Understanding (and approaches) to Cardiovascular risk in 2006

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Outline

- Scope of the problem
- A simplified model
- High Blood pressure
- Cholesterol
- Conclusion

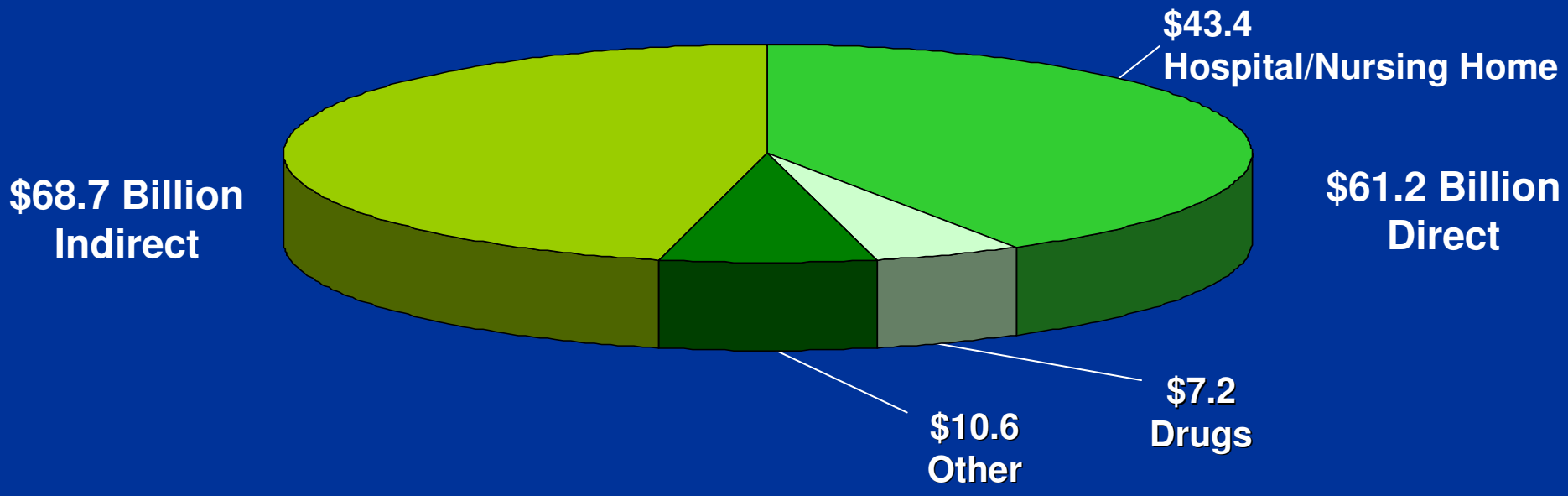
The Problem

- Nearly 1,000,000 infarctions each year
- Over 5.5 million persons with coronary disease and hyperlipidemia
- These number will double in the next 20 years

- Only 40% of those at risk are being treated

High Cost of CHD

Total US Costs for CHD Are Over $120 Billion/Year



- CHD is the leading cause of death in American men and women.
- An estimated 1.1 million Americans will have a new or recurrent myocardial infarction (MI) in 2003.

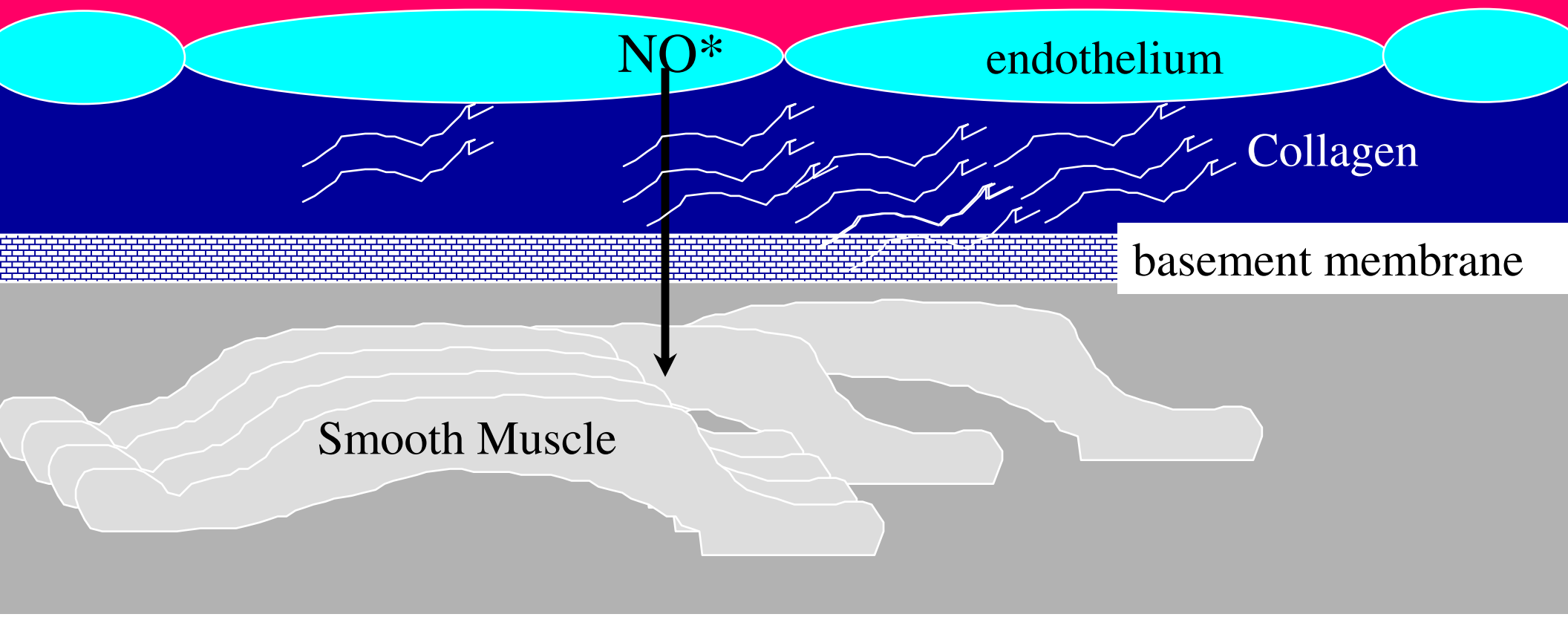
American Heart Association. *Heart Disease and Stroke Statistics – 2003 Update.*

Atherosclerosis: "A Response to injury"

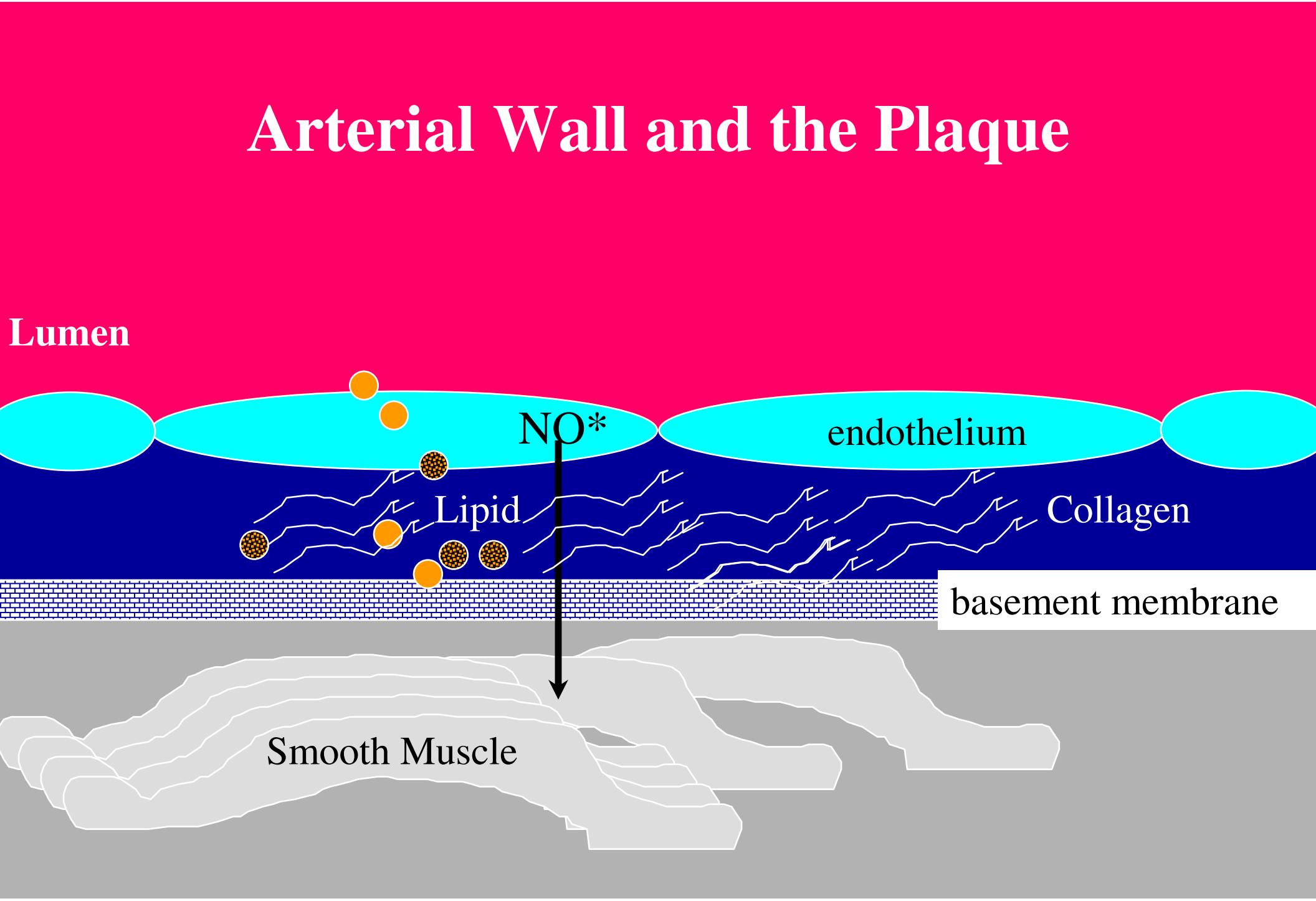
Initiation	**=**	**Endothelial damage**
Propagation	**=**	**Increased permeability to lipids and cells**
Evolution	**=**	**Cellular interactions and endothelial responses**

Modified from Schachter Int J Card 62:s3-s7; 1997

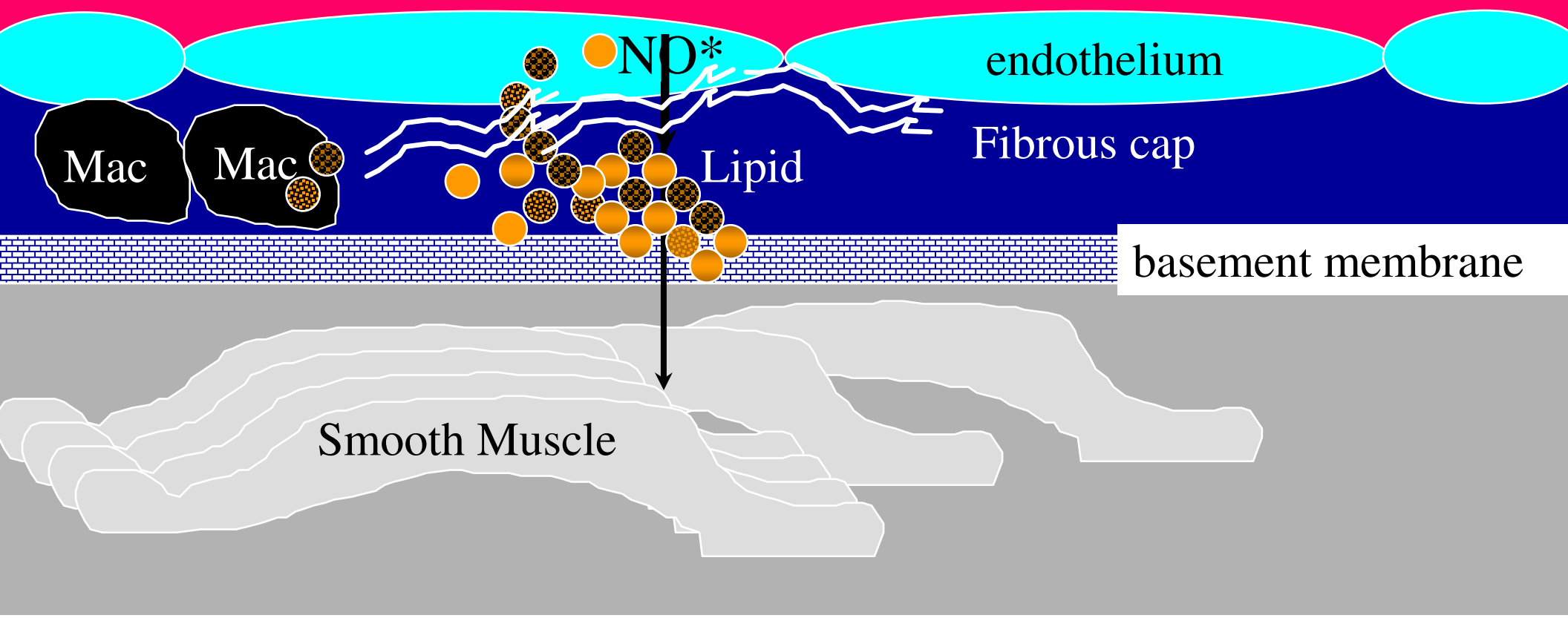
Arterial Wall
(Self Lubricating Teflon)



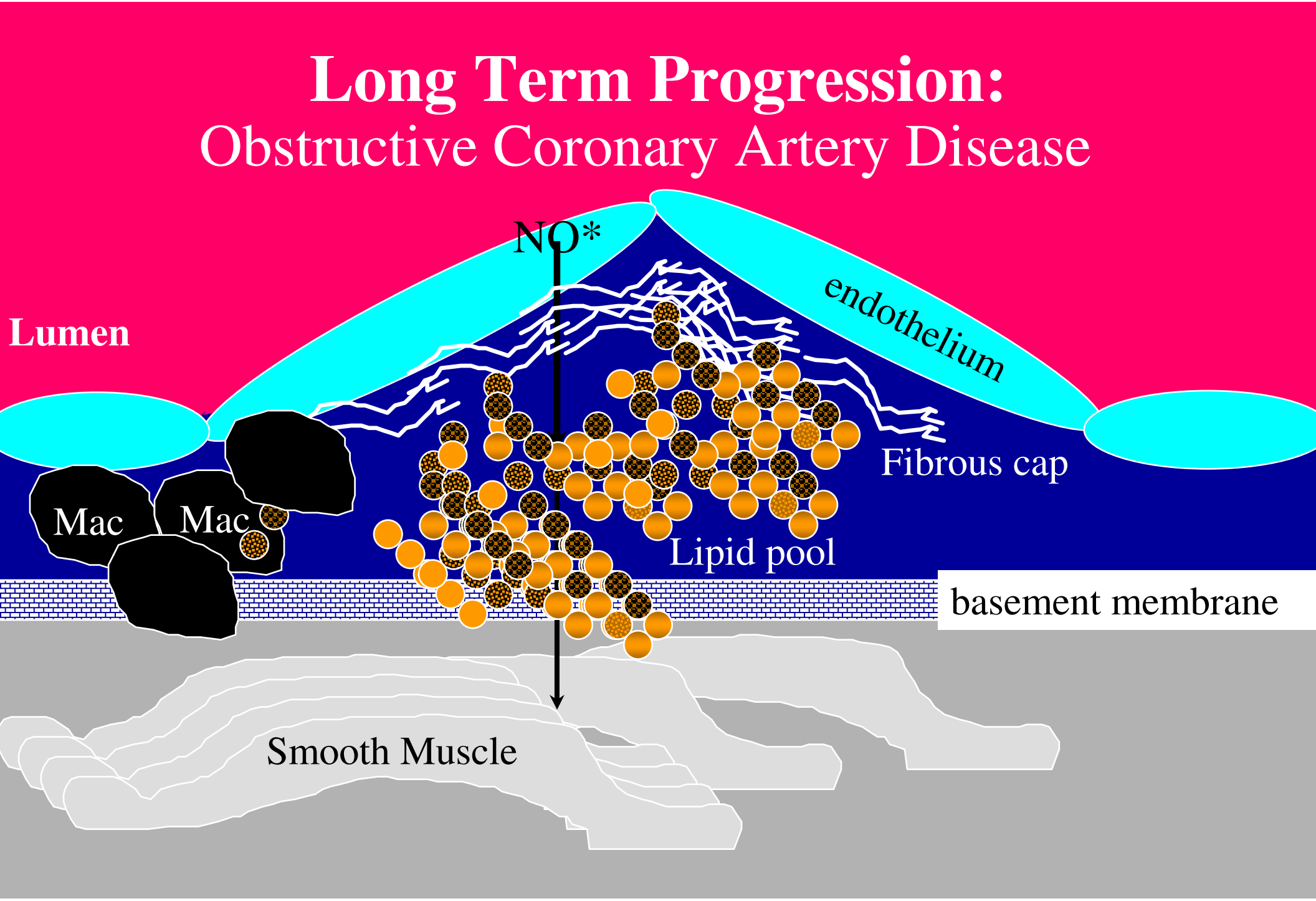
Arterial Wall and the Plaque



Initial Phases of Damage :
Repair versus Degradation

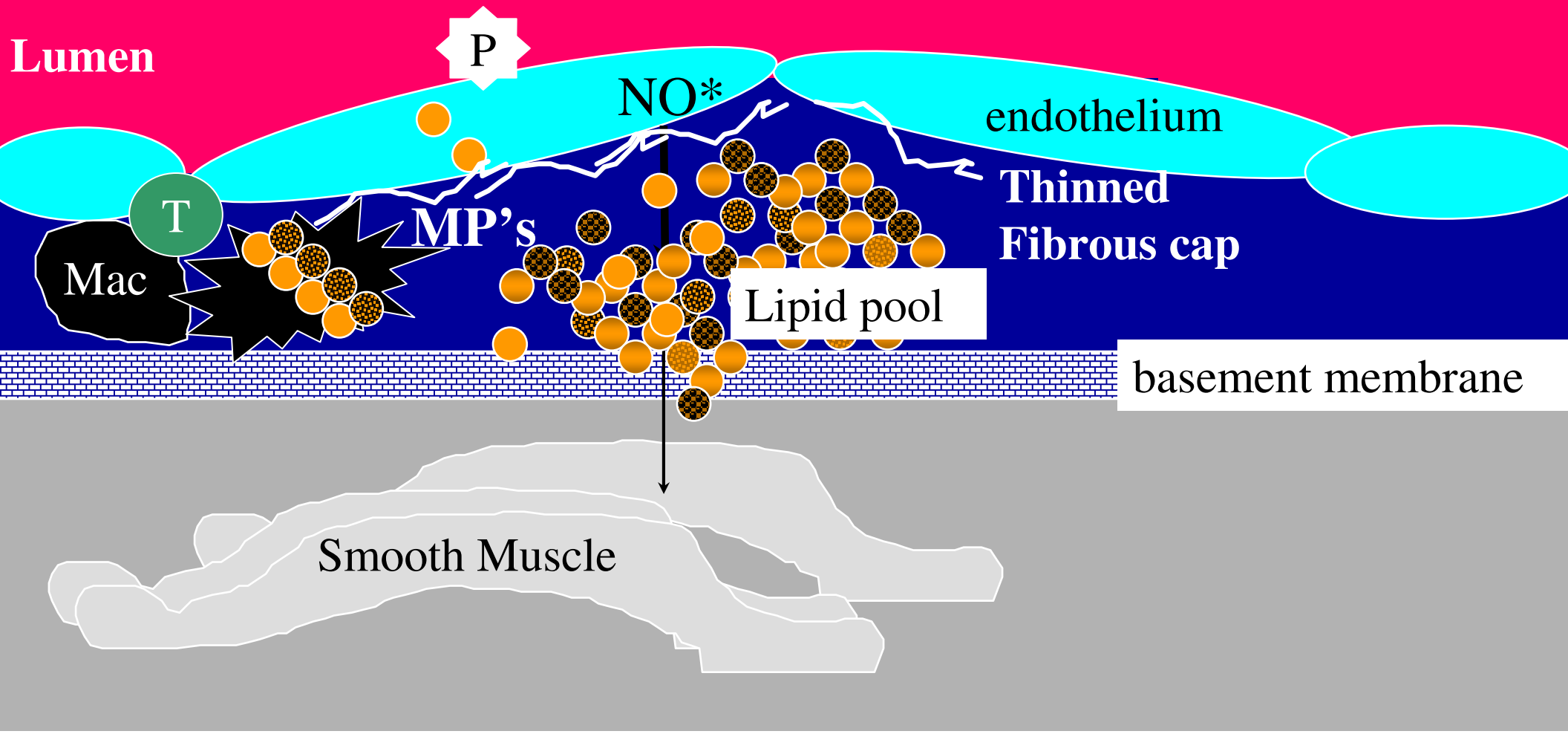


Long Term Progression:
Obstructive Coronary Artery Disease



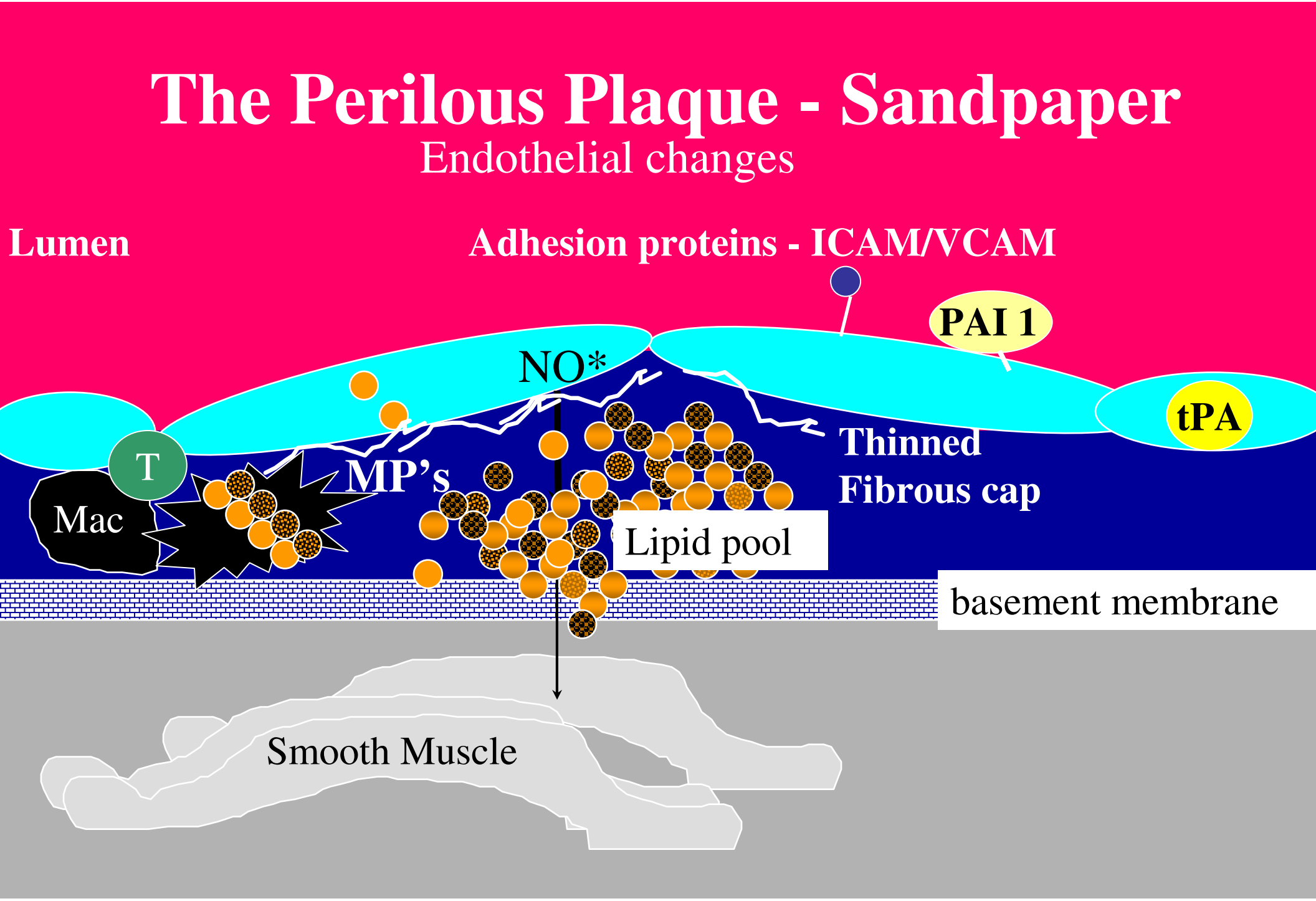
The Perilous Plaque

Degradation > repair

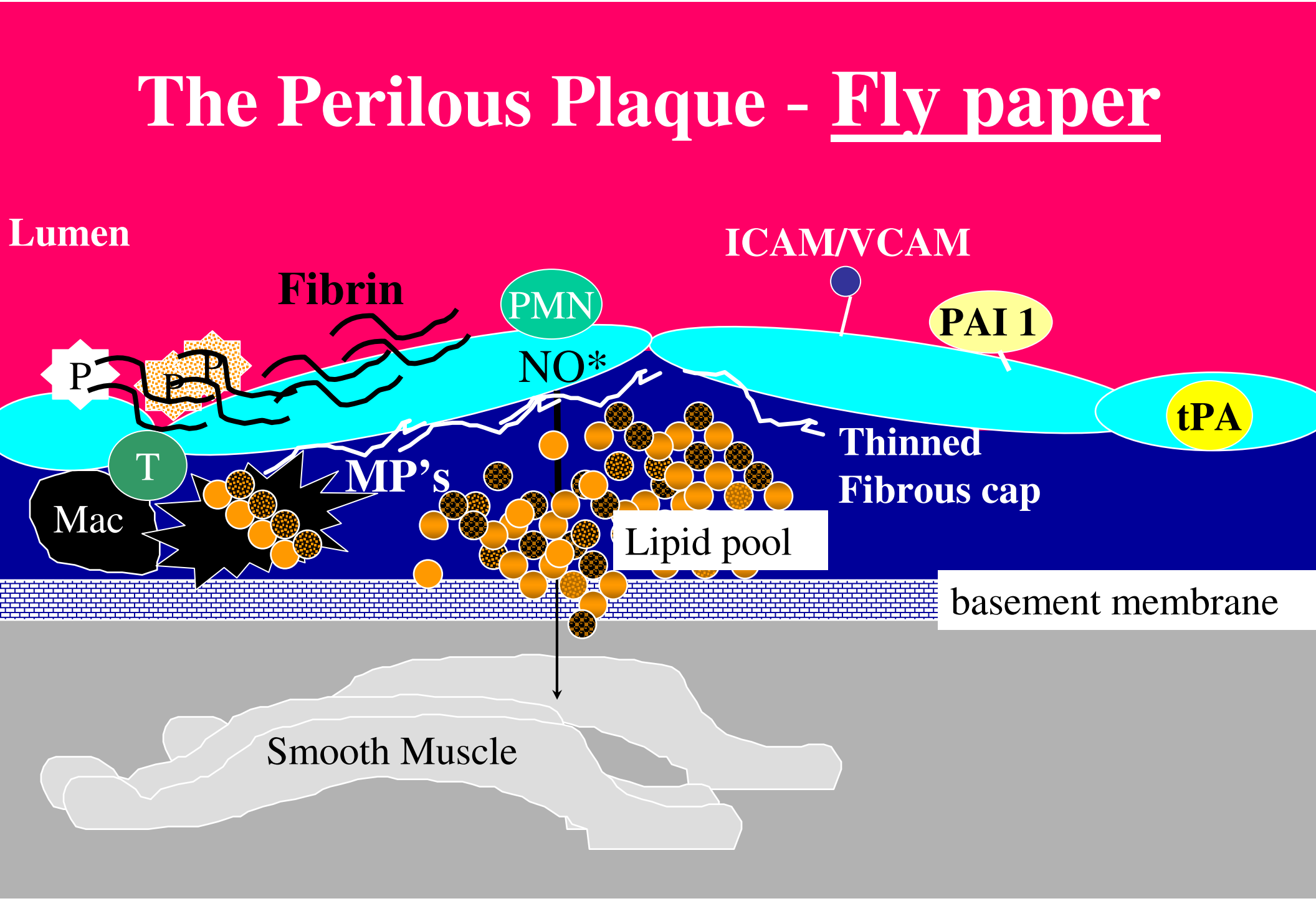


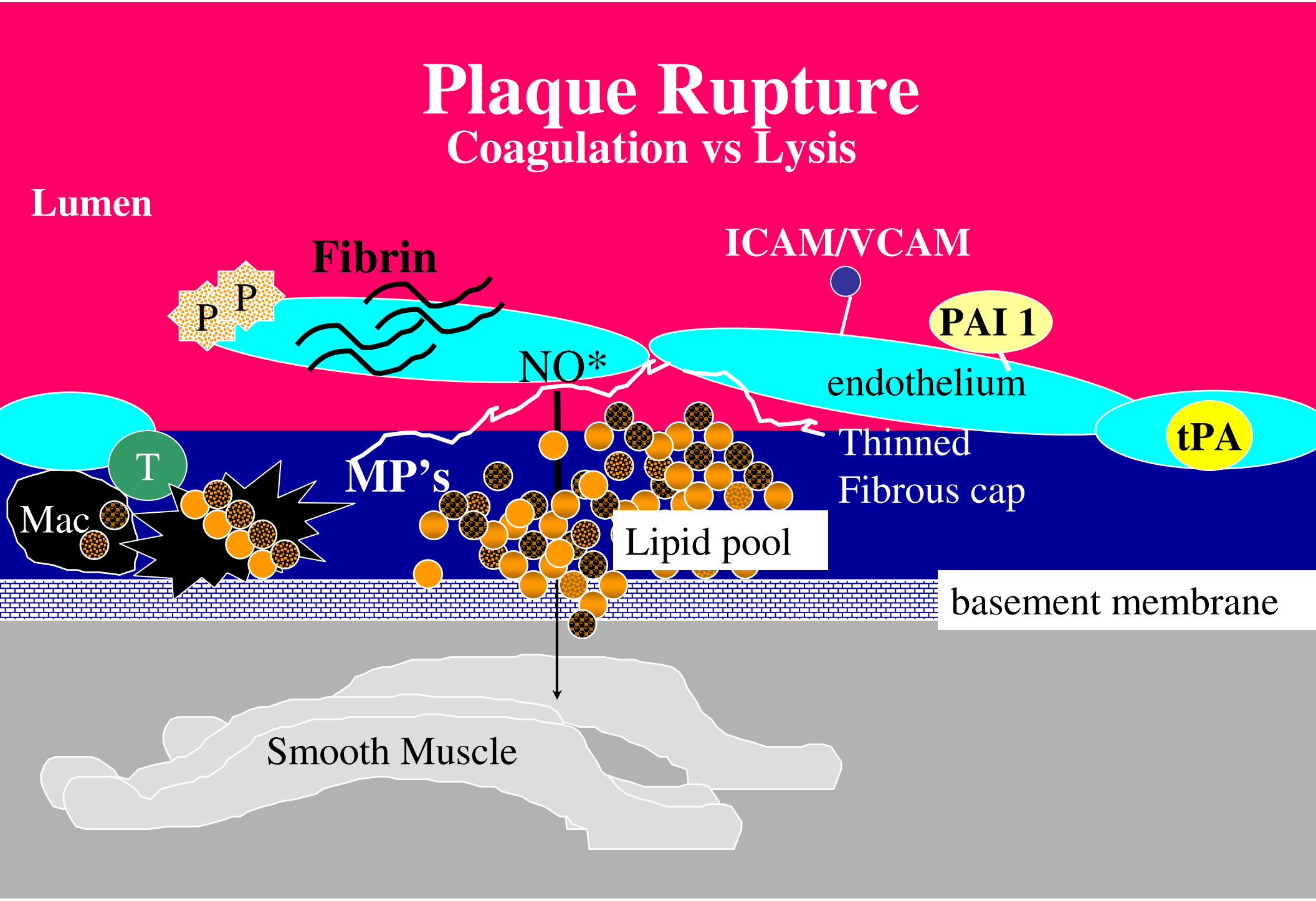
The Perilous Plaque - Sandpaper

Endothelial changes

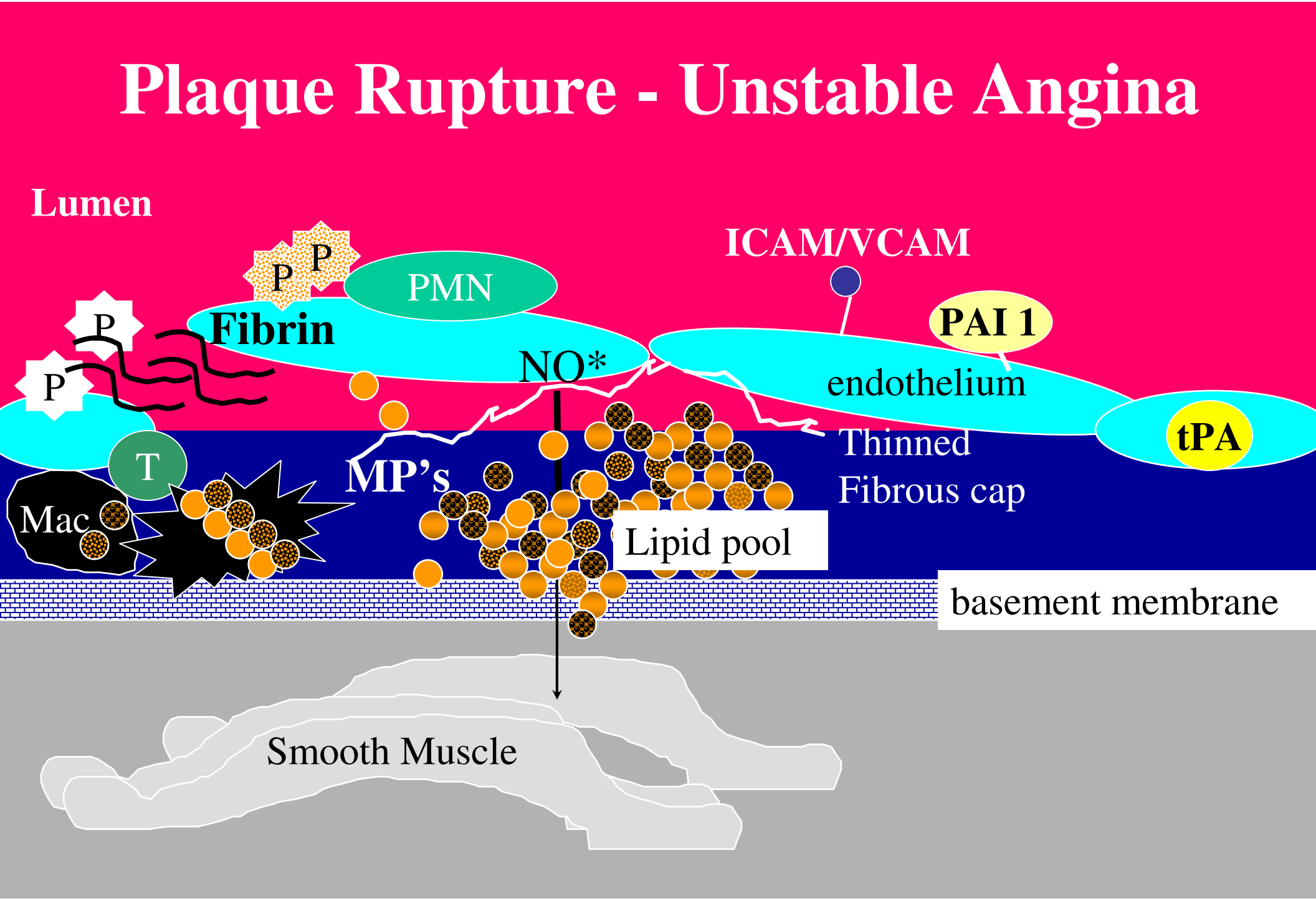


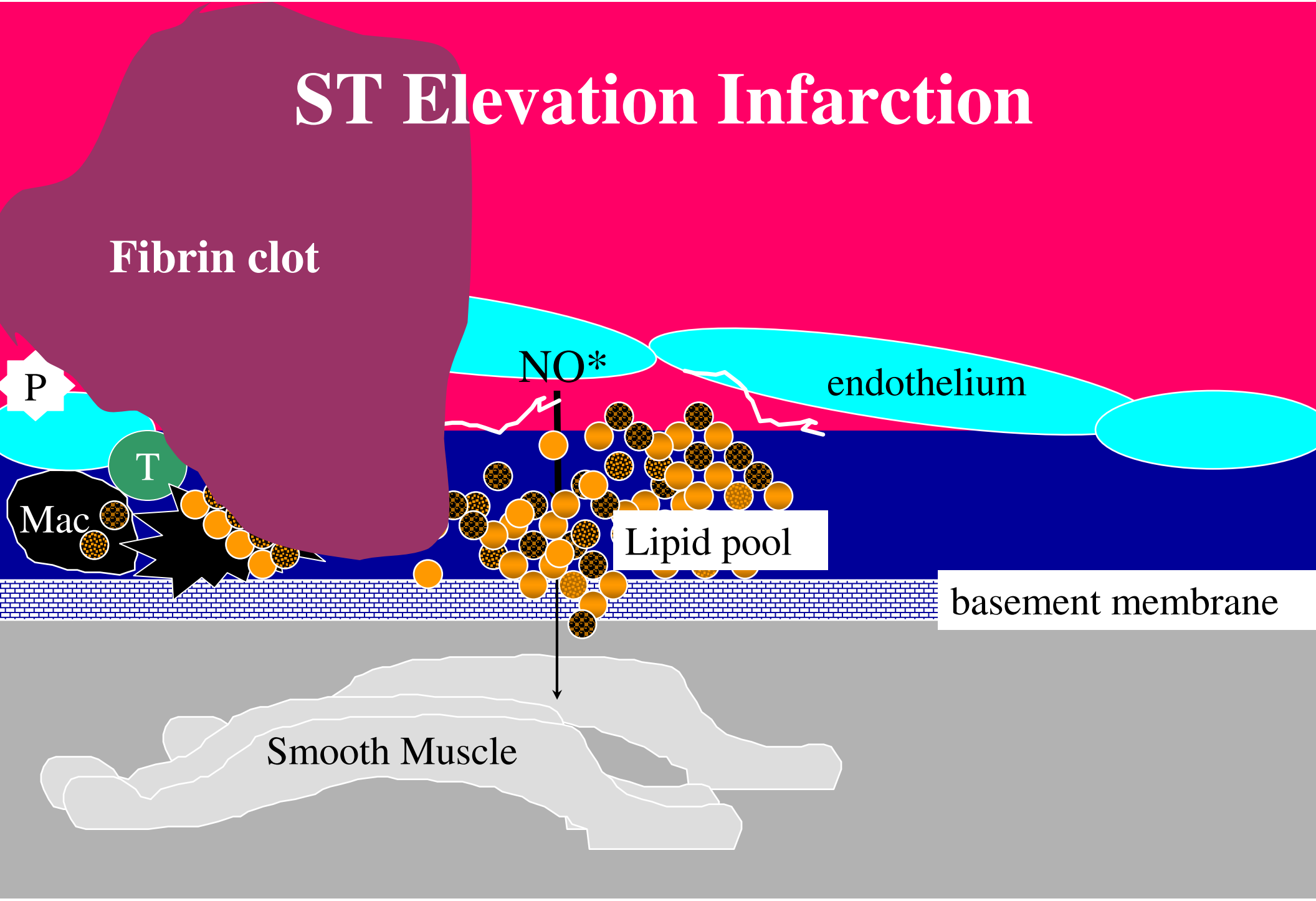
The Perilous Plaque - Fly paper




Plaque Rupture
Coagulation vs Lysis
Lumen
Fibrin
P
P
P
ICAM/VCAM
PAI 1
NO*
endothelium
tPA
Thinned
Fibrous cap
T
Mac
MP's
Lipid pool
basement membrane
Smooth Muscle

Plaque Rupture - Unstable Angina

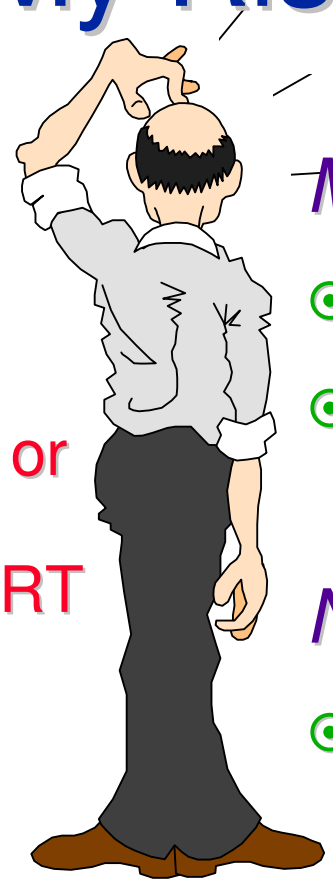



ST Elevation Infarction
Fibrin clot
NO*
endothelium
P
T
Mac
Lipid pool
basement membrane
Smooth Muscle

What are My Risk Factors?

Unmodifiable

- Age
  - male ≥ 45 years
  - female ≥ 55 years or premature menopause w/o ERT
- Family history of premature CHD
- Diabetes



Modifiable

- Smoking
- Hypertension

Negative Risk Factor

- HDL-C ≥ 60 mg/dL

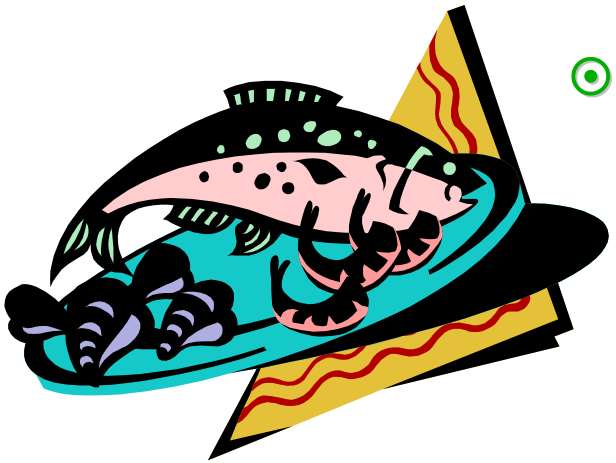
What drives “Blister” formation

- Diet
- Hypertension
- Cholesterol
- Bad Genes
- Diabetes
- Other factors

Dietary Intervention - Lyon Diet Heart Study

- Secondary Prevention investigating the Mediterranean type diet
- 605 patients in two groups followed for mean of 27 months
- Combined endpoint of cardiovascular events
  - 76% reduction in events - (14 versus 59)

AHA Step-Two Diet



- Total Fat
  - < 30% of total calories
    - Saturated fats: < 7% TCs
    - Poly unsaturated fats: 10% TCs
    - Monounsaturated fats: 10-15% TCs
- Carbohydrates
  - 55% or more of total calories
- Protein
  - 15% of total calories
- Cholesterol
  - < 200 mg/day
- Total Calories
  - To achieve and maintain desirable weight

Obesity and Risk

- Central obesity leads to:
  - Hypertension
  - Stickier cholesterol
    - Lowers HDL
    - Raises Triglycerides
  - Glucose intolerance (pre diabetes)
  - Elevated inflammatory marker levels

Hypertension

- Lower the blood pressure the better
- Lowest mortality associated with systolic (top) blood pressure of < 117.
- Too low is dizzy or problems with kidneys
- Goals are dependent on other disease states

Drugs for Hypertension – Diuretic (Latin for make me tinkle all day)

- Thiazide diuretic
  - HCTZ, Chlorthalidone, Dyazide
  - Most evidence with this class of diuretic
    - Huge study call ALLHAT proved this
- Potassium Sparing diuretic – Aldactone, Spironolactone
  - More commonly used in combination with a thiazide or for people with weak hearts (CHF)
- Loop diuretic – Lasix, Demadex, Bumex
  - NOT FOR HYPERTENSION

Drugs for Hypertension – ACE inhibitor

- Great for Blood pressure
  - Drug of choice if you also have vascular disease, DM or kidney disease
  - Proven in men; less so in women
  - Side effect
    - Cough
    - Swelling of lips in 1/3000 to 1/5000

Drugs for Hypertension – ARB

- Alternate for ACE
  - Work on the same mechanism
  - ACE prevents the key from being made, ARB is glue in the lock
  - Proven for kidney problems, weak heart if ACE intolerant

Drugs for Hypertension – Beta Blocker

- Slow the heart down
  - Protect heart from rhythm problems after a heart attack
  - Prevents angina (chest pain) by lowering rate
  - Side effect – numerous but not common
    - Depression
    - Impotence
    - Fatigue

Drugs for Hypertension – Calcium channel blocker

- Lower blood pressure by effecting calcuim
  - Three types
    - Dihydropyridine – Norvasc, Procardia
    - Diltiazem
    - Verapamil
- Good at treating the number not so much evidence

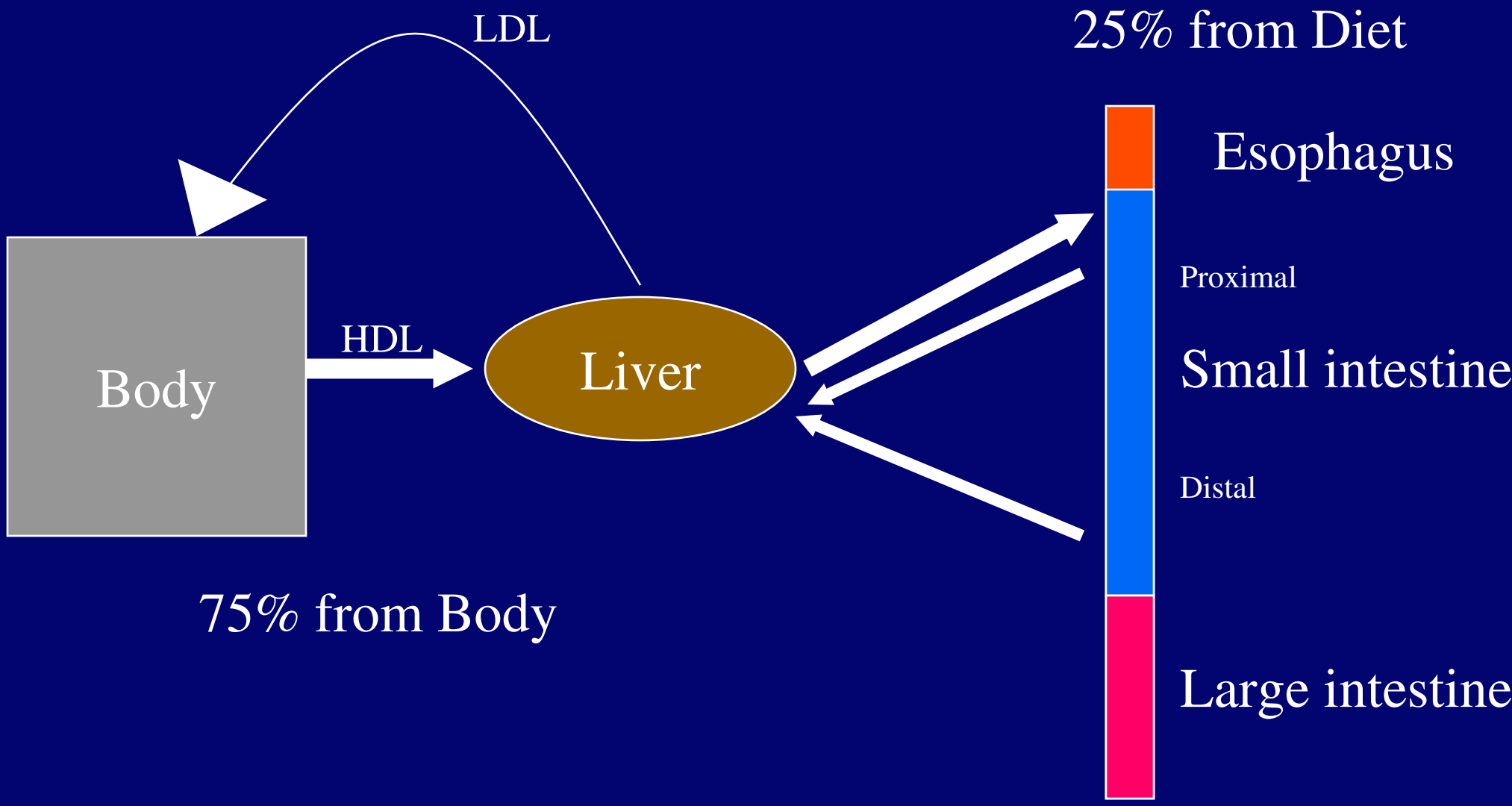
Drugs for Hypertension – Other drugs

- Clonidine
- Prazocin
- Hydralazine

Two Sources of Cholesterol

- What you eat
- What you make

Cholesterol Flow in Humans



Cholesterol levels

- In nature the balance between synthesis and uptake determines your cholesterol level
  - Born with LDL levels in the 40-60 range
  - In America diet plays a major role in cholesterol levels

Cholesterol effects

- Key component of cell membranes
- Key precursor of many hormones and other important molecules in the body
- Too much incites vascular damage

Cholesterol and Vascular Damage

- Impairs endothelial function
- Incites an inflammatory response
- Impairs vascular integrity

Drugs that lower cholesterol

- Diet
- Statins – Lipitor, Zocor, Pravachol, Crestor, Lescol, Advicor
- Ezetimibe – Zetia
- Fibrates - Lopid, Tricor
- Niacin

Benefits of Cholesterol Lowering Primary Prevention

- If your cholesterol is very elevated
  - 22% reduction in death
  - 34% reduction in heart attack
- If your cholesterol is “normal”
  - 34% reduction in first heart attack
  - 33% reduction in need for angioplasty

Benefits of Cholesterol Lowering Secondary Prevention

- If you have high or “normal” cholesterol
  - Reduction in total mortality of 24-30%
  - Reduction in cardiovascular events of 24-40%
  - Reduction in risk for stroke of 20-24%

How do I get these benefits?

- Get treated!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

    - Group of drugs called statins
    - Vitamin called Niacin

    - Other agents may not be as effective.

HMG-CoA reductase inhibitors

Lovastatin (Mevacor), Simvastatin (Zocor), Pravastatin (Pravachol), and Fluvastatin (Lescol)

- Effects on Lipids:
  - LDL-C: ↓ 20-40%
  - HDL-C: ↑ 5-15%
  - Triglycerides: ↓ 10-20%
- Major use is to lower LDL cholesterol
- Reduce risk of CHD (lovastatin, simvastatin & pravastatin - not shown with fluvastatin)
- Simvastatin has been shown to reduce total mortality as well

HMG-CoA reductase inhibitors

- Potential Side Effects:
  - Elevation of liver enzymes, myopathies
- Contraindications:
  - Absolute: Active or chronic liver disease
  - Relative: Concomitant use of cyclosporin, gemfibrozil, or niacin

How low should I go

- If you have active disease – LDL <70
  - Heart attack, Stroke, Cramping when you walk, Diabetes
- If you have stable disease – LDL < 100
- If you do not have disease but have risk – LDL < 130
  - Smoke, hypertension, strong family history, low HDL
- If you are at low risk - LDL < 160

Niacin (nicotinic acid)

- Effects on Lipids:
  - LDL-C: ↓ 10-25%
  - HDL-C: ↑ 15-35%
  - Triglycerides: ↓ 20-50%
- Useful in most lipid and lipoprotein abnormalities
- Reduces risk of CHD

Niacin (nicotinic acid)

- Potential Side Effects:
  - Flushing, hepatotoxicity, hyperglycemia, hyperuricemia or gout, and upper GI complaints; hepatotoxicity especially for sustained release
- Contraindications:
  - Absolute: Chronic liver disease
  - Relative: NIDDM, severe gout or hyperuricemia

Zetia

- Blocks cholesterol uptake in the first part of the intestine
- Low incidence of side effects
- Additive to a statin
- Works even if you have low dietary intake of cholesterol

Resins (bile acid sequestrants)

Cholestyramine, Colestipol

- Effects on Lipids:
  - LDL-C: ↓ 10-30%
  - HDL-C: ↑ 3-5%
  - Triglycerides: No effect or increase
- Major use is to lower LDL cholesterol
- Reduces risk of CHD

Resins (bile acid sequestrants)

- Potential Side Effects:
  - Upper and lower Gastrointestinal complaints
  - Decreased absorption of other drugs
- Contraindications:
  - Absolute: Familial Dysbetalipoproteinemia
Triglycerides > 500 mg/dL
  - Relative: Triglycerides > 200 mg/dL

Fibric Acid Derivatives (fibrates)

Gemfibrozil, Clofibrate

- Effects on Lipids:
  - LDL-C: ↓ 10-15% (variable)
  - HDL-C: ↑ 10-15%
  - Triglycerides: ↓ 20-50%
- Major use is to lower triglycerides
- *Reduces risk of CHD?*

Fibric Acid Derivatives (fibrates)

- Potential Side Effects:
  - Elevation of liver enzymes, myopathies, nausea, diarrhea, gallstones
- Contraindications:
  - Absolute: Patients with CHD
  - Relative: Concomitant use of HMG-CoA reductase inhibitors

Assessing Risk – NCEP Risk Calculator

- 5 factors are useful for predicting risk
  - Gender and Age
  - Cholesterol
  - Smoking status
  - HDL cholesterol
  - Systolic BP

Assessing Risk
NCEP Risk Calculator

- Gives 10 CV risk for Death or MI
- Tool for physicians to tailor therapy to absolute risk
- Can give one a notion of potential effectiveness of therapies
- Lets individuals compare themselves to expected risk for age

Assessing Risk
NCEP Risk Calculator

- Gives 10 CV risk for Death or MI

Assessing Risk
NCEP Risk Calculator

- Tool for physicians to tailor therapy to absolute risk

Assessing Risk
NCEP Risk Calculator

Can give one a notion of potential effectiveness of therapies

- 65 yo woman with TC 240, HDL 39 and SBP of 165 on HCTZ
- Risk = 22% 12 pts for age; but modifiable
  - Chol = 3 pts – falls to 11% if lower to < 160
  - HDL = 2 pts - falls to 14% if raise to > 60
  - HTN = 6 pts - falls to 5% if lower to < 120

Assessing Risk
NCEP Risk Calculator

- Lets individuals compare themselves to expected risk for age
  - Age expected risk = risk if all modifiable risk factors are optimal
  - Example Risk of 70 yo man with TC 150, non smoker, HDL 55 and SBP of 118 =
    - 12 pts for age = 10%

Role of CRP

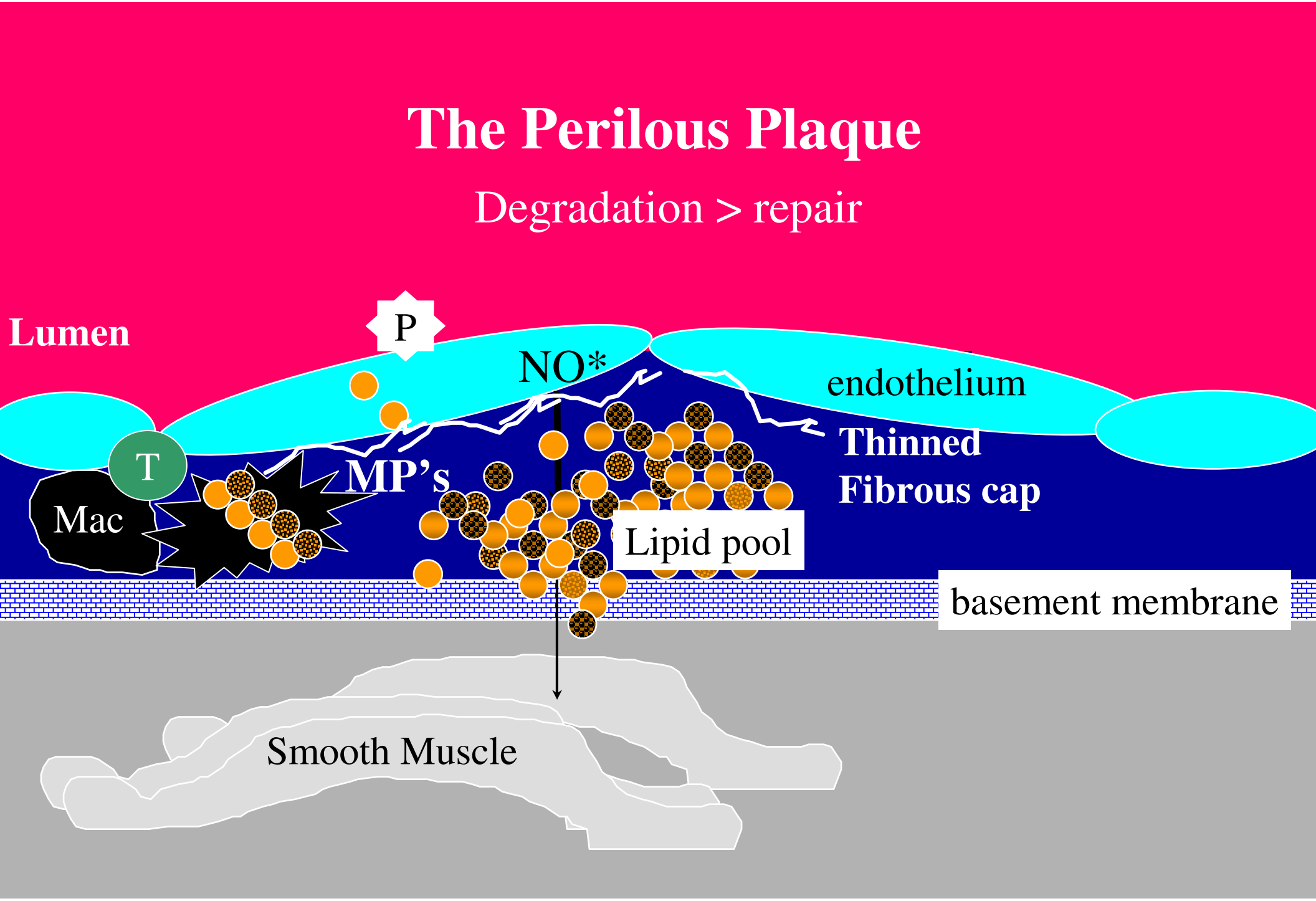
- Marker of inflammation in the body
- Elevated levels correlate very tightly with increased risk of cardiovascular events
  - In the blister and callous analogy events from blisters require two steps blister formation and blister rupture
  - Inflammation weakens the edge of the blister predisposing to rupture

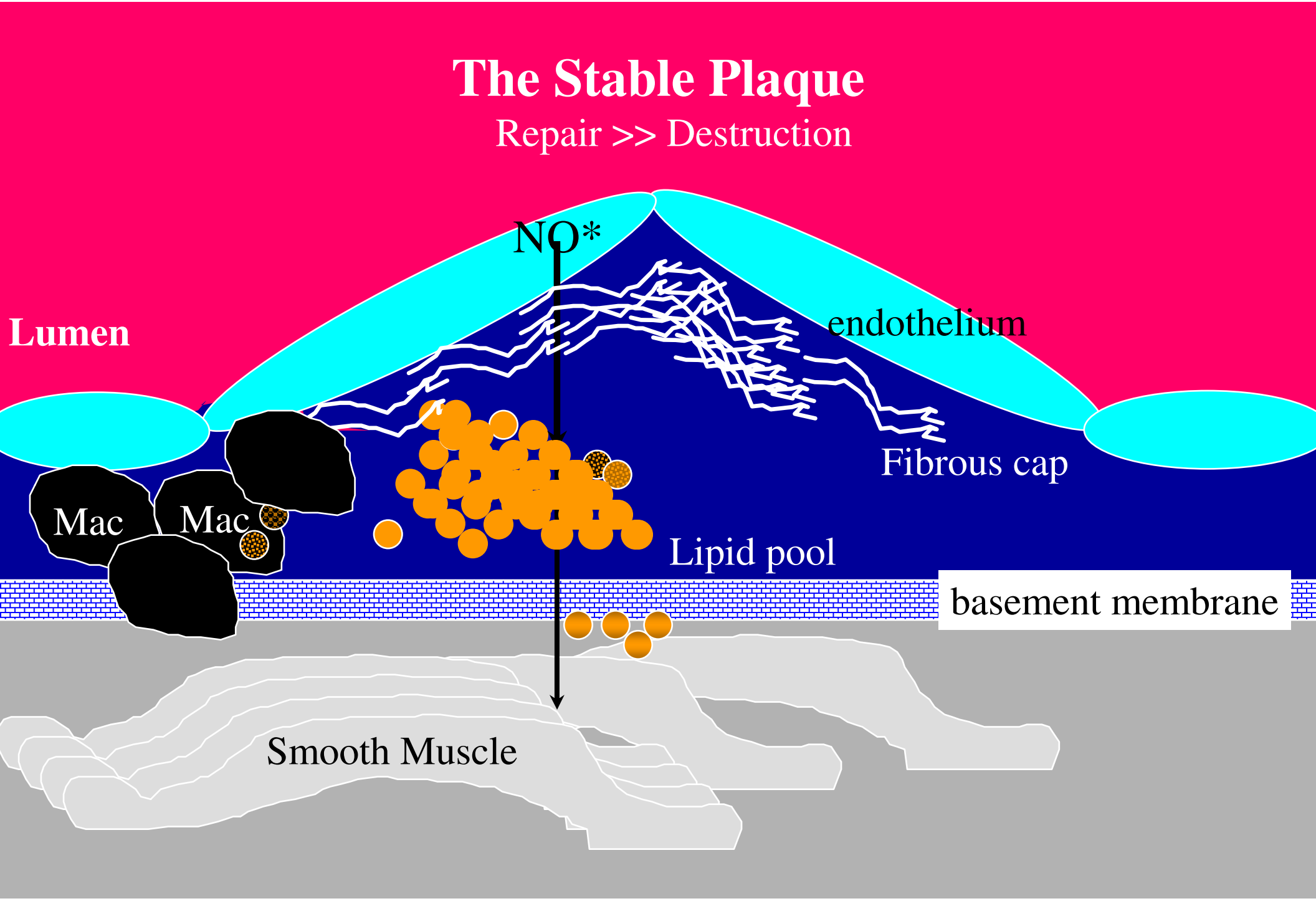
CRP

- Effectors of CRP
  - Cholesterol lowering
    - Statins
    - Zetia with statins
    - Niacin
    - Diet
  - Weight
  - Race
  - Other disease

CRP

- Desirable levels
  - Less than 3 is good
  - Less than 1 is great
  - Over 10 is not vascular in origin and investigation into other causes of inflammation should be considered


The Perilous Plaque
Degradation > repair
Lumen
P
NO*
endothelium
Thinned
Fibrous cap
T
Mac
MP's
Lipid pool
basement membrane
Smooth Muscle


The Stable Plaque
Repair >> Destruction
NO*
Lumen
endothelium
Fibrous cap
Mac
Mac
Lipid pool
basement membrane
Smooth Muscle

Other good things for preventing or healing "Blisters"

- Good diet
- Good management of other disease processes
- Good exercise habits
- Creating good habits and stopping bad ones
  - Too much alcohol
  - Any smoking
  - Too much stress

Conclusions

- Blisters are the enemy
  - Ruture easily and rupture =
    - Heart Attack
    - Heart Damage
- Callous' are the goal
  - Stable
  - If symptoms occur = Chest pain or new shortness of breath
    - not to worry. Consider it like recurrent knee or arm pain. Something easy to live with and fix if needed
- One gets to goal by paying attention to risk and treating it!!!!!!