THE UNIVERSITY OF JORDAN

Physiological, protective mechanism against blood loss, trauma

THROMBOSIS-

whenever there's unneccesary thrombosis, mutation in clotting system

PATHOLOGICAL ASPECTS

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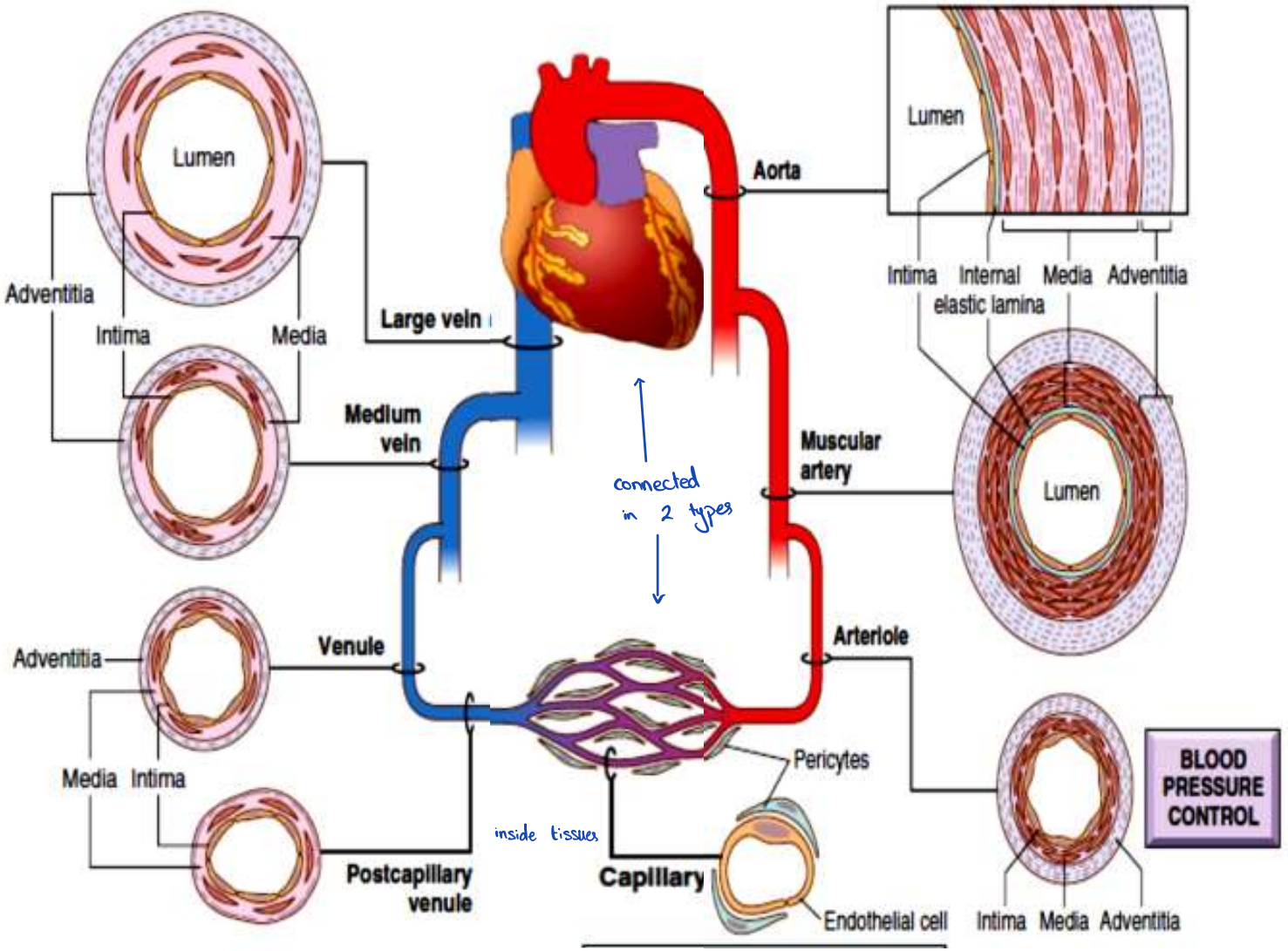
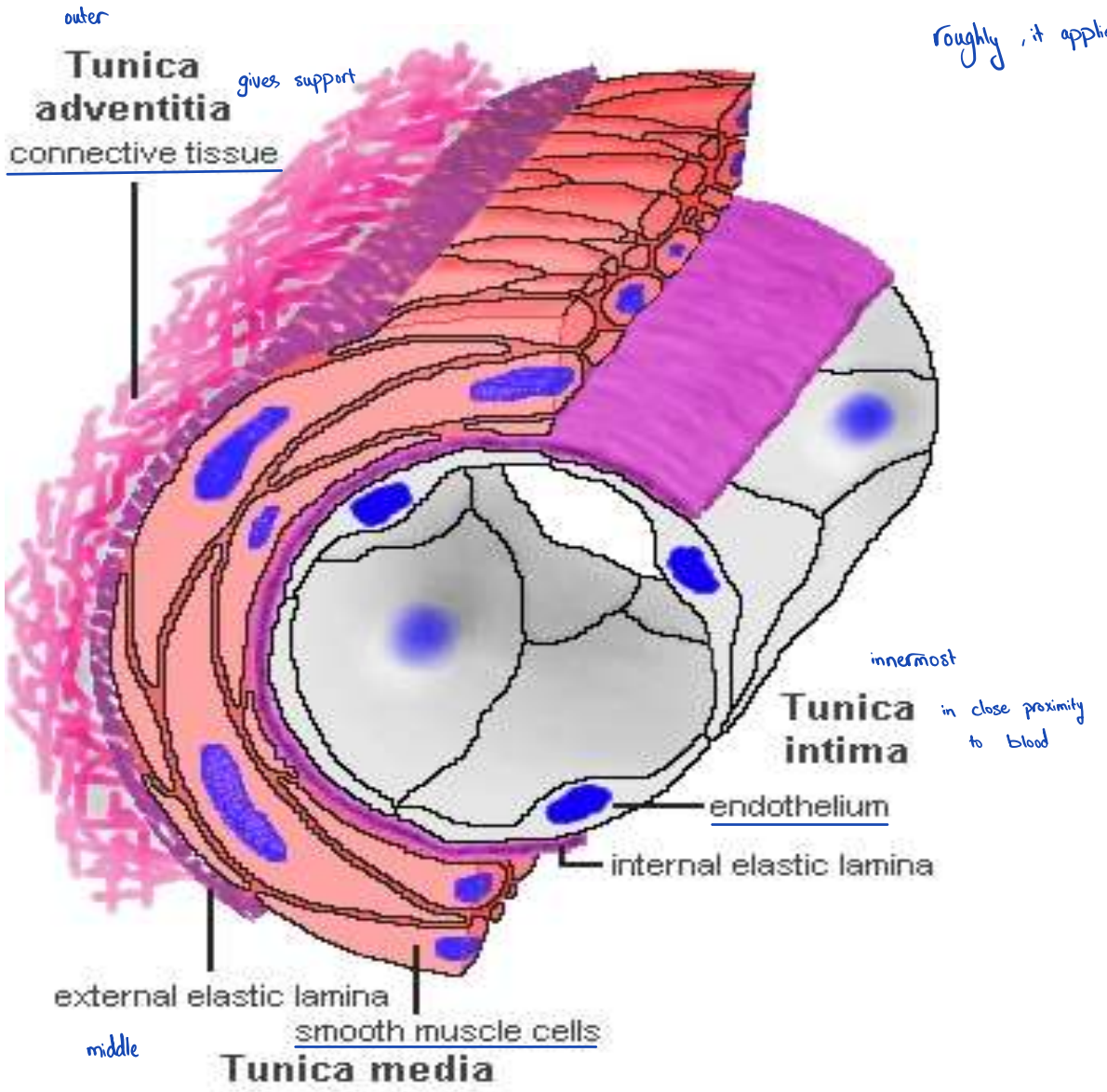
CARDIOVASCULAR SYSTEM

Venous circulation

Arterial circulation



NORMAL BLOOD VESSEL HISTOLOGY



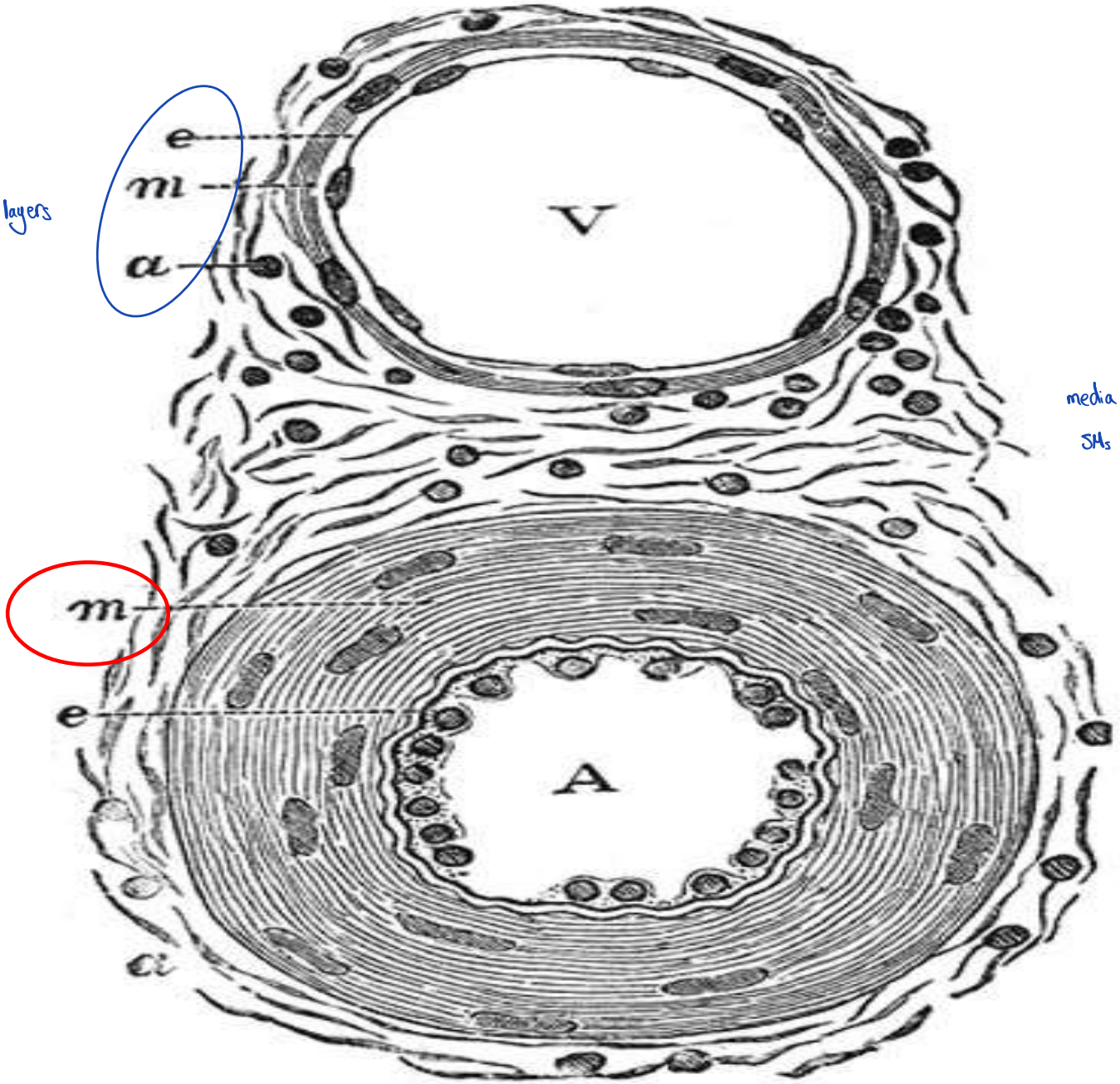
differences in structures

↓

diseases

ARTERY (A) VS VEIN (V)

same 3 layers

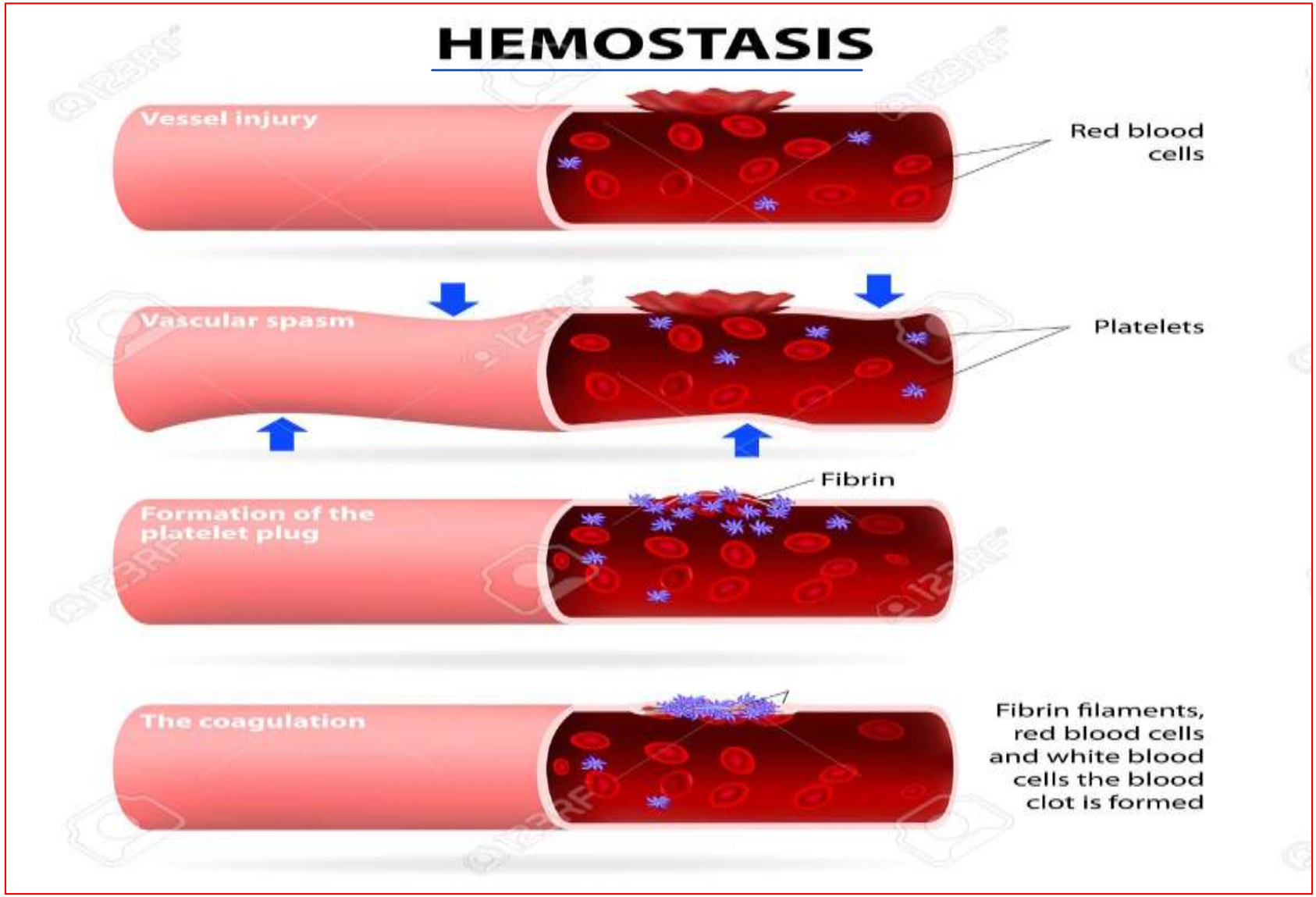


media is thicker in artries

SMs

PHYSIOLOGY OF THROMBOSIS

prevent blood loss by clotting system when there's a wound (physiological)



THROMBOSIS- PATHOLOGICAL ASPECTS

- Blood coagulation is a very important physiological event to protect our hemostasis, and life
- However, at certain points, this process can be pathological that may endorse injury and cause harm to our body

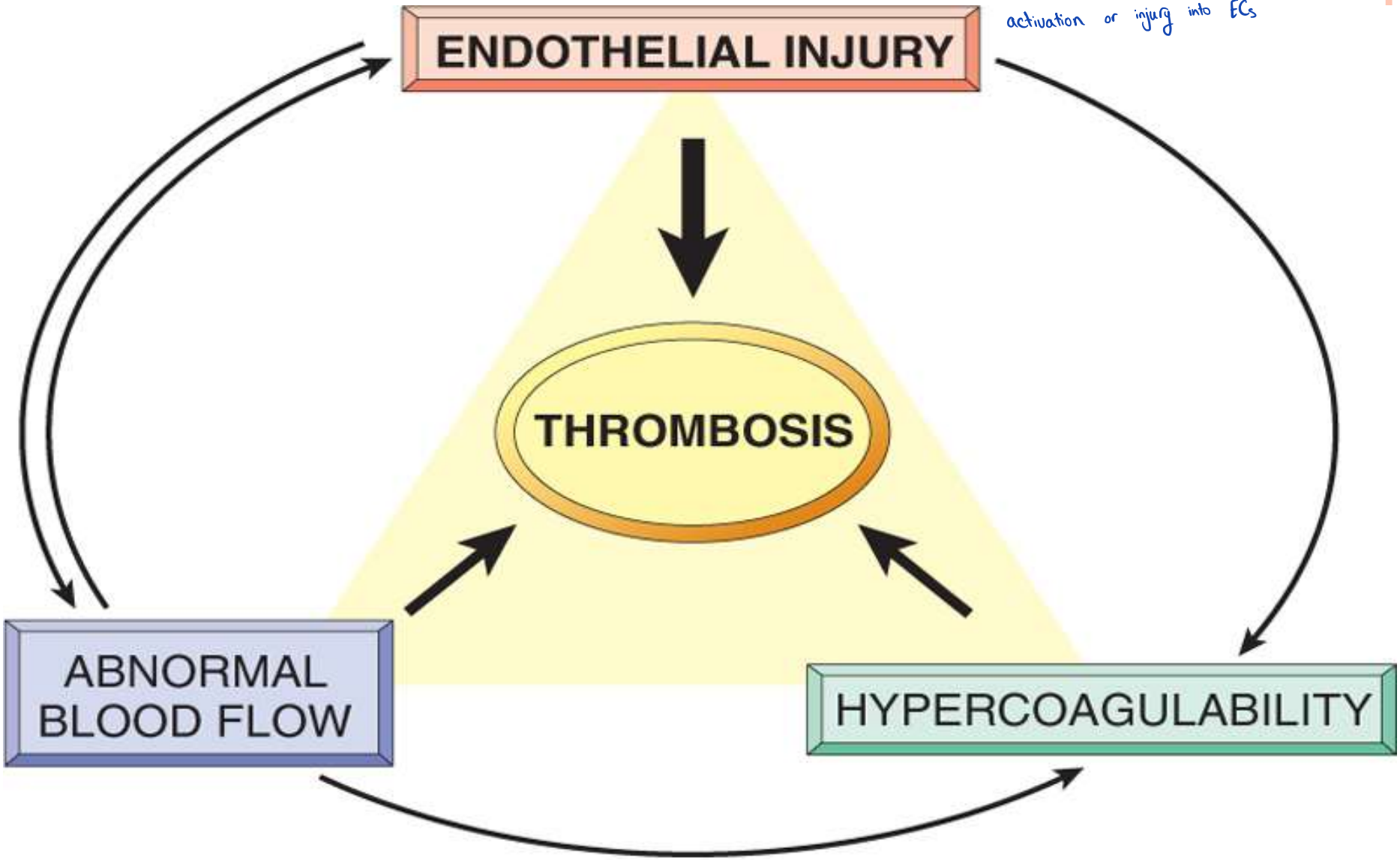
P. Thrombosis (unnecessary blood clotting)

- This happens whenever unnecessary blood clotting is activated
- **The "pathological" thrombosis is caused by the presence of at least one of 3 factors (together called Virchow's triad)**:

or a combination or one of them may cause the other

Virchow's triad

not by a wound or cut, changes in the environment which causes activation or injury into ECs



THROMBOSIS- PATHOLOGICAL ASPECTS

- **Pathogenesis (called *Virchow's triad*):**

1. ***Endothelial* Injury (Heart, Arteries)***
2. ***Stasis (abnormal blood flow)***
3. ***Blood Hypercoagulability***

*** Endothelial cells are special type of cells that cover the inside surface of blood vessels and heart.**

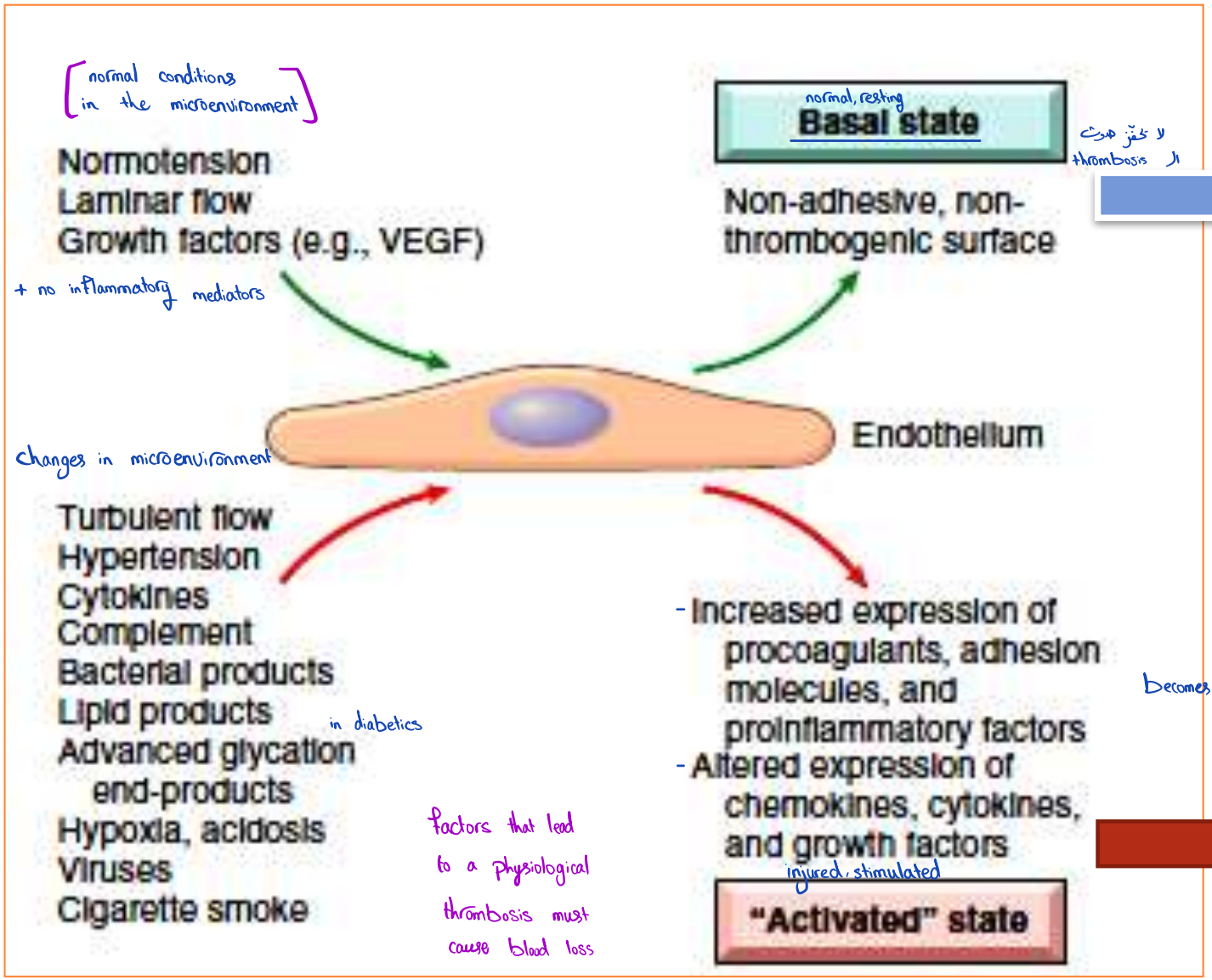
endocardium

*protective against pathological thrombosis *

normal ⟶ prevent P.T

injured ⟶ no prevention of P.T

Contribution of Endothelial Cells to Coagulation



لا تحفز حدوث thrombosis

No thrombosis

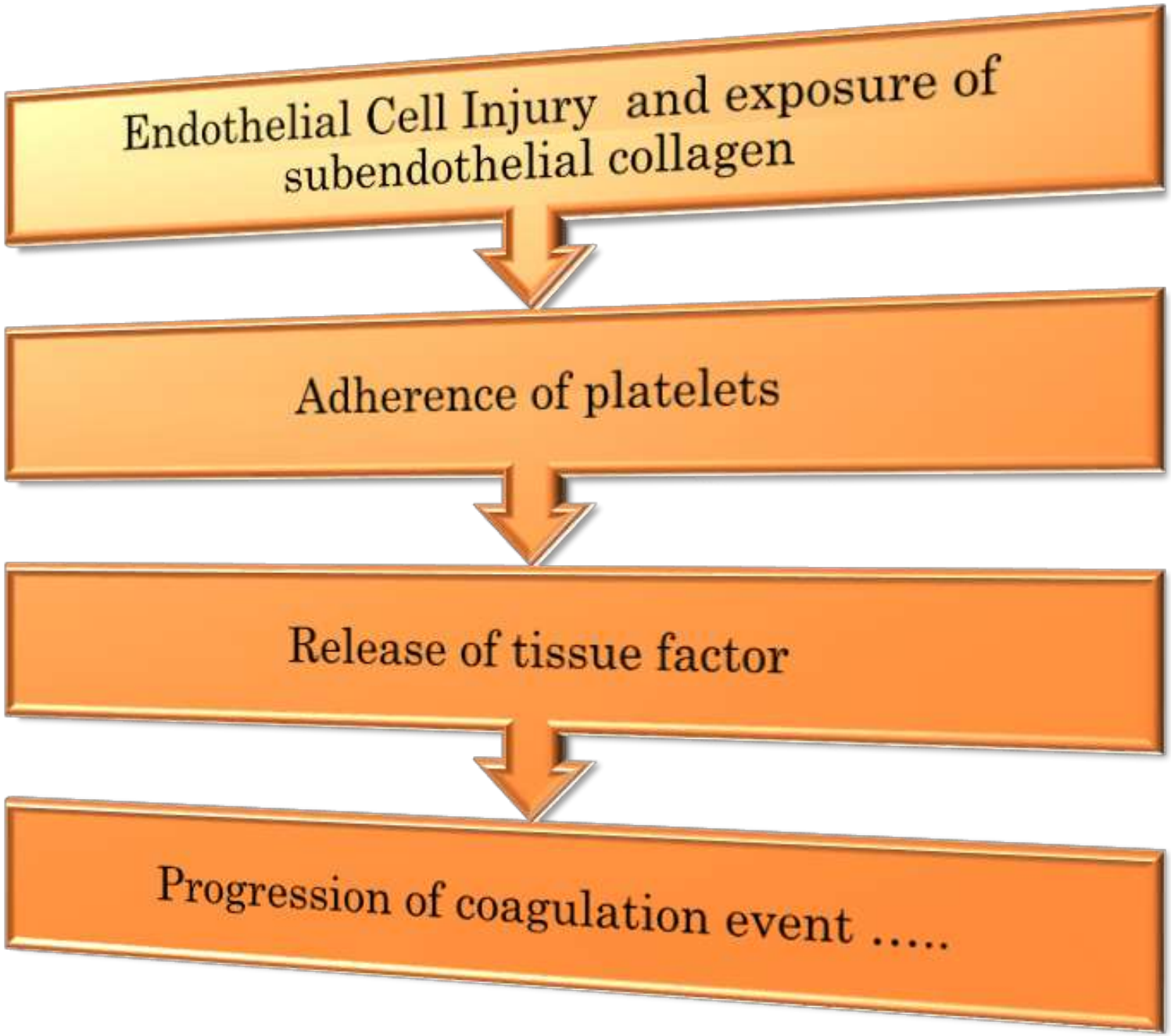
factors that lead to a physiological thrombosis must cause blood loss

Becomes pro-adhesive + pro-thrombogenic

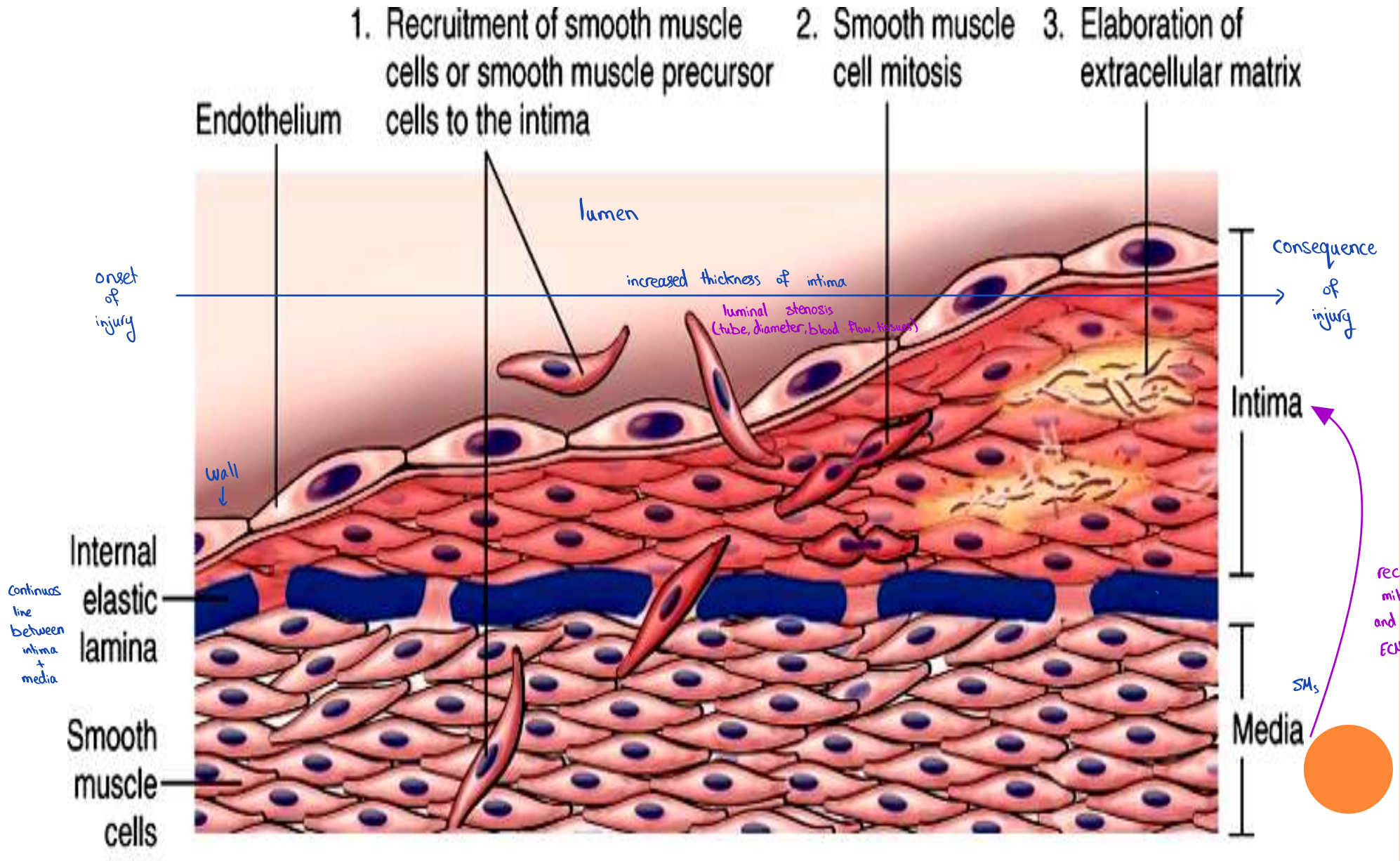
thrombosis

endothelial dysfunction

prothrombotic ? antithrombotic


Endothelial Cell Injury and exposure of subendothelial collagen
Adherence of platelets
Release of tissue factor
Progression of coagulation event .....

Response of Vascular Wall Cells to Injury



Response of Vascular Wall Cells to Injury

- **Injury results in a healing response**

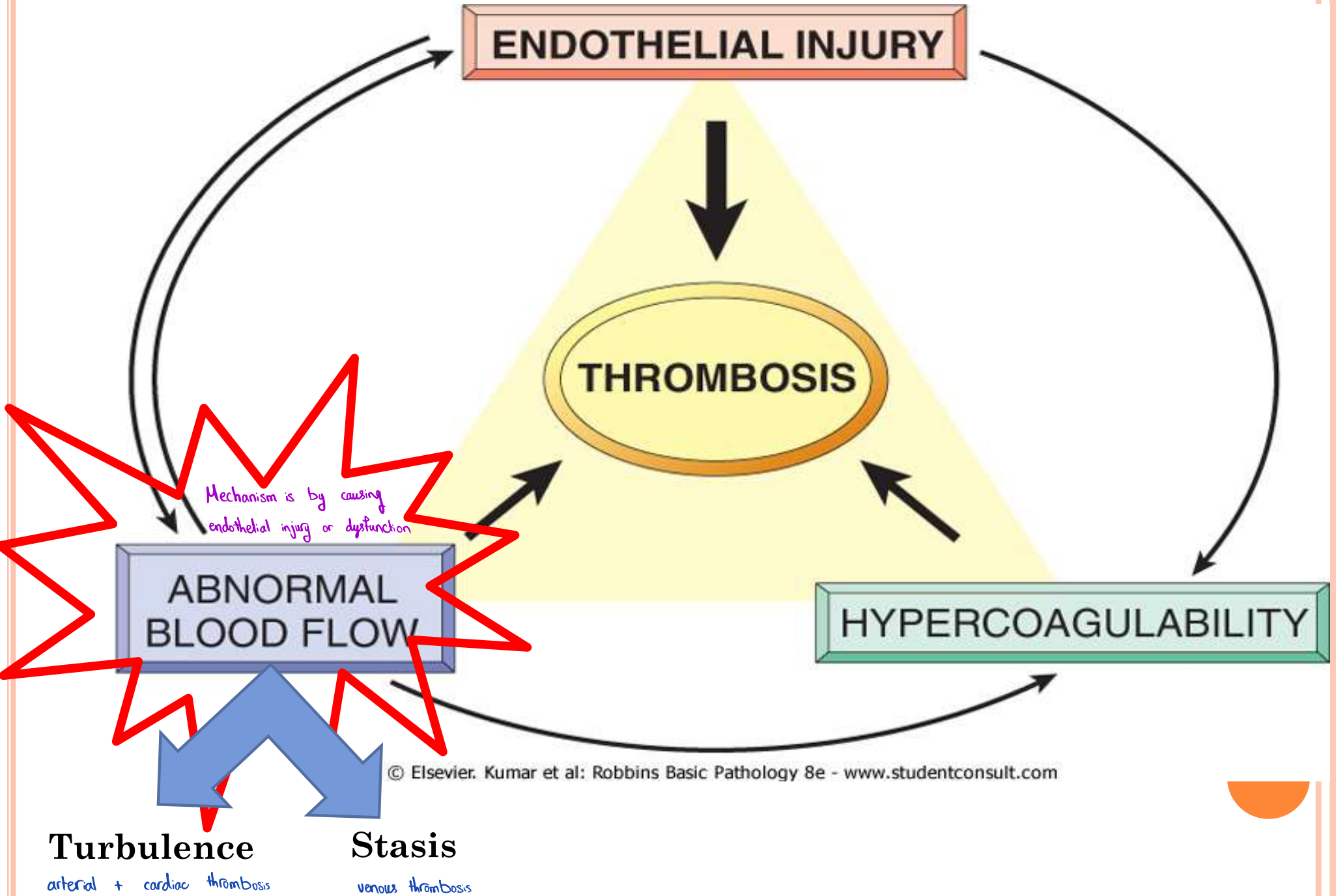
- **Pathologic effect of vascular healing:**

Excessive thickening of the intima →→
luminal stenosis & blockage of vascular flow

gen activators. Of note, however, *endothelium need not be denuded or physically disrupted to contribute to the development of thrombosis; any perturbation in the dynamic balance of the prothrombotic and antithrombotic effects of endothelium can influence clotting locally*. Thus, dysfunctional endothelium elaborates greater amounts of procoagulant factors (e.g., platelet adhesion molecules, tissue factor, PAI) and synthesizes lesser amounts of anticoagulant molecules (e.g., thrombomodulin, PGI_2, t-PA). Endothelial dysfunction can be induced by a variety of insults, including hypertension, turbulent blood flow, bacterial products, radiation injury, metabolic abnormalities such as homocystinuria and hypercholesterolemia, and toxins absorbed from cigarette smoke.

Causes of Endothelial injury

1. *Valvulitis*
2. *MI*
3. *Atherosclerosis*
4. *Traumatic or inflammatory conditions*
5. *Hypertension*
6. *Endotoxins*
7. *Hypercholesterolemia*
8. *Radiation*
9. *Smoking*
10. *……..etc.*



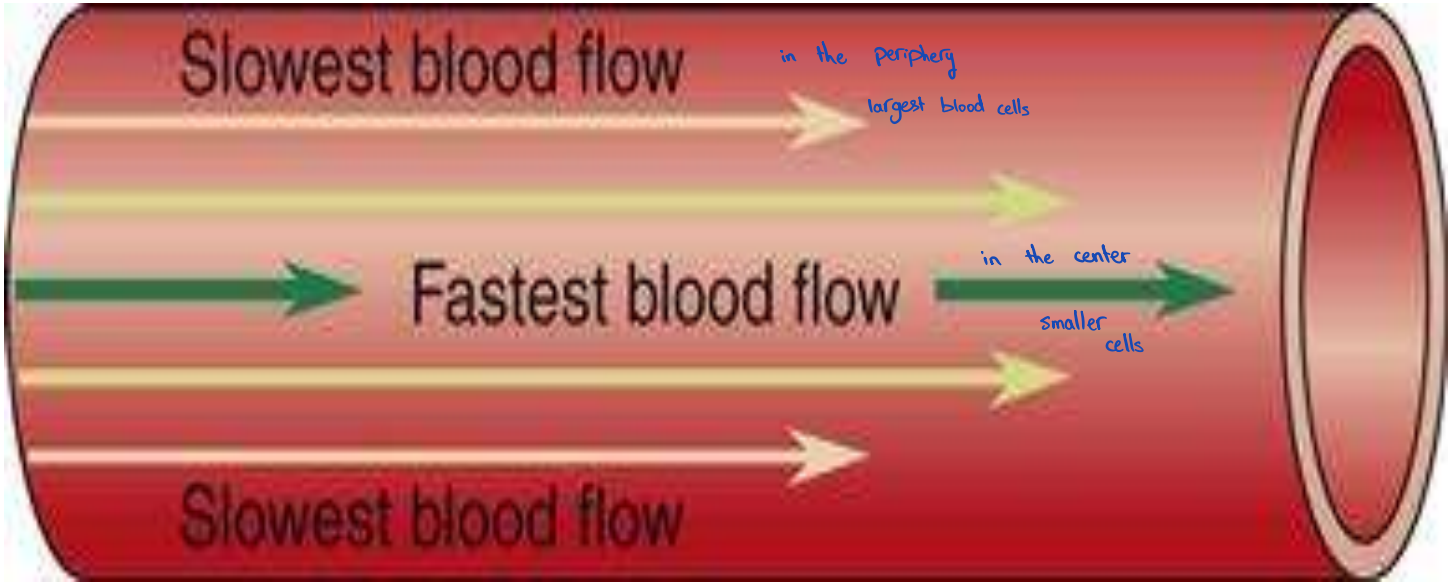
Turbulence

arterial + cardiac thrombosis

Stasis

venous thrombosis

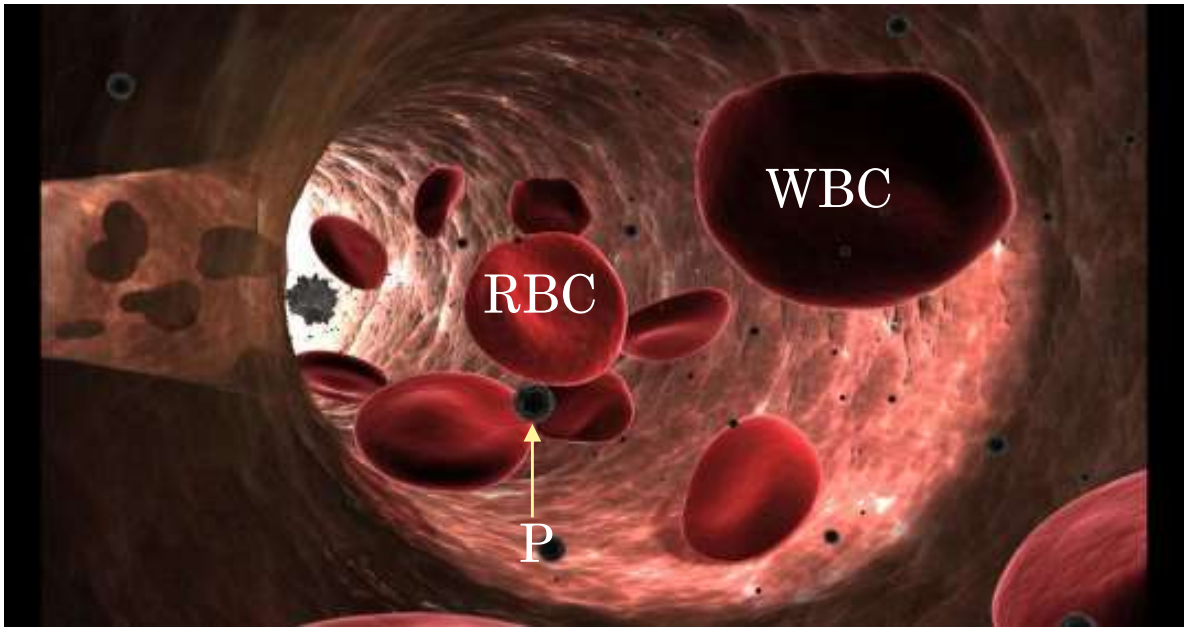
LAMINAR BLOOD FLOW (NORMAL)



in the periphery
largest blood cells

in the center
smaller cells

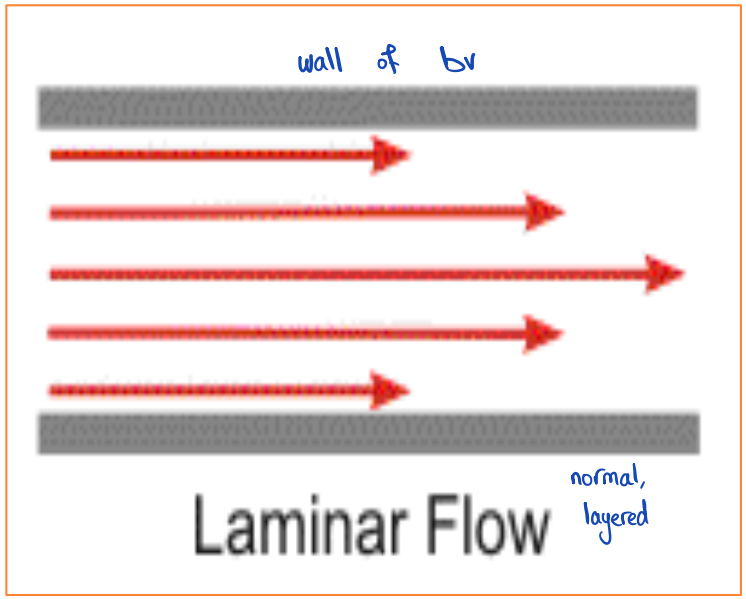
this prevents pathological thrombosis, platelets are kept away from ECs, so no unneccessary thrombosis



Laminar vs turbulent blood flow

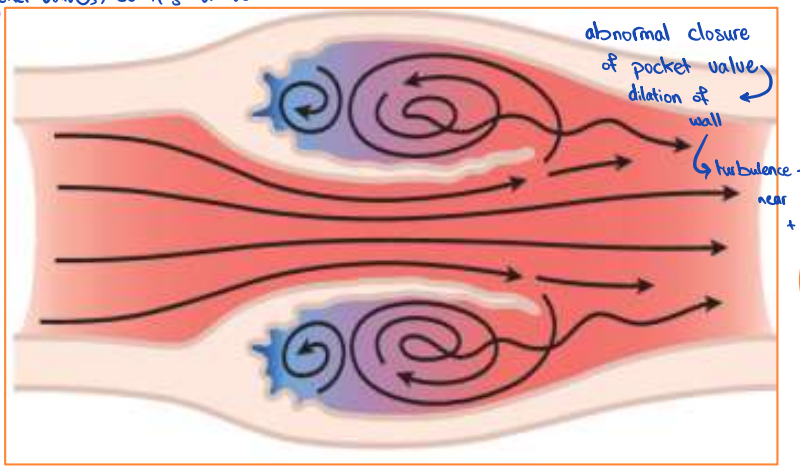
- Both promote endothelial cell activation and enhanced procoagulant activity, in part through flow-induced changes in endothelial gene expression.
- Stasis allows platelets and leukocytes to come into contact with the endothelium when the flow is sluggish.
- Stasis also slows the washout of activated clotting factors and impedes the inflow of clotting factor inhibitors.

higher chances of proximity of platelets to ECs + abnormal directions stasis + lower speed of blood flow

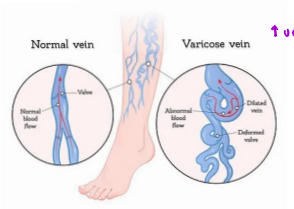


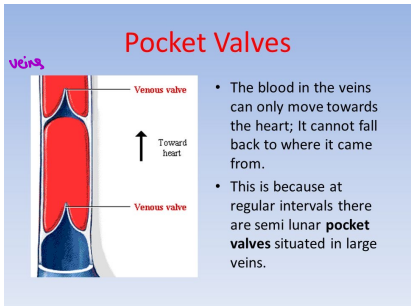
Turbulent Flow

we have pocket valves, so it's a vein



insufficiency leads to ↑ venous return → Varicose veins

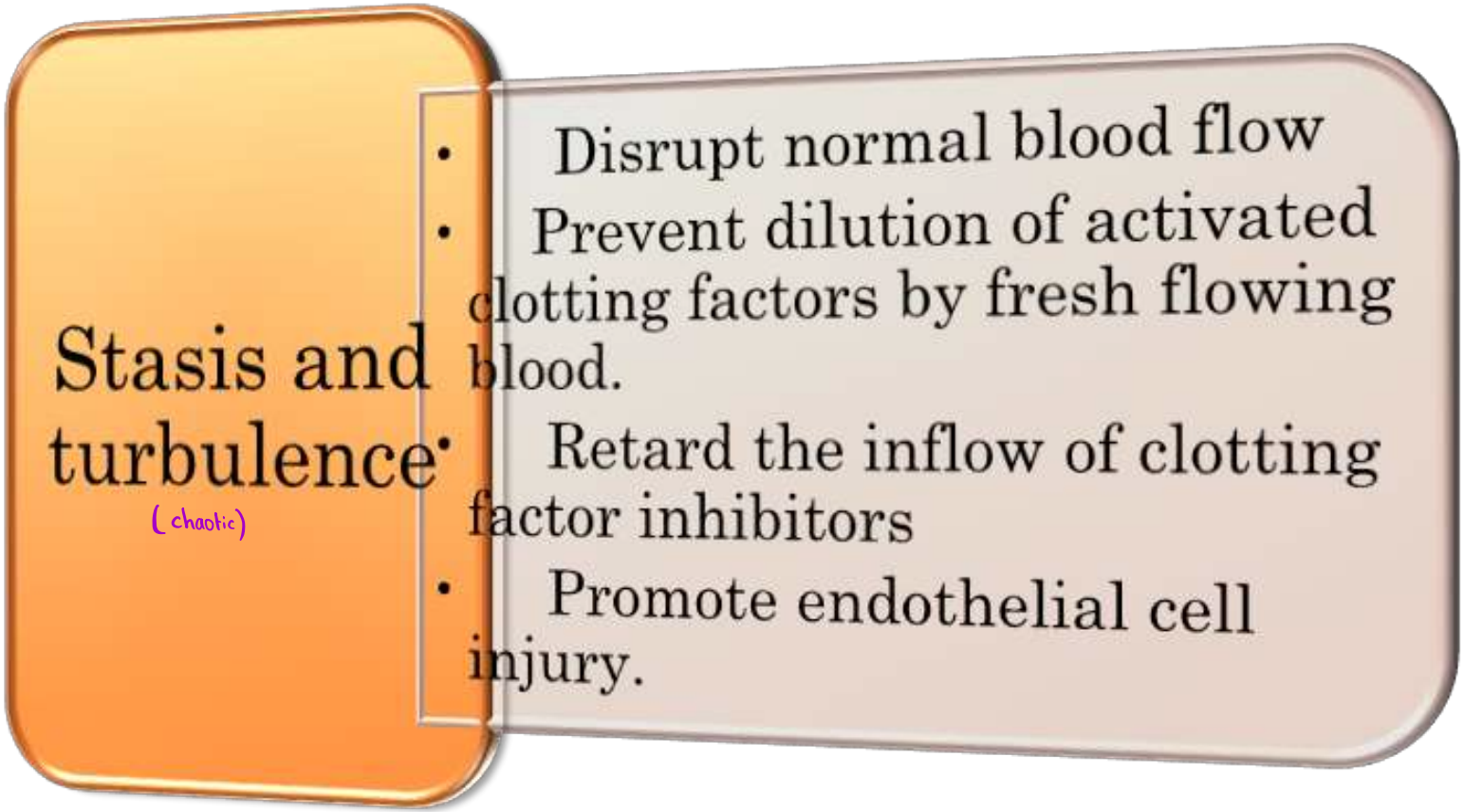




Stasis

slower than normal

- *Stasis is a major factor in **venous** thrombi*
- Normal blood flow is ***laminar (p***latelets flow centrally in the vessel lumen, separated from the endothelium by a slower moving clear zone of plasma)
- Stasis and turbulence cause the followings:



Causes of Stasis

1. ***Atherosclerosis***

in a number of clinical settings. Ulcerated atherosclerotic plaques not only expose subendothelial ECM but also cause turbulence.

2. ***Aneurysms***

cause turbulence. Abnormal aortic and arterial dilations called *aneurysms* create local stasis and consequently a fertile site for thrombosis

3. ***Myocardial Infarction (Non-cotractile fibers)***

Acute myocardial infarction results in focally noncontractile myocardium. Ventricular remodeling after more remote infarction can lead to aneurysm formation. In both cases, cardiac mural thrombi are more easily formed due to the local blood stasis

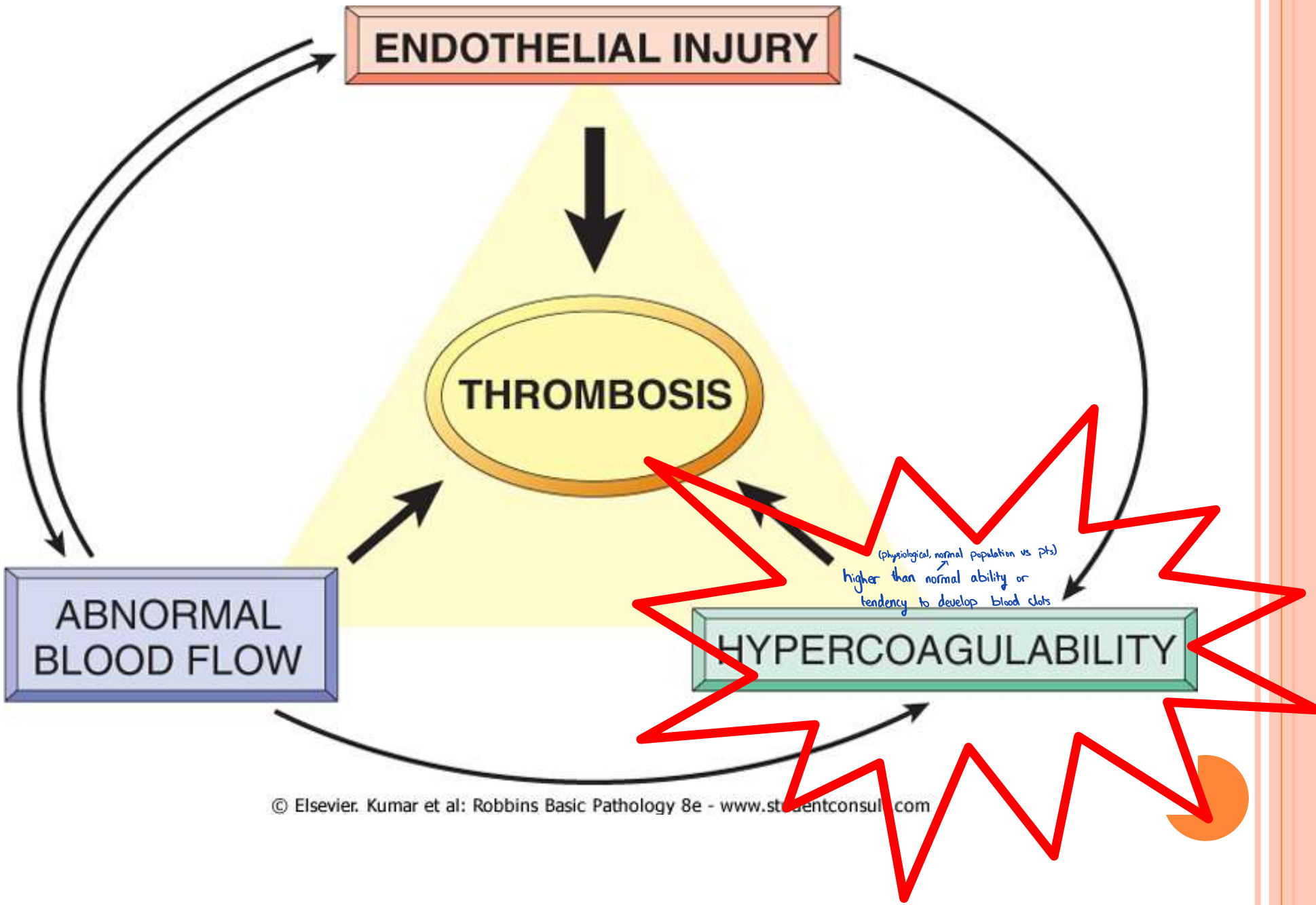
4. ***Mitral valve stenosis (atrial dilation)***

Mitral valve stenosis (e.g., after rheumatic heart disease) results in left atrial dilation. In conjunction with atrial fibrillation, a dilated atrium is a site of profound stasis and a prime location for the development of thrombi

5. ***Hyper viscosity syndrome (PCV and Sickle Cell anemia)***

Hyperviscosity syndromes (such as *polycythemia*) (Chapter 11) increase resistance to flow and cause small vessel stasis; the deformed red cells in sickle cell anemia (Chapter 11) cause vascular occlusions, and the resultant stasis also predisposes to thrombosis.

6. ***……..***


ENDOTHELIAL INJURY
THROMBOSIS
ABNORMAL BLOOD FLOW
HYPERCOAGULABILITY
(physiological, normal population vs pts)
higher than normal ability or tendency to develop blood clots
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Hypercoagulability

It is loosely defined as any alteration of the coagulation pathways that predisposes affected persons to thrombosis,

A. Genetic (primary):

- Inherited mutations in clotting factors or anti-clotting factors
- mutations in factor V gene and prothrombin gene are the most common causes of primary

In some situations (e.g., cardiac failure or trauma), stasis or vascular injury may be the most important factor. The hypercoagulability associated with oral contraceptive use and the hyperestrogenic state of pregnancy may be related to increased hepatic synthesis of coagulation factors and reduced synthesis of antithrombin III. In disseminated cancers, release of procoagulant tumor products (e.g., mucin from adenocarcinoma) predisposes to thrombosis. The hypercoagulability seen with advancing age has been attributed to increased platelet aggregation and reduced release of PGI_2 from endothelium. Smoking and obesity promote hypercoagulability by unknown mechanisms.

B. Acquired (secondary):

- Much more frequent than primary causes
- multifactorial & more complicated
- causes include: Immobilization, MI, AF, surgery, fractures, burns, Cancer, Prosthetic cardiac valves …etc

(slow blood flow (venous stasis which promotes activation of clotting factors)

MORPHOLOGY OF THROMBI

- **Can develop anywhere in the CVS (e.g., in cardiac chambers, valves, arteries, veins, or capillaries).**

- ***Arterial or cardiac* thrombi→ begin at sites of *endothelial injury* or turbulence; and are usually superimposed on an *atherosclerotic plaque***

- **Venous thrombi → occur at sites of stasis. Most commonly the veins of the lower extremities (90%)**

- **Thrombi are focally attached to the underlying vascular surface.**

- **The propagating portion of a thrombus is poorly attached →fragmentation and embolus formation**

2 parts : 1. adherant to bv
2. free end (propagating) → may lead to embolus formation

occur at sites of stasis. Thrombi are focally attached to the underlying vascular surface and tend to propagate **toward** the heart; thus, arterial thrombi grow in a retrograde direction from the point of attachment, while venous thrombi extend in the direction of blood flow. The propagating

due to the fast blood flow

due to the slower blood flow

Terms to remember ….

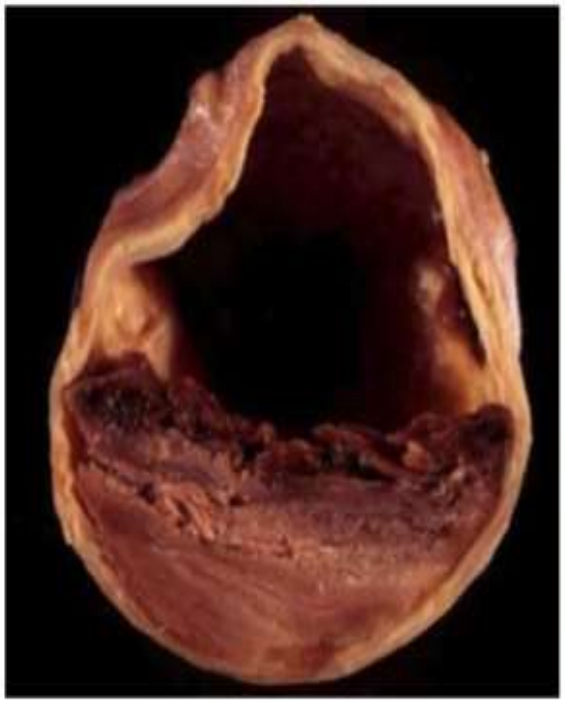
LINES OF ZAHN

macroscopic

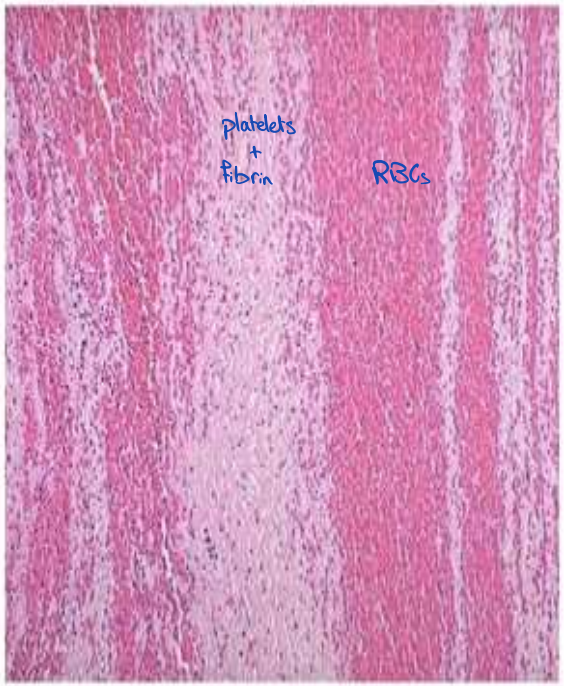
layers within blood clot

- gross and microscopically apparent laminations → only form in a flowing blood flow (alive)
- represent pale platelet and fibrin layers alternating with darker erythrocyte-rich layers
- Significance? distinguish **antemortem** (before death) thrombosis from postmortem clots (forensic issues to determine if it's the cause of death)
- postmortem (after death) blood clots are non-laminated clots *(no lines of Zahn)* (they form due to gravity)

gross



micro



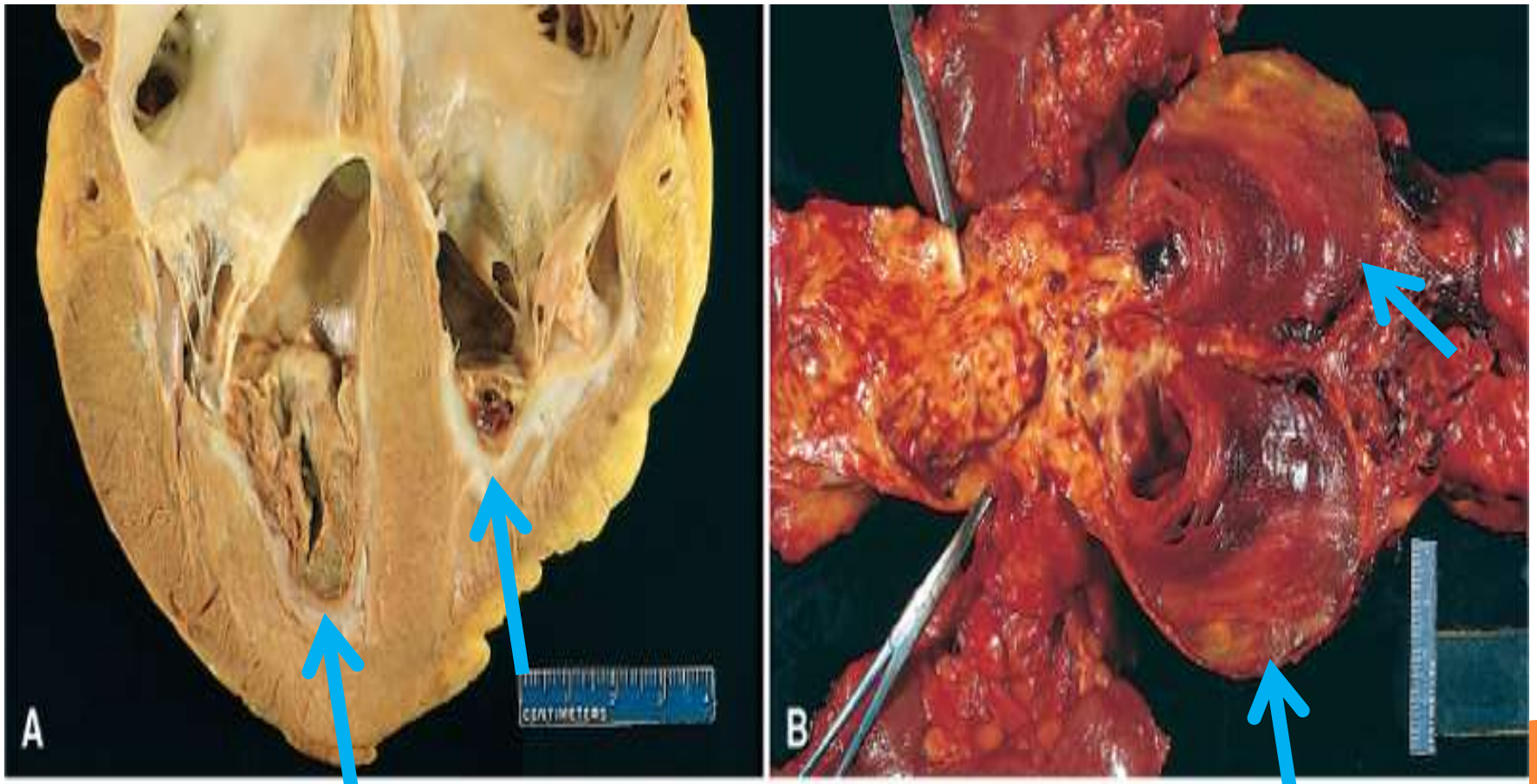
attached to a wall

MURAL THROMBI= - IN HEART CHAMBERS OR IN AORTIC LUMEN

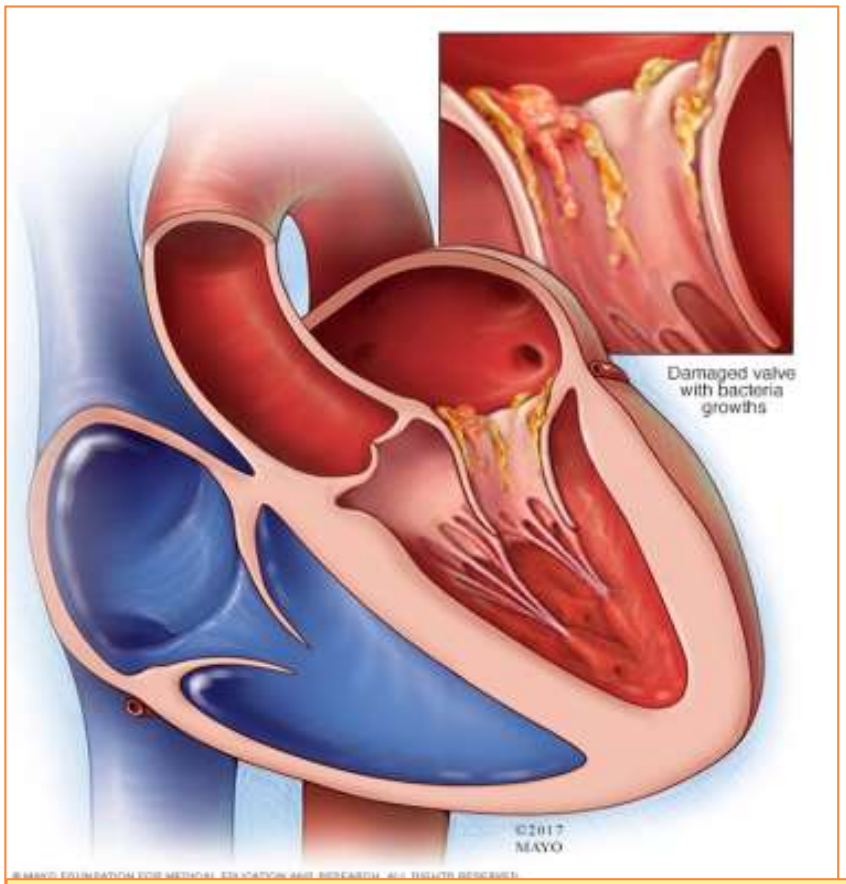
Describing heart & aortic thrombi

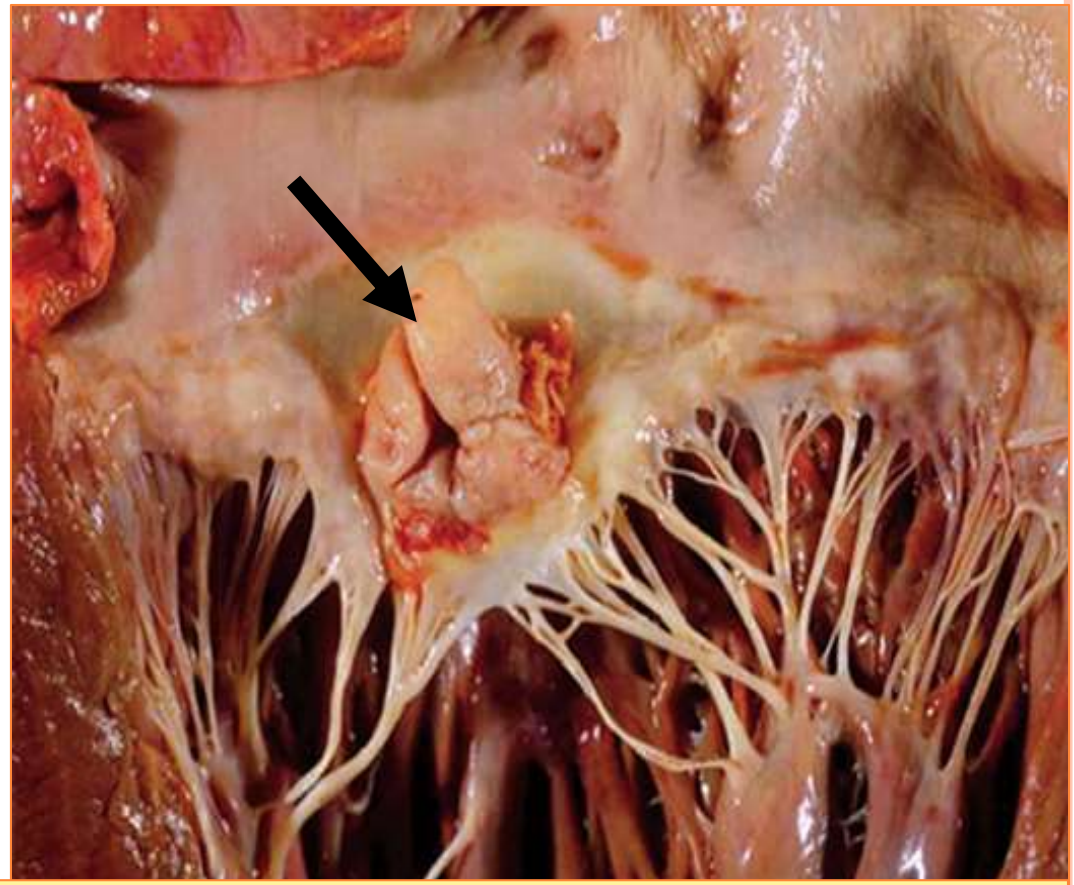
Thrombi occurring in heart chambers or in the aortic lumen are designated **mural thrombi.** Abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or myocardial infarction) or endomyocardial injury (myocarditis, catheter trauma) promote cardiac mural thrombi (Fig. 3–13, *A*), while ulcerated atherosclerotic plaques and aneurysmal dilation promote aortic thrombosis (Fig. 3-13, *B*).

endocardium



Cardiac Vegetations





= Thrombi on heart valves

Types:

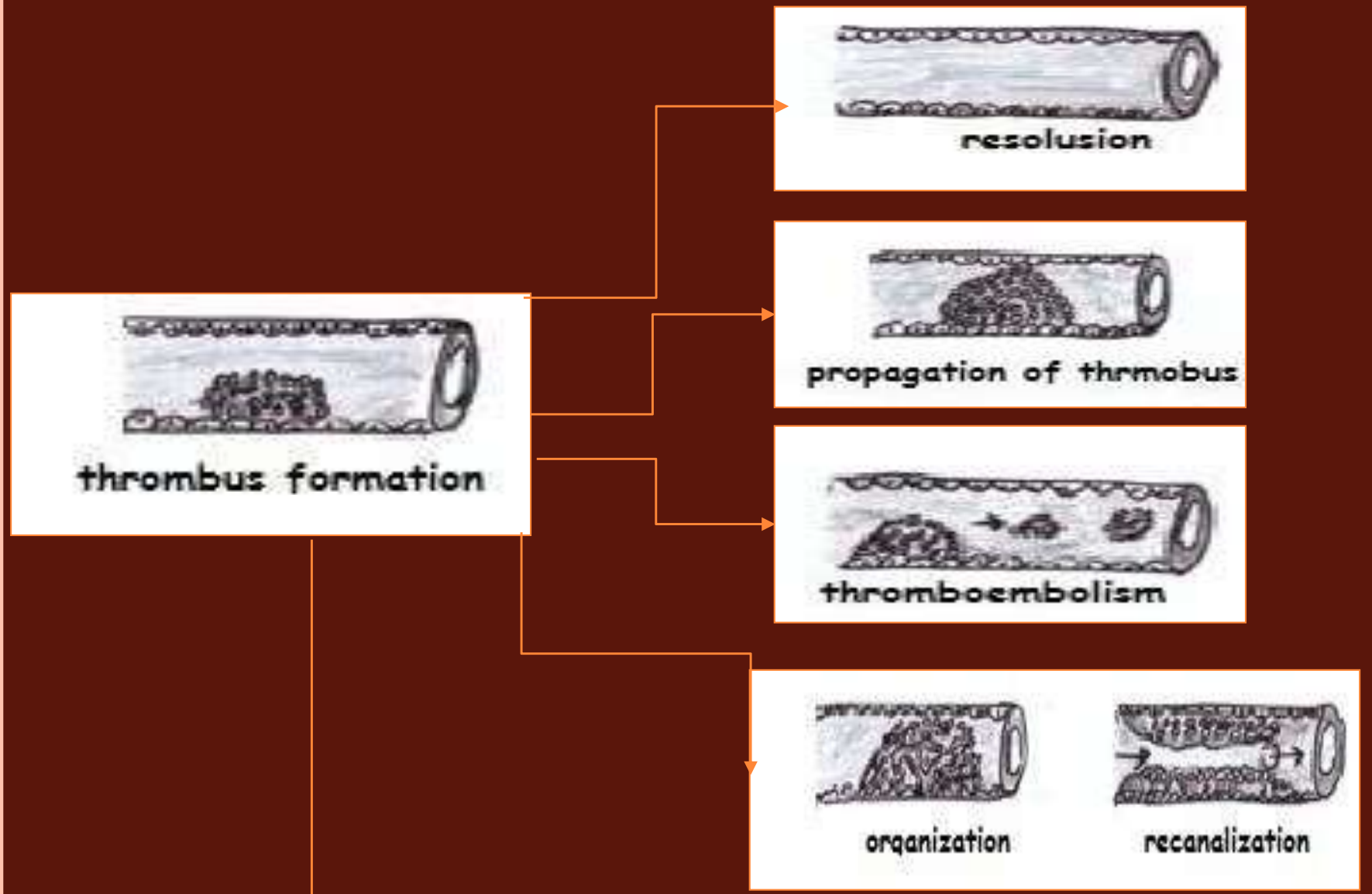
1- infectious (Bacterial or fungal blood-borne infections)

e.g. infective endocarditis

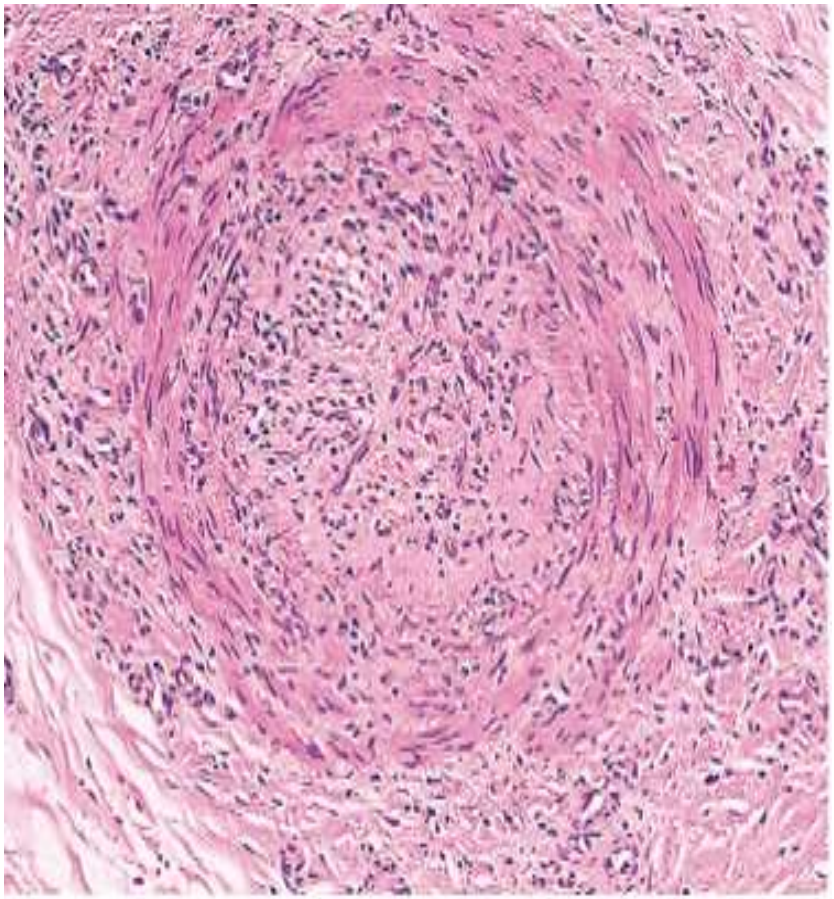
2-non- infectious: "Sterile vegetations" in a hypercoagulable state

e.g. rheumatic; non-bacterial thrombotic endocarditis

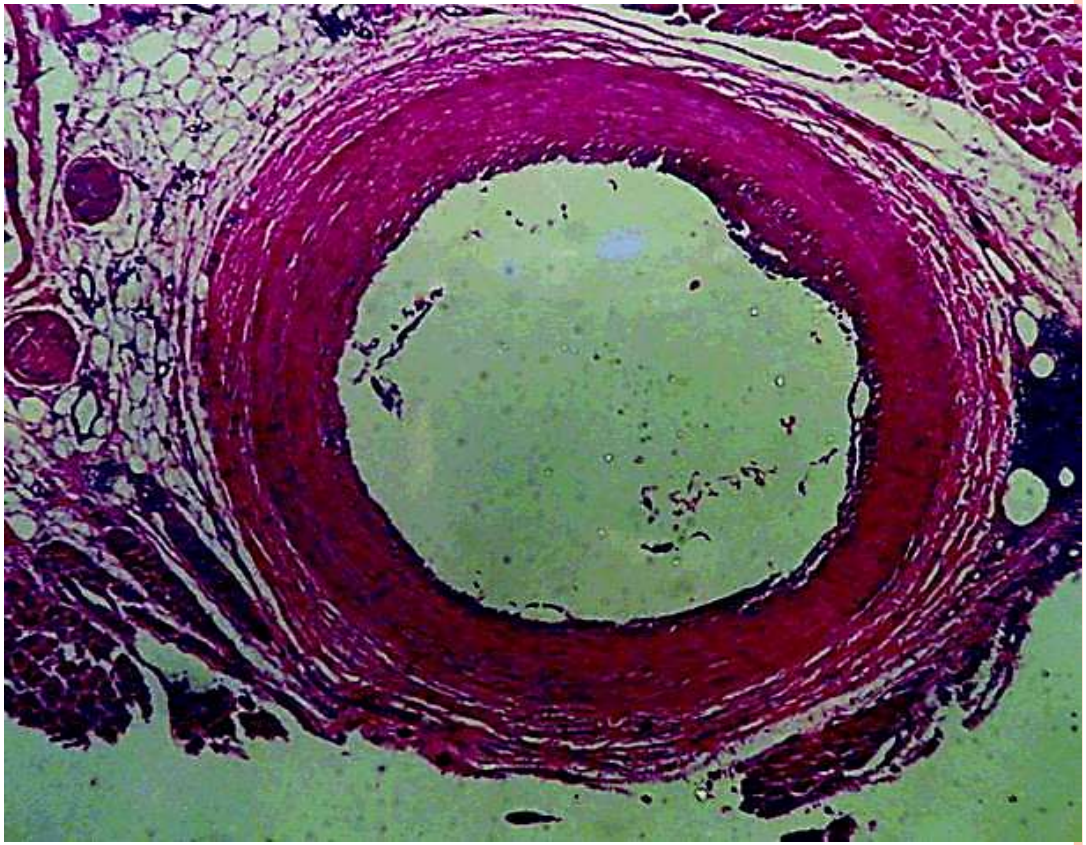
Fates of a thrombus



Organized arterial thrombus



A normal artery cross section for comparison



Fate of thrombi

occlusion of the lumen, bc it wasn't lysed exo or endogenously

1. ***Propagation*** → accumulate additional platelets and fibrin, eventually causing **vessel obstruction** (↑ risk of embolization + occlusion) → ischemia of downstream tissues
2. ***Embolization*** → Thrombi dislodge or fragment and are transported elsewhere in the vasculature (may go to a narrower lumen → obstruction)
3. ***Dissolution*** → Thrombi are removed by fibrinolytic (lysis) activity (endogenous or exogenous) (only in ***recent*** *thrombi)*
4. ***Organization* and recanalization*** → Thrombi induce inflammation and fibrosis. These can *recanalize* (re-establishing some degree of flow), or they can be incorporated into a thickened vessel wall (replacement of its components (platelets, fibrin, RBCs → fibrous tissue, worse, permanent)) (iatrogenic or self)

Organization and recanalization. Older thrombi become *organized* by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts into the fibrin-rich thrombus (Fig. 3–14). In time, capillary channels are formed that—to a limited extent—create conduits along the length of the thrombus, thereby reestablishing the continuity of the original lumen. Further recanalization can sometimes convert a thrombus into a vascularized mass of connective tissue that is eventually incorporated into the wall of the remodeled vessel.

**Organization refers to the ingrowth of endothelial cells, smooth cells and fibroblasts into the fibrin rich thrombus.*

complete dissolution. With older thrombi, extensive fibrin polymerization renders the thrombus substantially more resistant to plasmin-induced proteolysis, and lysis is ineffectual. This acquisition of resistance to lysis has clinical significance, as therapeutic administration of fibrinolytic agents (e.g., t-PA in the setting of acute coronary thrombosis) generally is not effective unless given within a few hours of thrombus formation.

5. ***Superimposed infection (Mycotic aneurysm)***

the wall of the remodeled vessel. Occasionally, instead of organizing, the center of a thrombus undergoes enzymatic digestion, presumably because of the release of lysosomal enzymes from entrapped leukocytes. If bacterial seeding occurs, the contents of degraded thrombi serve as an ideal culture medium, and the resulting infection may weaken the vessel wall, leading to formation of a *mycotic aneurysm* (Chapter 9).