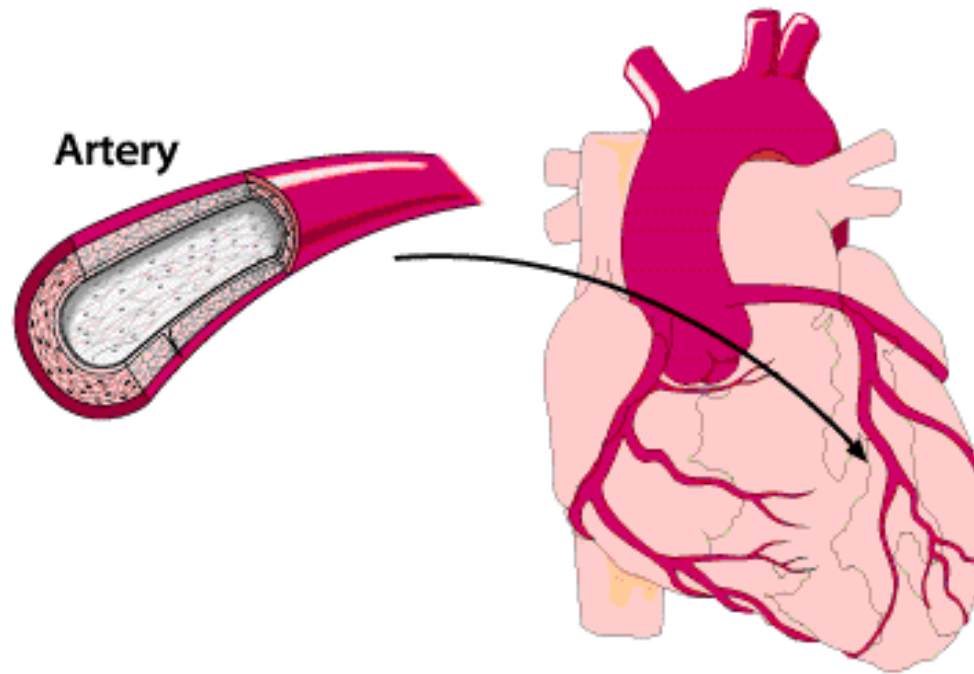


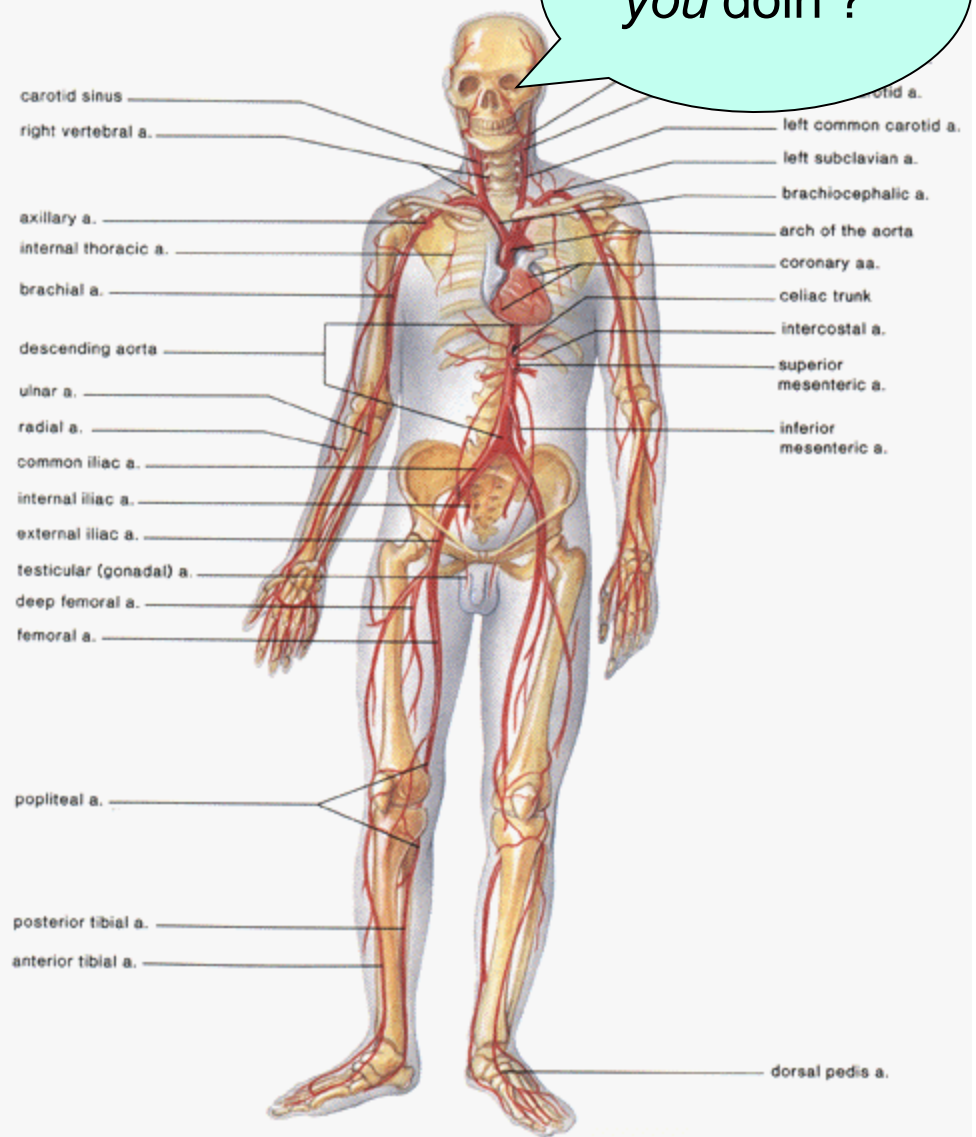
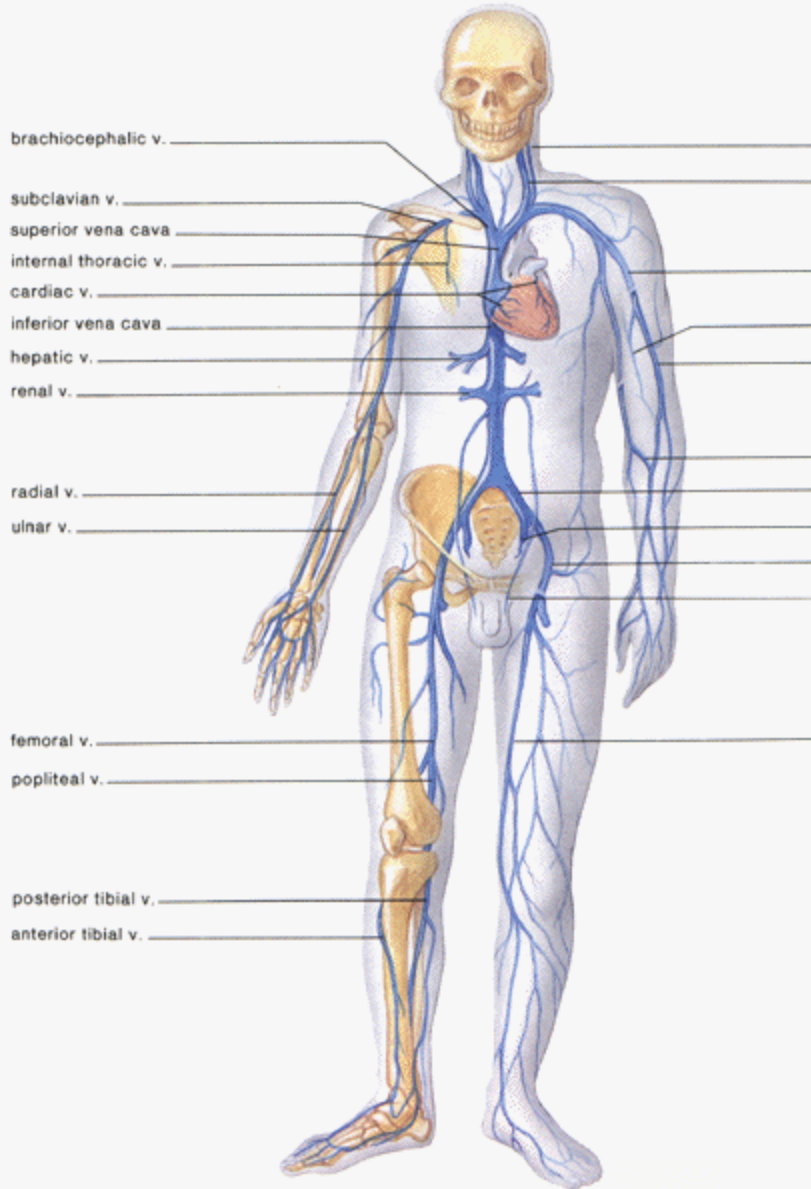
The Biology of Atherosclerotic Cardiovascular Disease



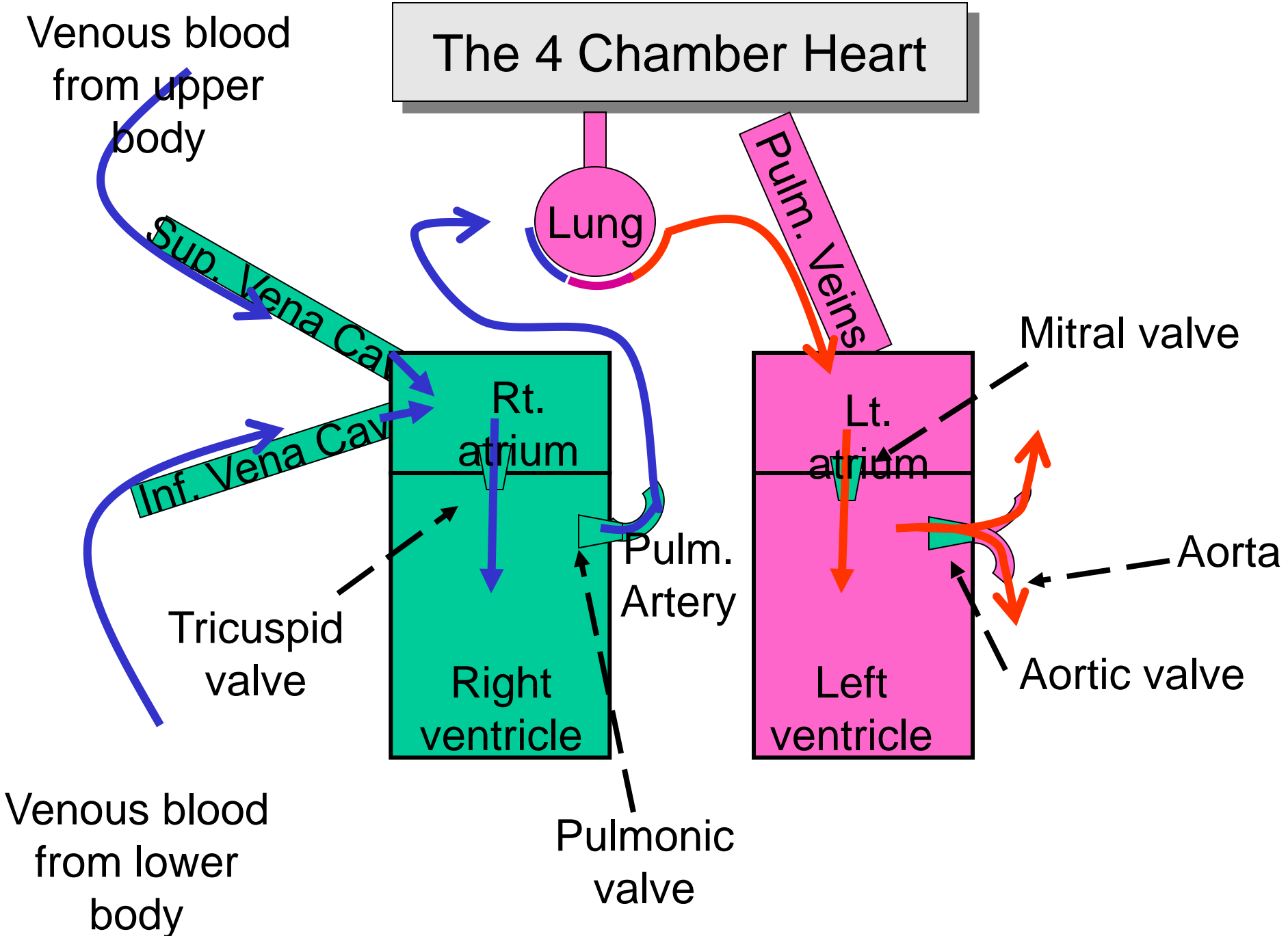
FYI

Venous & Arterial Systems

Hey, how you doin'?



The 4 Chamber Heart



Venous blood from upper body

Sup. Vena Cava

Inf. Vena Cava

Tricuspid valve

Rt. atrium
Right ventricle

Lung

Pulm. Artery

Pulmonic valve

Pulm. Veins

Lt. atrium
Left ventricle

Mitral valve

Aortic valve

Aorta

Venous blood from lower body

Small Veins & Capillaries

To heart,
neck, arms

Superior
Vena Cava

Pulm. a.

Pulm. v.

Aorta
Left
Atrium

Rt. Atrium

Aorta

Rt.
ventricle

Lungs

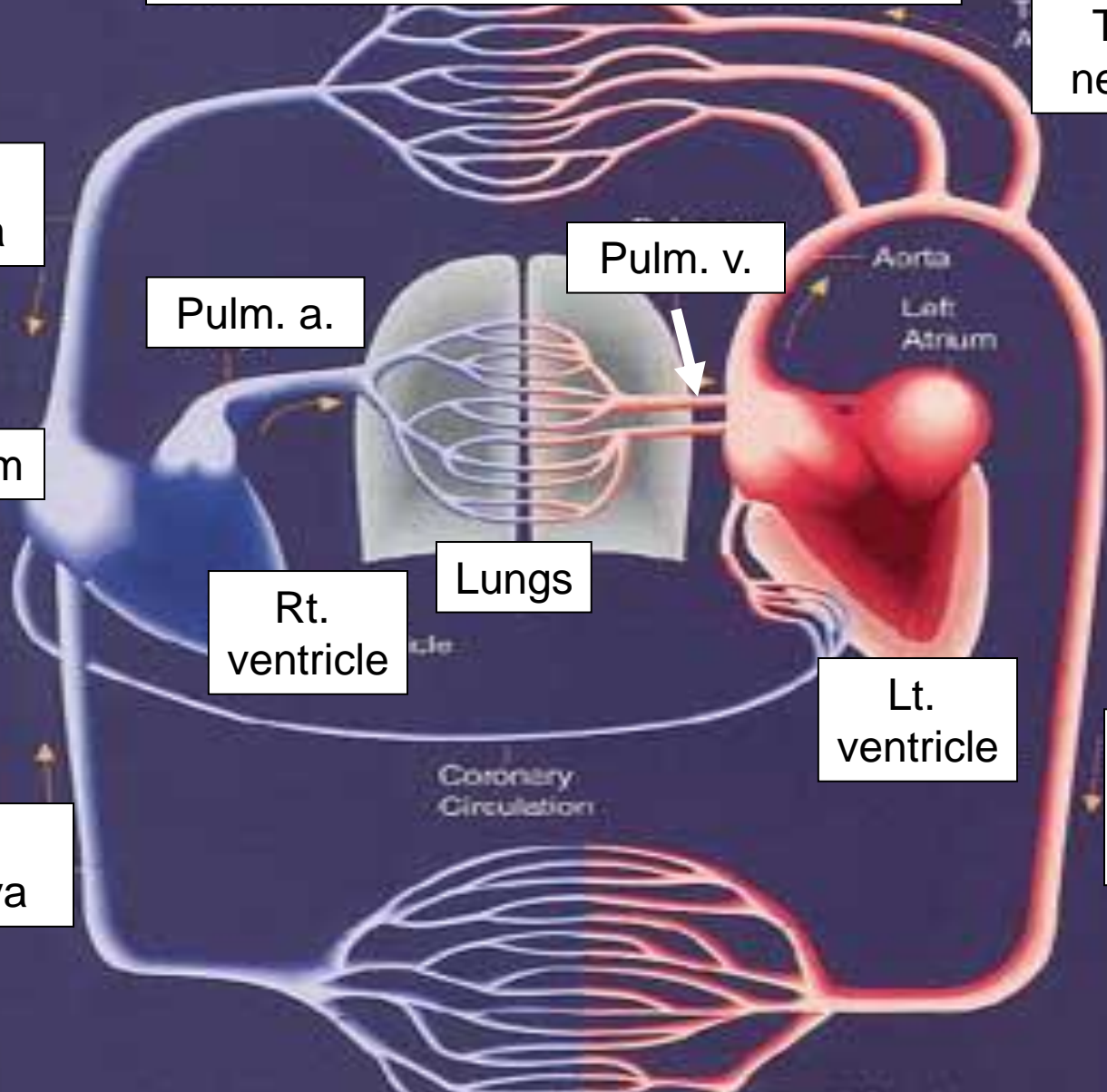
Lt.
ventricle

To abd.,
kidneys,
pelvis, legs

Inferior
Vena Cava

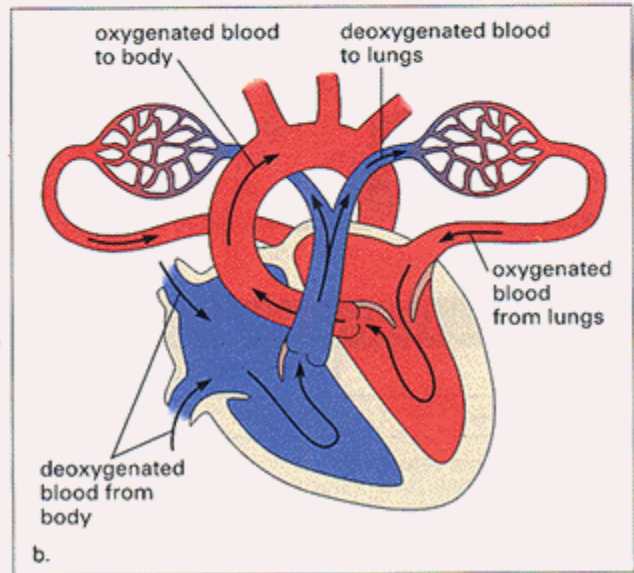
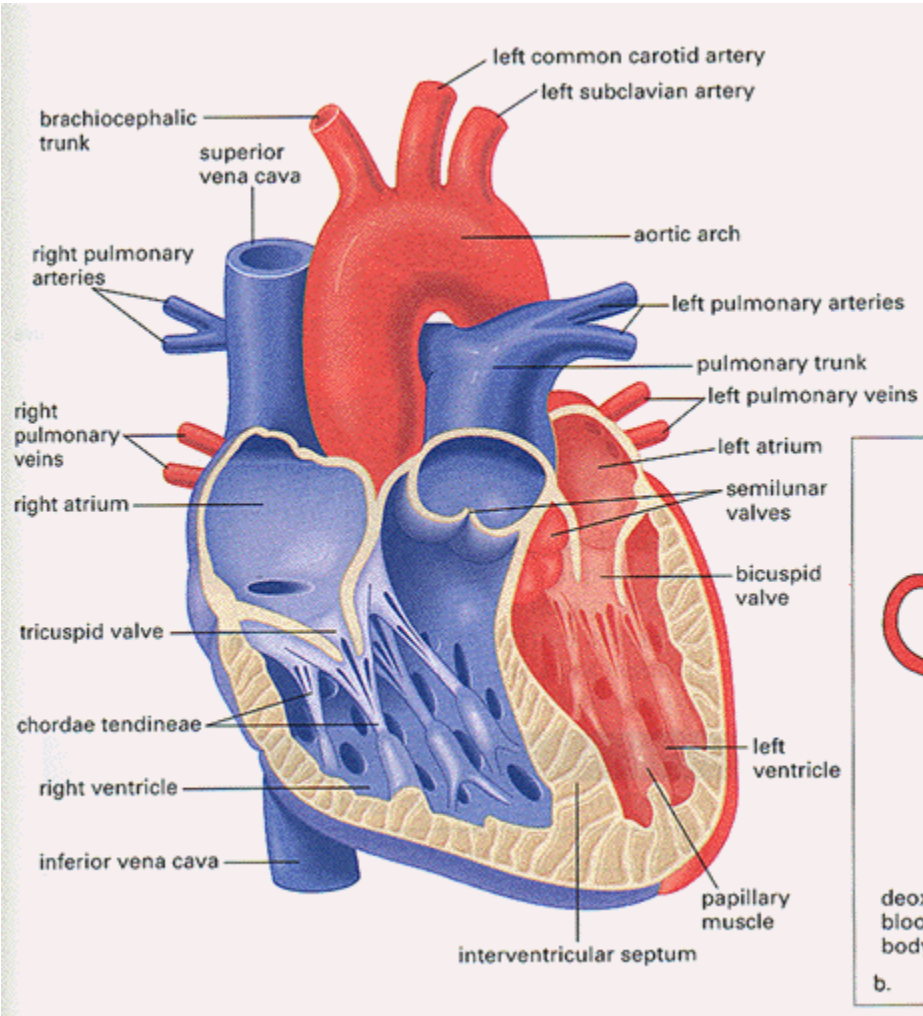
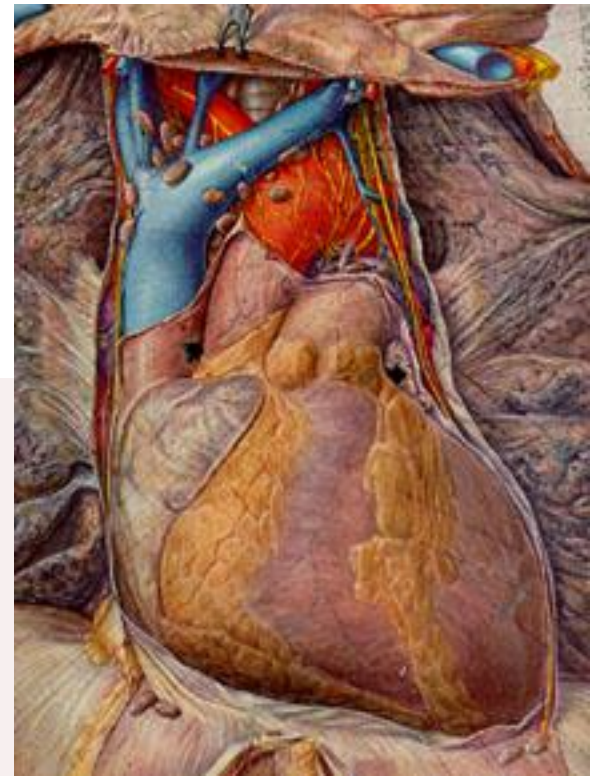
Coronary
Circulation

Small Veins & Capillaries

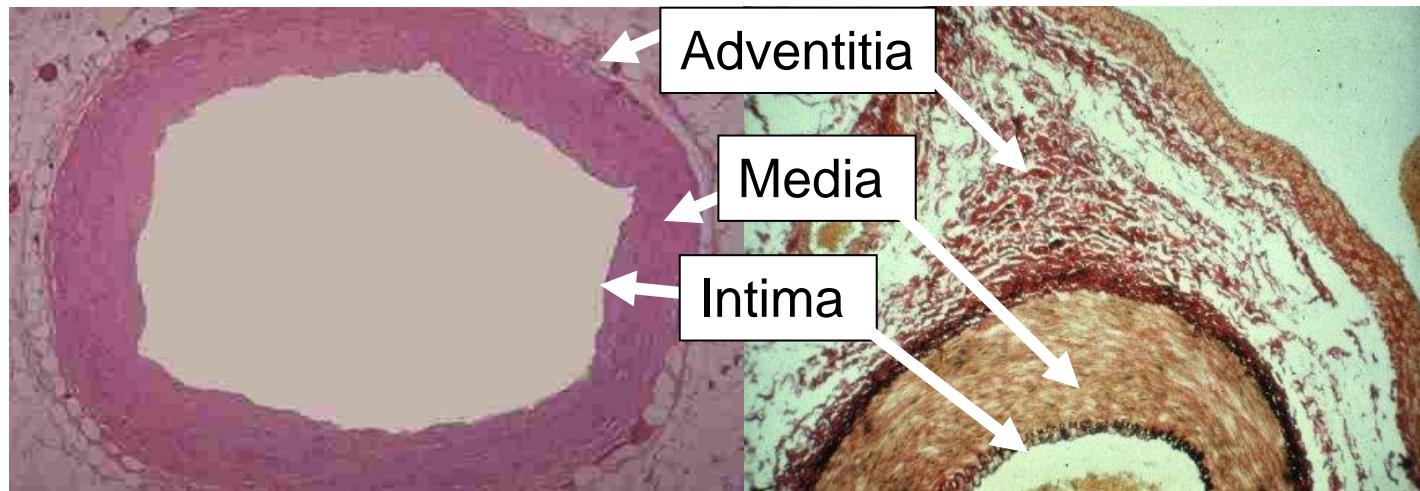
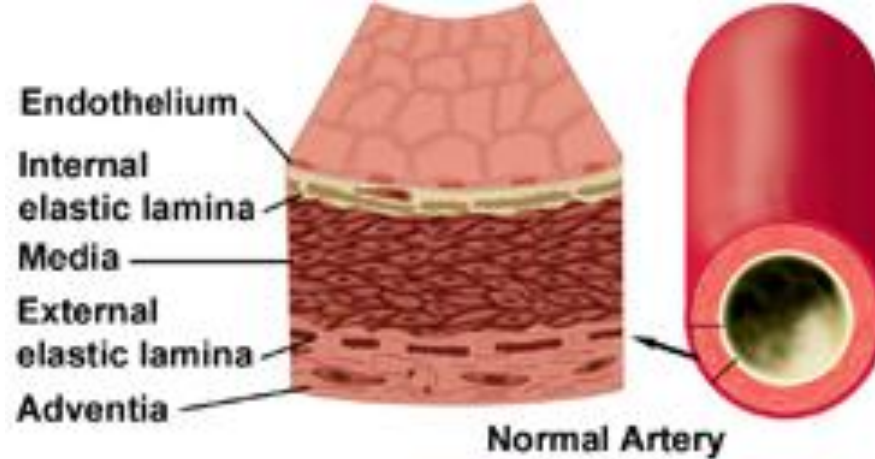


FYI

Anatomy of the Heart



Blood Vessels



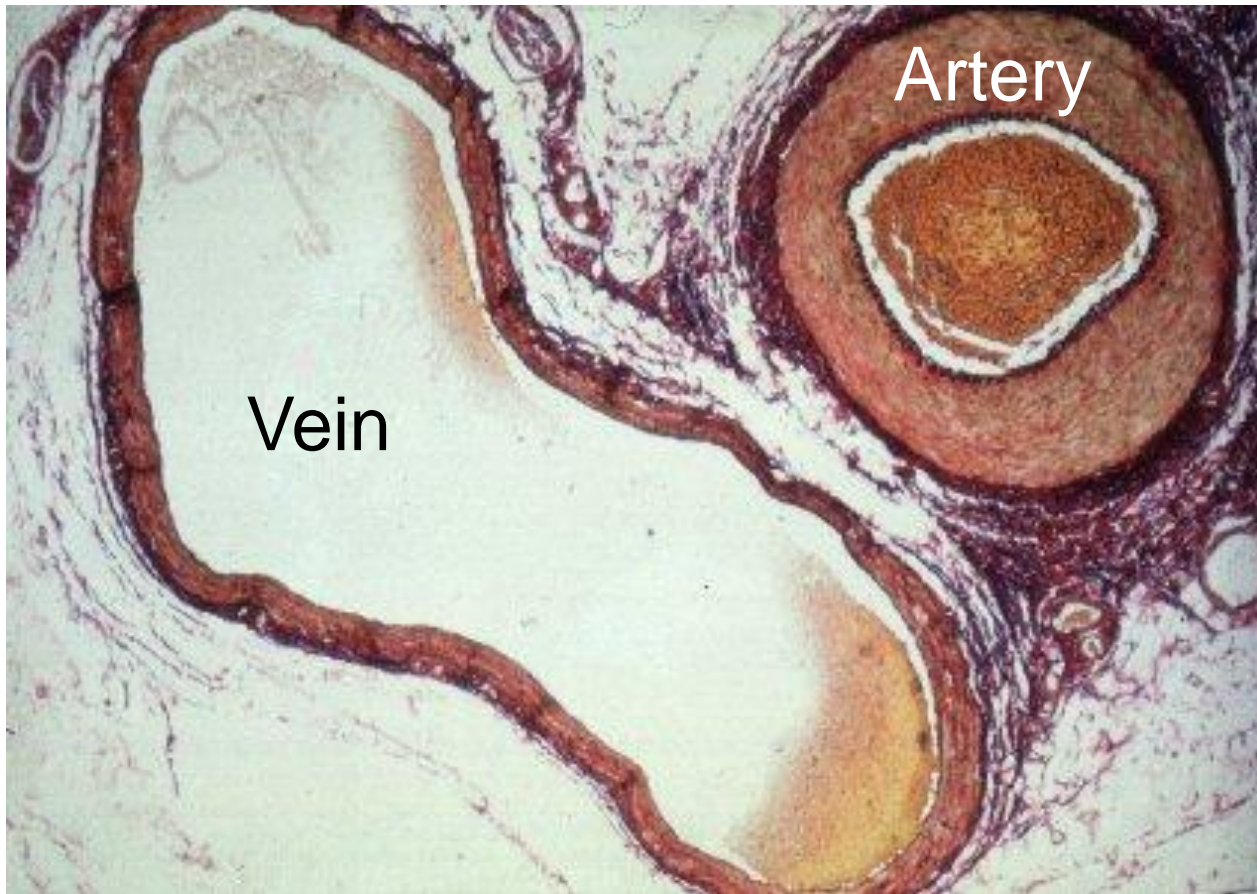
Veins & Arteries have 3 layers.

Intima: endothelial cells in contact with the blood. The internal elastic lamina forms the barrier between the intima and the underlying “tunica media.”

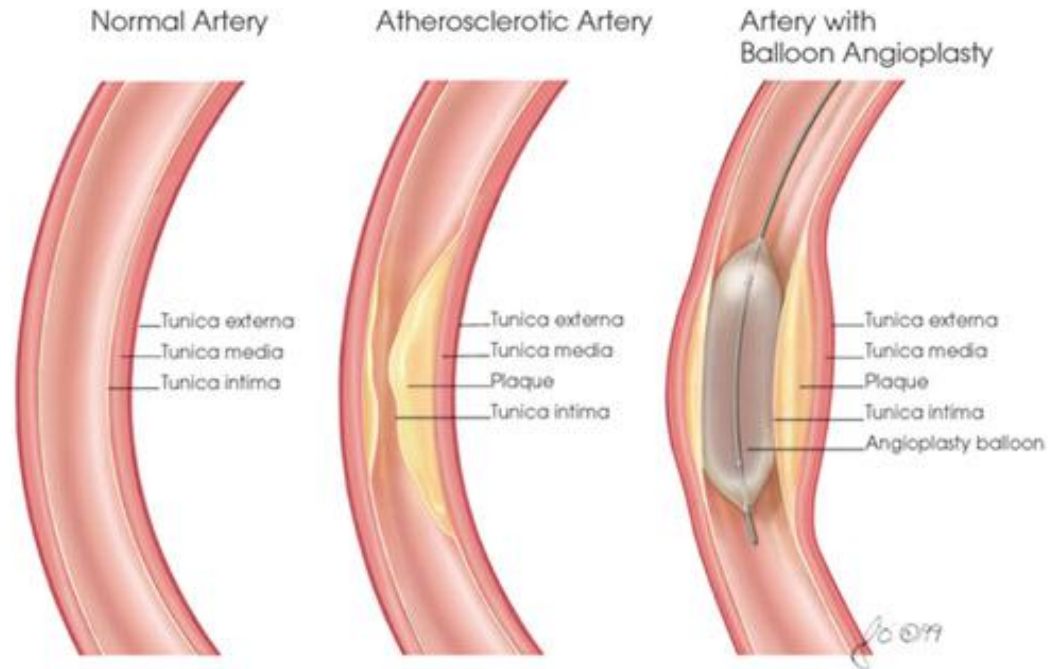
The **media** has multiple layers of smooth muscle cells. The outer layer of connective tissue is the **adventitia**.

Veins

- Have thinner walls; less media.
- Have a lower lumen pressure.
- Have valves that direct blood back toward the heart



Magnitude of the Problem



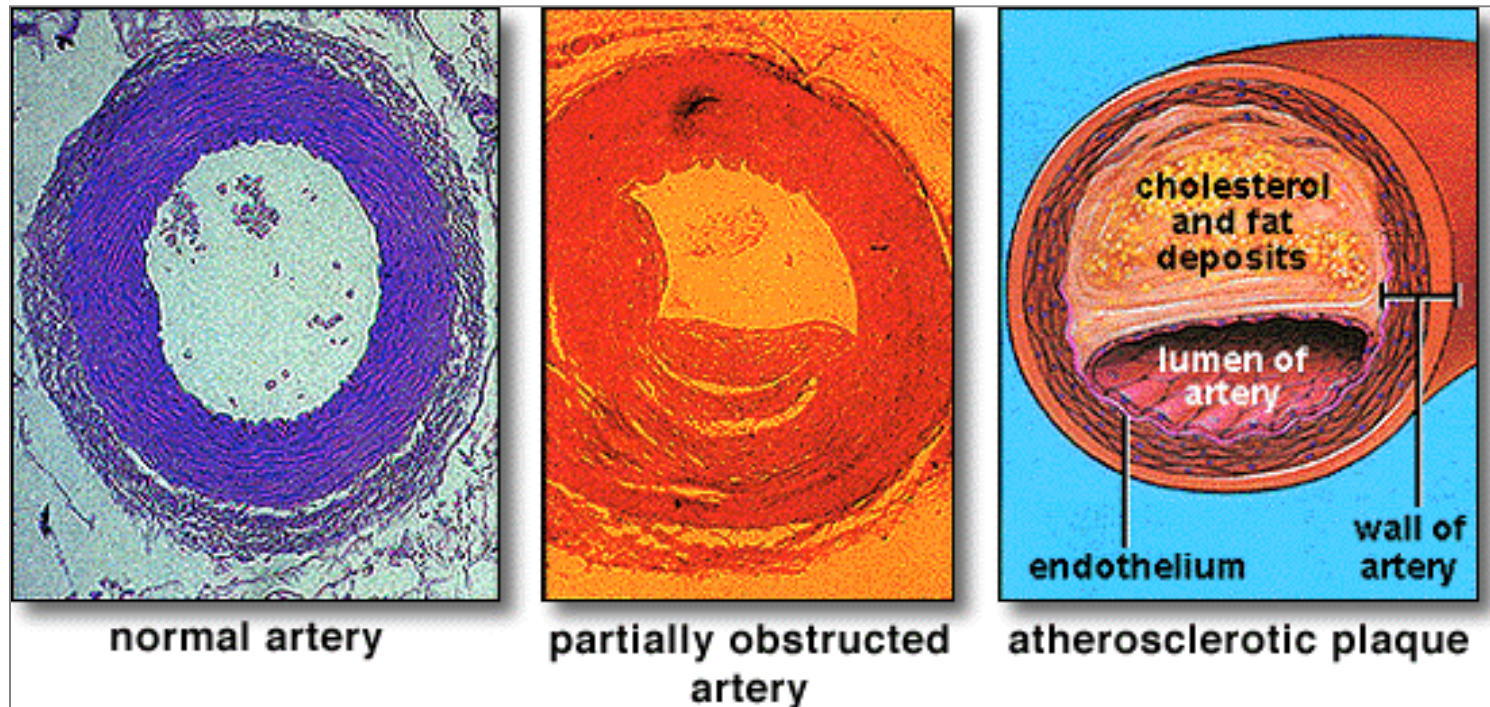
- Despite changes in lifestyle and “statins” to lower cholesterol, & angioplasty, cardiovascular disease is the #1 cause of death in the world.
- Atherosclerosis kills 800,000/year in US.
- Worldwide mortality is 12 million/year.

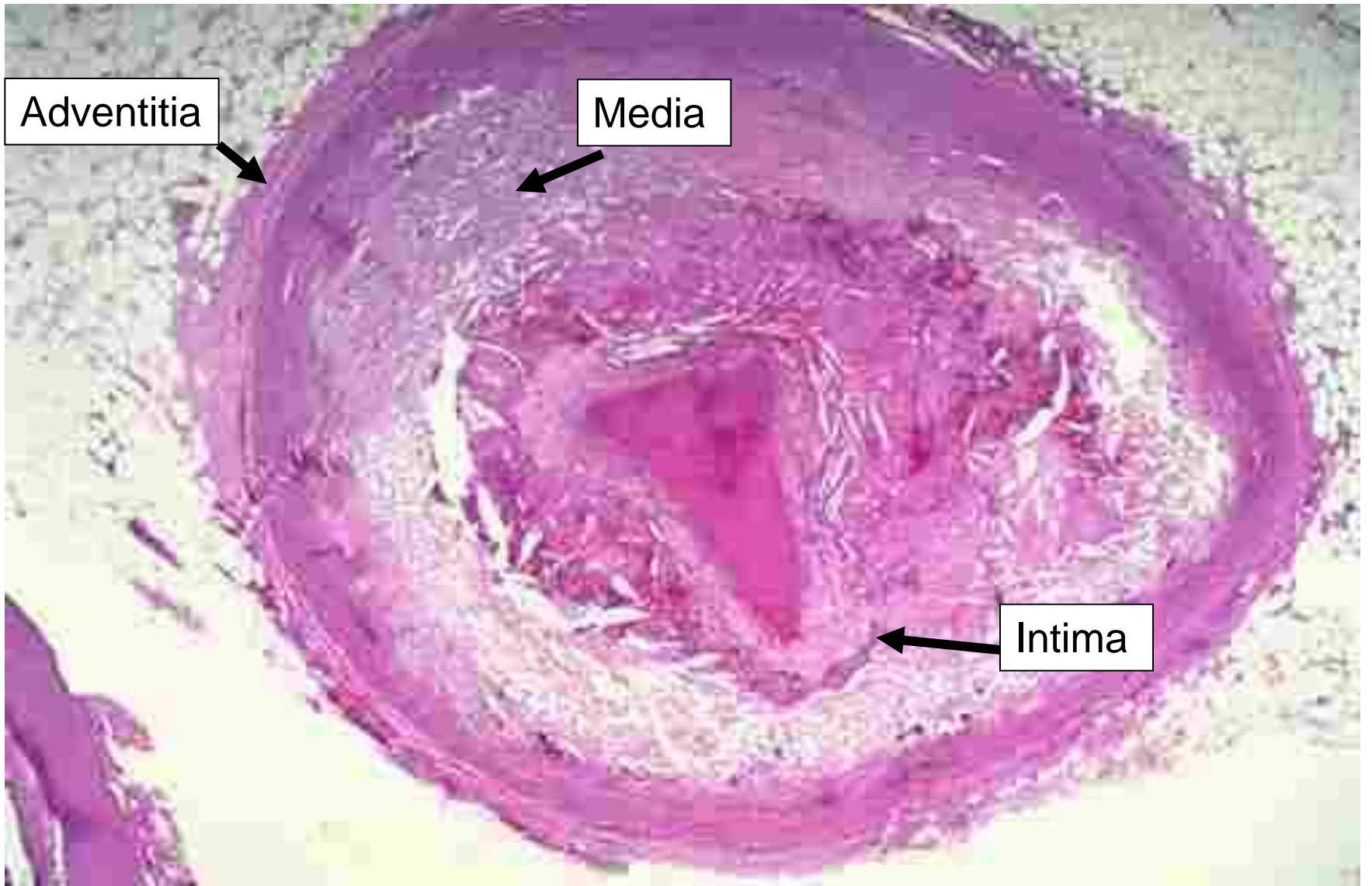
FYI

Atherosclerosis

Atherosclerosis is a disease process that produces blockages in arteries, mainly large and medium-sized arteries and can lead to **ischemia** (inadequate blood flow) of the heart, brain, or extremities.

When severe, it can produce "**infarction**," death of the tissue being supplied by the blocked artery.



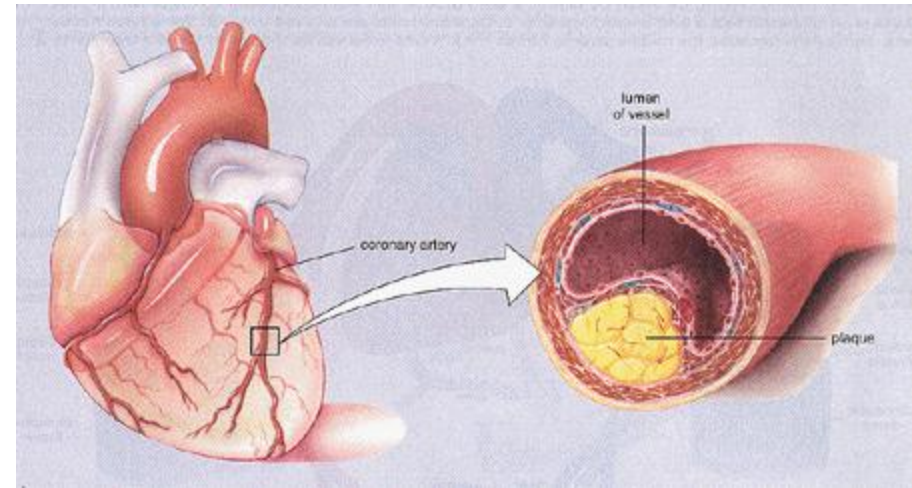
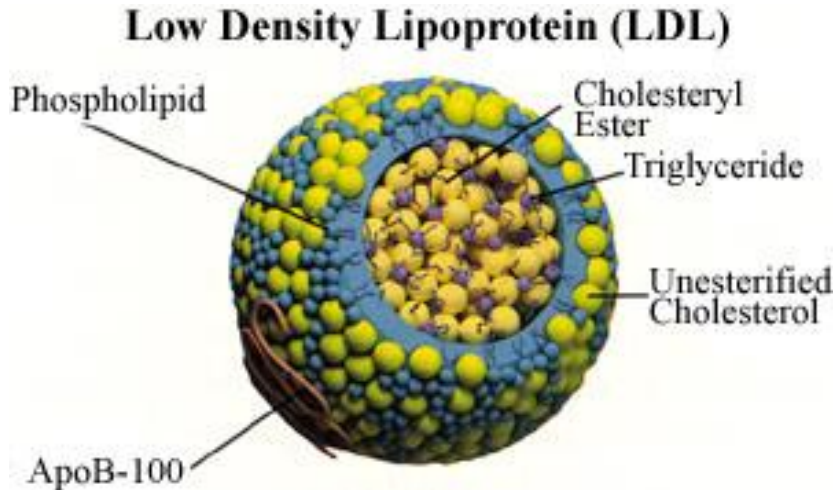


Adventitia

Media

Intima

Lipoproteins Transport Fatty Substances



Since high blood concentrations of cholesterol (especially in LDL), are a strong risk factor for atherosclerosis, many have believed that atherosclerosis is simply due to accumulation of lipids in the arterial wall.

In fact, the pathogenesis of atherosclerosis is more complicated & interesting than that.

Response To Injury Theory

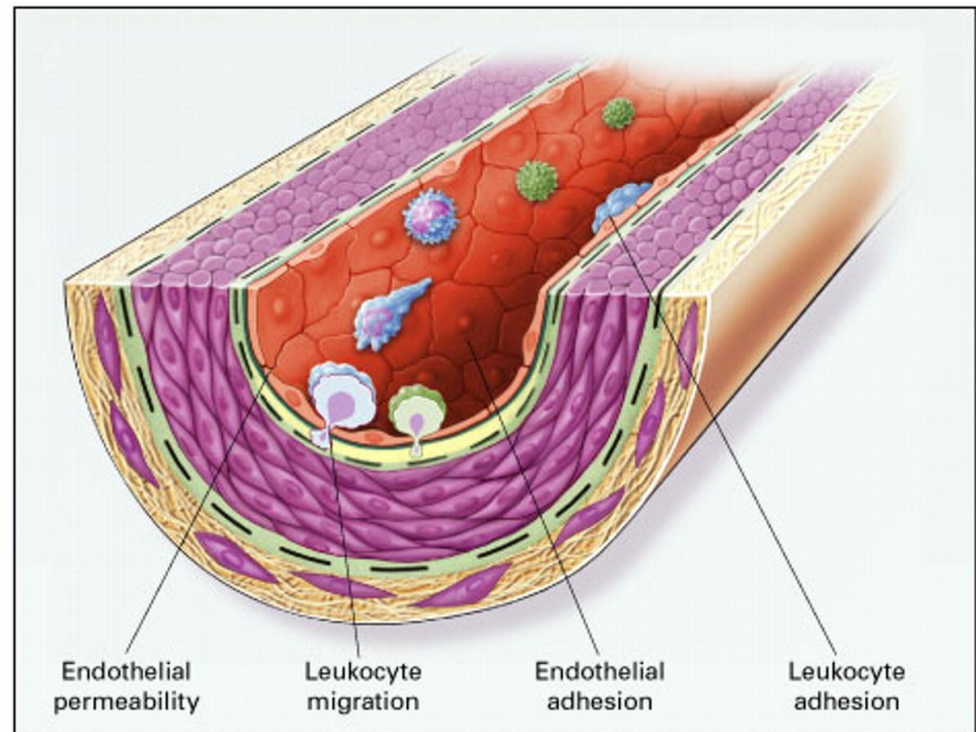
Atherosclerosis is initiated by endothelial injury and dysfunction due to:

- Elevated and modified LDL
- Free radicals caused by cigarette smoking
- Turbulent blood flow
- Hypertension
- Diabetes mellitus (glycation)
- Elevated plasma homocysteine concentrations
- Infectious microorganisms such as herpes viruses or *Chlamydia pneumoniae*

Endothelial Injury Triggers Responses

Earliest phase: injury stimulates inflammatory response:

- Increased adhesiveness of leukocytes (macrophages, T lymphocytes, and platelets) to endothelium
- Increased permeability
- Formation of vasoactive molecules, cytokines, and growth factors.



Inflammation

With infection or injury, mast cells release vasodilators that increase capillary permeability allowing plasma and leukocytes (white cells or WBCs) to leave the blood and enter tissue.

Cytokines, e.g. TNF & Il-1 induce the production of selectins, chemokines, and adhesion molecules on the inner surface of the endothelial cells that form the capillaries. Eventually integrins on the surface of the leukocyte bind to adhesion molecules on the inner surface of the endothelial cells. The leukocytes enter tissues by flattening out and squeezing between the endothelial cells.

The “Blood-Brain Barrier”:

The brain has “tight junctions” between endothelial cells making it hard for cells and large molecules to enter brain tissue.

LDL In Blood Vessels

In addition to supplying triglycerides to cells through action of lipoprotein lipase, LDL particles:

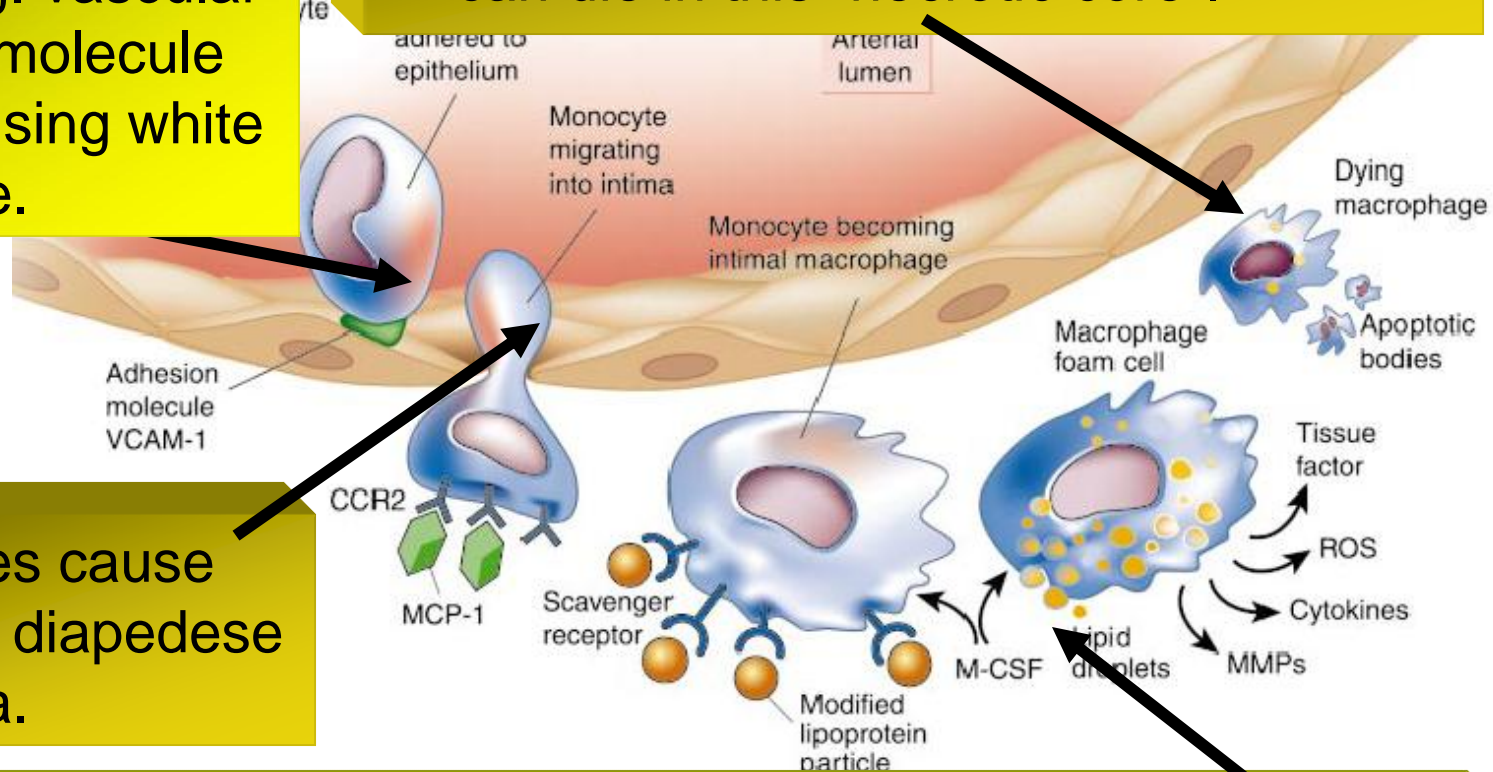
- Can be taken up by endothelial cells by endocytosis
- Can get beneath the endothelial cells due to increased permeability secondary to inflammatory changes. Inflammation also increases oxidation of LDL particles.

1) Injured endothelium makes adhesion molecules, e.g. vascular cell adhesion molecule (VCAM-1) causing white cells to adhere.

2) Chemokines cause monocytes to diapedese into the intima.

3) In the intima the monocyte becomes a macrophage expressing receptors that bind and take up lipoprotein particles modified by oxidation or glycation. This creates "foam cells", a hallmark of atheromas. Foam cells secrete inflammatory cytokines that amplify the inflammatory response, & also reactive oxygen species.

4) Eventually the macrophages congregate in a central core in the atherosclerotic plaque. Macrophages can die in this "necrotic core".



Monocytes migrating into the intima

Arterial Lumen

Monocyte differentiated to a macrophage

Foam Cell

Dying macrophage

Apoptotic bodies

VCAM-1

Intima

CCR2

MCP-1

Scavenger receptor

LDL being taken up by macrophage

M-CSF

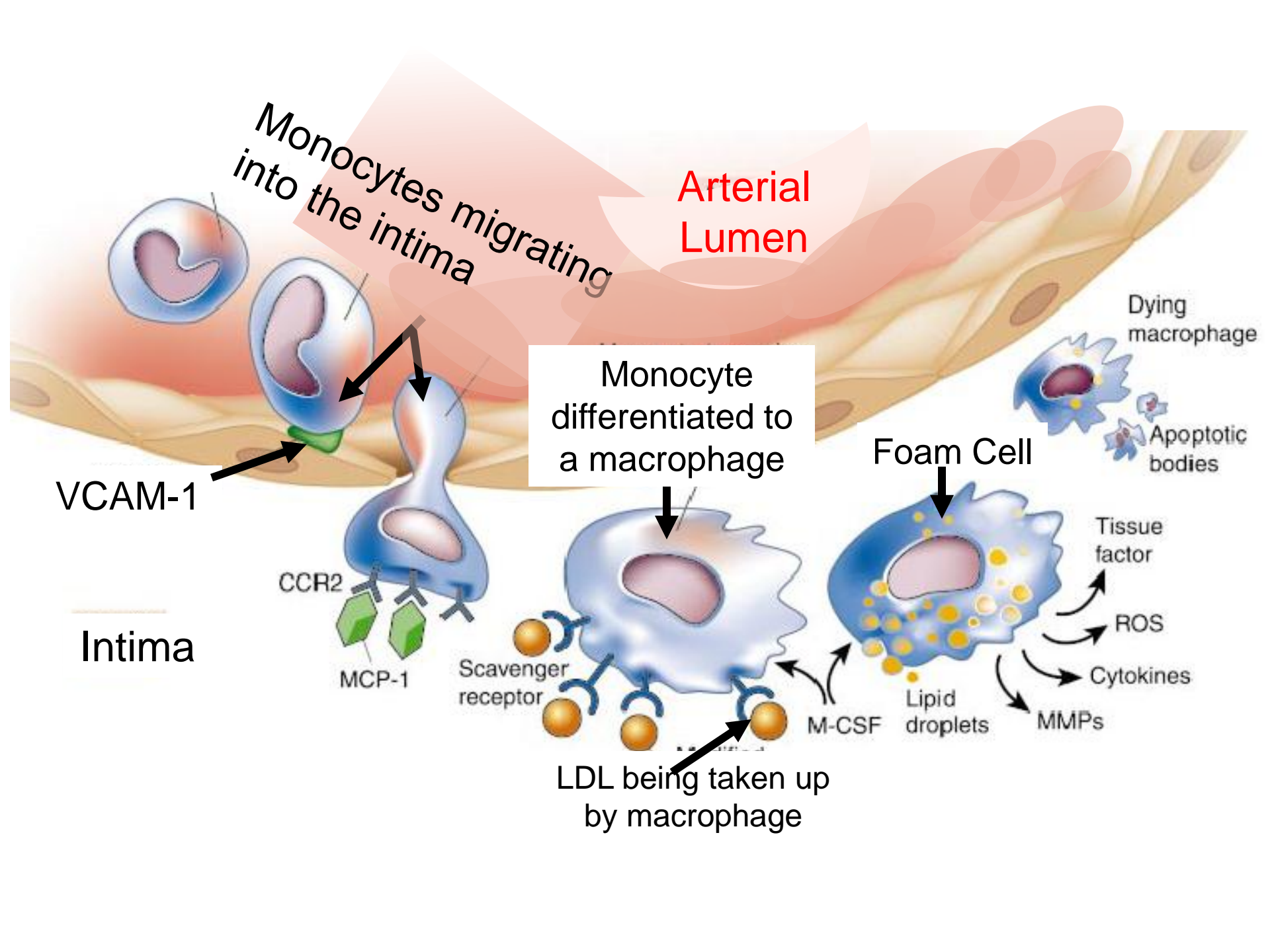
Lipid droplets

Tissue factor

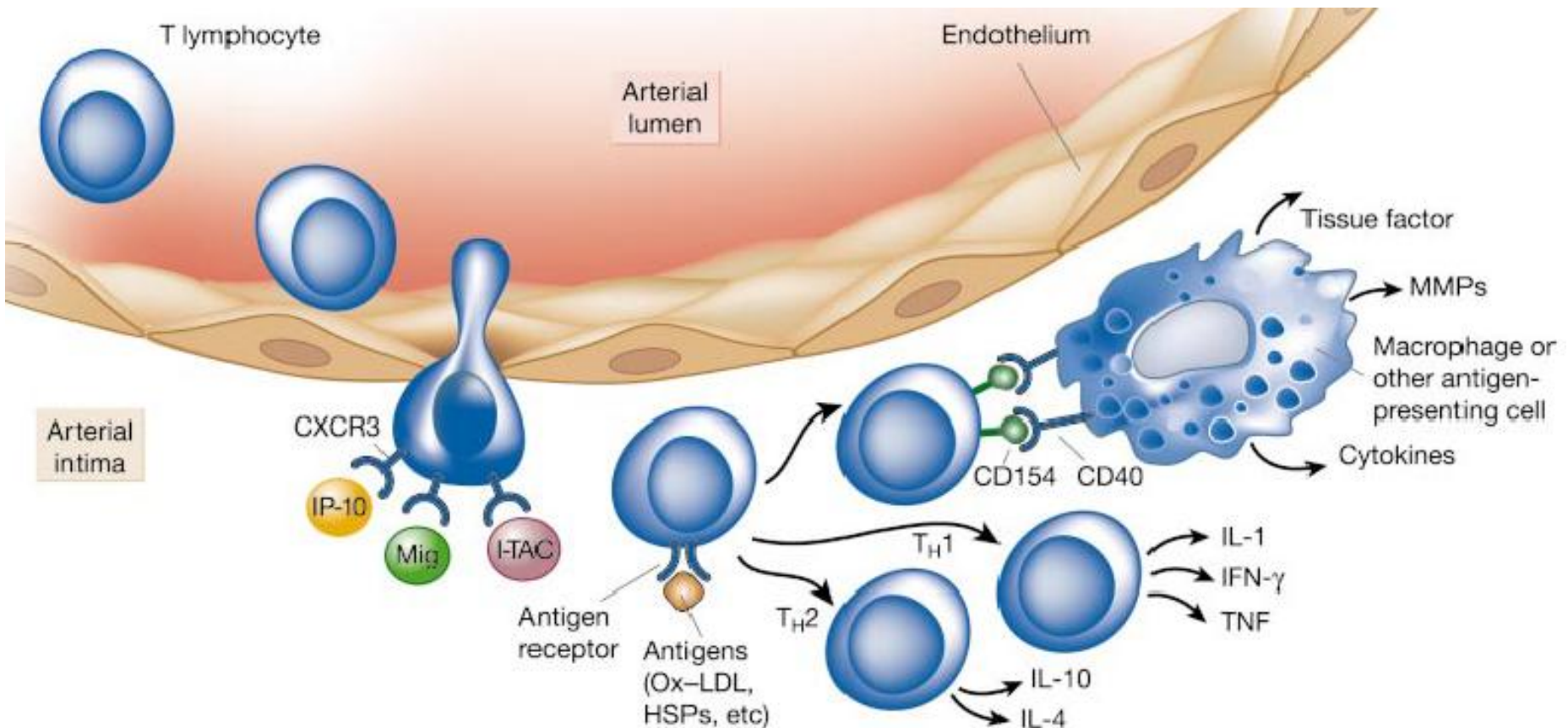
ROS

Cytokines

MMPs

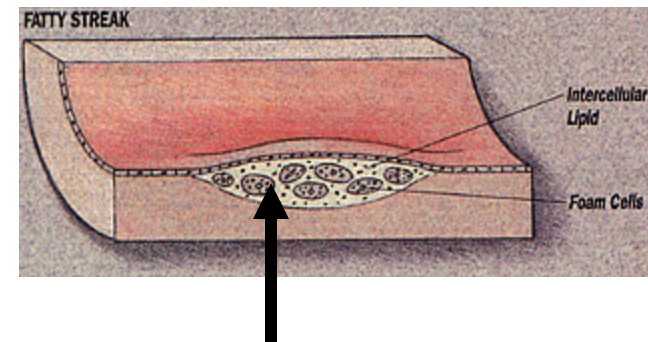
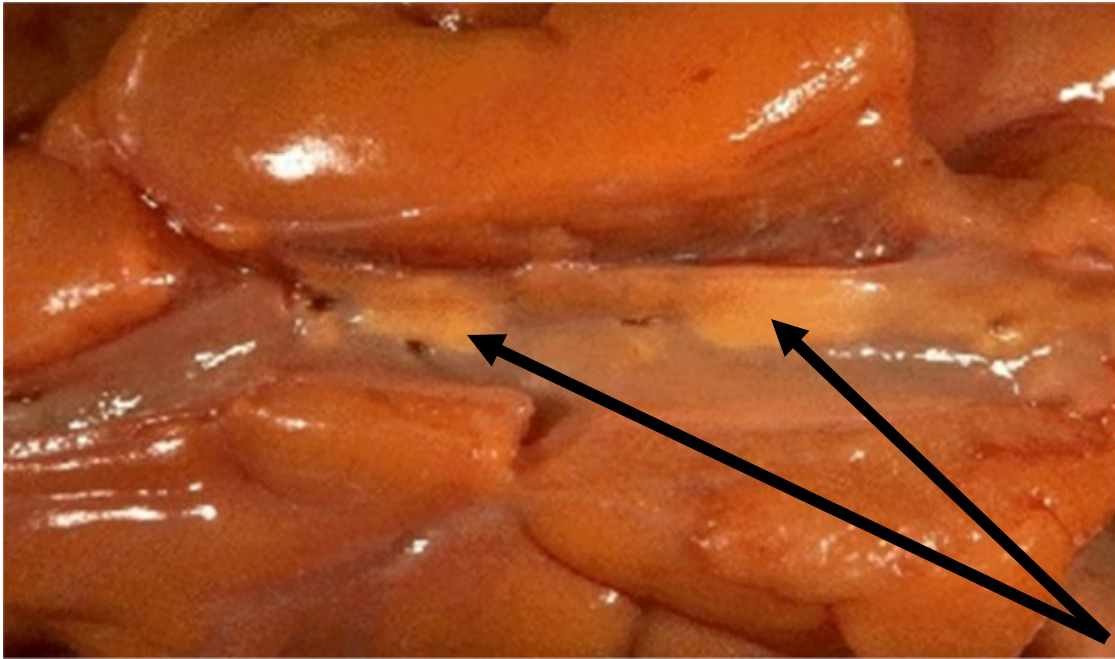


T Lymphocytes



Lymphocytes also bind to VCAM and enter the intima following chemoattractants. When the T cell encounters oxidized LDL, it produces cytokines that influence other cells and amplify the response.

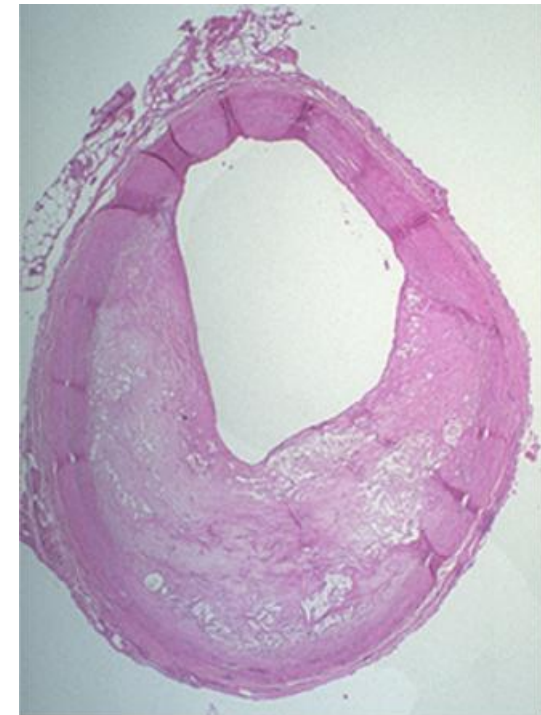
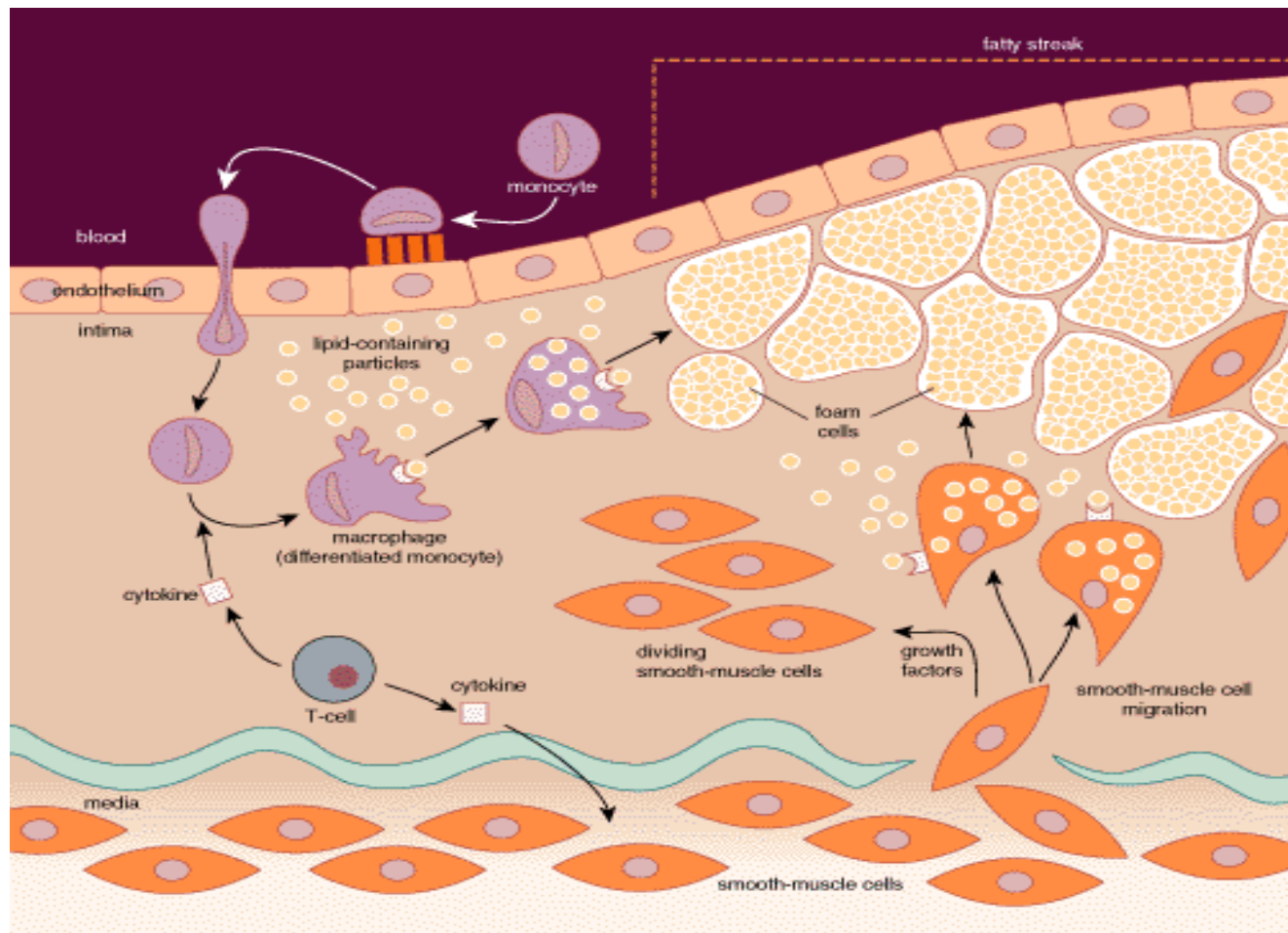
The Fatty Streak



A fatty streak consists of lipid-containing **foam cells** in the arterial wall just beneath the endothelium. It is the first obvious lesion during atherogenesis, and can be found in teenagers.

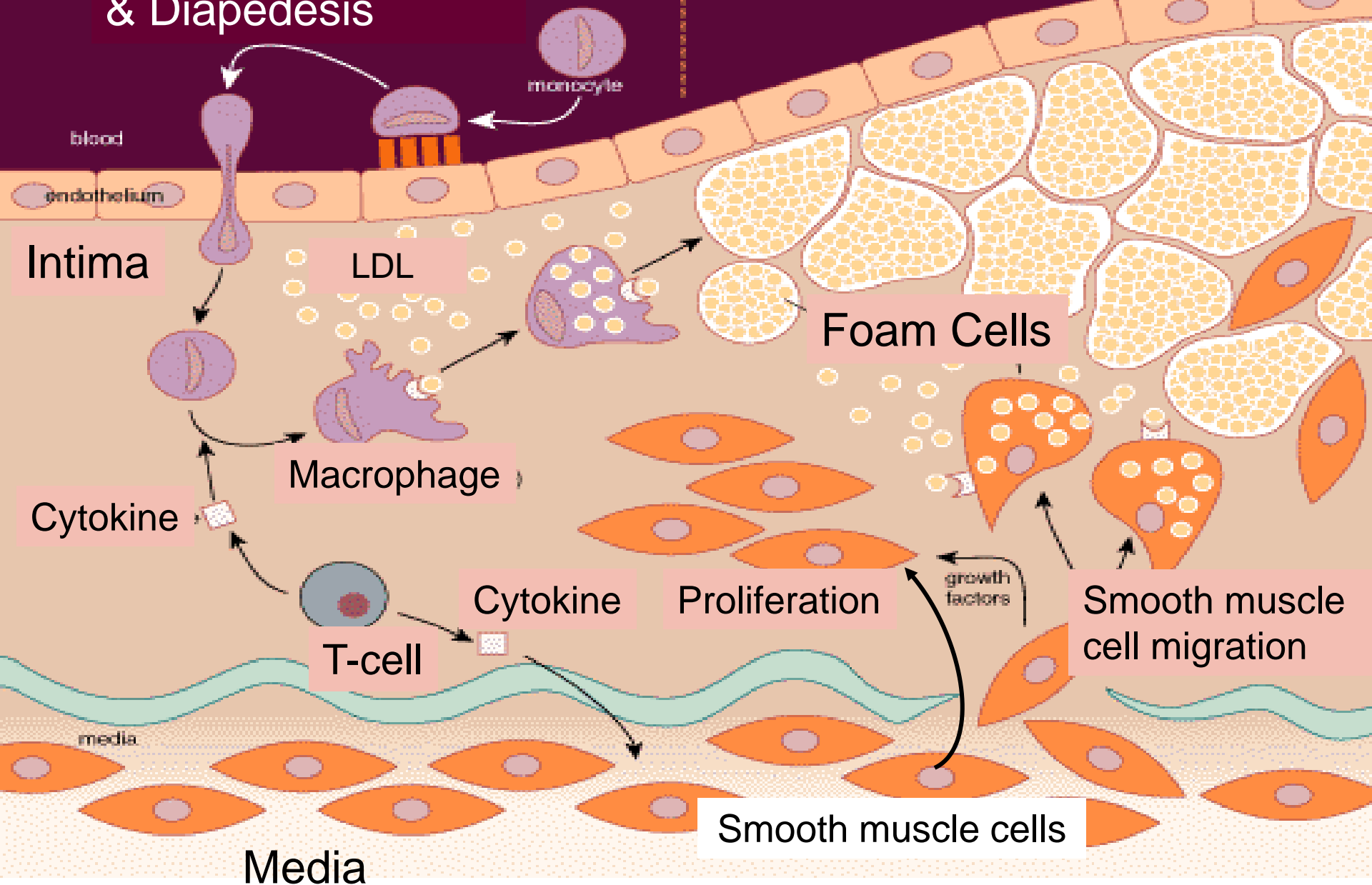
Smooth Muscle Cell Migration & Proliferation

Fatty streaks can slowly evolve into “**plaques**” or “**atheroma**” via migration & multiplication of smooth muscle cells stimulated by growth factors from leukocytes.



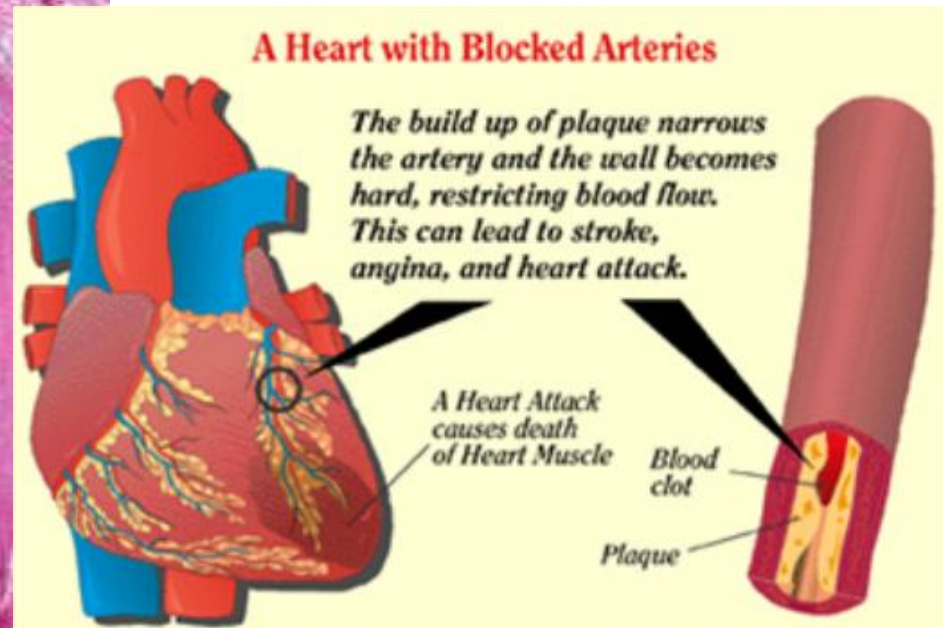
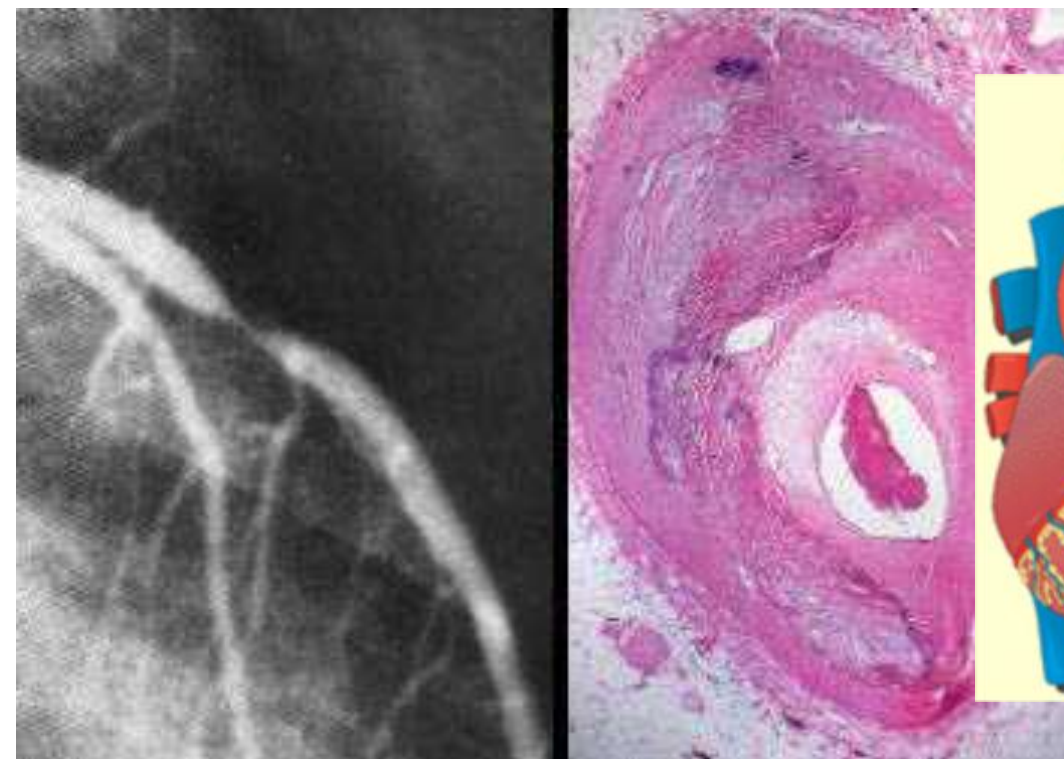
Monocyte Adhesion & Diapedesis

Fatty streak



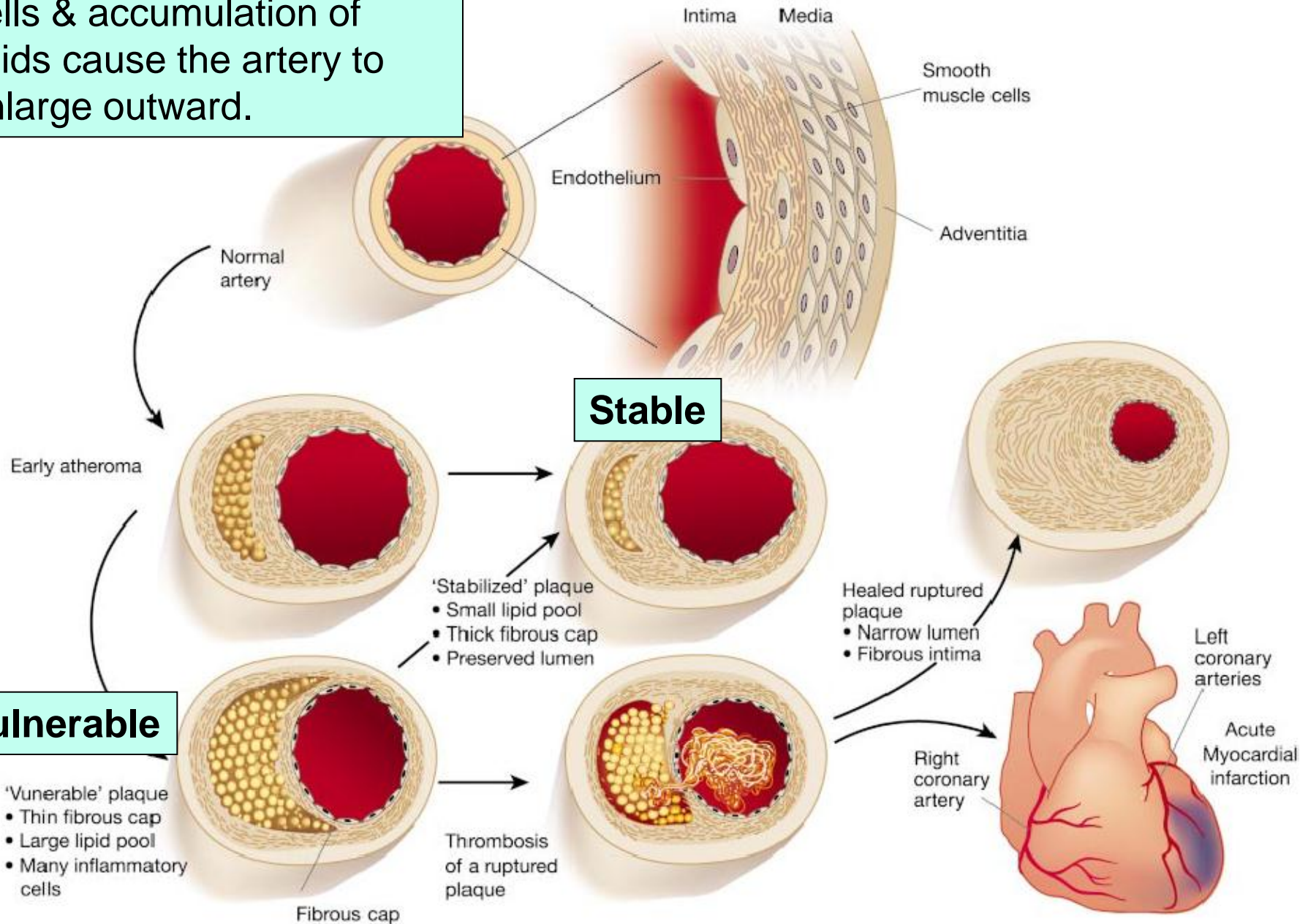
Ischemic Symptoms

Over time, the arterial lumen narrowed, impeding blood flow & leading to ischemic symptoms (e.g. **angina pectoris**), which would be more pronounced with increased demand (e.g. exercise). Ischemia implies that blood flow is inadequate to supply tissue demands. If severe enough **infarction** results.

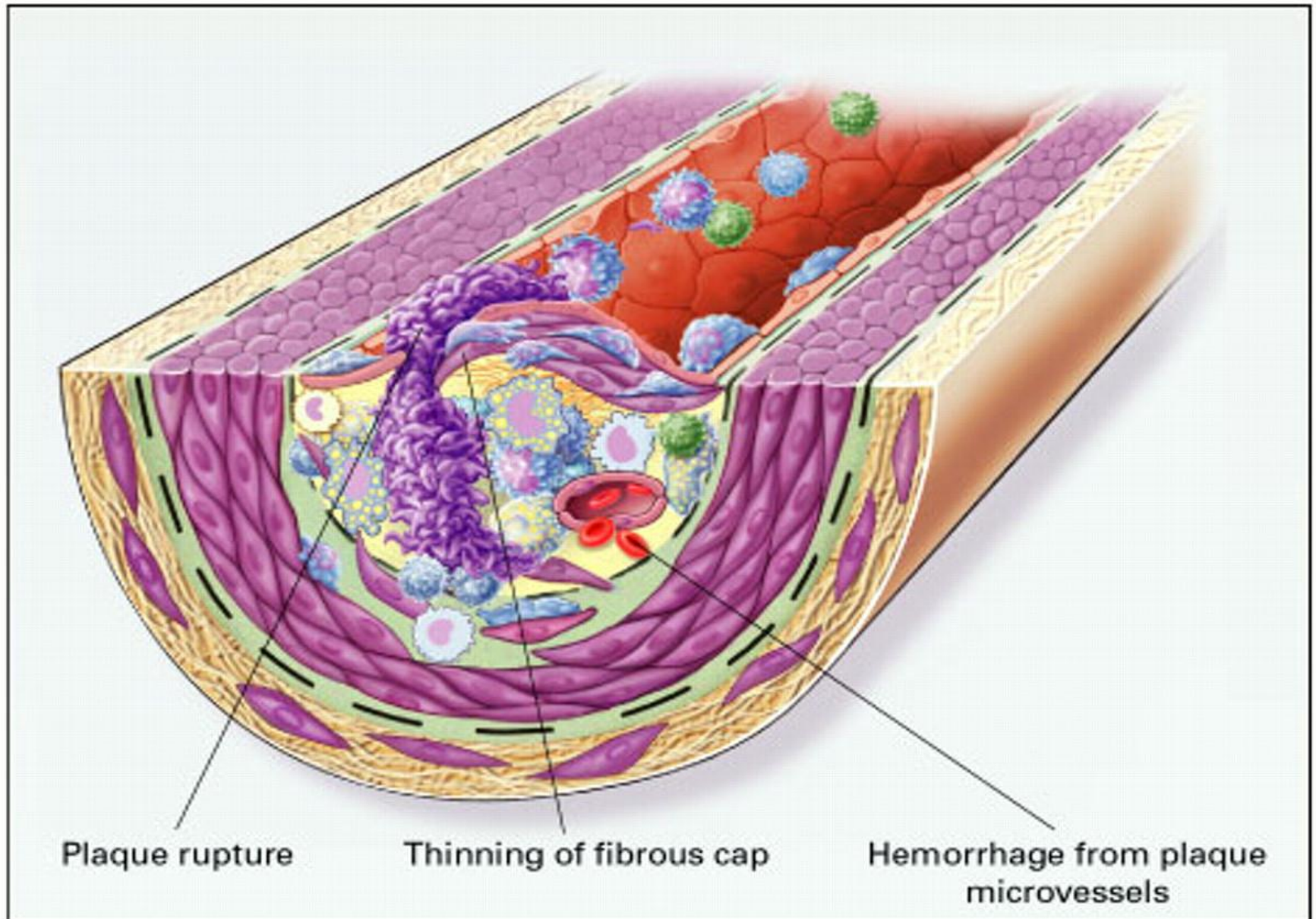


A Newer View of Infarction

In early atherogenesis, recruitment of inflammatory cells & accumulation of lipids cause the artery to enlarge outward.



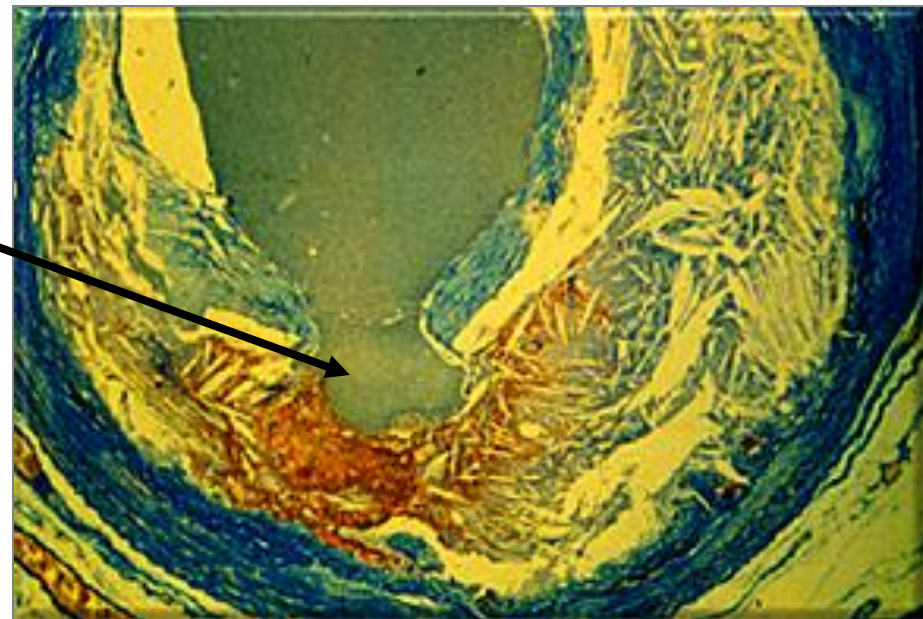
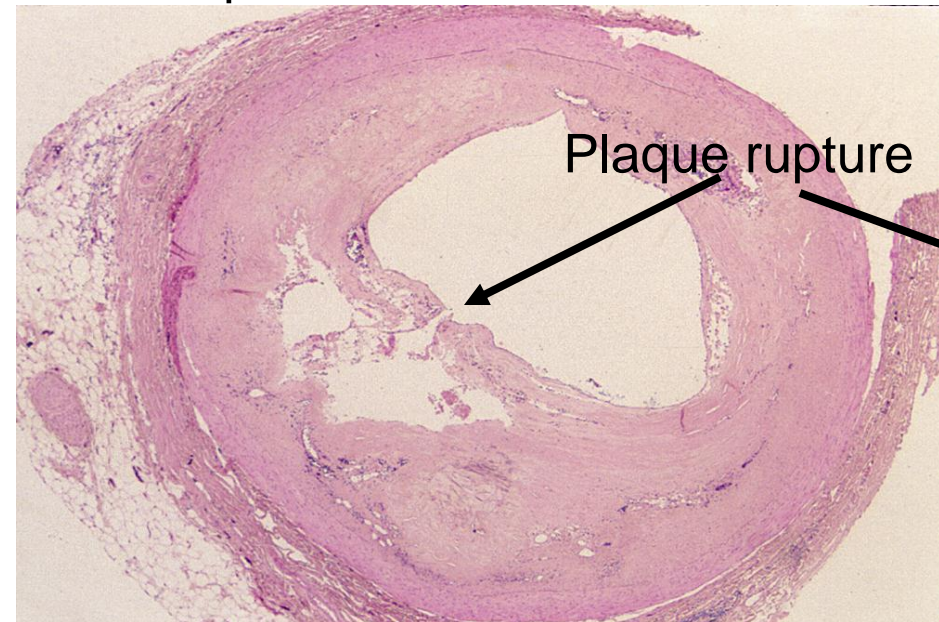
Rupture of the Fibrin Cap



Plaque Stability

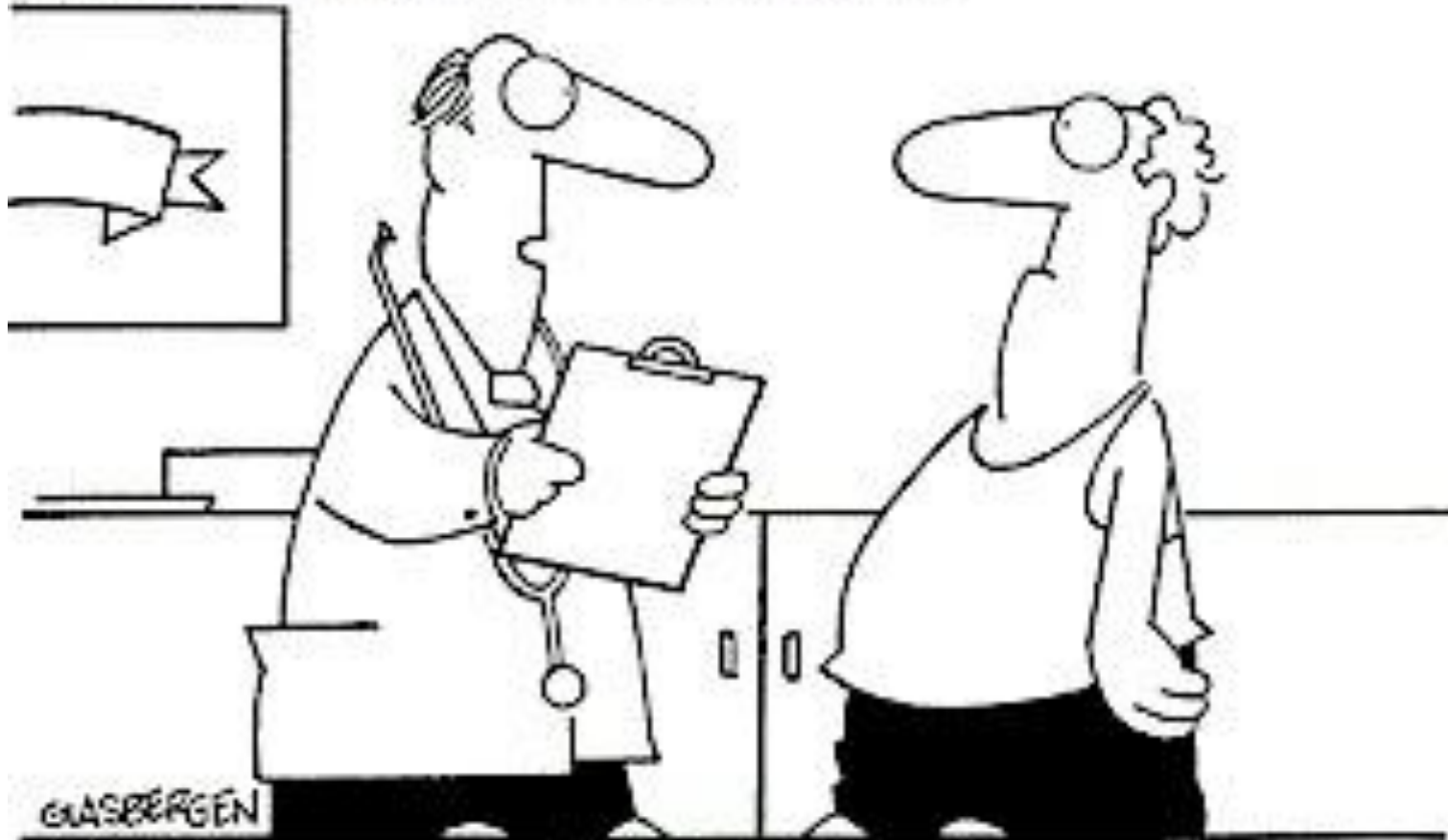
Older, advanced plaques may be less susceptible to rupture and renewed thrombosis because they have thicker fibrin caps. Also, lipid lowering can enhance plaque stability by reducing lipid content & inflammation.

- Thus, **older plaques** cause constriction and ischemic symptoms during increased demand (e.g., angina or heart attack during snow shoveling).
- **Newer plaques** with thin fibrin caps are less stable and may account for acute myocardial infarctions that sometimes occur with little provocation.



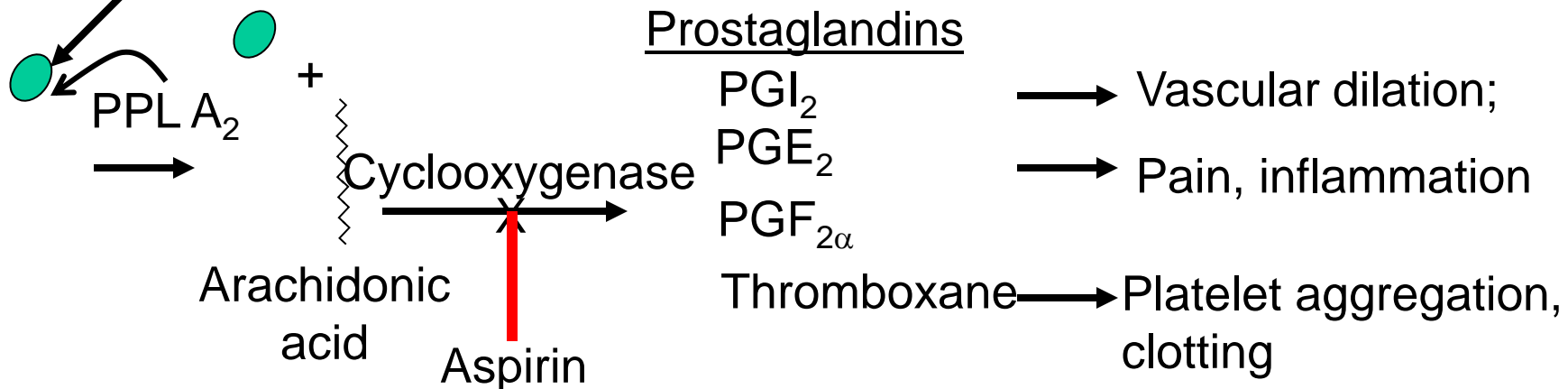
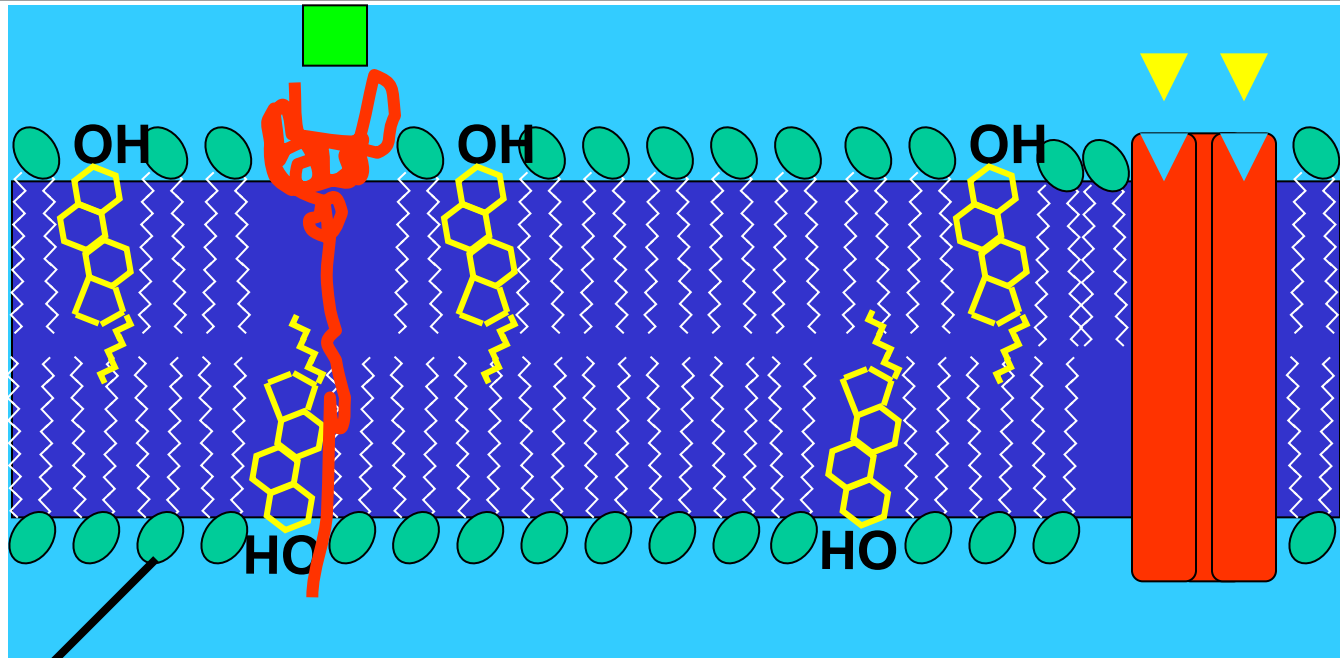
So How Does Aspirin Work?

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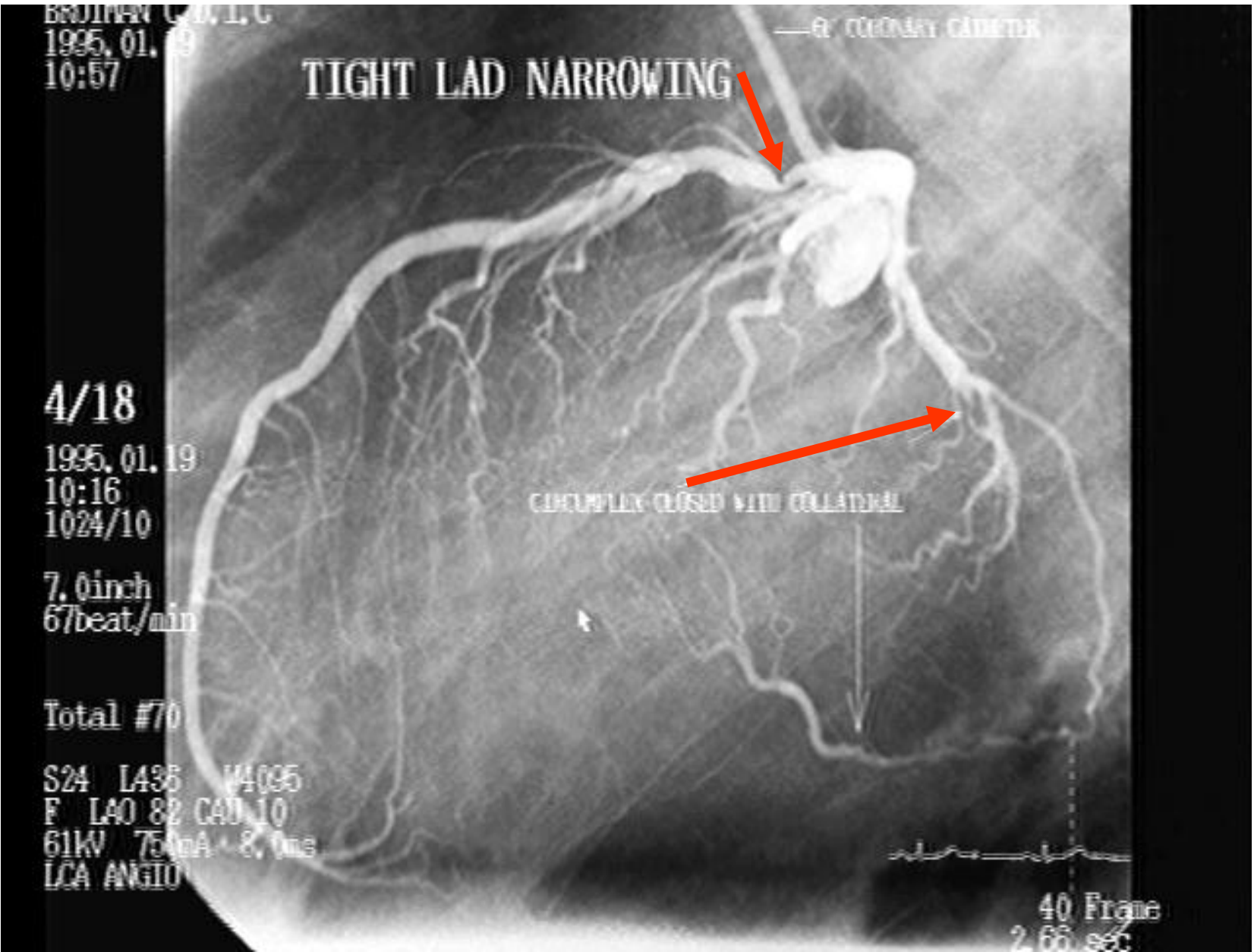


“An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger.”

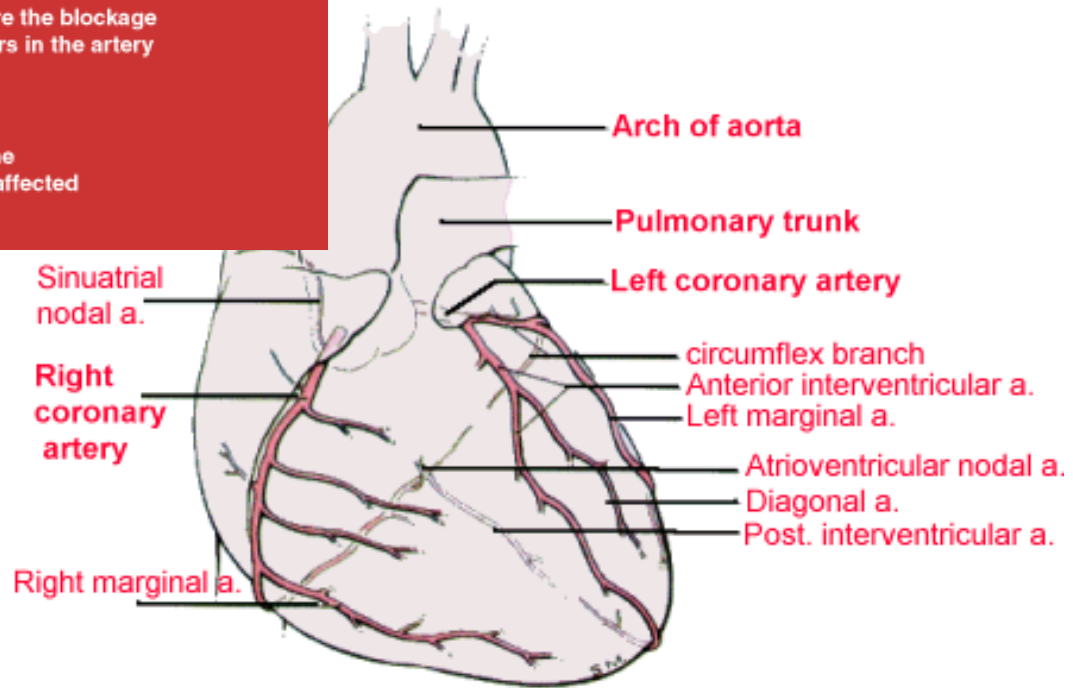
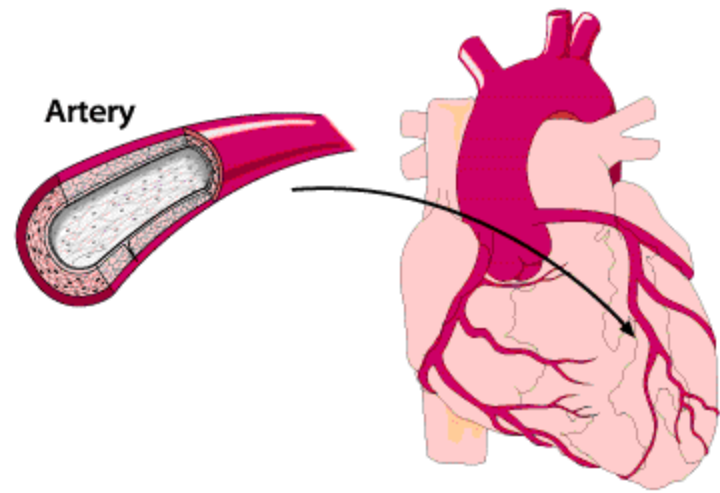
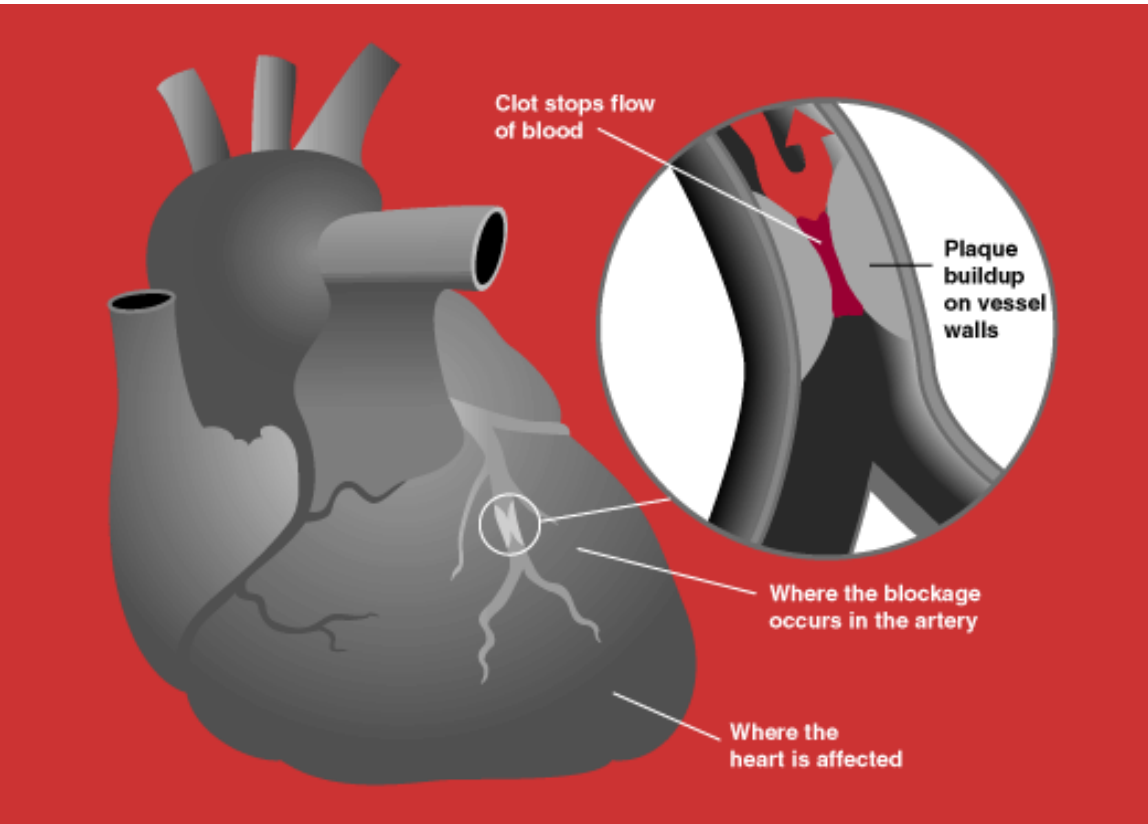
Aspirin Relieves Pain & Reduces Inflammation by Inhibiting Synthesis of Prostaglandins



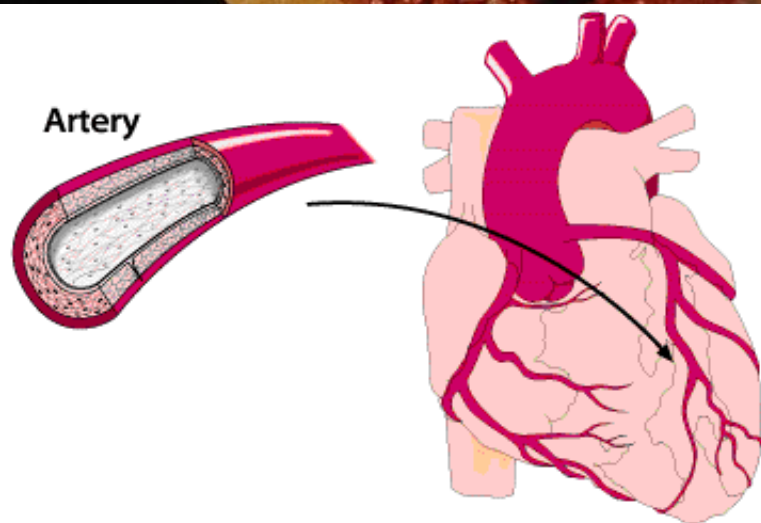
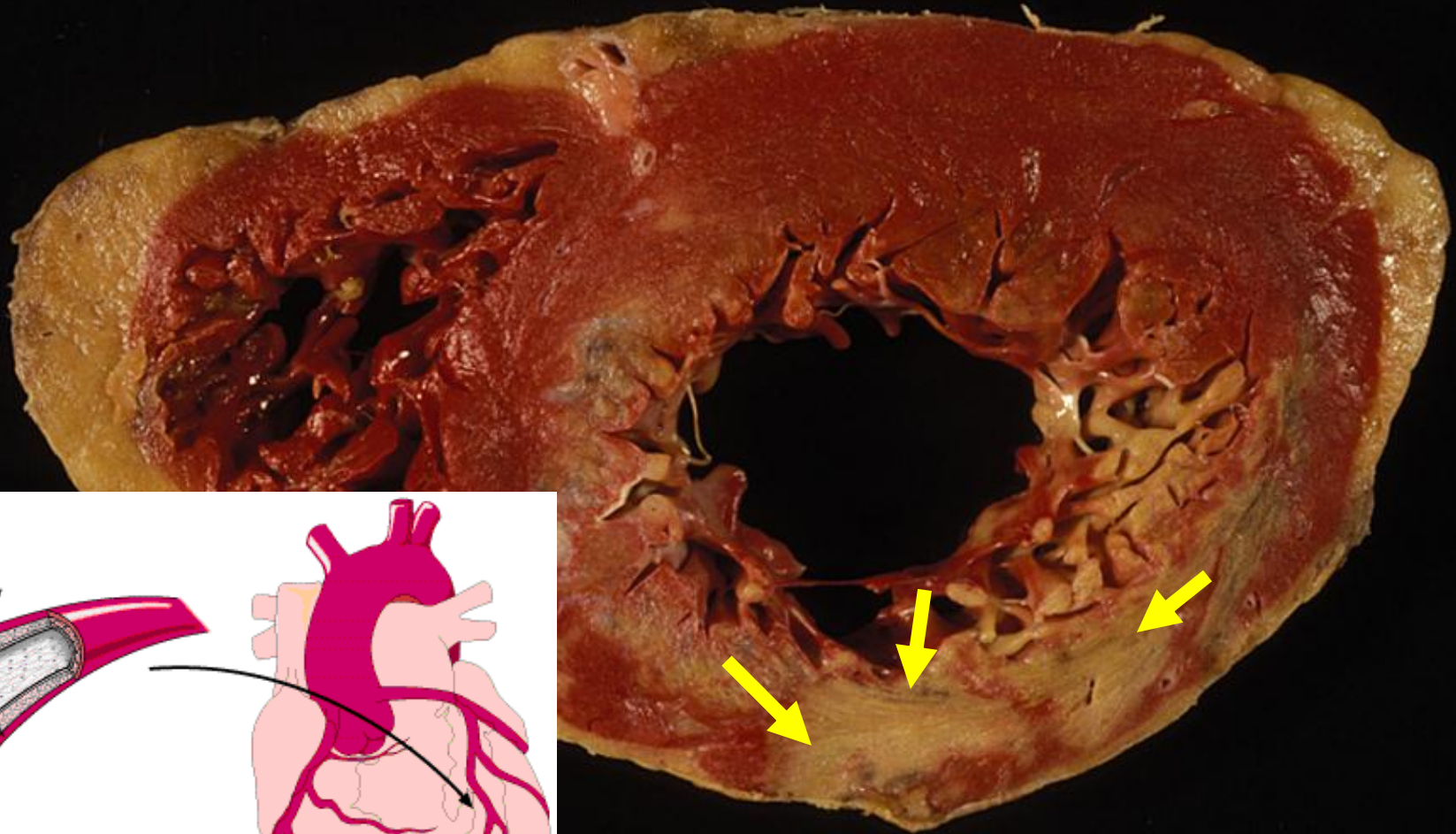
Coronary Angiography



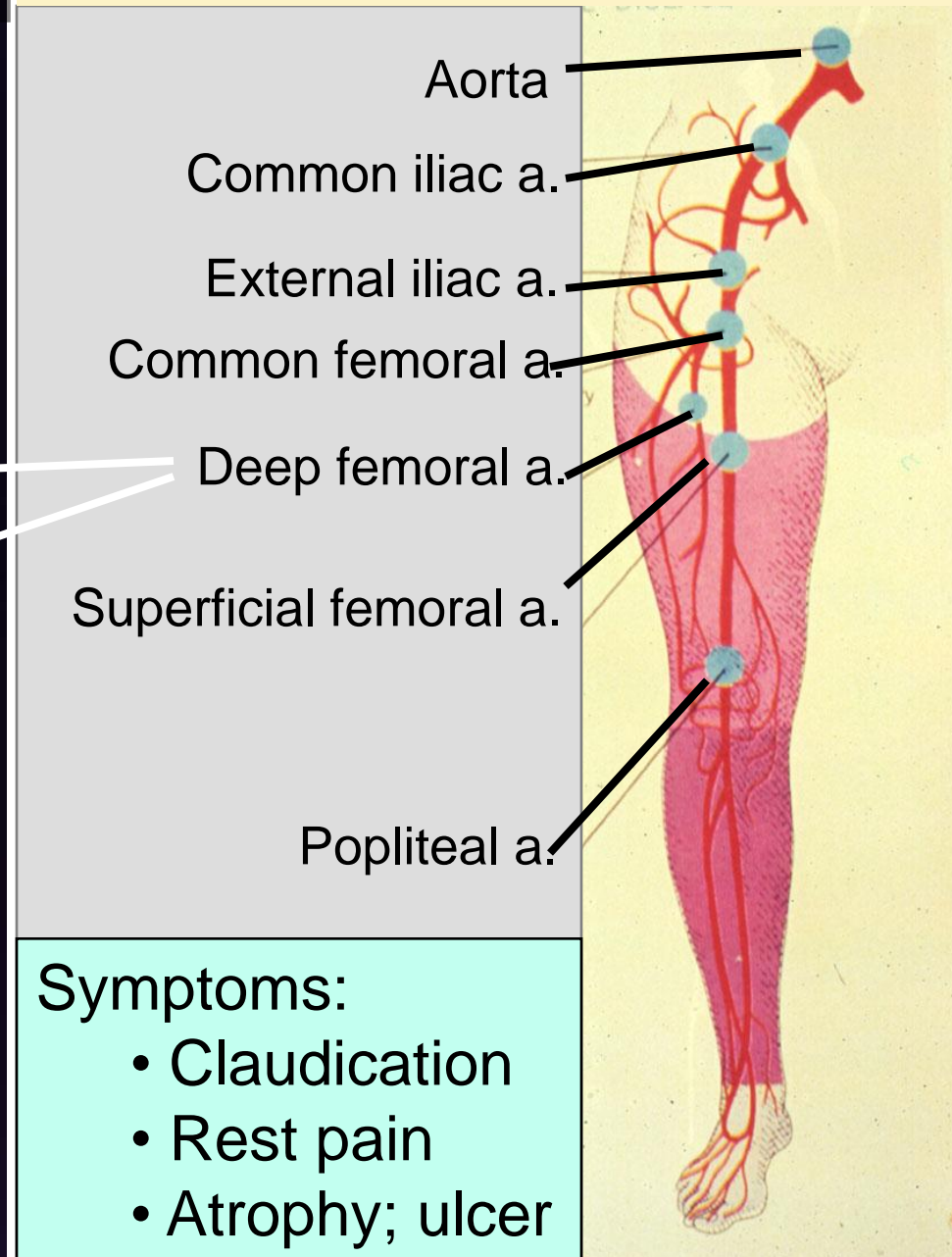
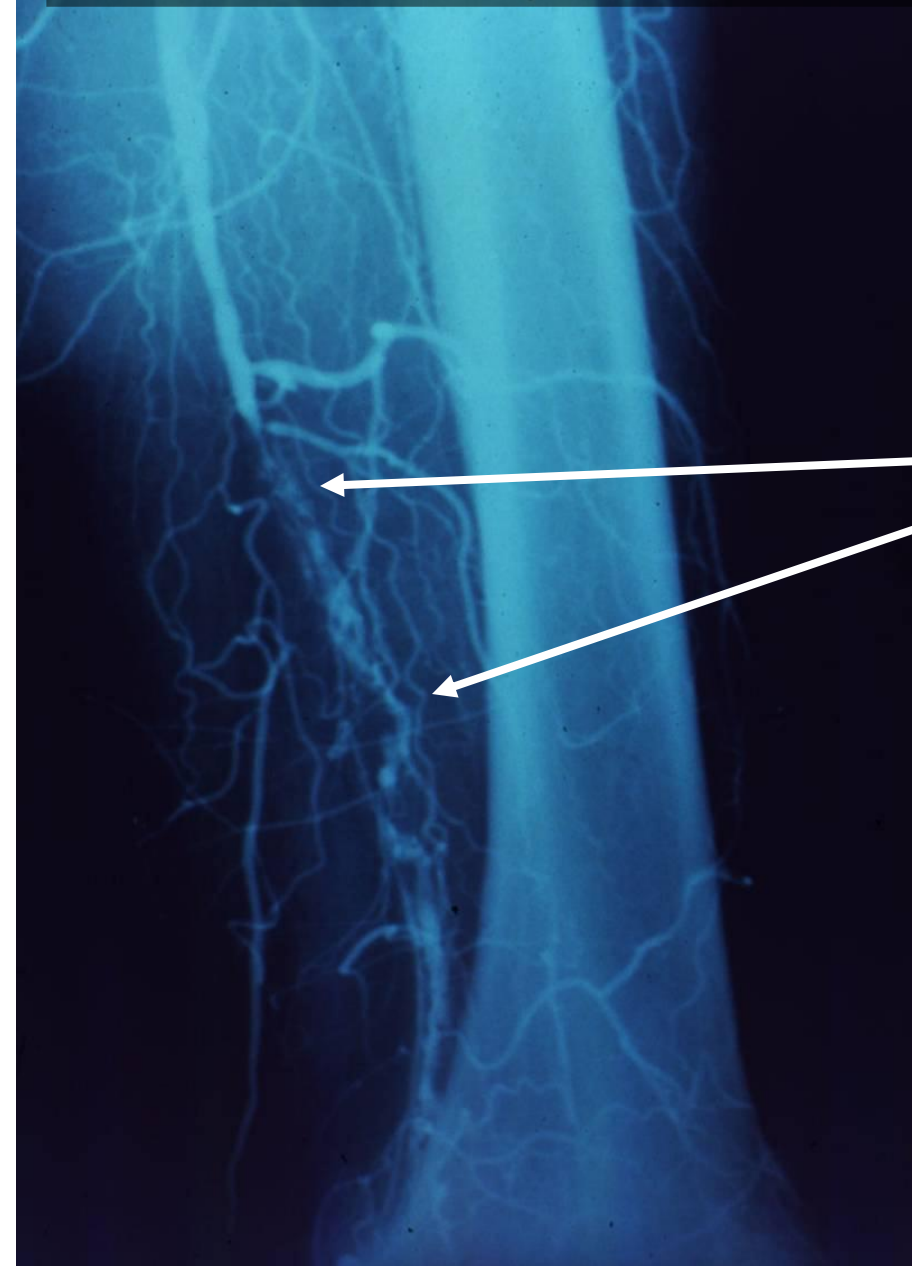
Myocardial Infarction



Acute Myocardial Infarction

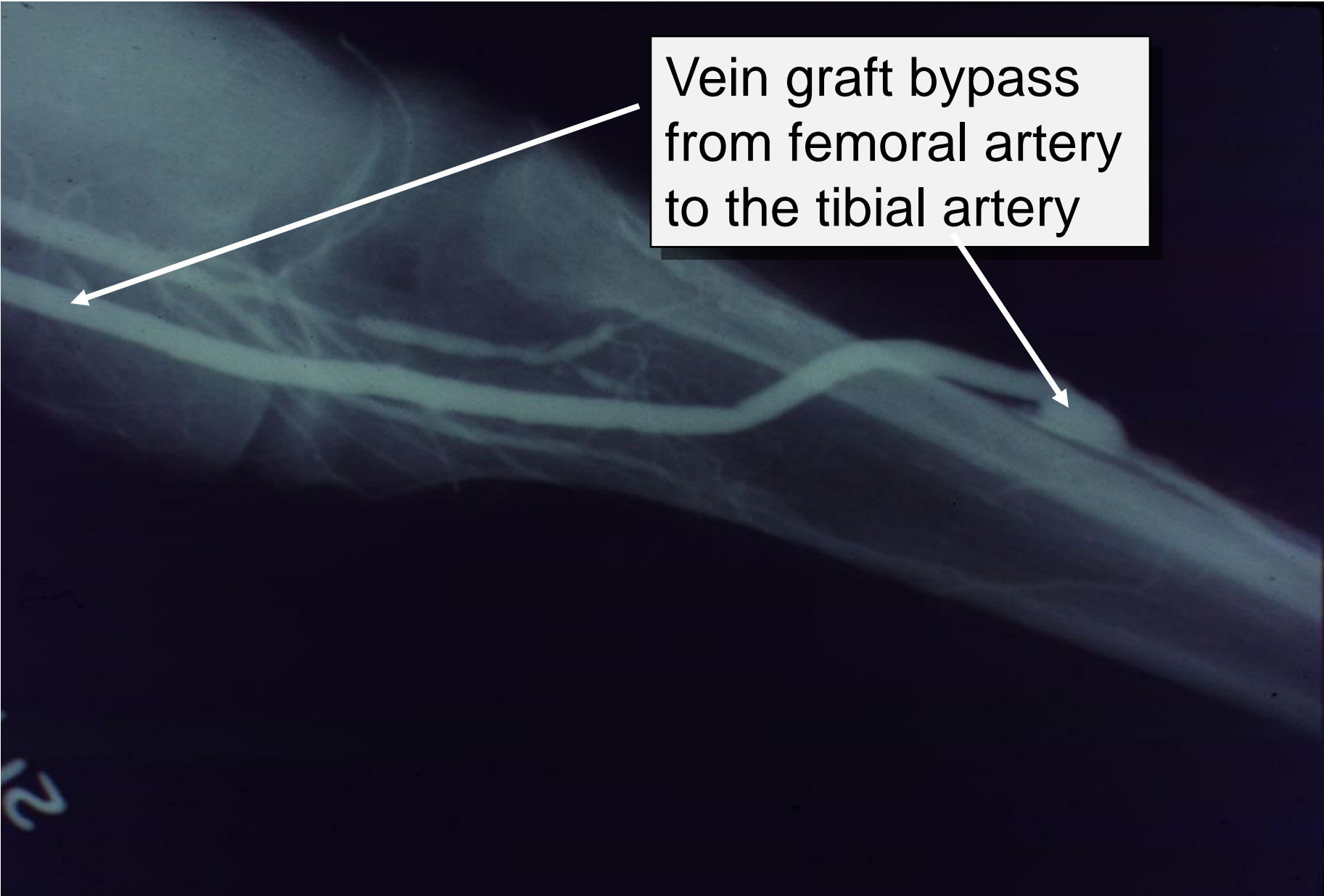


Occluded Femoral Artery



- Symptoms:
- Claudication
 - Rest pain
 - Atrophy; ulcer

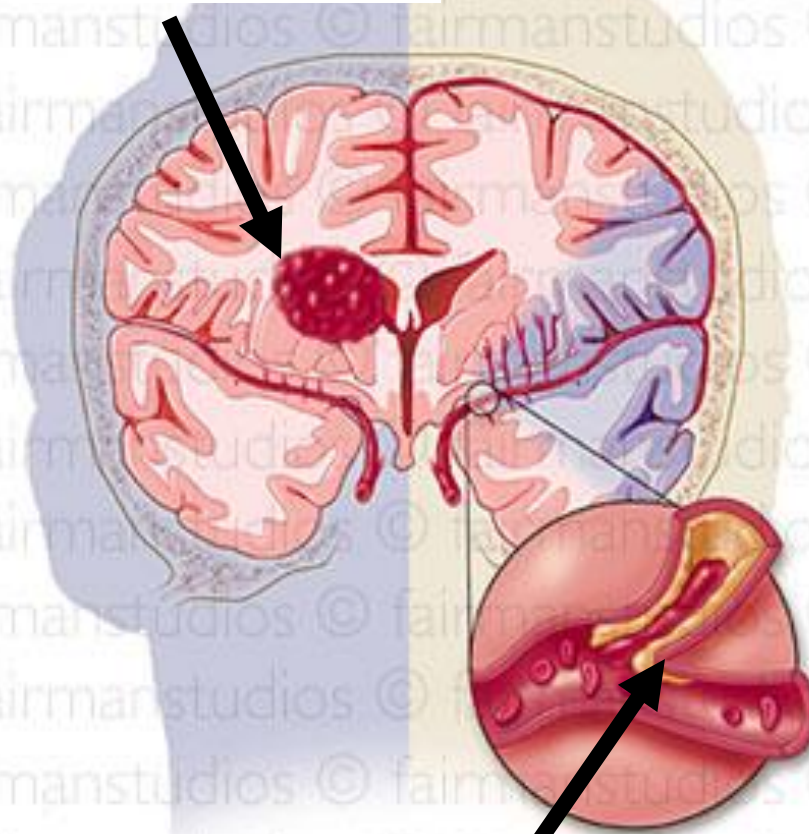
Vein graft bypass
from femoral artery
to the tibial artery



2

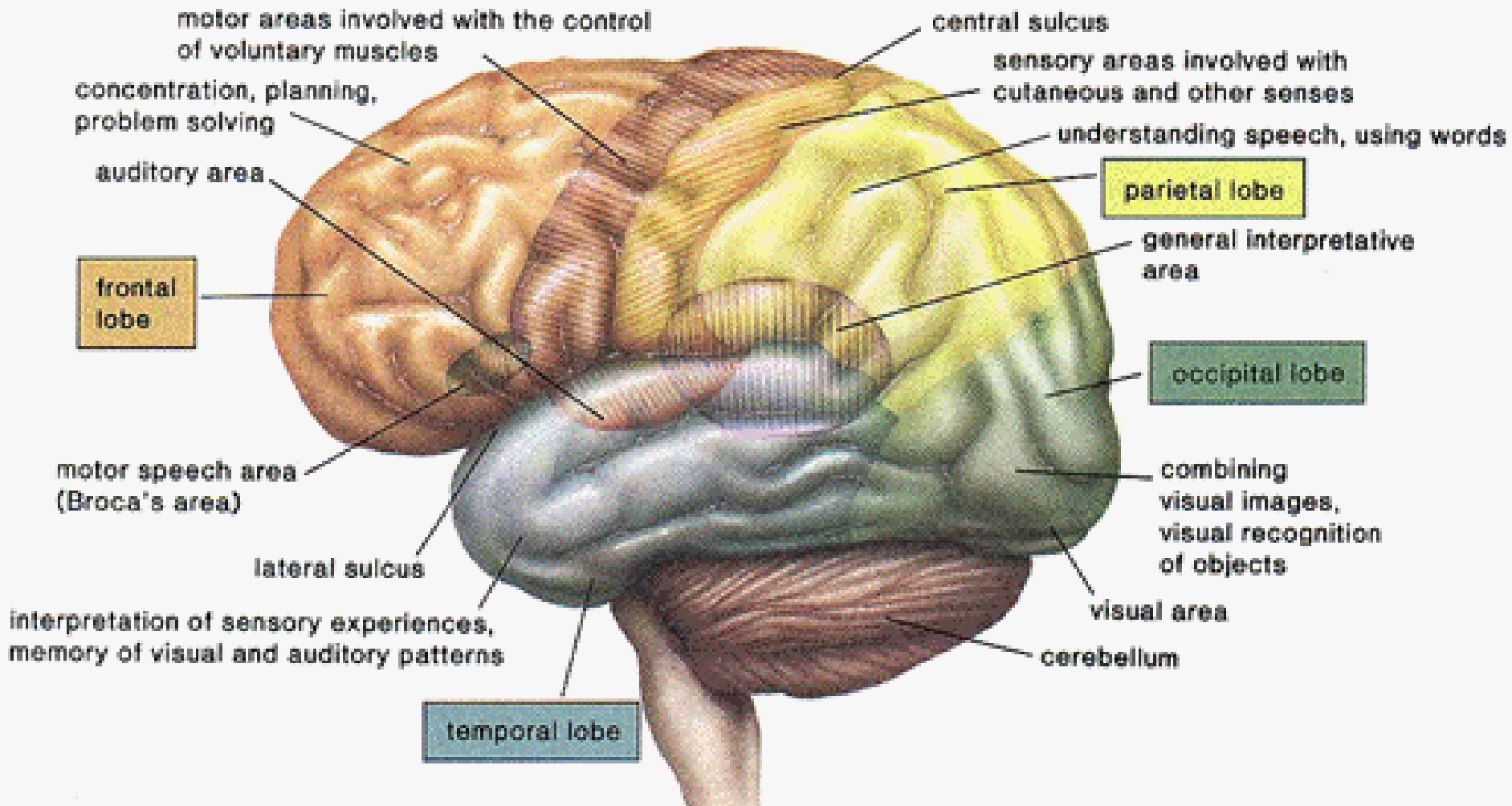
Cerebrovascular Disease (Stroke)

Hemorrhagic



Occlusive

Specialization In The Brain

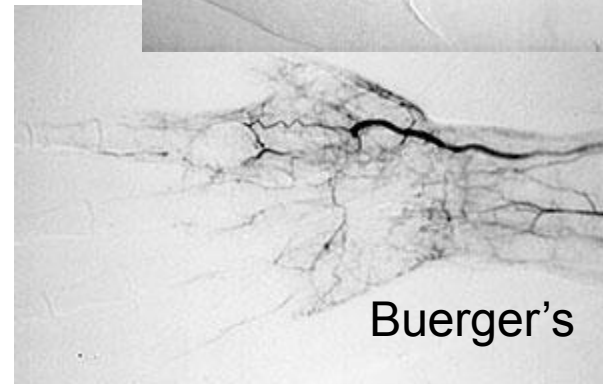
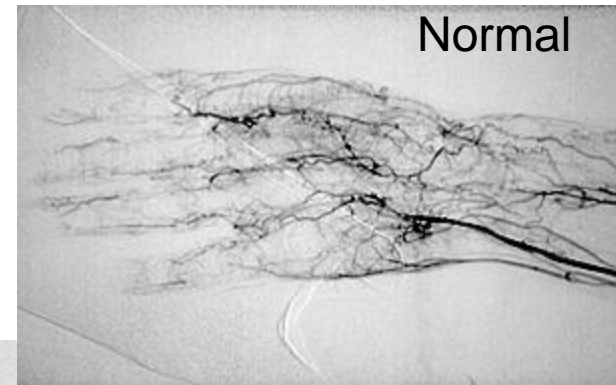
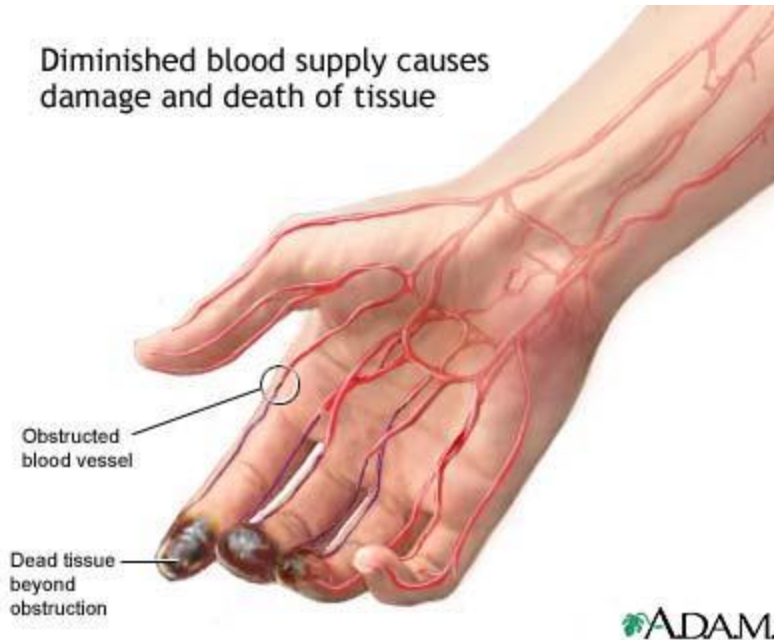


Strokes result in death of discrete brain areas. Sequelae of a stroke will depend on size and location of the affected area.

Buerger's Disease

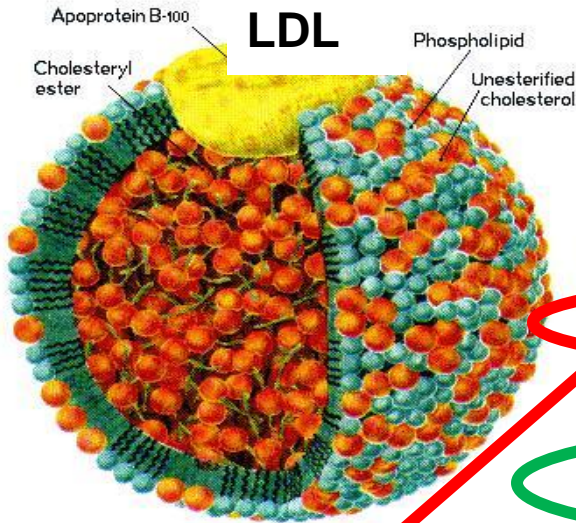
Acute inflammation and thrombosis (clotting) of arteries and veins — affected hands and feet.

Classic patient is a 20–40 year old male & a heavy cigarette smoker.



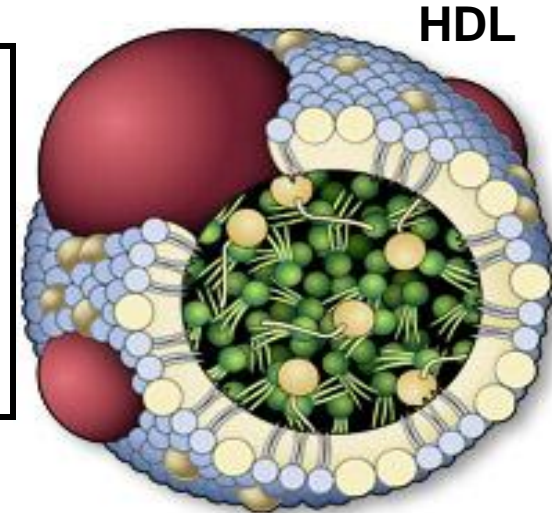
Total Cholesterol (mg/deciliter)

- Desirable: <200
- Borderline High: 200-239
- High: 240+



Total Fractionated into Lipoprotein Carriers

- Chylomicrons
- VLDL (very low density)
- LDL (low density)
- IDL (intermediate density)
- HDL (high density)



LDL (mg/deciliter)

<100	Optimal
100-129	Above optimal
130-159	Borderline high
160-189	High
>190	Very high

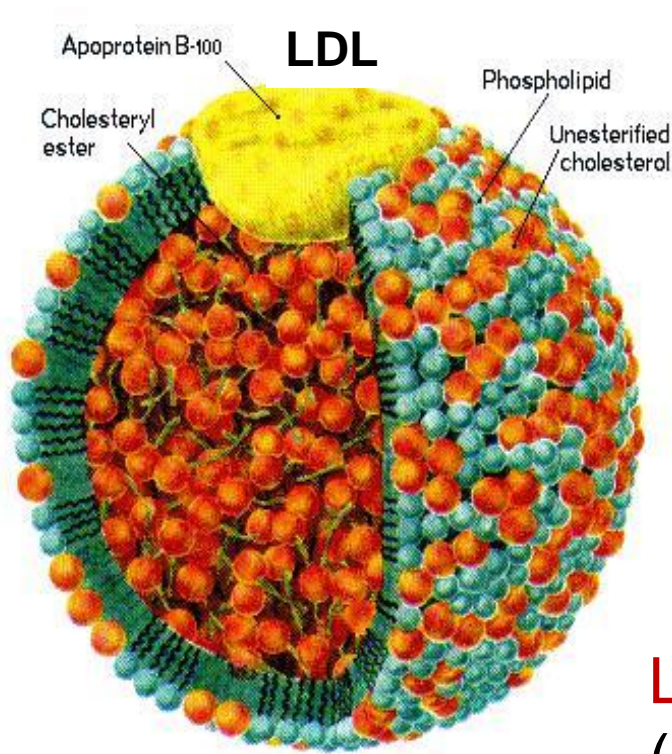
HDL Concentration (mg/deciliter)

<40	Low (High risk)
40-50	Average risk
60+	High (Low risk)

The French Paradox

The diet of the French is relatively high in fat (cream, rich sauces, desserts, cheese), but their incidence of heart disease is low compared with the rest of Europe. Also, the French consume more wine than any other population in Europe.

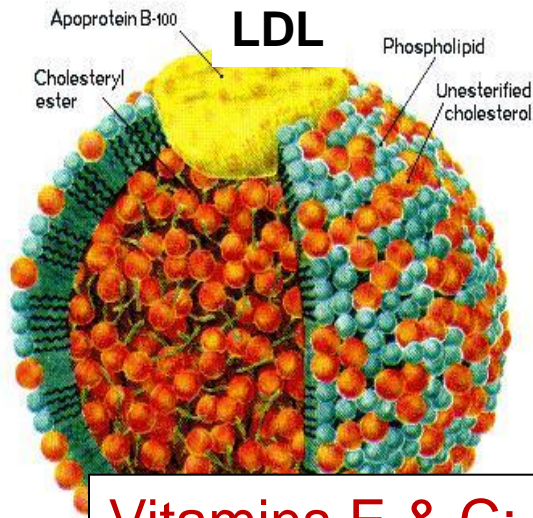
- Wine contains water, alcohol, and several dozen other compounds (e.g., ascorbic acid, sulfur dioxide, carbon dioxide, tartaric acid, and flavonoids).
- **Flavonoids:** antioxidants found in edible plants; they reduce oxidation of LDL and may reduce atherosclerosis.
- **Moderate intake of alcohol**, mostly in the form of wine, seems to protect against coronary heart disease although, some studies have not found any difference between beer, wine, and spirits. Proving benefit of one over others may be confounded by the influence of differences in education, diet, and life style.



Oxidized LDL

LDL may be modified by oxidation (loosing electrons) & glycation (attaching sugars in diabetes). Oxidized LDL is found in plaques in humans. LDL trapped in an artery undergoes oxidation and is taken up by macrophages. Internalization leads to formation of lipid peroxides (free radicals) and formation of foam cells.

Antioxidants



Vitamins E & C: anti-oxidants

- In animals with hypercholesterolemia, antioxidants reduce the size of lesions, and they reduce fatty streaks in nonhuman primates.
- Antioxidants increase the resistance of human LDL to oxidation in vitro in proportion to the vitamin E content of the plasma.
- Dietary intake of vitamin E intake from fruits & vegetables correlates inversely with the incidence of myocardial infarction.
- BUT, clinical trials have **not** demonstrated reduced MI in subjects taken vitamin supplements of C and E.

Homocysteine & Folic Acid

Homocysteine is toxic to endothelium and is prothrombotic. Inherited defects in enzymes that metabolize homocysteine cause severe atherosclerosis in childhood, with 1st myocardial infarction by age 20.

Many people without inherited defects have slightly elevated plasma homocysteine levels, and they have an increased risk of atherosclerosis. Folic acid normalizes their homocysteine concentrations. Trials are under way to determine whether this prevents progression or atherosclerosis.

American Heart Association has not yet said that high homocysteine levels are a major risk, & they don't recommend widespread use of folic acid & B vitamins to reduce the risk of heart disease and stroke.

Hypertension (High Blood Pressure)

Hypertension promotes inflammation and increases formation of reactive oxygen species.

These reduce formation of **nitric oxide** by the endothelium, increase leukocyte adhesion, and increase peripheral resistance.

Smoking & Atherosclerosis

Smoking increases risk of atherosclerosis, myocardial infarction, peripheral vascular disease, and stroke.

- Components of tobacco smoke, or their metabolites, **generate reactive oxygen species** and **reduce antioxidants**, contributing to endothelial dysfunction.
- Smoking also **increases platelet aggregation** and the plasma concentrations of **fibrinogen** which both contribute to the occlusion of arteries.

Infection & Atherosclerosis

Herpes viruses (Cytomegalovirus) and *Chlamydia pneumoniae* have been found in atheromatous plaques, & increased antibodies to these agents are associated with increased risk of new infarction in patients who have had myocardial infarction.

Periodontal disease is associated with increased risk of atherosclerosis, even after adjusting for other risk factors. Mouth organisms e.g. *Porphyromonas gingivalis* & *Streptococcus sanguis* have been found in plaques., and *P. gingivalis* infection accelerated atherosclerosis in a mouse model.

Injection of CMV, Chlamydia, or *P. gingivalis* experimentally does not induce atherosclerosis, but they do accelerate atherosclerosis in animal models.

Role of Infection Is Unclear

Some believe that total “**pathogen burden**” i.e., the **cumulative exposure** to multiple atherogenic infectious agents might enhance risk.

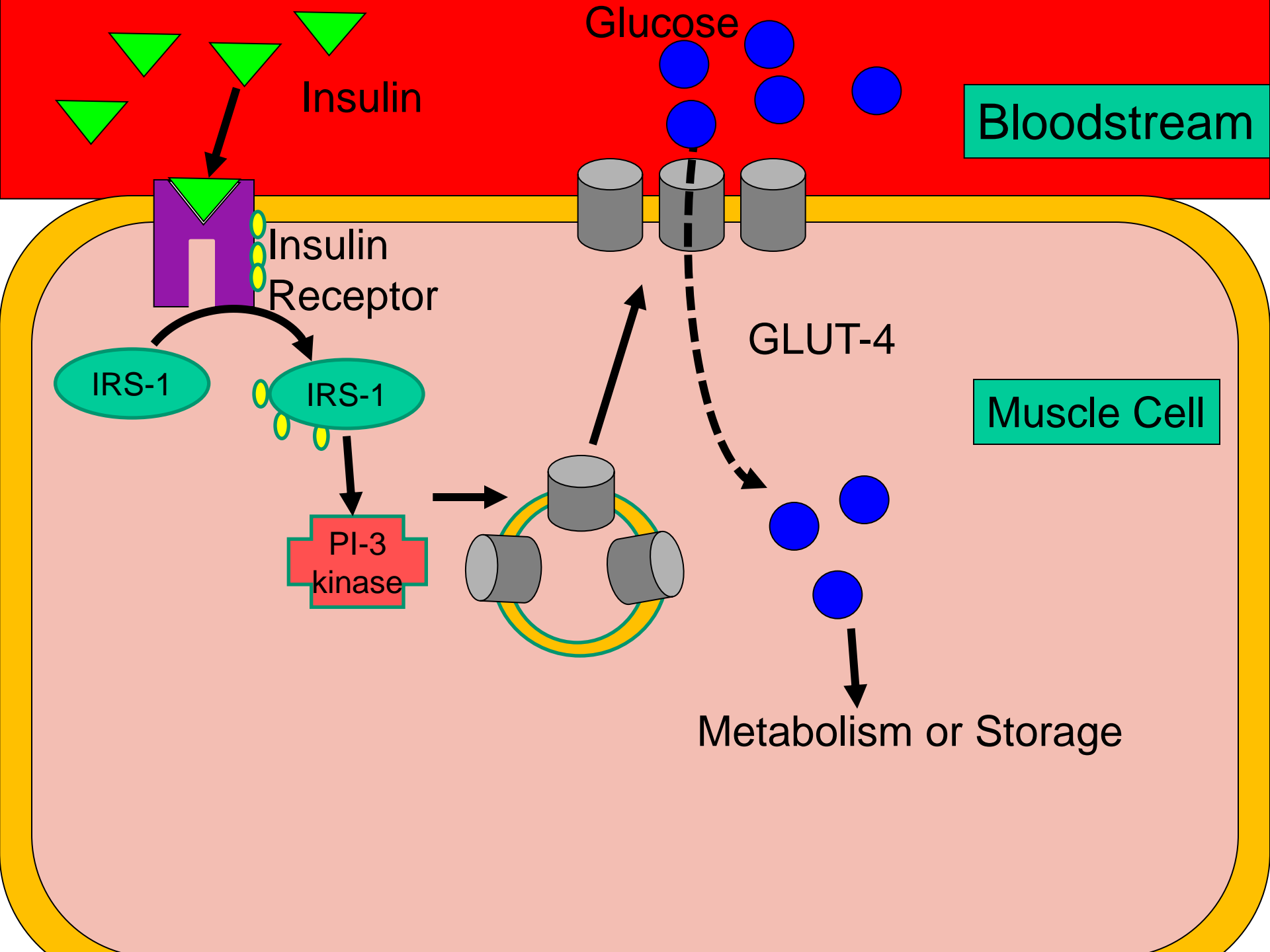
- Atherosclerosis is an inflammatory disease. The triggers of inflammation are incompletely understood but may be infectious as well as noninfectious.
- Circulating inflammatory markers (e.g., C-reactive protein) are associated with increased risk.

It may be that infection, combined with other factors, contributes to atherosclerosis in some patients, but there is no direct evidence that infectious agents cause atherosclerosis, and there is the potential for confounding by socioeconomic factors.

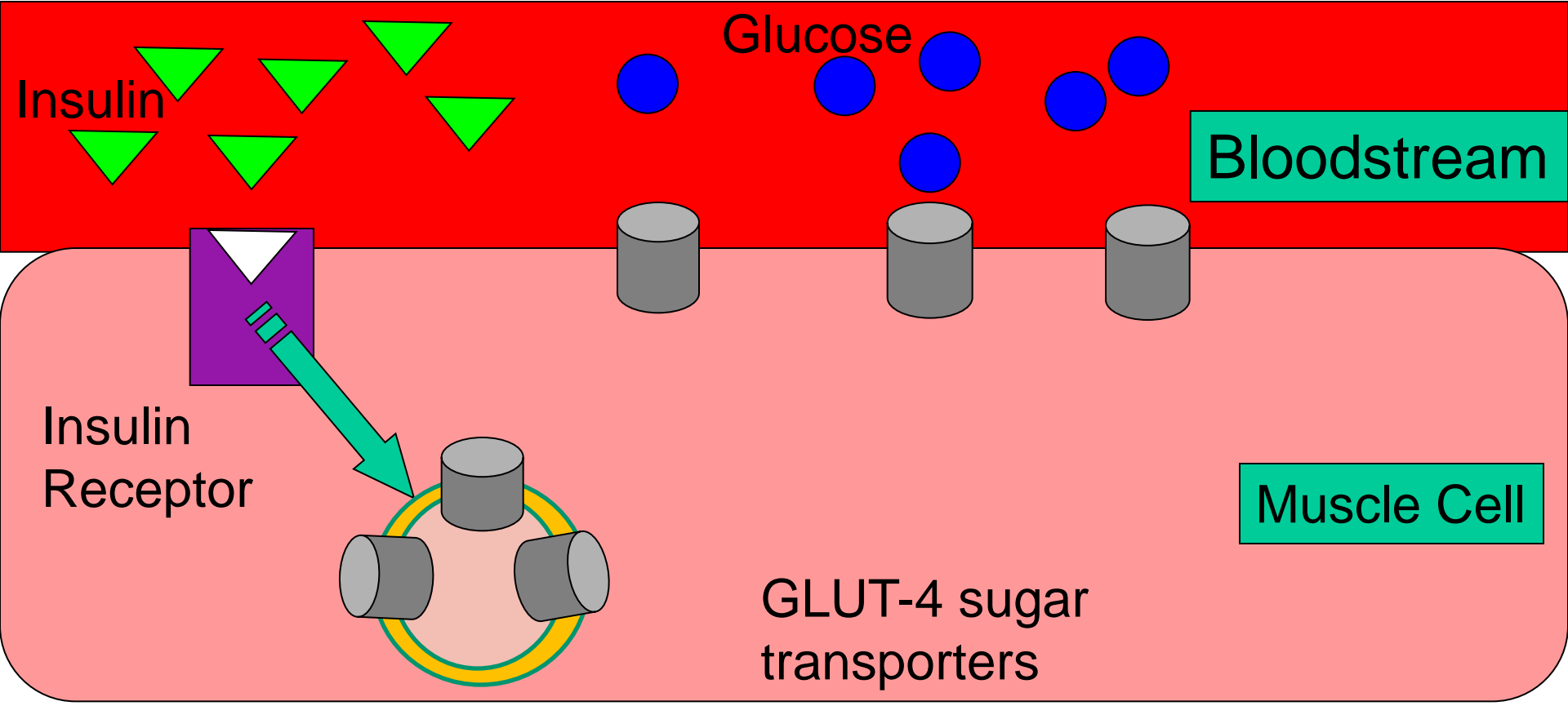
Dysfunction of Endothelial Cells May Play a Central Role

Endothelial dysfunction (perhaps from inflammation) may lead to:

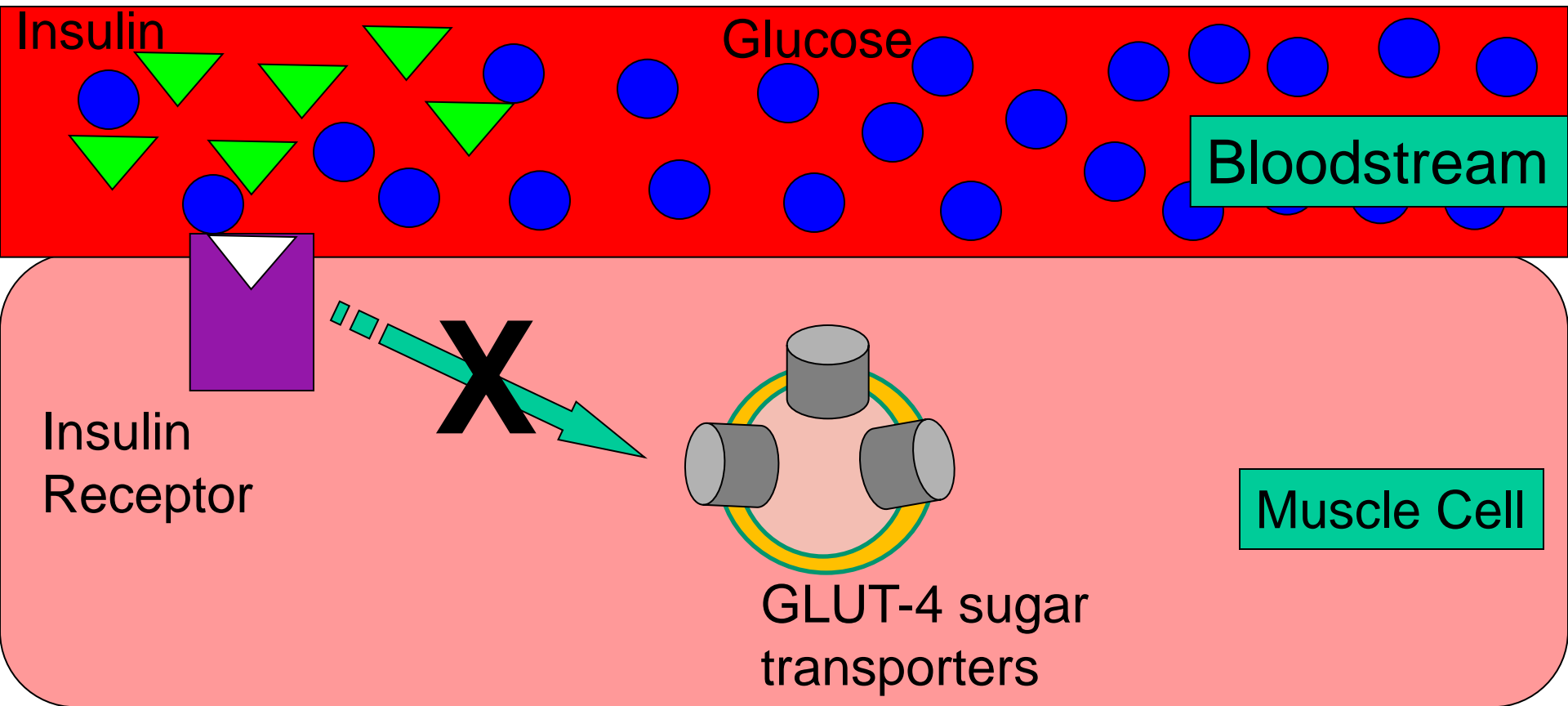
- Increased coagulation of blood
- Leaky blood vessels
- Increased vascular tone or constriction causing hypertension
- Secretion of growth factors that stimulate blood-vessel walls to hypertrophy, narrowing the lumen.



Insulin facilitates entry of glucose into muscle and fat cells by increasing insertion of GLUT-4 transporters into cell membranes.



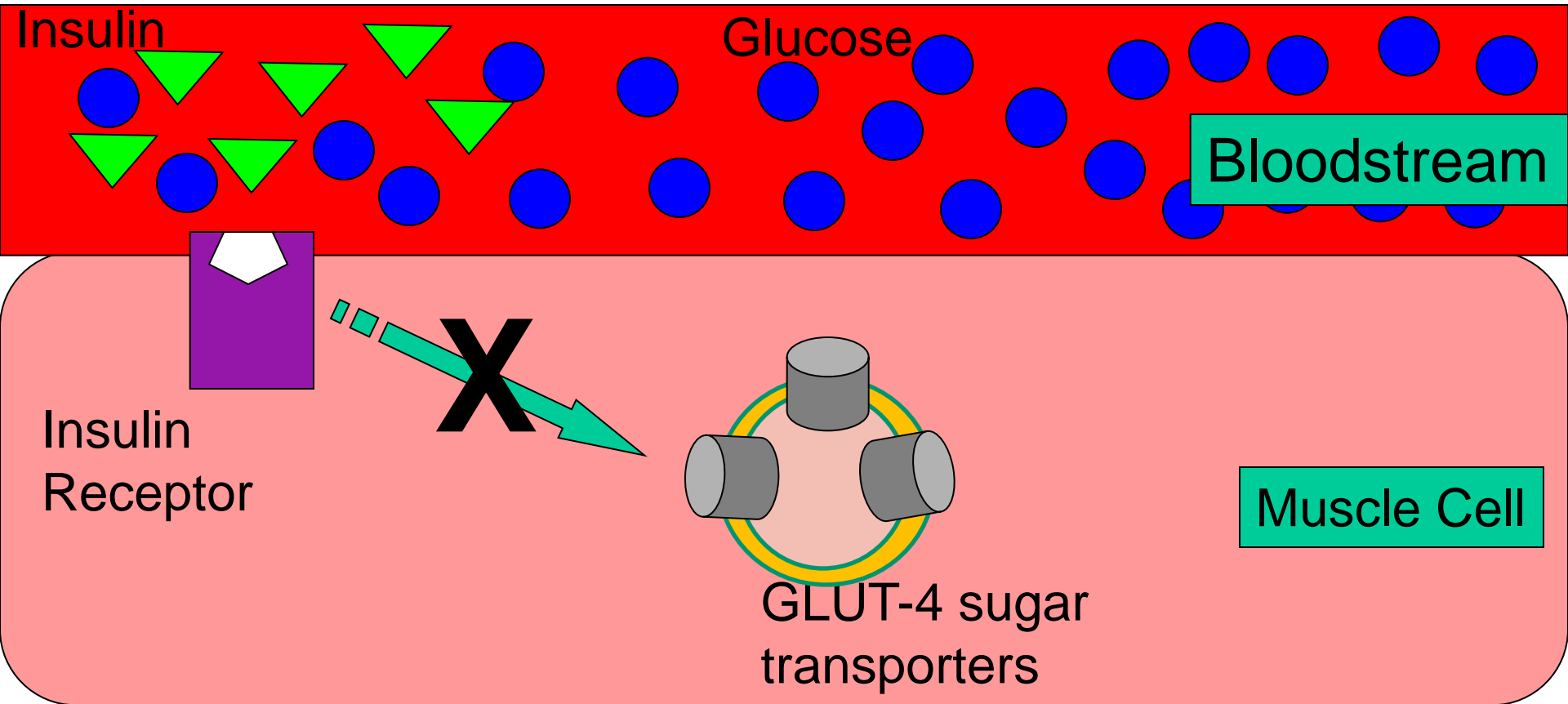
Type I Diabetes Mellitus: Autoimmune damage to insulin producing cells in the pancreas leads to loss of insulin.



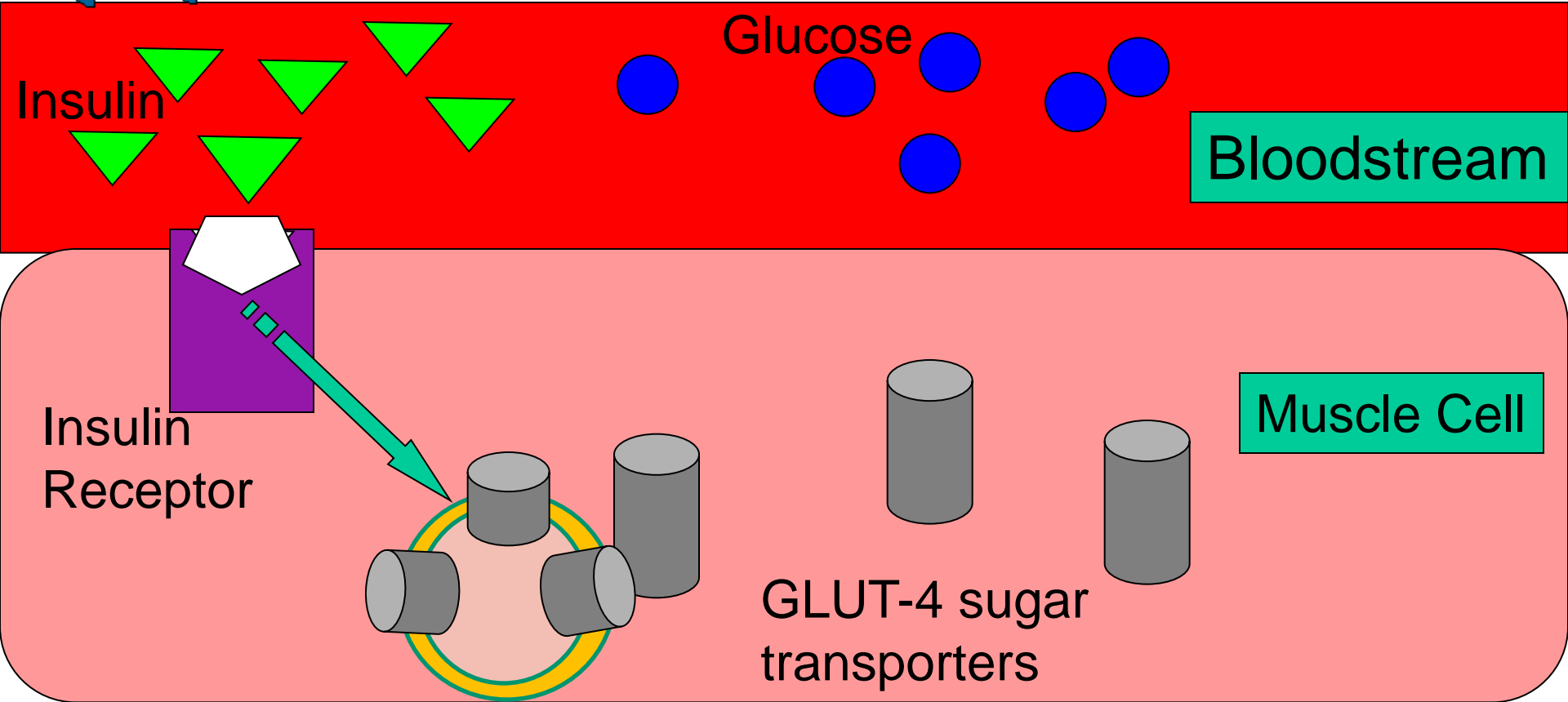
If untreated, high levels of blood sugar begin to “spill” into urine. Fat is broken down for energy.

Results: Weight loss, hunger, X-S urination, ketoacidosis.

Type II Diabetes Mellitus: There is adequate insulin, but interaction between insulin & receptor is abnormal.



Exercise somehow promotes interaction of insulin with its receptors and facilitates insertion of GLUT-4 transporters.



Type 1 and 2 Diabetes = Endothelial Dysfunction

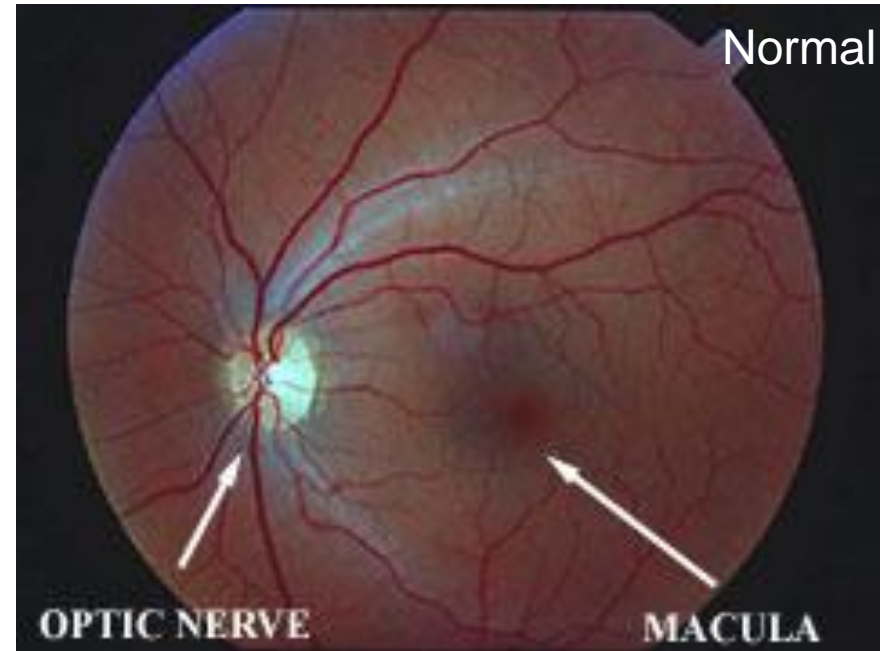
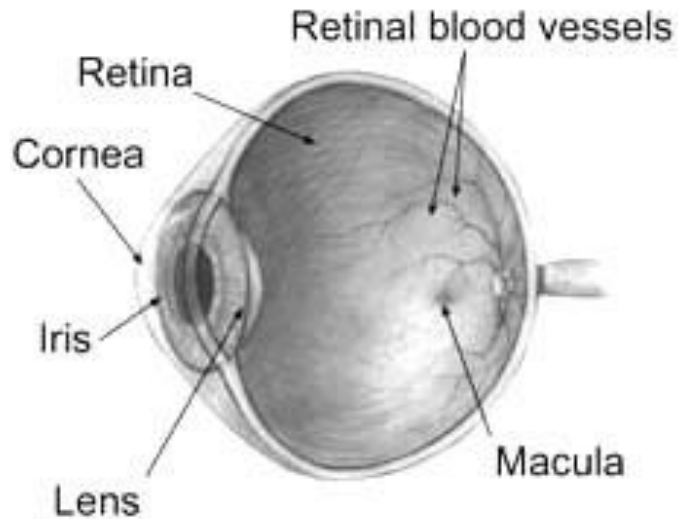
Lipid abnormalities due to impaired activity of lipoprotein lipase & increased secretion of VLDL from liver).

- Increased triglycerides.
- Decreased HDL cholesterol.
- Concentrations of LDL cholesterol are normal, but the LDL particles are smaller and denser than normal and circulate longer.

PLUS

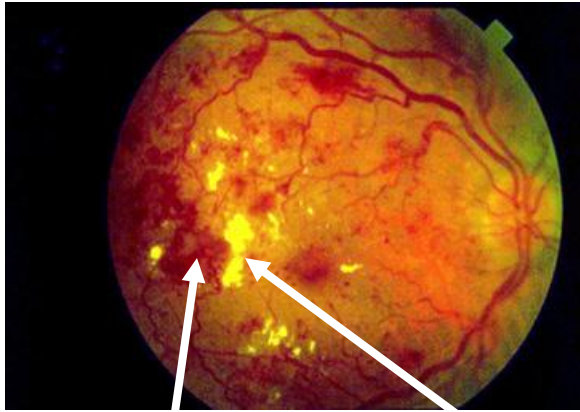
- Glycosylation of lipoproteins (attachment of sugar molecules to the surface of lipoproteins) & other proteins.
- Oxidation of LDL by reactive oxygen species.

Normal Microvasculature (Blood Vessels)

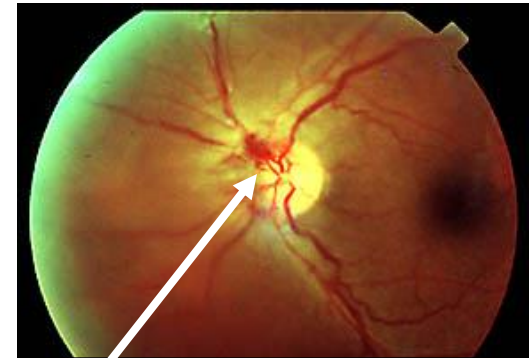


An ophthalmoscope can be used to view small blood vessels on the surface of the retina.

Microvascular Complications of Diabetes



Hemorrhages and edema



New vessel formation



A larger bleed



Consequences for Diabetics

- 4x greater risk of heart disease & stroke
- 70% of diabetics will die from vascular disease (CAD, stroke, peripheral vascular disease)
- Blindness
- Renal failure
- Amputations
- Cataracts

Prevention of Complications

Control blood glucose, lipids, BP, & other risk factors (smoking, inactivity, obesity). Take low-dose aspirin.

Details FYI

Blood glucose

- HbA1c (the long-term average glucose level) <6.5 %
- Reduce postprandial hyperglycemia.

BP: Systolic BP<130 mmHg; Diastolic BP<85 mmHg.

Blood lipids

- HDL-cholesterol >40 mg/dl
- Triglycerides <170 mg/dl
- LDL-cholesterol <100 mg/dl (**statins** if necessary)
- Total/HDL-cholesterol ratio <4.0
- Total cholesterol <200 mg/dl

If these targets can be sustained, the risk of cardiovascular disease is low, but relatively few patients are being controlled this carefully.

Different Types of Triglycerides (Fats & Oils)

Solid at room temperature:

Coconut butter is a fat with mostly saturated fatty acids.

Lard is animal fat, which is rich in saturated fatty acids.

Liquid at room temperature:

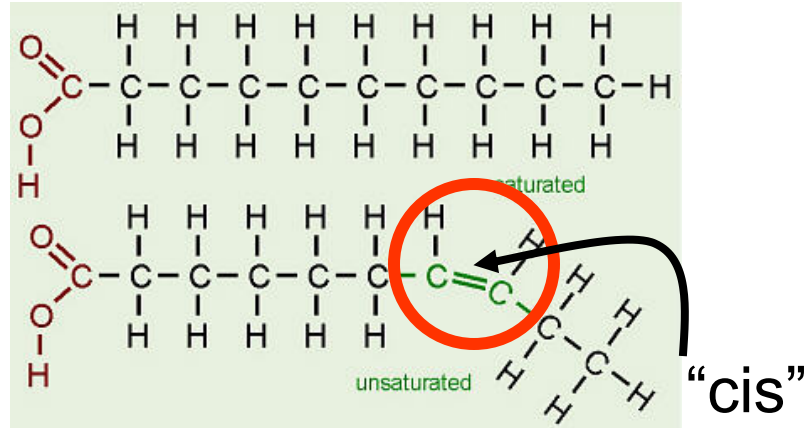
Olive oil is a fat with a high amount of oleic acid (monounsaturated).

Corn oil is a fat with a high amount of polyunsaturated fatty acids (2 double bonds).

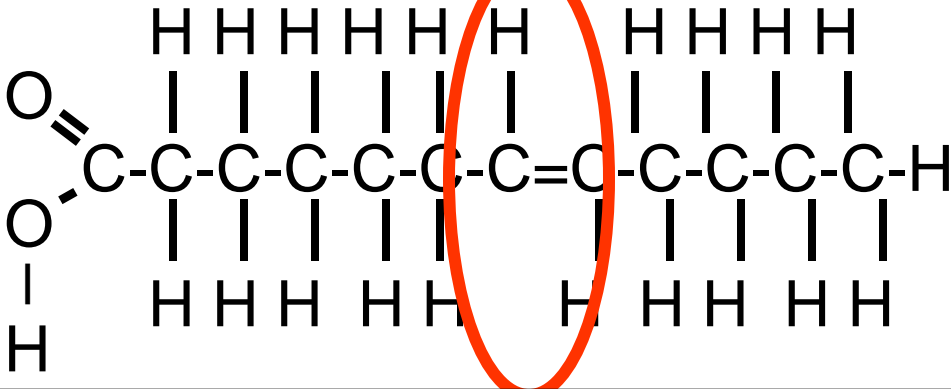
Fish oils are fats with unusually long fatty acids (20 or 22 carbon atoms) with 5 or 6 double bonds.

“Partially Hydrogenated” & “Trans” Fatty Acids

Saturated fatty acids (e.g. stearic acid) have straight carbon chains. (MP=72°)



“trans”
(across)



Most naturally occurring **unsaturated fatty acids**, e.g. oleic acid have “**cis**” double bonds, with hydrogen atoms attached on the same side of the chain. This causes a bend that prevents tight packing. (MP=13°)

Trans fatty acids have double bonds with hydrogens attached on opposite sides of the chain, so the chain is fairly **straight**, like a saturated fatty acid and packs tighter. (MP=44°).

Trans Fatty Acids

Found mainly in partially hydrogenated fats such as margarines. American Heart Association (AHA) & American Society of Clinical Nutrition/American Institute of Nutrition (ASCN/AIN) recommend reducing total and saturated fats in the diet and trans fatty acids to reduce heart disease and certain types of cancer.

The health effects of trans fatty acids remain uncertain, although their consumption is associated with elevated levels of serum cholesterol and triglycerides, which are associated with increased risk of cardiovascular disease.

The Metabolic Syndrome

(Syndrome X, insulin resistance syndrome, dysmetabolic syndrome)

A collection of risk factors that increase risk of heart disease, stroke, & diabetes seen in >20% of Americans.

Diagnosed if you have three or more of the following:

- Waistline of 40" or more for men; 35" or more for women
- Blood pressure >130/85 mm Hg or are on medications
- Serum triglyceride level > 150 mg/dl
- Fasting blood glucose (sugar) level > 100 mg/dl or are on glucose lowering medications
- HDL < less than 40 mg/dl (men) or < 50 mg/dl (women)

The Jupiter Study

“Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment.

We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.”

Results

“Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; $P < 0.00001$), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; $P = 0.0002$), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; $P = 0.002$), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; $P < 0.00001$), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; $P < 0.00001$), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; $P = 0.02$). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes.”

Editorial - The Jupiter Study

“The relative risk reductions achieved with the use of statin therapy in JUPITER were clearly significant. However, **absolute differences in risk are more clinically important than relative reductions** in risk in deciding whether to recommend drug therapy, since the absolute benefits of treatment must be large enough to justify the associated risks and costs.”

“The proportion of participants with hard cardiac events in JUPITER was reduced from 1.8% (157 of 8901 subjects) in the placebo group to 0.9% (83 of the 8901 subjects) in the rosuvastatin group; thus, **120 participants were treated for 1.9 years to prevent one event.**”