ACS pathophysiology: an Update

חיים דננברג

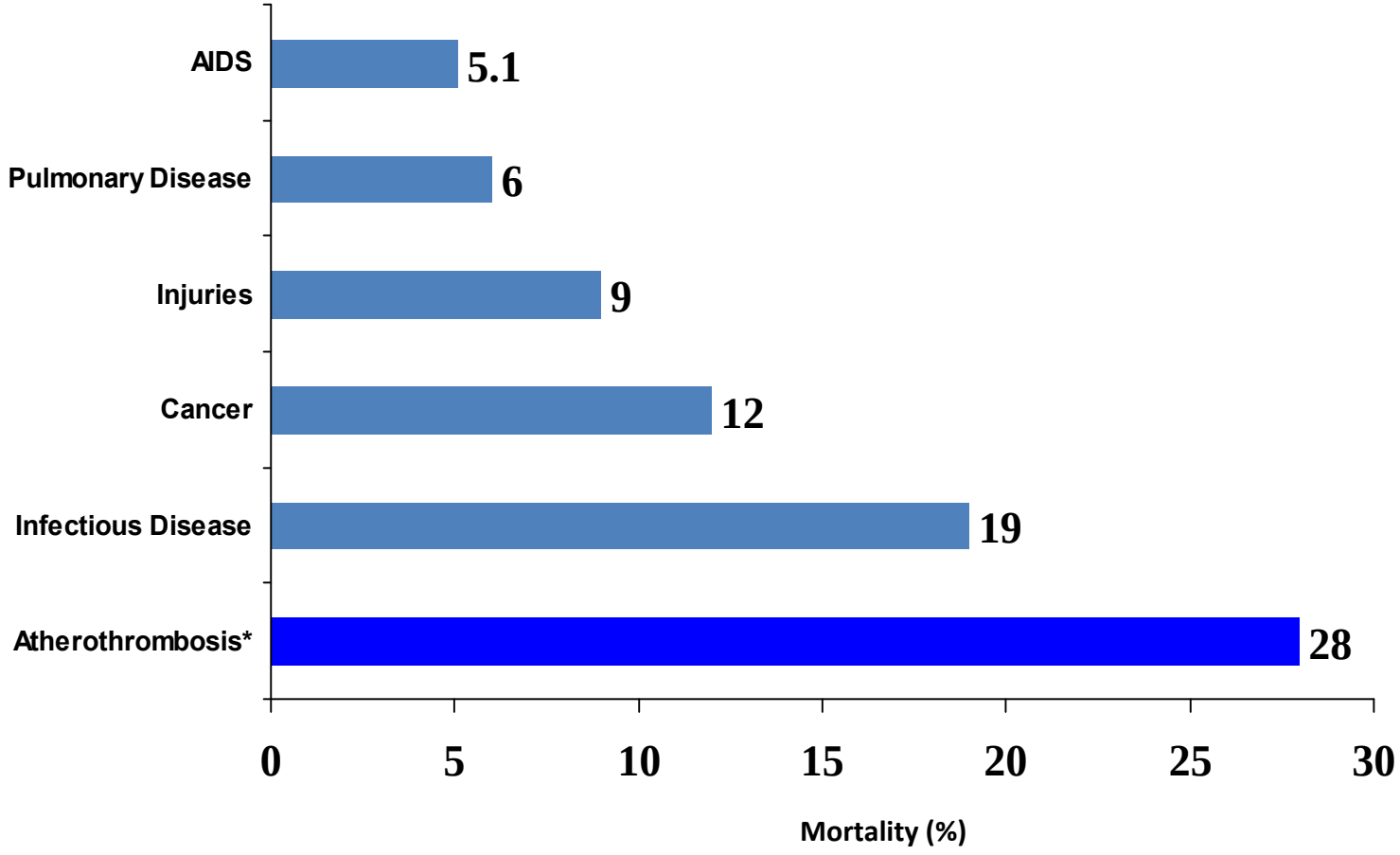
המרכז הרפואי הדסה

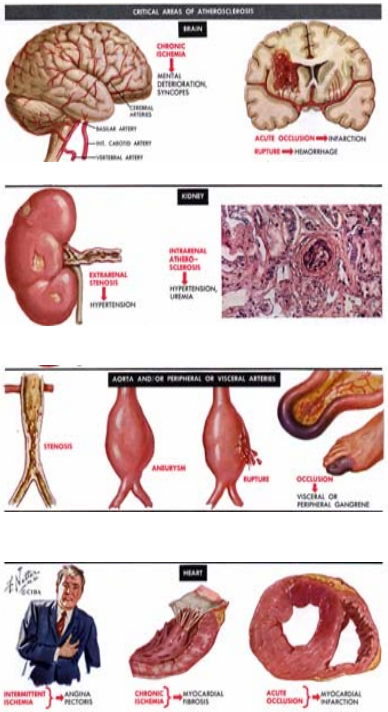
ירושלים

השתלמות למתמחים בקרדיולוגיה

קיסריה, 2 נובמבר 2010

Atherothrombosis is the Leading Cause of Death Worldwide



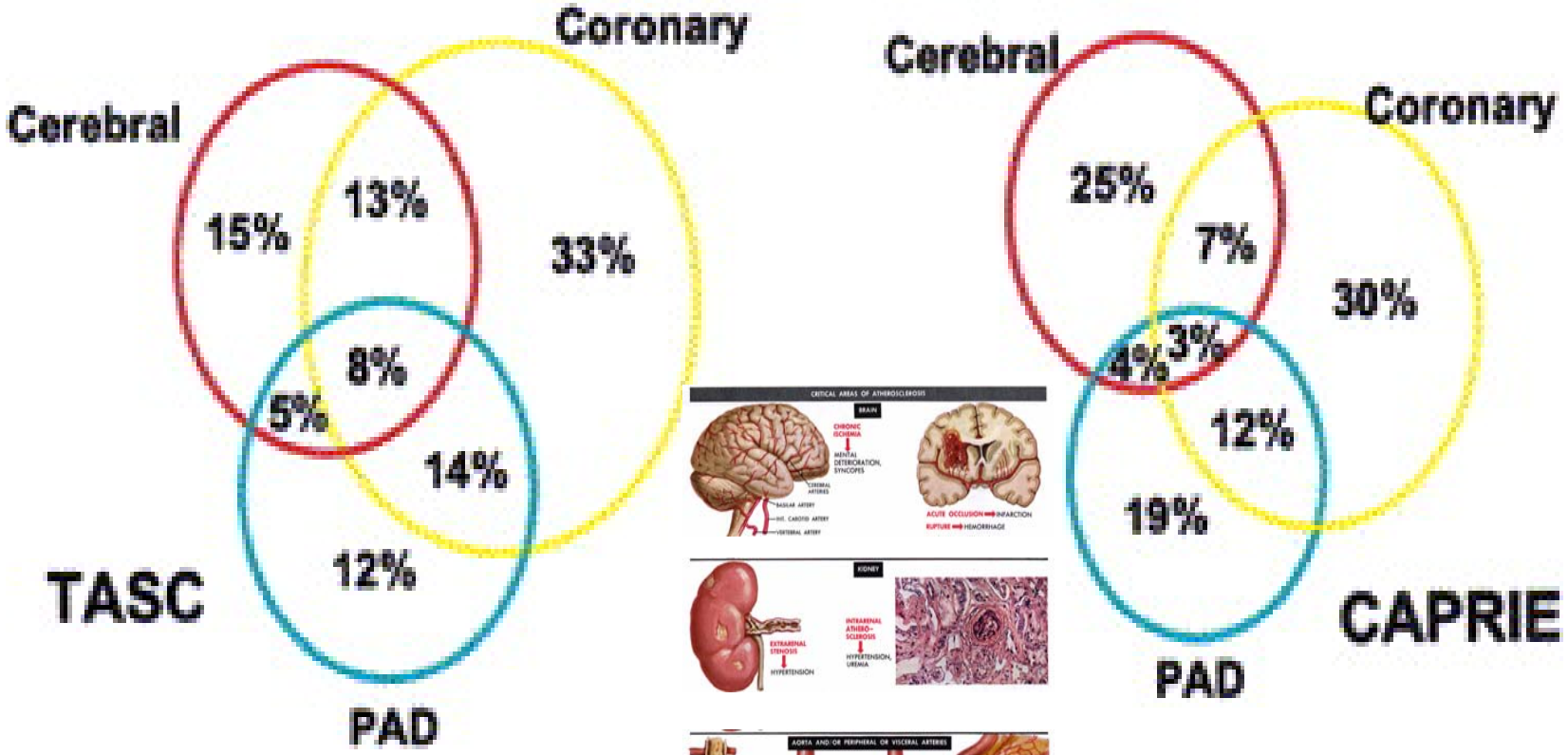


*Ischemic heart disease, cerebrovascular disease, inflammatory heart disease and hypertensive heart disease

†Worldwide defined as Member States by WHO Region (African, Americas, Eastern Mediterranean, European, South-East Asia and Western Pacific)

The World Health Report, 2002, WHO Geneva, 2002.

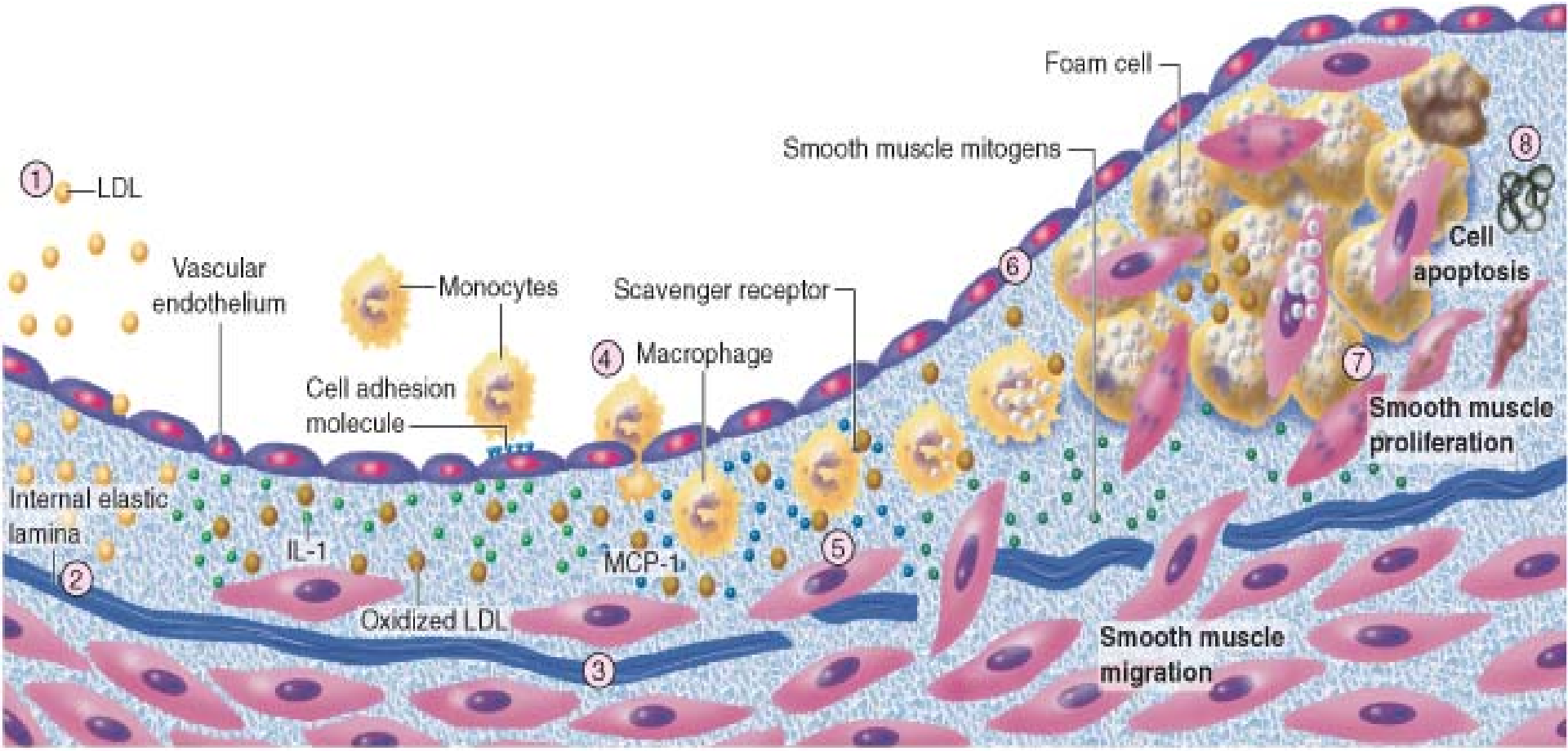
Atherothrombosis: a systemic disease



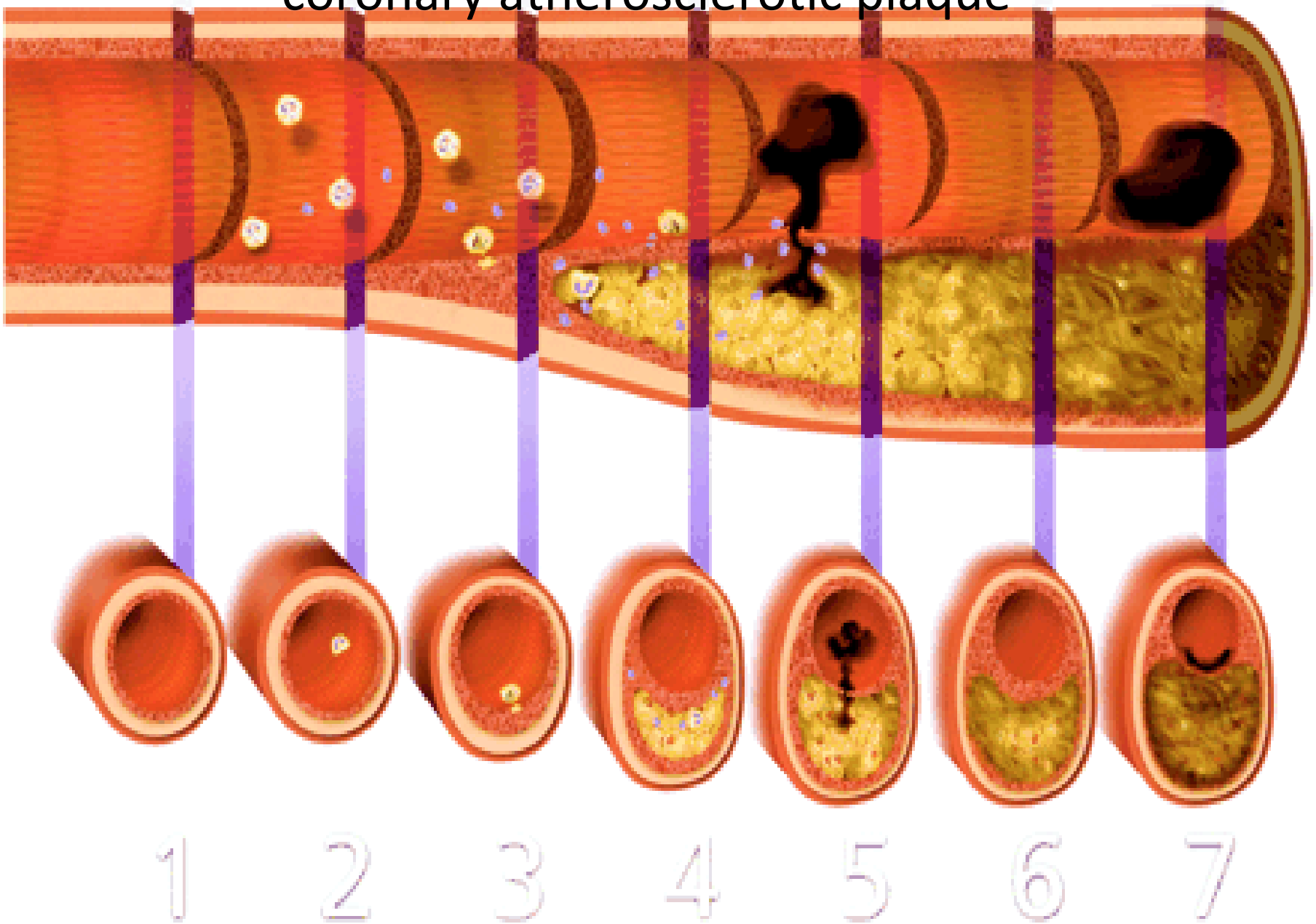
~2,000

~20,000

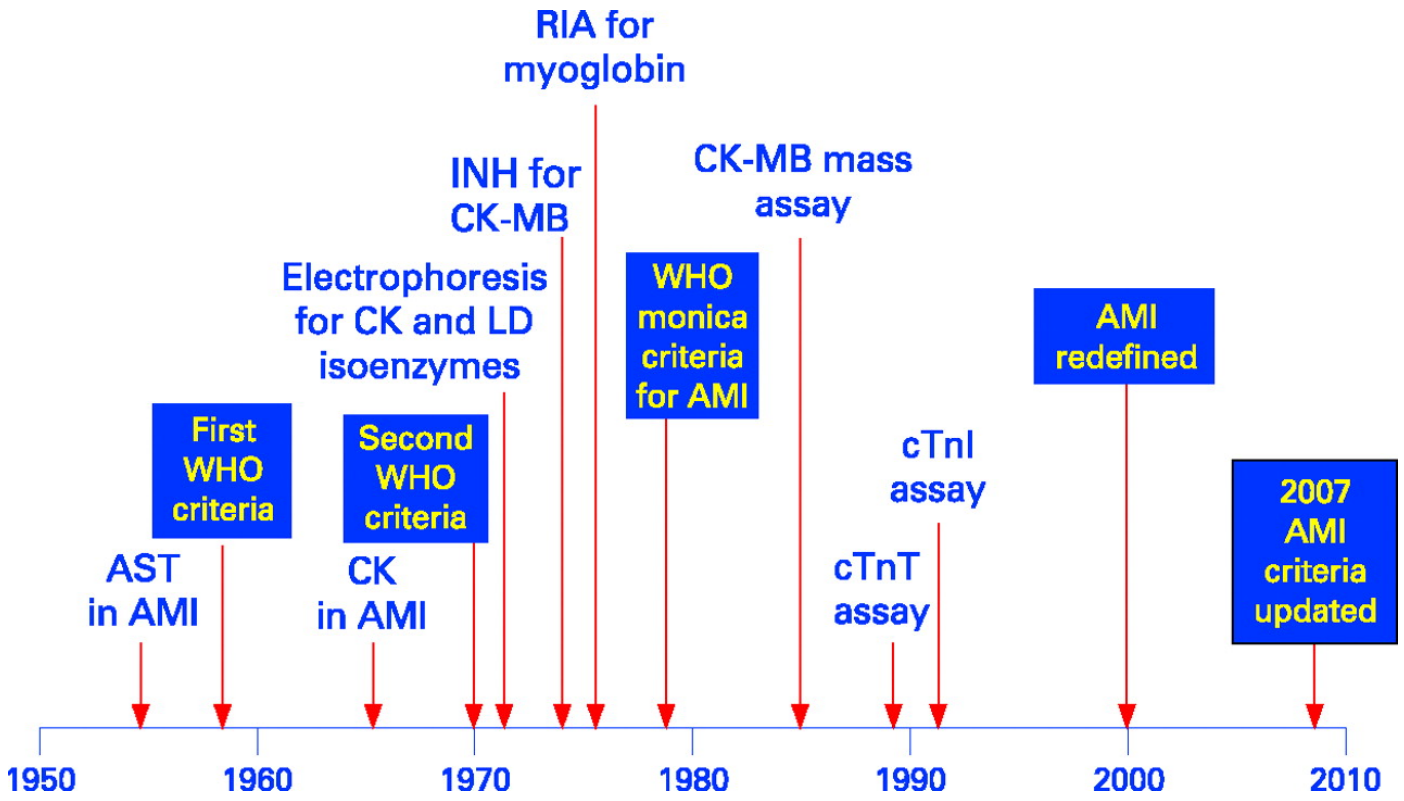
Evolution of the atherosclerotic plaque



Initiation, progression, and complication of human coronary atherosclerotic plaque



History of biomarkers and the definition of acute myocardial infarction (AMI).



Alpert, J. S et al. Heart 2008;94:1335-1341

New (universal) MI definition

- **Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection**

- **Type 2: MI secondary to ischemia due to oxygen demand:supply imbalance (coronary artery spasm, embolism, anemia, arrhythmias, hypertension, or hypotension)**

- **Type 3: Sudden unexpected cardiac death accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood**

- **Type 4a: MI associated with PCI**
- **Type 4b: MI associated with stent thrombosis (definite)**

- **Type 5: Myocardial infarction associated with CABG**

Elevations of troponin in the absence of overt IHD

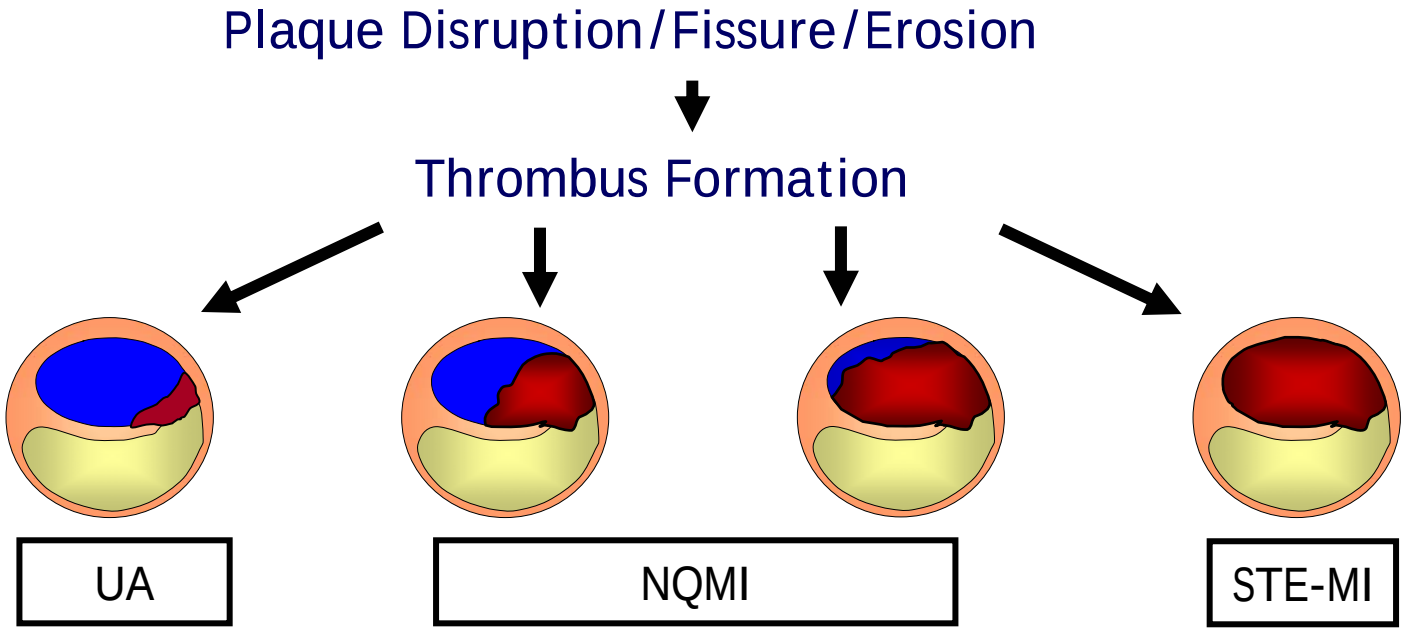
Table 2 Elevations of troponin in the absence of overt ischemic heart disease

Cardiac contusion, or other trauma including surgery, ablation, pacing, etc.
Congestive heart failure—acute and chronic
Aortic dissection
Aortic valve disease
Hypertrophic cardiomyopathy
Tachy- or bradyarrhythmias, or heart block
Apical ballooning syndrome
Rhabdomyolysis with cardiac injury
Pulmonary embolism, severe pulmonary hypertension
Renal failure
Acute neurological disease, including stroke or subarachnoid haemorrhage
Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, and scleroderma
Inflammatory diseases, e.g. myocarditis or myocardial extension of endo-/pericarditis
Drug toxicity or toxins
Critically ill patients, especially with respiratory failure or sepsis
Burns, especially if affecting >30% of body surface area
Extreme exertion

Modified from Jaffe *et al.*,[4] and French and White.[5]

Thygesen, K. et al. Circulation 2007

Thrombus Formation and ACS



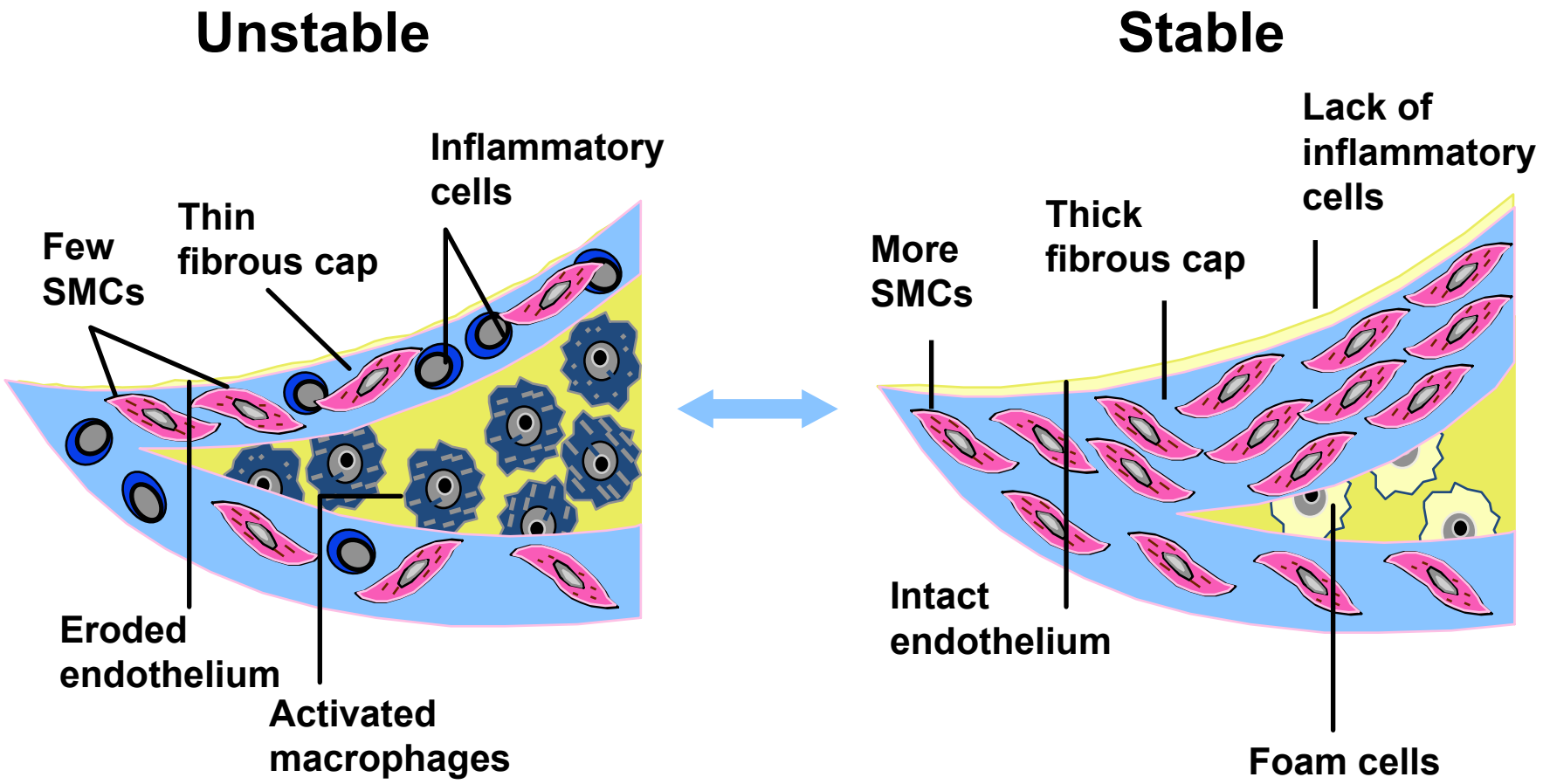
Old Terminology:

New Terminology:

Non-ST-Segment Elevation Acute Coronary Syndrome (ACS)

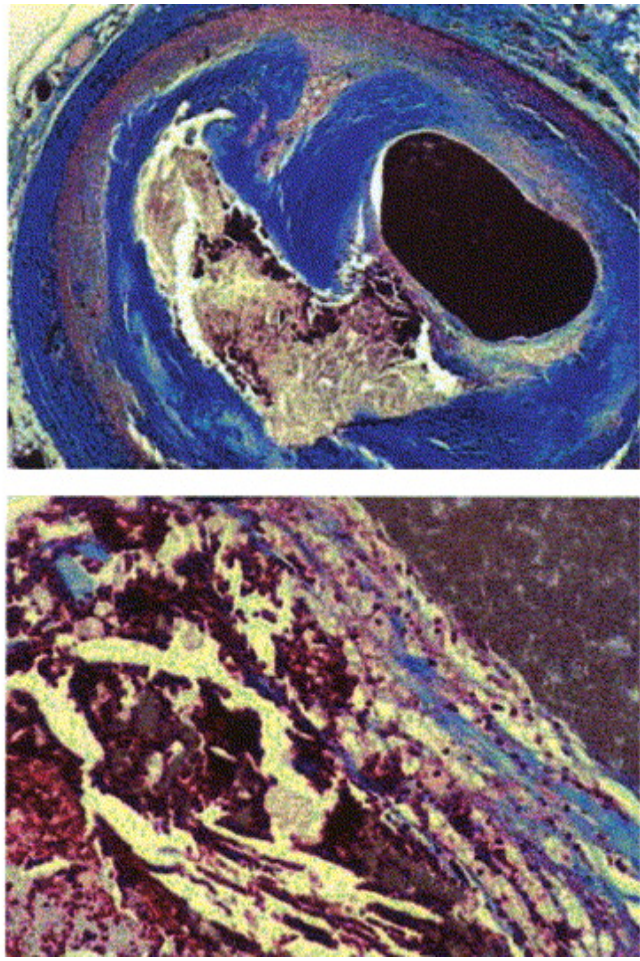
ST-Segment Elevation Acute Coronary Syndrome (ACS)

Characteristics of Unstable and Stable Plaque

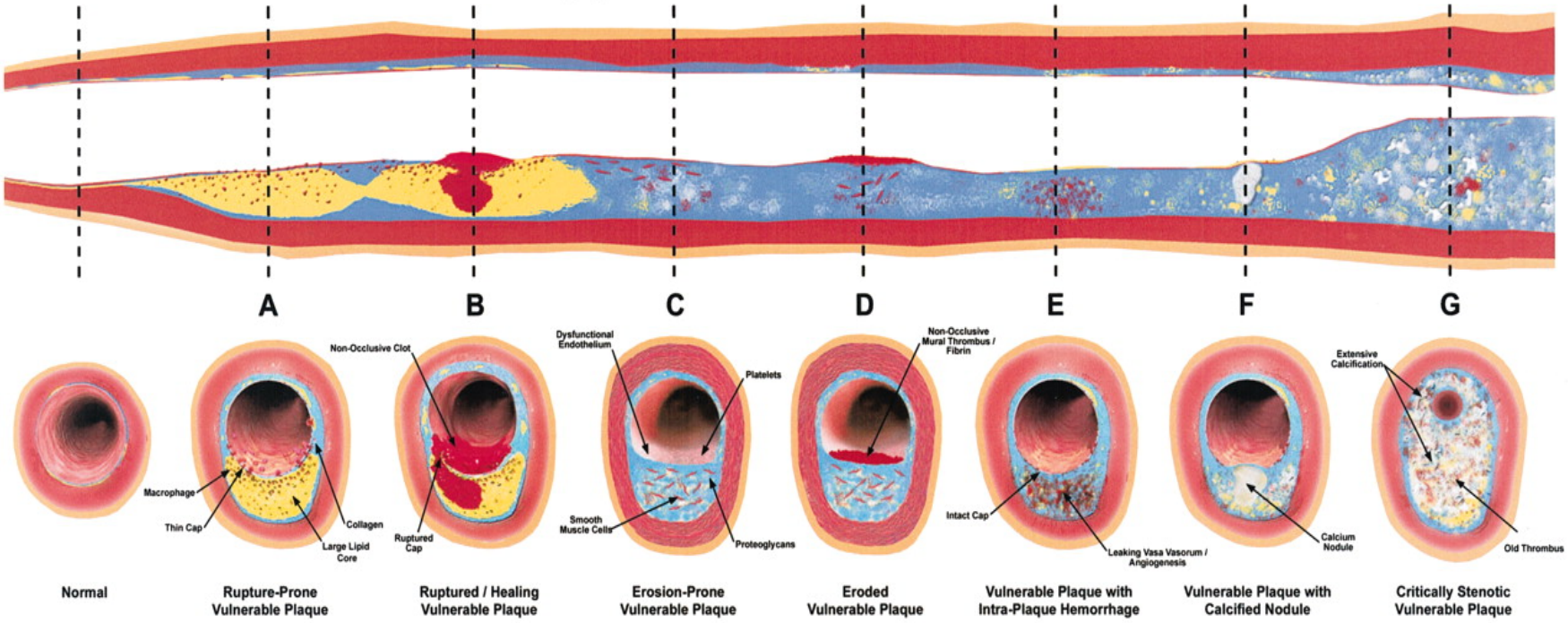


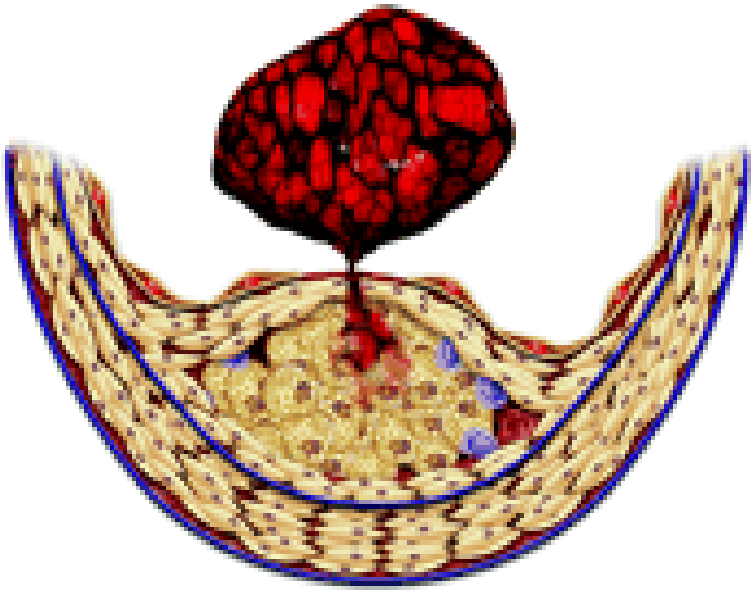
Vulnerable plaque

1. **Thin, friable fibrous caps. (cap thickness < 60 micron)**
2. **Thick infiltrate of macrophages (>25 per high-magnification field)**
3. **Lipid-rich central core (40% of its volume), with an abundant amount of lipid-laden macrophage foam cells derived from blood monocytes.**
4. **Blood vessels from the vasa-vasorum penetrating the plaque**
5. **Fractures in the internal elastic lamina**

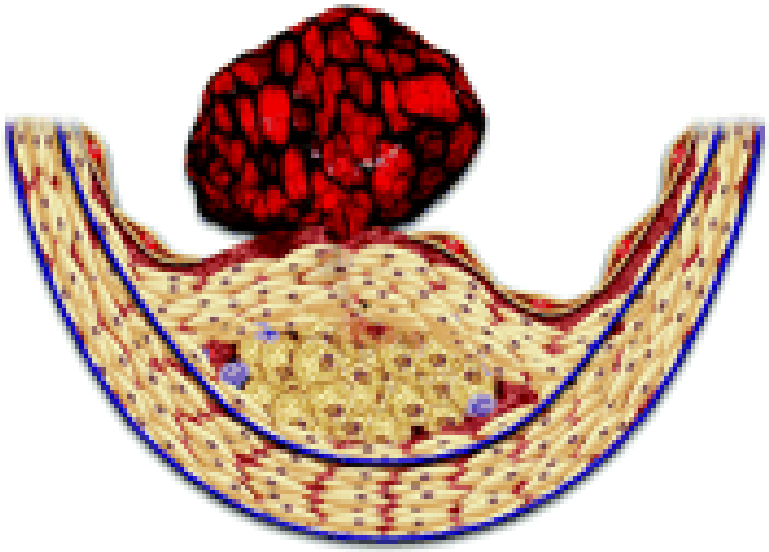


Different Types of Vulnerable Plaque

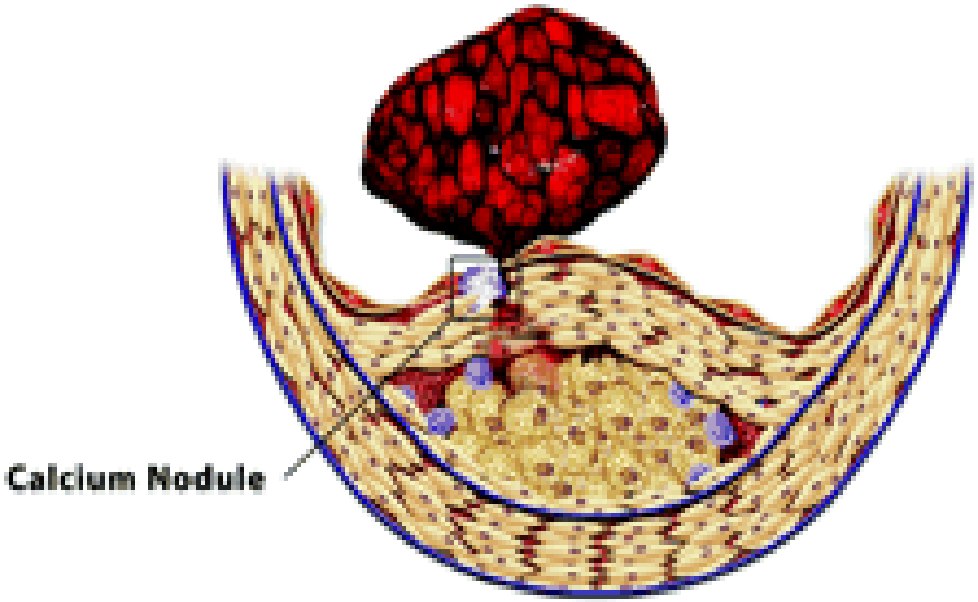




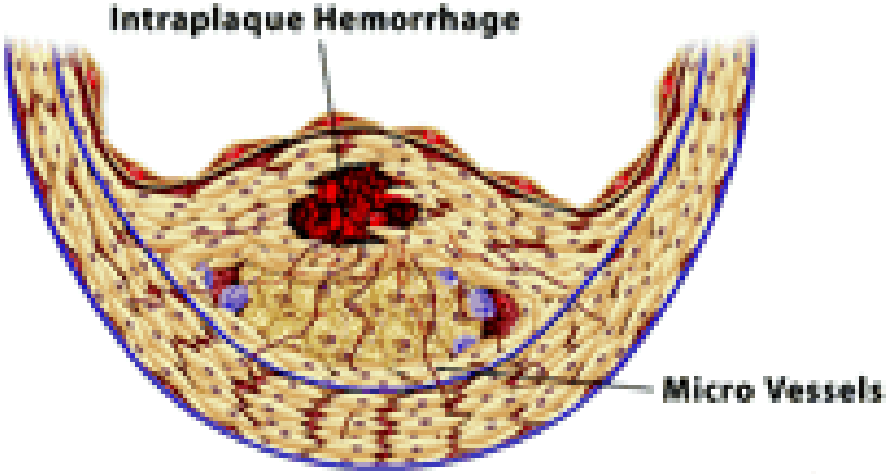
Rupture of Fibrous Cap



Superficial Erosion



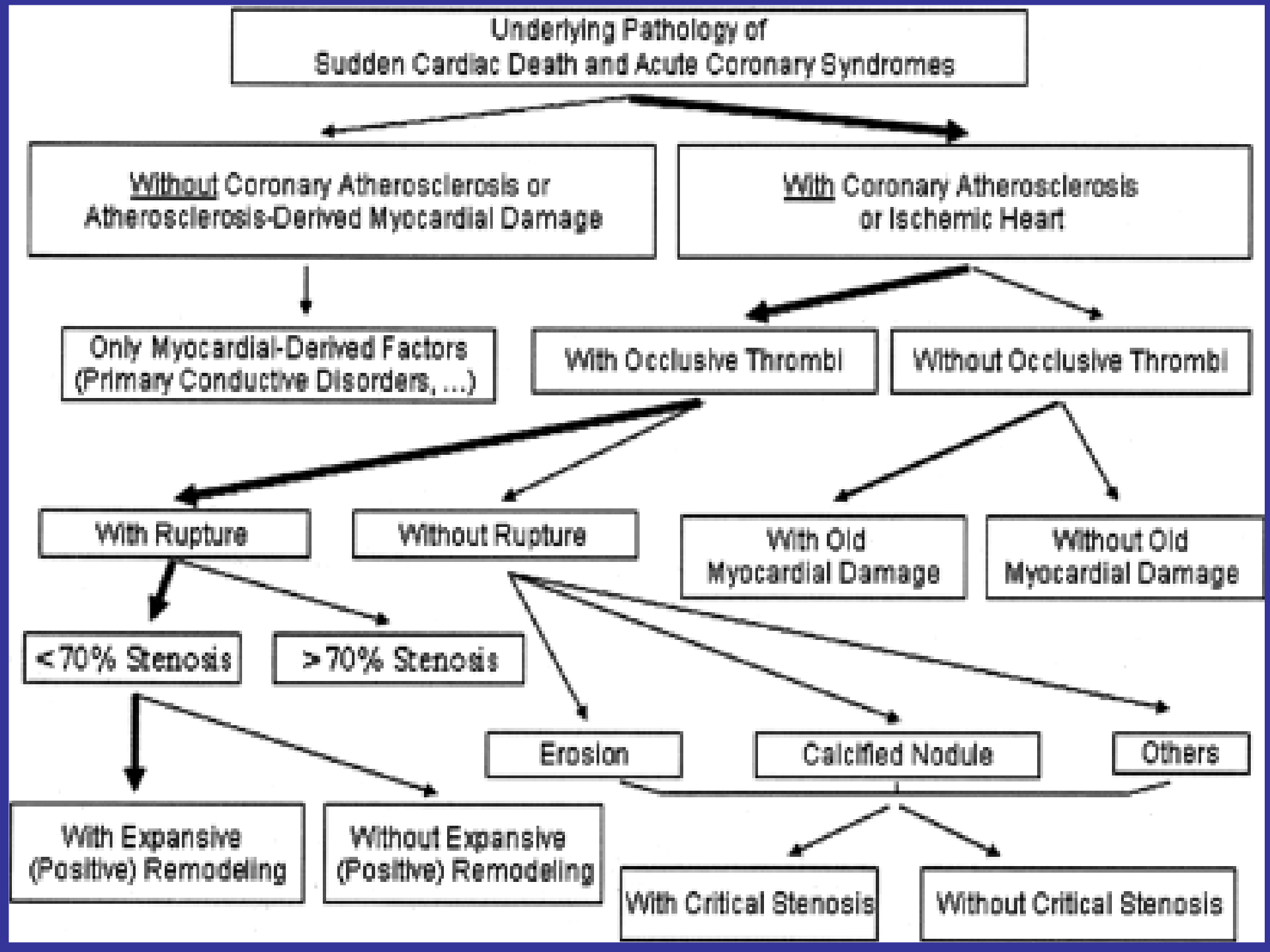
Erosion of Calcium Nodule

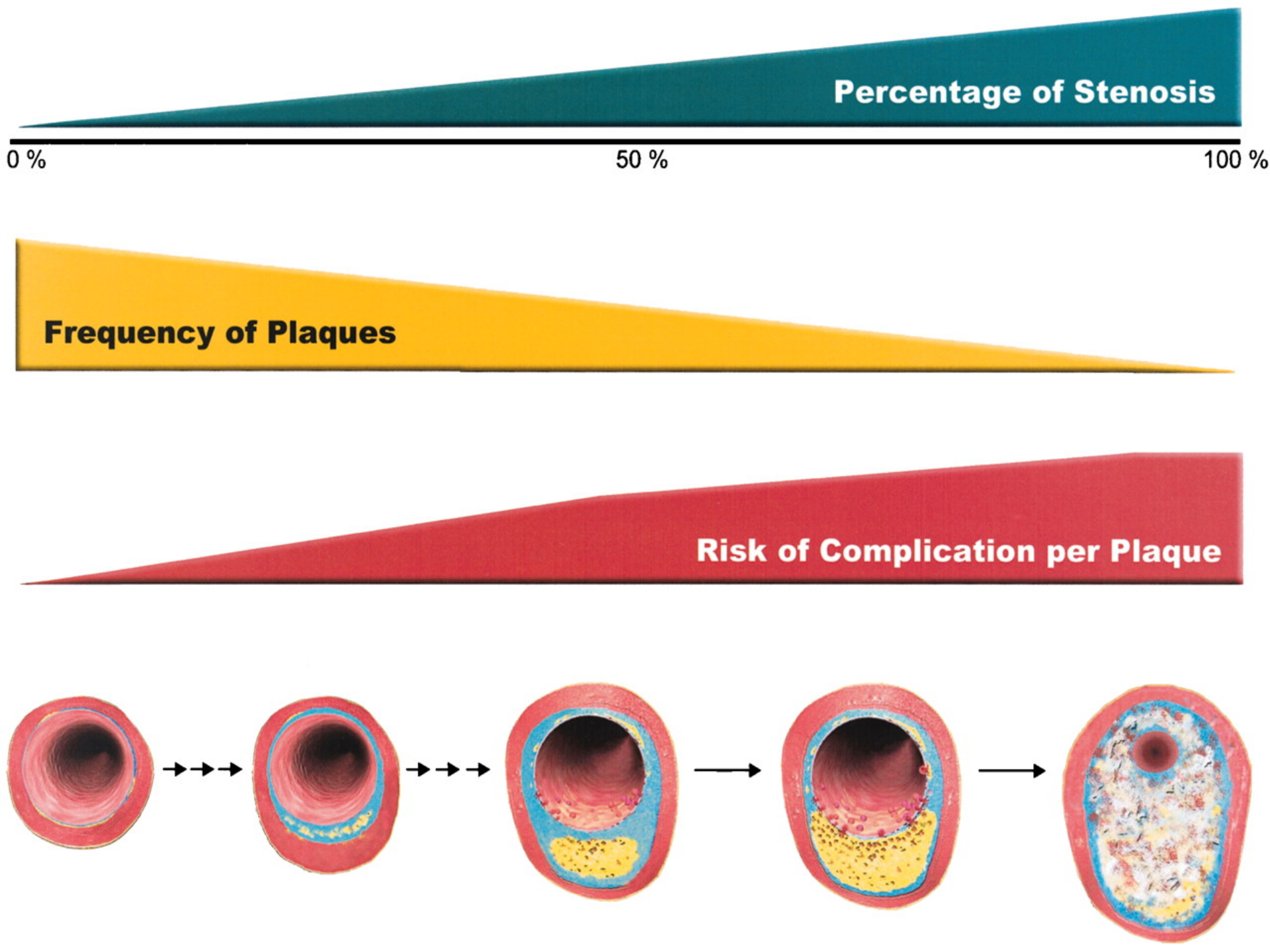


Intraplaque Hemorrhage

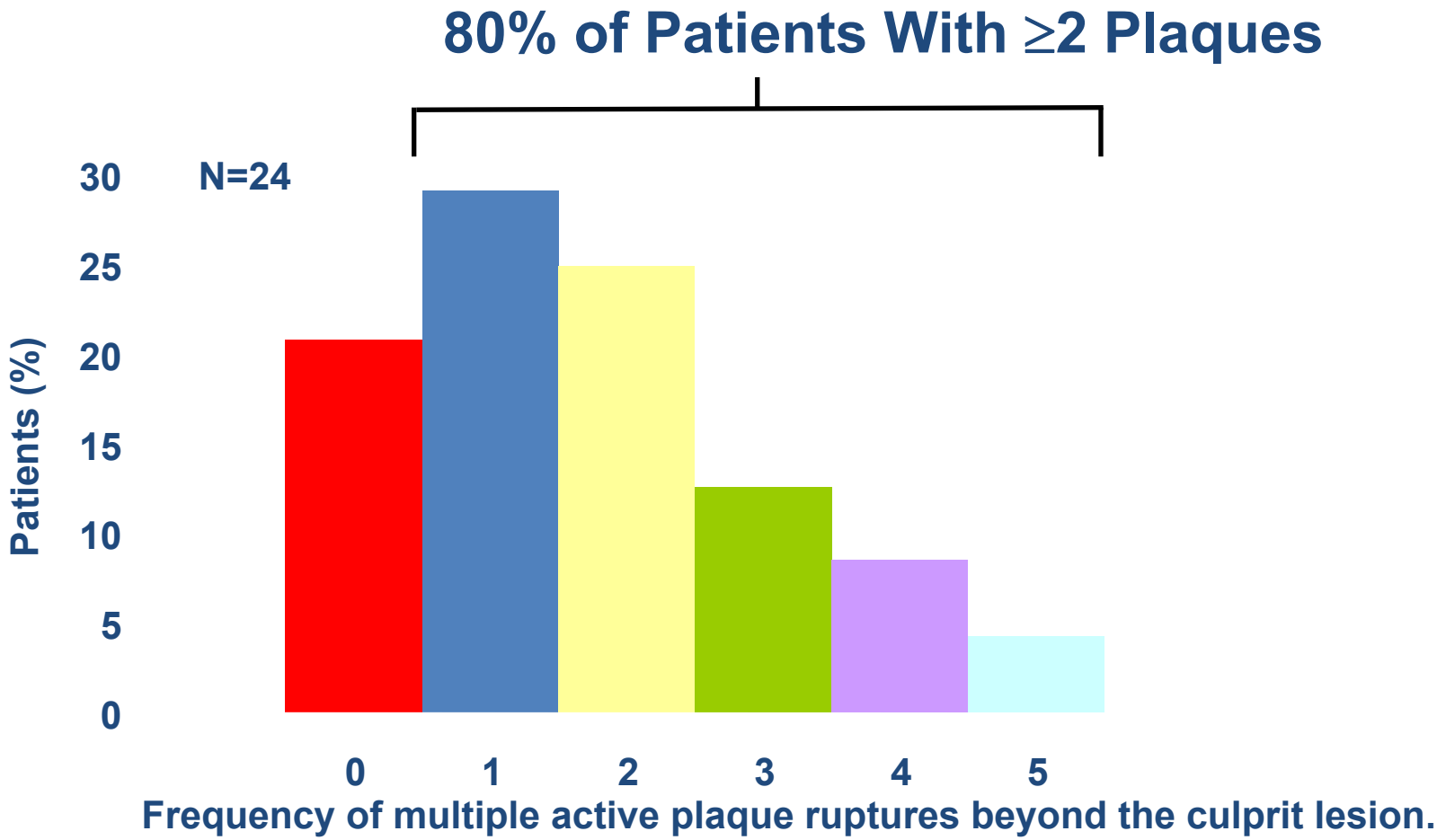
Plaque Erosion

- **30% to 40% of coronary thrombosis occurs at sites at which plaque rupture cannot be identified**
- **of 50 consecutive cases of sudden cardiac death attributable to coronary thrombosis, in which 22 had superficial erosion of a proteoglycan-smooth muscle cell–rich plaque (Farb. Et al).**


Underlying Pathology of
Sudden Cardiac Death and Acute Coronary Syndromes
Without Coronary Atherosclerosis or
Atherosclerosis-Derived Myocardial Damage
With Coronary Atherosclerosis
or Ischemic Heart
Only Myocardial-Derived Factors
(Primary Conductive Disorders, ...)
With Occlusive Thrombi
Without Occlusive Thrombi
With Rupture
Without Rupture
With Old
Myocardial Damage
Without Old
Myocardial Damage
<70% Stenosis
>70% Stenosis
Erosion
Calcified Nodule
Others
With Expansive
(Positive) Remodeling
Without Expansive
(Positive) Remodeling
With Critical Stenosis
Without Critical Stenosis

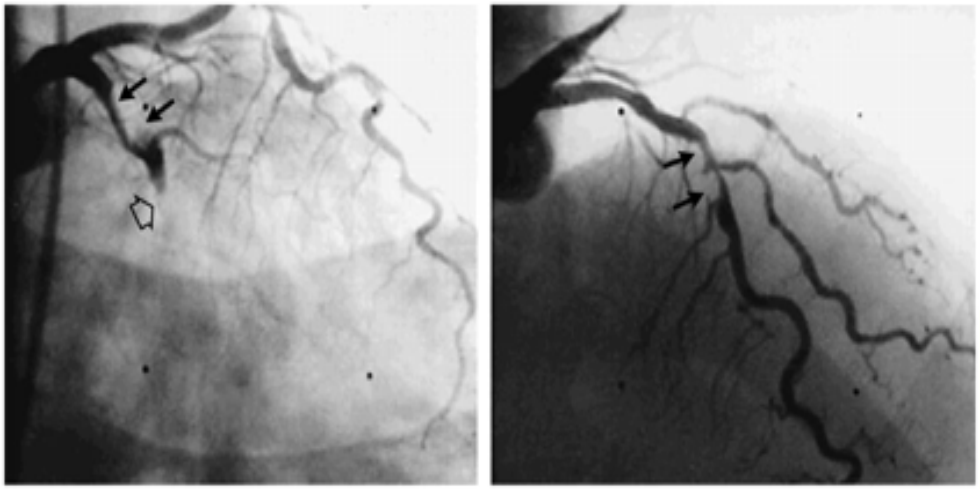

Percentage of Stenosis
0 %
50 %
100 %
Frequency of Plaques
Risk of Complication per Plaque

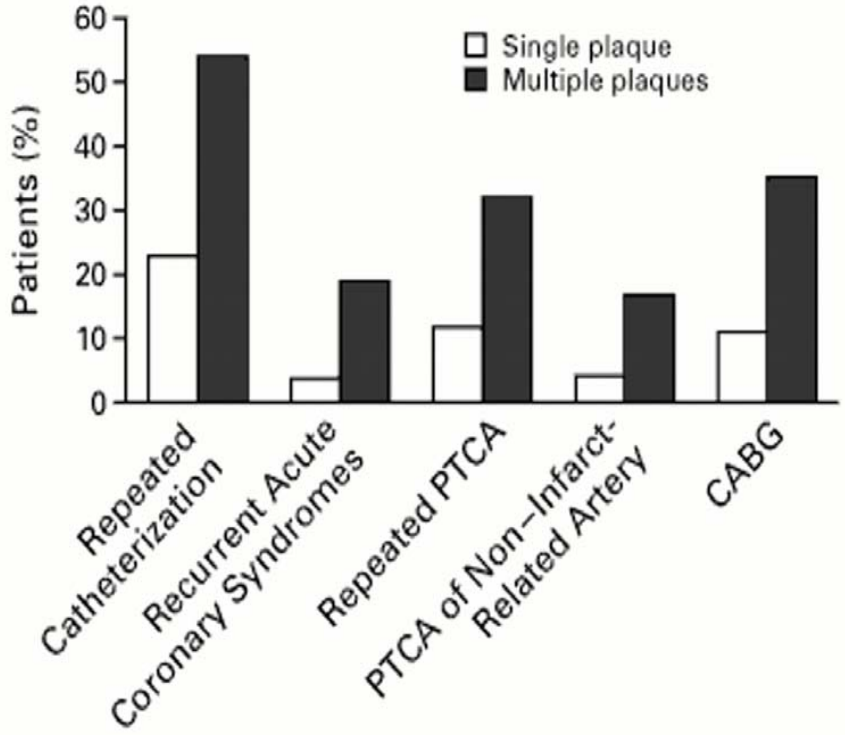
ACS a Systemic Disease:
Frequency of Multiple "Active" Plaques



Adapted from Rioufol G, et al. *Circulation.* 2002;106:804-808.

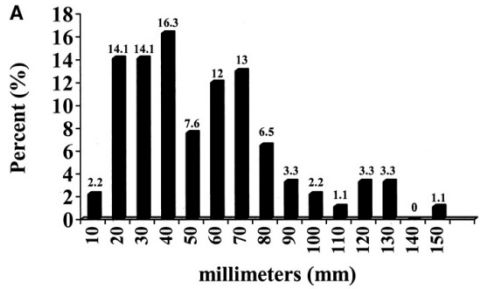
Multiple Complex Coronary Plaques in Patients with AMI

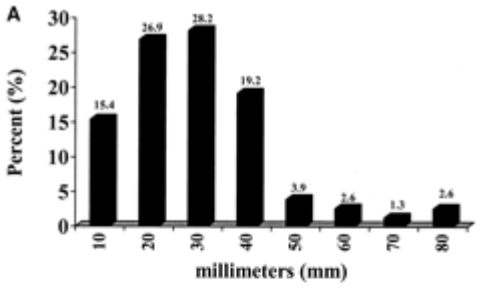


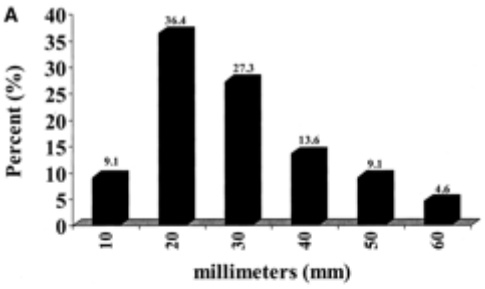


Goldstein et al. NEJM 2000

Coronary Artery Spatial Distribution of Acute Myocardial Infarction Occlusions



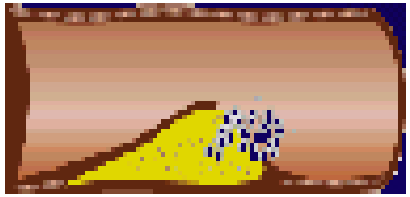




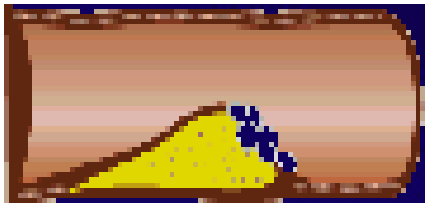
RCA **LAD** **LCx**

Wang, J. C. et al. Circulation 2004;

Pathogenesis of Acute Coronary Syndromes: the integral role of platelets



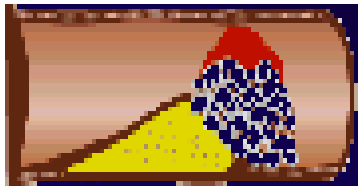
Plaque Fissure or Rupture



Platelet Adhesion

Platelet Activation

Platelet Aggregation

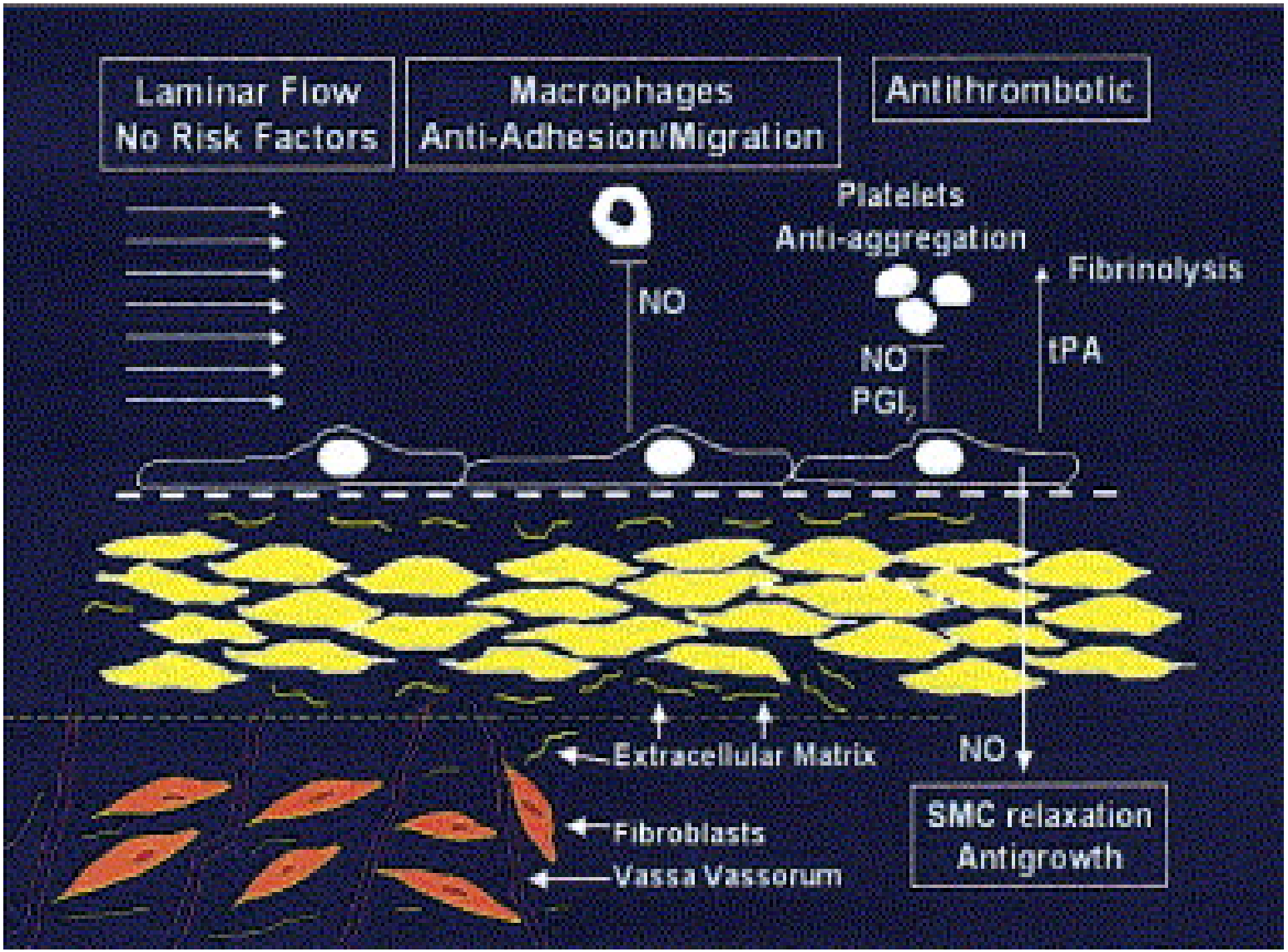


Thrombotic Occlusion

3 Major systems involved

- Vessel wall
  - Endothelium
- Platelets
- Coagulation cascade

Endothelial Dysfunction



Anti-coagulant Properties of the Endothelium

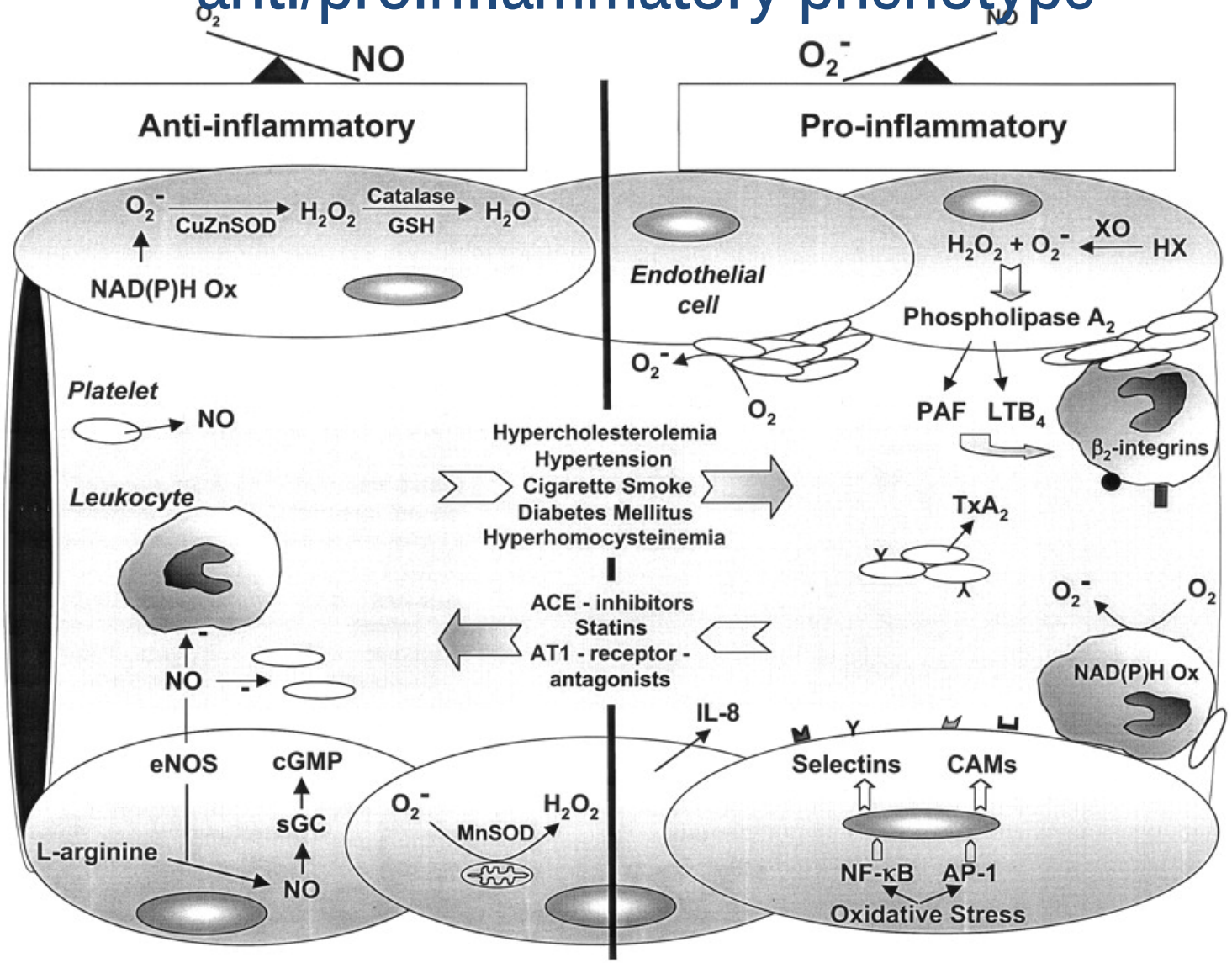
-Endothelial cells produce t- PA which activates fibrinolysis via plasminogen to plasmin

- Heparin-like molecules (proteoglycans), which activate anti-thrombin III (inactivates thrombin, other clotting factors)

- Thrombomodulin – transmembrane proteoglycan binds thrombin – activates protein C (by cleavage) - process occurs on thrombomod. (protein C , inactivates Va & VIIIa)

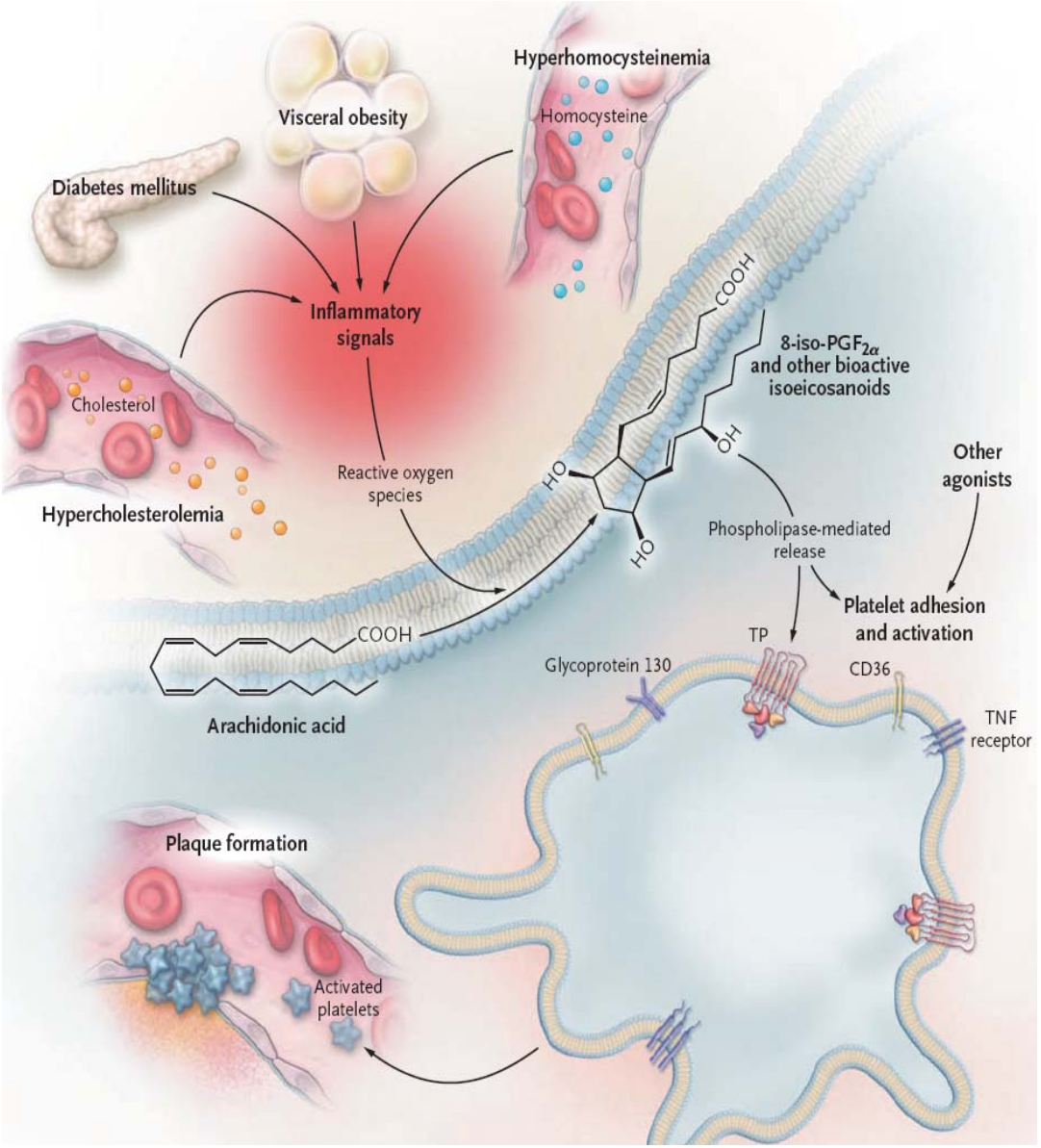
- TFPI – tissue factor pathway inhibitor – released from endothelial cells (and from platelets), inhibits TF-VIIa & Xa

Superoxide-NO balance affects the vascular anti/proinflammatory phenotype

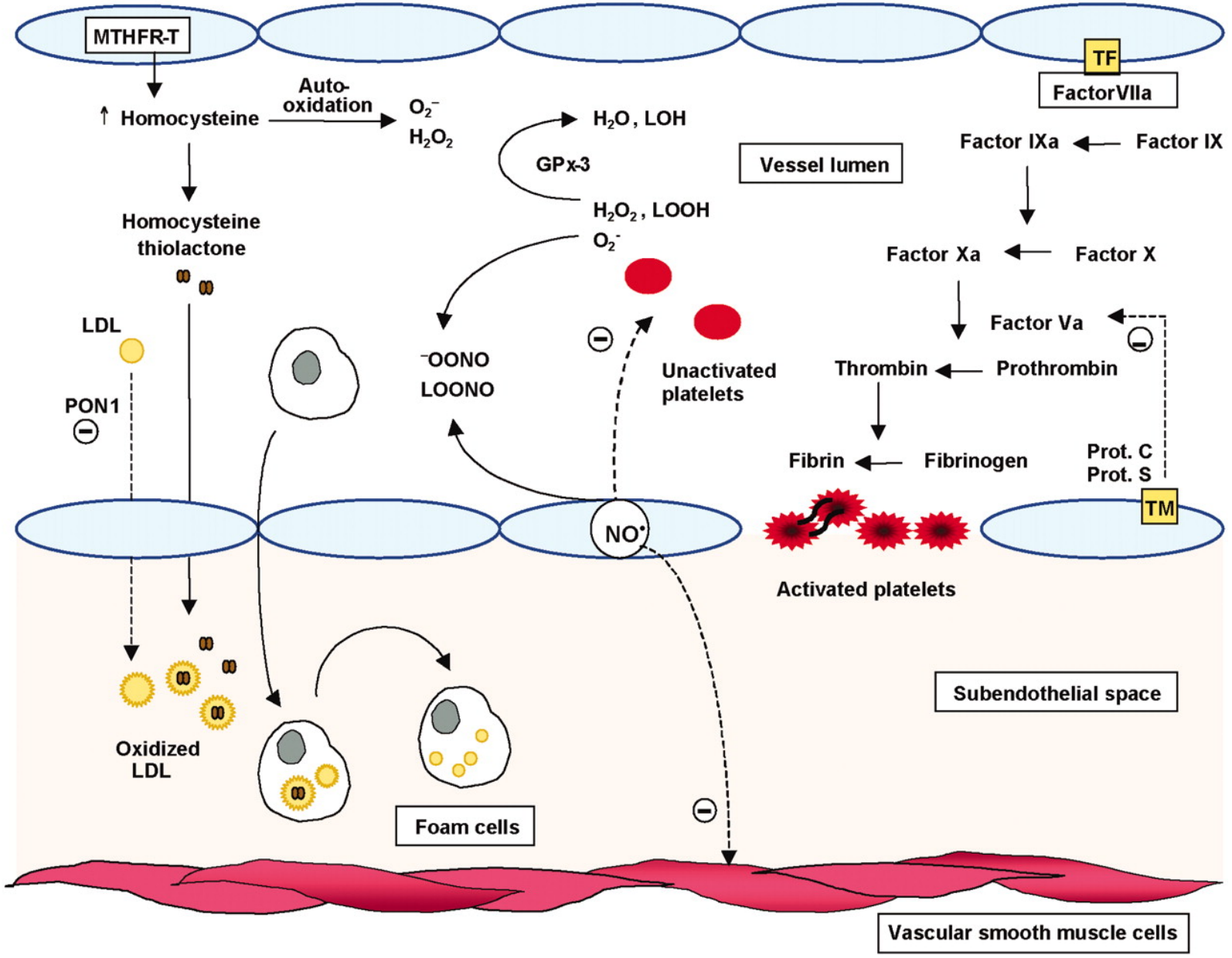


Granger, D. N. et al. Hypertension 2004;43:924-931

Isoprostanes: between inflammation and thrombosis



Vascular hemostatic and antioxidant defense mechanisms

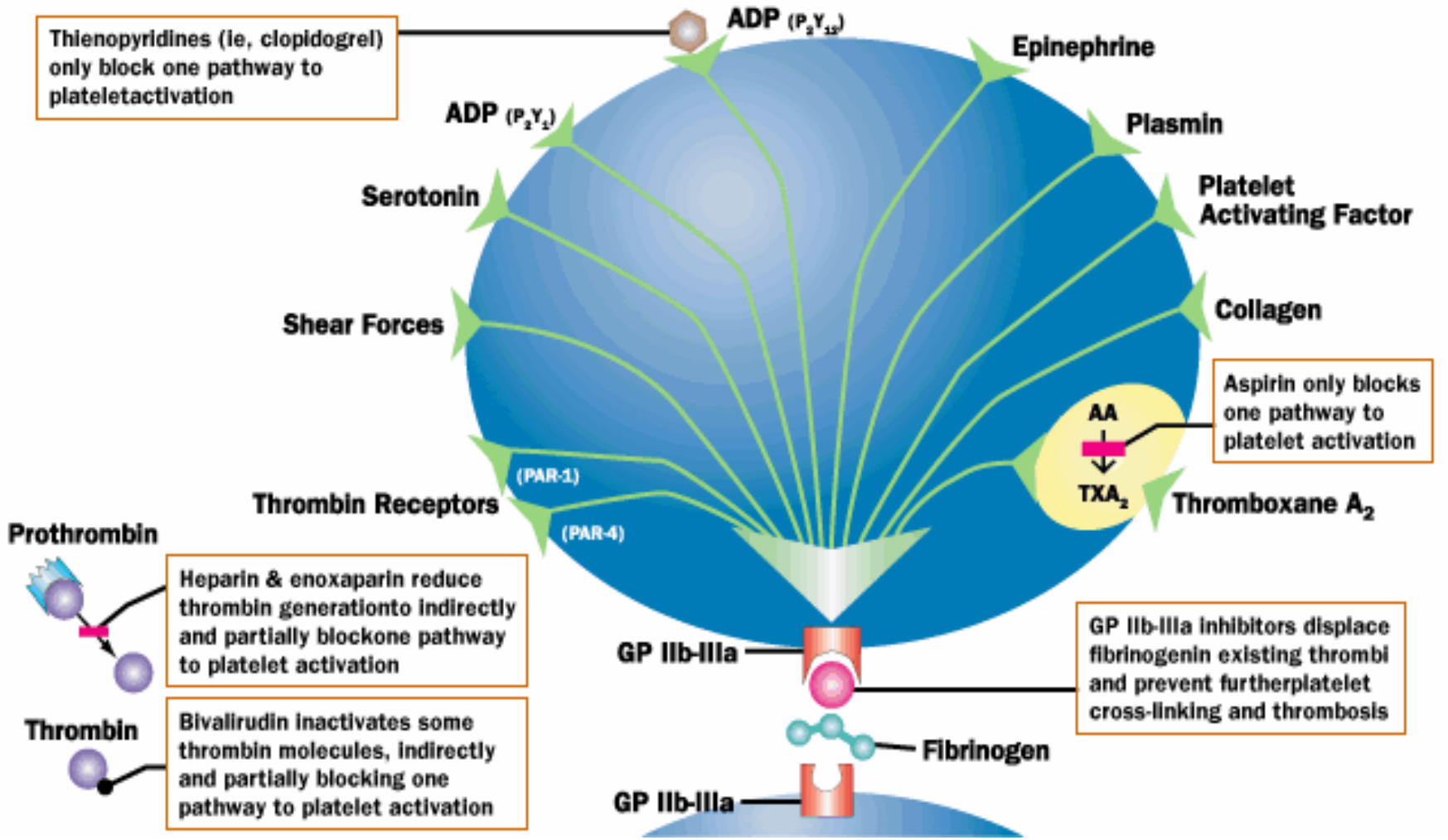


Voetsch, B. et al. Arterioscler Thromb Vasc Biol 2004;24:216-229

Platelet Adhesion

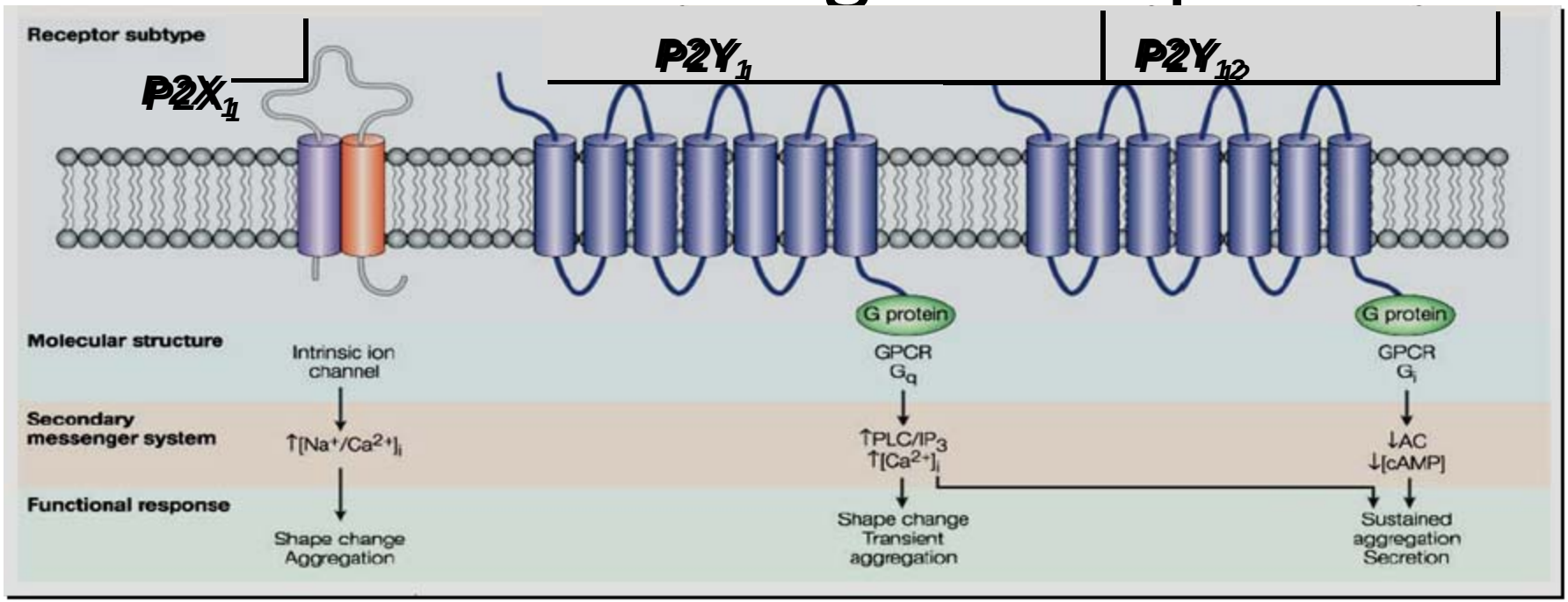
- Platelets are the first cells to thether and adhere to injured vascular wall (subendothelium)
- Adhesion is mediated by vWF – a mutimetric protein synthesized by both endothelial cells and megakaryocytes (stored in α granules) – present in plasma and ECM – serves as “an anchor”
- Platelet receptor – GPIb (part of the GP Ib/IX-V complex)
- Binding occurs only under high shear stress conditions !

Platelet Activation



Active Metabolite of Clopidogrel

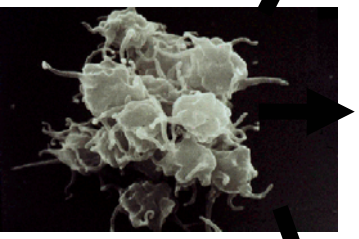
Platelet Purinergic Receptors



Platelet Activation

- Release from alpha and dense granules
- Dense granules: ADP, serotonin
- Alpha granules: vWF, finbrinogen, fibronectin, growth factors (PDGF), PF4, factor V

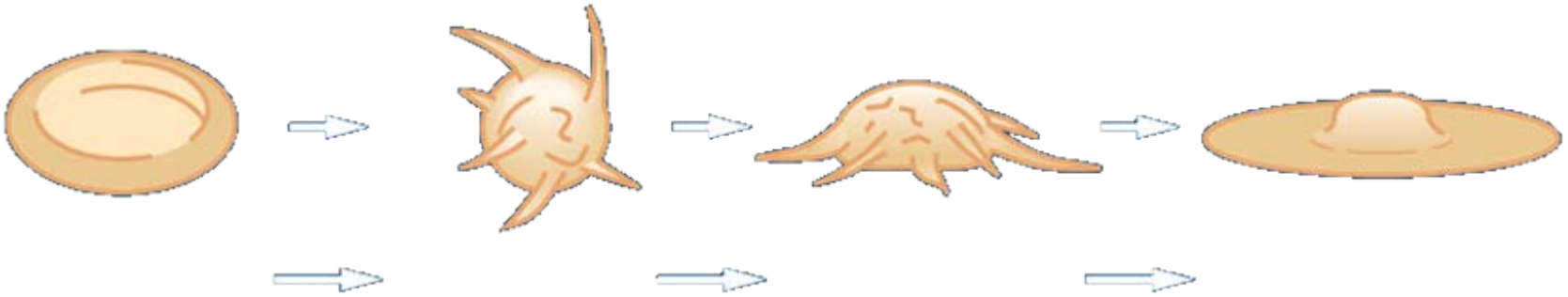
- Activated platelets also synthesize (denovo) TxA2 from arachidonic acid



UD16_MOUSE UDP glucuronosyltransferase 1-6 precursor
TRA1_MOUSE TNF receptor associated factor
TLR5_HUMAN Toll/interleukin-1 receptor-like protein 3
TAST_HUMAN Trophinin-associated protein
SEP6_MOUSE Septin 6
SACS_HUMAN Sacsin
Q9Z2V7 Lymphocyte specific formin related protein
Q9Y6V0 Piccolo protein [Fragments)
Q9HCV9 HSPC164/HSPC169
Q9H233 BCL-6 corepressor
Q9BZG3 Acid phospahatase variant
Q96QE3 ATPbinding protein
Q96PH3 Proliferation potential-related protein
Q925P2 CEA related cell adhesion molecule 2
Q91ZT8 Ankyrin repeat and SOCS box containing protein 9
Q91W89 Alpha-mannosidase 2C1
Q8TDN5 Retinoblastoma-associated factor 600
Q8TDL7 Spermatogenesis associated factor
Q8TCH0 Nebulin-related anchoring protein
Q8R099 Similar to compliment component 1
Q14393 Growth arrest specific protein, Gas 6
PSD2_HUMAN 26S proteasome subunit p97
MS1P_HUMAN Site-1-protease
MGD2_HUMAN Melanoma-associated antigen D2
MAP2_HUMAN Microtubule-associated protein 2
MAGB_HUMAN Melanoma-associated antigen 11
HPS3_HUMAN Hermansky-Pudlak syndrome 3 protein)
FCGA_HUMAN CD32
ECEL_MOUSE Endothelin-converting enzyme-like 1
COTR_MOUSE Serpin
CFAH_HUMAN Compliment H
ACRO_HUMAN Acrosin
SNX2_MOUSE Nexin
S23A_HUMAN Protein transport protein Sec 23A
Q9QXA1 Cysteine and histidine-rich protein
Q9EPX2 Papilin
Q9DBX8 Vacuolar protein sorting 11
MM02_HUMAN MMP2, metalloproteinase
IC1_MOUSE Plasma protease C1 inhibitor

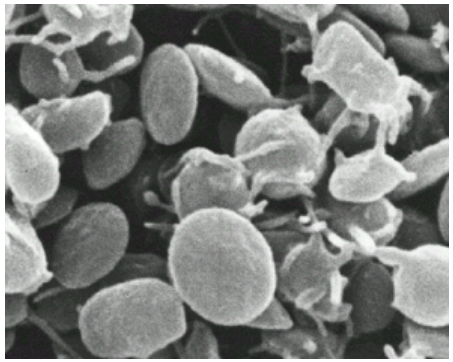
ATS7_HUMAN ADAMS TS 7
CATW_HUMAN Cathepsin W
HS9A_HUMAN Heat shock protein HSP 90-alpha
TAC2_MOUSE Transforming acidic coiled-coil-containing protein 2
SG2_HUMAN Secretogranin II
Q9DC90 Proprotein convertase subtilisin/kexin type 4
Q9D7C0 Transcript expressed during hematopoiesis 1
Q925U0 Ooocyte secreted factor
CANS_MOUSE Calcium-dependent protease, small subunit
EMBP_HUMAN Proteoglycan 2, bone marrow
GILT_HUMAN Gamma-interferon-inducible protein IP-30)
IBA4_HUMAN ITBA4 protein
TPIS_MOUSE Triosephosphate isomerase
MHYB_MOUSE Myosin heavy chain
P97315 Cysteine rich protein
NP25_MOUSE Neuronal protein NP25
CD63_MOUSE CD63
WDNM_MOUSE protease inhibitor
TNF8_HUMAN Tumor necrosis factor ligand superfamily member 8.
MABC_HUMAN Mannose Binding Protein
KLK5_MOUSE Kallikrein
IL13_MOUSE Interleukin 13
ABP_HUMAN Diamine oxidase
OXDD_HUMAN D-aspartate oxidase
O00391 Quiescin
Q9JHQ5 Leucine zipper transcription factor-like
Q9DCA5 Ribosome biogenesis protein Brix
Q9BWF3 RNA binding protein motif
Q920Q2 Deoxyribonucleotidyl transferase
CAZ1_MOUSE F-actin capping protein
SPCB_MOUSE Spectrin
PKP4_HUMAN Plakophilin 4
MOES_MOUSE Moesin
CADH_HUMAN Cadherin-17
CTA4_MOUSE Cell recognition molecule Casp4

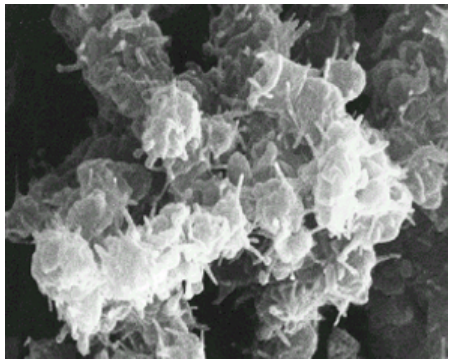
Platelet Aggregation



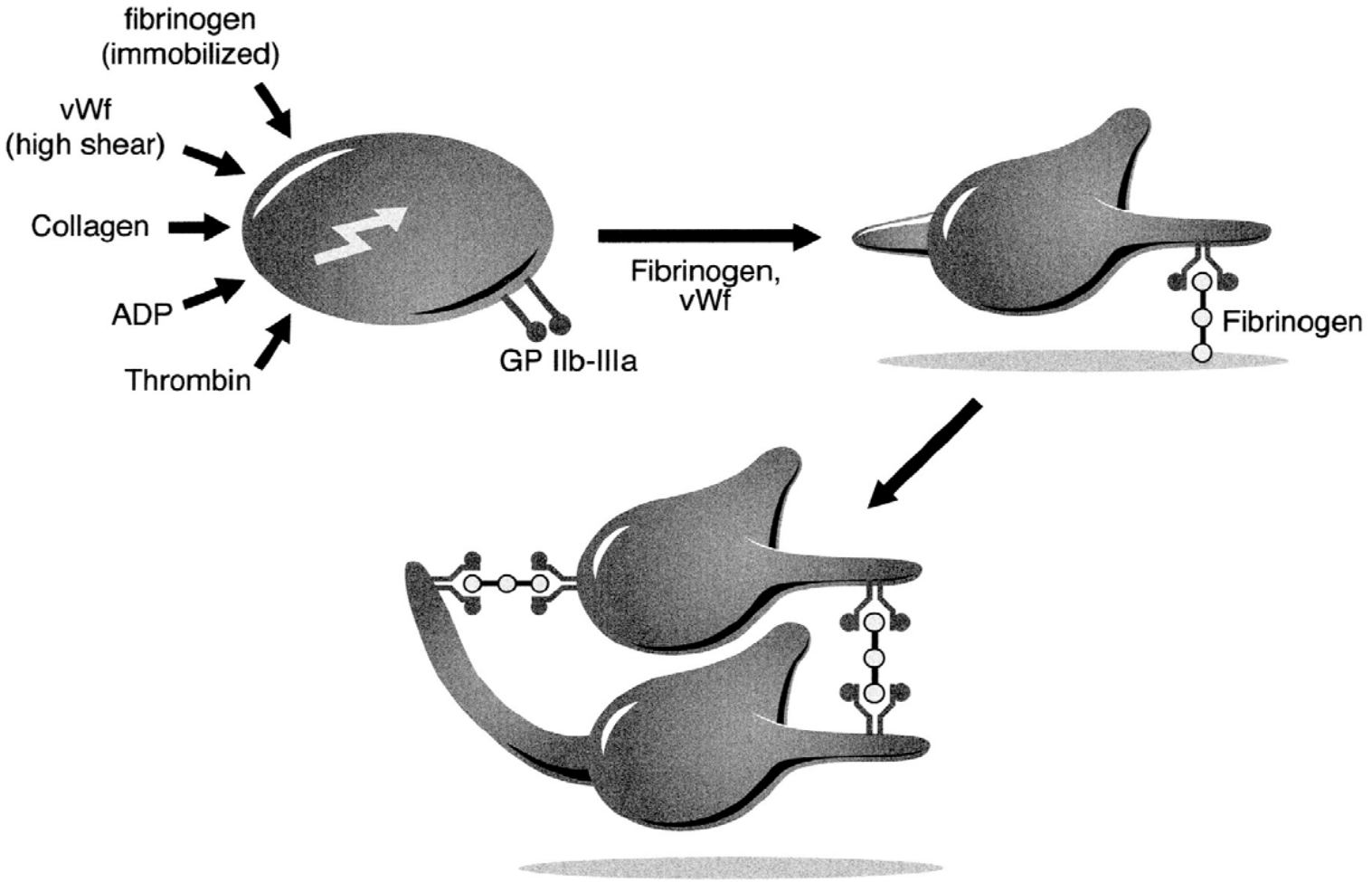
FIRM, BUT REVERSIBLE ADHESION

IRREVERSIBLE ADHESION





Platelet Aggregation



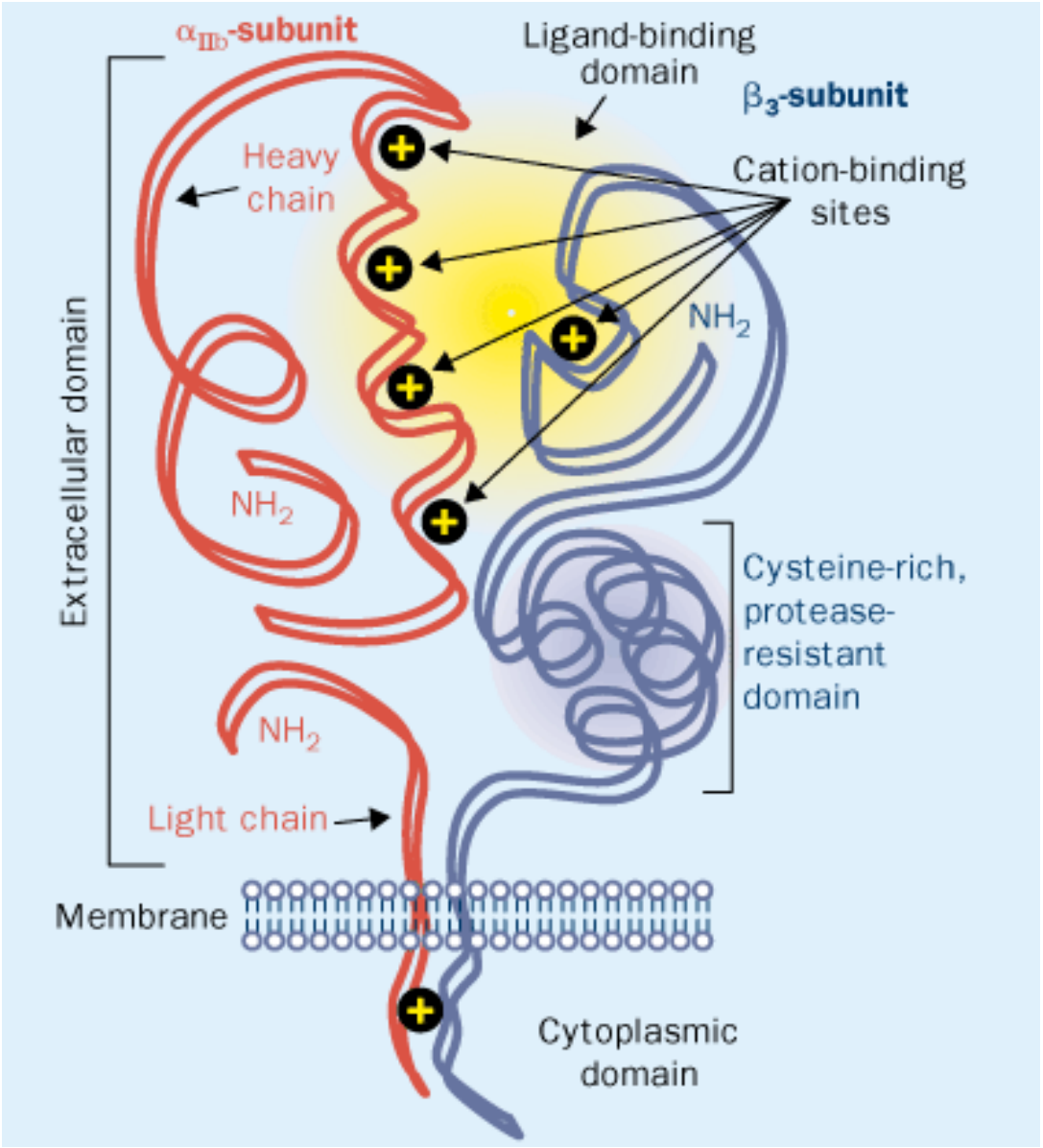
GP IIb/IIIa Receptor

- Mediates platelet aggregation
- Member of the integrin receptor family – can interact with both extracellular and cytoskeletal molecules
- One of the most abundant cell surface receptors (50-80,000 receptors per resting platelet, 15% of surface protein)
- Ca+ ions are critical for maintenance of both structure and function
- In the resting platelet the receptor has minimal binding affinity for ligands – fibrinogen and vWF

GP IIb/IIIa Receptor – cont.

- Upon activation of the platelet, conform. change of the receptor → high affinity ligand binding state + clustering of receptors on platelet surface
- Biderctional signaling occurs (→ initiate numerous cellular responses)
- All ligands are characterized by the arginine-glycine-aspartate (RGD) sequence → implicated as the binding sites to the GP IIb/IIIa receptor
- Fibrinogen is a divalent ligand – each molecule can bind simultaneously to two GP IIb/IIIa receptors on adjacent platelets → cross-linking

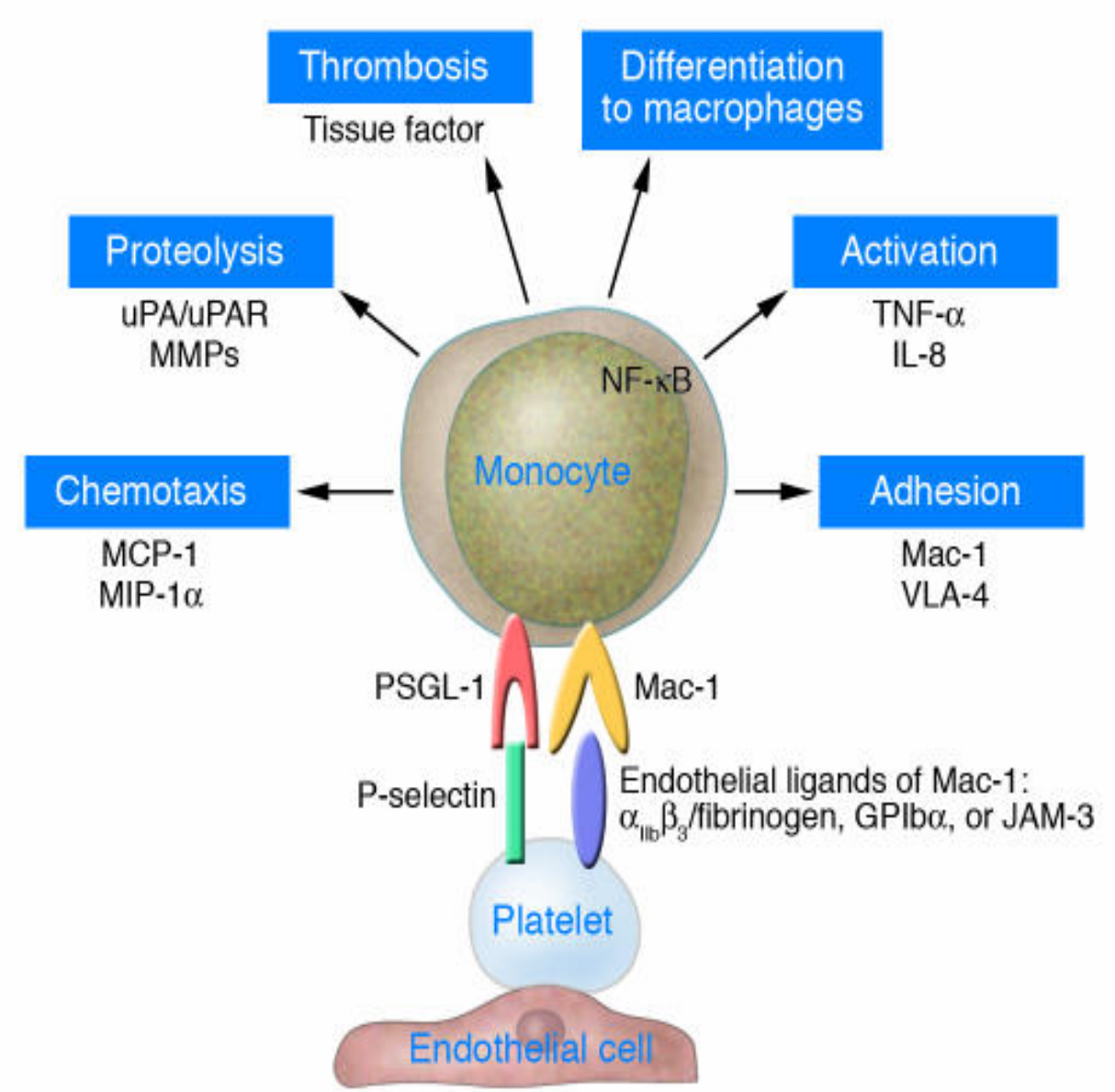
Schematic depiction of integrin $\alpha_{IIb}ß_3$



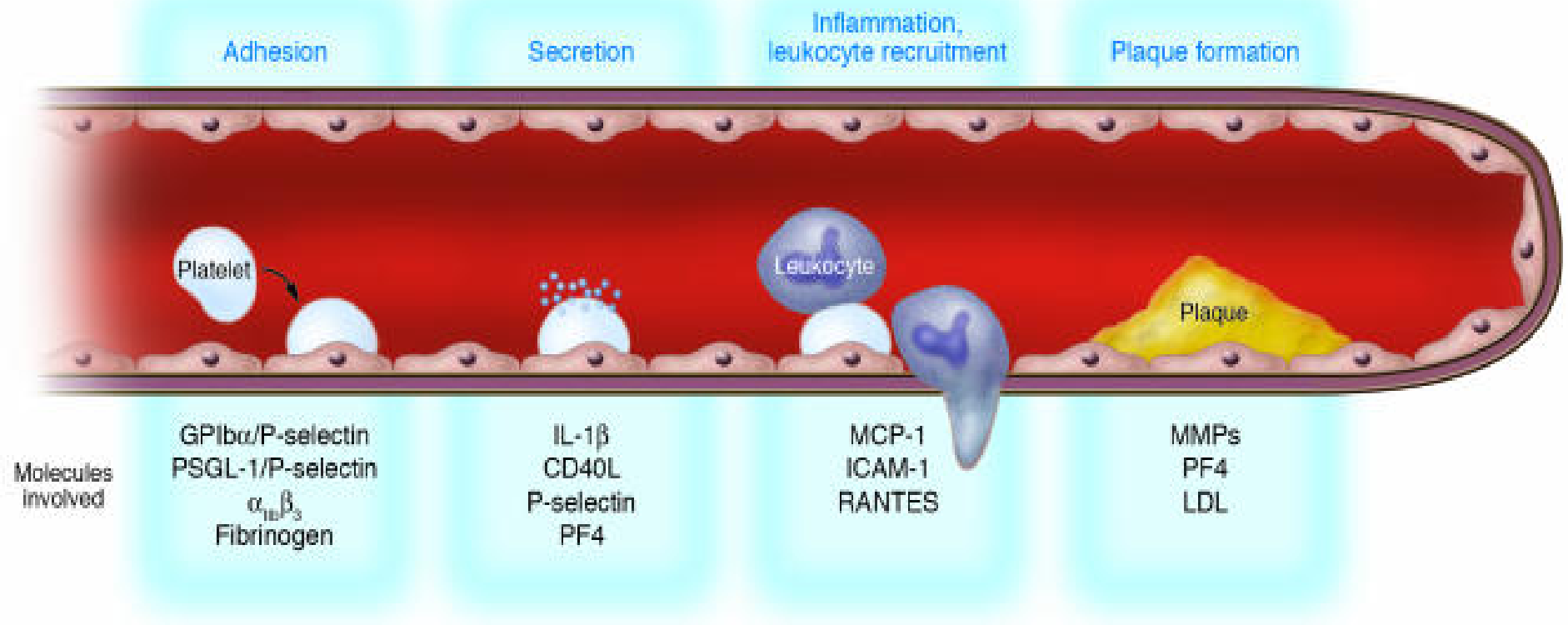
Both subunits composed of a short cytoplasmatic tail, a single transmembrane domain and a large extra-cell. domain that consists of a series of linked domains

Both subunits are a product of a single gene located on chrom. 17

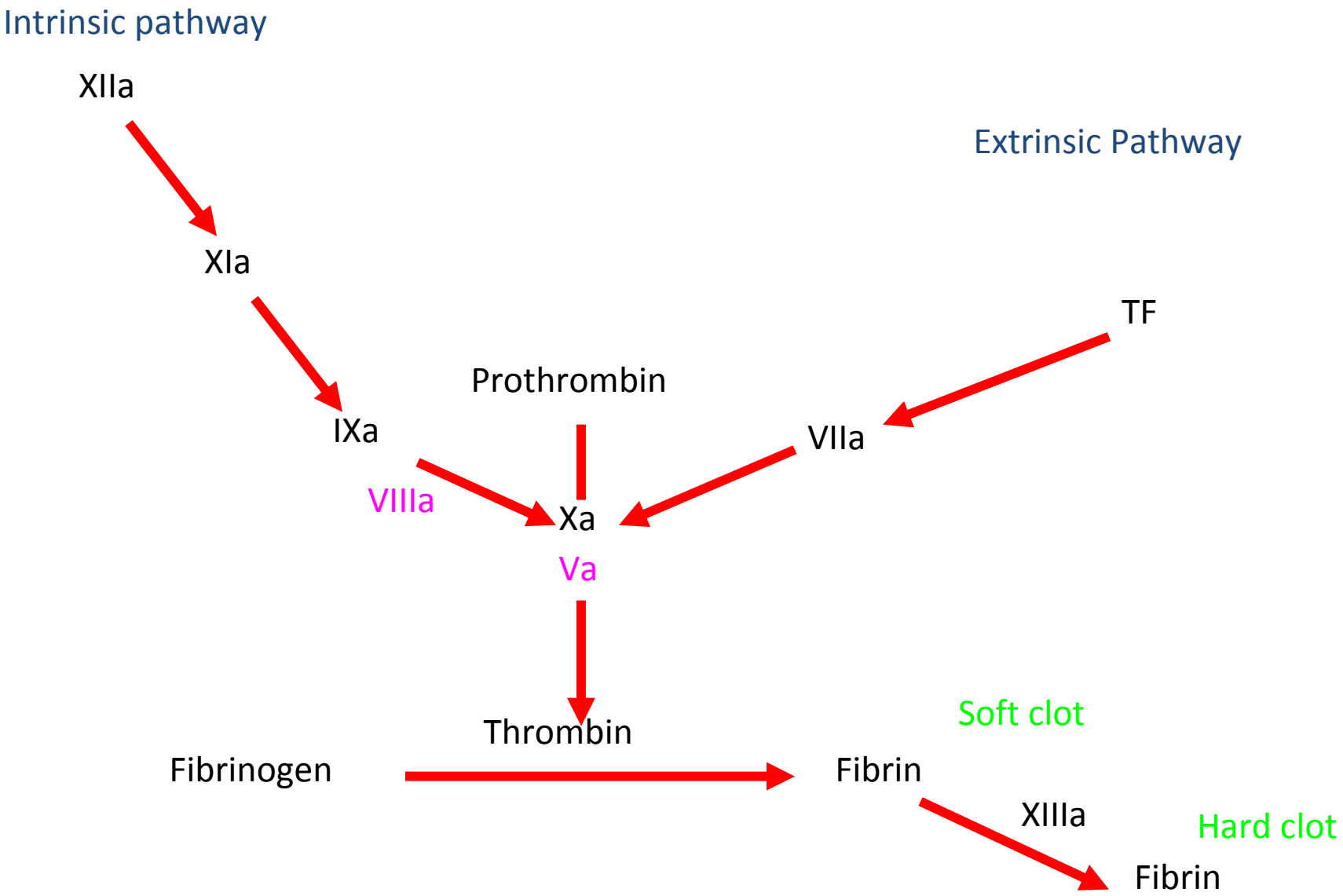
Platelets and inflammation



Platelets in atherogenesis

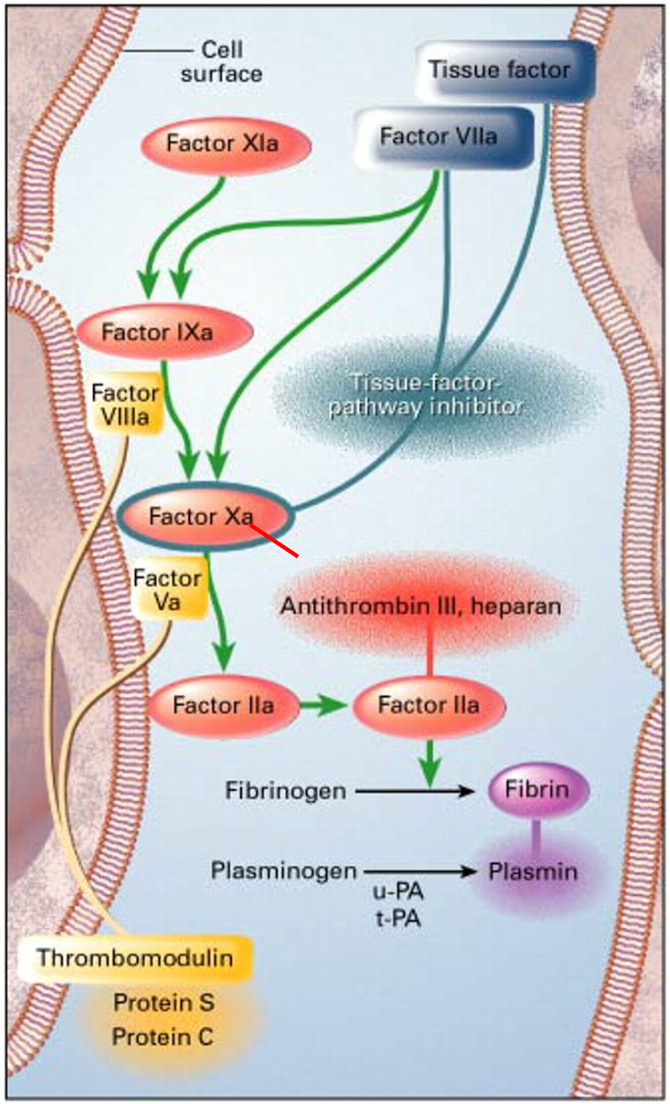


“Classic Coagulation Cascade”



“Classic Coagulation Cascade”

Localization to sites of vascular injury. Protease complexes assemble on PL membranes of activated platelets, endothelial cells and monocytes.
(The coagulation cascade occurs very slowly in fluid phase plasma and with resting cells)

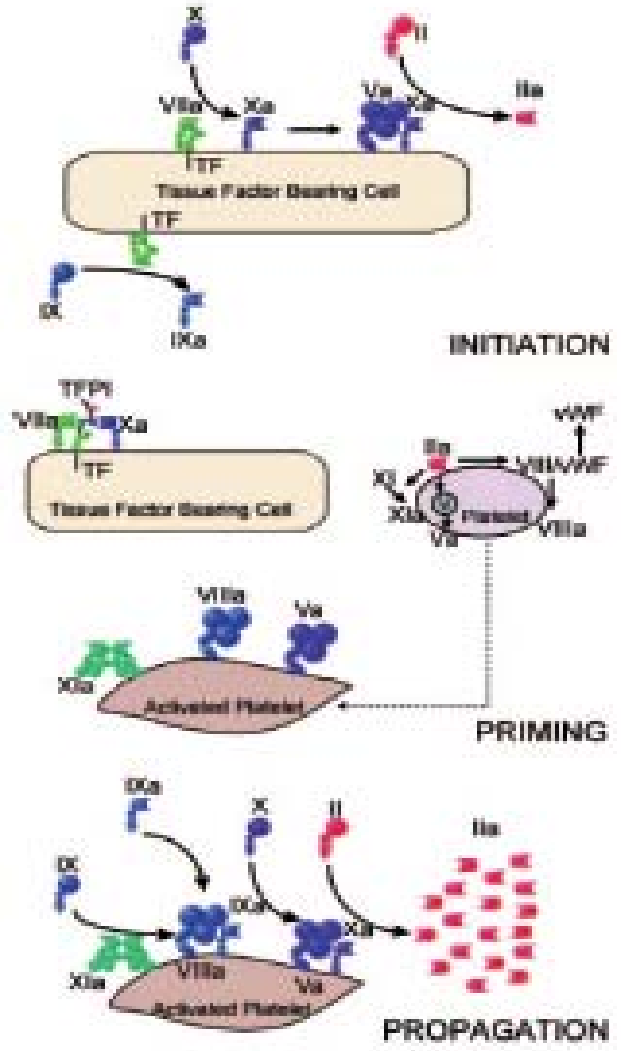


4 major Anti-thrombotic Pathways (TFPI, Prot C/S, ATIII, Plasmin)

Rosenberg et al NEJM 1999

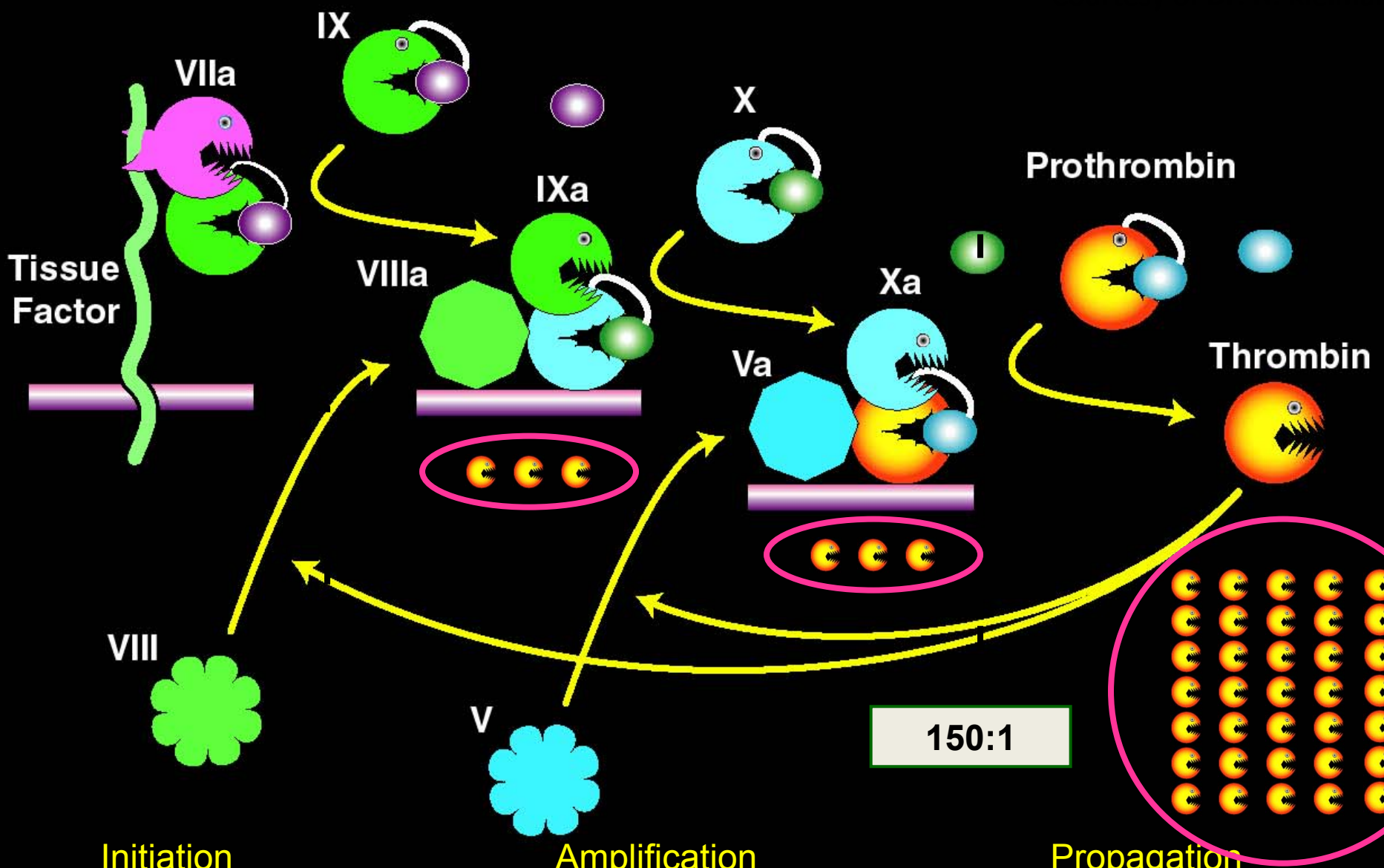
Current View of the Coagulation System

- Initiation by vessel wall injury which exposes blood to cells with TF on their surface → TF/FVIIa activates FX → Xa + Va cleaves II → small amounts of IIa (thrombin)
- Minute amounts of thrombin produced initially than lead to a marked increase in activation of FXI, FIX, FVIII, FV and marked generation of thrombin.
- Priming invloves adherence and activation of platelets.The small amounts of initial thrombin activates platelets → release of FV + PL surface for protease activation
- Propagation – an explosive increase in thrombin generation mediated by the classic "intrinsic system" → FXI, FIX → Fxa/VIIIa/Va on activated platelets → IIa + fibrin formation



Schneider D et al, Circulation 2007

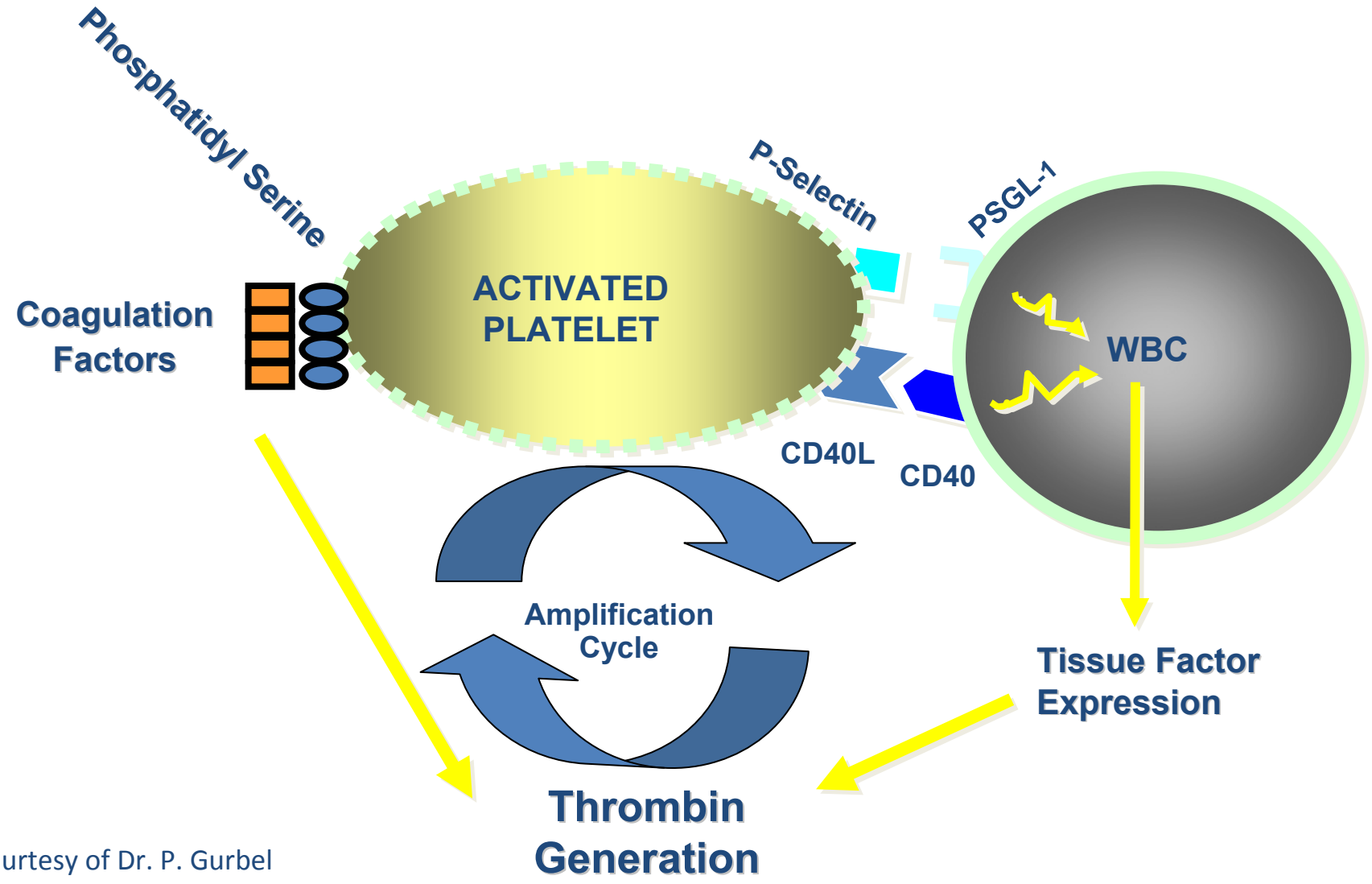
Enzymatic Amplification in the Coagulation Cascade



Role of Platelets in Current View of the Coagulation System

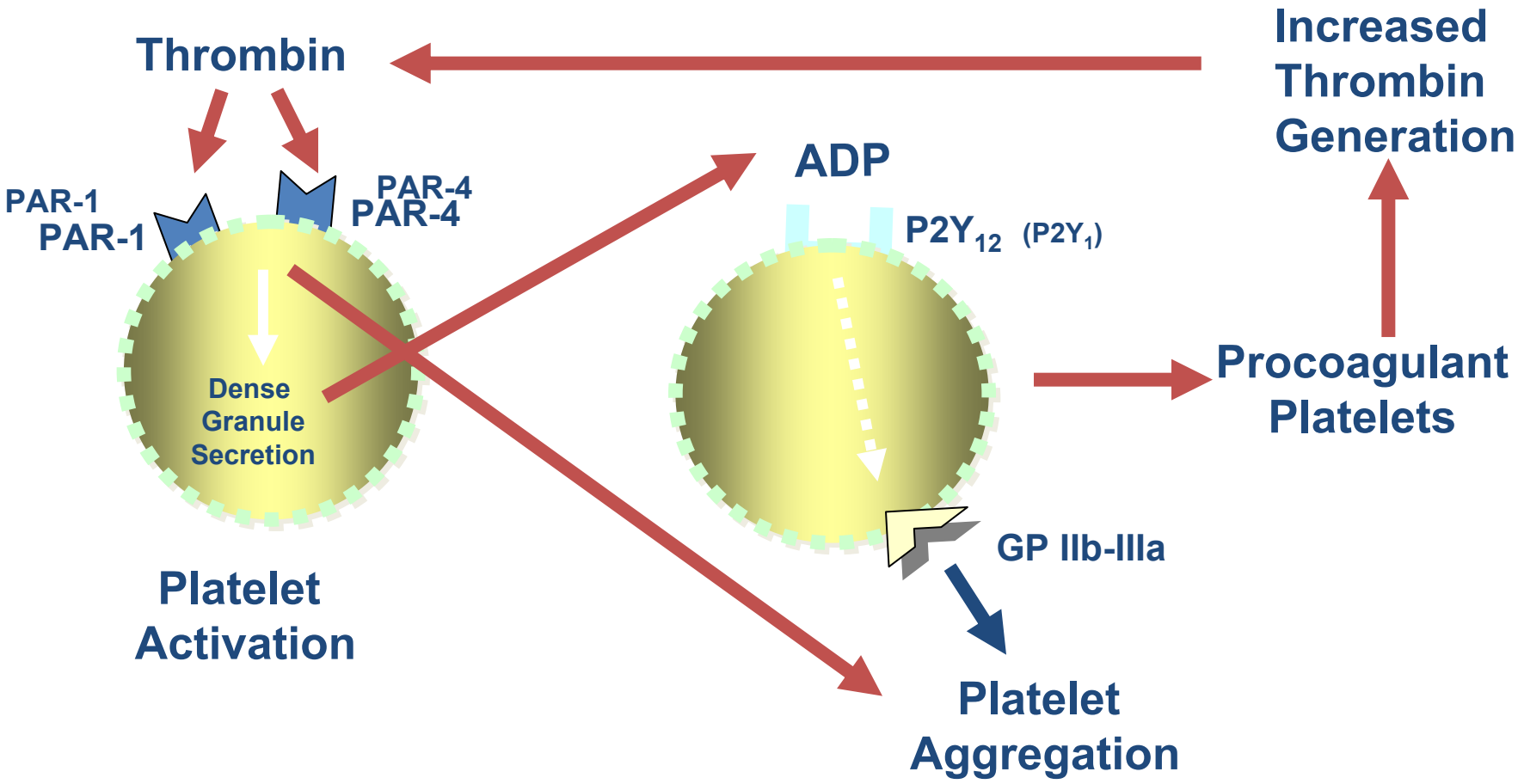
- Adherence after vascular injury
- Formation of platelet-platelet aggregates (GP IIb/IIIa) and platelet-WBC aggregates (P-selectin)
- Release of platelet granule products – Ca, FV, fibrinogen
- Recruitment of additional activated platelets (ADP, TXA2)
- Stimulation of vasoconstriction (serotonin)
- Formation of thrombin promoted by PL surface on which the coagulation complexes form (priming + proagation)
- Change in shape with pseudopod extension

The Platelet as a Mediator of Coagulation



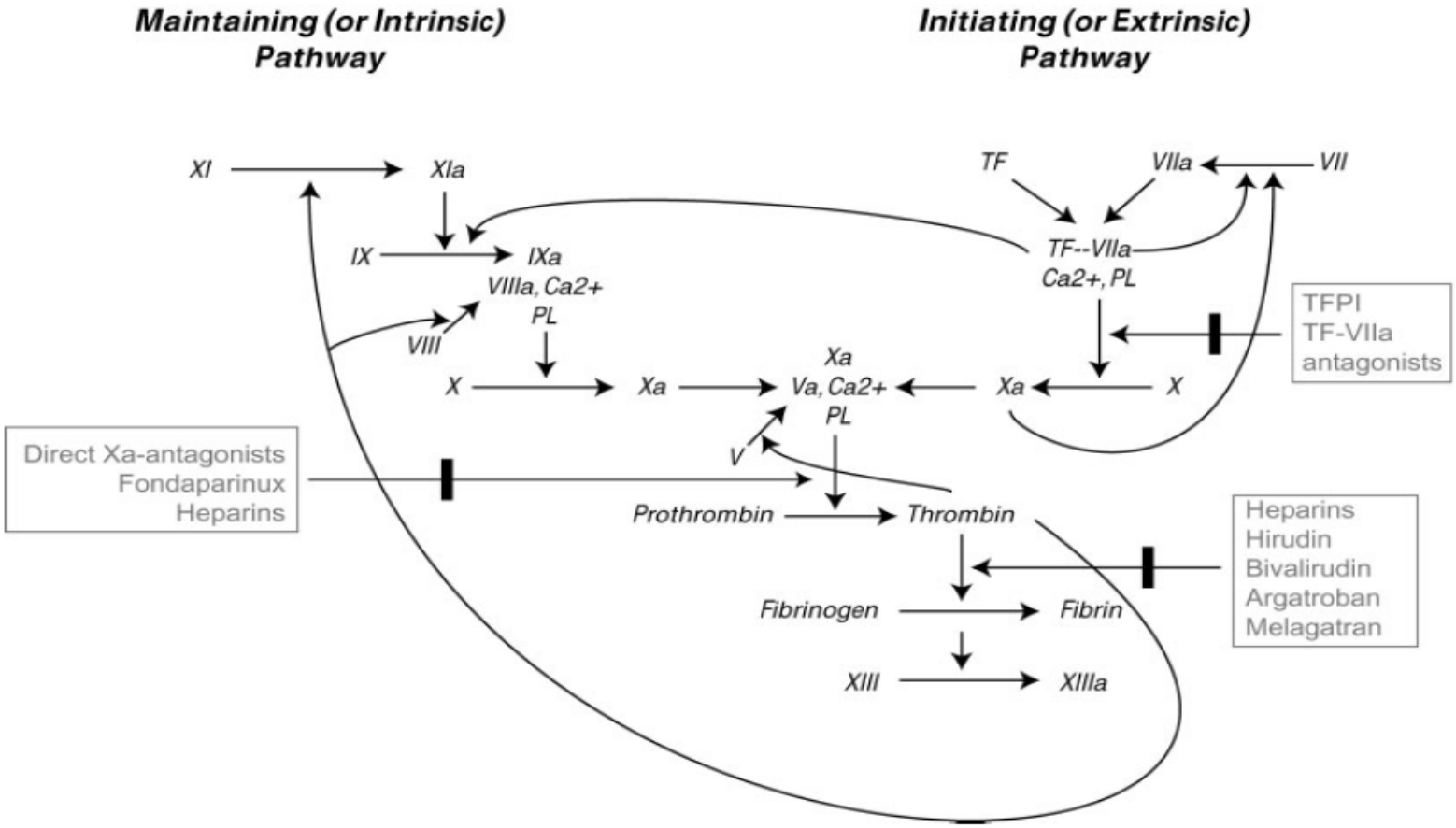
Courtesy of Dr. P. Gurbel

Central Role of ADP and Thrombin Crosstalk: a "Viscous" Cycle



Courtesy of Dr. P. Gurbel

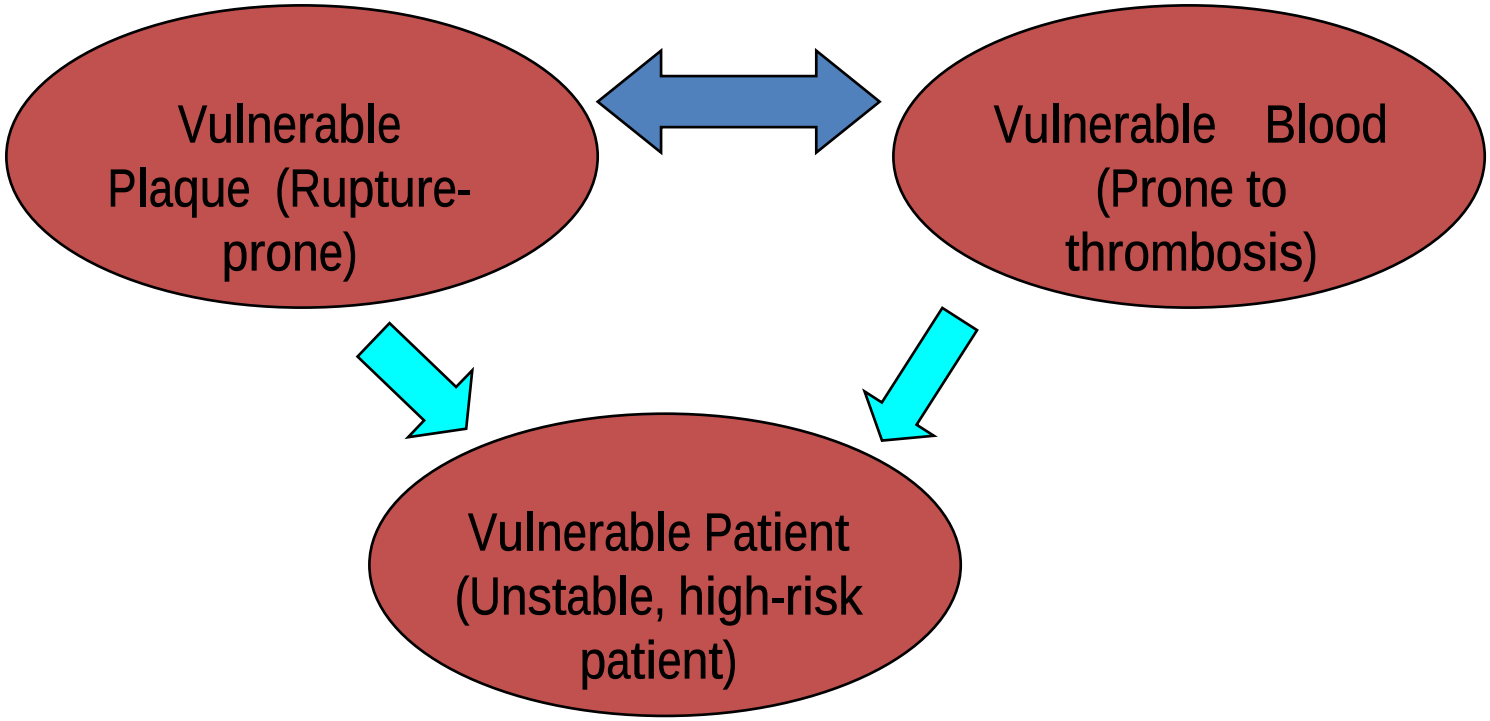
Current View of the Coagulation System



Del Conde et al CCI, 2003

The Virchow Triad of Thrombogenicity

- Local vessel wall substrates
  - Plaque components, inflammation, post-injury..
- Rheology
  - Shear stress, vasoconstrictor, bifurcation, post-intervention…
- Systemic factors of circulating blood
  - Metabolic&hormonal factors, hemostasis…




VULNERABLE PLAQUE
VULNERABLE PATIENT
VULNERABLE BLOOD
VULNERABLE MYOCARDIUM


בהצלחה, אל תעבדו קשה מדי!

שאלה 1:

מה שכיחות מחלת כלי דם משולבת – לבבית, מוחית והיקפית – בקרב חולי אתרותרומבוזיס?

1) **פחות מ 10%**
2) **15-25%**
3) **30-40%**
4) **45-55%**
5) **מעל 75%**

שאלה 2:

מה מהבאים אינו מאפיין רובד רגיש (vulnerable plaque)?

1) ליבה שומנית (lipid core)
2) תכולת קולגן גבוהה
3) ייצור NO נמוך ע"י האנדותל המצפה
4) Fibrous cap דק
5) ריבוי וזה-וזורום (vasa vasorum)

שאלה 3:

מבין הבאים, מי איננו תורם לתהליך הדלקתי-טרשתי בדופן העורק ולחוסר יציבות (Vulnerability) הרובד הטרשתי?

1. Vascular cell adhesion molecule-1
2. Monocyte chemoattractant protein-1
3. Interferon Gamma
4. Smooth muscle cells
5. T Lymphocytes

שאלה 4:

מי מהסמנים (מרקרים) הבאים אינו קשור בהגברת הסיכון לאירועים קרדיו-וסקולרים ותמותה קרדיאלית?

1. IL-6
2. Soluble CD 40 ligand
3. BNP
4. Angiotensin type II receptor
5. CRP

שאלה 5:

מבין השיטות הבאות איזו היא הפחות רגישה לאבחנה וזיהוי של Vulnerable plaque?

1. IVUS
2. Angioscopy
3. Thermography
4. MRI
5. Optical Coherence Tomography


בהצלחה, אל תעבדו קשה מדי!