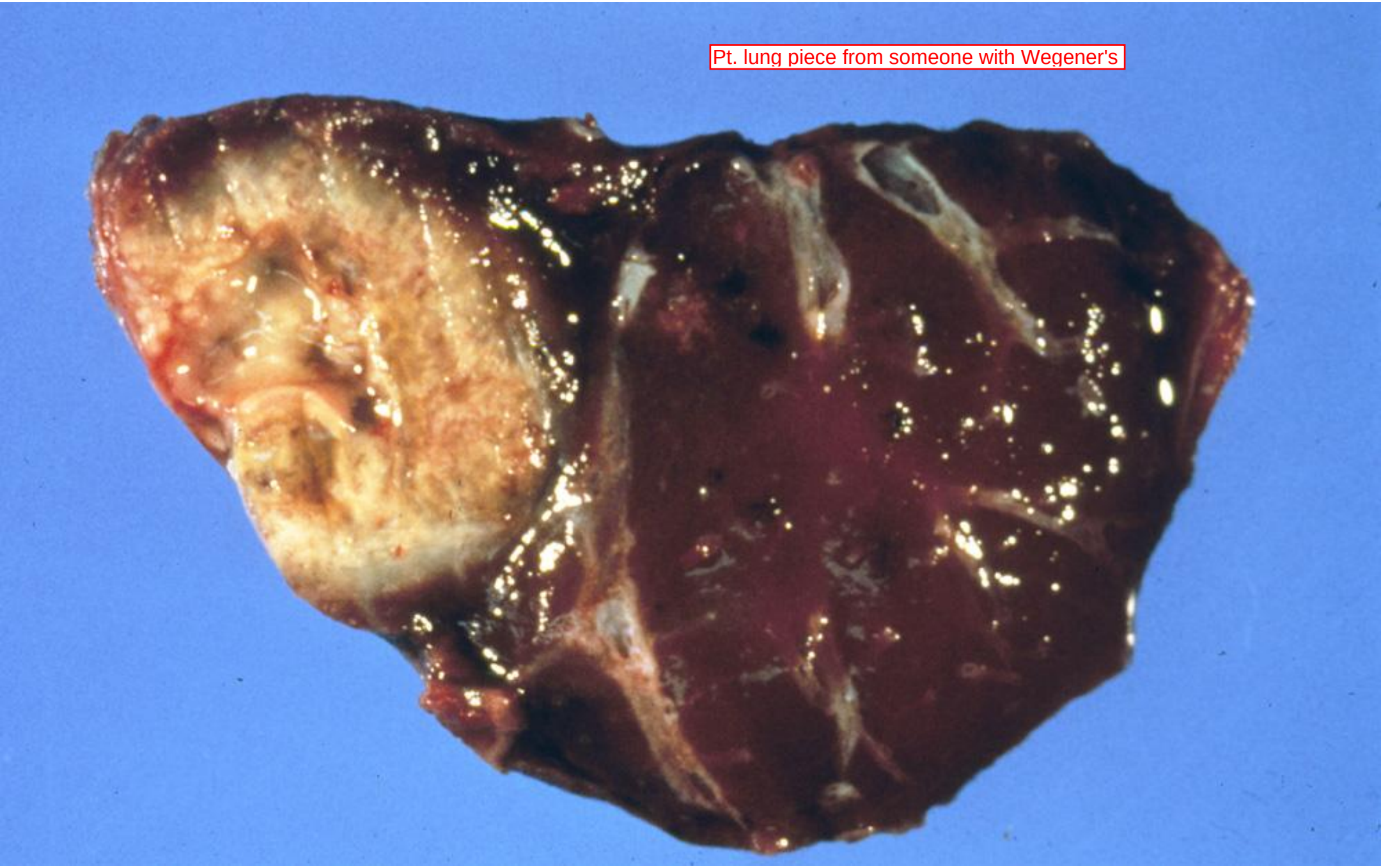
He read this slide.

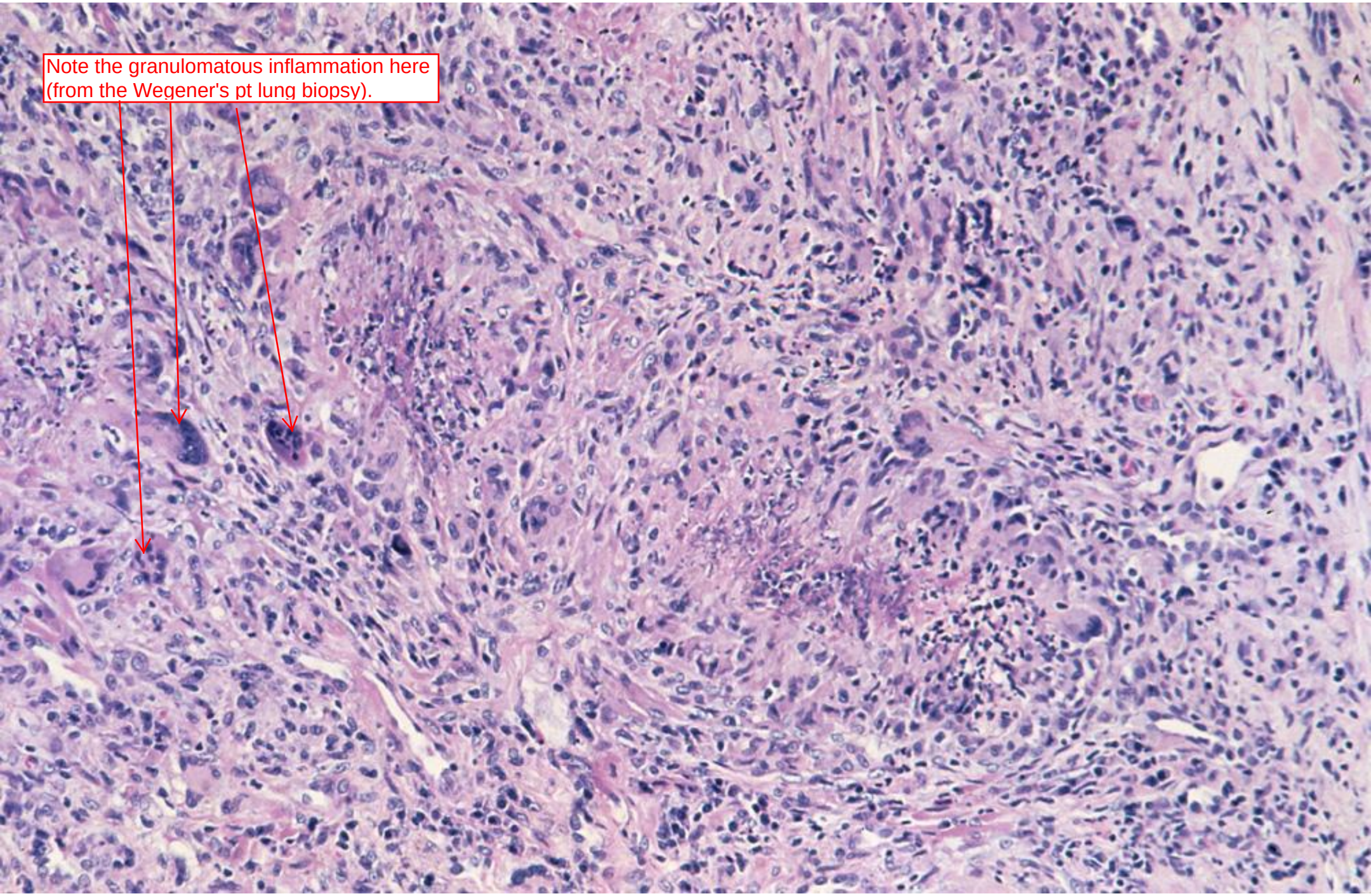
Wegener's granulomatosis: histology

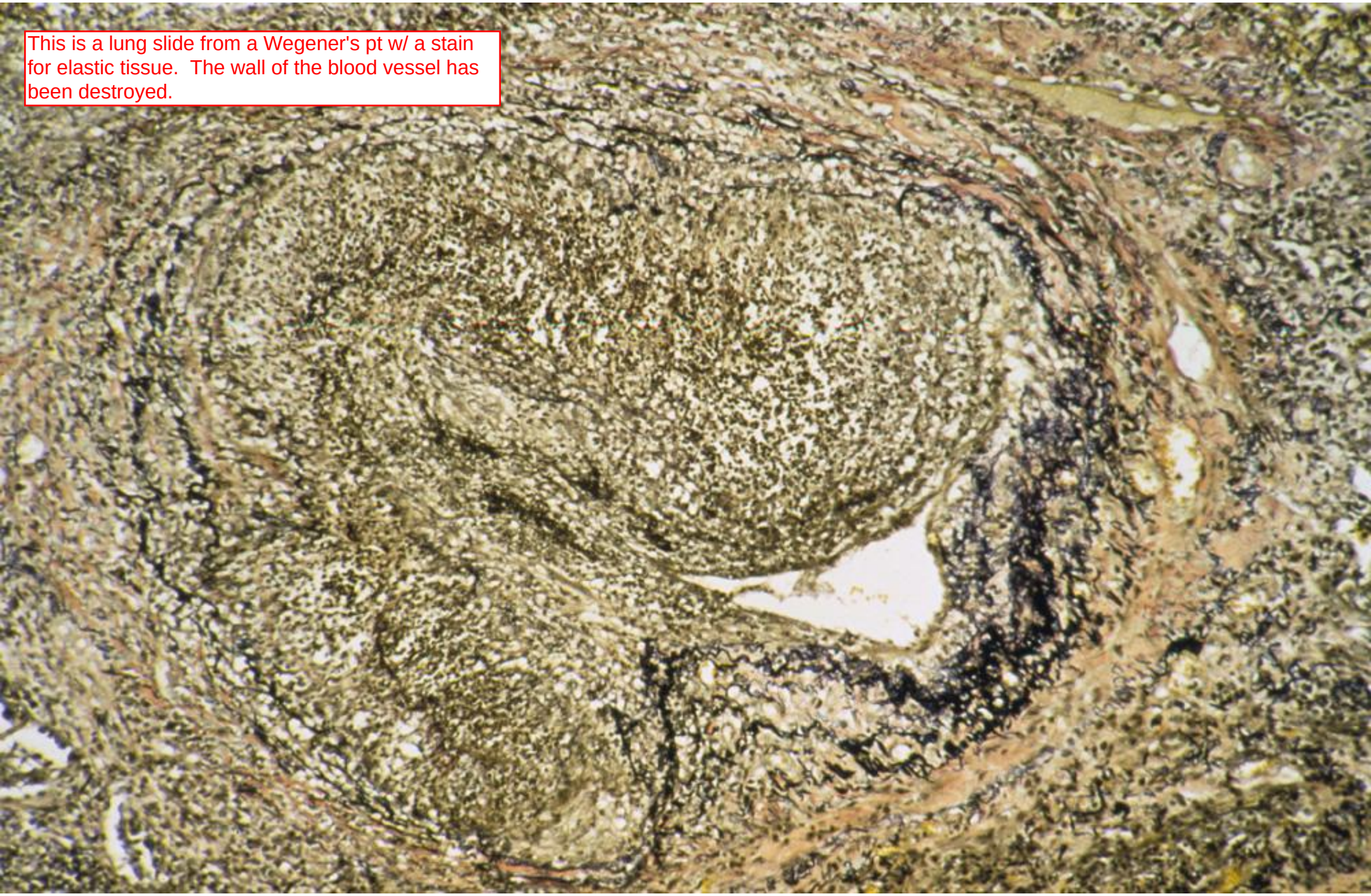
Necrotizing granulomas of upper respiratory tract (ear, nose, sinuses, throat)

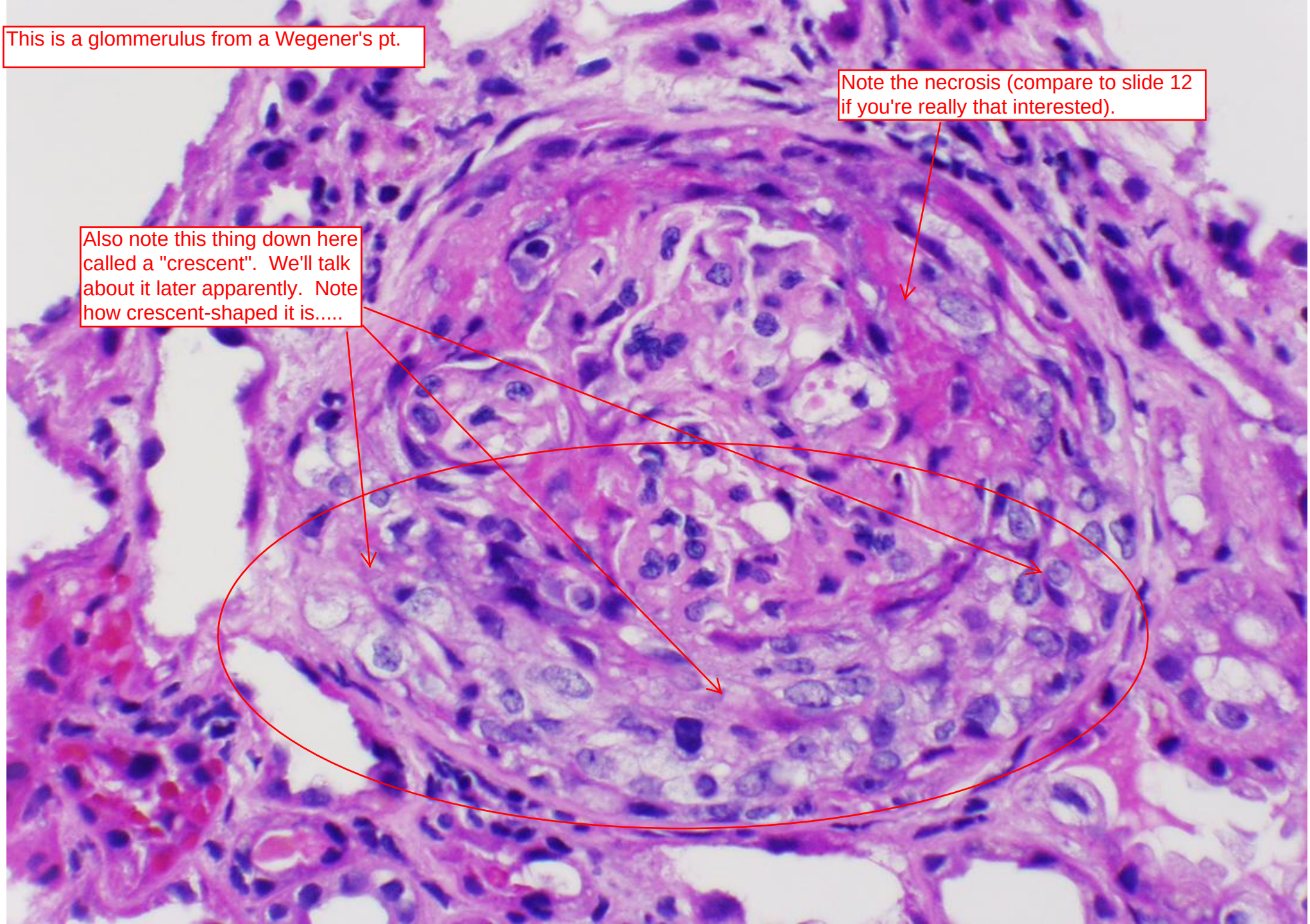
Necrotizing granulomatous vasculitis in other organs, especially lungs

Necrotizing glomerulonephritis, often with crescents ← "Don't worry about it" for now.


Pt. lung piece from someone with Wegener's


Note the granulomatous inflammation here
(from the Wegener's pt lung biopsy).


This is a lung slide from a Wegener's pt w/ a stain for elastic tissue. The wall of the blood vessel has been destroyed.


This is a glommerulus from a Wegener's pt.
Note the necrosis (compare to slide 12 if you're really that interested).
Also note this thing down here called a "crescent". We'll talk about it later apparently. Note how crescent-shaped it is.....

Lol, he didn't get to talk about Kawaski disease (it's a real thing, supposedly) but he meant to talk about it here.