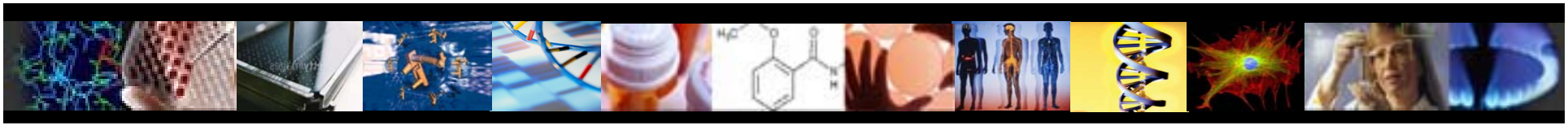
Demystifying Medicine
Part II

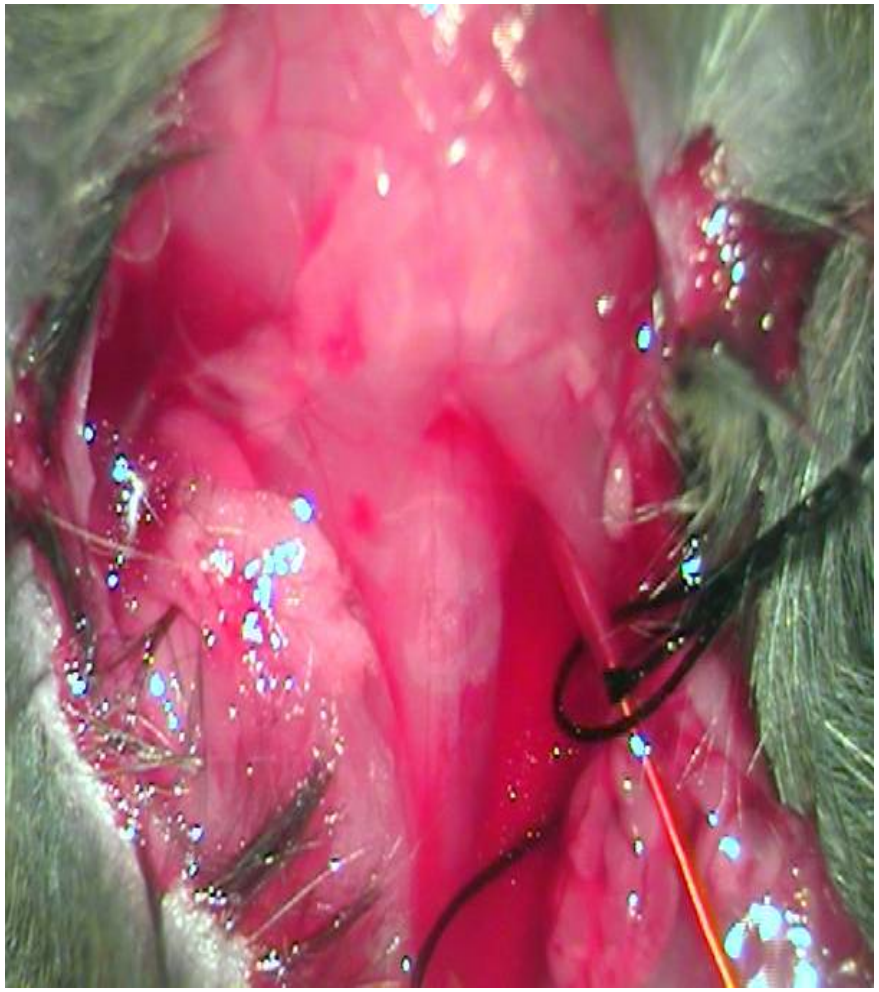
Genetics, Aging, and Heart Disease



Elizabeth G. Nabel, M.D.
Director
National Heart, Lung, and Blood Institute
National Institutes of Health

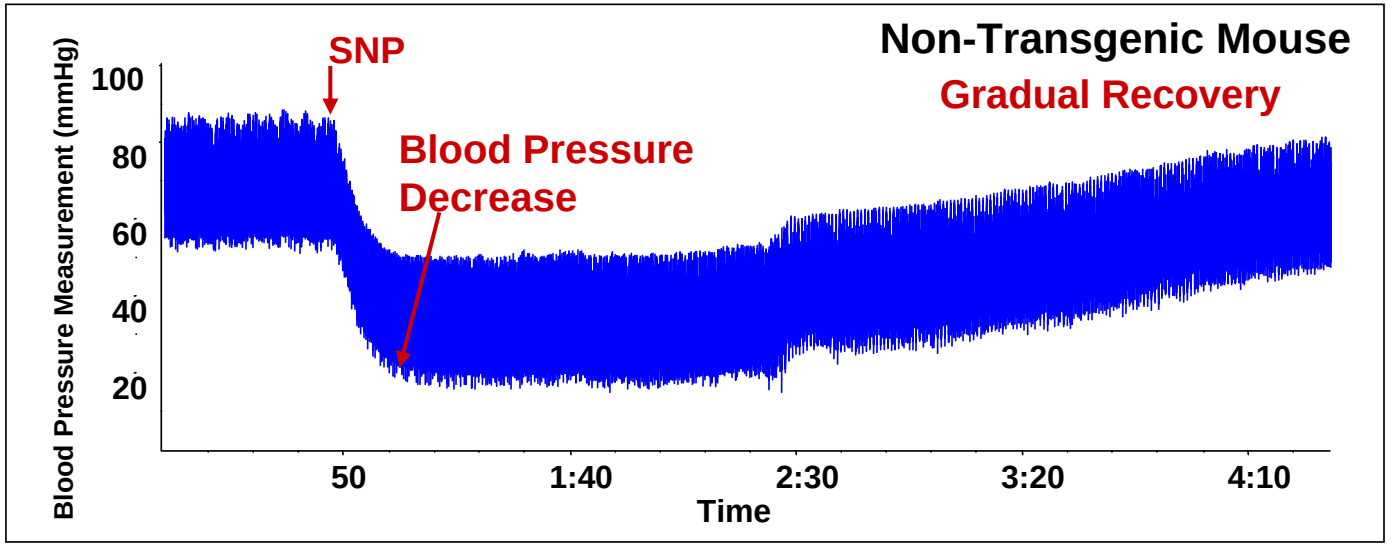
April 11, 2006

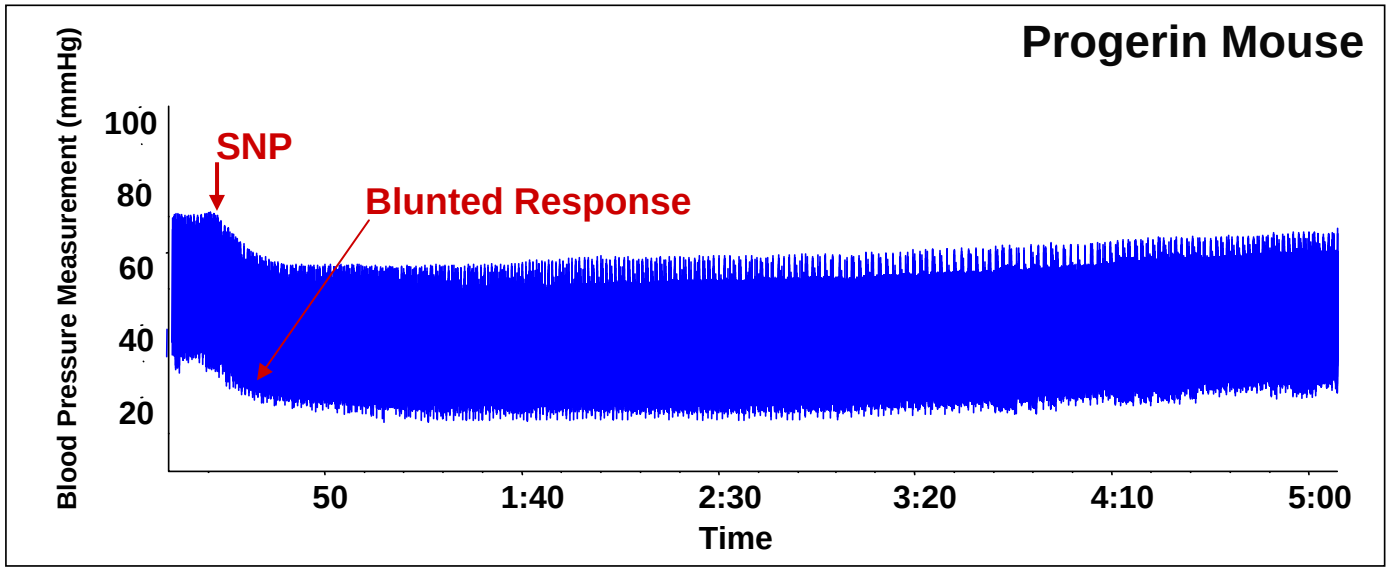
Blood Pressure Measurements



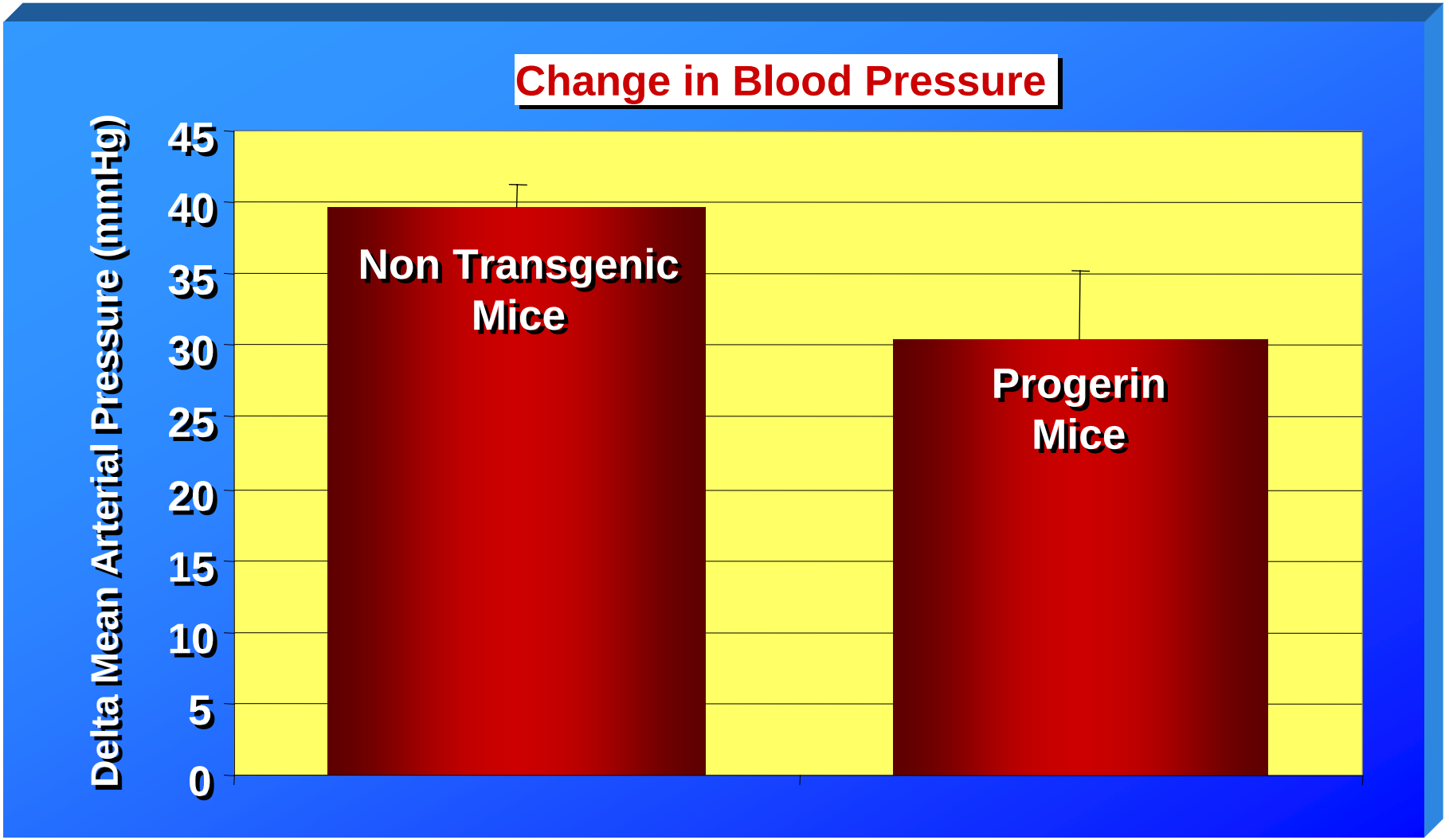
- **1 - 3% Isoflurane anesthesia**
- **Cannulation of the right carotid artery with a Millar conductance catheter**
- **2 infusions of 0.9% saline or sodium nitroprusside 0.1 mg/kg into the left jugular vein**
- **Continuous measurements of blood pressure over two hours using ARIA single-Segment Pressure-Volume Conductance System**

Impaired Maintenance of Blood Pressure upon Infusion of Sodium Nitroprusside (SNP) in Progerin Mice

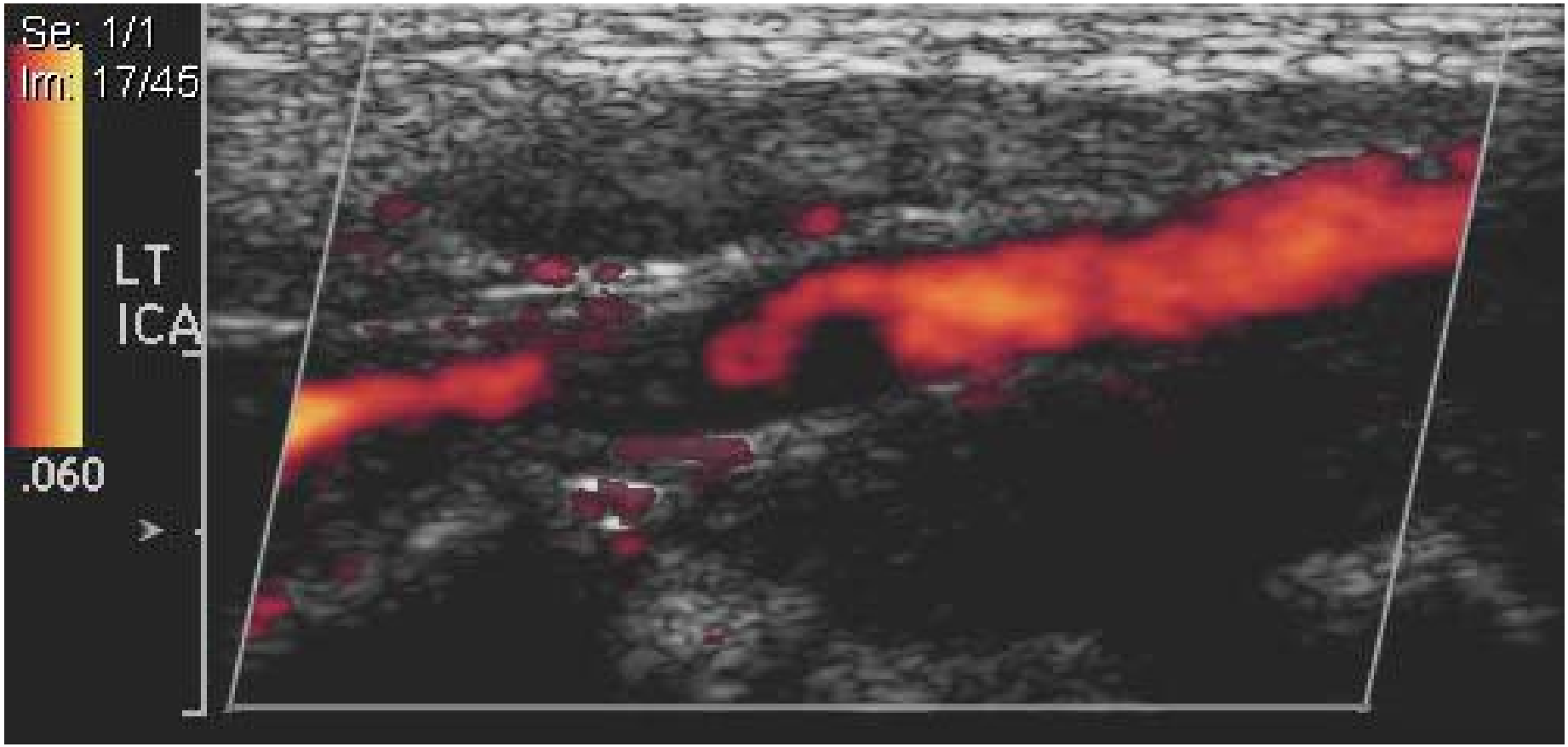




Blunting of Blood Pressure Response in Progerin Mice



Complete Occlusion of the Left Common Carotid Artery in a 9 year old child with HGPS



Vascular Remodeling in HGPS

VOLUME 8 No. 1 JAN/FEB 1999

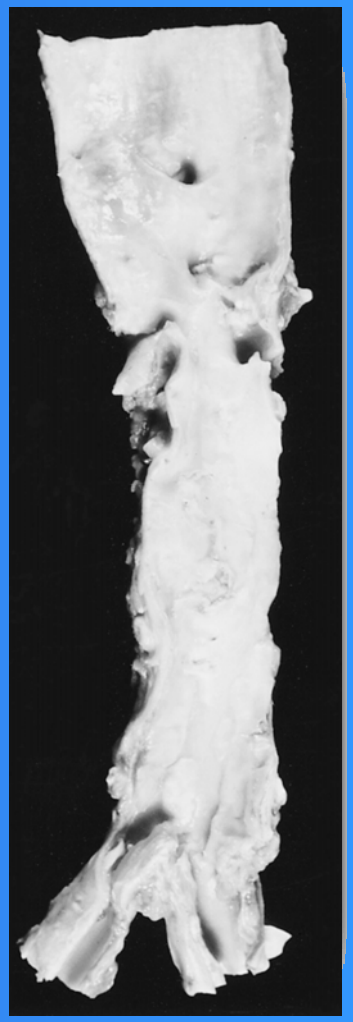
Cardiovascular Pathology

Histological and Ultrastructural Features of Atherosclerosis in Progeria

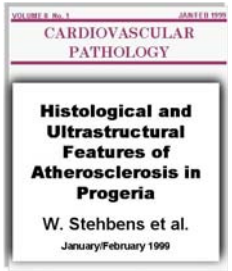
W. Stehbens et al.

January/February 1999

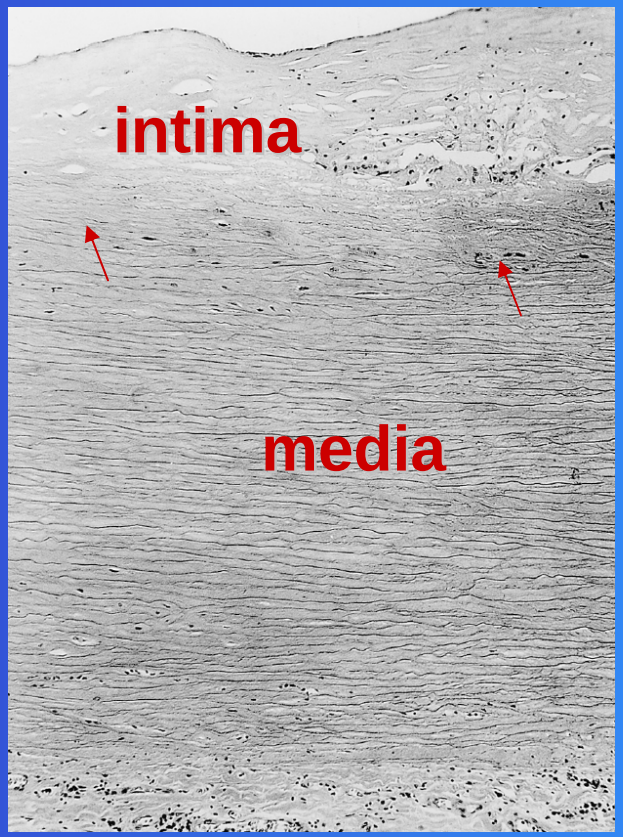
Vol. 8 No. 1

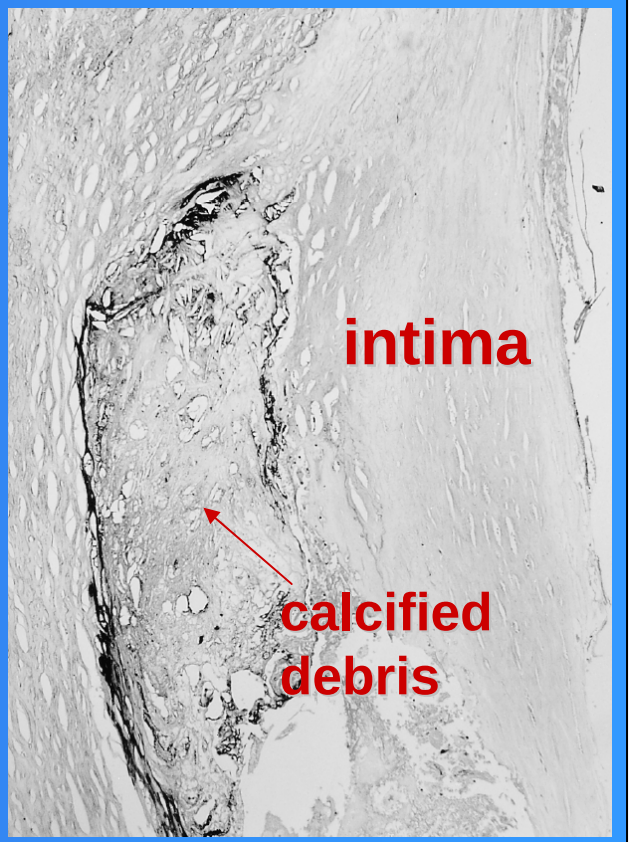


Histological Features of Vascular Remodeling in HGPS



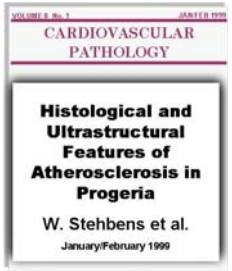
Atherosclerotic aortic showing relative acellularity of intima and media with round cell infiltration, partially calcified caseous debris and loose superficial dissection of intimal tissue with thrombus.



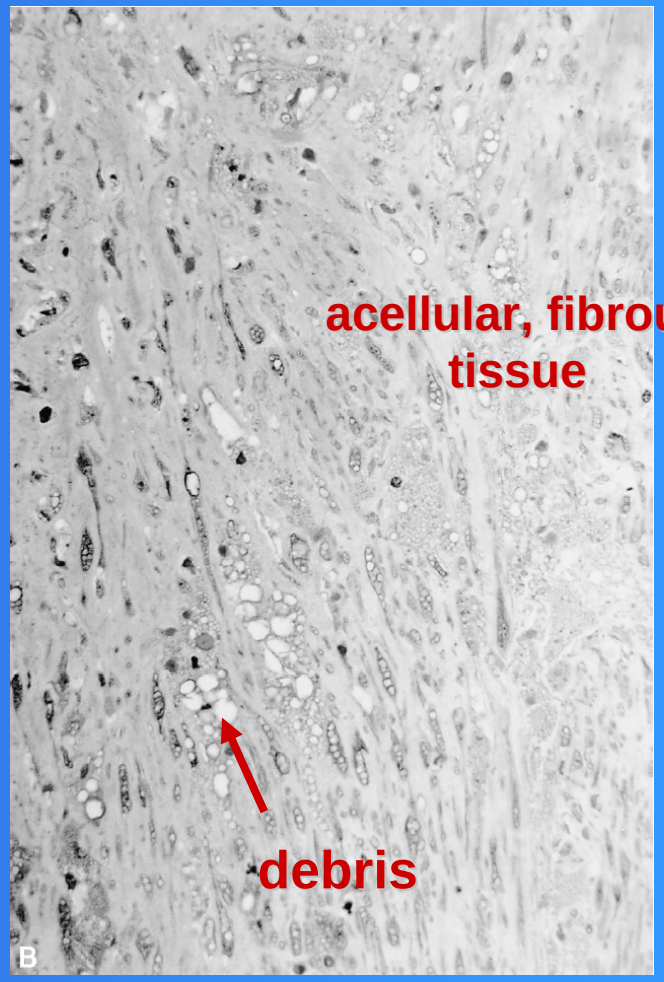


Stehbens et al, *CardiovascPathol* 1999;8:29-39

Loss of vascular smooth muscle cells and replacement by fibrosis

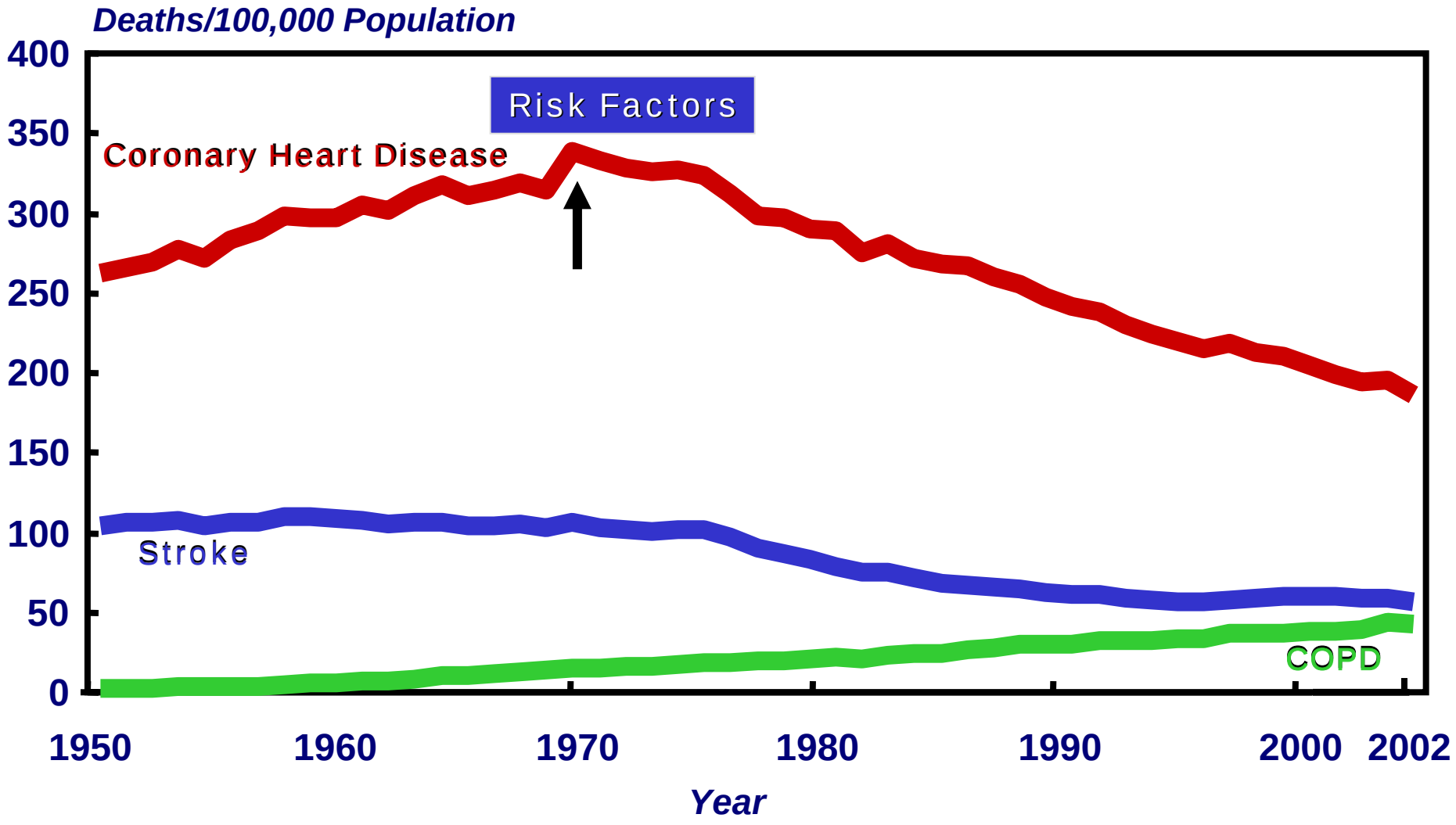


Atherosclerotic aortic intima exhibiting fibrotic tissue overlying caseous debris deep in intima.



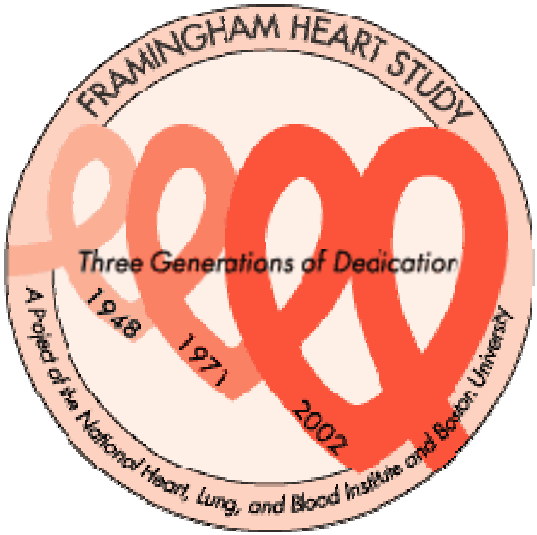
Stehbens et al, *CardiovascPathol* 1999;8:29-39

Age-Adjusted Death Rates for Coronary Heart Disease, U.S., 1950-2002

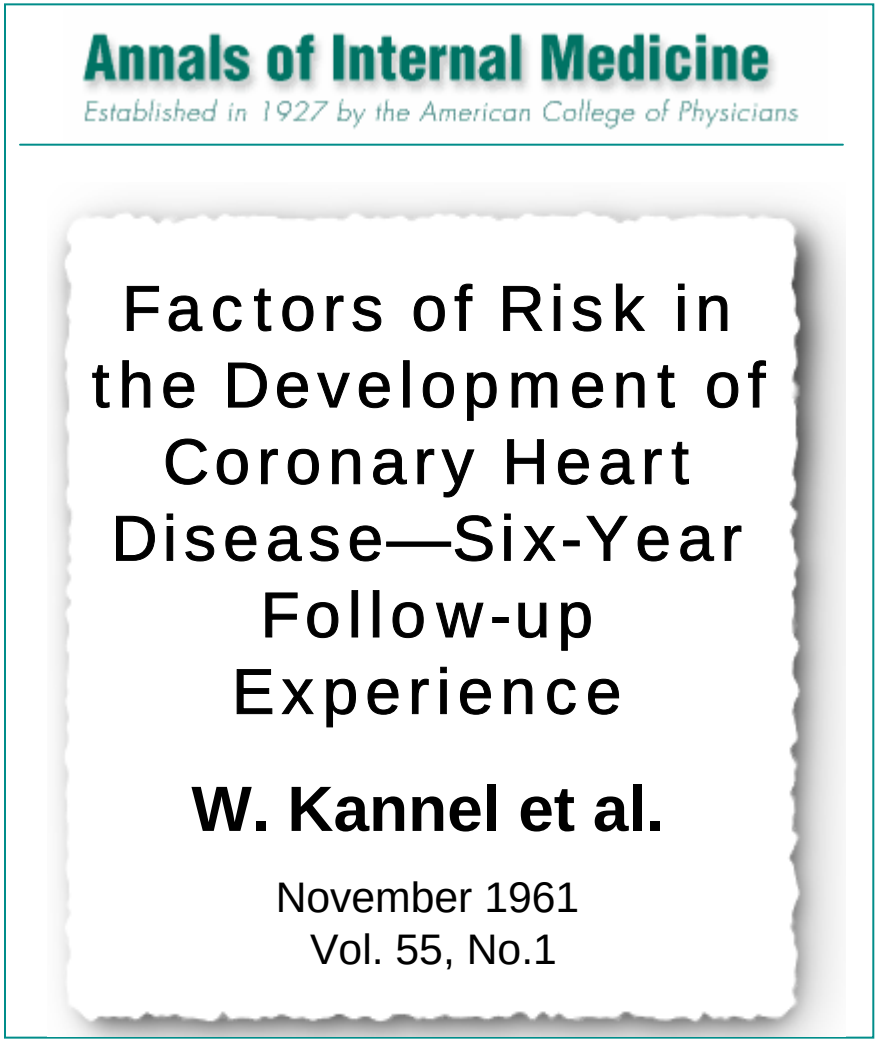


Framingham Heart Study

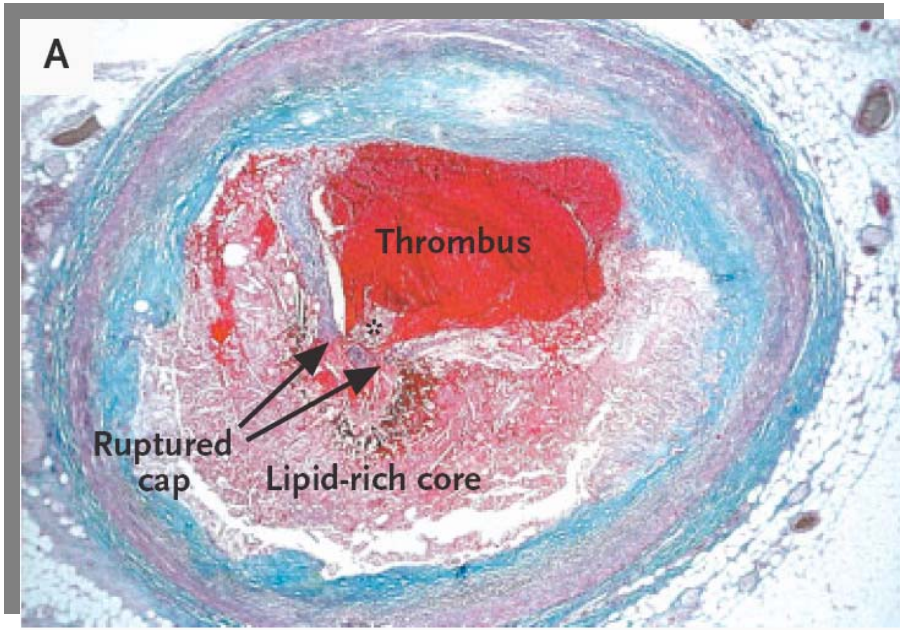
Downtown Framingham, MA (circa 1960)

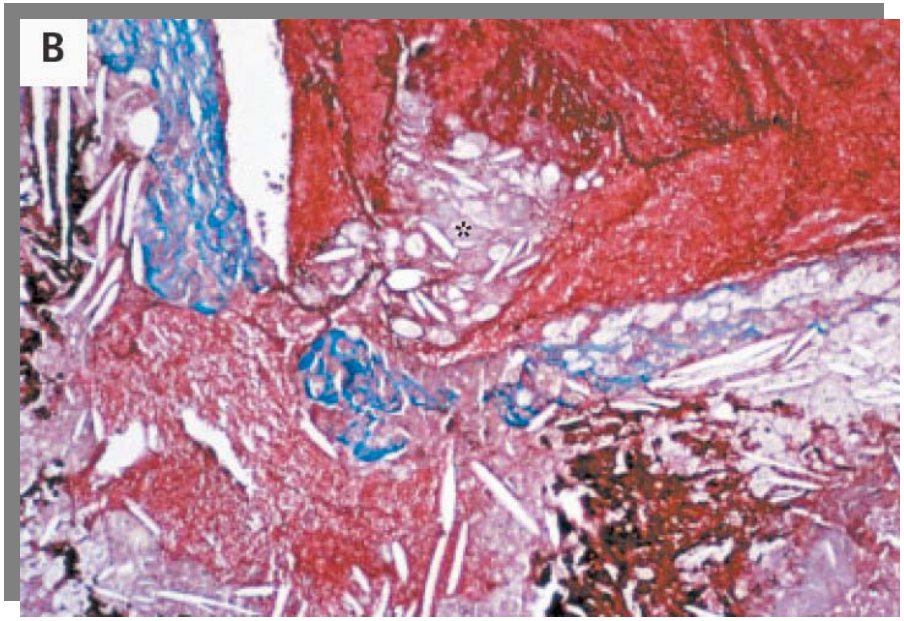


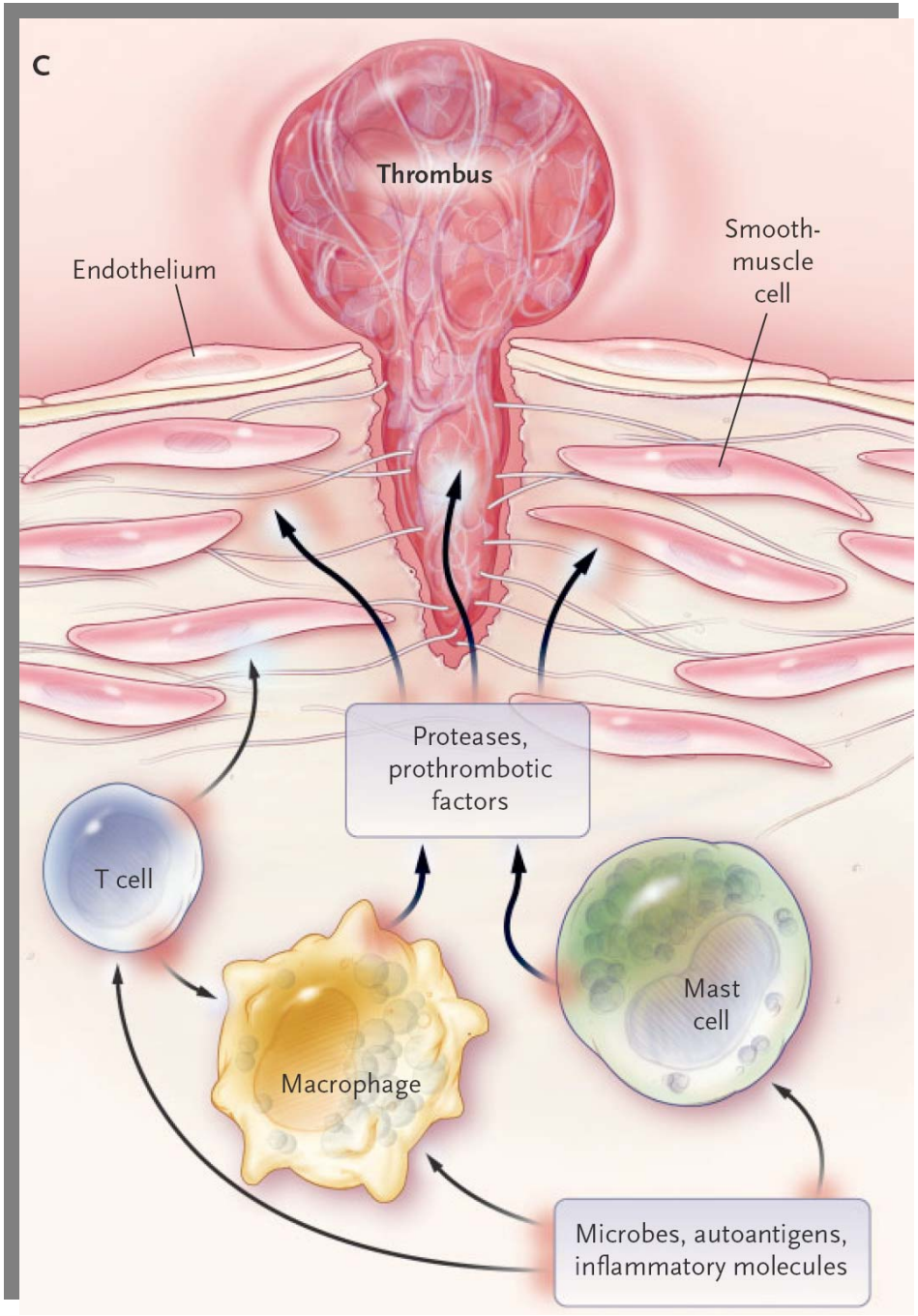
“Factors of Risk” for CVD



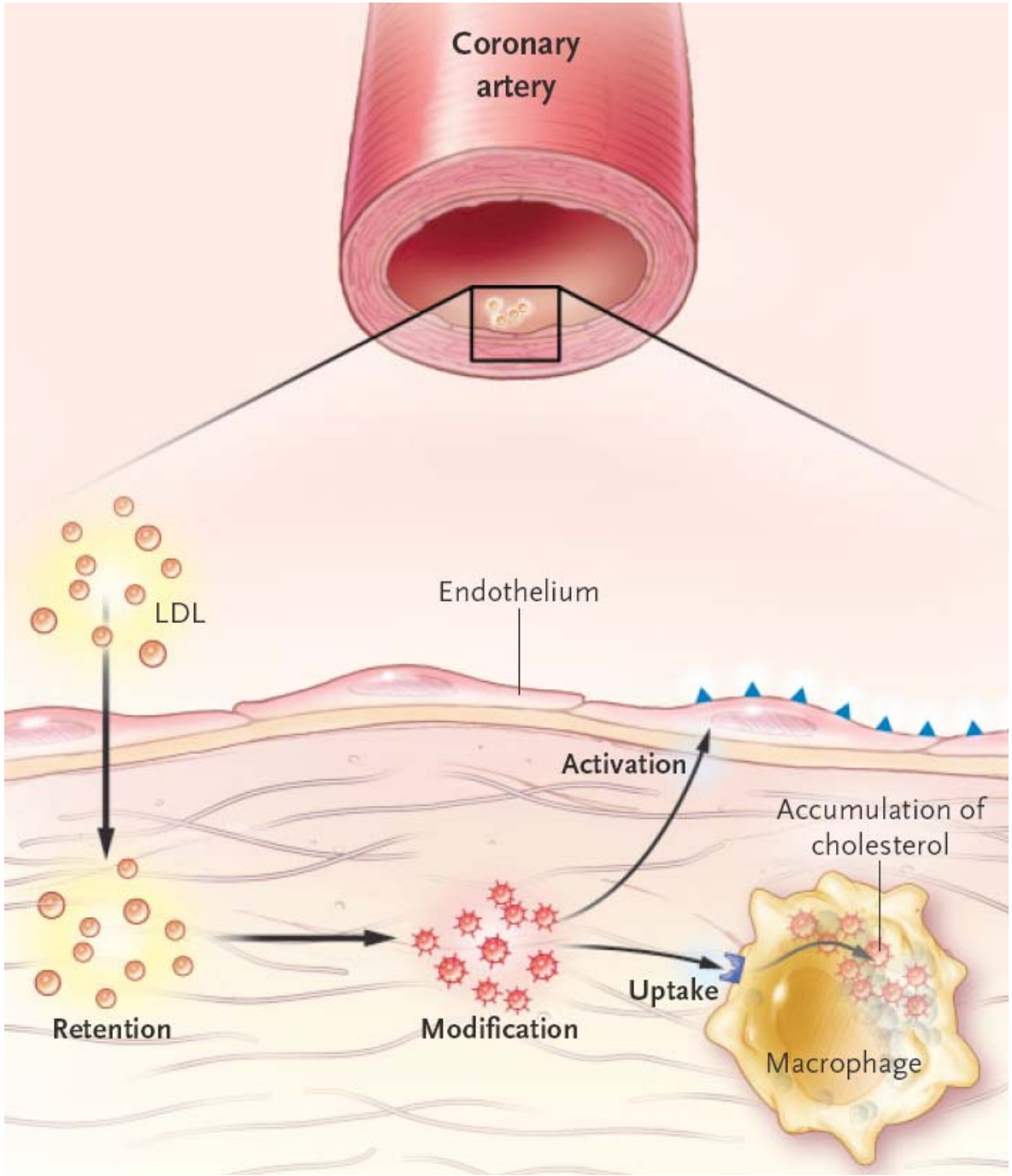
- **High Blood Pressure**
- **Increased Cholesterol**
- **Smoking**
- **Diabetes**
- **Family History**
- **Male Gender**



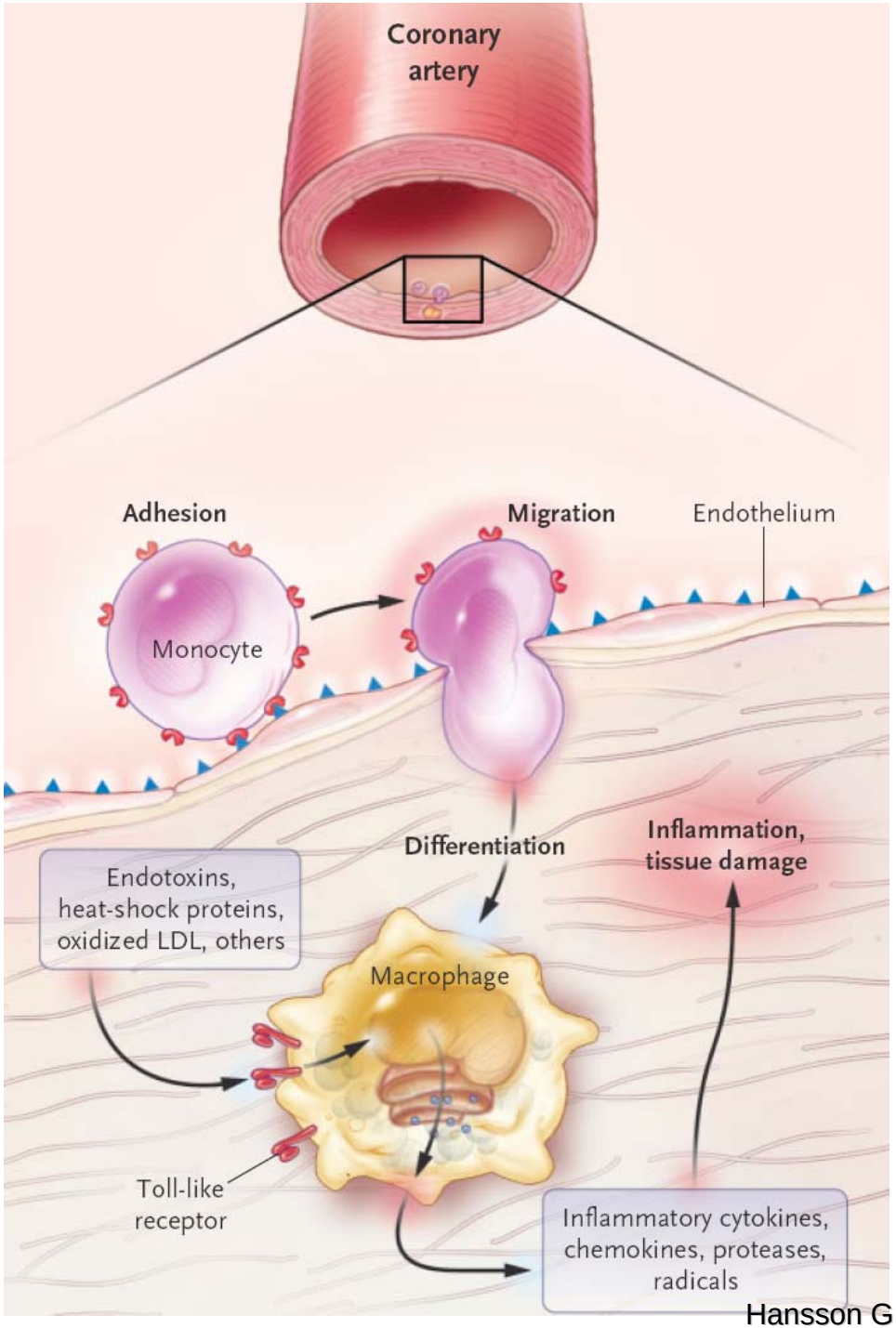




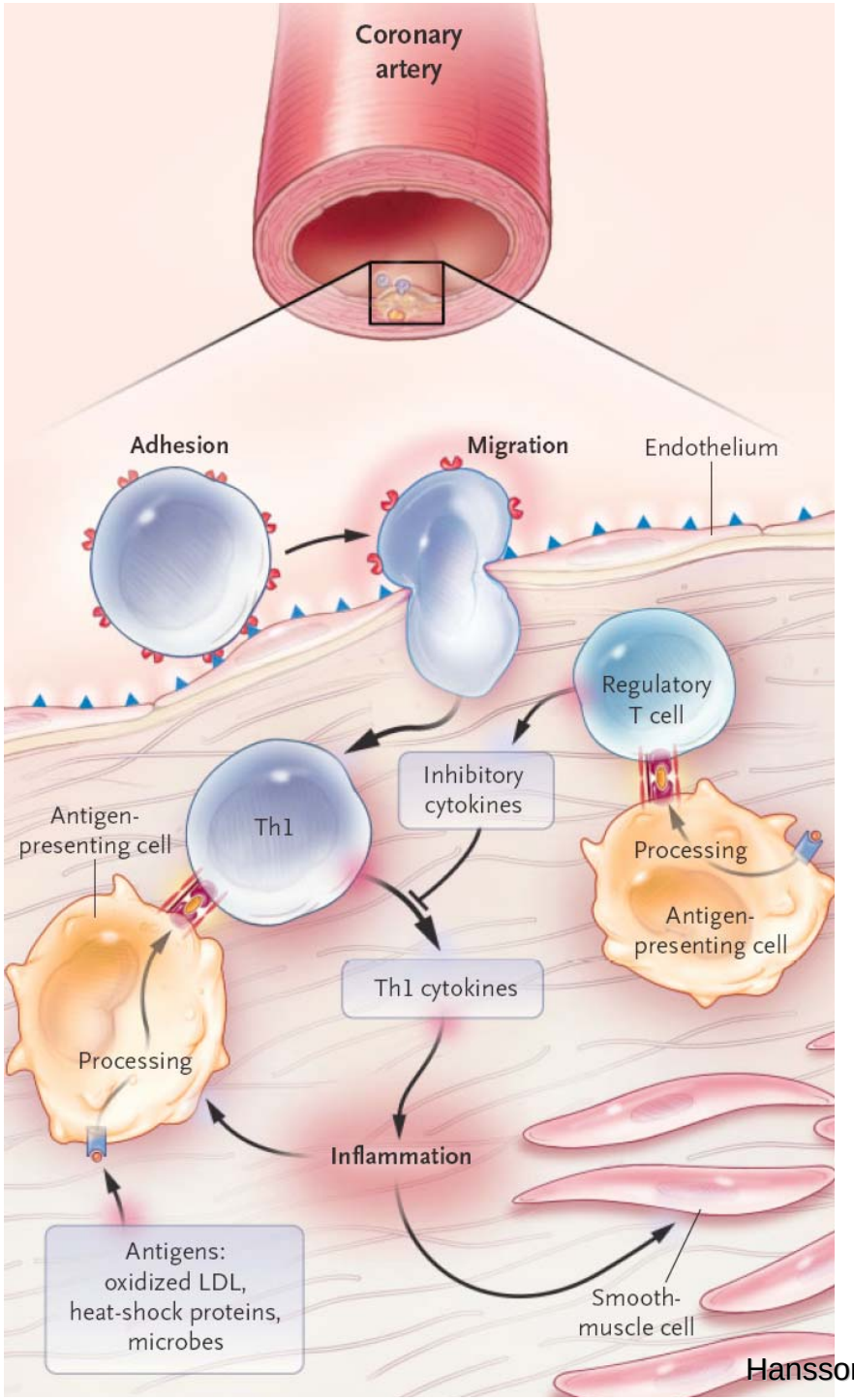
Hansson G., *N Engl J Med* 2005;352:1685



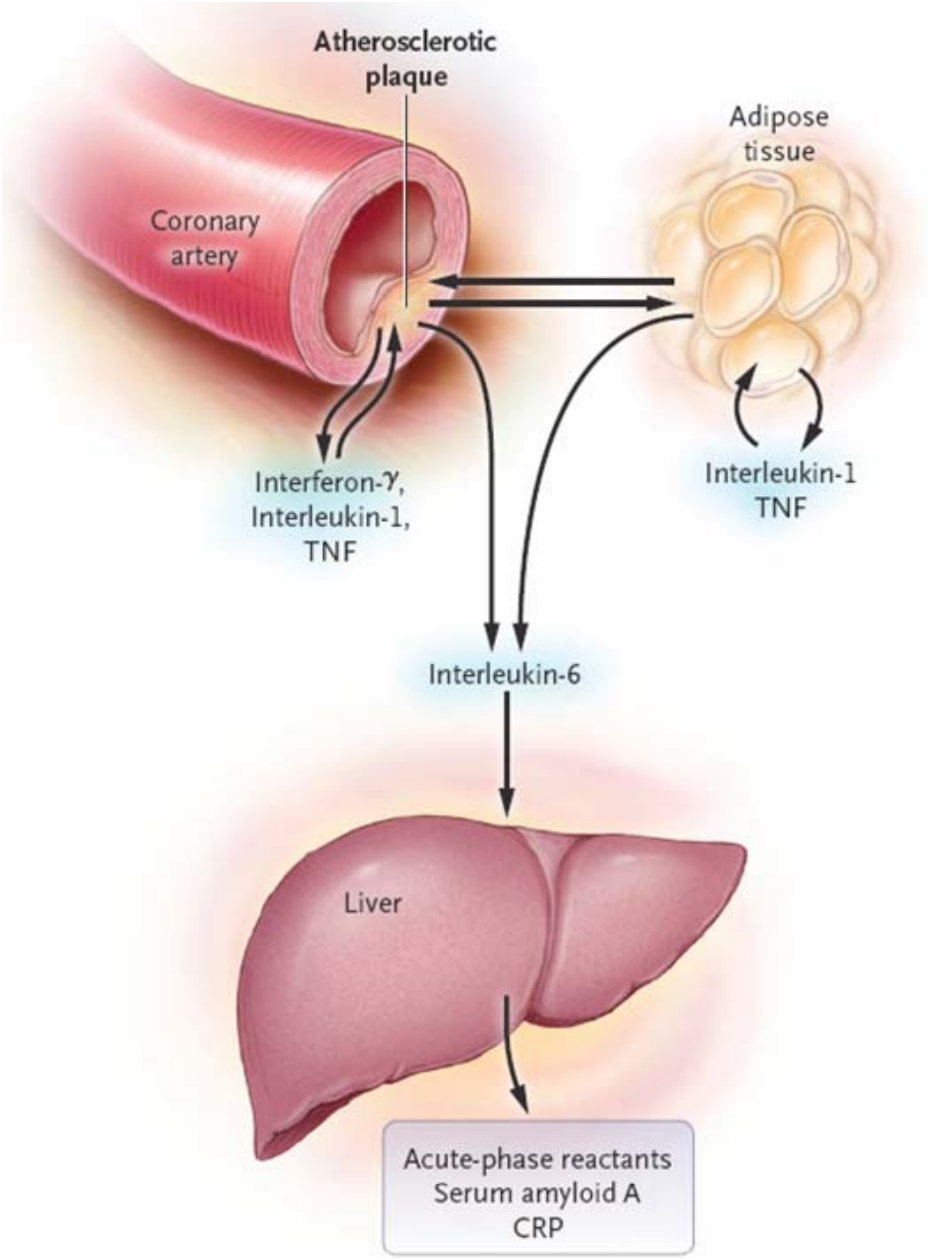
Hansson G., *N Engl J Med* 2005;352:1685



Hansson G., *N Engl J Med* 2005;352:1685

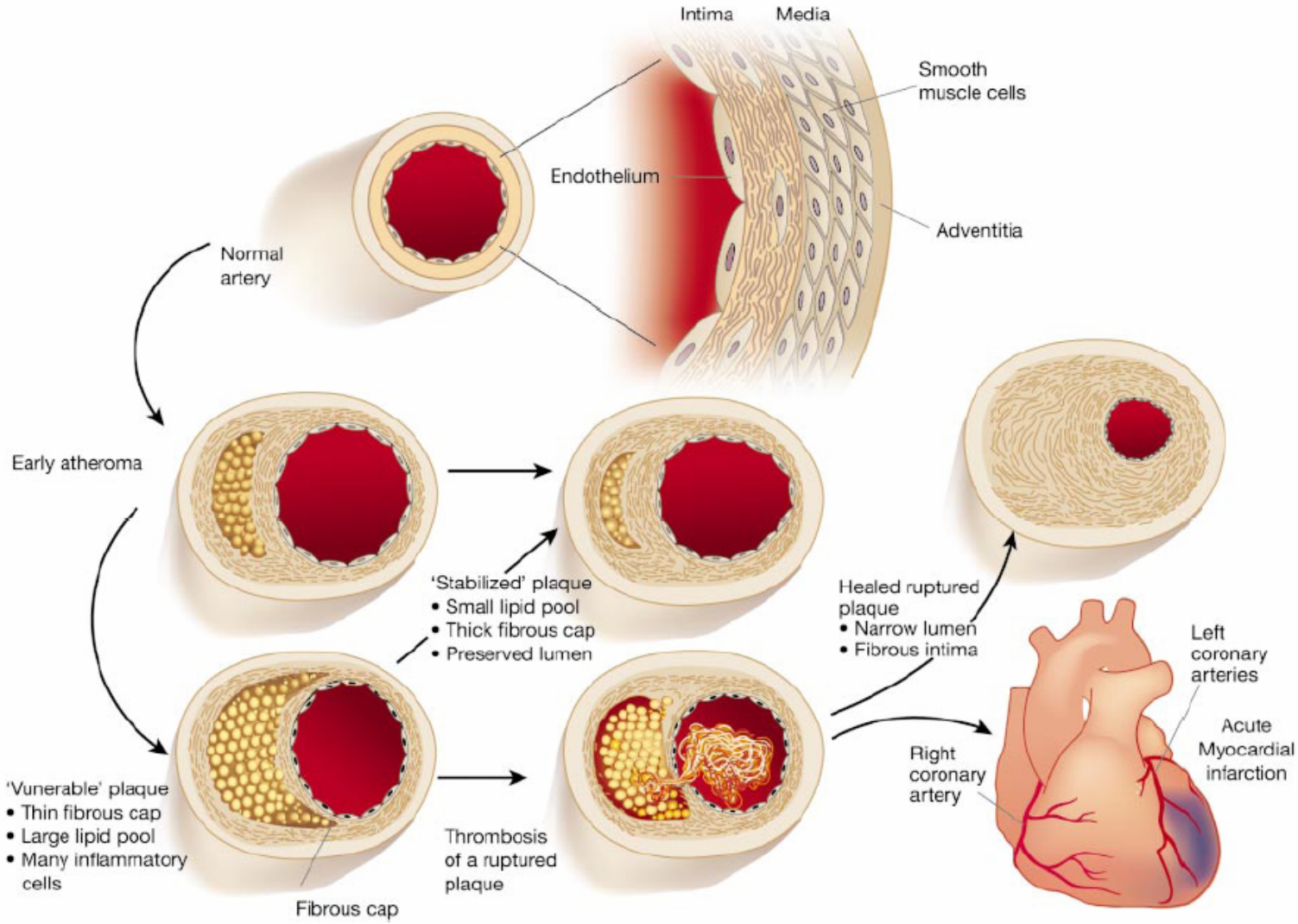


Hansson G., *N Engl J Med* 2005;352:1685



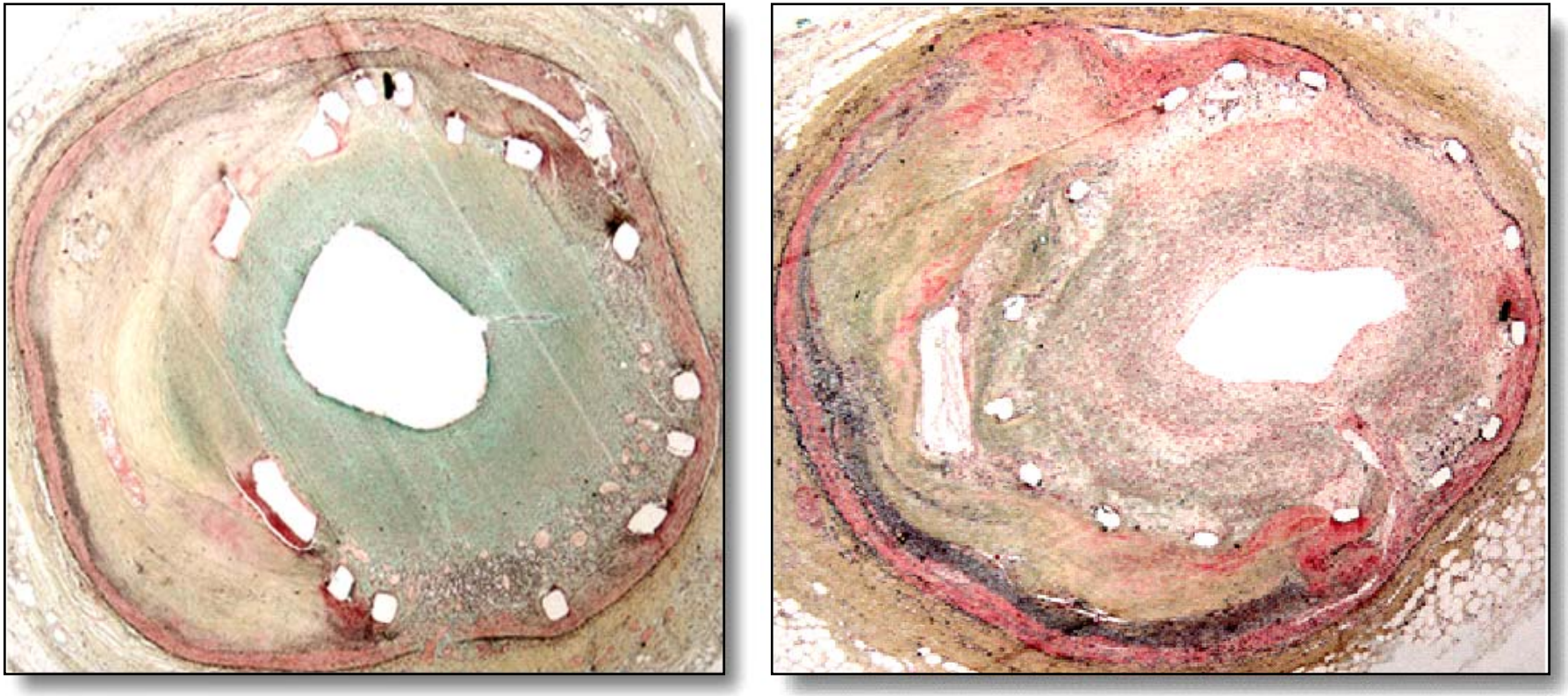
Hansson G., *N Engl J Med* 2005;352:1685

Schematic of the Life History of an Atheroma



Libby et al., *Nature* 2002;420:868-74

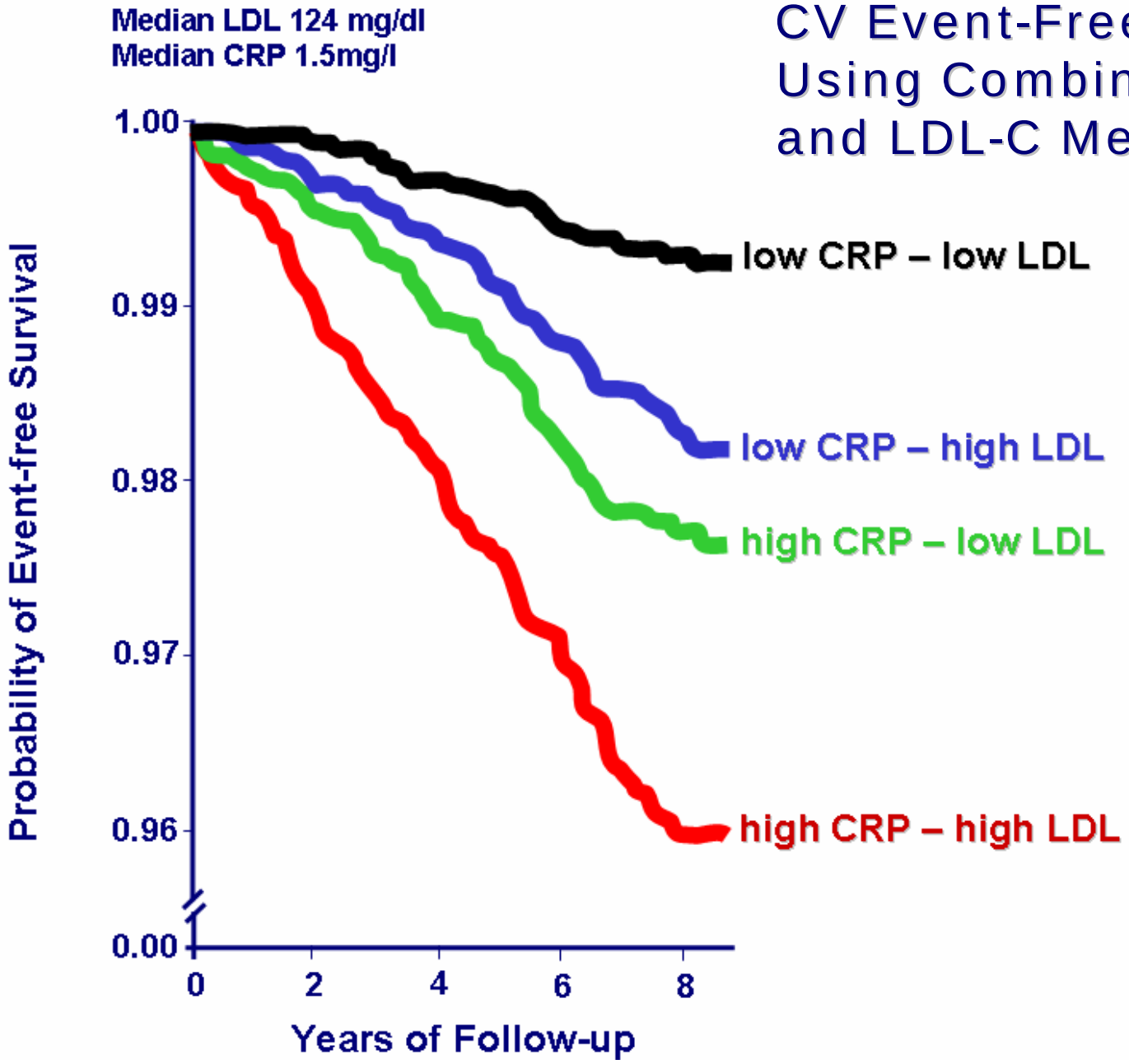
Atherosclerosis in Human Coronary Arteries



Farb et al., *Circulation* 2002;105:2974

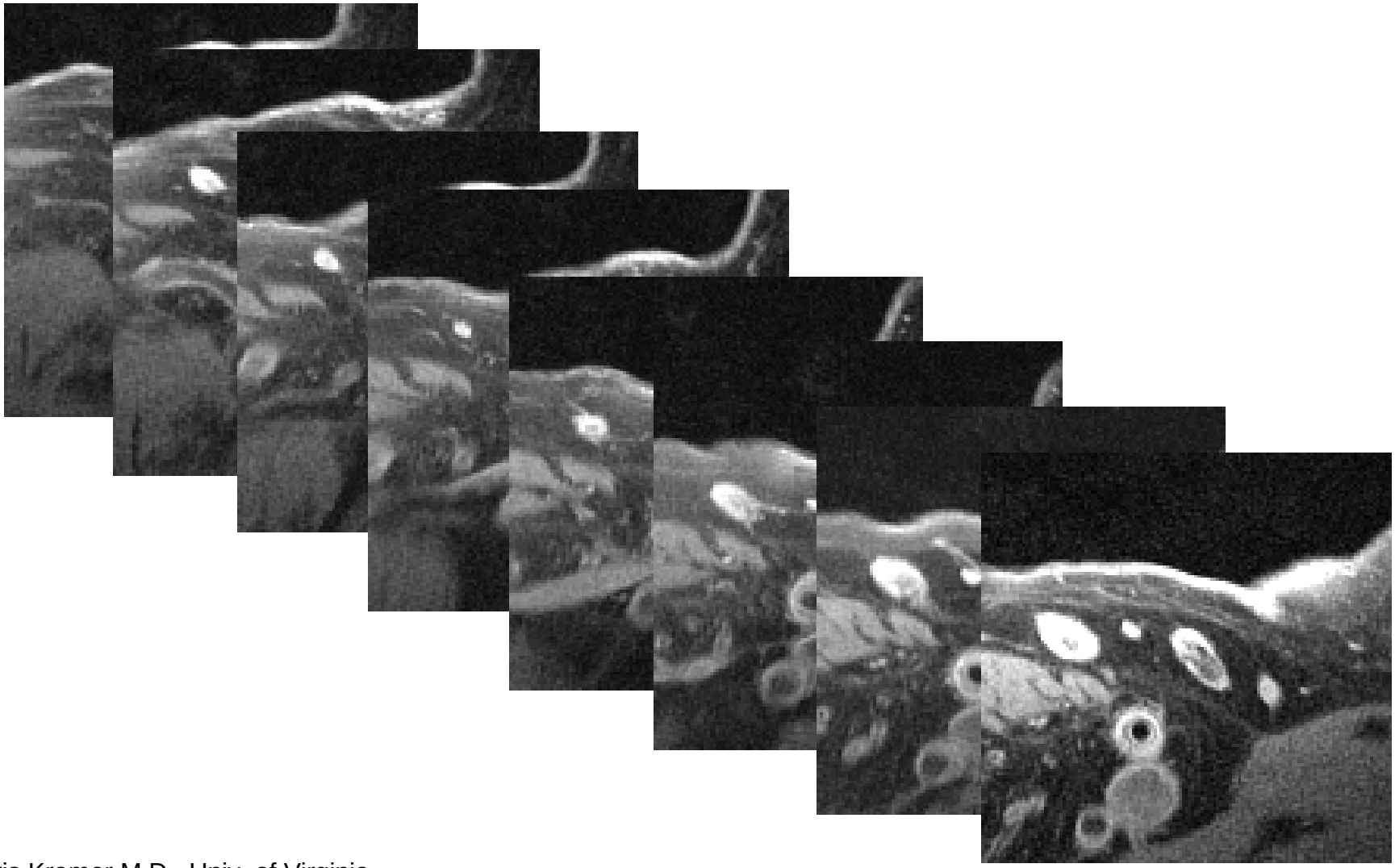
Atherosclerosis

CV Event-Free Survival Using Combined hsCRP and LDL-C Measurements



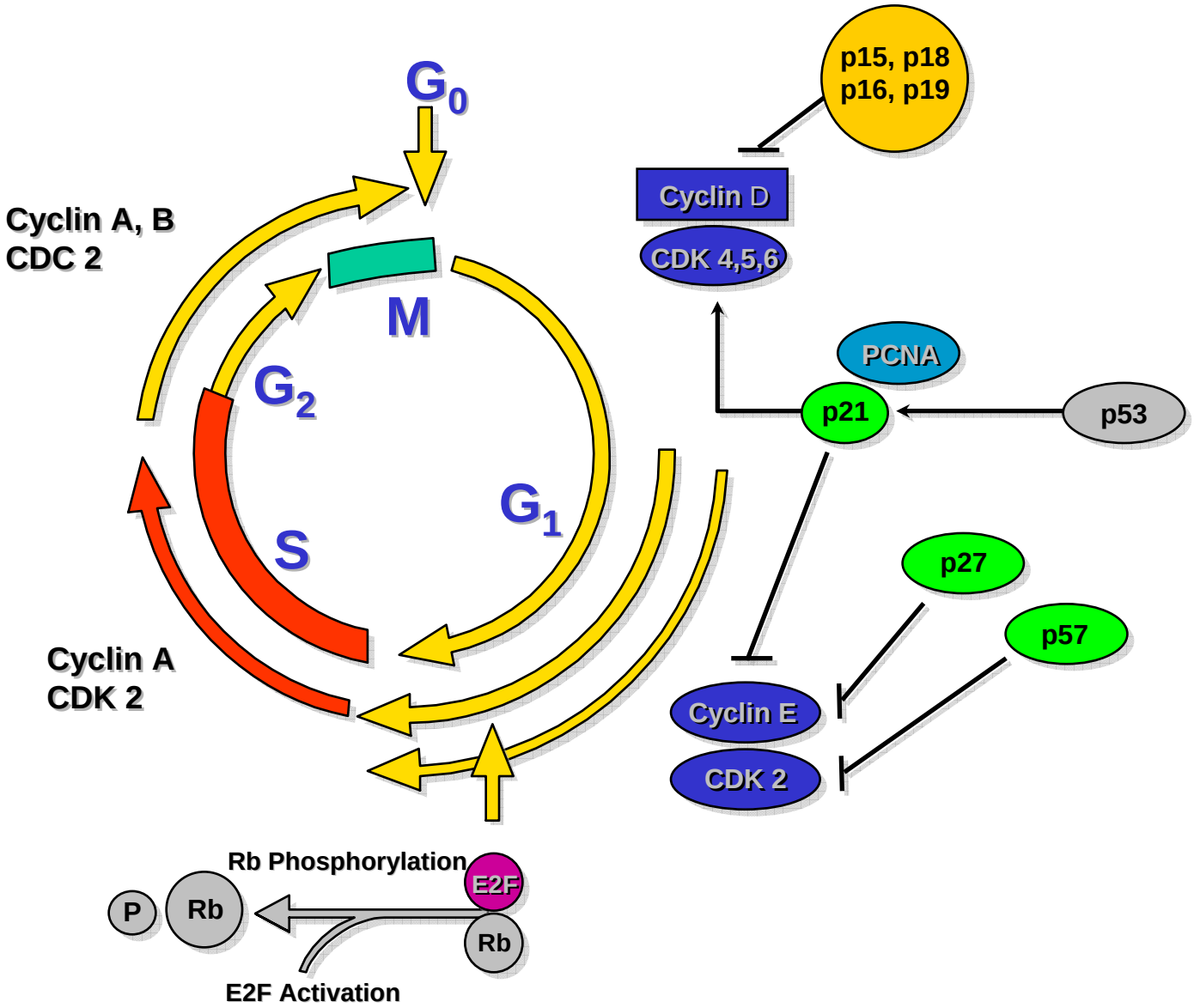
Ridker et al, *N Eng J Med* 2002;337:1557

Imaging: Plaque Volume Quantification

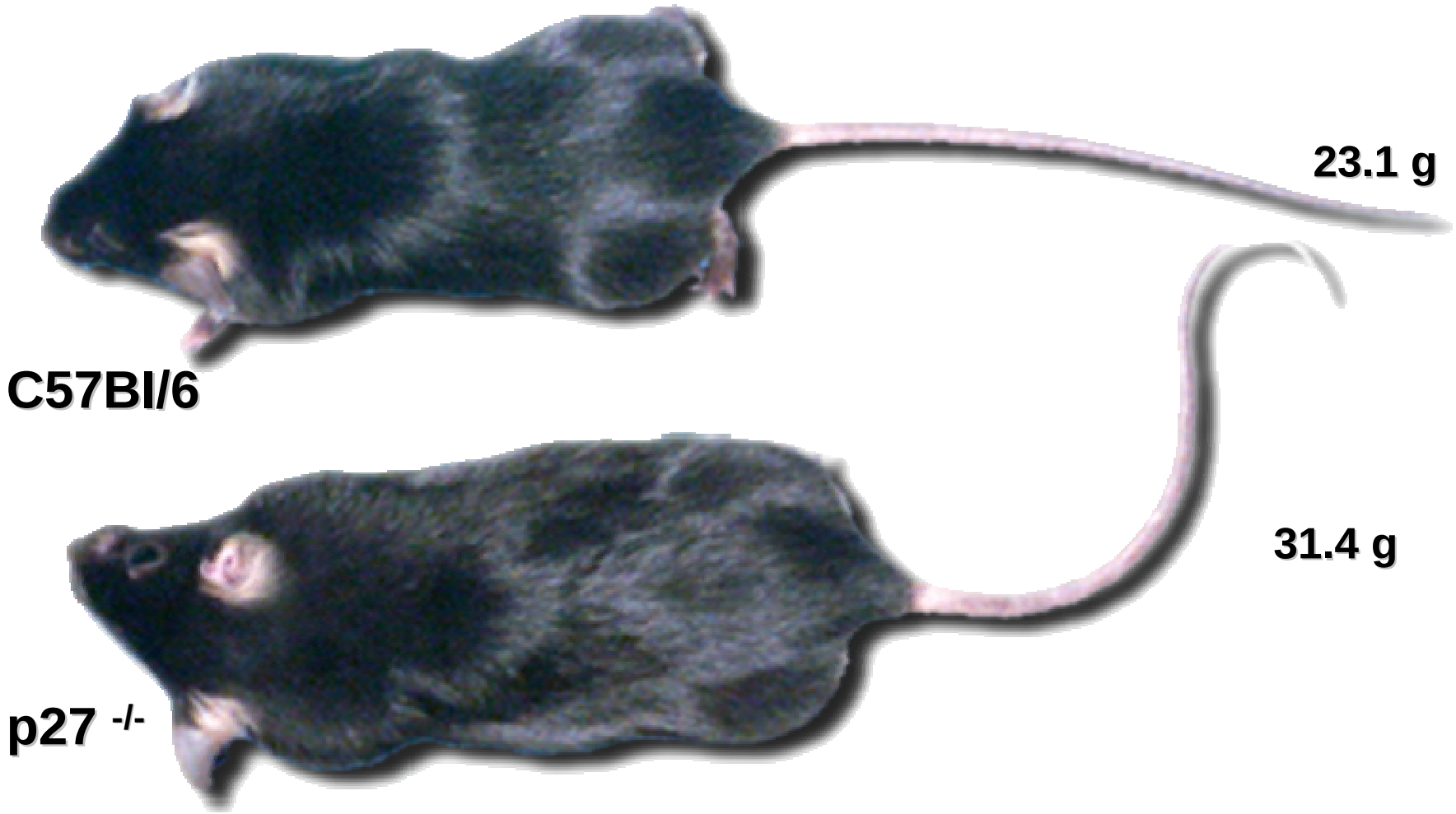


Chris Kramer M.D., Univ. of Virginia

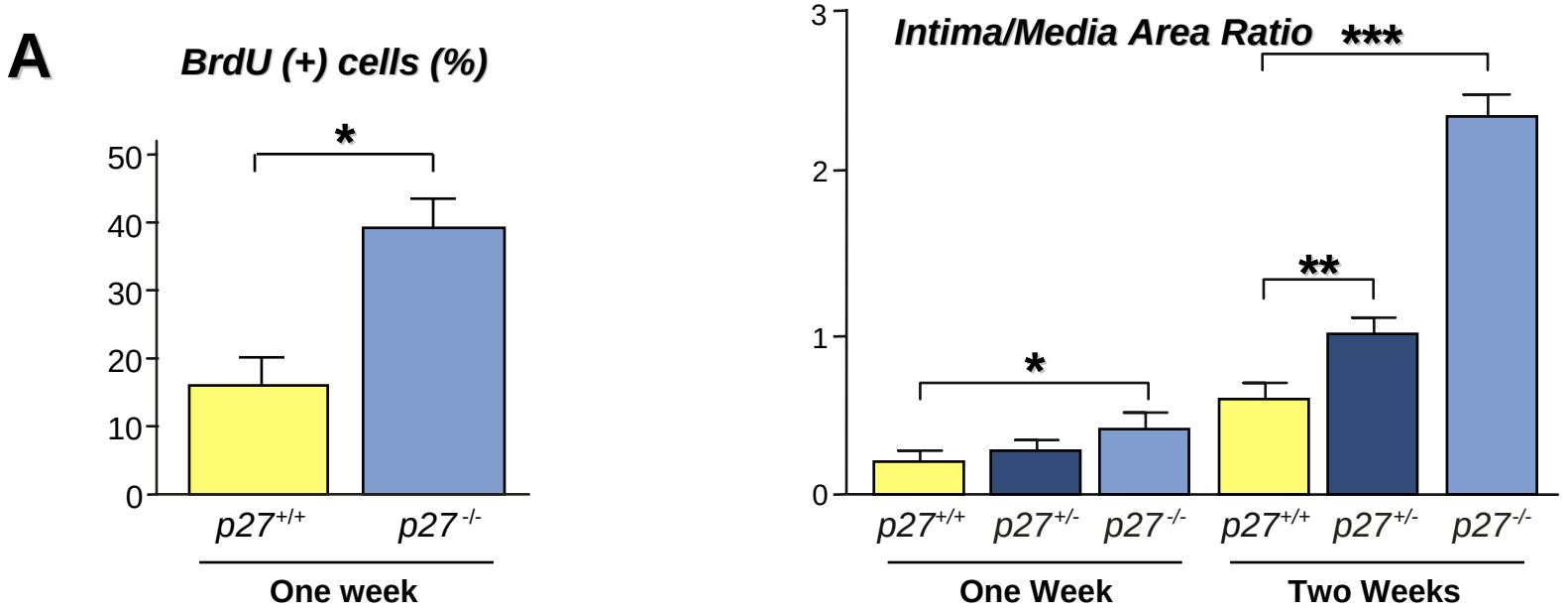
Cell Cycle

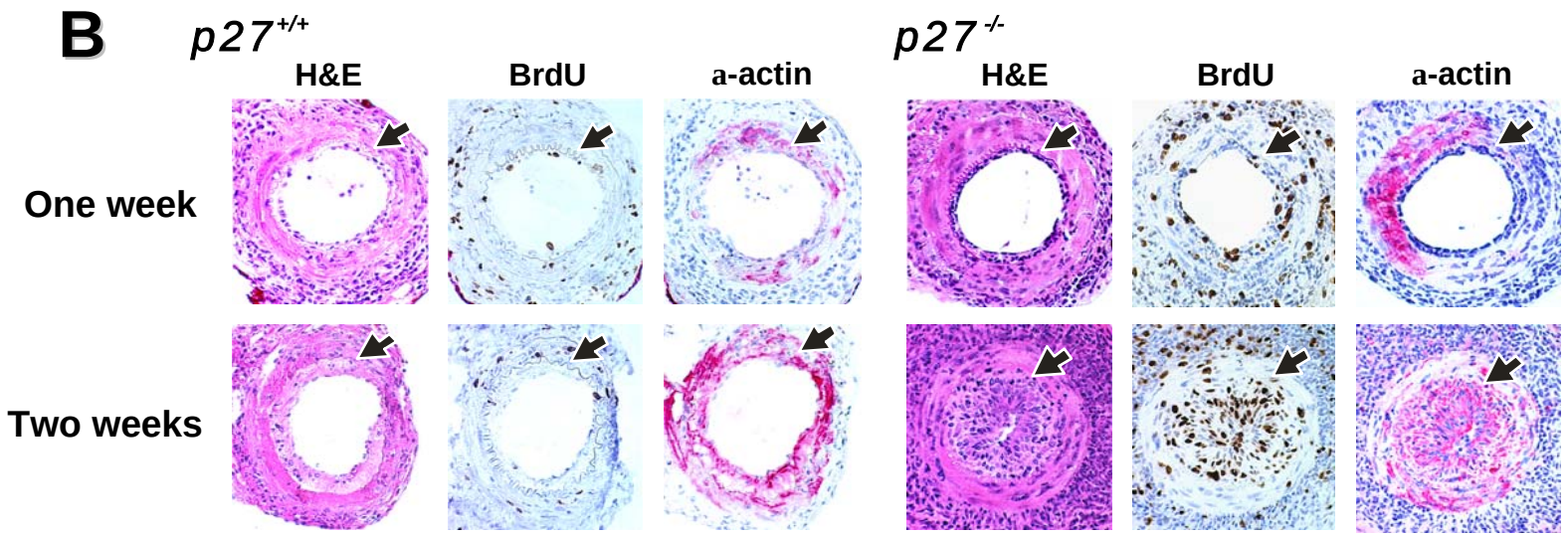

G0
M
G2
G1
S
Cyclin A, B
CDC 2
Cyclin A
CDK 2
p15, p18
p16, p19
Cyclin D
CDK 4,5,6
PCNA
p21
p53
p27
p57
Cyclin E
CDK 2
Rb Phosphorylation
P
Rb
E2F
Rb
E2F Activation

p27$^{-/-}$ Mice Display Abnormal Cell Growth in Many Organs



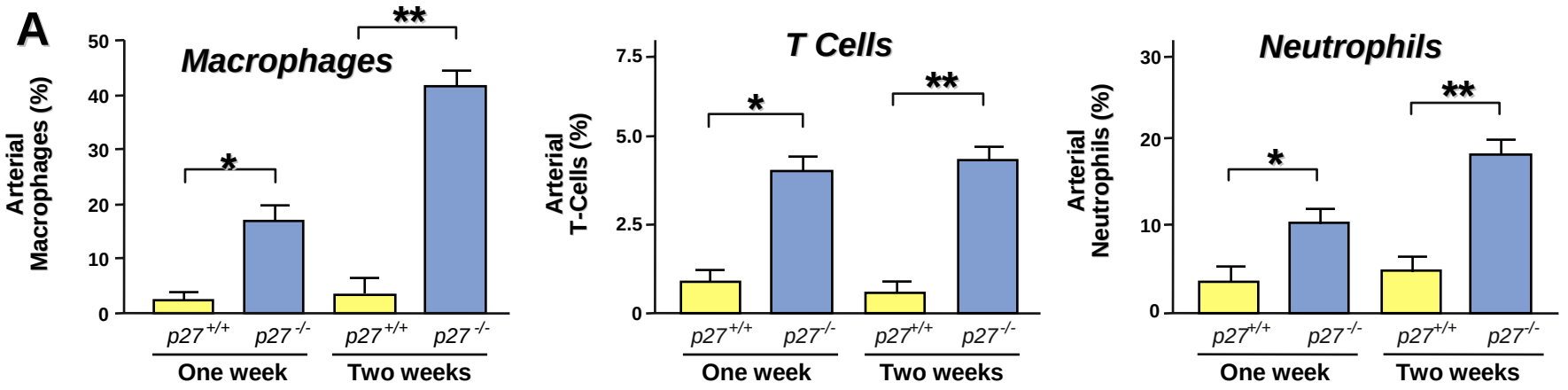
Impaired Wound Healing in *p27*$^{-/-}$ Mice

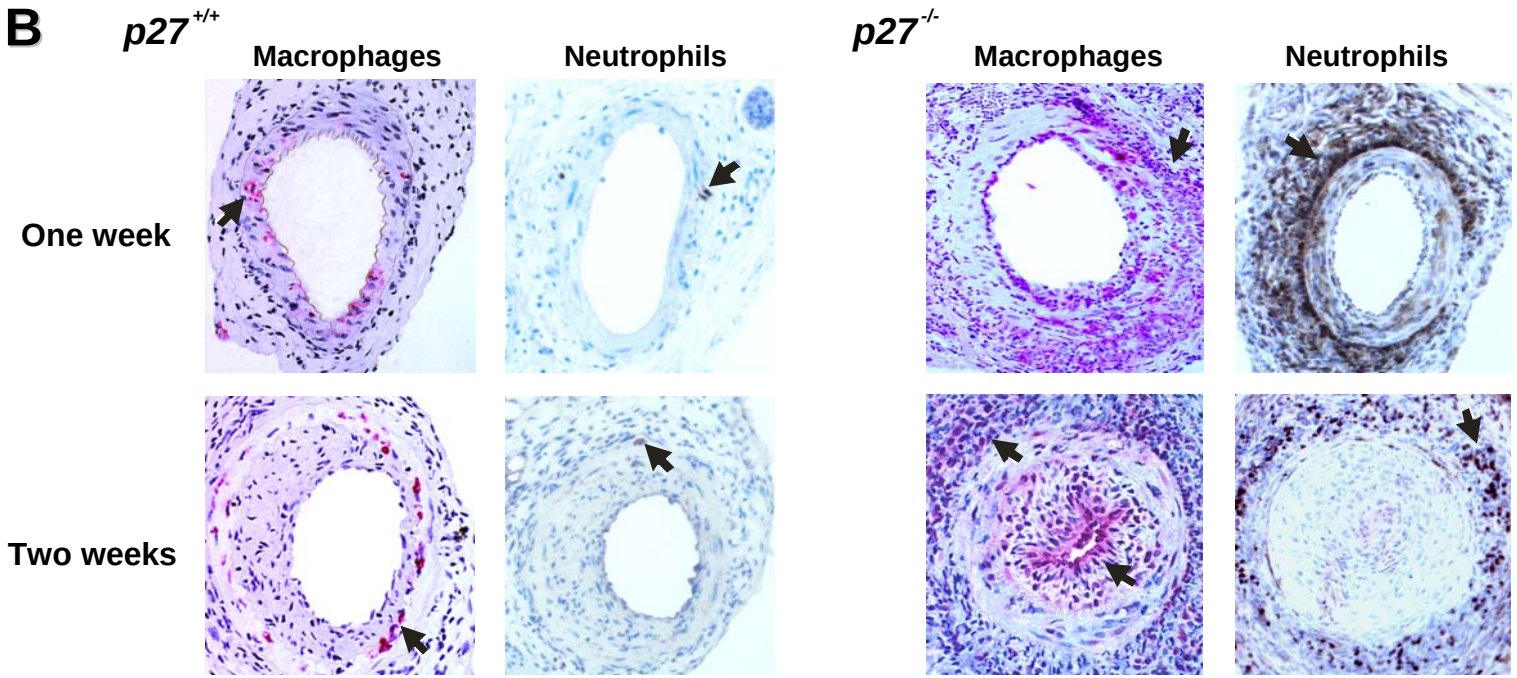




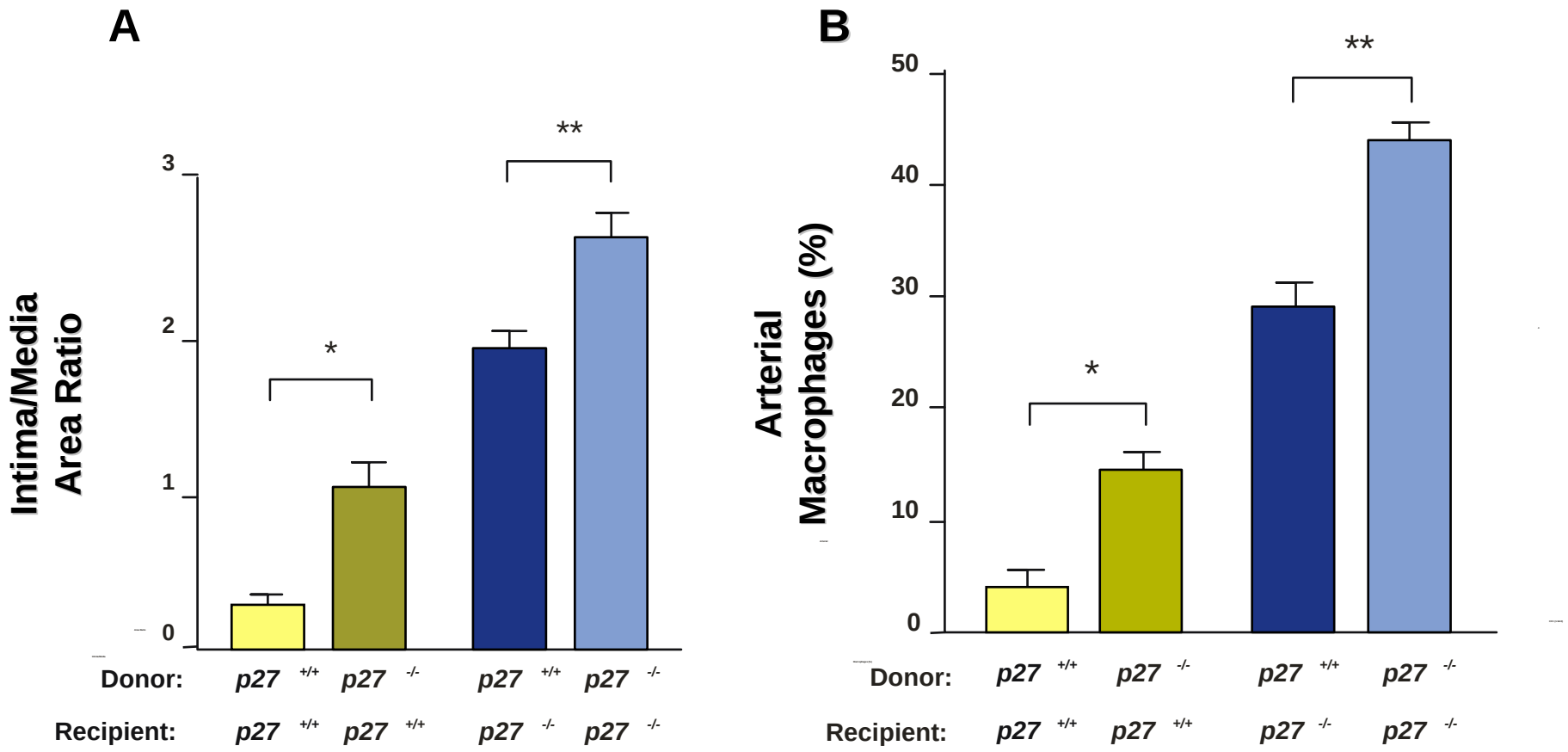
Boehm et al., *J Clin Invest* 2004;114:419

$p27^{Kip1}$ Mediates the Inflammatory Response to Vascular Injury

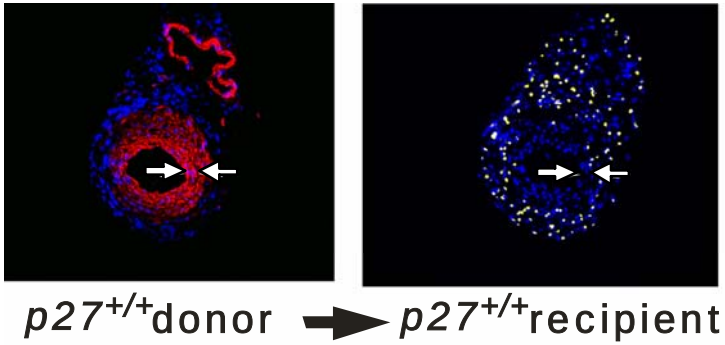




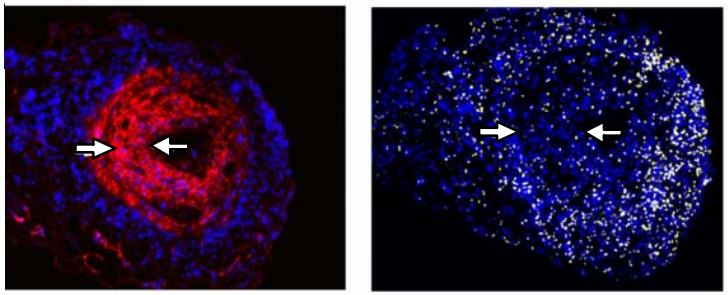
p27^{Kip1} Regulates Bone Marrow Cells that Repopulate Injured Arteries



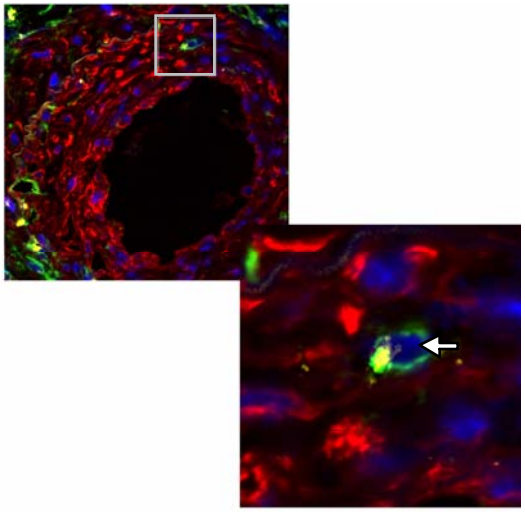
p27$^{-/-}$ BM Derived Cells Reconstitute the Intima and Adventitia of Vascular Lesions

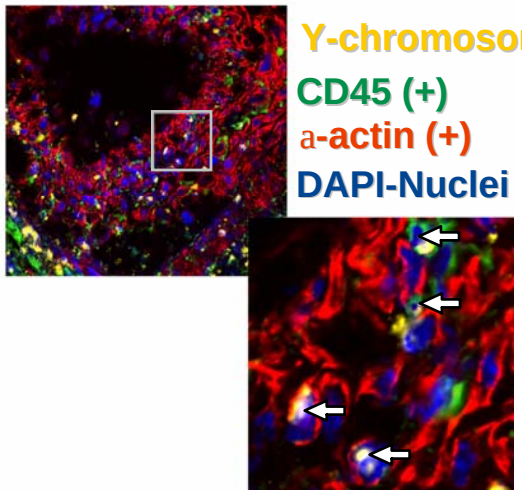


p27$^{+/+}$donor → *p27*$^{+/+}$recipient

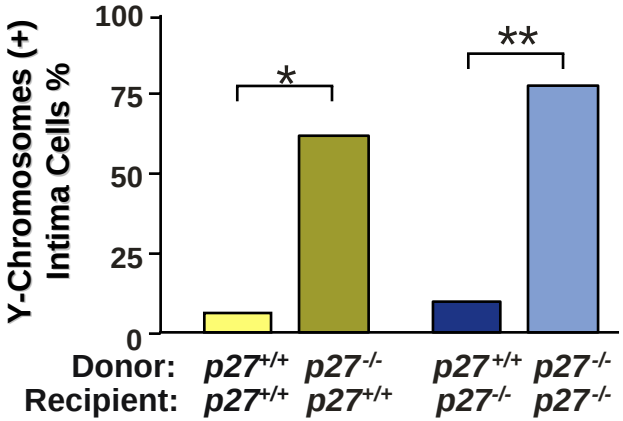


p27$^{-/-}$ donor → *p27*$^{+/+}$recipient

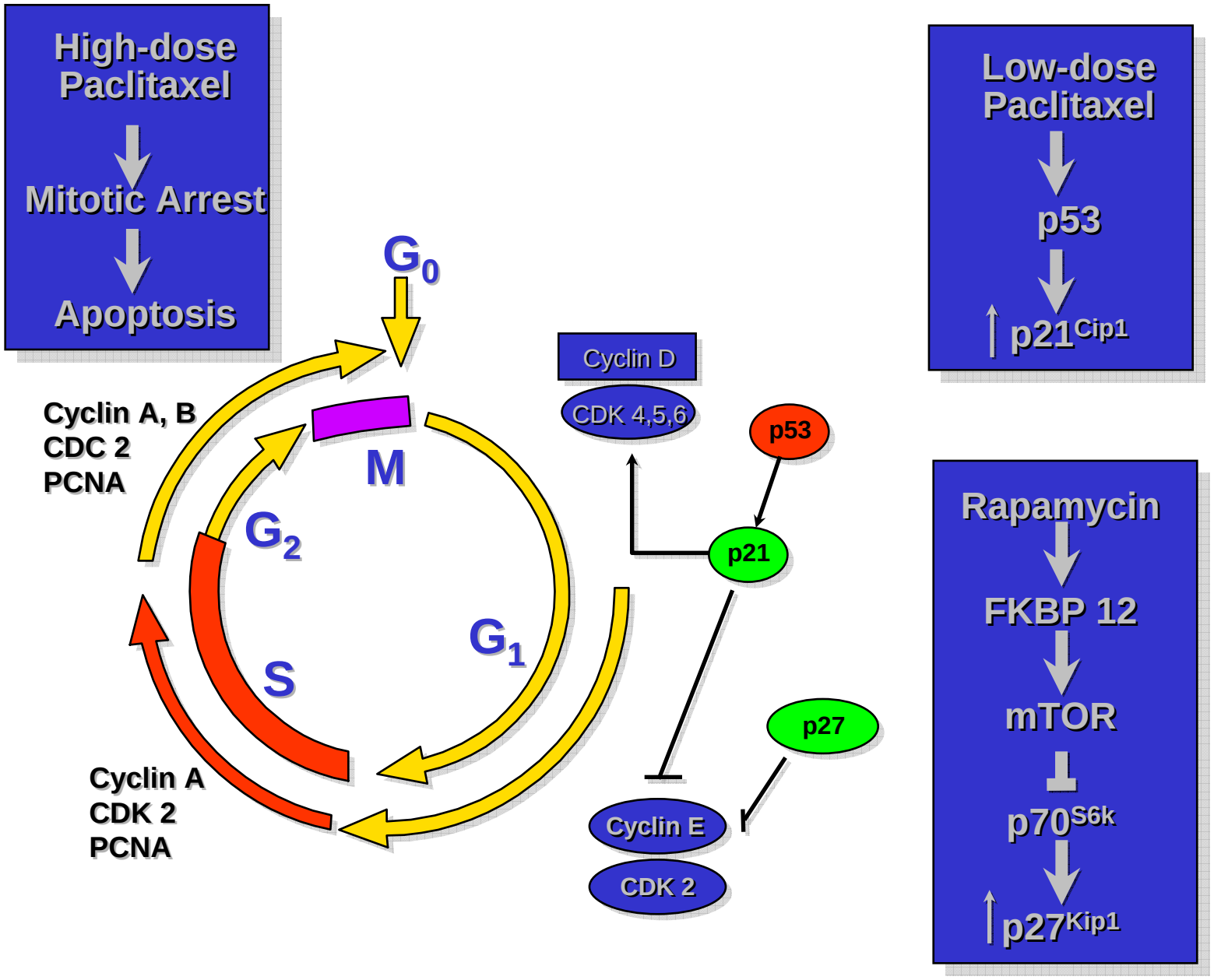




Y-chromosome(+)
CD45 (+)
a-actin (+)
DAPI-Nuclei



Drug Eluting Stents



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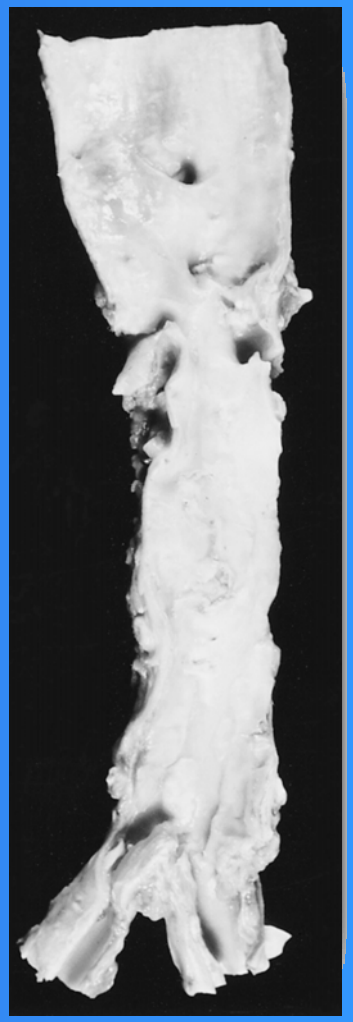
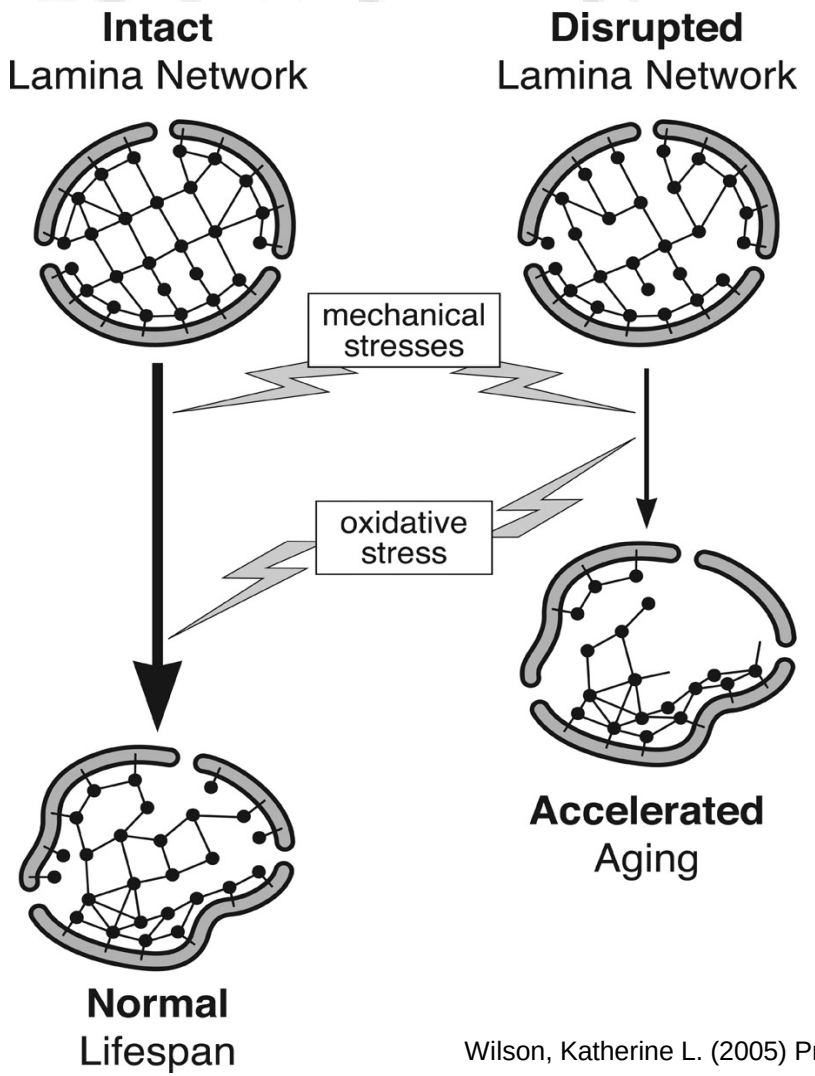


The Integrity of the Nuclear Lamina is linked Lifespan of Cells



Wilson, Katherine L. (2005) Proc. Natl. Acad. Sci. USA 102, 18767-18768

Progeroid Syndromes Associated with Impaired Genome Stability

Syndrome (affected genes)	Affected process
Cockayne syndrome (*CSA, CSB*)	Transcription-coupled DNA repair
Cerebro-oculo-facio-skeletal syndrome (*CSB, XPG, XPD*)	Transcription-coupled and global genome nucleotide excision repair
Trichothiodystrophy (*XPB, XPD, TTDA*)	Transcription-coupled and global genome nucleotide excision repair
Xeroderma pigmentosum + Cockayne syndrome (*XPB, XPF, XPD, XPG*)	Transcription-coupled and global genome nucleotide excision repair
Xeroderma pigmentosum + DeSanctis–Cacchione syndrome (*XPA, XPC, XPD*)	Global genome nucleotide excision and transcription-coupled repair
Ataxia telangiectasia (*ATM*)	DNA damage response
Nijmegen breakage syndrome (*NBS1*)	DNA damage response and repair
Bloom syndrome (*BLM*)	DNA repair and recombination
Werner syndrome (*WRN*)	DNA repair and recombination
Fanconi anaemia (*FANC* genes, *BRCA2*)	DNA crosslink repair
Dyskeratosis congenita (*DKC1, TERC1*)	Telomere maintenance
Hutchinson–Gilford progeria syndrome (*LMNA*)	Lamina function
Atypical Werner syndrome (*LMNA*)	Lamina function
Restrictive dermopathy (*LMNA, ZMPSTE24*)	Lamina function
Seip syndrome (*LMNA*)	Lamina function

*Mitochondrial DNA disorders that lead to premature ageing might also be considered to be caused by genetic instability.

Thanks to Nabel Lab Members:

http://nabel-lab.genome.gov/

- **Tom Cimato**
- **Santhi Ganesh**
- **Thomas Langenickel**
- **Michele Olive**
- **Stephen Pan**
- **Xuan Qu**
- **Hong San**
- **Adong Yu**
- **Jeannette Bears**

Manfred Boehm

Martin Crook

Thanks to the Collins Lab!