

“Erosion, Intraplaque hemorrhage: The other Face of Vulnerability”

*Angioplasty Summit 2005, TCT Asia Pacific,
Seoul, April 28-30, 2005*



Renu Virmani, MD
CVPath, A Research Service of the International
Registry of Pathology
Gaithersburg, MD

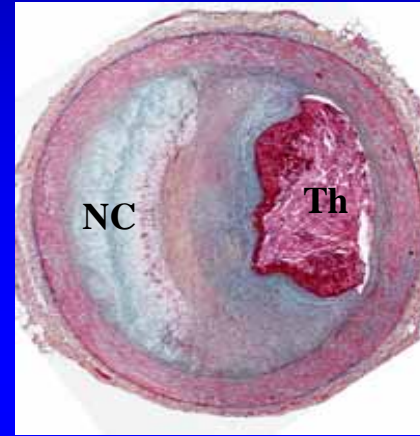
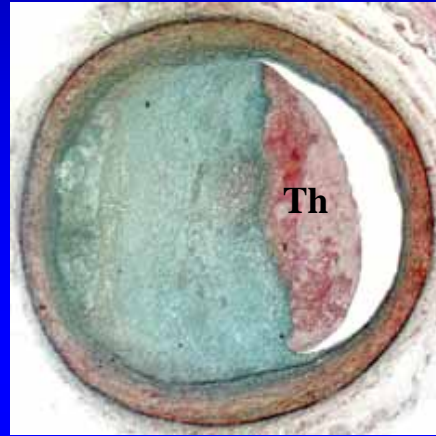
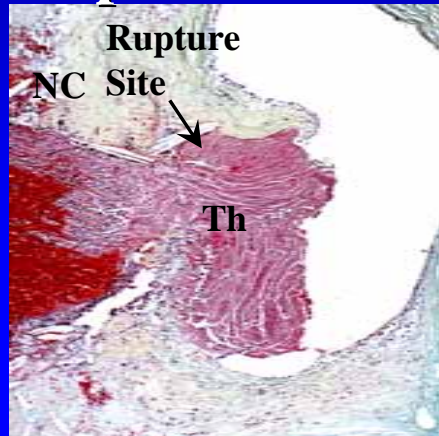
Lesions with Thrombi

- *Plaque Rupture*
- *Plaque Erosion*
- *Calcified Nodule*

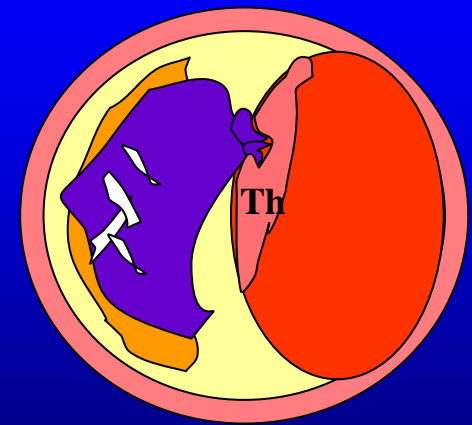
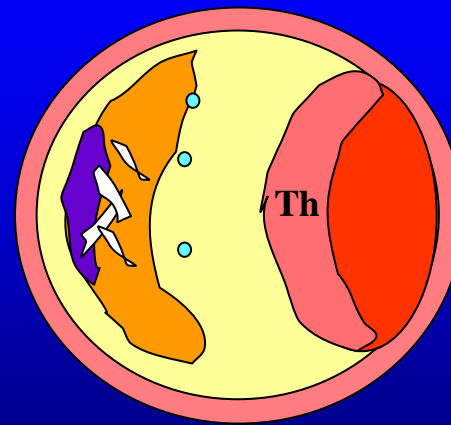
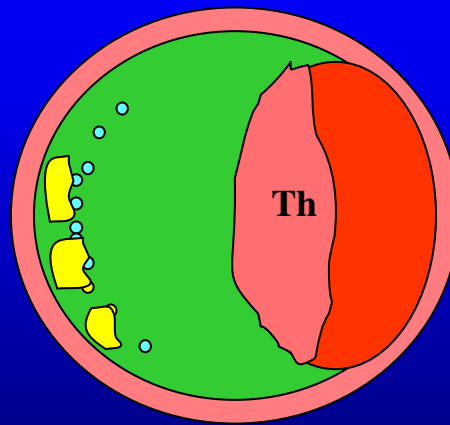
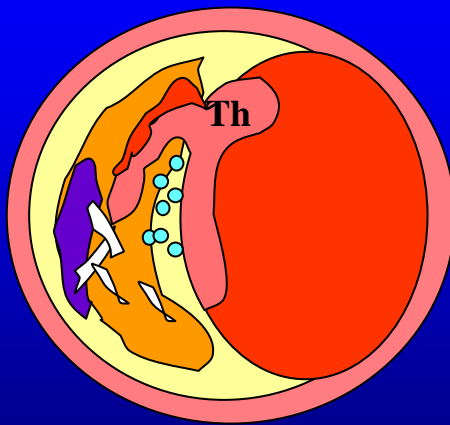
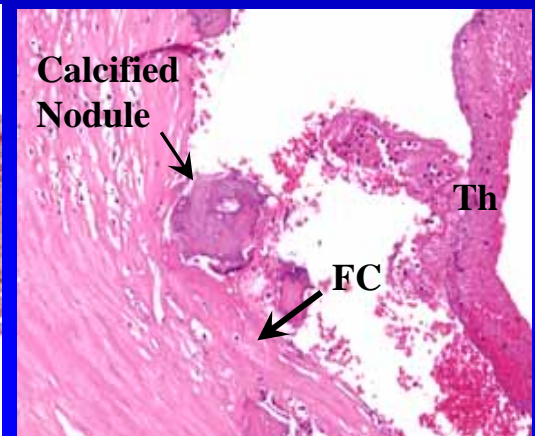
Causes of Coronary Thrombosis

Erosion

Rupture

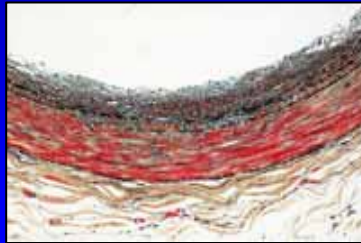


Calcified nodule

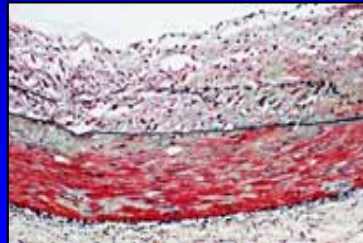


Development of Human Coronary Atherosclerosis

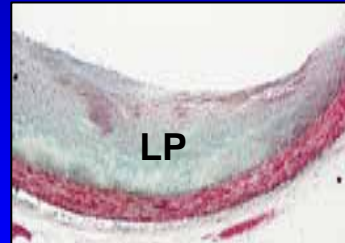
Intimal thickening



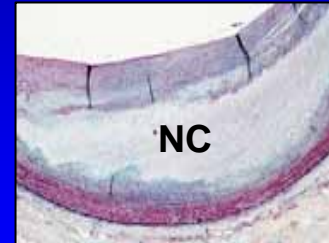
Intimal xanthoma



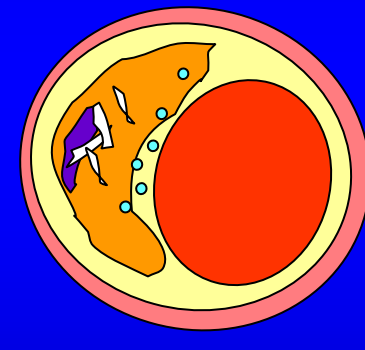
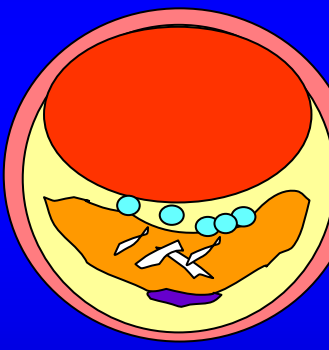
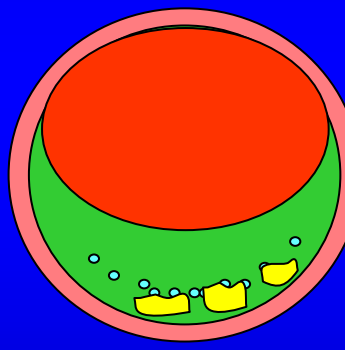
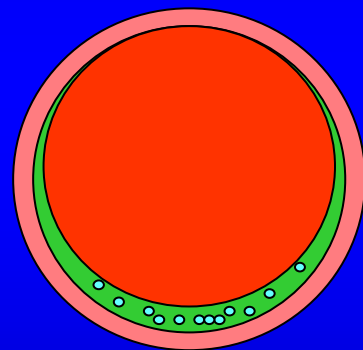
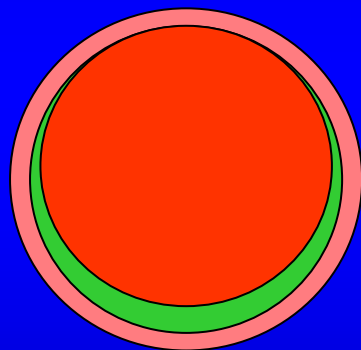
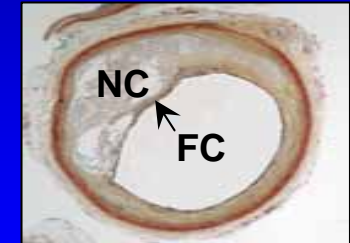
Pathologic intimal thickening



Fibrous cap atheroma

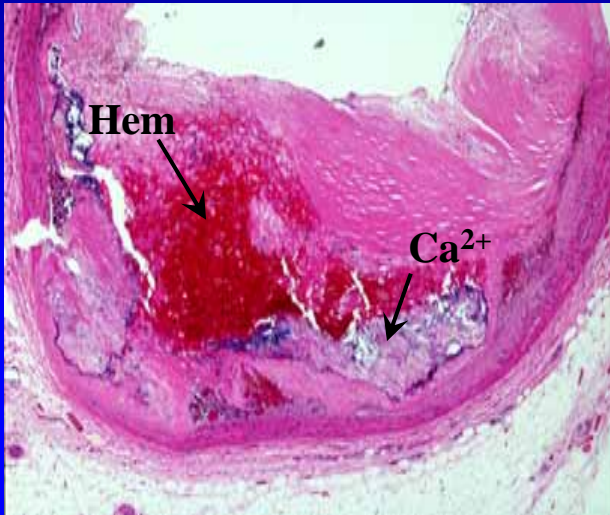


Thin-cap Fibroatheroma

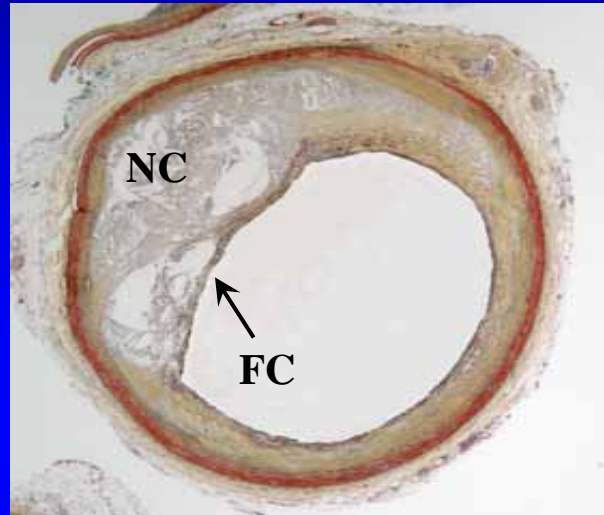


● Smooth muscle cells	● Calcified plaque
● Macrophage foam cells	● Hemorrhage
● Extracellular lipid	● Thrombus
● Cholesterol clefts	● Healed thrombus
● Necrotic core	● Collagen

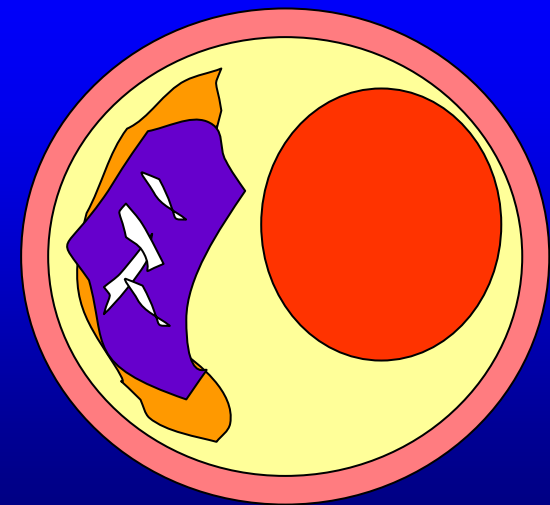
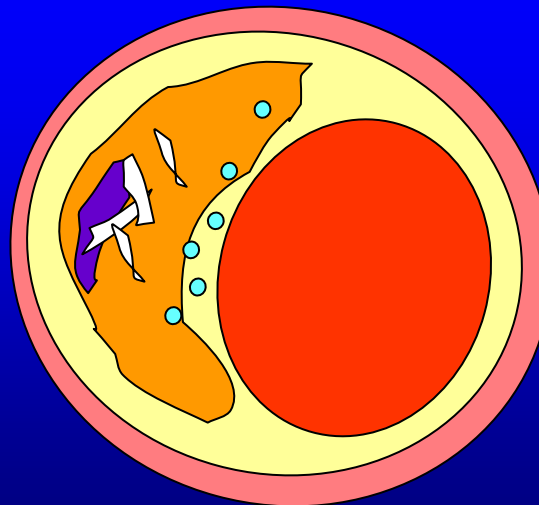
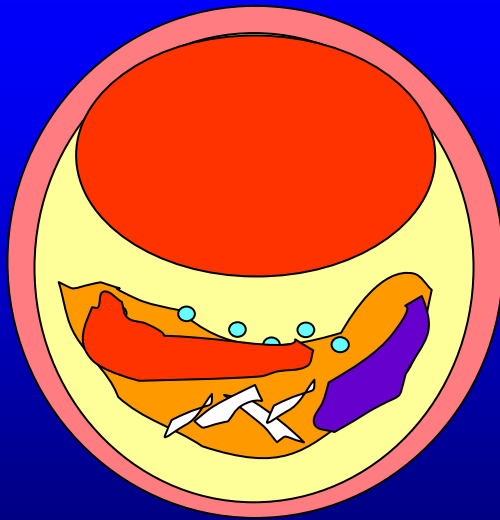
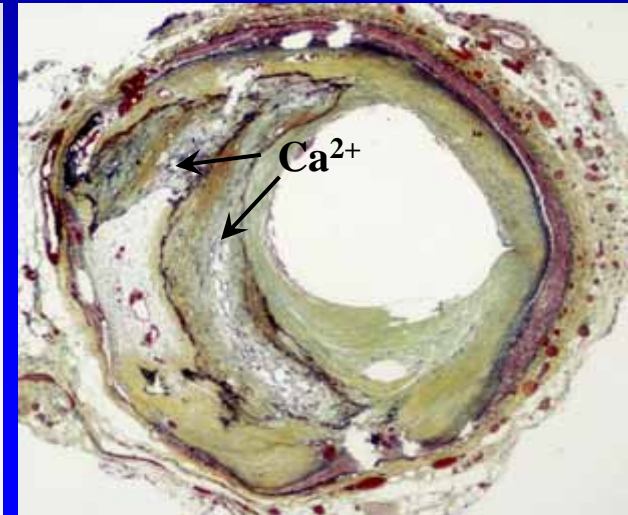
**Fibrous cap atheroma
with hemorrhage**



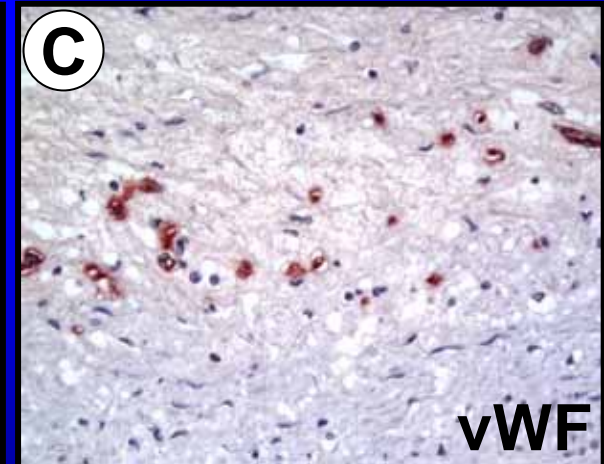
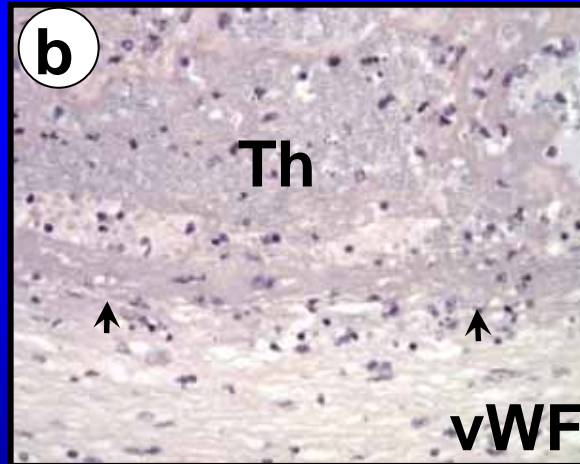
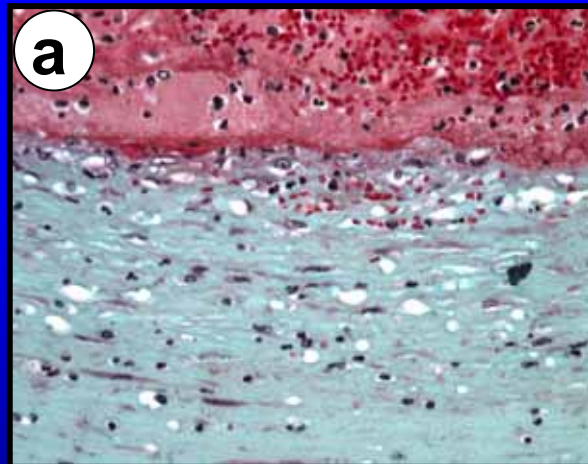
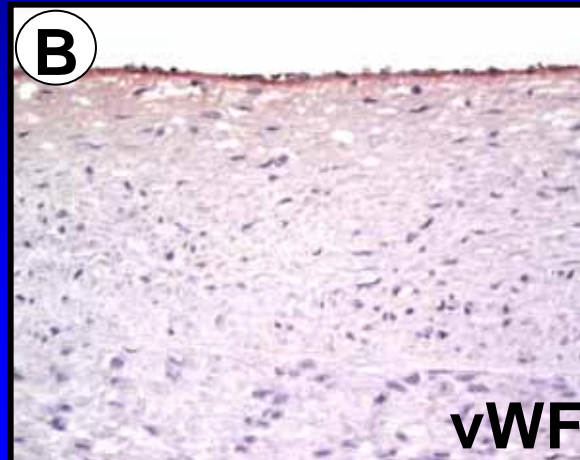
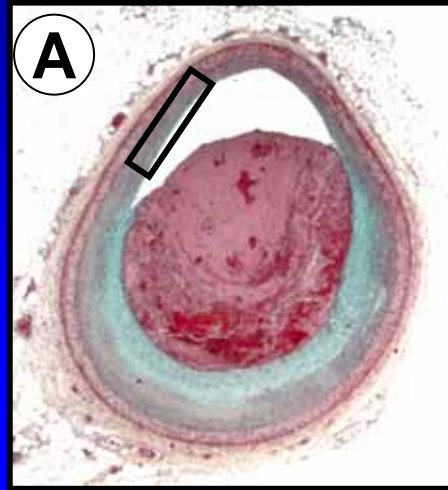
**Thin fibrous cap
atheroma**



Fibrocalcific plaque



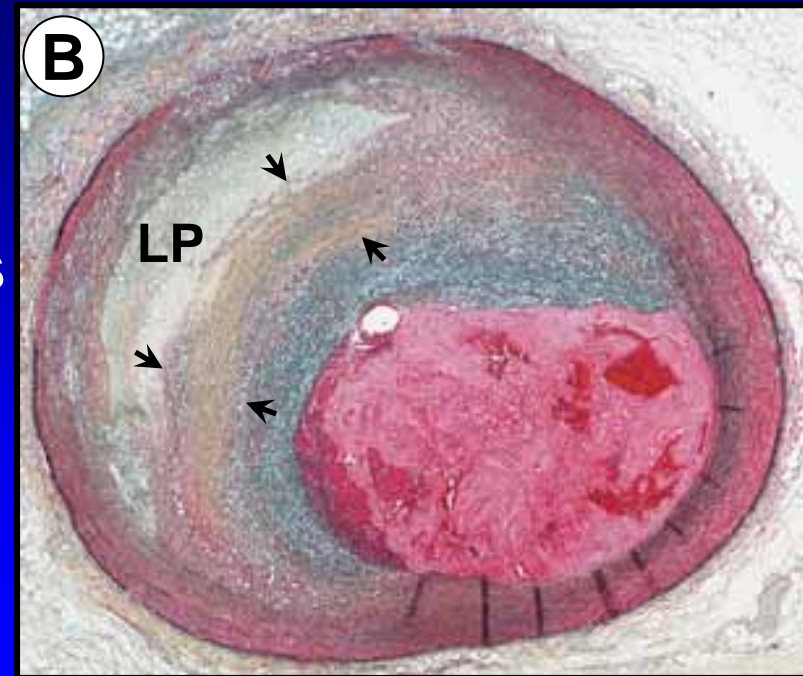
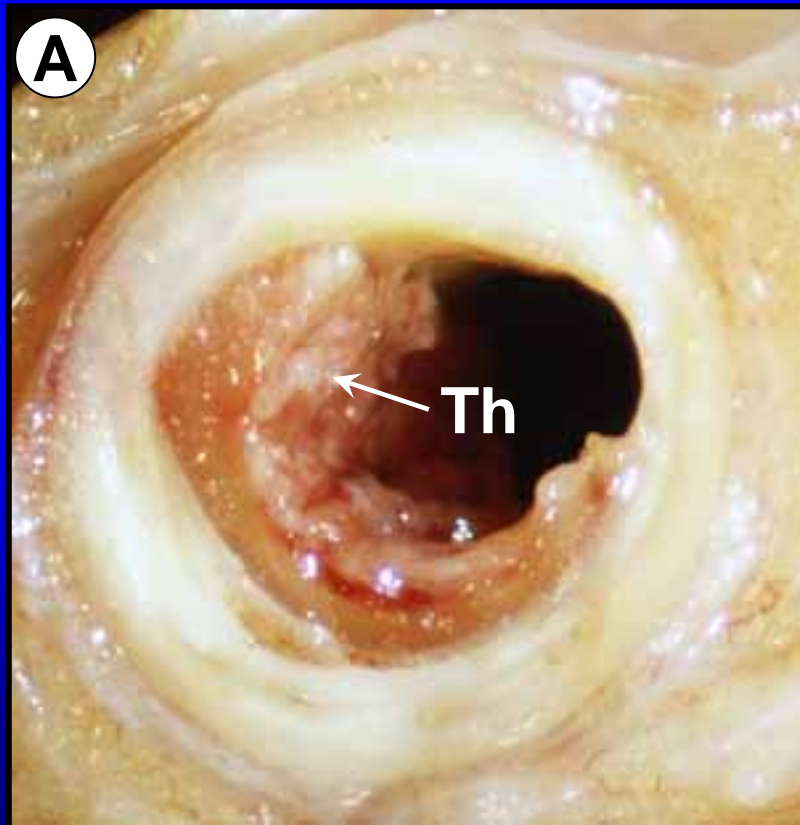
The Endothelium in Fatal Plaque Erosion



Coronary Thrombosis: Plaque Erosion

→: Occlusive thrombus

↓: Left anterior descending artery



↓: Eroded intima with thrombus

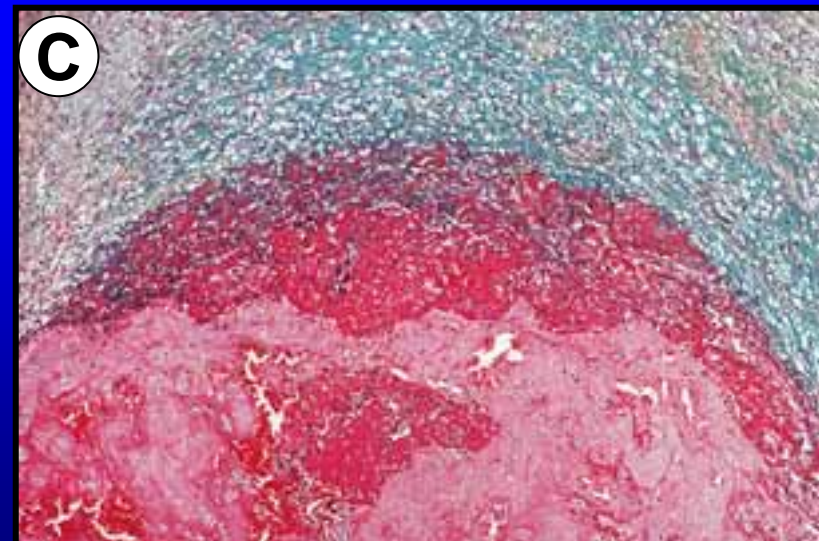
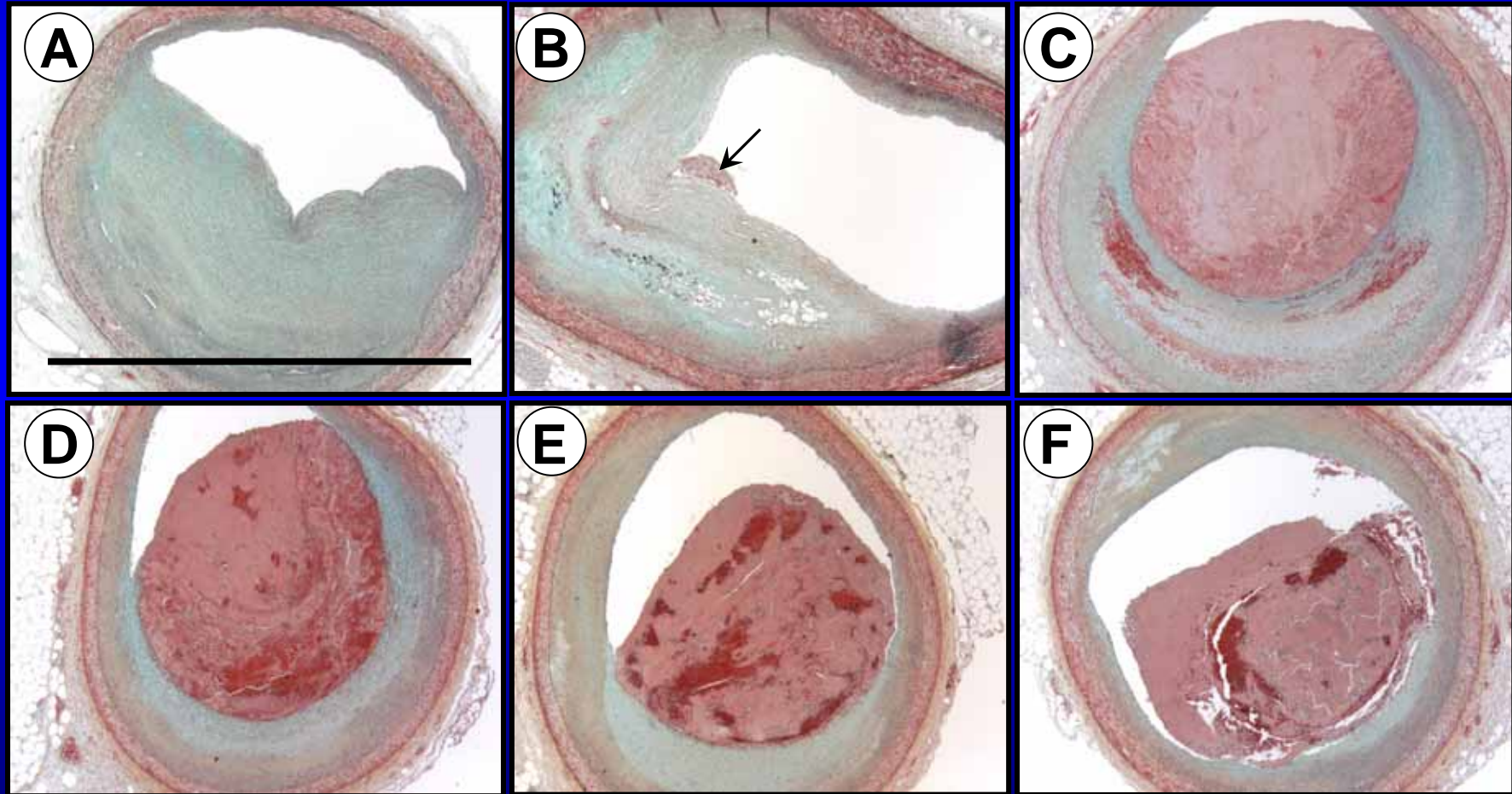


Fig. 4-2

Serial Sections of Plaque Erosion in a 38-Year-Old Female Sudden Coronary Death Victim

PROXIMAL LEFT ANTERIOR DESCENDING \longrightarrow

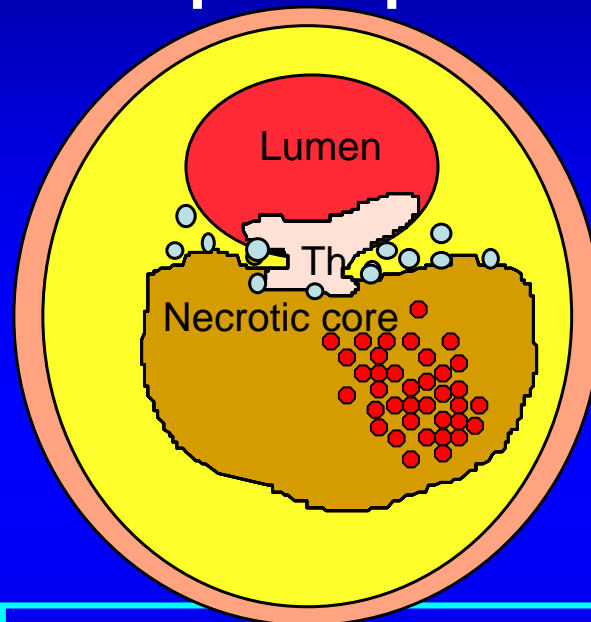


DISTAL

Fig. 4-3

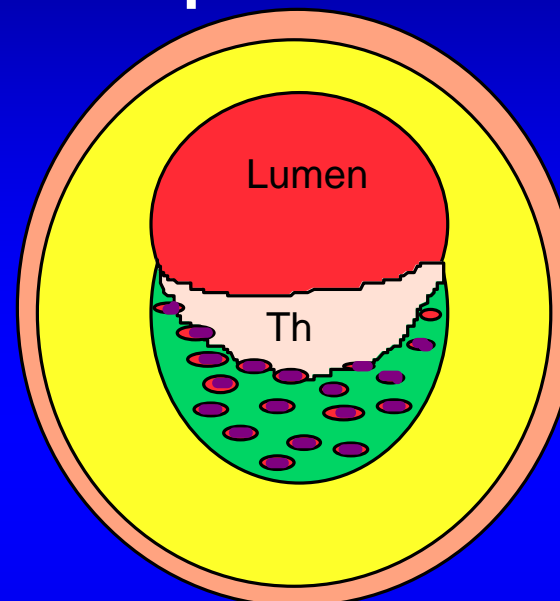
Clinical and Morphologic Difference in Plaques Associated with Luminal Thrombi

Plaque Rupture



45-55% thrombi in SCD
M>F, Older, Ca⁺⁺
Eccentric = concentric,
↑ Hemorrhage
Greater % stenosis
Macs, T cells,HLADr

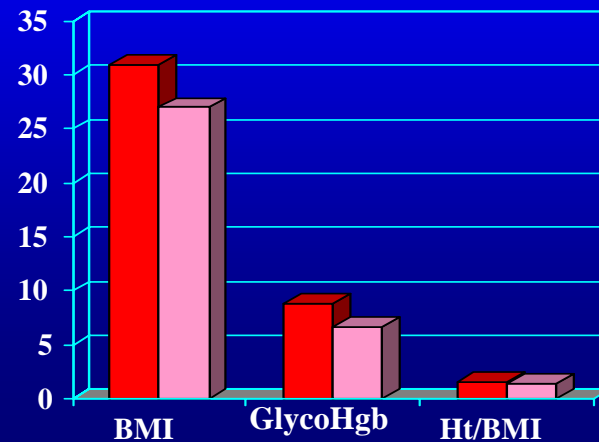
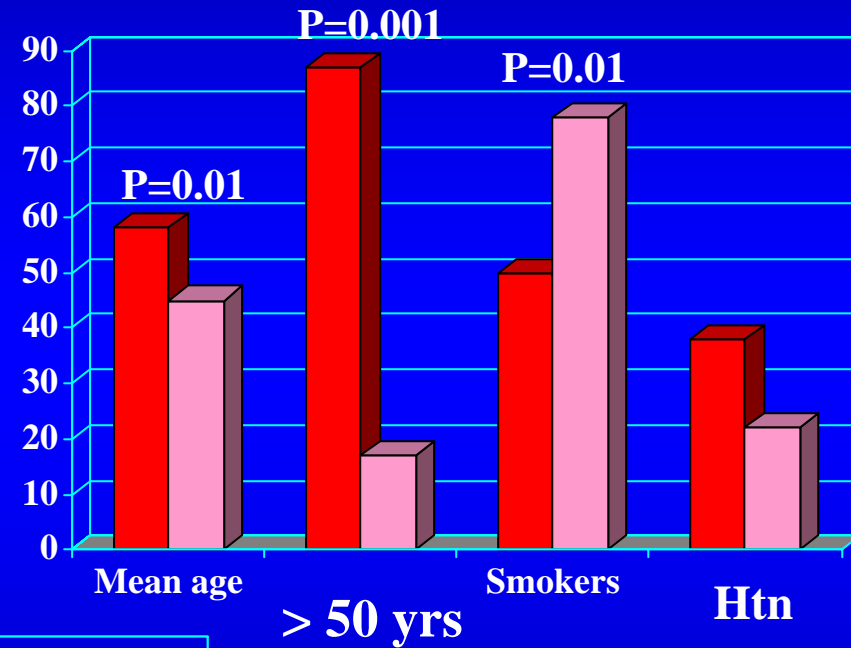
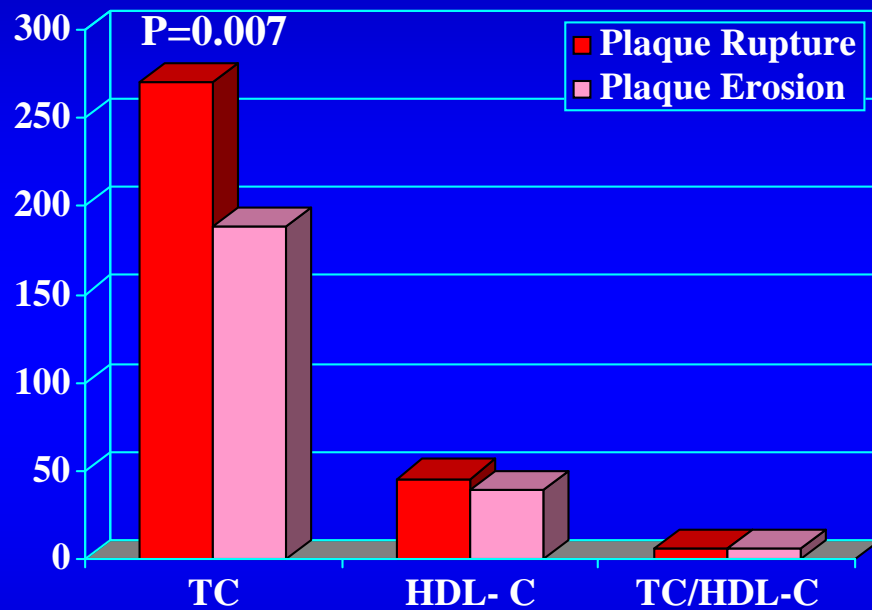
Plaque Erosion



35-40% thrombi in SCD
M=F, younger
Usually eccentric
Lesser % stenosis
SMC rich,
proteoglycans(versican)
& hyaluronan

Fig. 4-4

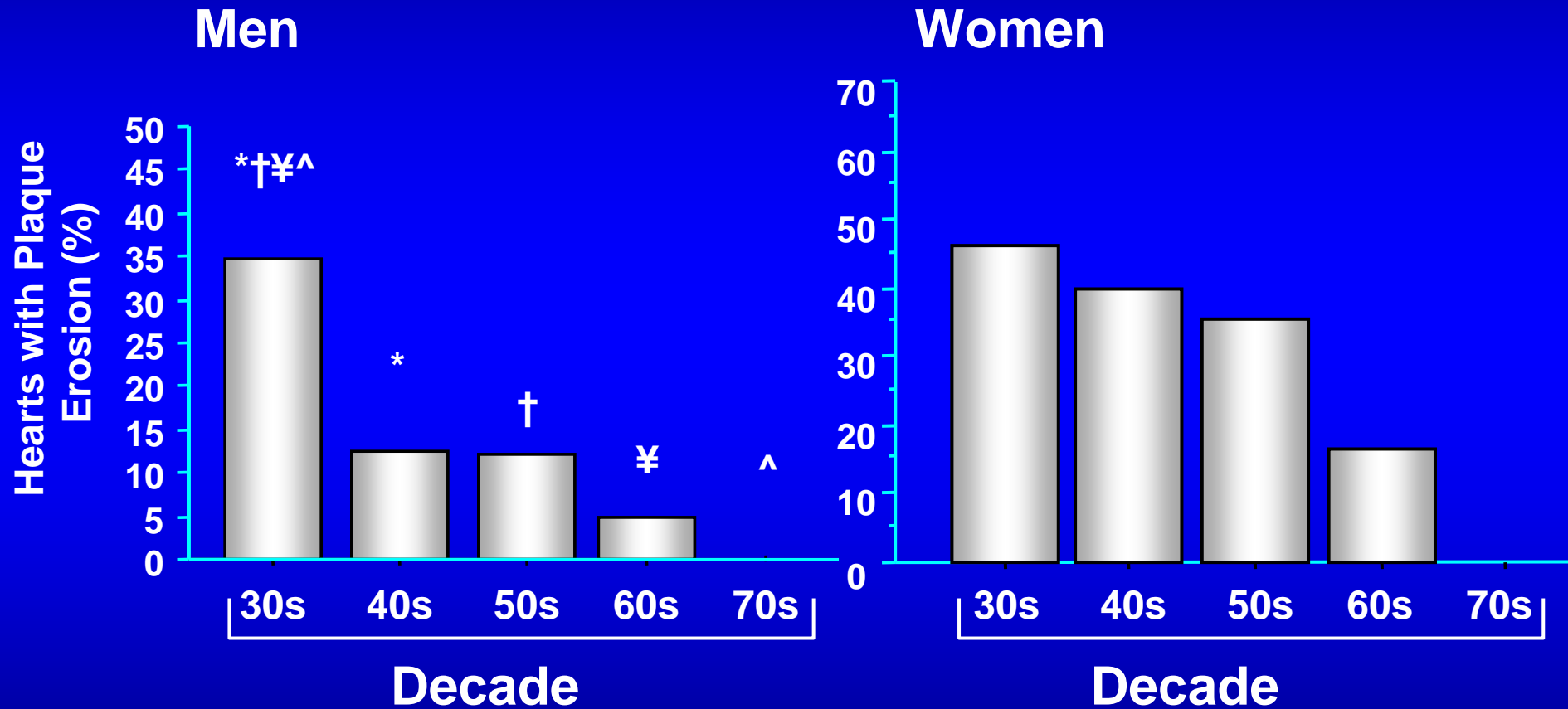
51 Women with Severe Coronary Atherosclerosis



Frequency Distribution of Percent Cross-sectional Area Stenosis by Plaque in Coronary Thrombosis

% Stenosis	Mean Age	All Cases	Plaque Rupture	Plaque Erosion
50-59	42±5	4(8%)	1(4%)	3(14%)
60-69	46±7	9(18%)	4(14%)	5(23%)
70-79	49±10	21(42%)	11(39%)	10(45%)
80-89	50±5	8(16%)	5(18%)	3(14%)
90-99	52±16	8(16%)	7(25%)	1(5%)
Total	49±10	50(100%)	28(100%)	22(100%)

Plaque Erosions in Men and Women Stratified by Age



*P=0.01, †P=0.02, ¥p=0.01, ^P=0.03

All P > 0.05

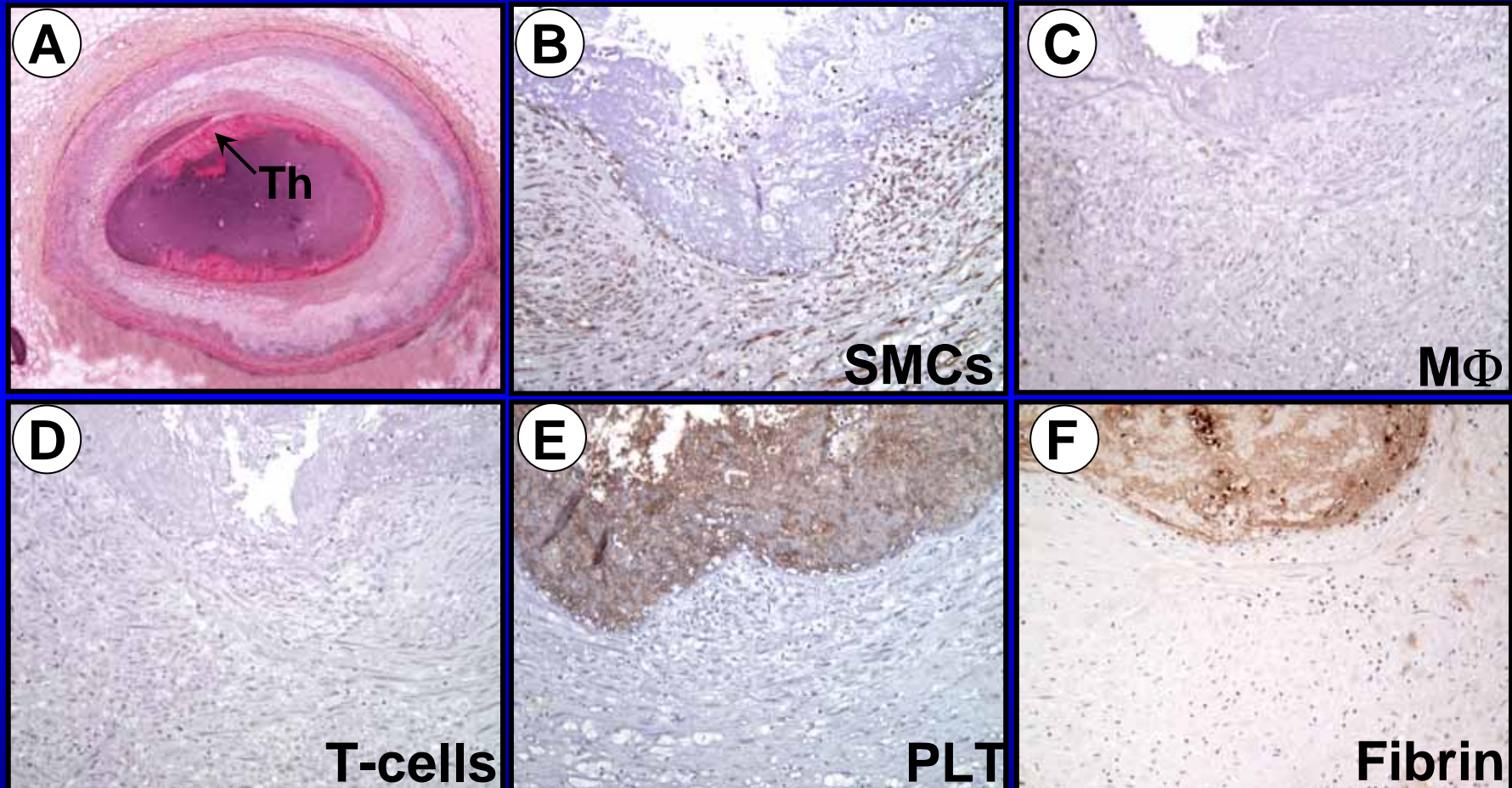
Plaque Erosion and Inflammation

SCD victims <40 yrs in age

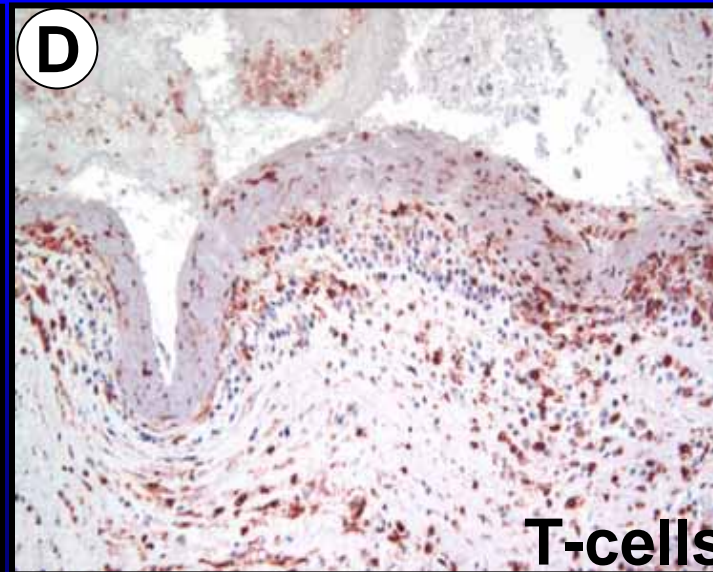
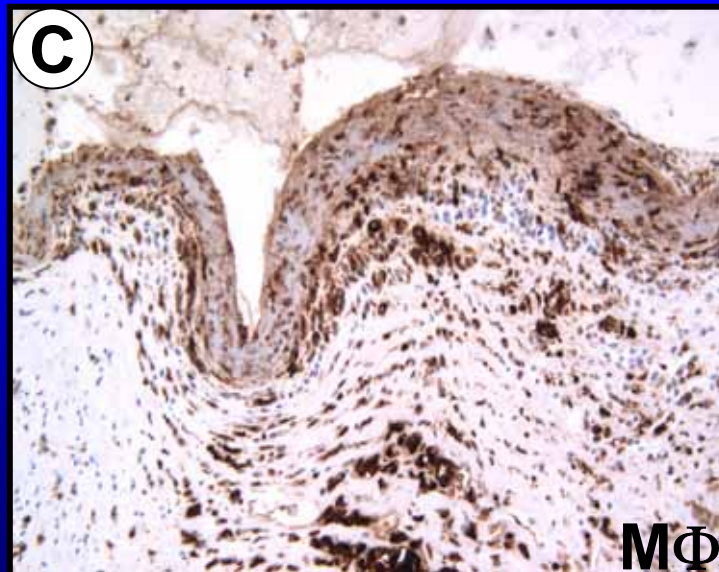
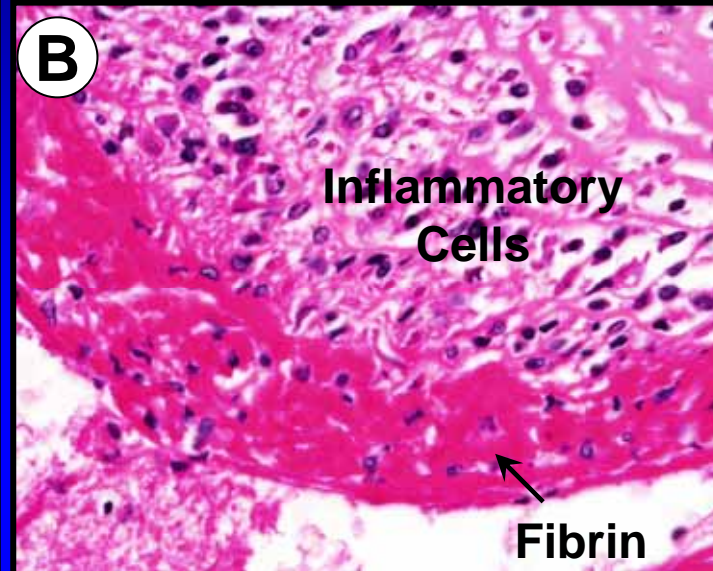
- Of 23 cases of plaque erosion, 5 occurred on a fibrous plaque without lipid deposits, 17 had pathologic intimal thickening, and 1 had a fibroatheroma.
- Organizing thrombus in 11, and organized at the base in 12. Severe inflammation observed in 2 cases

Cell Type	Erosion	Rupture	P value
SMC's (cells /mm ²)	794±334	164±177	<0.0001
Macrophages (cells /mm ²)	251±159	585±219	0.0007
T-cells (cells /mm ²)	1.3±0.8	6.4±1.3	0.008

Acute Plaque Erosion No Thrombus Organization

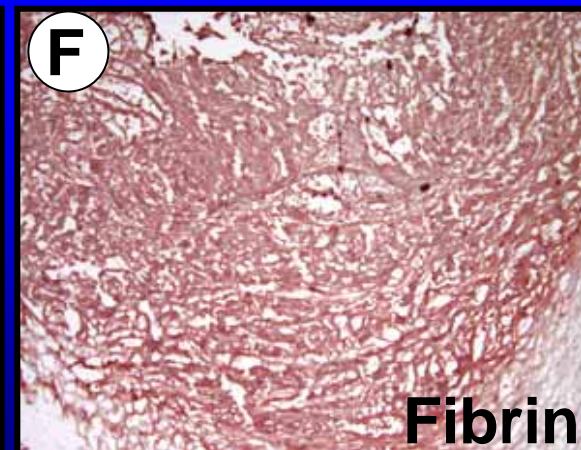
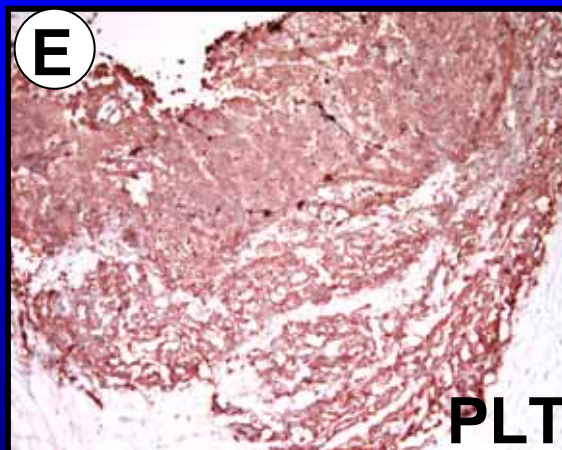
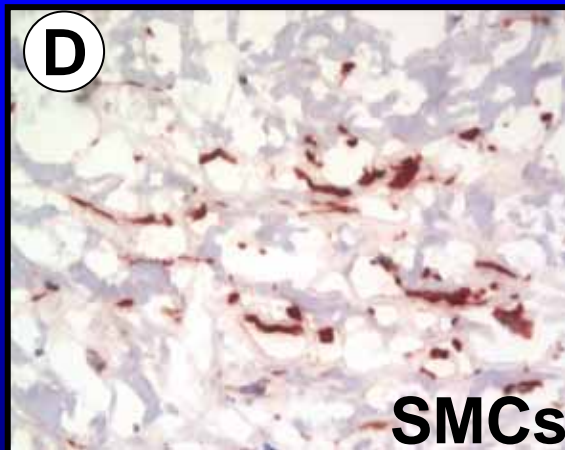
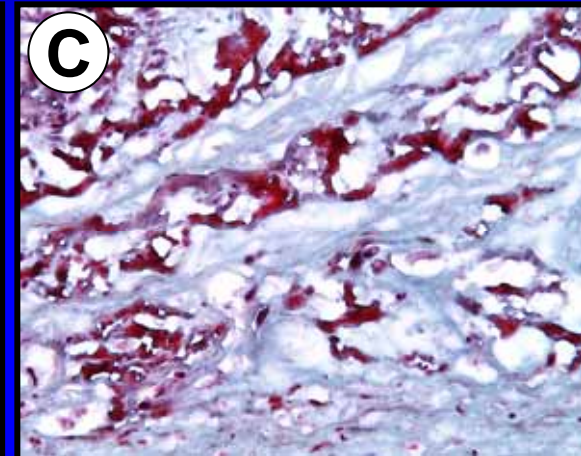
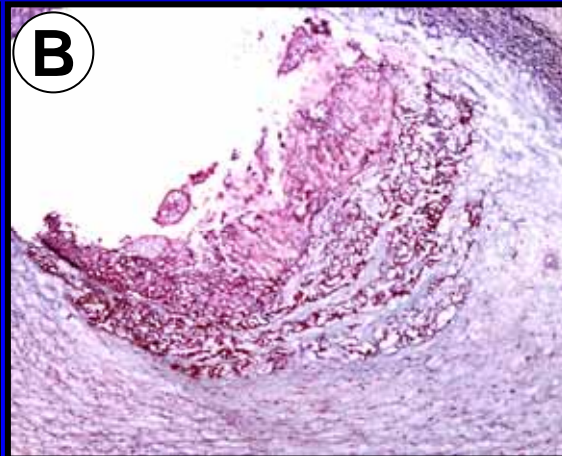
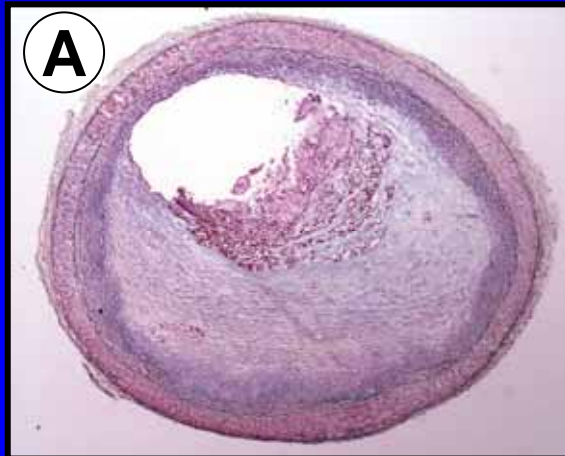


“Inflamed” Erosion

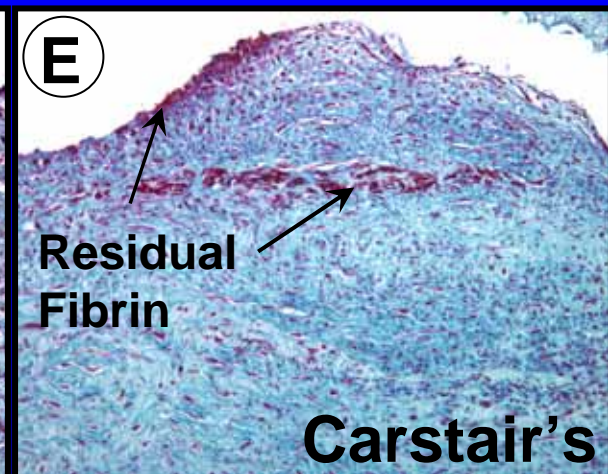
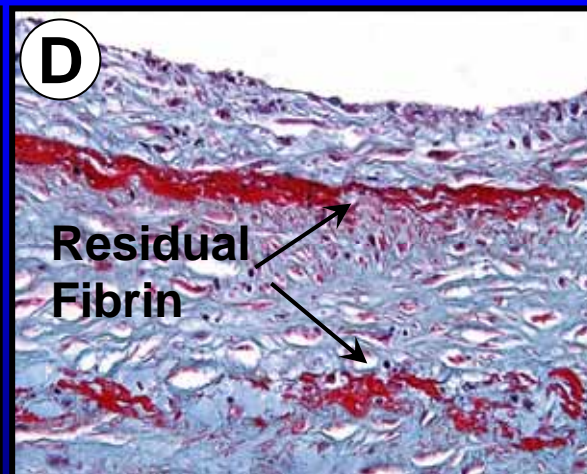
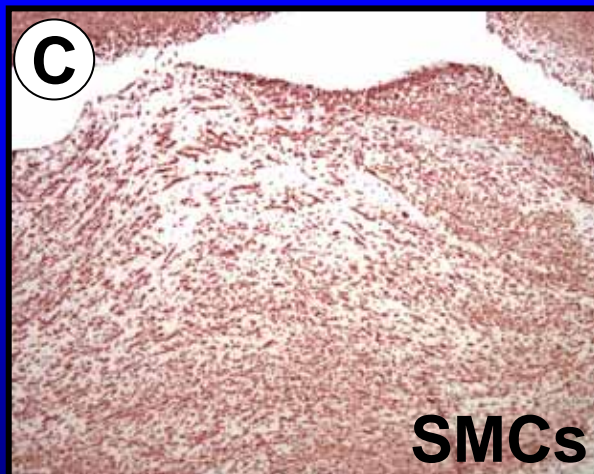
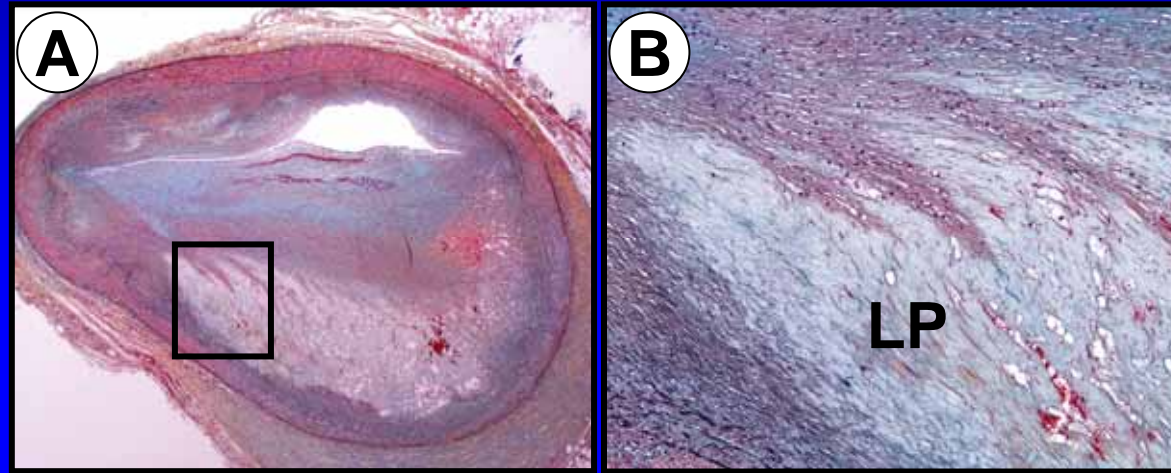


Plaque Erosion

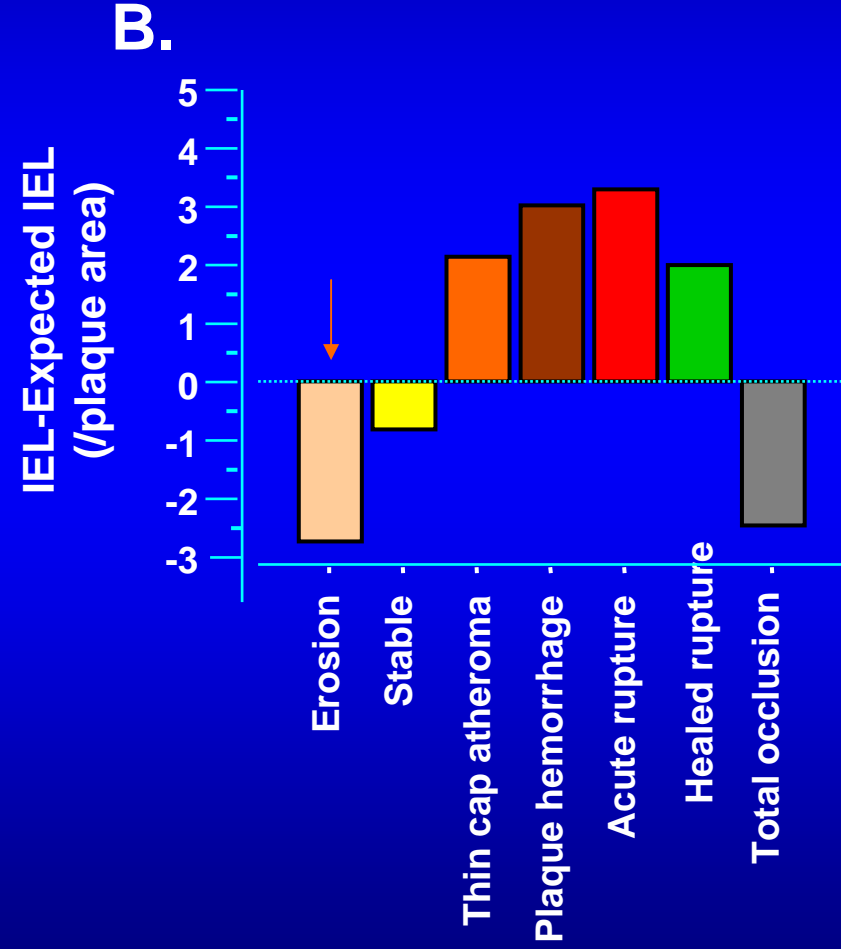
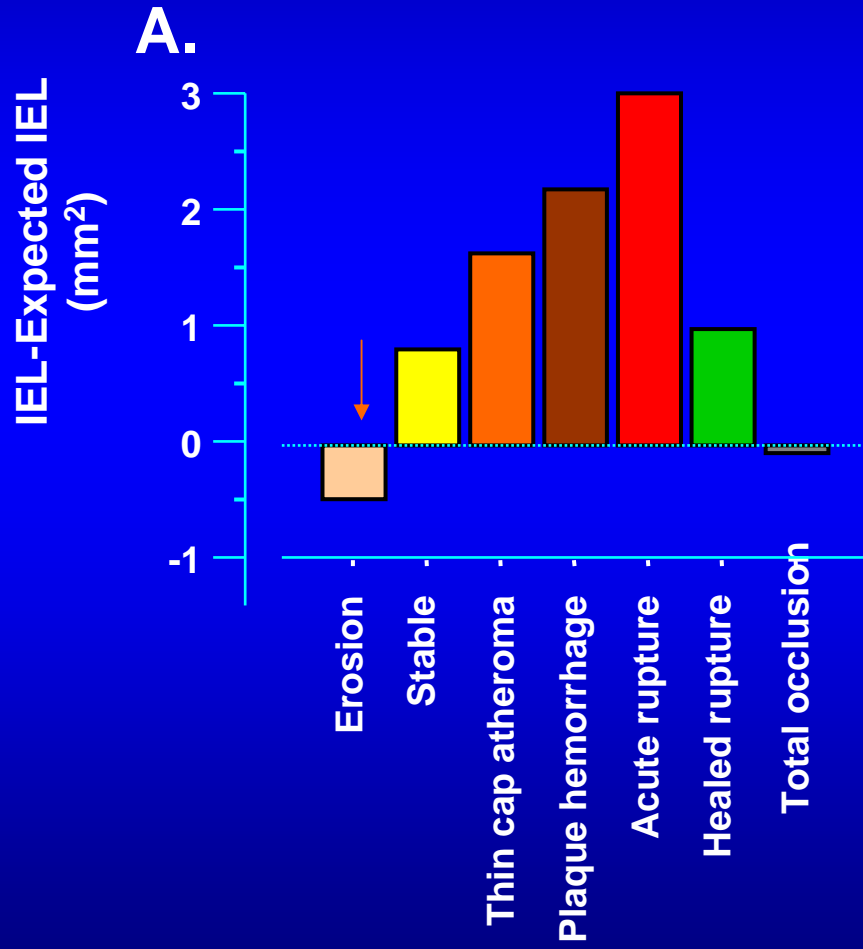
Early Thrombus Organization



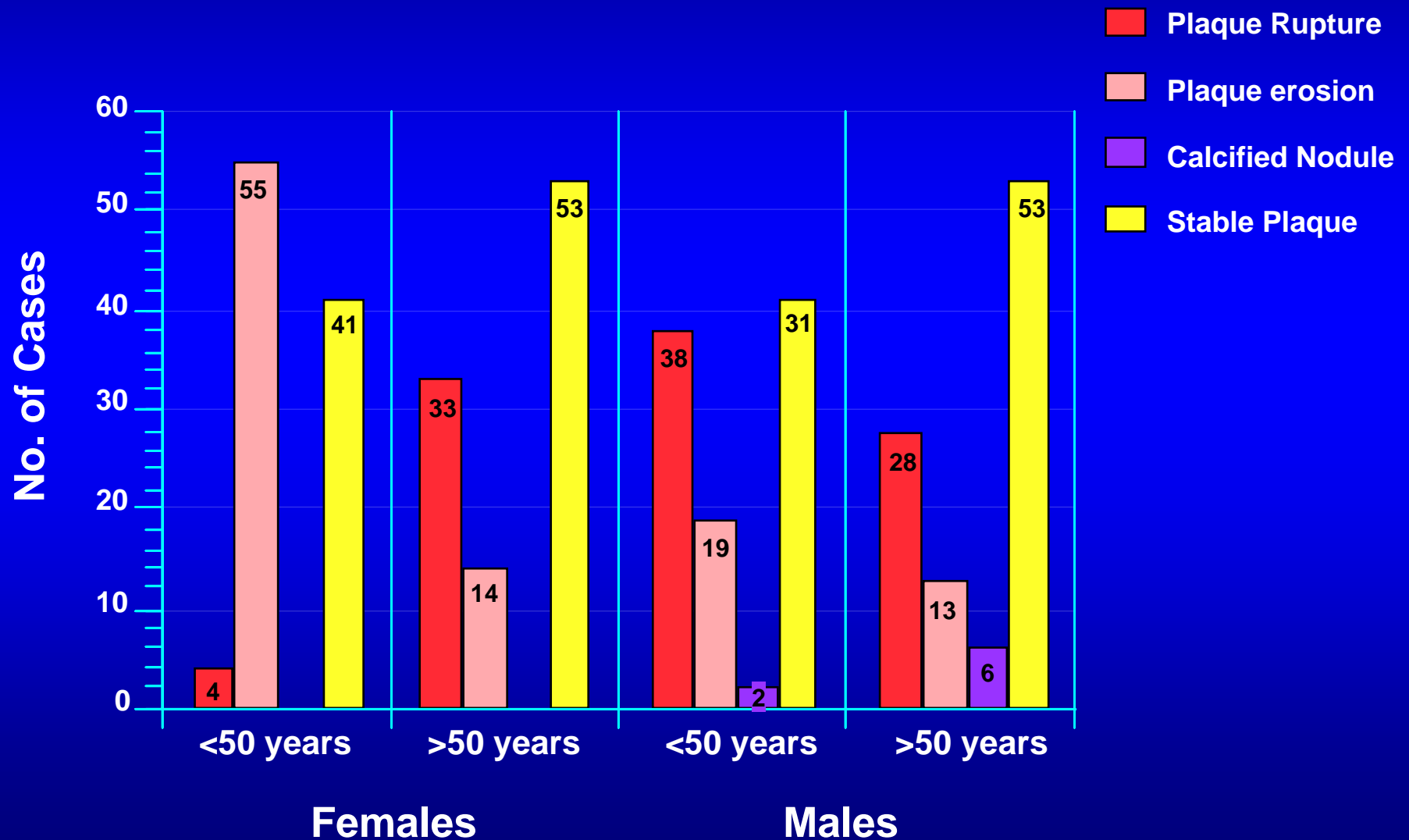
Plaque Erosion Organized Thrombus



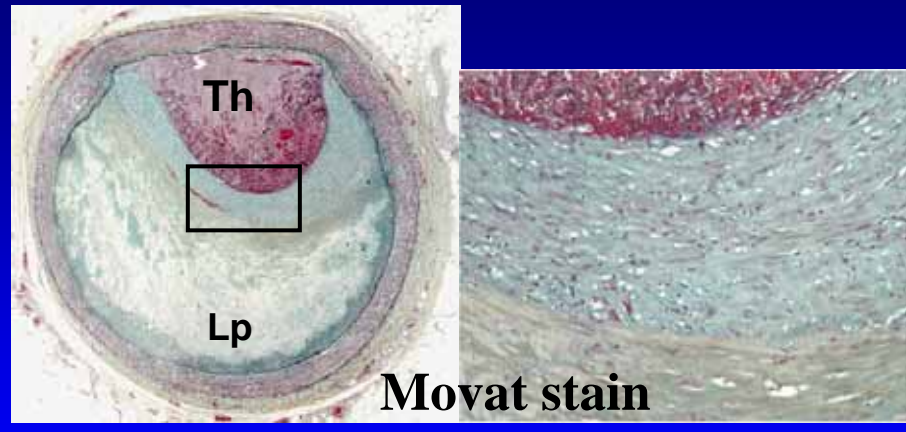
Remodeling in Varying Coronary Lesion Morphologies



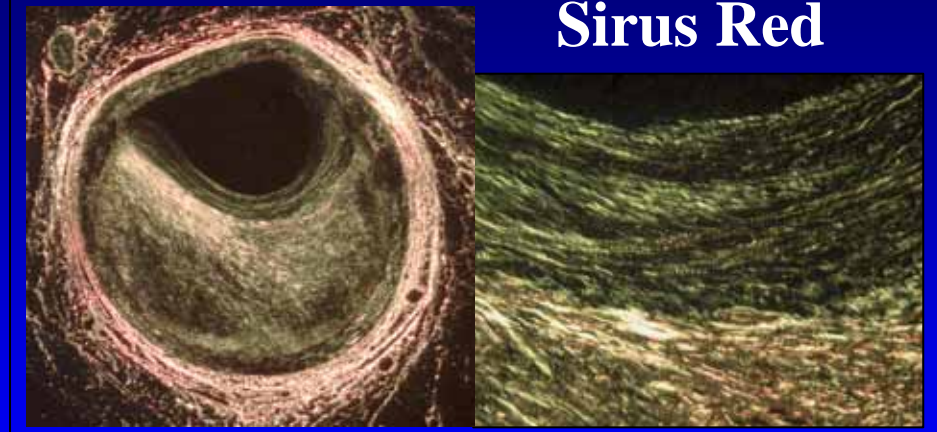
Influence of Age on Coronary Thrombosis in Men and Women



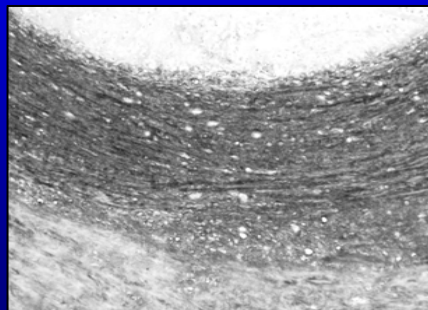
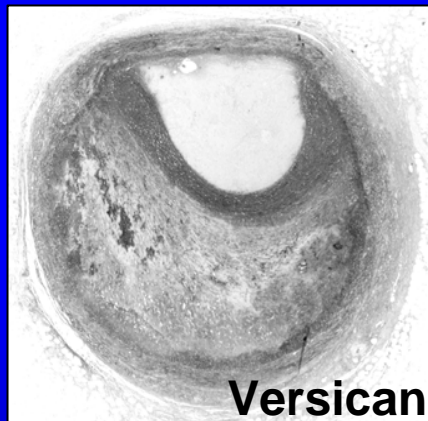
A **Plaque erosion and Matrix**



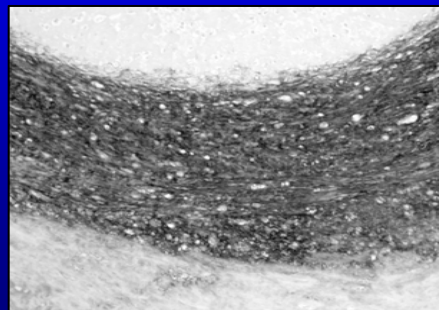
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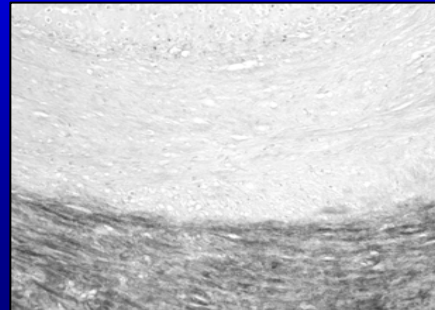
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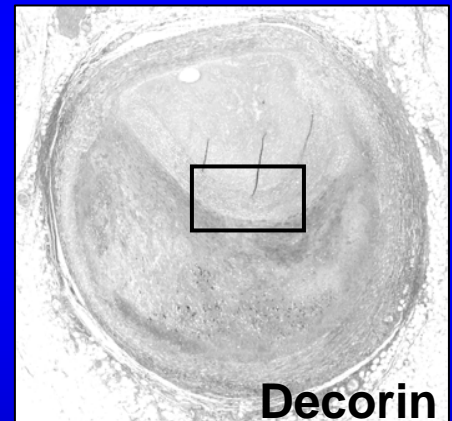
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E

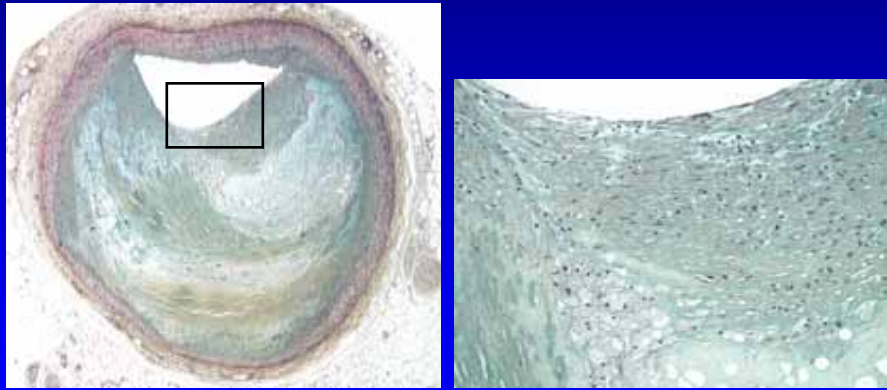


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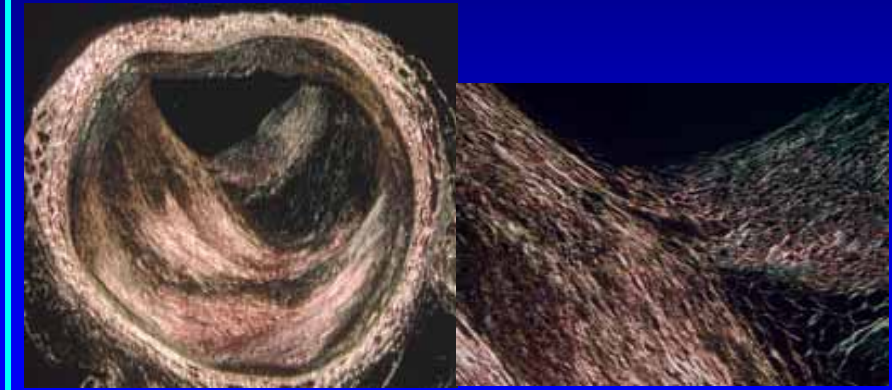


Stable Plaque

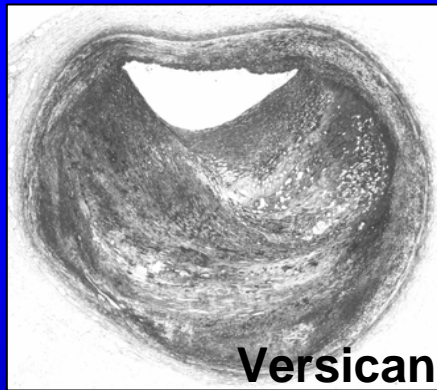
A



B

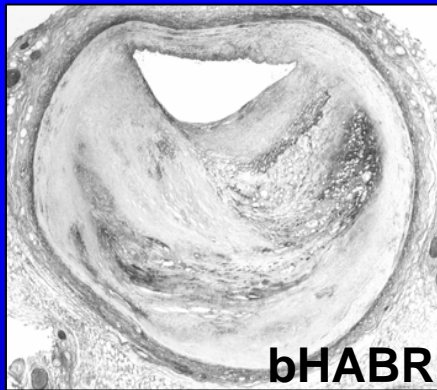


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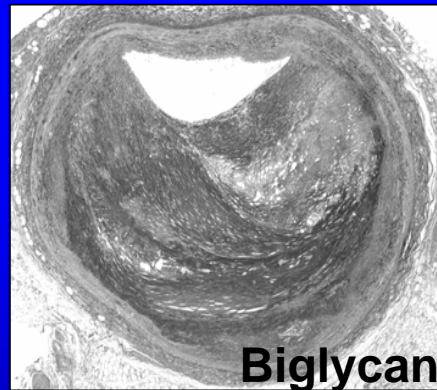
Versican

D



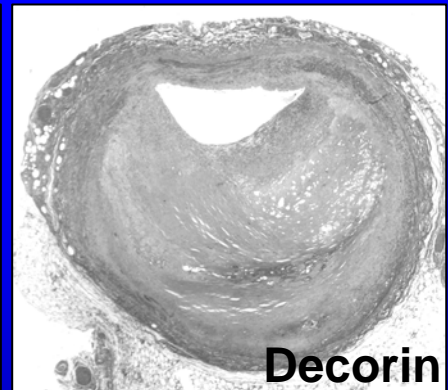
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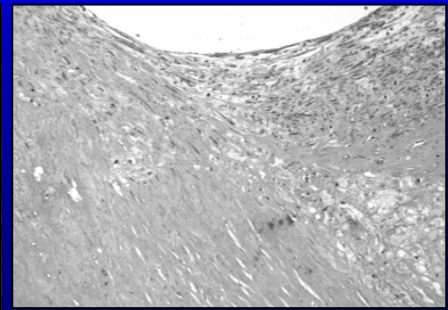
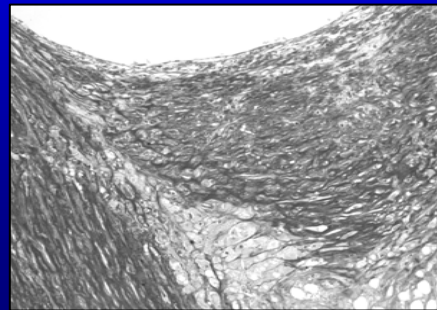
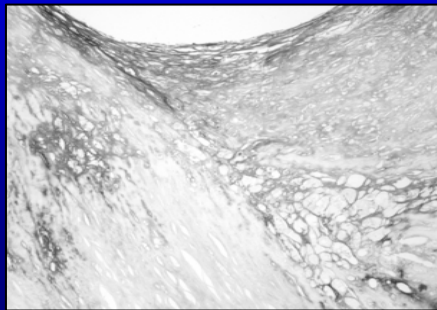
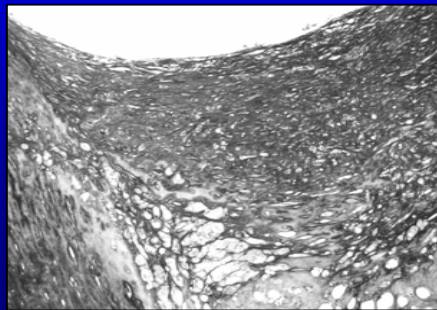


Biglycan

F



Decorin



Distribution of Proteoglycans in Plaque Erosion

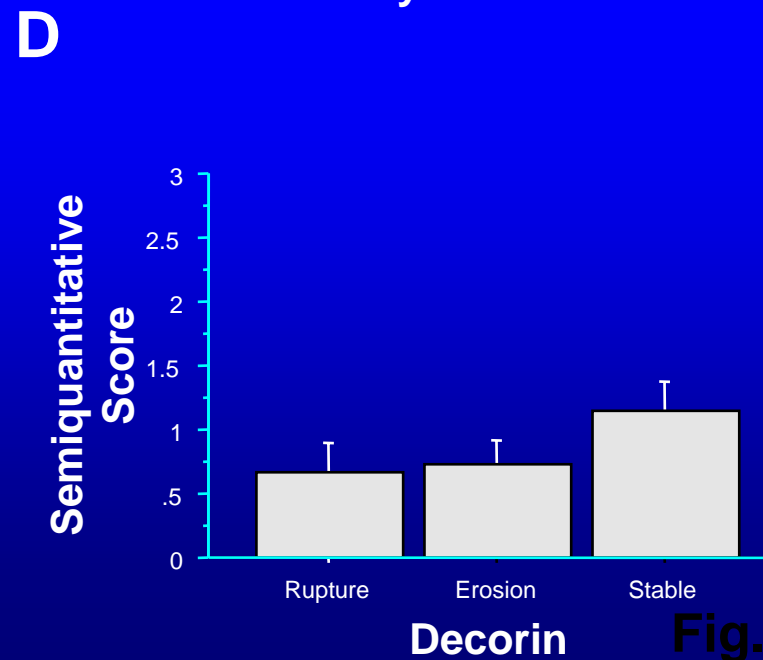
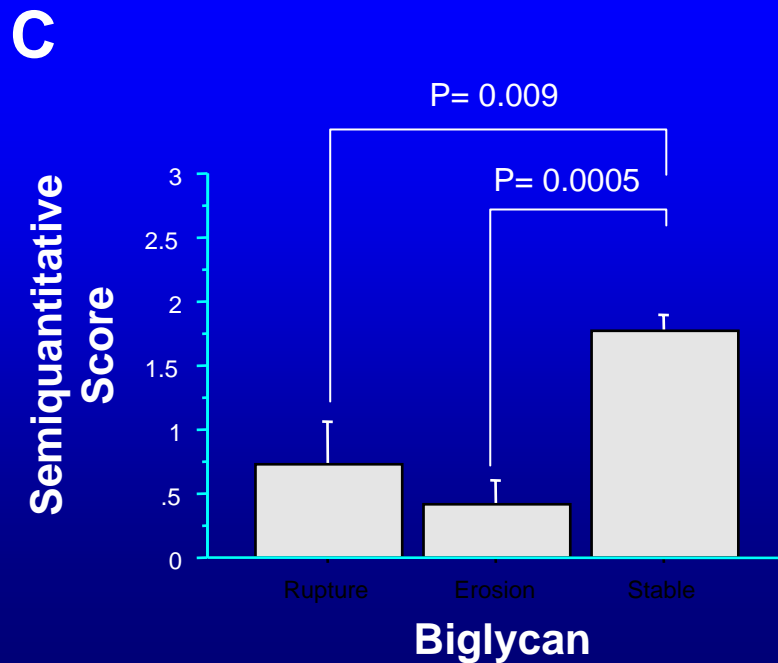
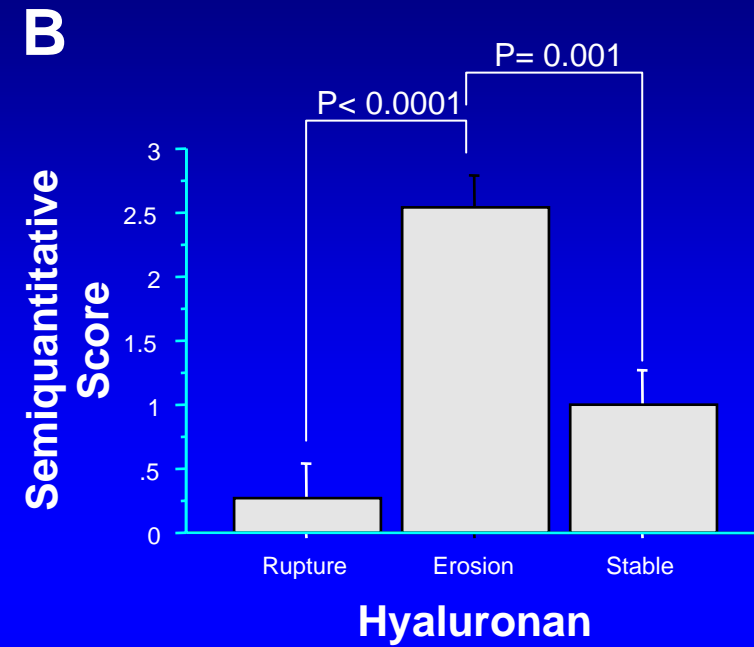
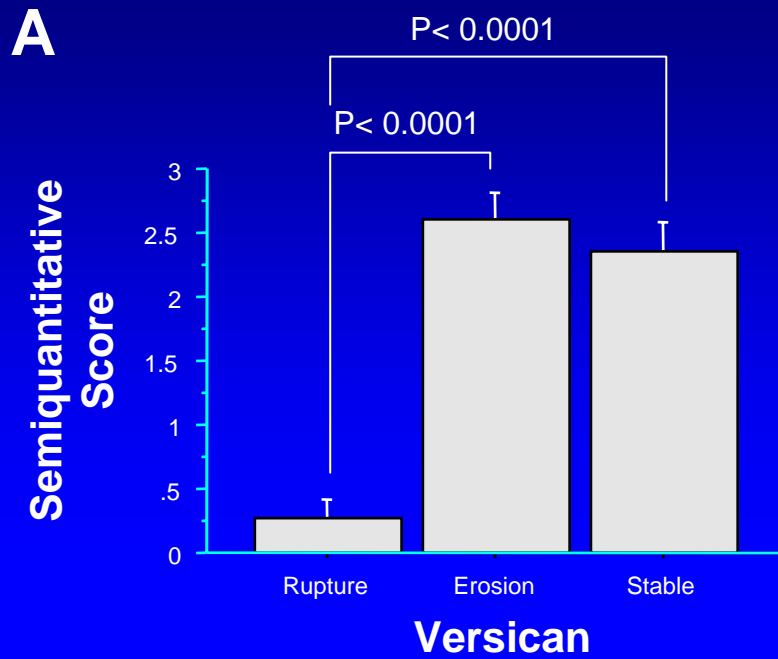
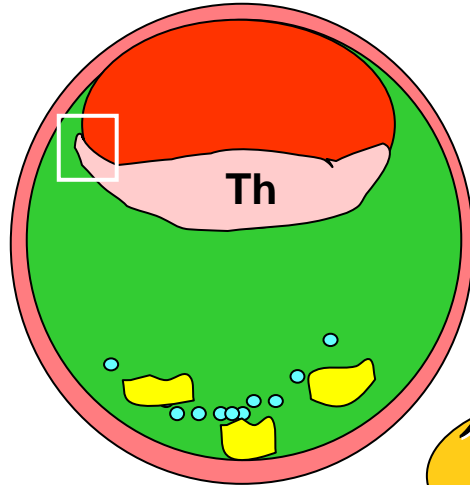
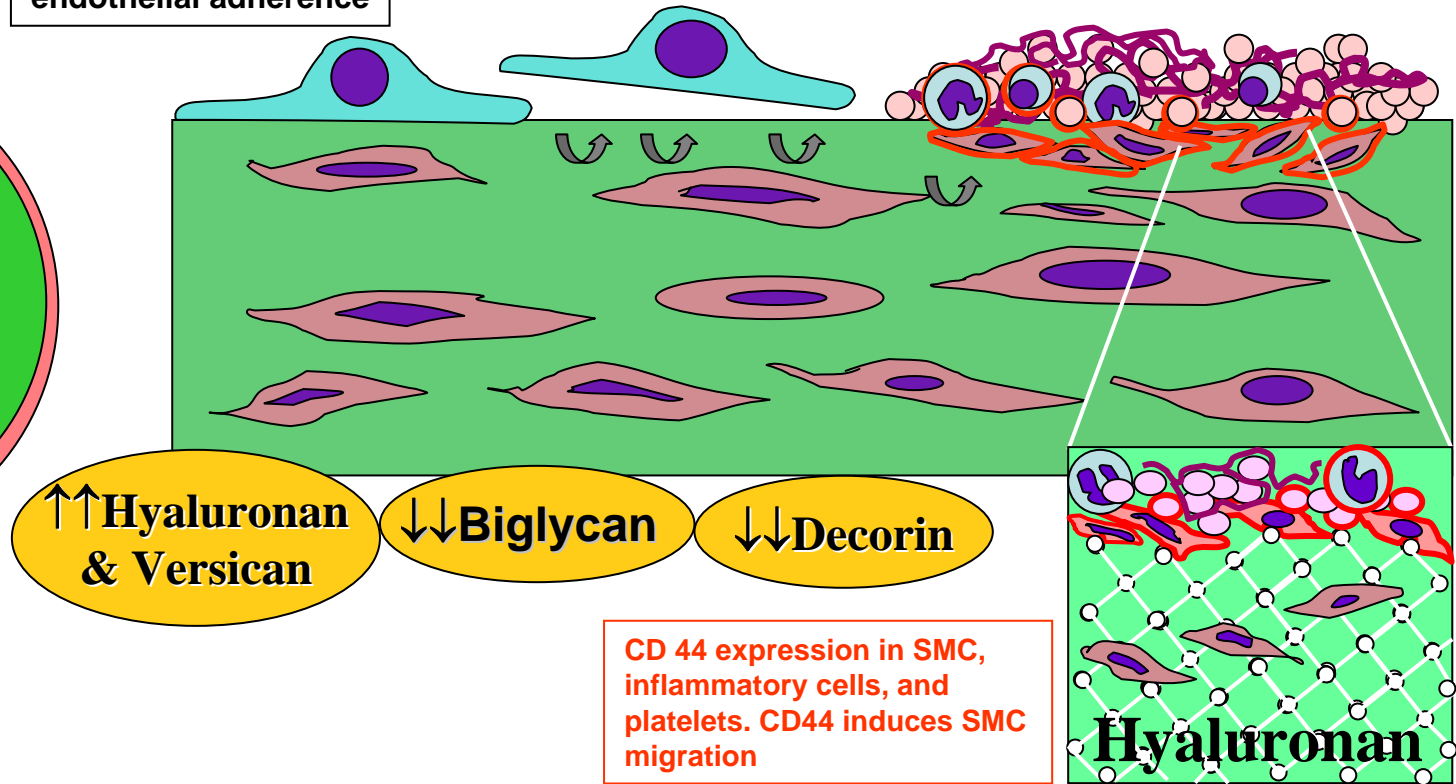
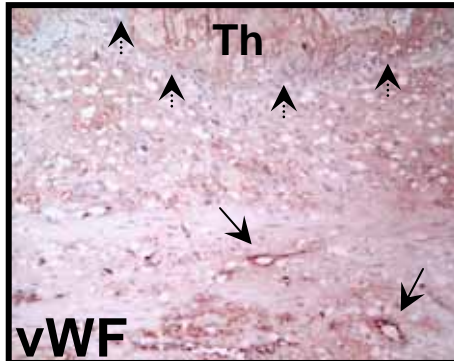
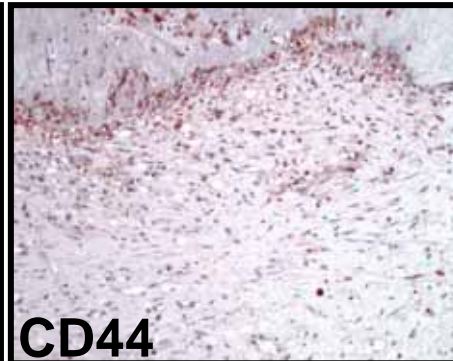
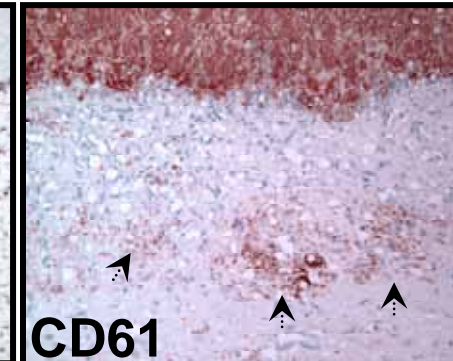
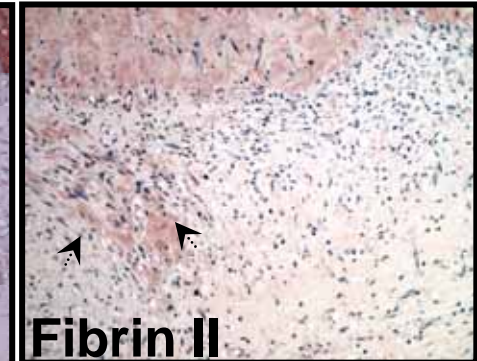


Fig. 4-12

A**Plaque Erosion**

HA interferes with endothelial adherence

HA: ↑ fibrin polymerization
Promotes adherence
platelets
macrophages

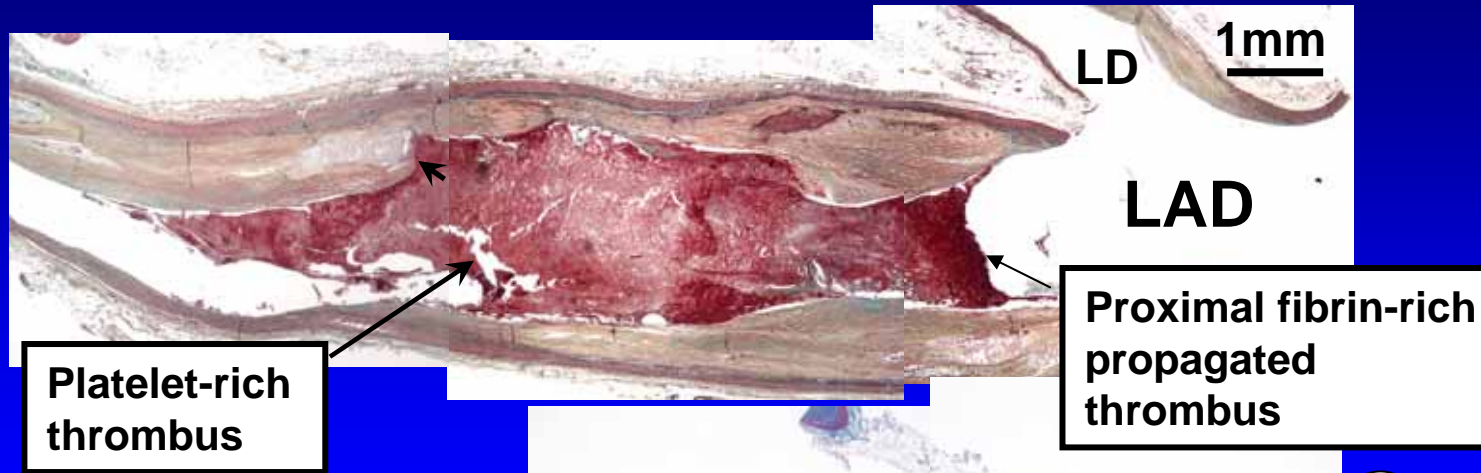
**B****C****D****E**

Role of Hyaluronan and CD44 at Sites of Plaque Erosion

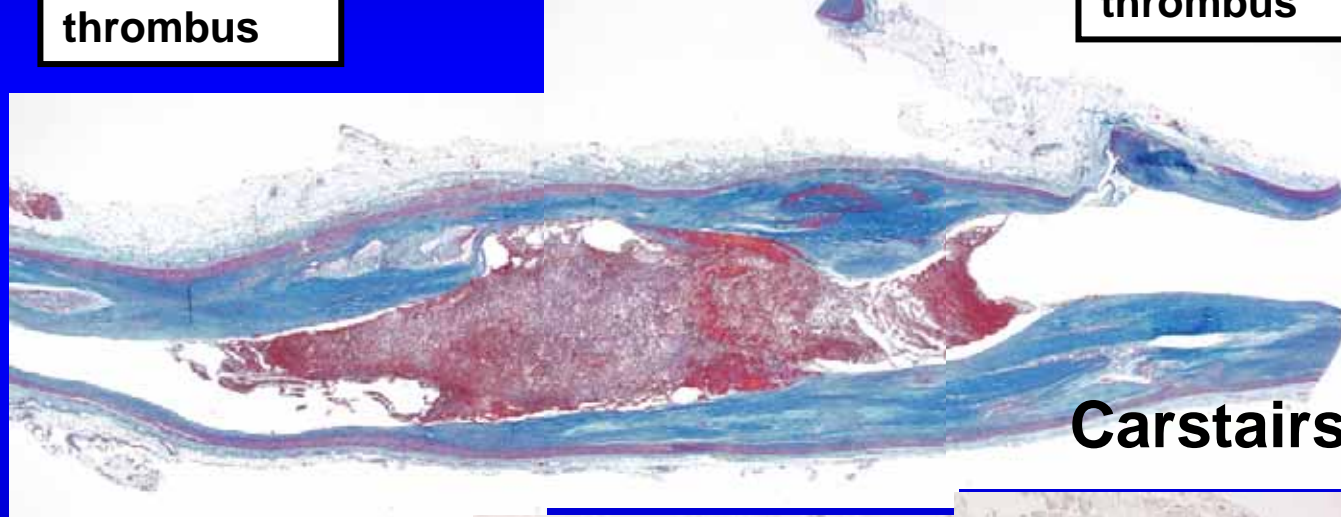
- Increased hyaluronan at plaque thrombus interphase
- Hyaluronan may interfere with the integrity of normal vascular endothelium - endothelial cells from large vessels have lower potential for adherence to hyaluronan. Endothelial cells in culture demonstrate decreased cell growth and increased propensity to apoptosis.
- Hyaluronan binds to CD44 and CD44 receptors have been shown to mediate the adhesion of platelets to hyaluronan, The deendothelialized surface of erosion may expose hyaluronan, thereby promoting platelet attachment via CD44. CD44 promotes atherosclerosis by mediating inflammatory cell recruitment.

Thrombus Propagation in Plaque Rupture

A



B



C



D

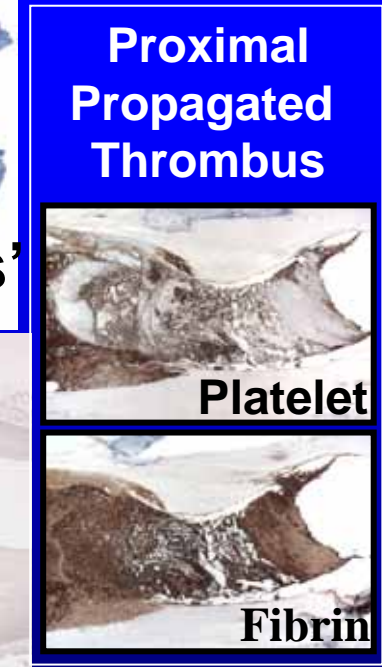
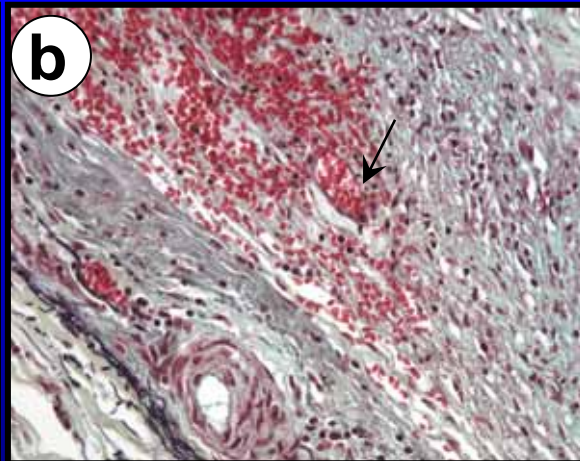
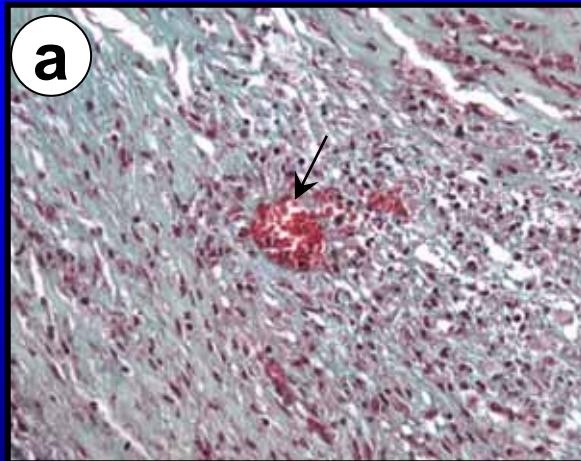
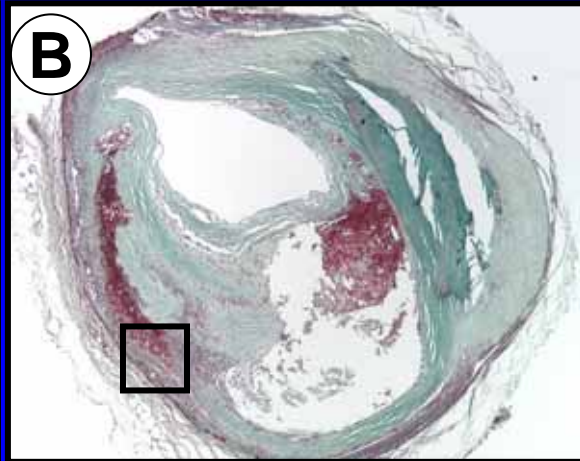
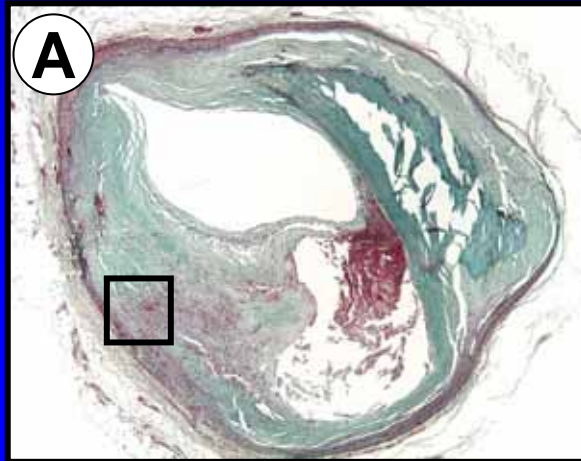


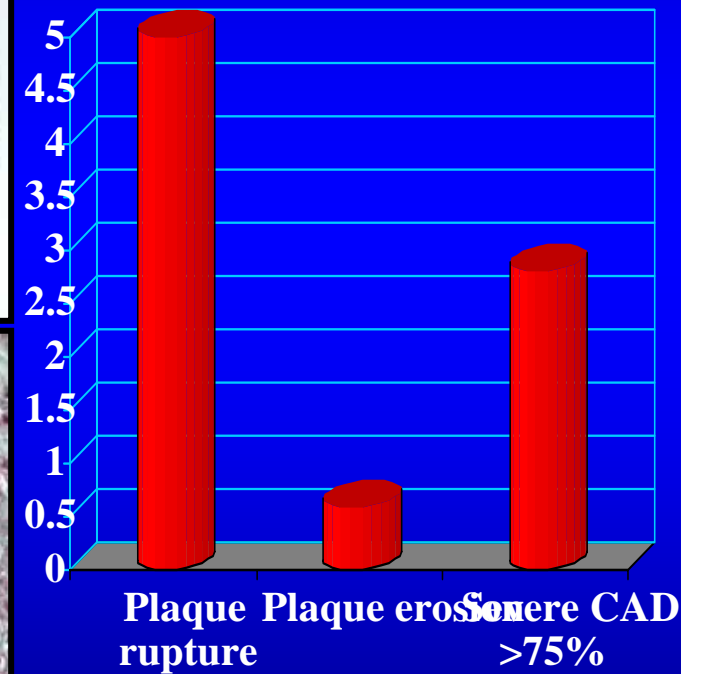
Fig. 3-15

Thin-cap Fibroatheroma

Recent Intraplaque Hemorrhage is seen at Multiple sites in Patients Dying SCD



Plaque Hemorrhage



Intraplaque Hemorrhage and Progression of Coronary Atherosclerosis

- **Conversion of a stable, asymptomatic lesion to an unstable, ruptured plaque involves many processes, the most studied of which is inflammation, cellular breakdown, and expansion of the acellular, lipid rich, necrotic core.**
- **Commonly believed that death of macrophages and SM foam cells, in addition to the aggregation of lipoproteins, contribute to the accumulation of extracellular free cholesterol within unstable plaques.**
- **Contribution of intraplaque hemorrhage to the expansion of necrotic core has not been explored.**

Consequence of Extravasated Erythrocytes Outside the Vasculature

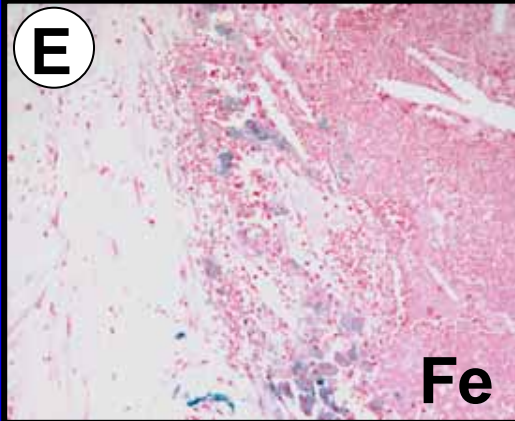
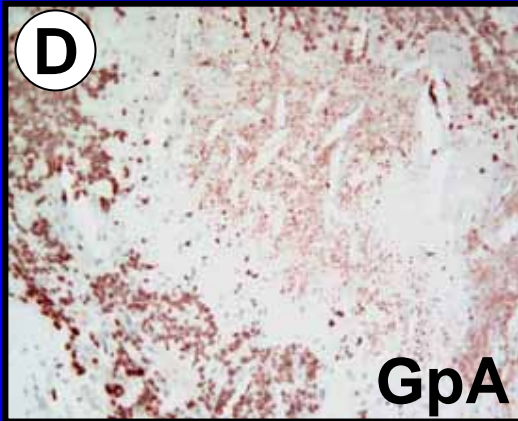
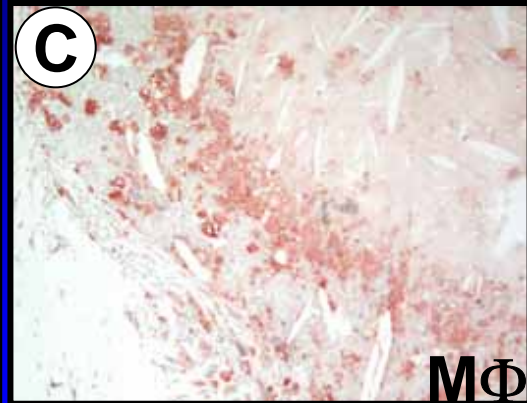
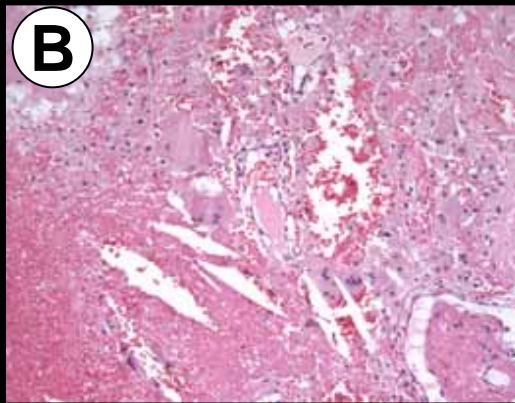
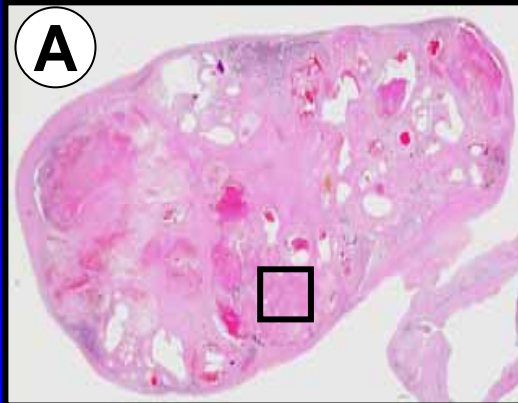
- Free cholesterol content of erythrocyte membrane exceeds that of all other cells in the body, with lipid constituting 40% of the weight
- Yeagle in 1985 showed that extravasated erythrocytes contain free cholesterol and Arbustini et al. in 2002 showed macrophage infiltration in intimal plaques in pulmonary trunk of patients with pulmonary hypertension at sites containing erythrocyte membranes

We examined tissues from nonvascular location to determine the effect of hemorrhage

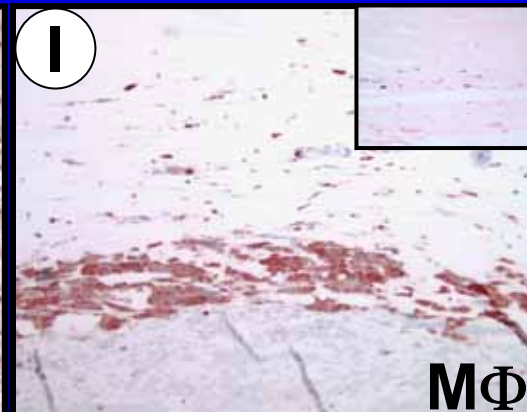
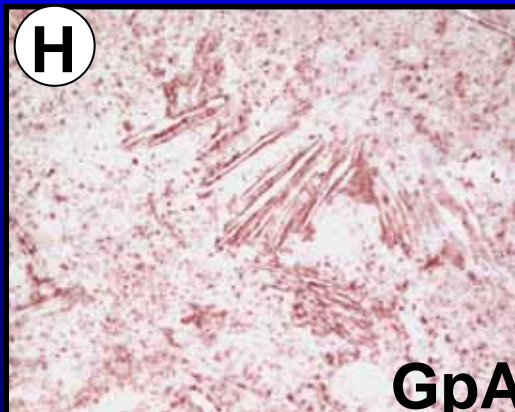
- Pericardial hemorrhage
- Intratumor hemorrhage (atrial hemangiomas, hemorrhagic pericarditis, papillary carcinoma of kidney etc)

Intracardiac Hemangioma (A-F) and Hemorrhagic Pericarditis (G-I)

Intracardiac hemangioma



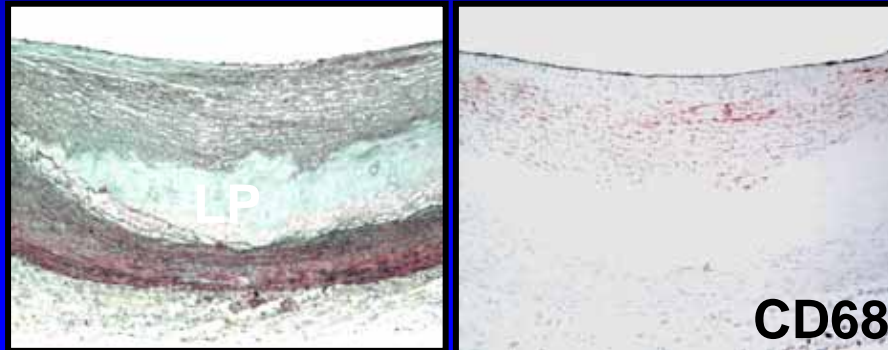
Hemorrhagic pericarditis



Plaque Types Studied

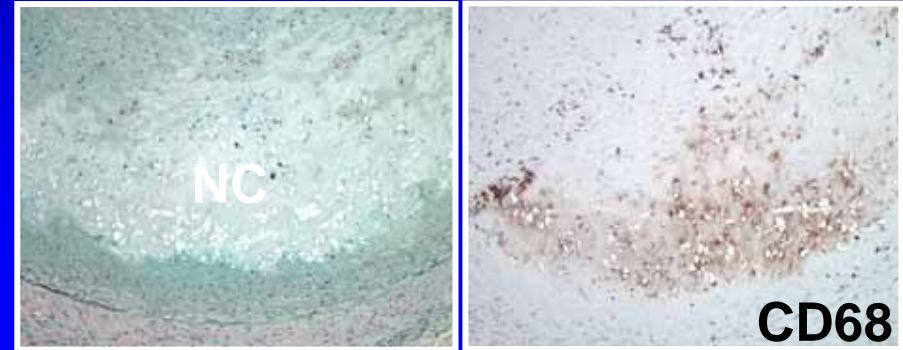
A.

Pathologic Intima Thickening



B.

Fibroatheroma 'Early' Core



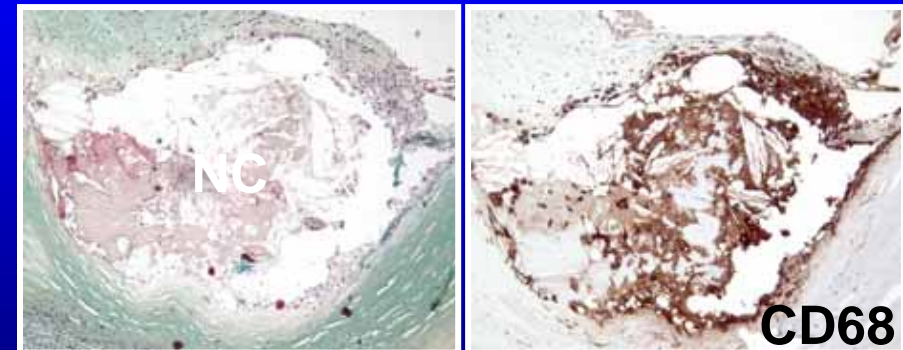
C.

Fibroatheroma 'Late' Core

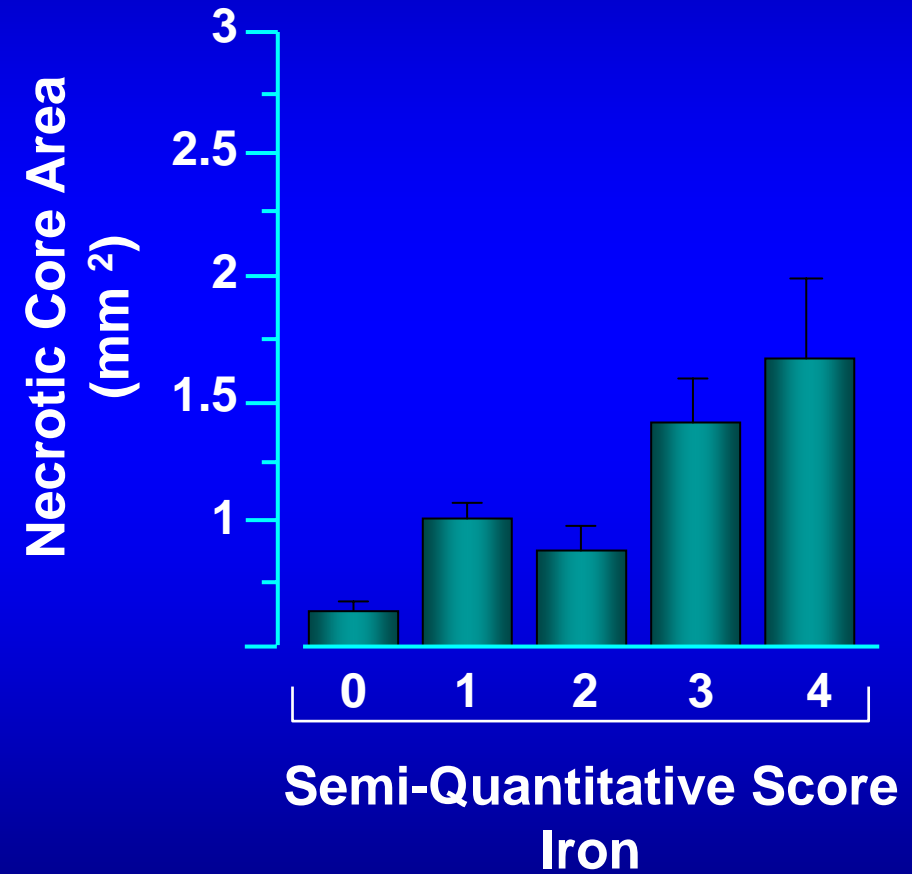
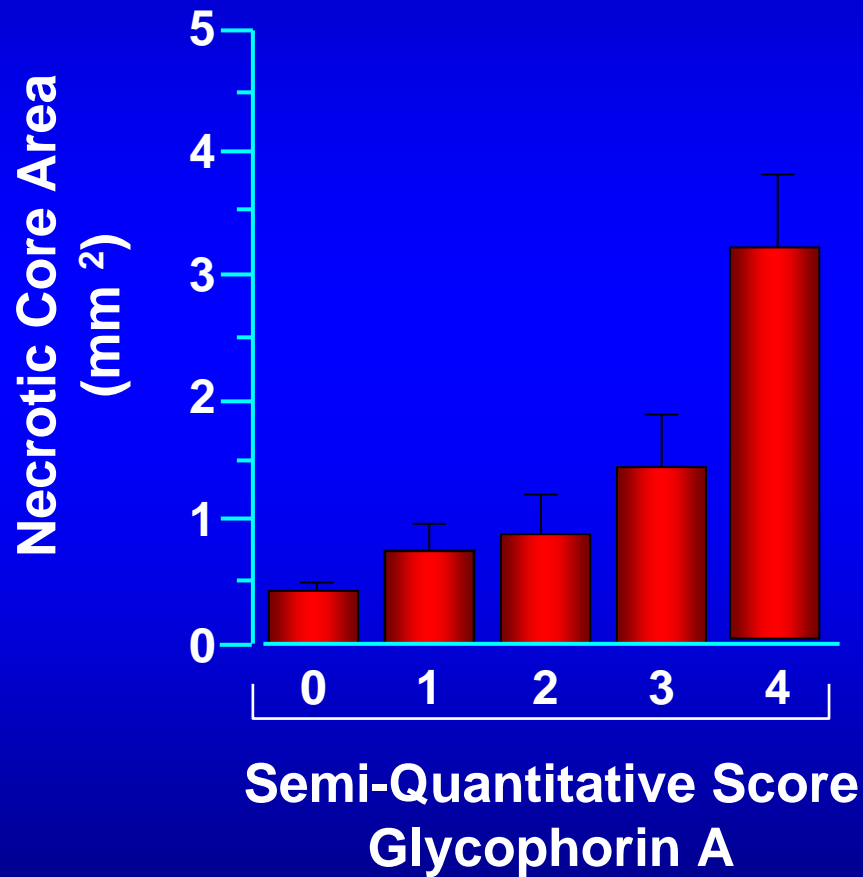


D.

Thin Cap Fibroatheroma



Extent of Glycophorin A and Iron Accumulation Relative to Necrotic Core Size

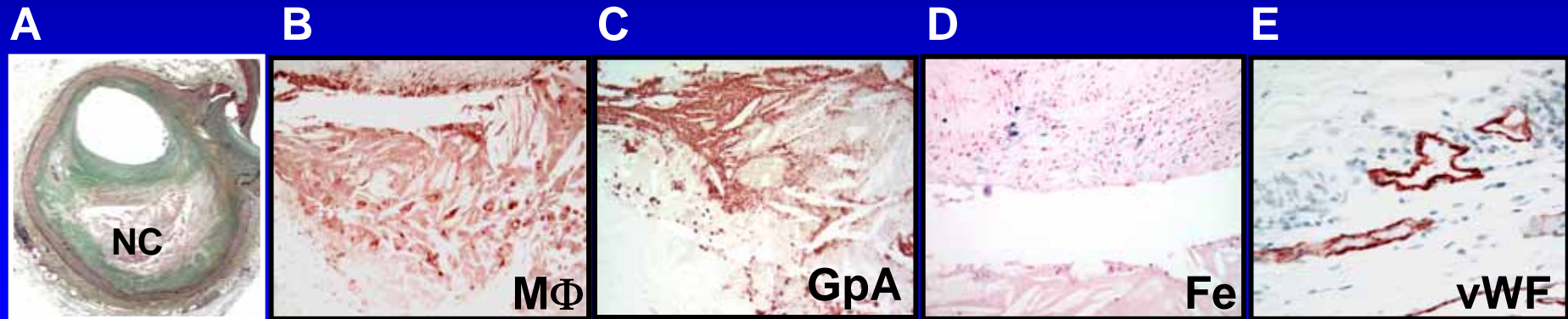


Morphometric Analysis of Hemorrhagic Events in Human Coronary Plaques from Sudden Death Victims

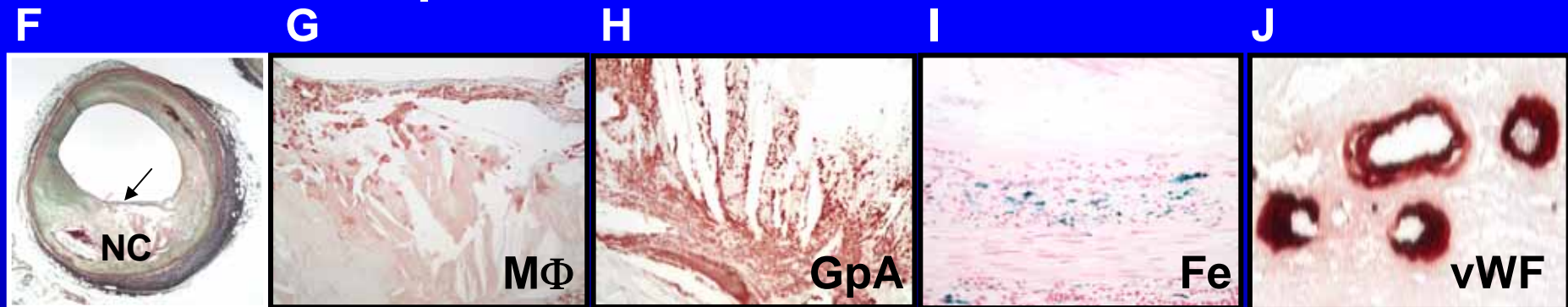
Plaque Type	GpA Score	Iron	Necrotic Core (mm ²)	MΦ (mm ²)
PIT no core (n=129)	0.09±0.04	0.07±0.05	0.0	0.002±0.001
FA early core (n=79)	0.23±0.07	0.17±0.08	0.06±0.02	0.018±0.004
FA late core (n=105)	*0.94±0.11	*0.41±0.09	*0.84±0.08	*0.059±0.007
TCFA (n=52)	*1.60±0.20	*1.24±0.24	*1.95±0.30	*0.142±0.016

Values are reported as the means±SE, *p<0.001 versus early core. The number in parenthesis represent the number of lesions examined;the total number= 365. MΦ = macrophages

Fibrous Cap Atheroma (Late Necrosis)



Thin Fibrous Cap Atheroma



Plaque hemorrhage contributes to enlargement of the necrotic core

- Importance has been shown in human plaques - red cell membrane contributes to free cholesterol and larger necrotic cores.
- Macrophage accumulation is triggered by crystallization of cholesterol from erythrocyte membrane and foreign body reaction as seen in cholesterol granulomas and e.g., receptors on erythrocytes bind a wide array of chemokines, MCP-1; lipid oxidation from senescent RBCs or iron-catalyzed reactions may liberate potent chemoattractants

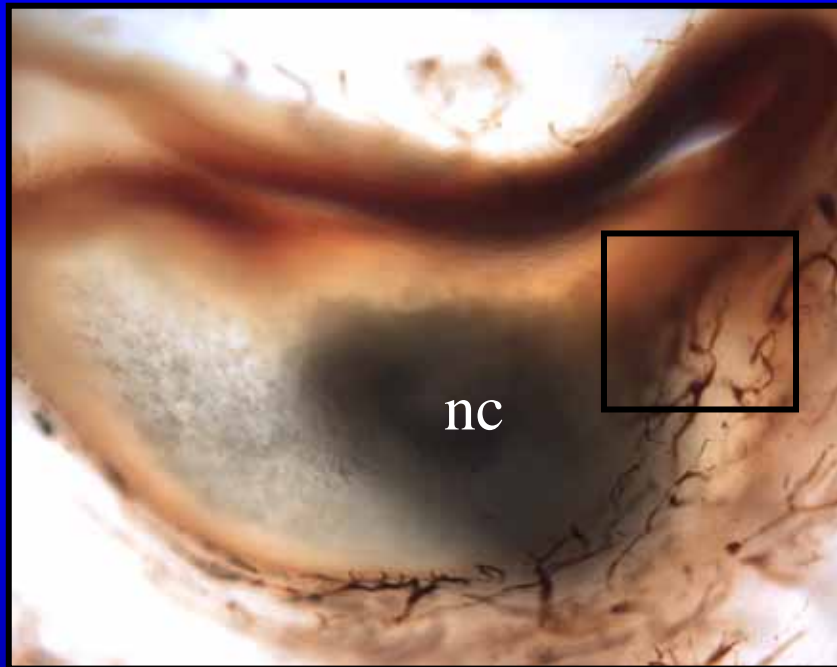
Plaque Vasa Vasorum

- **Plaque capillaries are observed in atherosclerotic plaques with plaque thickness > 0.5 mm, suggesting that wall ischemia may be a determinant of neovascularization.**
- **Heistead and Armstrong reported a 5 fold increase in intimal/medial blood flow from proliferating micro vessels in monkeys fed a high cholesterol diet for 17 months. (Atherosclerosis 1986)**
- **Plaque Vv may be a potential source of inflammation within the plaque [expression of VCAM-1, ICAM-1 and E-selectin has been shown in plaque Vv (O'Brian, et al. AJP 1994).**
- **Inflammation and matrix composition of atherosclerotic plaques may also influence angiogenesis.**

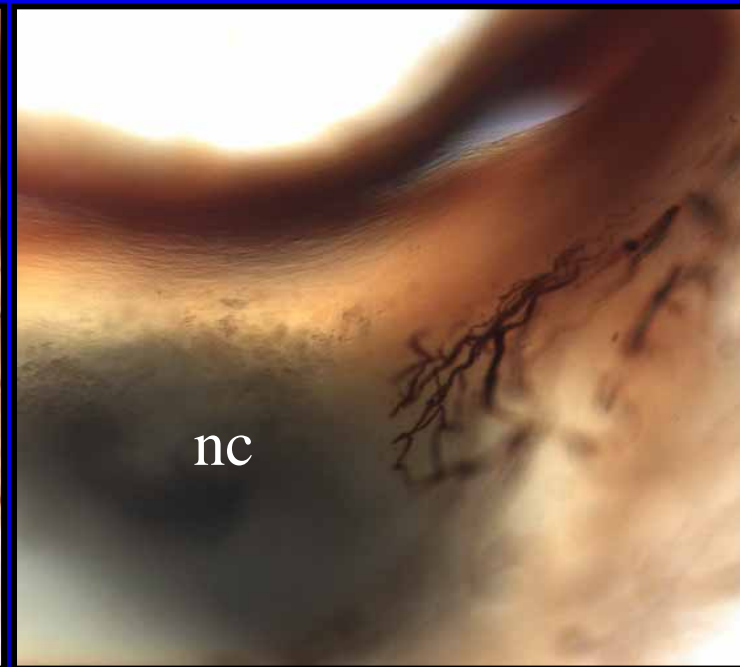
Intraplaque Vasa Vasorum in Coronary Plaques with a Necrotic Core

150 μ m thick sections stained with Ulex

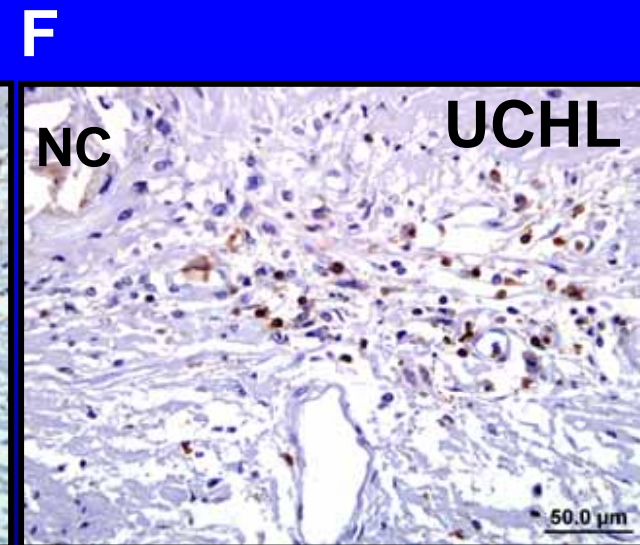
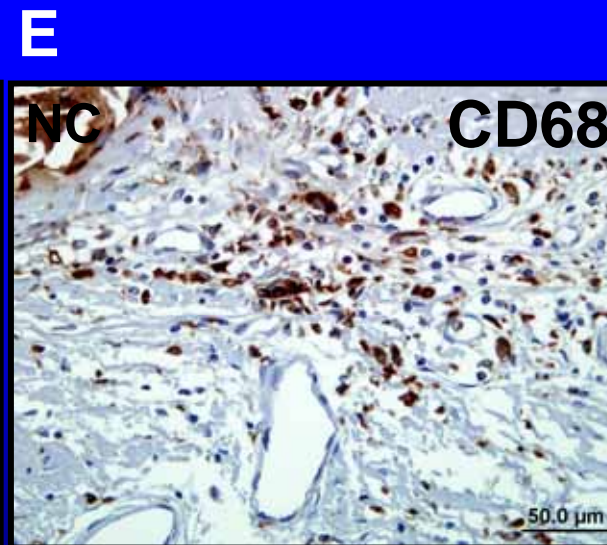
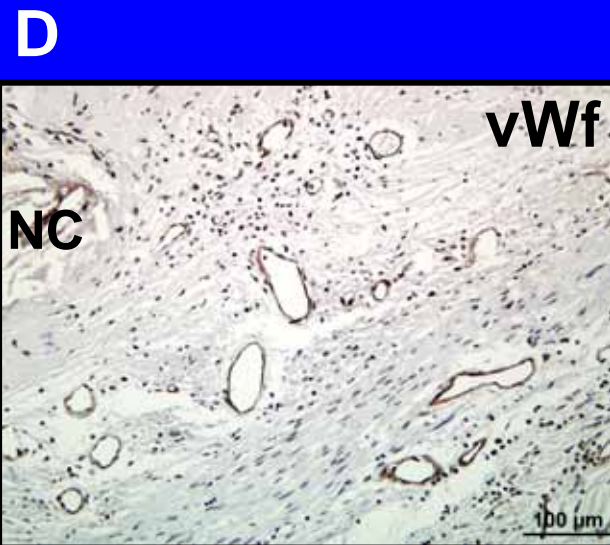
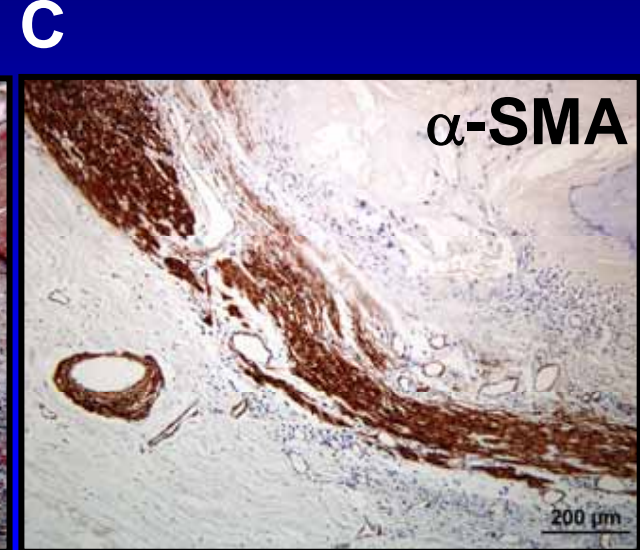
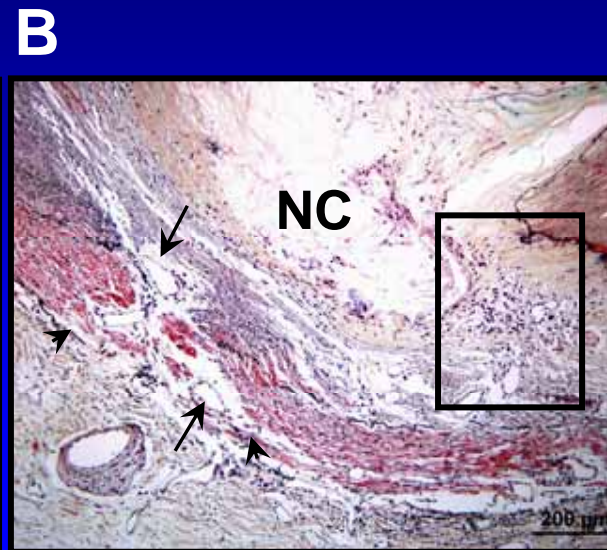
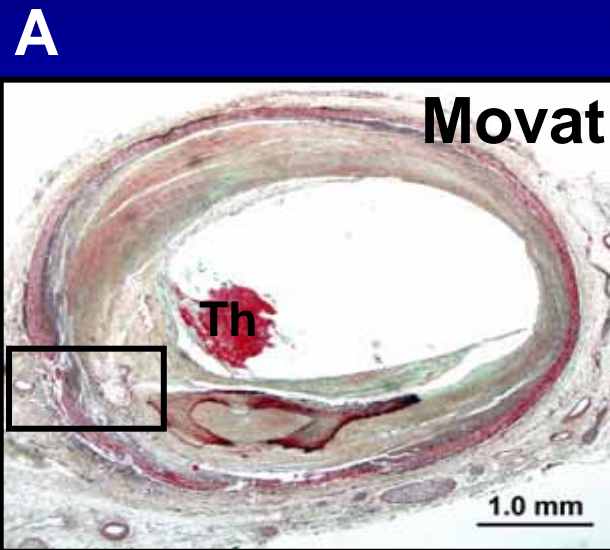
A



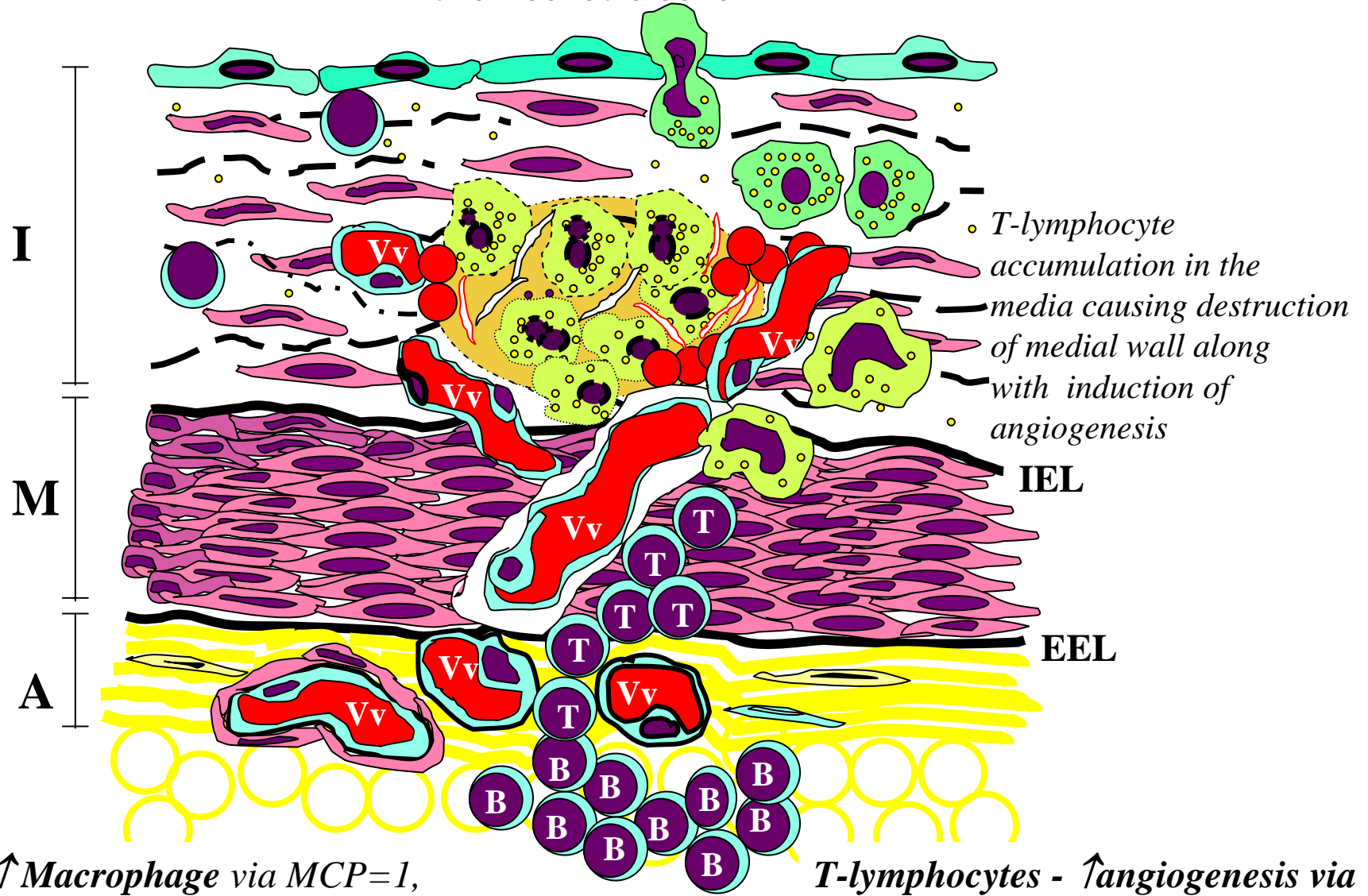
B



Vasa Vasorum in Plaque Rupture



Mechanism of coordinated angiogenesis and inflammation in the progressive enlargement of the necrotic core



↑ Macrophage via MCP=1, M-CSF within plaque - ↑ VEGF = ↑ angiogenesis

T-lymphocytes - ↑ angiogenesis via Toll-like receptors (TLR) 2 and 4 CD40/CD40L

Erosion, and Intraplaque Hemorrhage: The other face of vulnerability

Conclusions:

- The dominant cause of coronary thrombosis is plaque rupture (commoner in men), followed by erosion (more common in women).
- Erosion lesions are rich in smooth muscle cells with paucity of macrophages, and majority do not have an underlying necrotic core. Usually seen in younger individuals and in females who often present with atypical chest pain
- Total cholesterol and HDL are not associated with erosion
- Underlying base of the thrombus is rich in proteoglycans and hyaluronan. It is conceivable that plaque erosion has a different etiology possibly secondary to vasospasm of the arterial wall rather than atherosclerotic.

Erosion, and Intraplaque Hemorrhage: The other face of vulnerability

Conclusions:

- Intraplaque hemorrhage is commonly seen in coronary arteries of patients dying with plaque rupture
- Red cell membranes contribute to enlargement of the necrotic core (lipid core expansion) and ↑ in macrophage content
- Angiogenesis of atherosclerotic plaques contribute to plaque hemorrhages
- Angiogenesis of the intima occurs at sites of medial destruction where T-lymphocytes accumulate
- Understanding the relationship of angiogenesis, inflammation and plaque progression are key to understanding atherosclerosis and its progression.

Acknowledgments

- Allen Burke, M.D.
- Frank Kolodgie, Ph.D.
- Andrew Farb, M.D.
- Elena Ladich, M.D.
- Robert Kutz, M.S.
- You-hui Liang, M.D.
- Hedwig Avallone
- Lila Adams

