Lipid Disorders

Role of Cytochrome P450 7A1(CYP7A1) / 7 Alpha-Hydroxylase /Cholesterol 7-Alpha -Monooxygenase

- **Cytochrome P450 7A1** is enzyme in **ER of Hepatocytes**
- **Encoded by *CYP7A1 gene***
- **Important role in cholesterol catabolism**
- **Catalyzes first rate limiting step in bile acid biosynthesis**
- **Oxidizes Cholesterol at position 7** using molecular Oxygen
- **Converts Cholesterol** to **7-Alpha Hydroxy Cholesterol**
- **Regulates Cholesterol level**

- Bile acids provide feedback inhibition for CYP7A1
- **Inhibition** of cholesterol 7-alpha-hydroxylase **(CYP7A1) represses bile acid biosynthesis**
- **When blood cholesterol levels are high CYP7A1 is upregulated** by **nuclear receptor LXR**
- To increase production of bile acids and reduce level of cholesterol in hepatocytes.
- **When blood cholesterol levels are low it is downregulated by** Sterol Regulatory Element Binding Proteins **(SREBP)**

Salient Biochemical Features
Defect in CYP7A1 Gene

- **Inherited** through family
- Signs of **premature cholesterol gallstone disease**
- **Defective Cholesterol Catabolism**
- **LDL Cholesterol levels elevated** in blood
- Substantially **elevated TAG**
- **Nonresponsive Statin therapy**
- **Increases risk of Atherosclerosis**

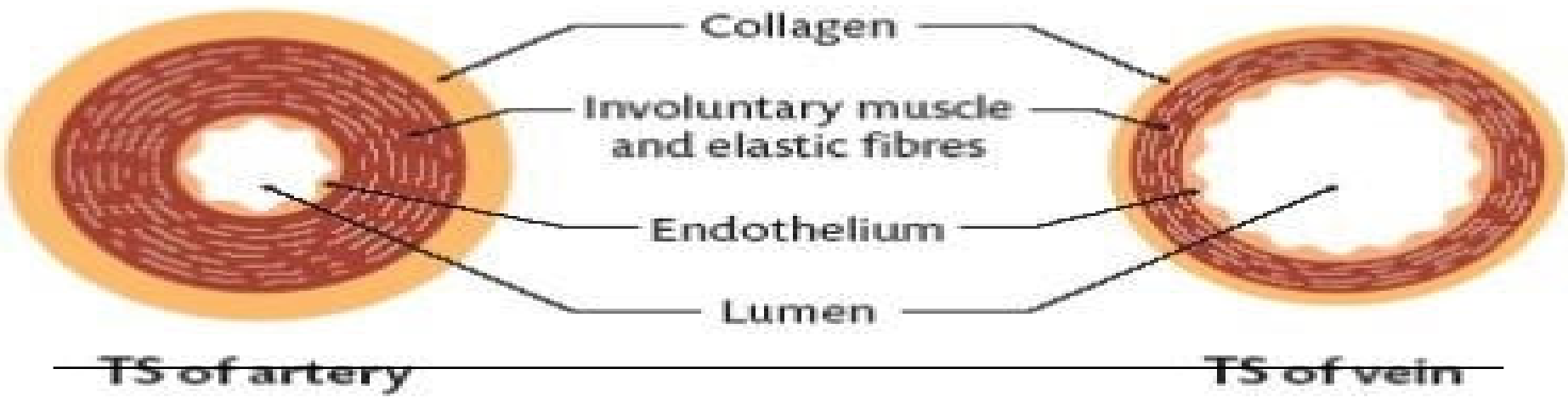
Atherosclerosis Diseased Arteries

Study Of Atherosclerosis

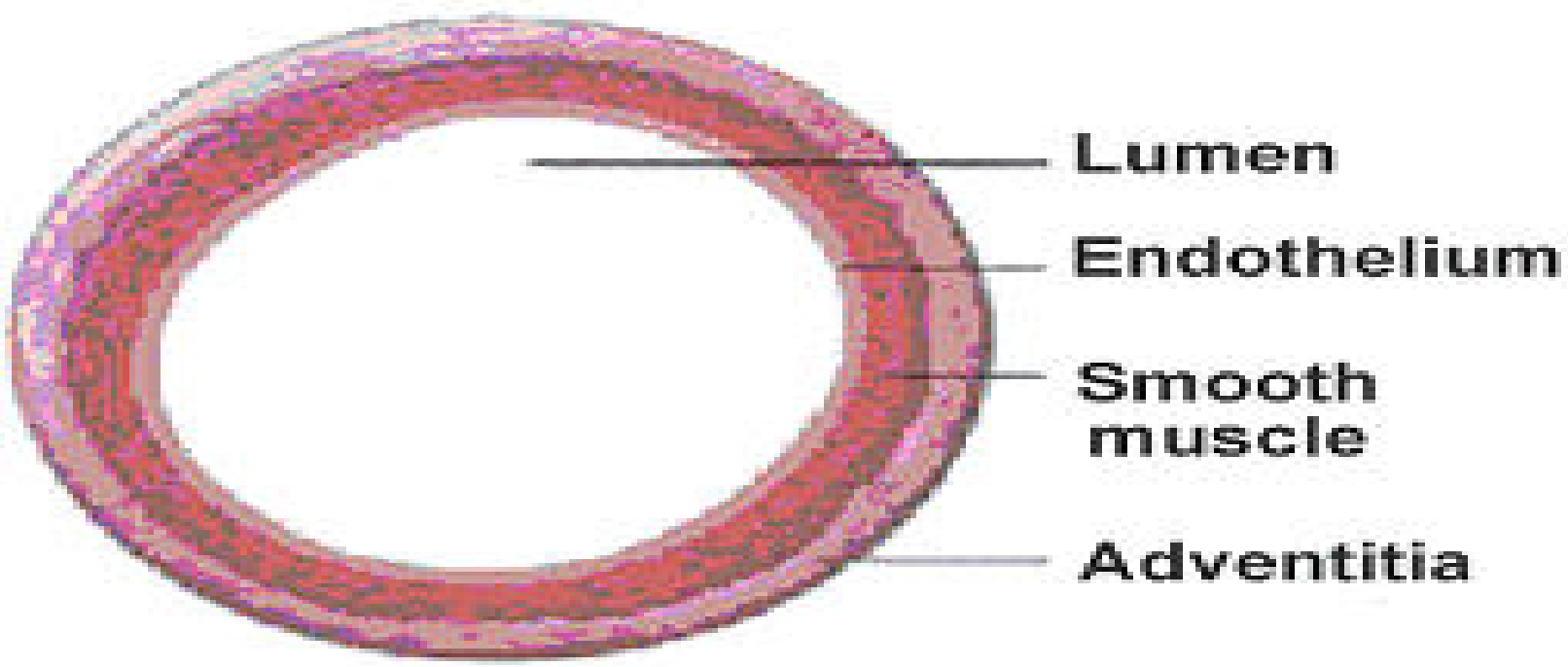
- Features of Normal and Atherosclerosed artery
- Risk of development
- Process of development
- Consequences
- Diagnosis
- Management
- Prevention and Reduction

Features Of Normal Arterial Wall

- **Lumen of healthy arterial wall** is lined by:
  - –**Confluent layer of Endothelial cells**



Normal Endothelium Controls Important function Of Arterial wall



Normal vessel

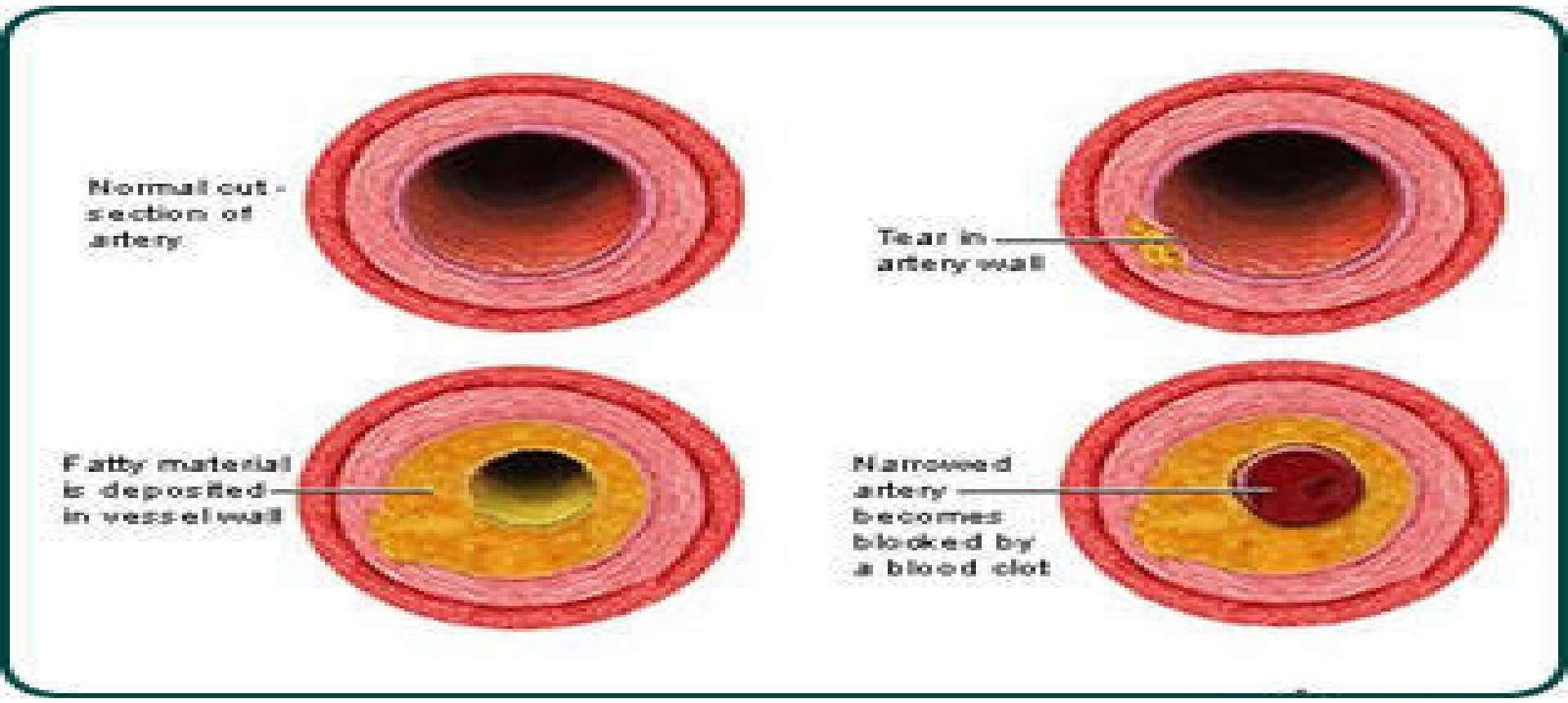
- **Normal healthy arterial endothelium:**
- **Arteries are soft and Elastic**
- **Repels cells** and **inhibits blood clotting**
- **Regulates tissue and organ blood flow by**
  - Ability of blood vessels to dilate- **vasodilatation**
  - Ability of blood vessels to constrict- **vasoconstriction**

Arteriosclerosis

What Is Arteriosclerosis?

- **Arteriosclerosis** is **non-specific term** used to describe
- **Hardening and thickening of wall of medium or large arteries.**

Atherosclerosis is a form of Arteriosclerosis



What Is Atherosclerosis?

- Term **Atherosclerosis**, comes from **Greek words**

  –**Atheros-** meaning **"gruel" or "paste"**

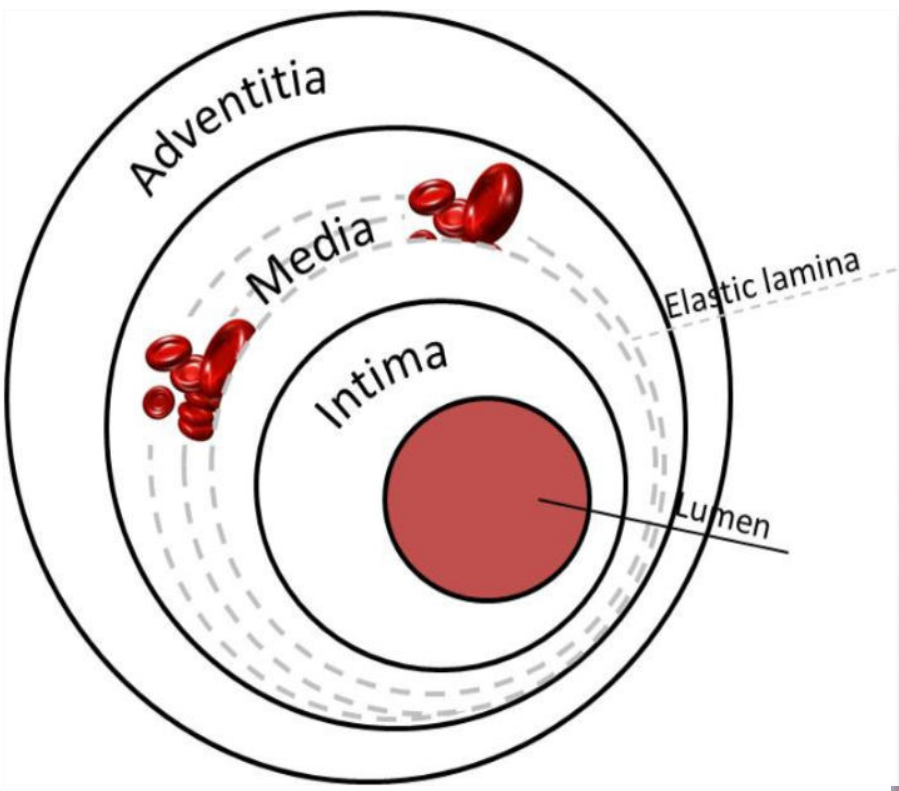
  –**Sclerosis-** meaning **"hardness".**

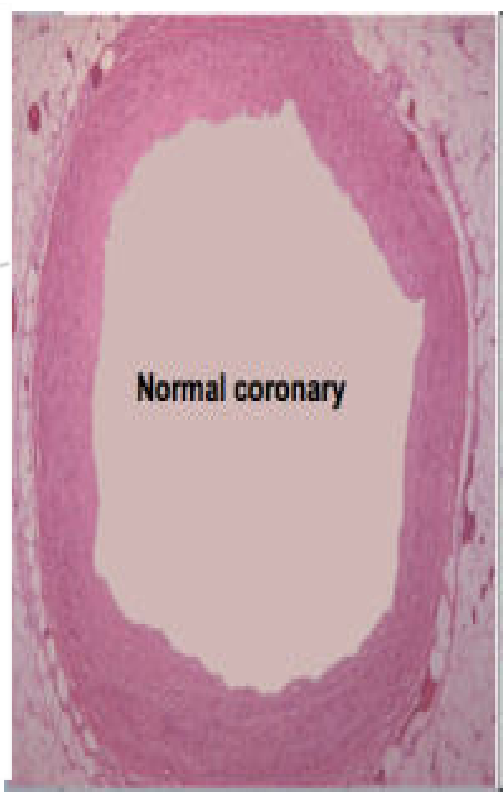
Terms related to Atherosclerosis

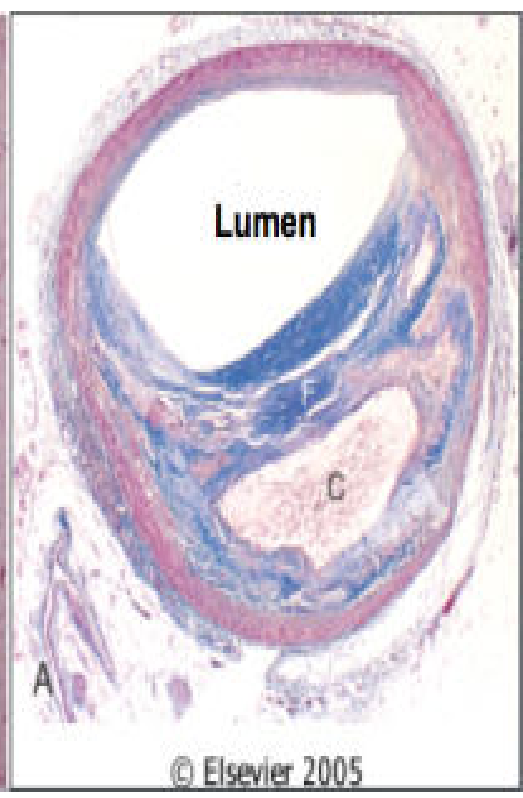
- Many terms are associated to Atherosclerosis:
  - ❖Atheroma
  - ❖Atherosclerotic Plaques
  - ❖Fibro Fatty Lesions
  - ❖Fibrous Plaques

- **Atherosclerotic Plaque Results From Accumulation of :**
  - –Lipids
  - –Connective tissue
  - –Inflammatory cells
  - –Smooth Muscle cells
  - –Foam Cells
  - –Minerals
- In an intima of blood vessels.

Atherosclerosis is Hardening of Blood Vessels due to formation of Fibro Inflammatory Fatty Lesions/Plaques







- **Atherosclerosis are abnormal**

Diseased/defective arteries.

  - **Becomes hard and non elastic**
  - **Less or non Functional**
  - **Decreased diameter of lumen**
  - **Obstruct normal blood flow to cells/tissues/organs.**

Causes Of Atherosclerosis

Risk Factors For Atherosclerosis

- Risk factors which accelerate progression of Atherosclerosis and endothelial dysfunction are:

–Oxidative Stress due to free radicals
–Dyslipidemias/Dyslipoproteinemias
–Hypercholesterolemia
–Other Cardiovascular risk factors

Improper Dietary Habits

- Eating an imbalanced diet
- Excess of Refined Sugars
- Excess of Saturated fatty acids
- Use of Trans Fatty acids

- Smoking
- Age and Sex
- Physical inactivity
- Stressful life style

- Hormonal Imbalances

❖ Diabetes mellitus

❖ Metabolic Syndrome

Unchangeable Risk factors of Atherosclerosis

- **Age**
- **Genetic Alterations**
- **Male gender**
  - Men are at grater risk than are premenopausal women, because of the protective effects of natural Estrogens.
- **Family history of premature coronary heart disease**
  - Several genetically determined alterations in lipoprotein and cholesterol metabolism have been identified.

Changeable Risk Factors Of Atherosclerosis

- **Hyperlipidemias:**
  - Presence of Hyperlipidemia is **strongest risk factor for Atherosclerosis** in persons younger than 45 years of age.
  - Both primary and secondary hyperlipidemia increases risk.

Dyslipidemias directly associated with increased risk of Atherosclerosis

- **Elevated TAG (above reference range)**
- **Increased LDL (above reference range)**
- **Decreased HDL (Below reference range)**
- **Increased HDL (above reference range)**

❖Hypertension

❖High blood pressure produces **mechanical stress on vessel endothelium.**

❖**Major risk factor for atherosclerosis in all age groups**

❖May be as important or **more important than hypercholesterolemia after age of 45 years.**

❖**Blood Pressure >160 mmHg increases risk for MI**

- **Regulation of Hypertension may reduce risk of Atherosclerosis.**

- Substances toxic to endothelial cells:
  - Homocysteine
  - C-Reactive Protein

Less Well Established Risk Factors

- **High Serum Homocysteine Levels**
  - Homocysteine is derived from **metabolism of dietary Methionine**
  - Homocysteine inhibits elements of anticoagulant cascade and is **associated with endothelial damage**.
- **Infectious agents**
  - Presence of some organisms (*Chlamydia pneumoniae, herpesvirus hominis, cytomegalovirus*) in atheromatous lesions has been demonstrated by immunocytochemistry
  - Organisms may play a role in atherosclerotic development by initiating and enhancing inflammatory response.
- **Elevated serum C-Reactive Protein**
  - ~~It may increase likelihood of thrombus formation~~
  - Inflammation marker

How An Atherosclerotic Plaque Developed?

Common Arteries Atherosclerozied

- **Aorta** and its branches
- **Coronary arteries**
- **Large vessels** that supply **Brain**
- **Peripheral arteries**

Pathogenesis Of Atherosclerosis

- Pathogenesis of Atherosclerosis includes:
  - **Genetic Factors**
  - **Environmental Factors**

3 Stages of Atherosclerosis:

1.Initiation and Formation

2.Adaptation

3.Clinical

Development of Atherosclerosis

- Key event is **damage to endothelium**
- Damaged endothelium becomes **more permeable to Lipoproteins.**
- Lipoproteins **move** below **endothelial layer** (get lodged into intima).

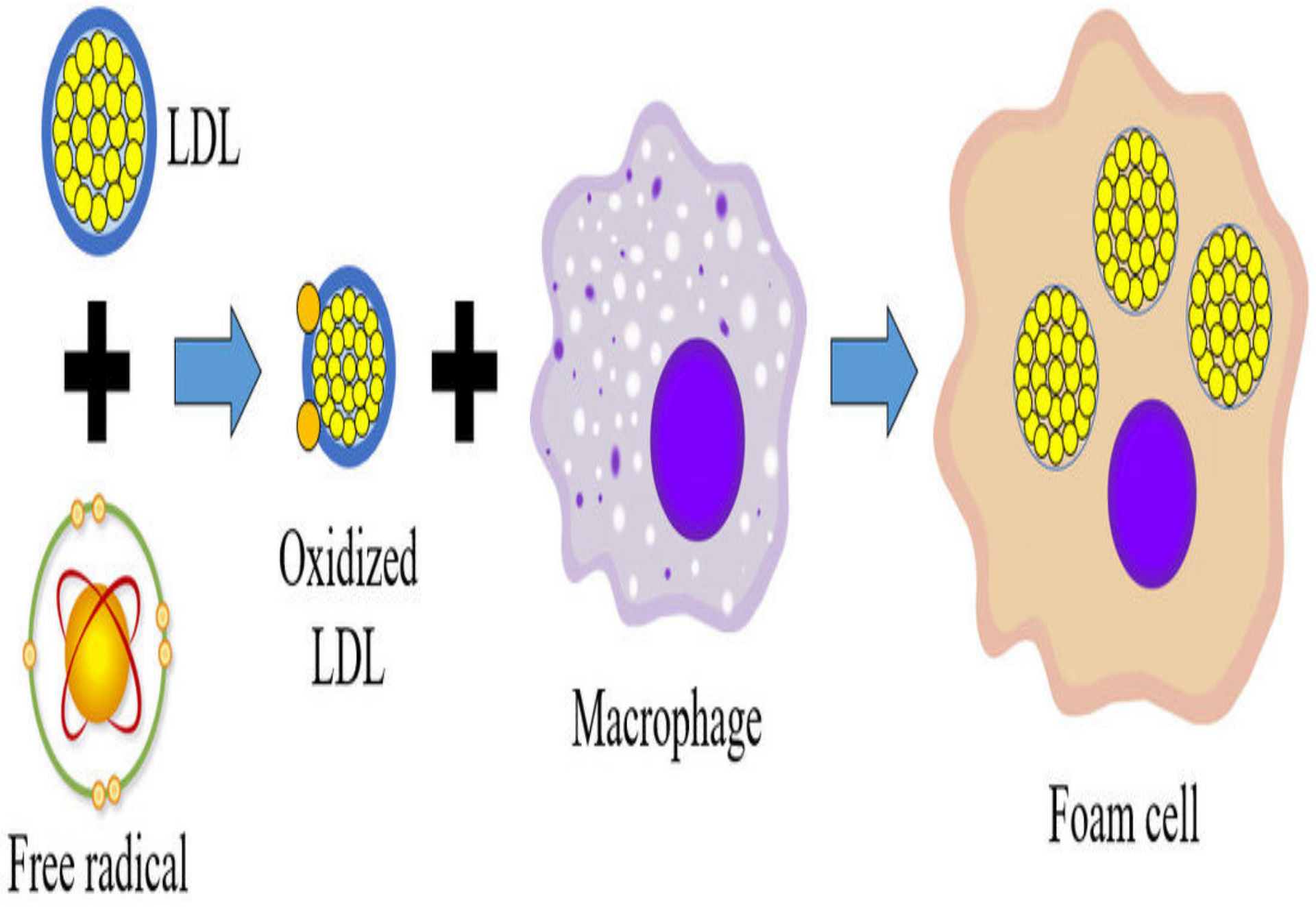
- **Damaged Endothelium looses its cell-repellent quality.**
  - **Inflammatory cells move into vascular wall.**
  - Further **Endothelial injury occurs** by **attachment of leukocyte** (lymphocyte and monocyte) and **Platelet adherence**
  - **Smooth muscle cell emigration and proliferation**

- **Activated macrophages** releases **free radicals that oxidizes LDL.**

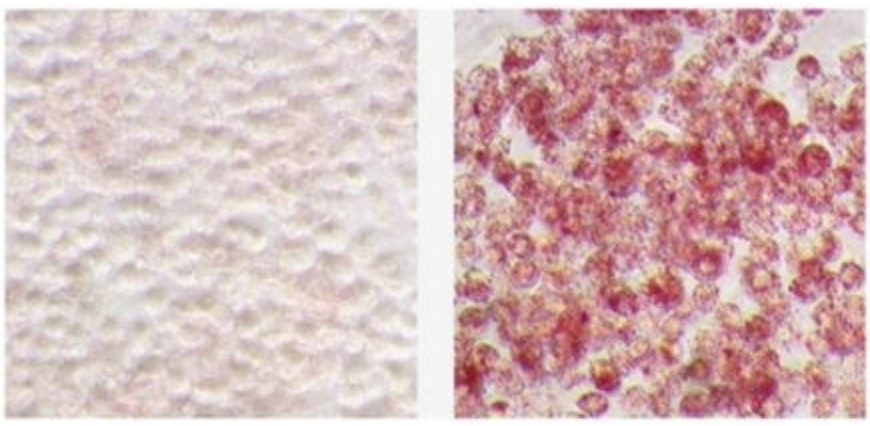
❖**Lipid Engulfment by Macrophages**

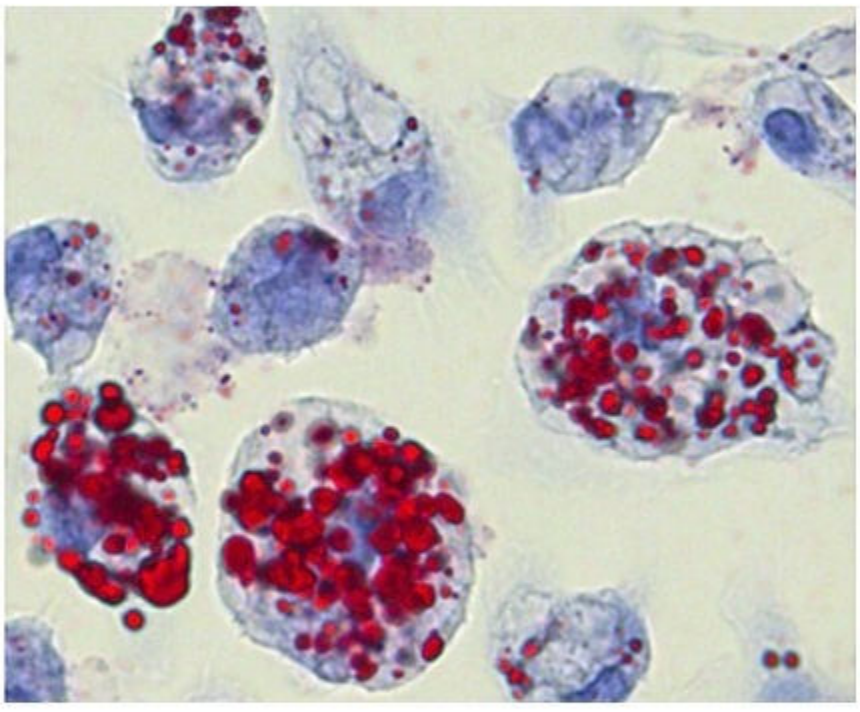
❖**Oxidized LDL engulfed by Macrophages transform** to form **Foam cells**

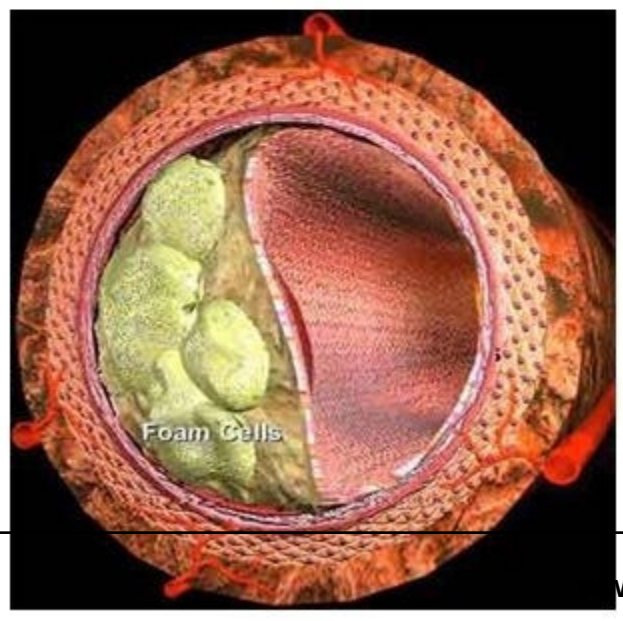
❖Subsequent **development of an atherosclerotic plaque with lipid core**



Foam Cells



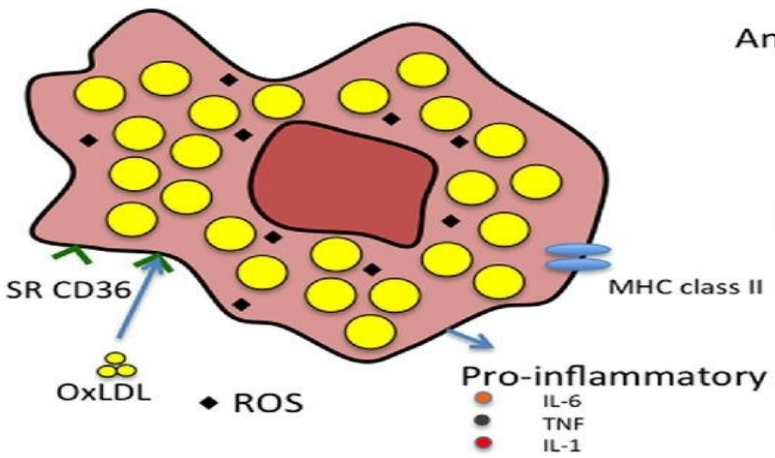




Foam cells are unable to metabolize and efflux the cholesterol that they have accumulated. As a result, they die which exacerbates the inflammatory conditions in and around the atherosclerotic lesion.

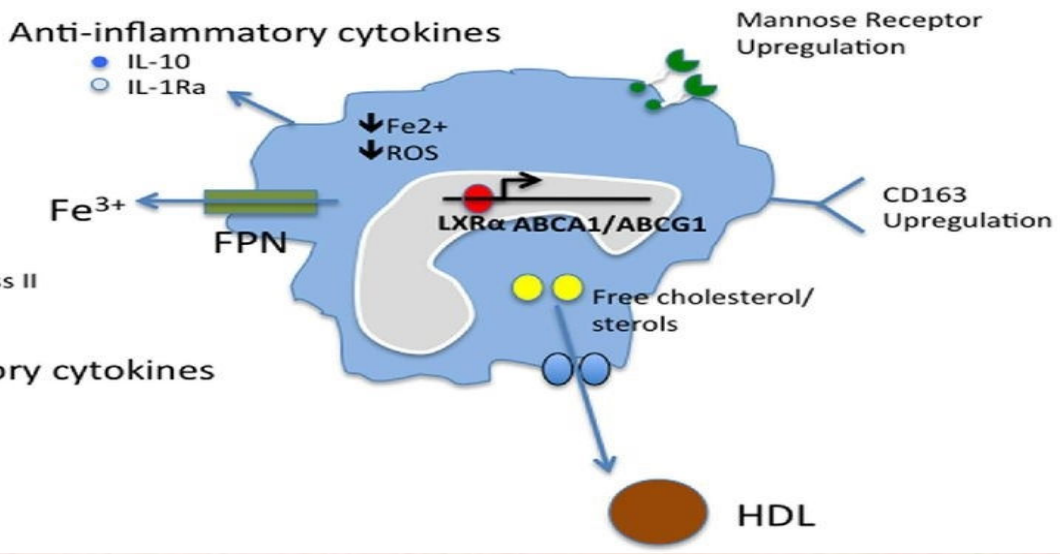
Foamy Macrophage

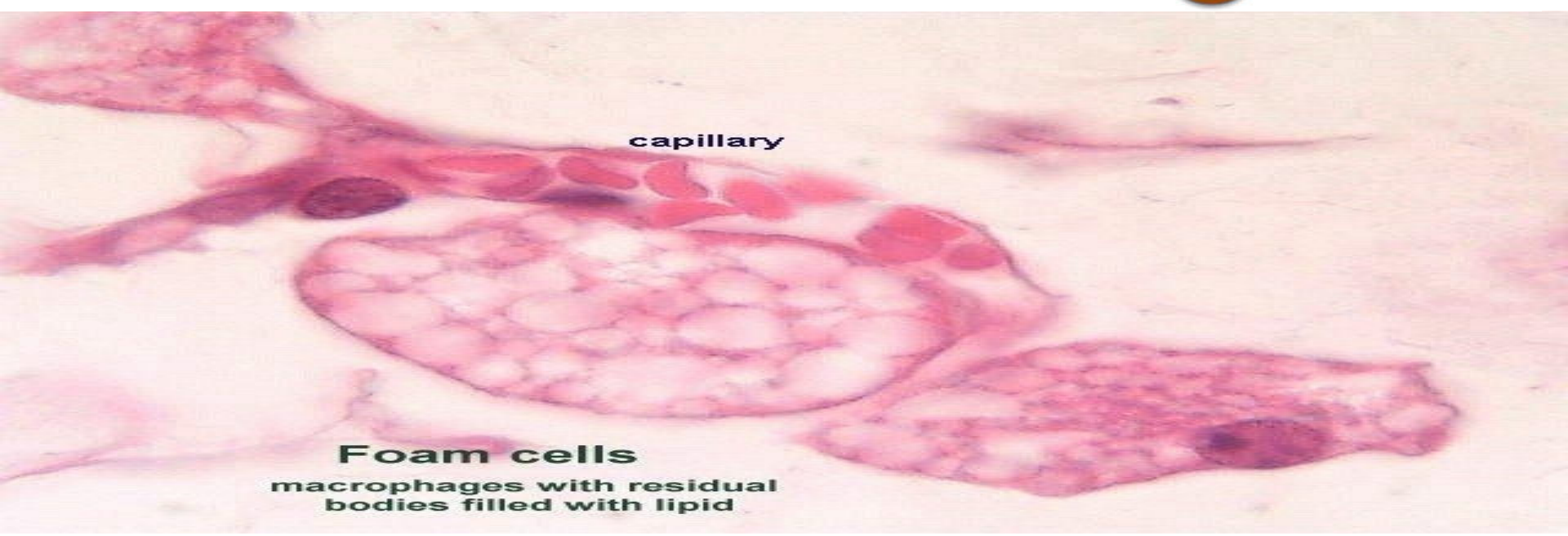
Stimulus: oxLDL
+ Cytokine production – pro-inflammatory
+ MHC class II expression
↑Lipid uptake
↑Reactive Oxygen Species (ROS)



M(Hb) Macrophage

Stimulus: Hb:Hp
+ Cytokine production – anti-inflammatory
↓lipid uptake
↑cholesterol efflux
↓intracelluar iron and ROS





Effects Of Oxidized LDL

• Oxidized LDL is Toxic to Endothelium:

- Causes **Endothelial loss**
- Exposure of subendothelial tissue to blood components
- **Chemotactic effect**
  - **Lymphocytes and Monocytes**
  - **Smooth muscle cells from arterial media**
- Stimulates production of Cytokines, adhesion molecules in endothelium;
- Inhibits endothelium derived releasing factor (EDRF), **favoring vasospasm**
- Stimulates specific immune system (production of antibodies against oxidized LDL).

- **Activated Macrophages also ingest oxidized LDL** to **become foam cells,**
- Which are present in all stages of atherosclerotic plaque formation.
- **Lipids released from necrotic foam cells accumulate** to form **lipid core of unstable plaques/Fatty streaks.**

- Endothelial disruption leads :
  - **Platelet adhesion** and **aggregation**
  - **Fibrin deposition**

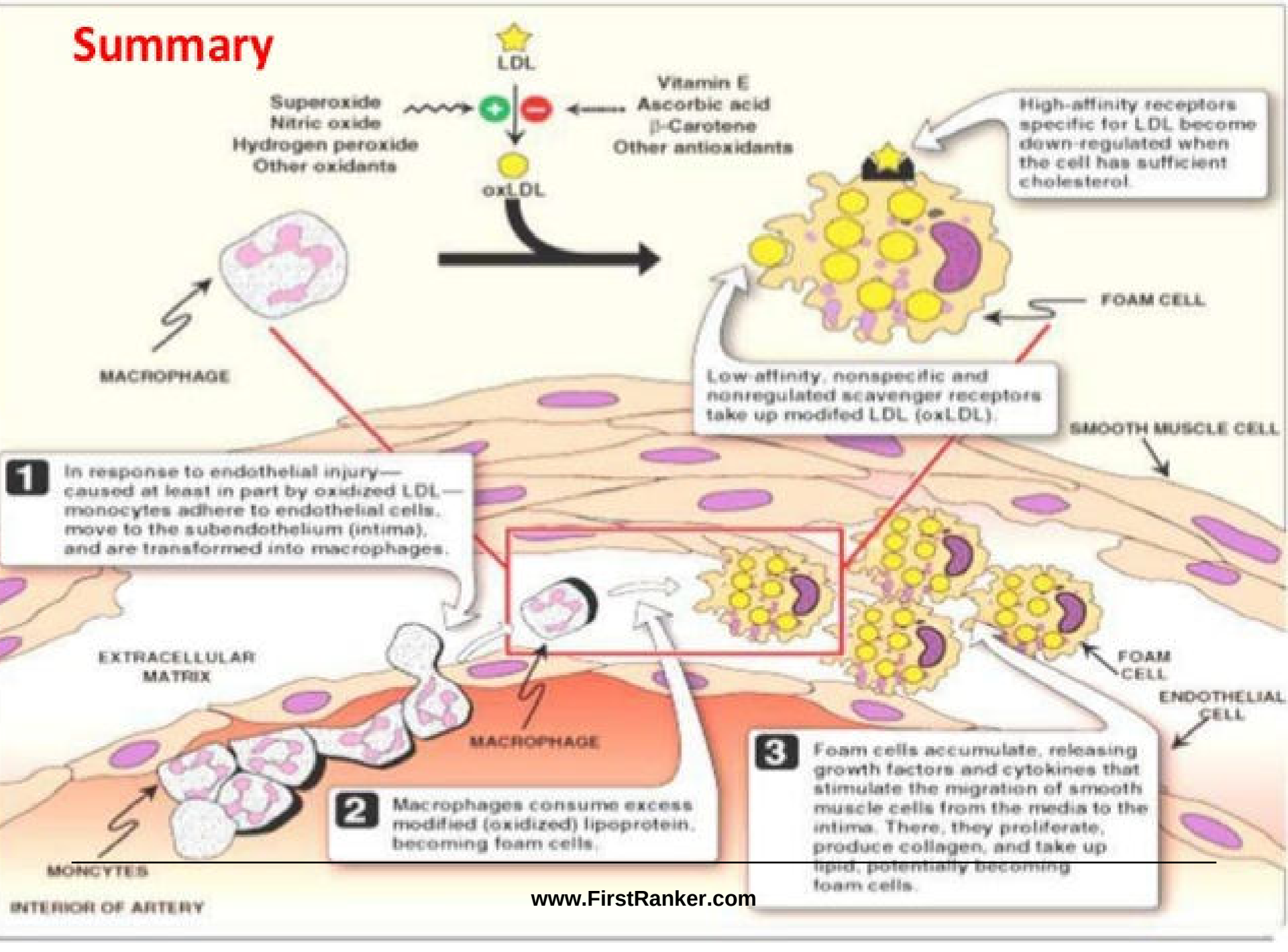
- **Platelets and activated macrophages release various factors that are thought to promote growth factors**

- This modulate proliferation of smooth muscle cells and **deposition of extracellular matrix in lesions: Elastin, Collagen, Proteoglycans.**

- Thus **Connective tissue synthesis** and **Calcium fixation** determinates stiffness of blood vessels.

- Which causes further **ulceration of Atheromatous plaque.**

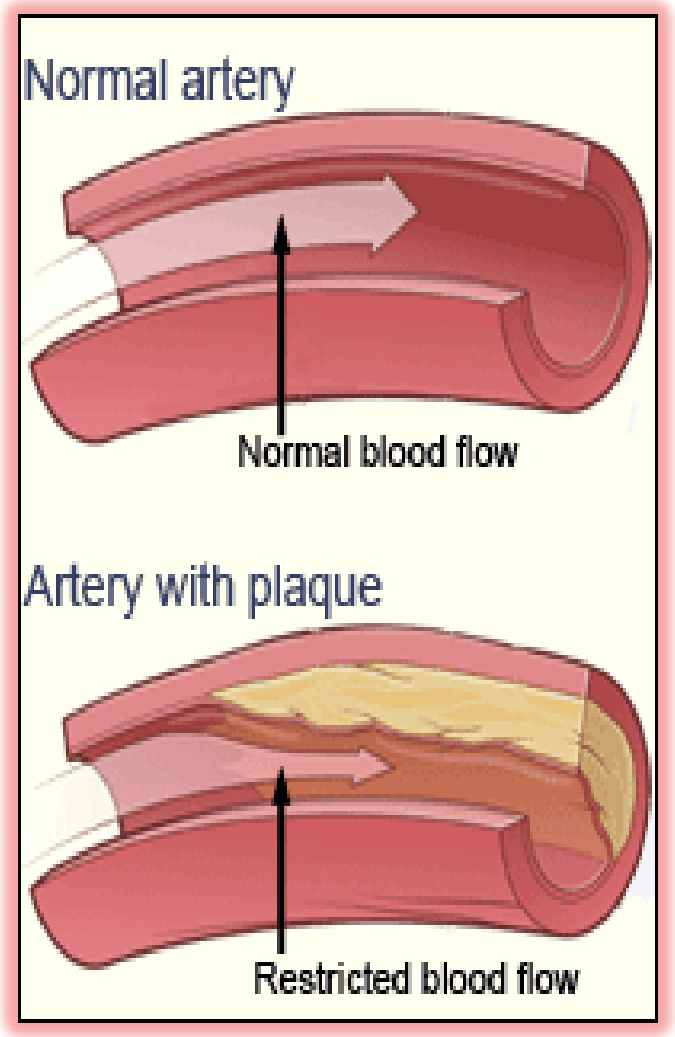
Summary

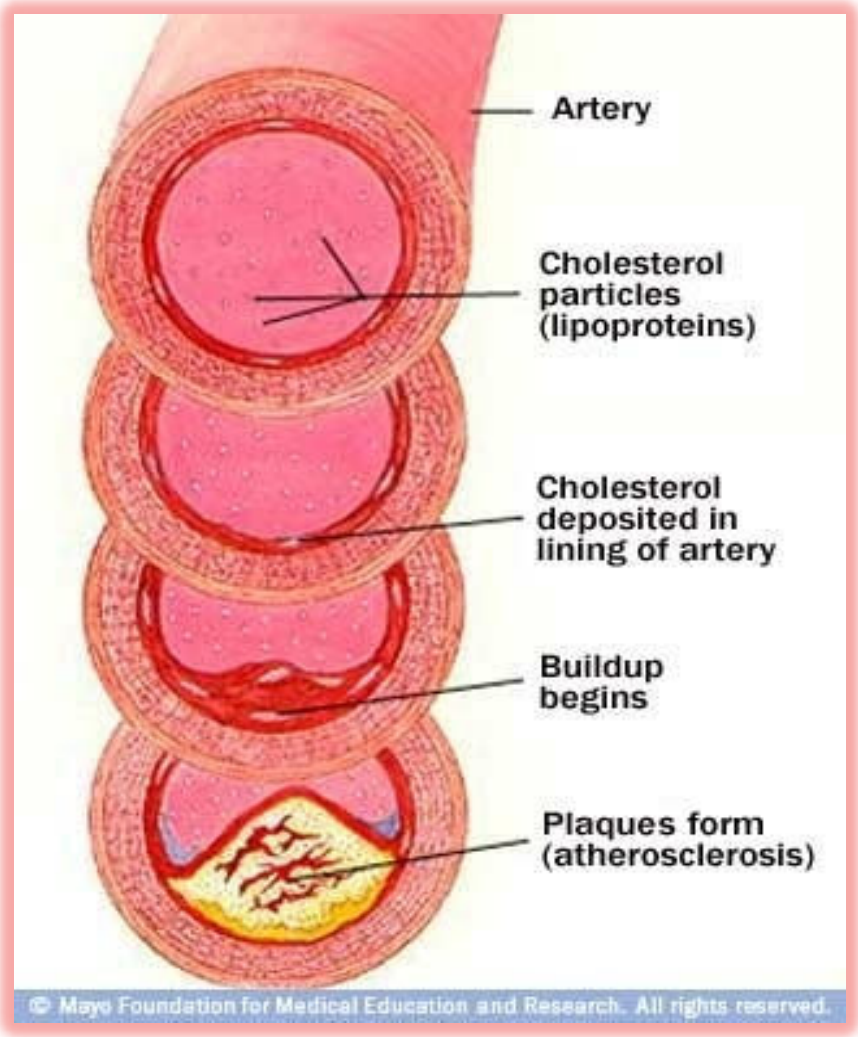


Summary Of Pathogenesis Of Atherosclerosis

- **Accumulation of Lipids in vessel wall**
- Plasma Lipoproteins
- Low-density lipoproteins LDL
- **LDL transported inside macrophages to vessel walls**
- **Damage to Endothelium**
- **Adhesion of Macrophages**
- **Inflammation at the site**
- **Fatty Streaks**
- **Foam cells**
- **Small Thrombi**
- **Calcification**
- **Plaque formation**
- **Ulceration**
- **Stiffening and Hardening of blood vessels**

Building Up of Atherosclerotic Plaque





Lesions Associated with Atherosclerosis

- **Lesions** associated **with Atherosclerosis** are of **three types**:
  - **Fatty streak**
  - **Fibrous Atheromatous plaque**
  - **Complicated Lesion**
- **Latter two** are **responsible for clinically significant manifestations** of disease.

- **More advanced complicated lesions** are characterized by:
  - **Hemorrhage**
  - **Ulceration**
  - **Scar tissue deposits**

- As a result of all pathogenic mechanism
- **Atherosclerosis** can be defined as **vicious inflammatory process**.

Modern Theory of Atherosclerosis

- **Multifactor Theory:**

– **Structural and functional injury of vascular endothelium**
– Role of lipoproteins **in initiation and progression of lesions**
– Response to **injury of immune cells and smooth muscle cells**
– **Role of growth factors and cytokines in inflammation**
– **Role of repeated thrombosis in lesions progression.**

- Endothelial monolayer overlying an intima contacts blood.
- Hypercholesterolemia promotes accumulation of LDL particles (light spheres) in intima.
- Lipoprotein particles often associate with constituents of the extracellular matrix, notably proteoglycans.
- Sequestration within intima separates lipoproteins from some plasma antioxidants and favors oxidative modification.
- Modified lipoprotein particles (darker spheres) may trigger a local inflammatory response responsible for subsequent steps in lesion formation.
- Increased expression of various adhesion molecules for leukocytes recruits monocytes to the site of a nascent arterial lesion.
- Once adherent, some white blood cells will migrate into intima.

- Migration of leukocytes probably depends on chemoattractant factors including modified lipoprotein particles themselves and chemoattractant cytokines depicted by the smaller spheres, produced by vascular wall cells in response to modified lipoproteins.
- Leukocytes in evolving fatty streak can divide and exhibit increased expression of receptors for modified lipoproteins (scavenger receptors).
- These mononuclear phagocytes ingest lipids and become foam cells, represented by a cytoplasm filled with lipid droplets.
- As fatty streak evolves into a more complicated atherosclerotic lesion, smooth-muscle cells migrate from media (bottom of lower panel), through internal elastic membrane (solid wavy line), and accumulate within expanding intima where they lay down extracellular matrix that forms the bulk of the advanced lesion.

Consequences Of Atherosclerosis

OR

Effects/Complications Of Atherosclerosis

- Atherosclerosis is a **chronic process**
- Atherosclerosis **affects almost all people with variable severity.**

- Atherosclerosis **develop over several decades.**
- If Congenital in origin It **may starts as early as infancy** and **childhood,**
- **Progress very slowly during life.**

- **Atherosclerosis** contributes to **more mortality** and

- **More serious morbidity** than any other disorder in the western world.

- **Atherosclerosis affects** the **intimal lining of endothelium of**

- **Large and Medium-sized elastic and muscular arteries of body.**

- **Atherosclerotic plaque formation**

- **Narrows diameter of blood vessel lumen.**

- **Atherosclerosis leads** to the **narrowing or complete blockage of arteries /Occlusion by:**
  - **Endothelial Dysfunction**
  - **Lipid deposition**
  - **Inflammatory reaction in vascular wall**
  - **Ulcerative Lesions**

Atherosclerosis Brings Alterations Of Arteries :

- **Aneurysm**-Excessive localized swelling of blood vessel
- **Stenosis**-Abnormal narrowing of vessel
- **Occlusion**-Closing of blood vessel
- **Thrombosis**-Local clotting of blood
- **Embolism** -blockage of vessel by lodging of blood clot/fat globule
- **Fissure**-Small tear with bleeding
- **Ulceration**-Removal of top layer
- **Calcification-** Accumulation of Calcium Salts

- **Atherosclerosis , can and does, occur in almost any artery in the body.**
- **Atherosclerosis of coronary arteries is very crucial**
- **This blocks,blood circulation to Heart**
- **Which fails cardiac muscle to sustain.**

- **Atherosclerosis leads to disease of cardiovascular system affecting blood vessel wall.**

- **Causing Ischemic Heart Disease which** is **leading cause of death in developed countries.**

Complications of Atherosclerosis

- 1. **Acute Occlusion:**

  Thrombosis

  Occlusion

  Ischemia, Infarction

- 2. **Chronic Stenosis:**

  Chronic ischemia

  Atrophy

  Eg. Renal atrophy in renal artery stenosis, ischemic atrophy of skin in DM

- 3. **Aneurysm Formation:**

  Extension to media

  Aneurysm

  Aneurysmal rupture eg. Abdominal aortic aneurysm
- 4. **Embolism:**

  Of atherosclerotic plaque or of thrombi

- **Thrombosis** is most important complication of Atherosclerosis.

- It is caused by slowing and turbulence of blood flow in region of plaque and ulceration of plaque.

PHYSIOPATHOLOGICAL CONSEQUENCES OF THE PLAQUE

- Coronary Artery Disease (CAD) : Angina, MI
- Cerebro Vascular Disease (CVD)
- Peripheral Artery Disease (PAD)
- Ischemic Stroke (Brain infarct)
- Secondary Erectile Disorder (ED)
- Chronic Renal Ischemia (Renal failure)

- **Atherosclerosis commonly leads to:**
  - **Myocardial infarction**
  - **Stroke**
  - **Gangrene of extremities**

Biochemical Alterations In Atherosclerosis

Biochemical Basis Of Atherosclerosis

- **Low Blood supply** to Cells/Tissues
- **Low Nutrient and Oxygen Supply** to cells
- **Low Metabolism in cells**
- **Low Oxidative Phosphorylation**
- **Low ATP production** in cells
- **Low Cellular Activity**
- **Cellular/Tissue/Organ Dysfunction**
- **Irreversible Damage of cells/tissues/organ/system**

Diagnosis Of Atherosclerosis

- Checking Lipid Profile/Lipoproteins
- B.P
- ECG
- Angiography
- EEG
- Color Doppler
- MRI

Management Of Atherosclerosis

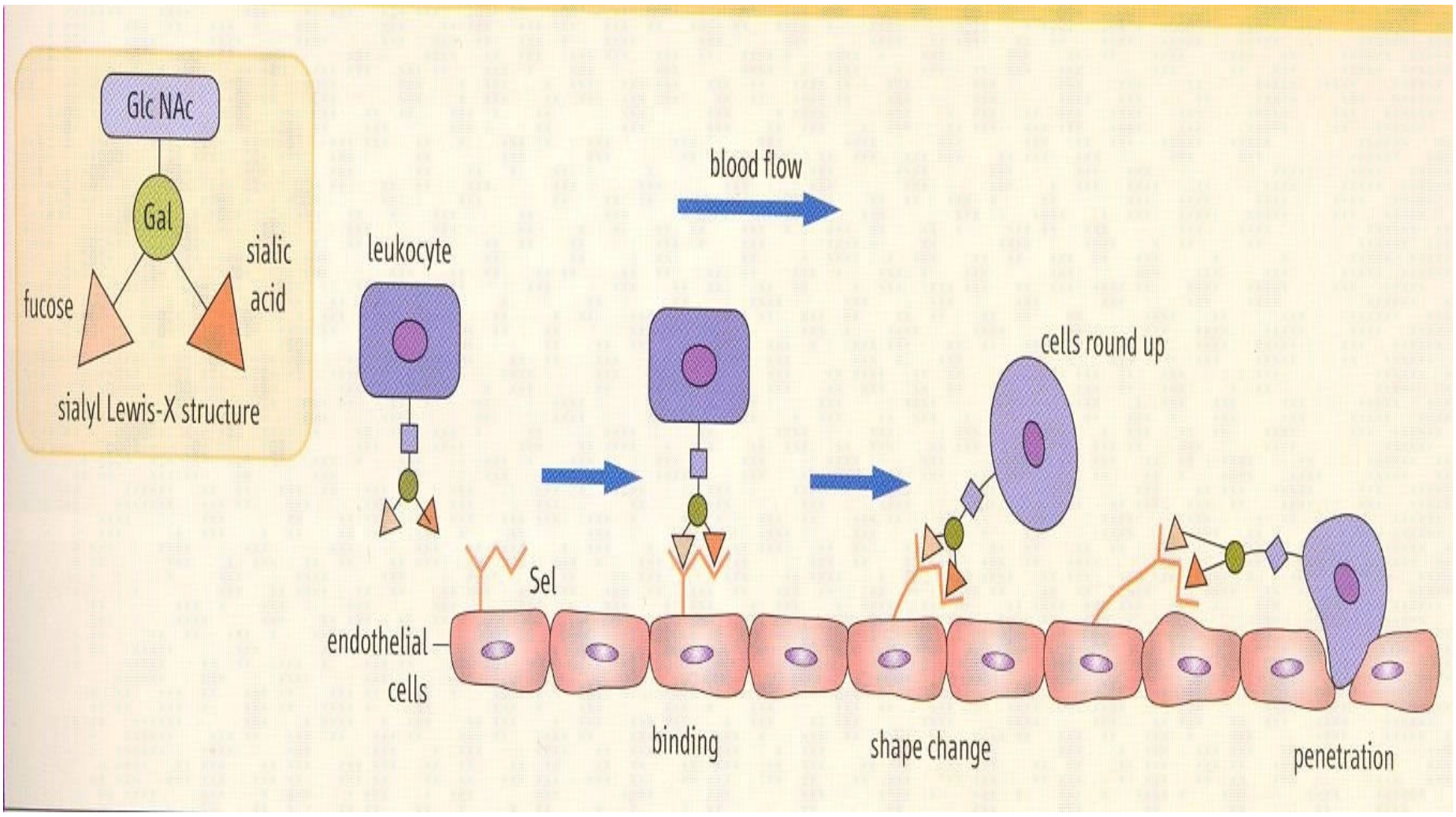
- Reducing the risk factors
- Correcting the underlying causes
- Angioplasty
- Other Surgeries

Reduction Of Atherosclerosis Risk

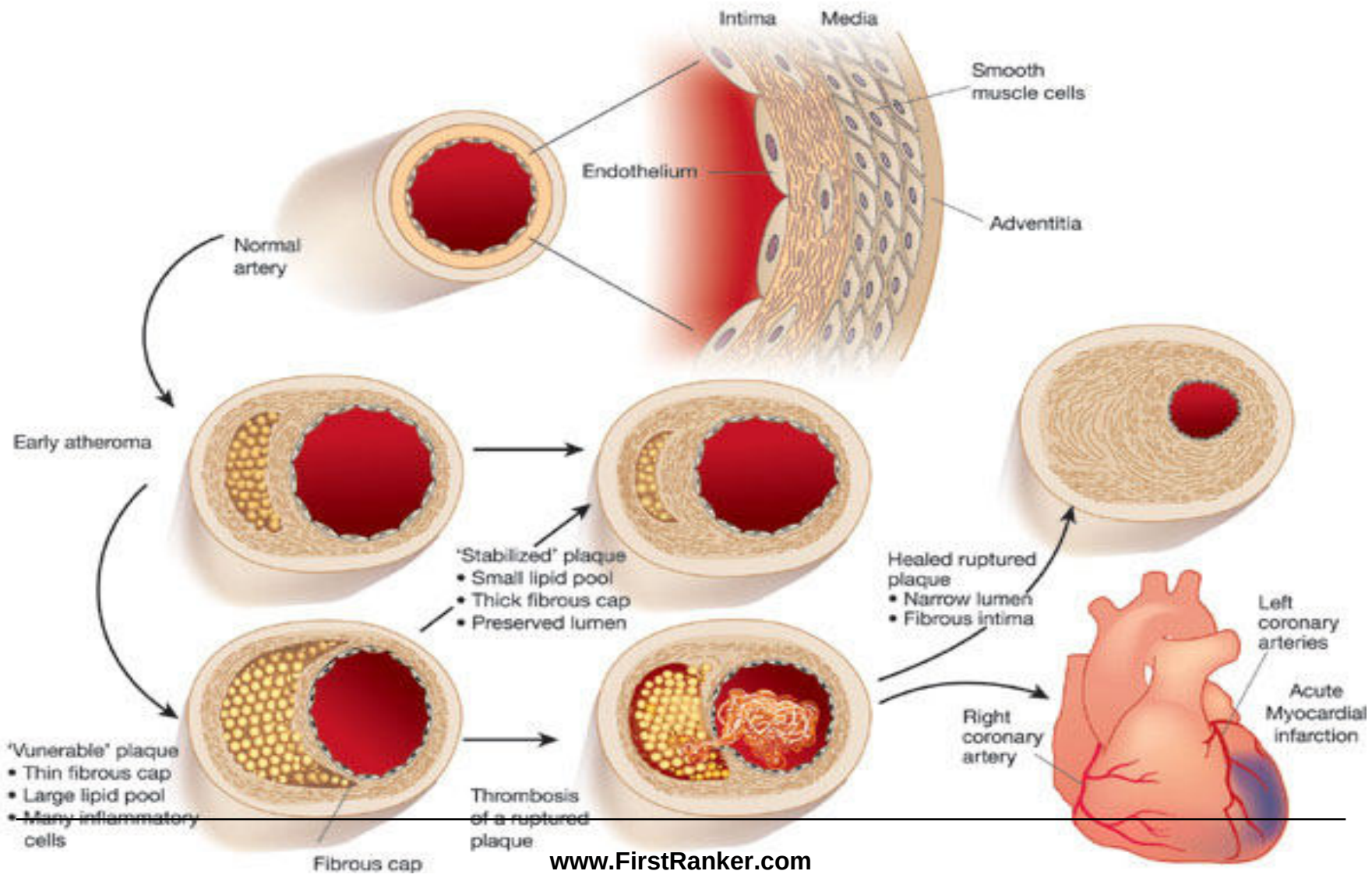
Risk of atherosclerotic event can be decreased by:

- Normal Balanced diet
- Physically active life
- Regular Exercise
- Smoking cessation
- Control of high blood pressure
- Intake of Antioxidants
- Drugs Statins, Ezetimibe

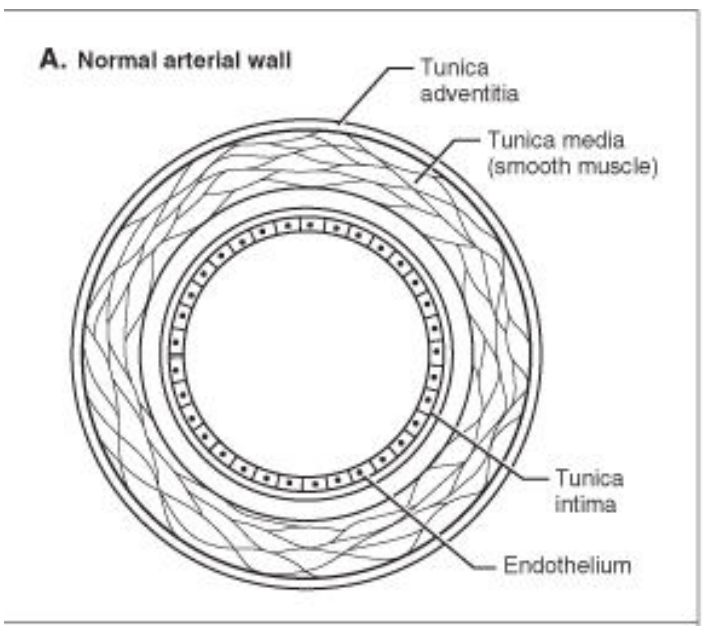
Development of Atherosclerosis

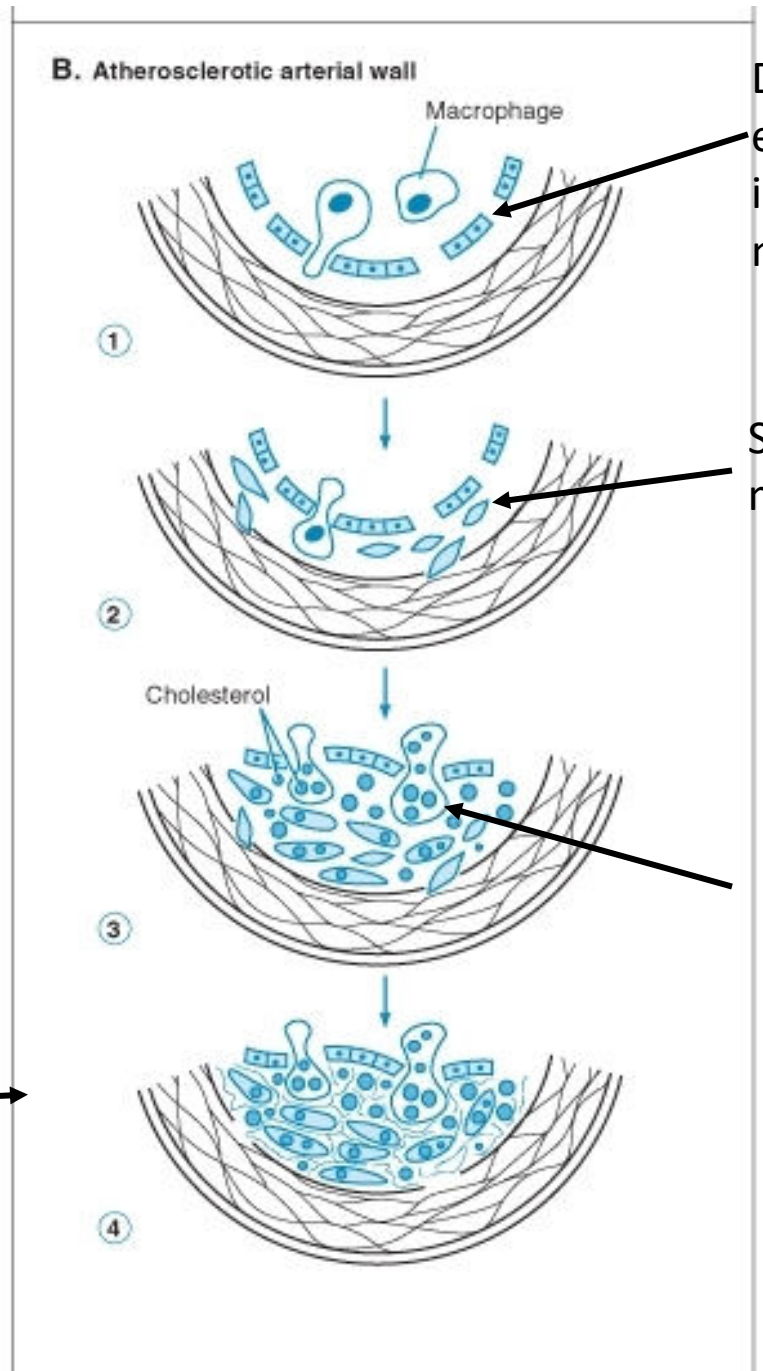


Process of Atherogenesis



Progression of CHD





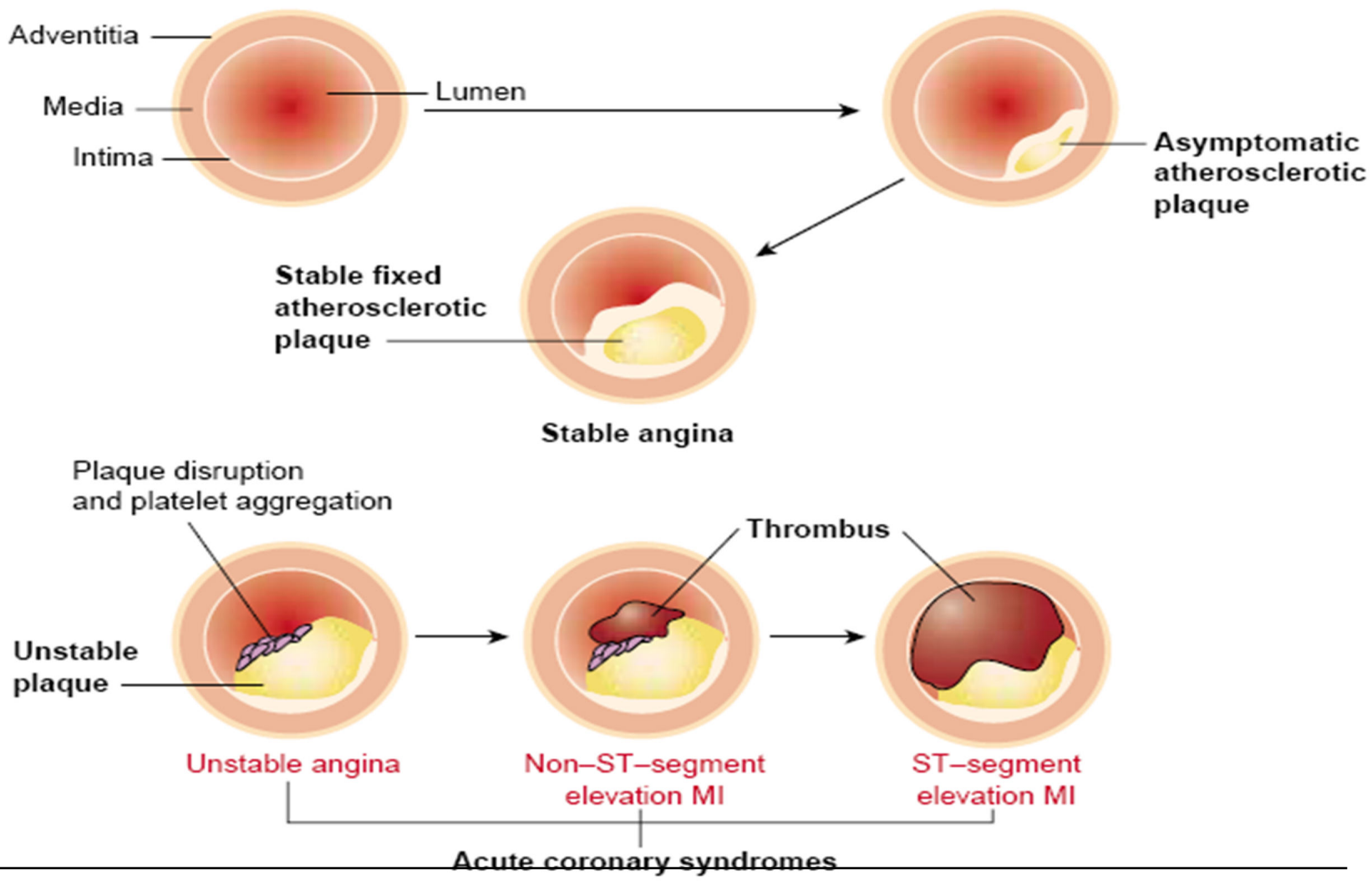
Damage to endothelium and invasion of macrophages

Smooth muscle migration

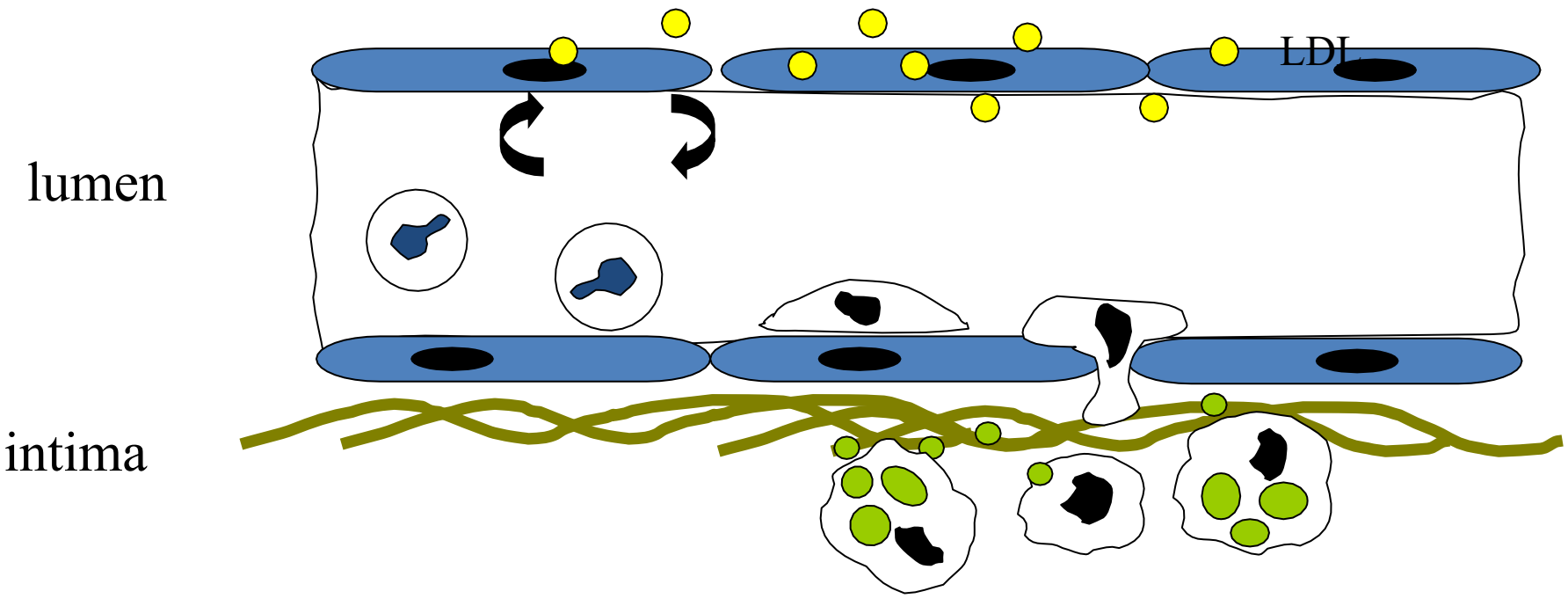
Cholesterol accumulates around macrophage and muscle cells

Collagen and elastic fibers form a matrix around the cholesterol, macrophages and muscle cells

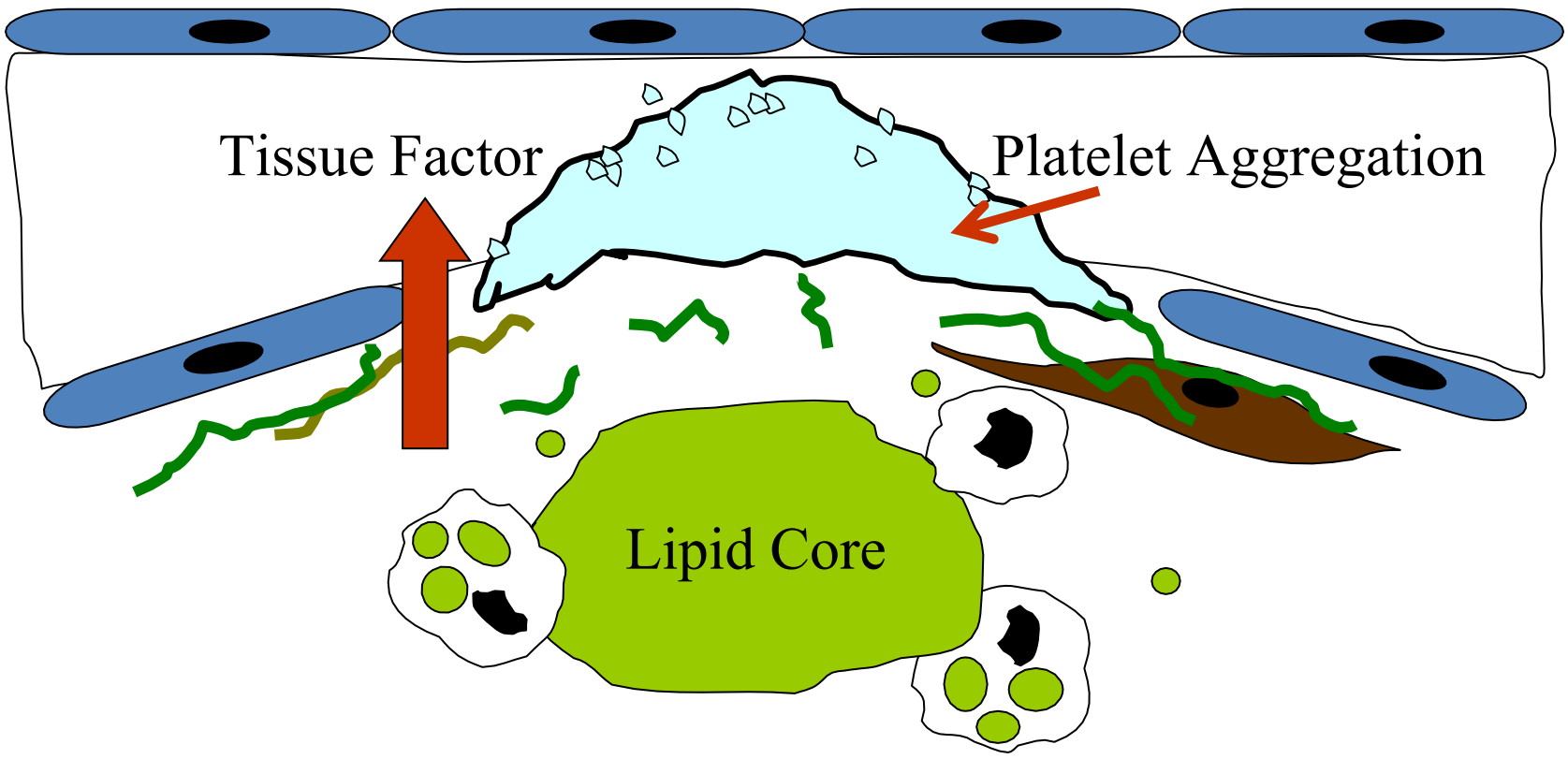
Pathogenesis of Coronary Heart Disease (CHD)



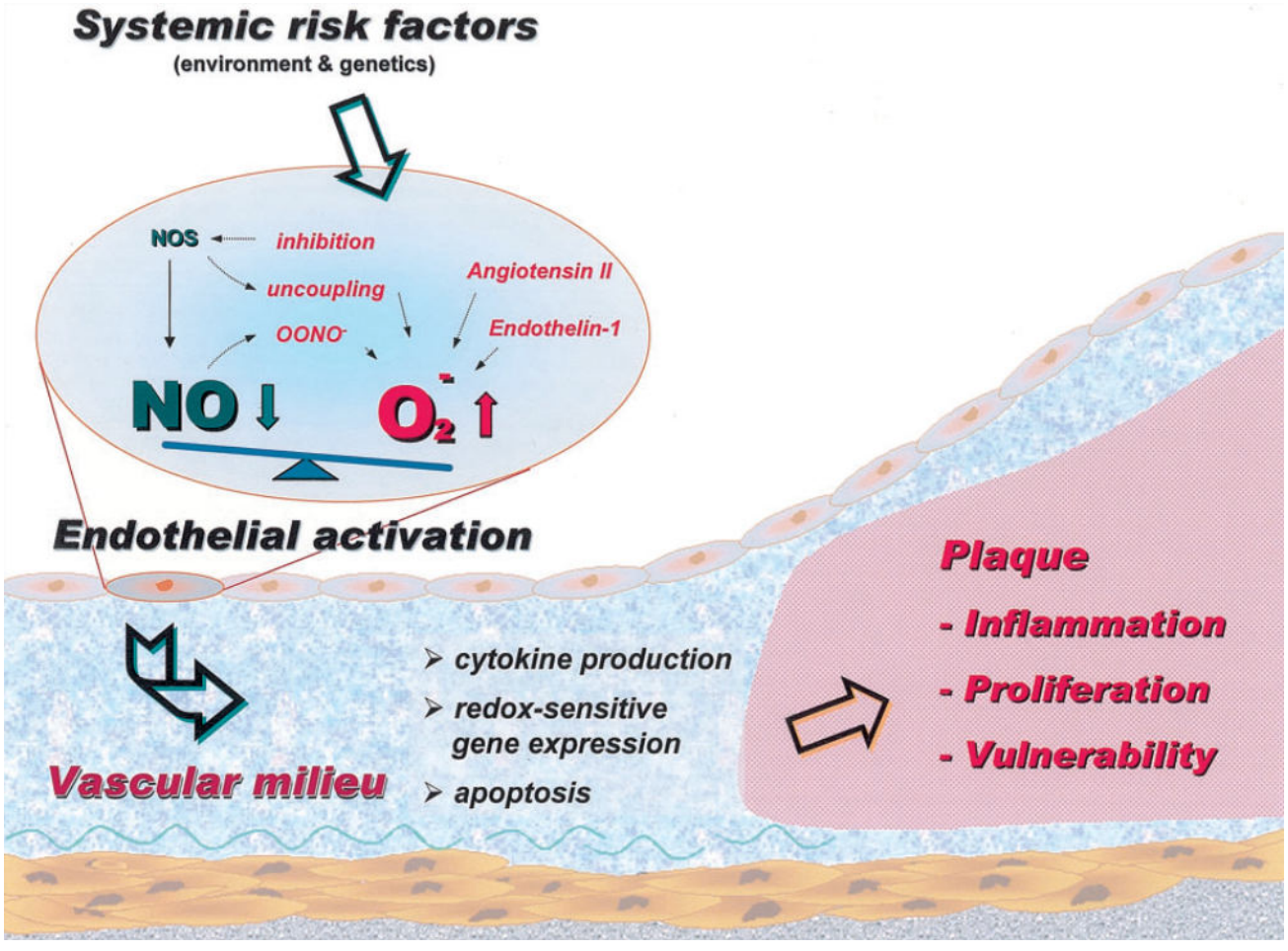
Monocyte Recruitment



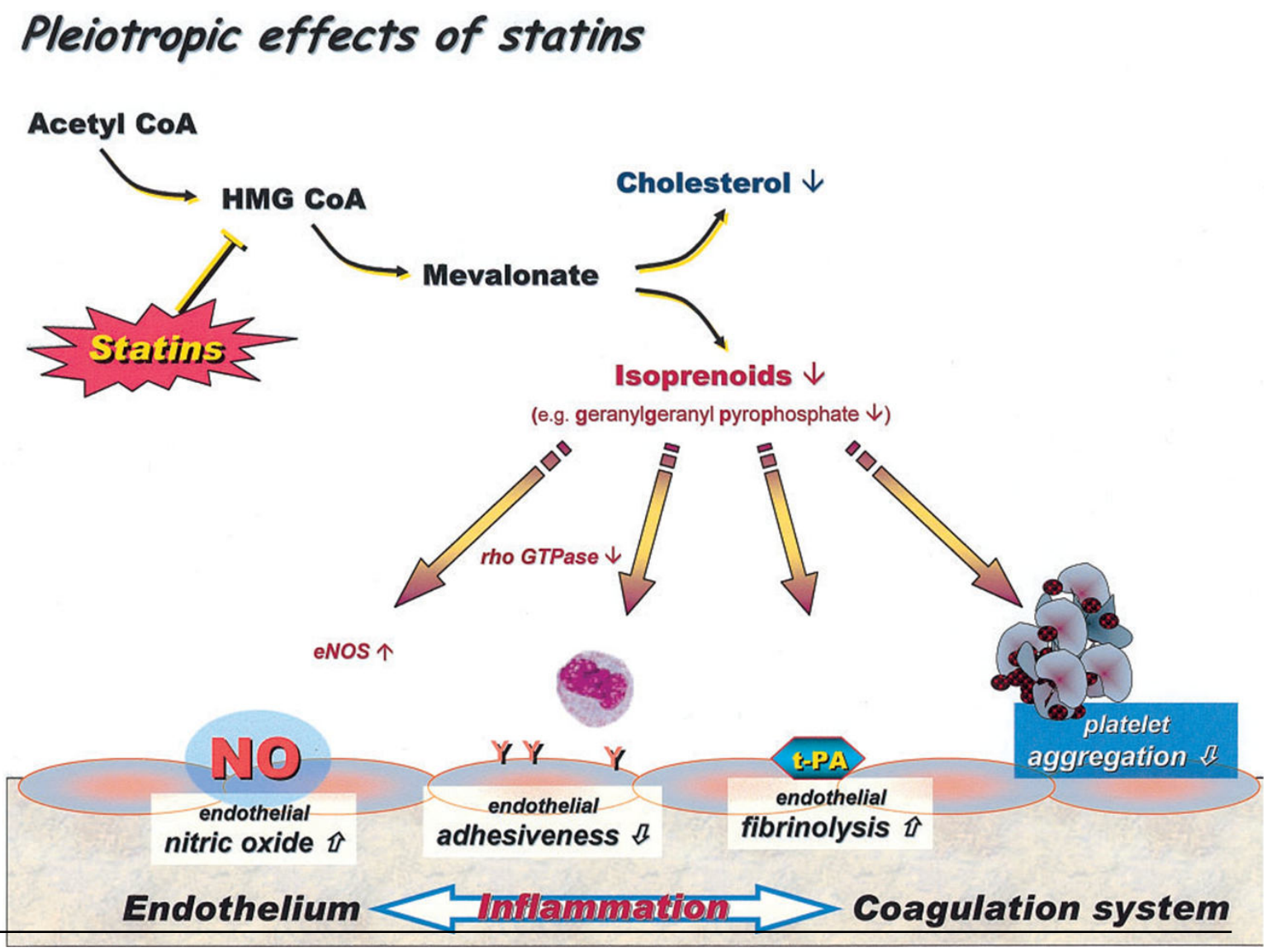
Plaque Rupture and Thrombosis



NO Inactivation Due to Oxidative Stress

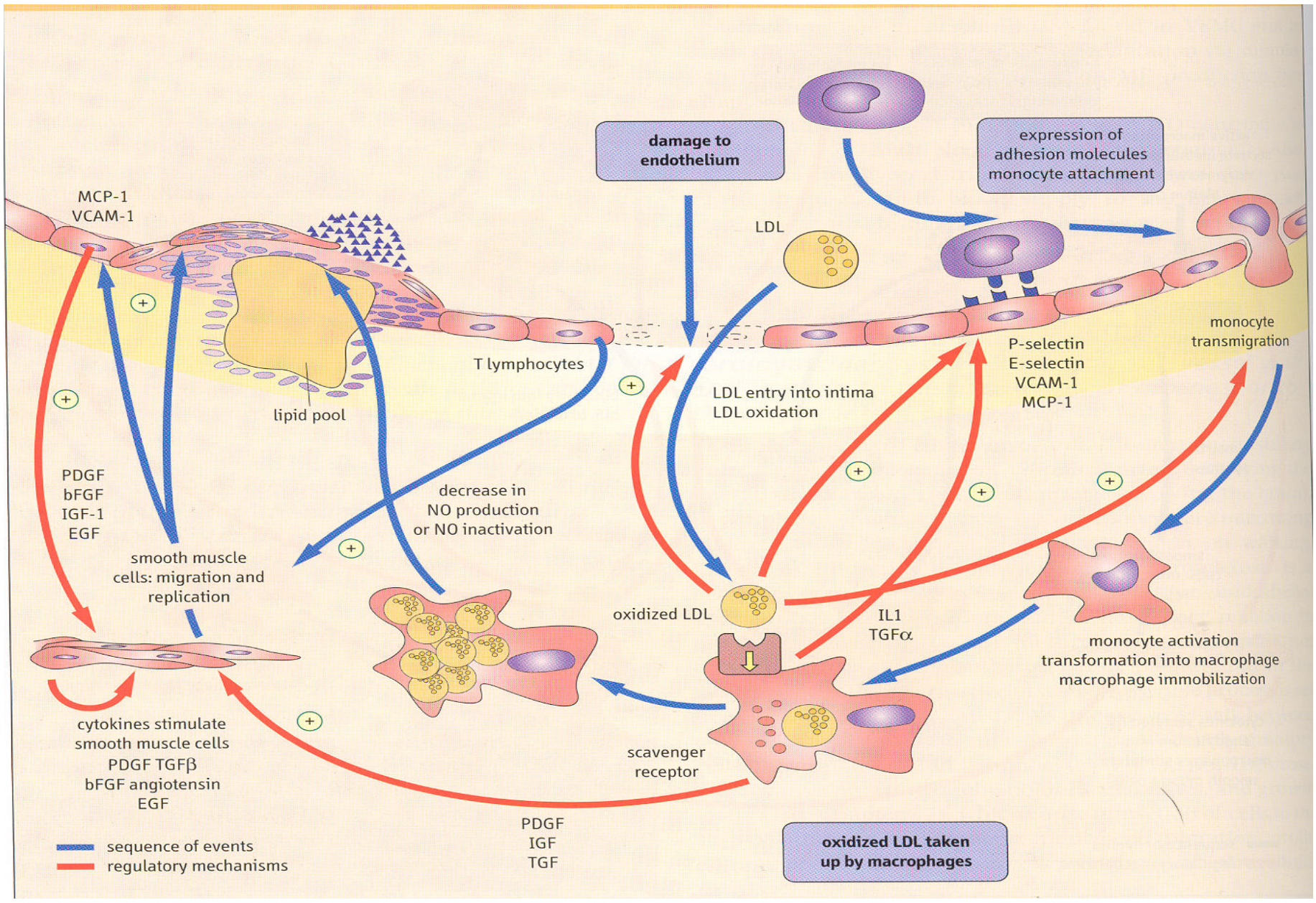


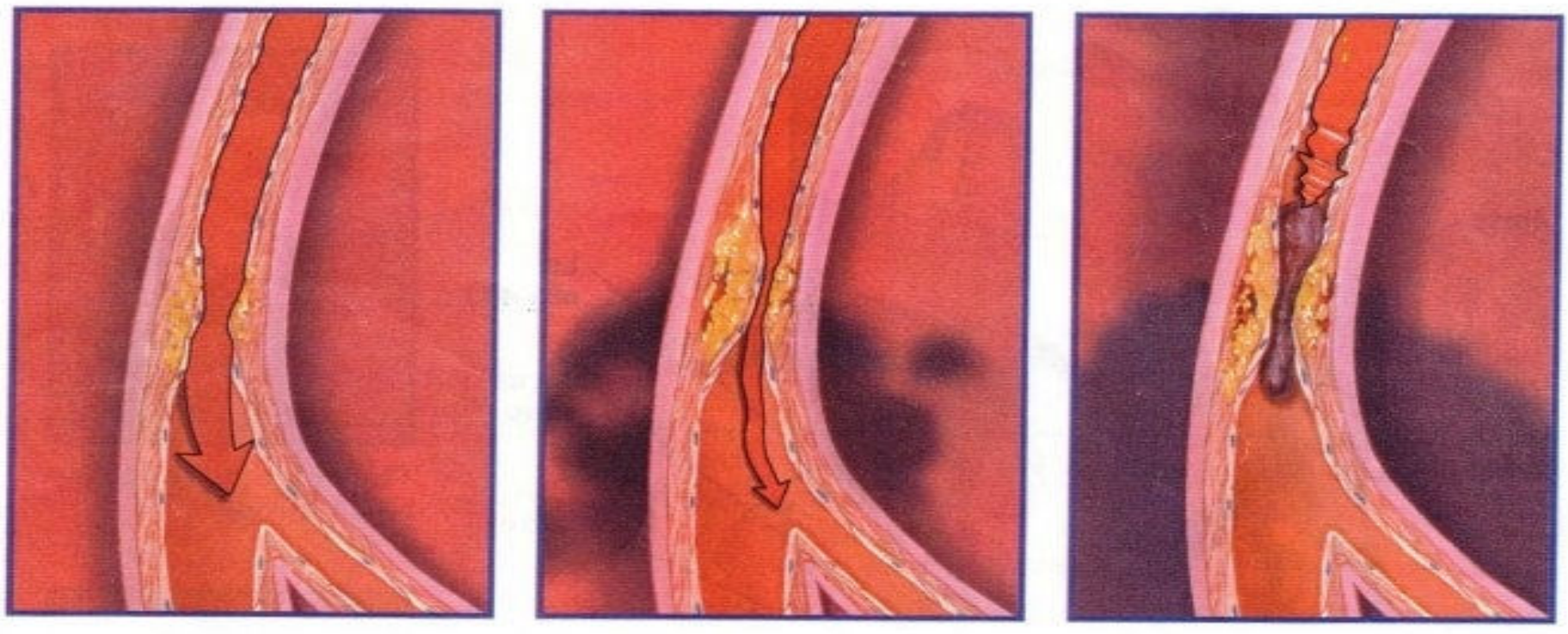
Schächinger V., Zeiher A.M.: Nephrol Dial Transplant (2002): 2055



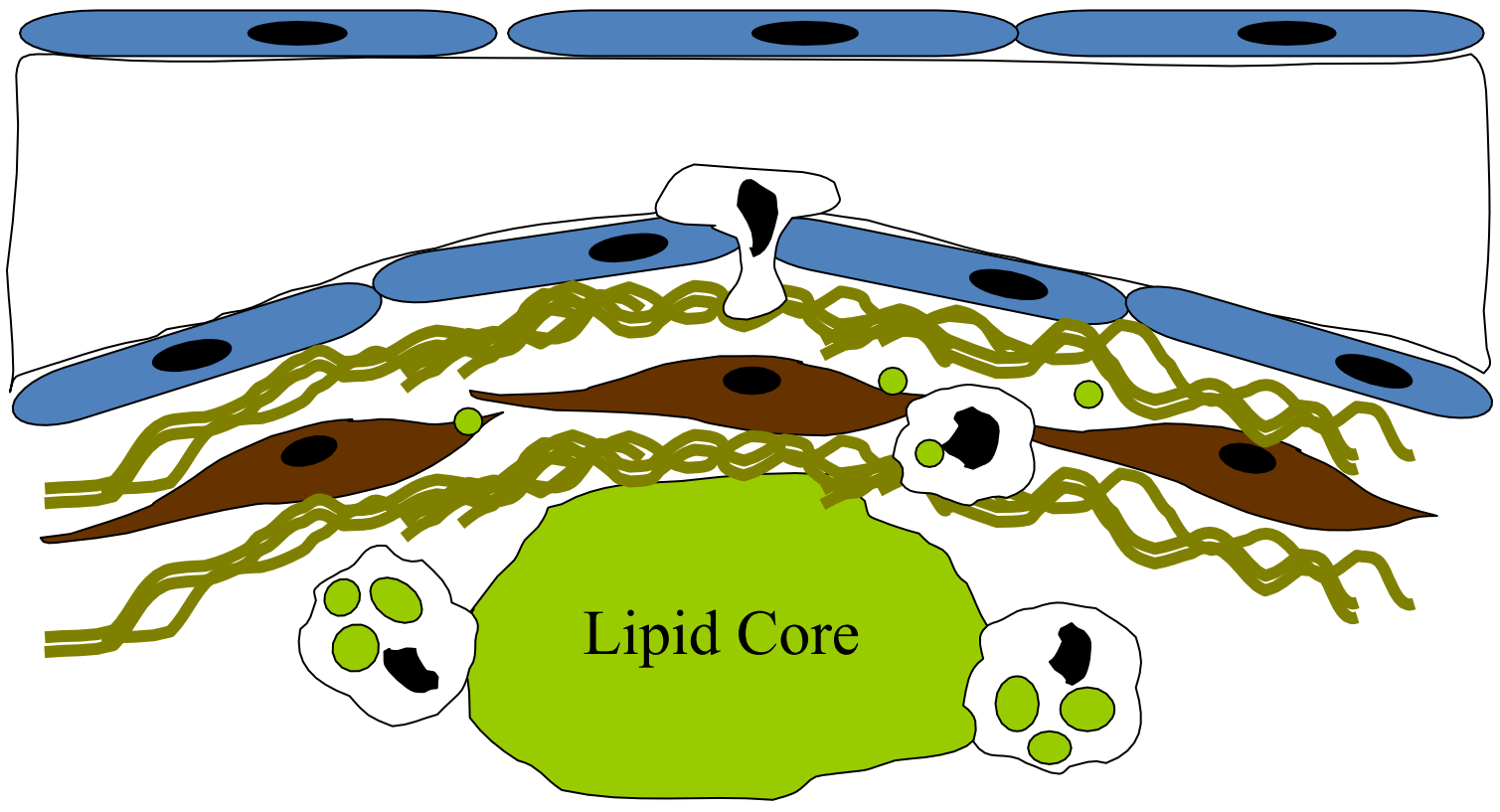
Schächinger V., Zeiher A.M.: Nephrol Dial Transplant (2002): 2055

Process of Atherogenesis – an overview

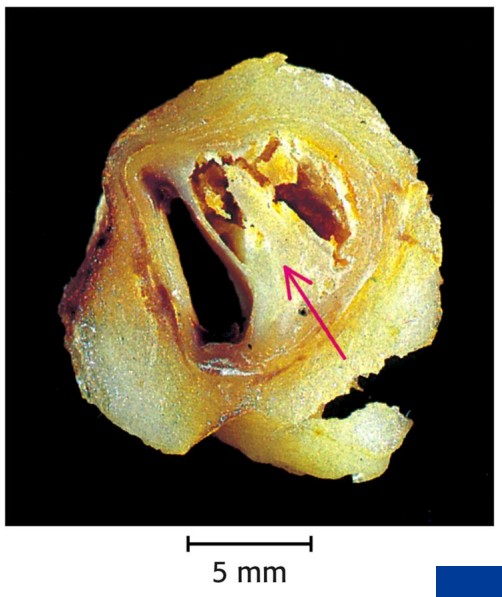


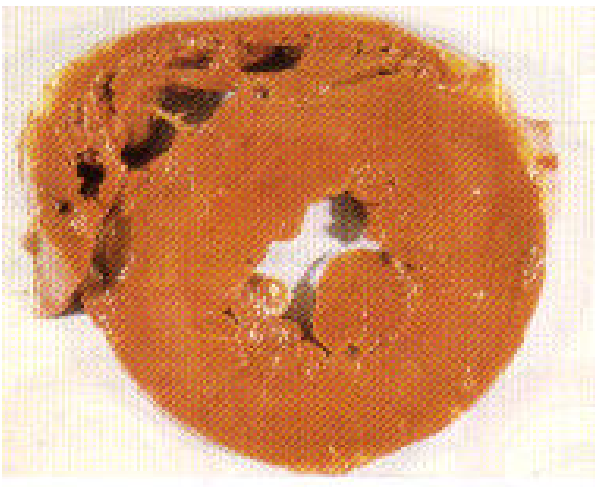


Formation of Atherosclerotic Plaques

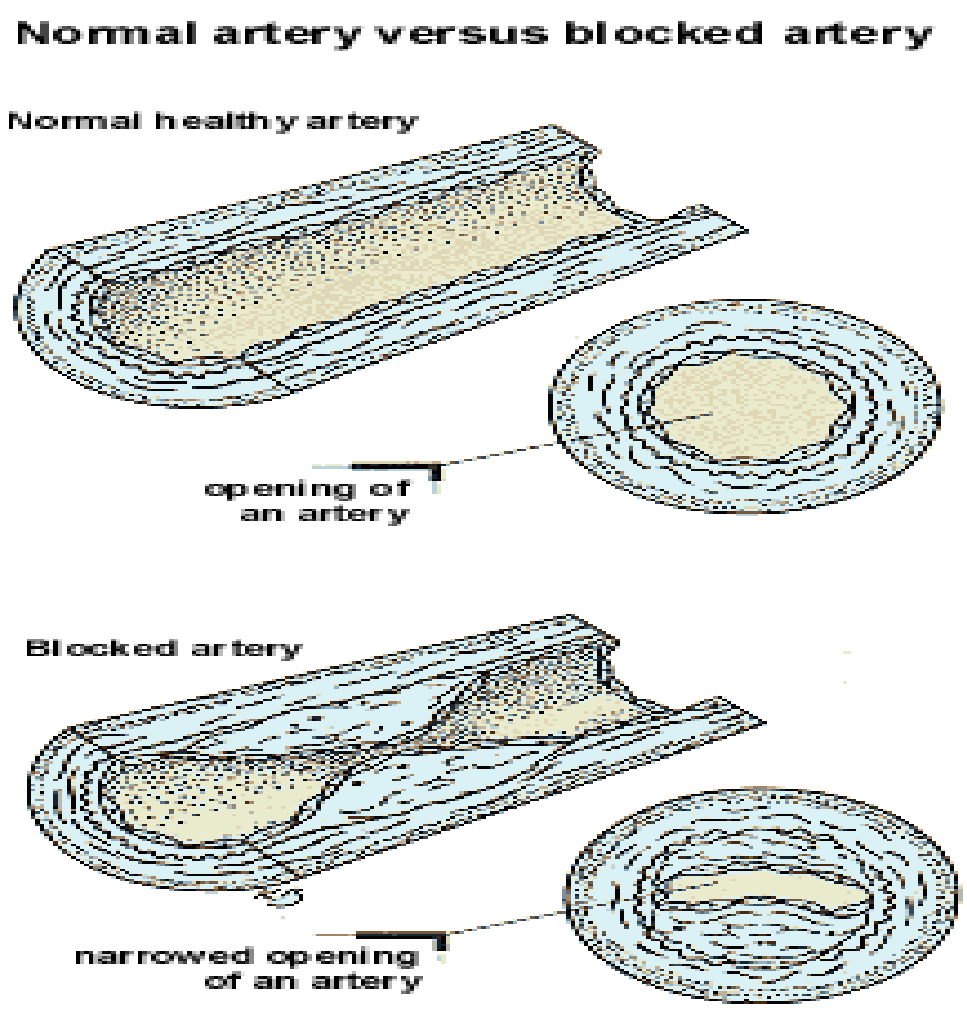


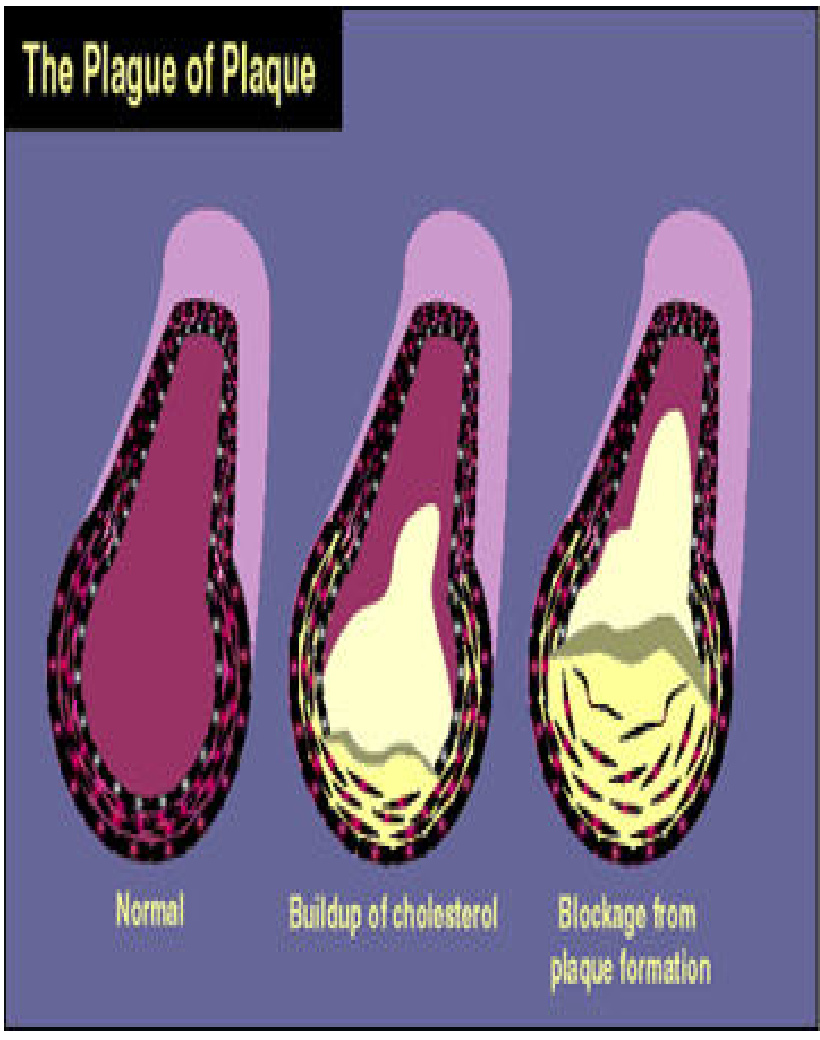
Plaque Build up in Artery

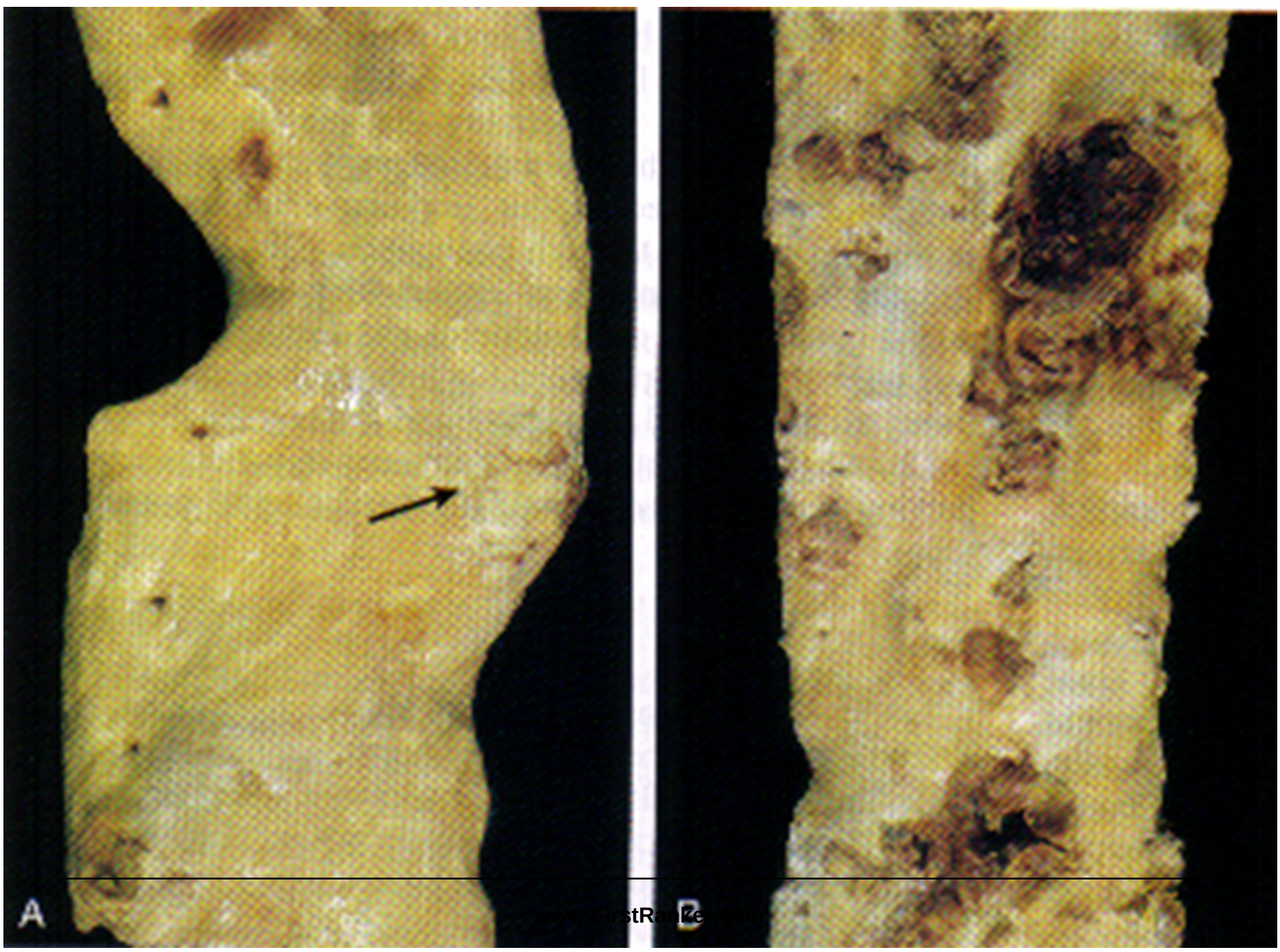


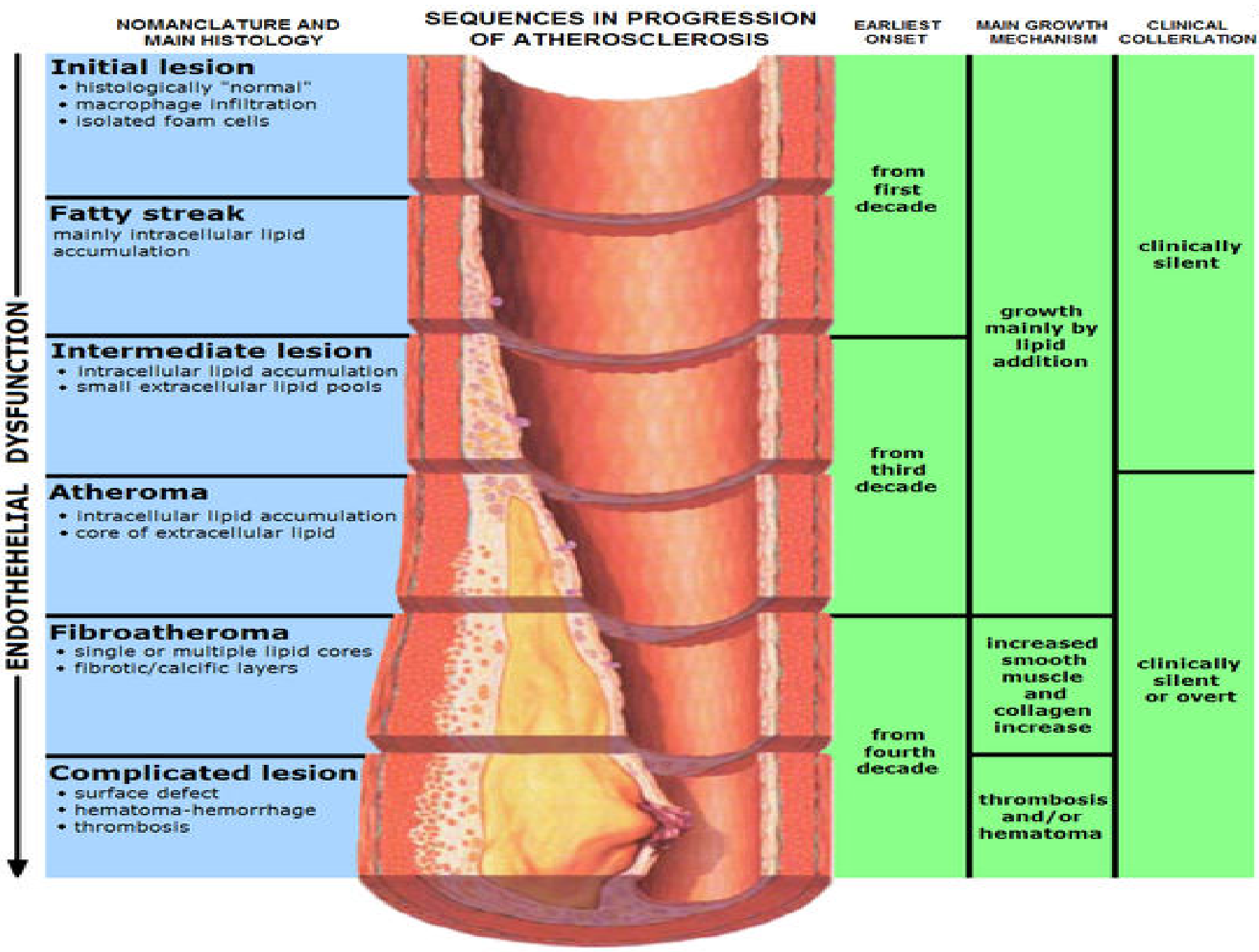


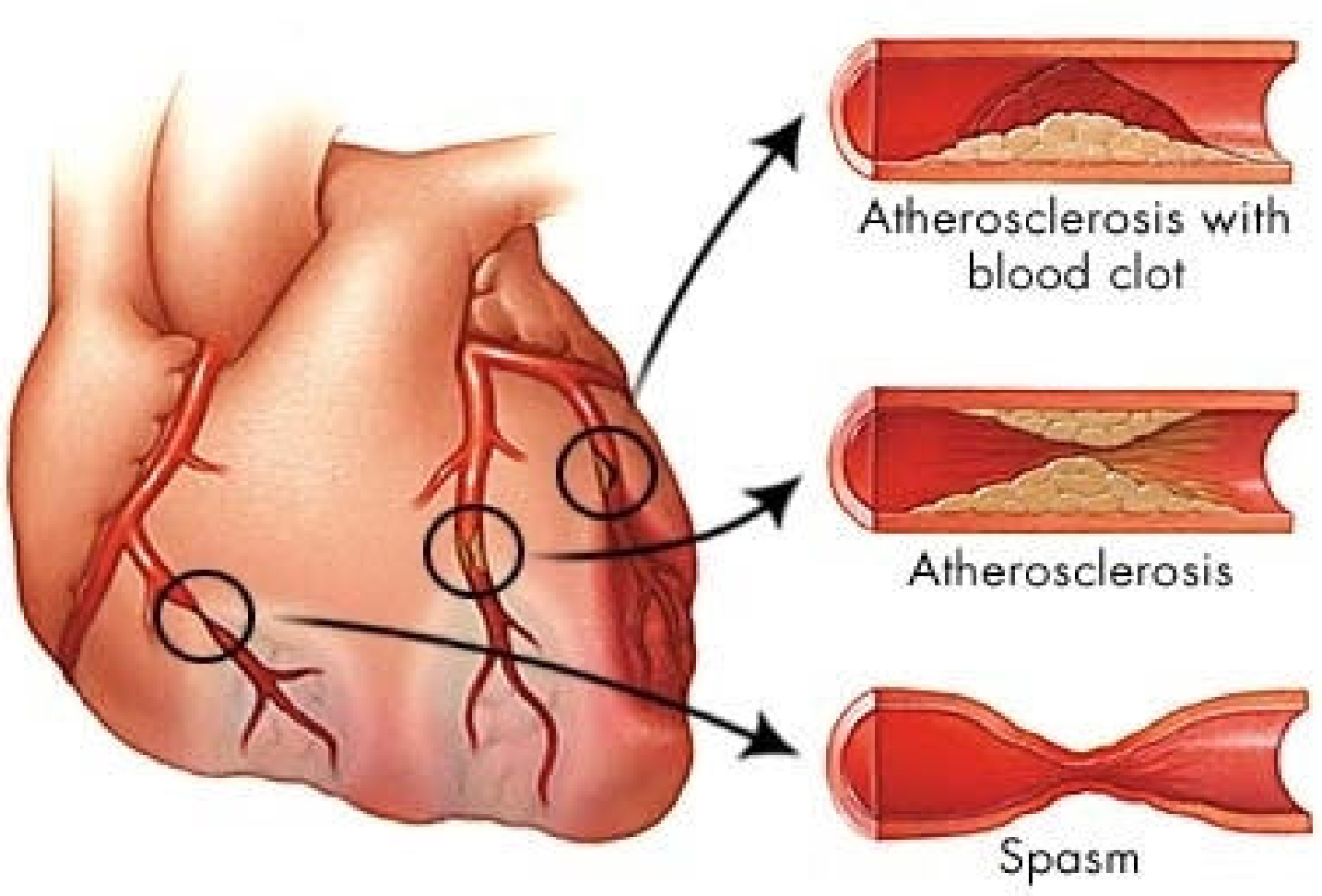
Overview of Artery

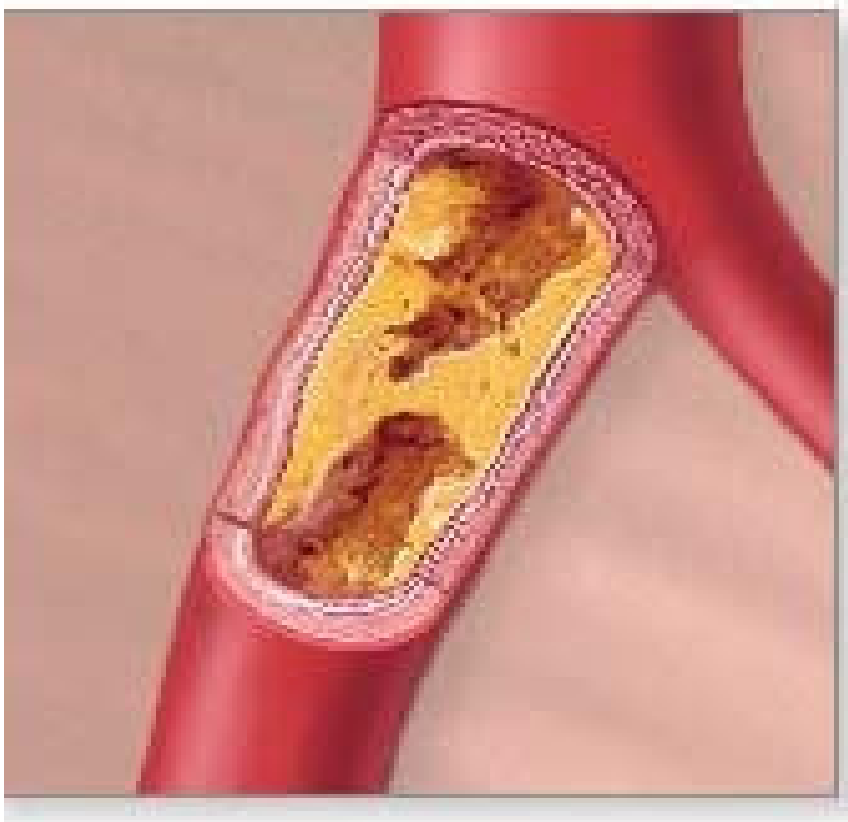




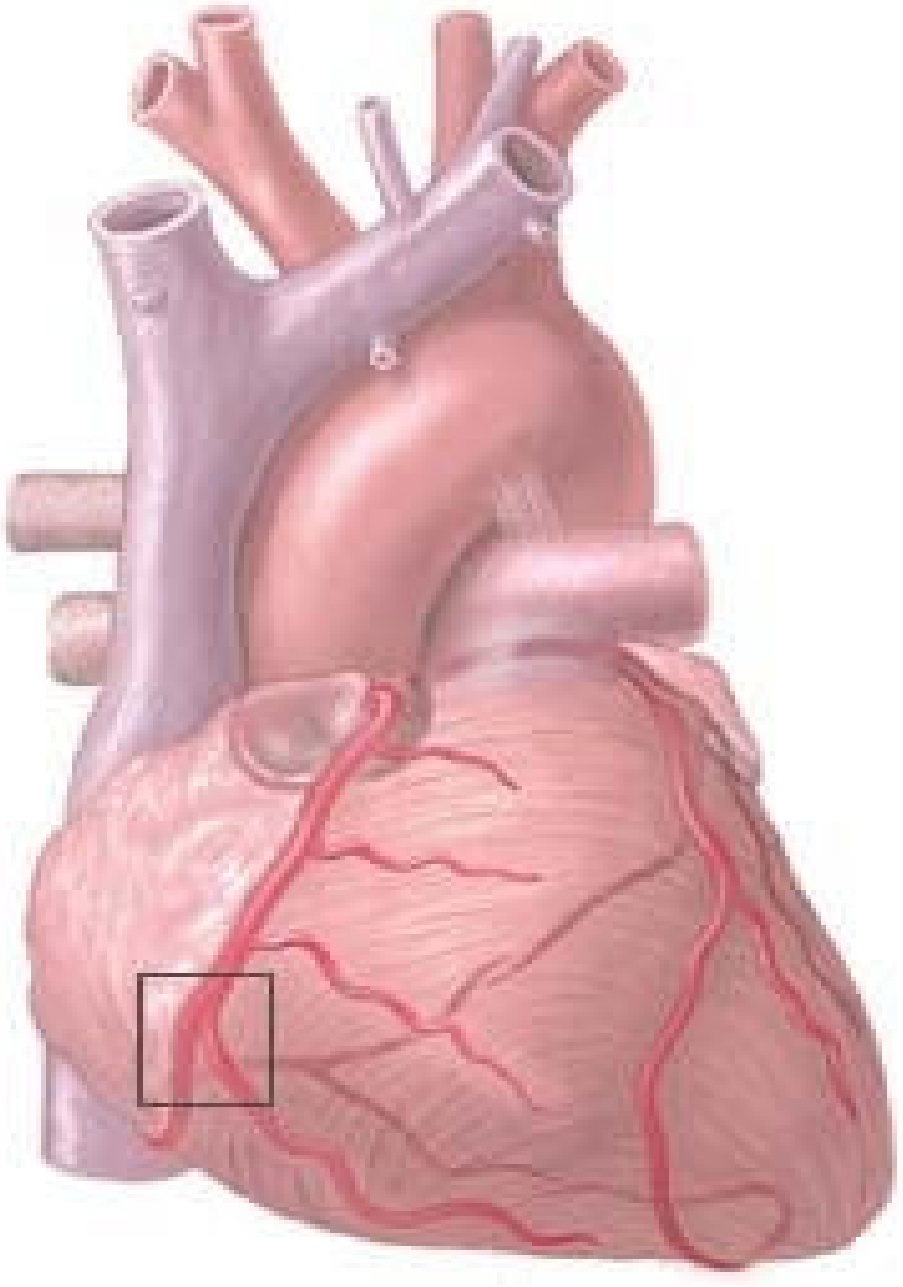


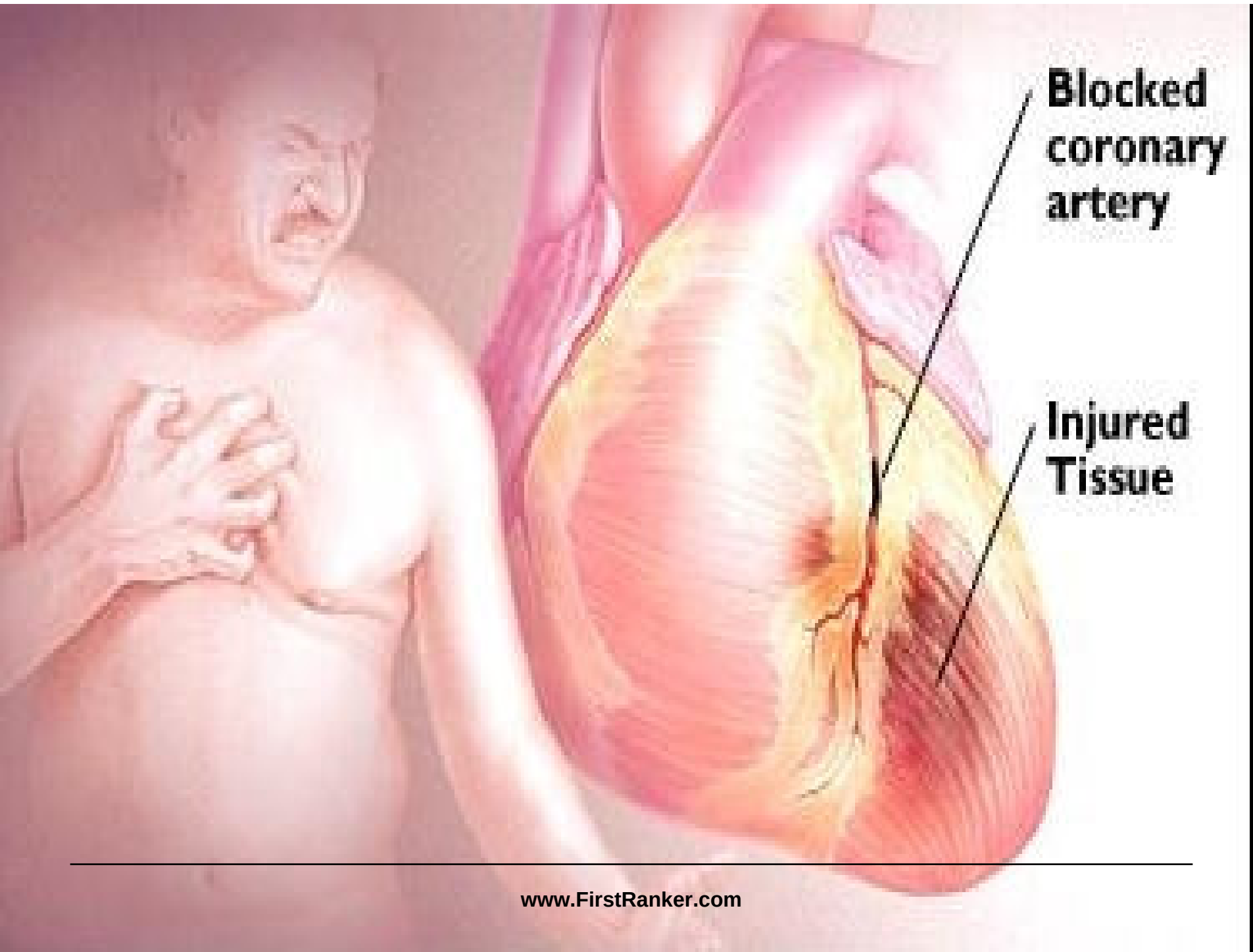






Blockage in right coronary artery





Cardio Vascular Disorders (CVD)

Coronary Artery Disease (CAD)
OR
Coronary Heart Disease(CHD)
OR
Ischemic Heart Disease(IHD)

Coronary Heart Disease

- Term **Coronary Heart Disease** (CHD) describes Heart disease caused by ***impaired coronary blood flow***.
- In most cases, it is **caused by Atherosclerosis of coronary arteries** which supply Myocardium.

Clinical Manifestations

- **Clinical manifestations of Atherosclerosis depend on:**
  - **Vessels involved**
  - **Extent of vessel obstruction**

- **Atherosclerotic Lesions produce their effects through:**
  - **Narrowing of the blood vessel** and production of Ischemia;
  - **Sudden vessel obstruction** caused by Plaque hemorrhage or rupture;
  - **Thrombosis and formation of emboli** resulting from damage to the vessel endothelium;

Coronary Artery Diseases Can cause:

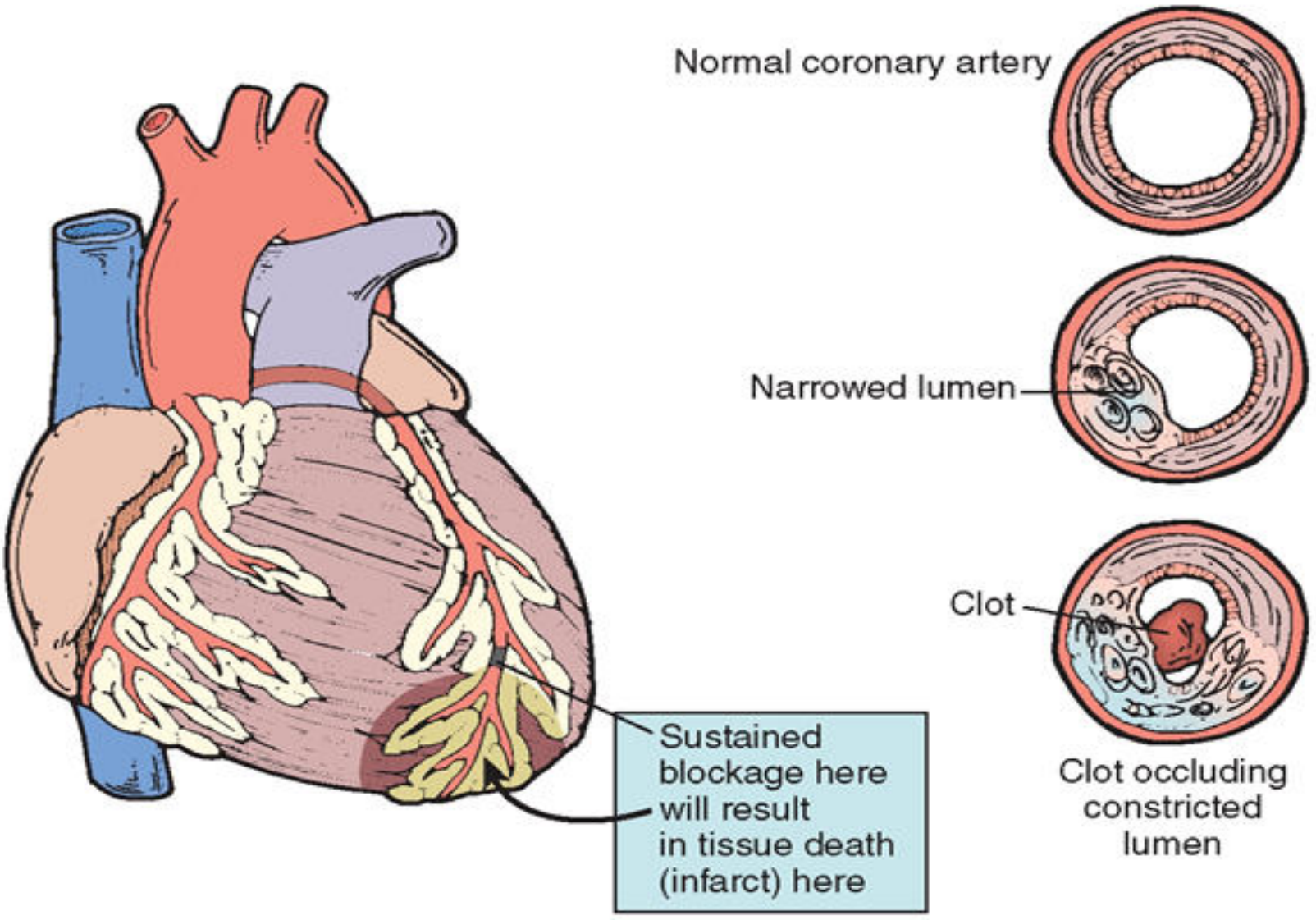
- Angina/Chest Pain
- Myocardial Infarction /Heart attack
- Cardiac dysrhythmias
- Conduction defects
- Heart failure
- Sudden death

Myocardial Infarction

Myocardial Infarction

- MI is an **irreversible damage** to Myocardium(Heart tissue)

- Acute myocardial infarction (AMI), **also known as a heart attack**



- **AMI** is caused due to associated **Atherosclerotic disease of the coronary arteries.**

Risk Factors OF MI

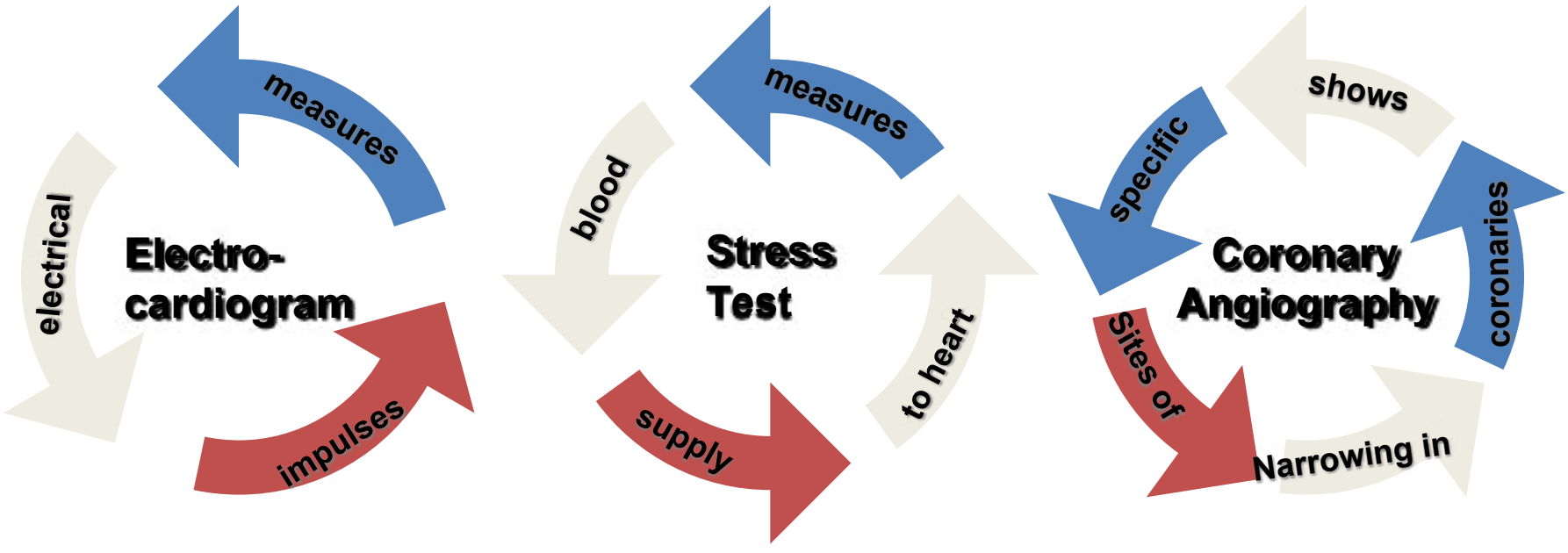
Uncontrollable

- Sex
- Hereditary
- Race
- Age

Controllable

- High blood pressure
- High blood cholesterol
- Smoking
- Physical activity
- Obesity
- Diabetes
- Stress and Anger

Screening and Diagnosis



Diagnosis Of MI

1. Pain

- **Severe and Crushing,**
- **Constricting, Suffocating.**
- **Usually is Sub Sternal,** radiating to the left arm, neck, or jaw
- **Gastrointestinal Complaints**
  - **–Sensation of Epigastric distress**
  - **–Nausea and Vomiting**

ECG

- **Elevation of the ST segment** usually indicates acute myocardial injury.

- When the **ST segment is elevated without associated Q waves**, it is called a ***Non–Q-wave Infarction***.

Diagnostic Biochemical Markers Of MI Enzymes and Proteins

- **Lipid Profile**
- **CK –MB**
- **AST**
- **LDH 1 and LDH2**
- **Trop T and Trop I**
- **Myoglobin**
- **Homocysteine**
- **hs CRP**
- **LP-PLA2**

- ***Creatine kinase* (CK),** formerly called *creatinine phosphokinase,* is an intracellular enzyme found in muscle cells. Muscles, including cardiac muscle, use ATP as their energy source.
- Creatine Phosphate, which serves as a storage form of energy in muscle, uses CK to convert ADP to ATP.
- **CK exceeds normal range within 4 to 8 hours** of myocardial injury and declines to normal within 2 to 3 days.
- There are three isoenzymes of CK, with the MB isoenzyme (CK-MB) being highly specific for injury to myocardial tissue.

- ***Myoglobin*** is an **Oxygen-Storing Protein**, that is normally present in cardiac and skeletal muscle.
- It is a small molecule that is released quickly from infarcted myocardial tissue and becomes **elevated within 1 hour after myocardial cell death,** with peak levels reached within 4 to 8 hours.
- It **rapidly eliminates through urine** (low molecular weight).
- Because myoglobin is present in both cardiac and skeletal muscle, it is **not cardiac specific**.

- ***Troponin complex* consists** of three subunits
  - **Troponin C**
  - **Troponin I**
  - **Troponin T**
- These subunits are released during myocardial infarction.
- Cardiac muscle forms of both Troponin T and Troponin I are used in diagnosis of myocardial infarction.
- **High sensitive Cardiac Troponin I** is current Biomarker validation in research of early diagnosis of AMI

- **Troponin I (and Troponin T) rises more slowly than myoglobin**
- This may be useful for diagnosis of infarction, even up to 3 to 4 days after the event.
- It is thought that cardiac Troponin assays are more capable of detecting episodes of myocardial infarction **in which cell damage is below that detected by CK-MB level.**

Effects of Acute Myocardial Infarction (AMI)

- The principal biochemical consequence of AMI is
- The **conversion from aerobic to anaerobic metabolism**
- With **inadequate production of energy(ATP)** to sustain normal Myocardial function.

- I**schemic area ceases to function** within a matter of minutes, and
- **Irreversible Myocardial cell damage occurs after 20 to 40 minutes of severe ischemia**.

Treatment

- **Reperfusion**
- **(Re-establishment of blood flow)**
- **Thrombolytic therapy**
  - **–Streptokinase/ Urokinase**
- **Revascularization procedures**

– **Early Reperfusion** (within 15 to 20 minutes) after onset of ischemia can **prevent necrosis.**

– **Reperfusion after a longer interval** can salvage some of the myocardial cells that would have died because of longer periods of ischemia.

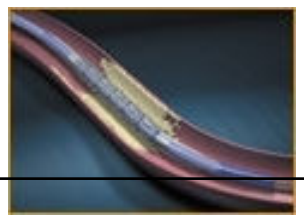
Treatment 1) Stenting

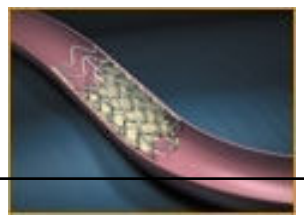
• **A Stent (narrow expandable tube**) is introduced into a blood vessel on a **balloon catheter** and advanced into the blocked area of the artery

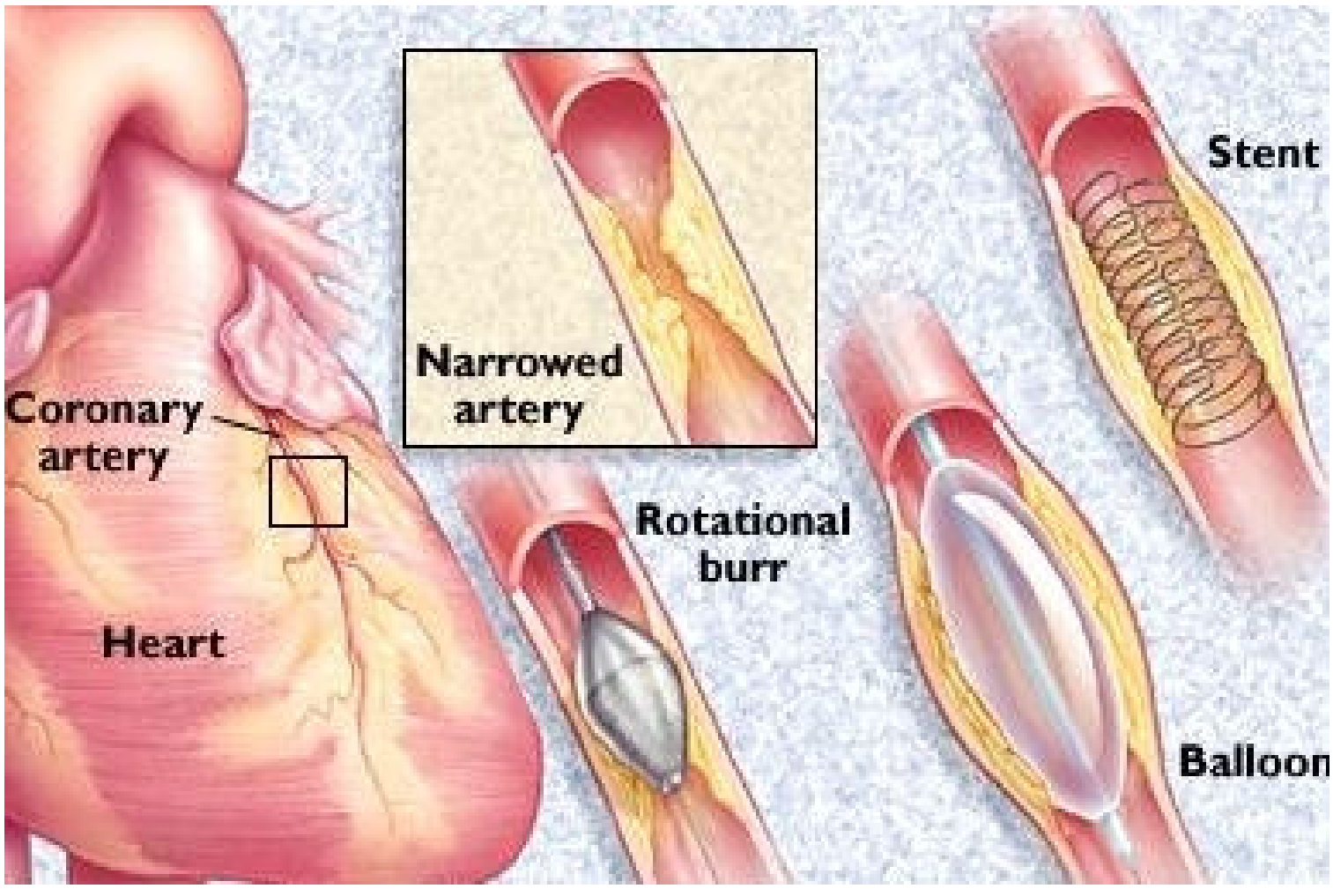
• The **balloon is then inflated** and causes the stent to expand until it fits the inner wall of the vessel, conforming to contours as needed

• The balloon is then deflated and drawn back

•The stent stays in place permanently, holding the vessel open and improving the flow of blood.







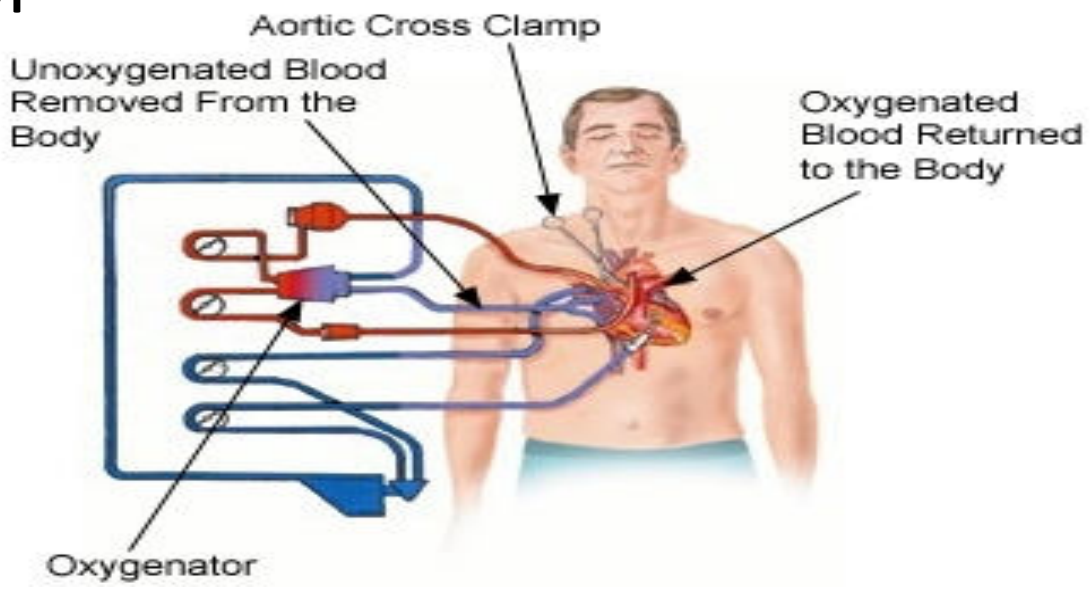
Treatment 2) Angioplasty

- **Balloon catheter** is passed through the guiding catheter to the area near the narrowing. A guide wire inside the balloon catheter is then advanced through the artery until the tip is beyond the narrowing.
- The angioplasty catheter is moved over the guide wire until the balloon is within the narrowed segment.
- Balloon is inflated, compressing the plaque against the artery wall
- Once plaque has been compressed and the artery has been sufficiently opened, the balloon catheter will be deflated and removed.

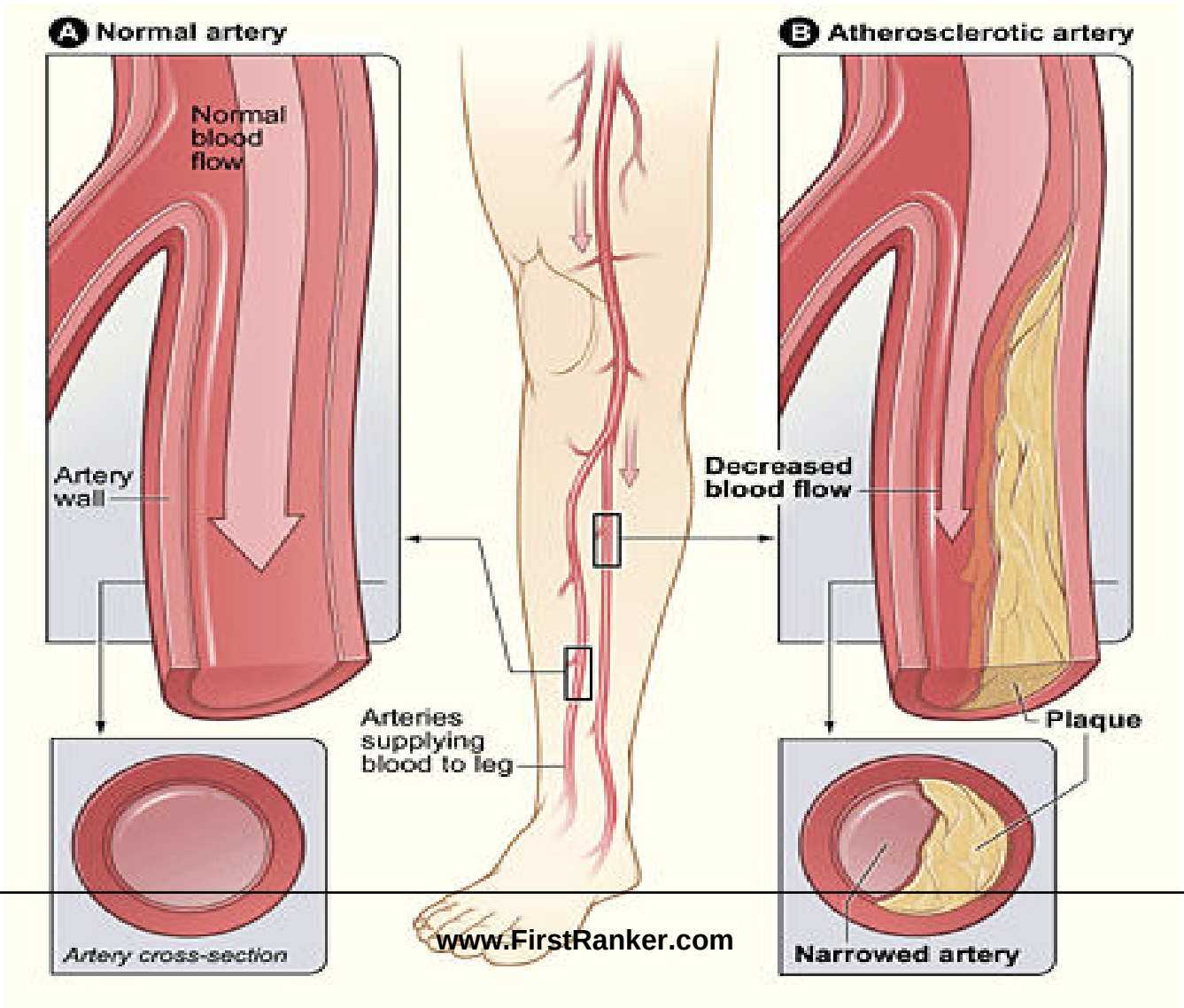
Treatment

3) Bypass surgery

- healthy blood vessel is removed from leg, arm or chest
- blood vessel is used to create new blood flow path in your heart
- the “bypass graft” enables blood to reach your heart by flowing around (bypassing) the blocked portion of the diseased artery. The increased blood flow reduces angina and the risk of heart attack.



Peripheral Arterial Disease (PAD)



Peripheral Arterial Disease (PAD)

- **PAD** refers to the **obstruction of large arteries** in lower extremities of leg
- It possess, **inflammatory processes** leading to **stenosis, an embolism, or thrombus** formation.

Risk of PAD

- Risk of PAD also increases in individuals who are:
  - **Over the age of 50**
  - **Male Obese**
  - **With a family history of vascular disease, heart attack, or stroke.**

Symptoms OF PAD

- About **20% of patients with mild PAD may be asymptomatic;**
  - **Symptoms of PAD include:**
    - **Pain, weakness, numbness, or cramping in muscles** due to decreased blood flow
    - **Sores, wounds, or ulcers that heal** slowly or not at all
    - **Noticeable change in color** (blueness or paleness) or **temperature** (coolness) when compared to the other limb
    - **Diminished hair and nail growth** on affected limb and digits.

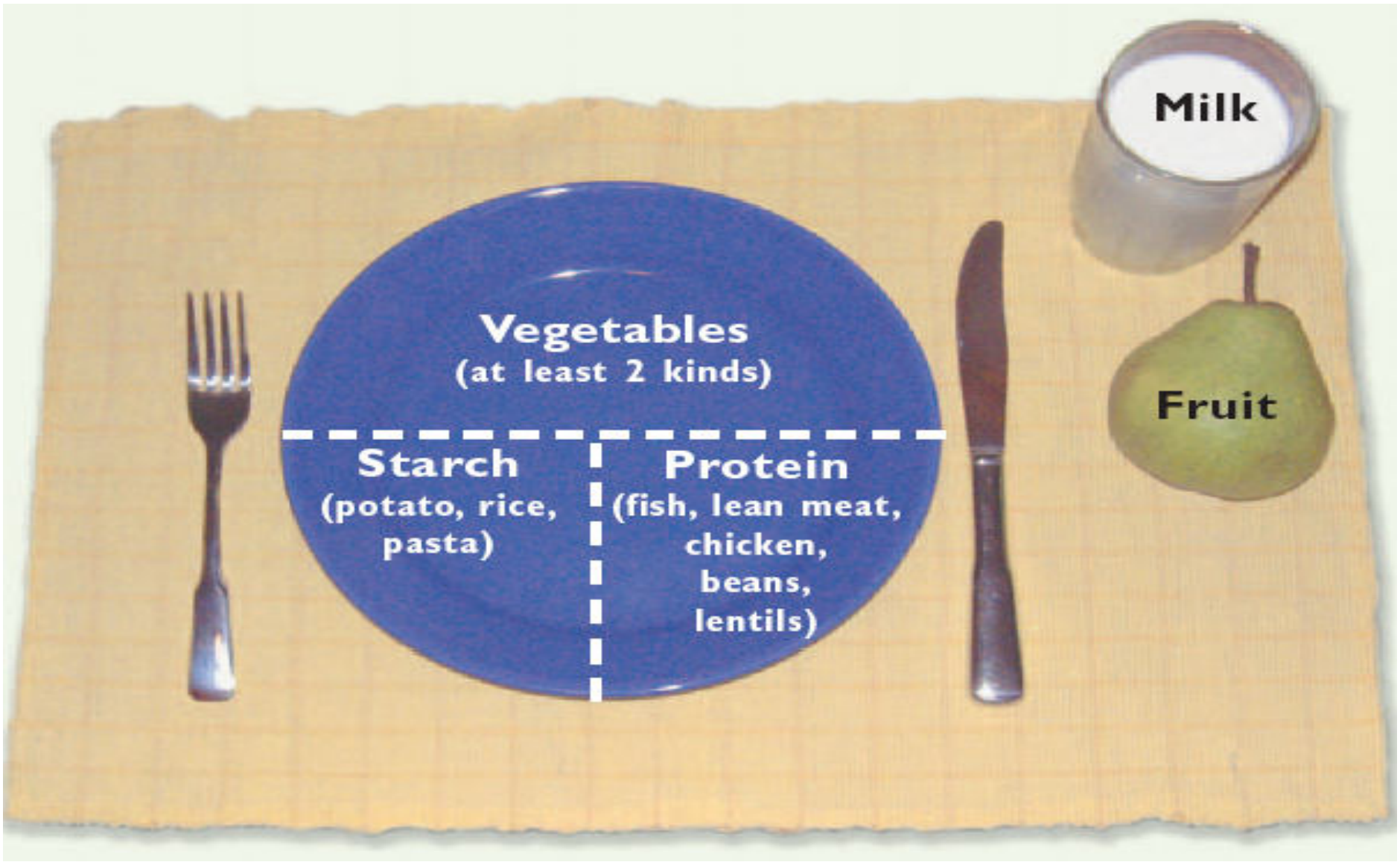
Prevention Of Dyslipidemias And Its Consequences And Complications

Prevention

Live Sensible Implement

- Get regular medical checkups
- Eat a Heart-Balanced healthy diet
- Control your blood pressure
- Check your Blood Cholesterol
- Don’t smoke and drink Alcohol
- Exercise regularly
- Maintain a healthy weight
- Manage stress

THE HEALTHY PLATE



FOODS THAT LOWER LDL CHOLESTEROL

1. Oats
2. Barley and Whole grains
3. Beans
4. Eggplant and okra
5. Nuts
6. Vegetable oils (canola, sunflower, safflower)
7. Apples, grapes, strawberries, citrus fruits
8. Soy
9. Fatty Fish
10. Fiber supplements

- Eat meat sparingly
- Add Fish to your diet
- Go for Nuts
- Eat Fruits and Vegetables
- Increase Complex Carbohydrates and fiber
- Opt for low-Fat dairy products
- Cut down on Saturated fat in cooking
- Avoid Palm and Coconut oils (Rich in SFAs)
- Avoid Trans Fats
- Reduce Dietary Cholesterol
- Reduce Salt intake
- Watch the Snacks

Blood Cholesterol levels increase by eating these products

- **Refined Sugars**
- **Beef**
- **Poultry**
- **Fish**
- **Milk**
- **Eggs**
- **Cheese**
- **Yogurt**

EXERCISE

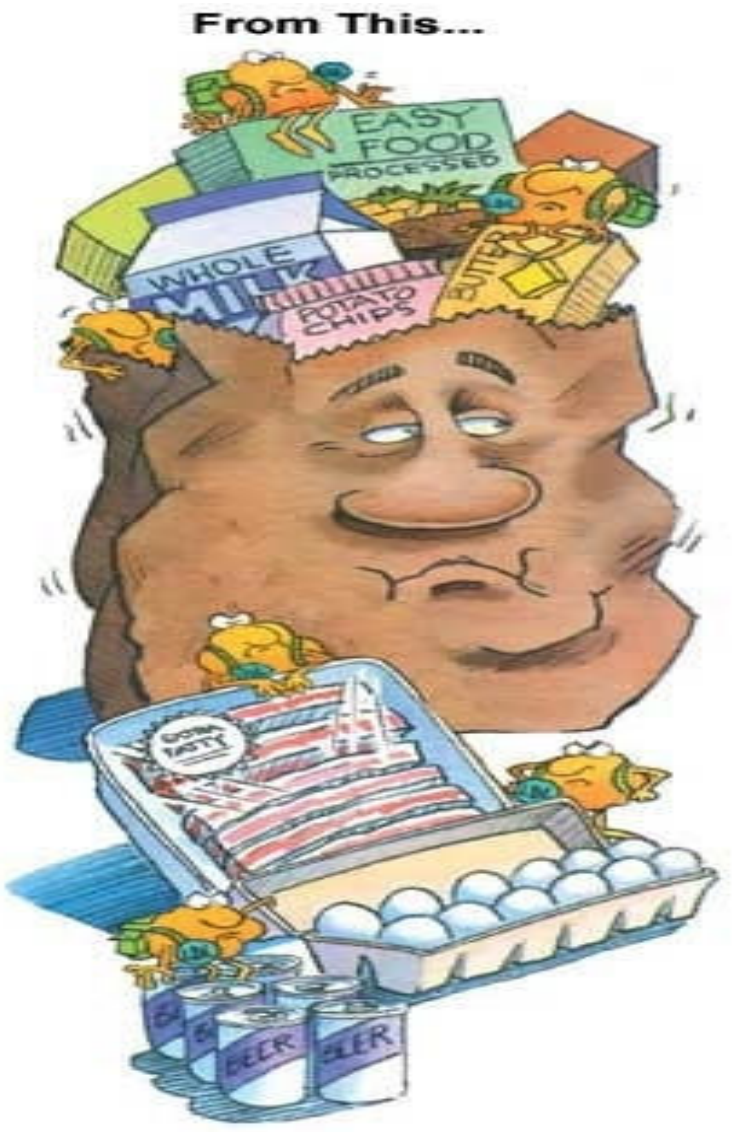
- ***Aerobic exercise (jogging, swimming, brisk walking, bicycling, etc)***

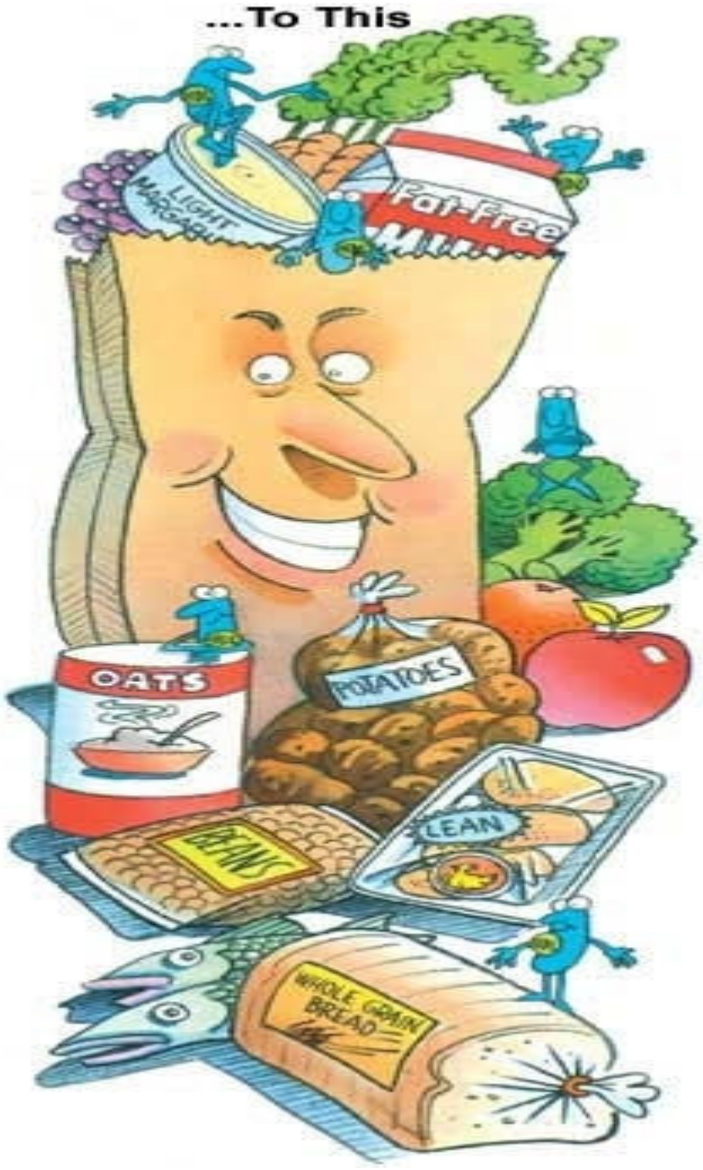
STRESS REDUCTION STEPS

- **Be Spiritual**
- **Balance All Actions**
- **Make and Follow Right protocols**
- **Be Planned and Organized**
- **Manage works based on priority**
- **Involve In work which you are chosen for**
- **Be Obedient and Have Patience**
- **Be Happy with what get**
- **Not expect too much in life**
- **Repent, Accept But Do Not Repeat**
- **Ventilate And Communicate**

Summary To Prevent

- **Eat right**
- **Watch your weight** -even a modest drop in weight can make a difference
- **Be Active** - start a program of light exercise for at least 30-45 minutes every day
- **Lower your stress levels**. Practice stress reduction techniques
- **Stop smoking and drinking alcohol**
- **Be Spiritual**





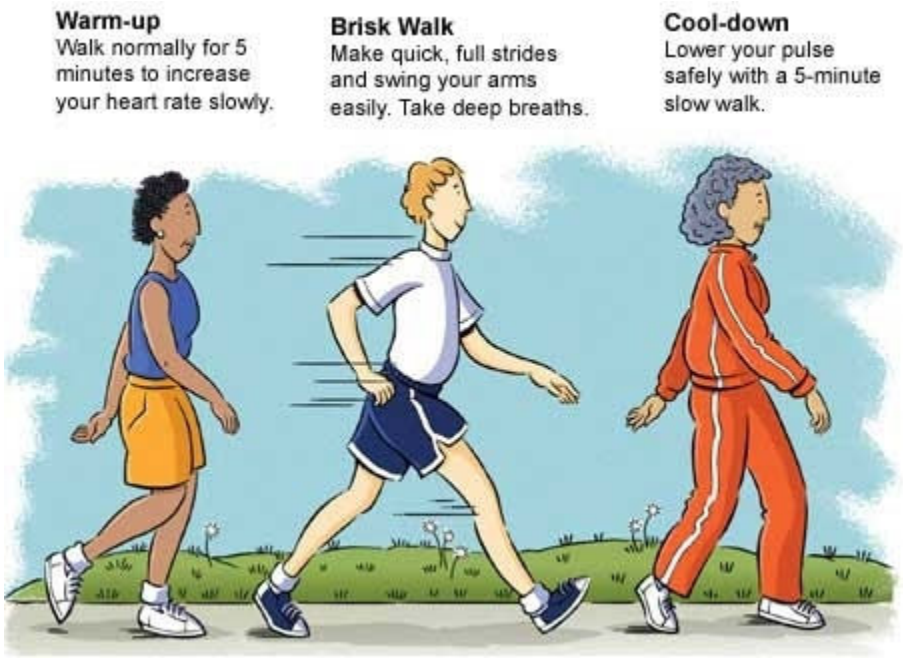
Avoid
Unhealthy eating

Promote
Healthy eating

Relaxation

Visit your doctor regularly

Check your weight



Exercise regularly

Balance intake with output

Inborn Errors Of Lipid Metabolism

Inborn Error Of Lipid Metabolism	Enzyme Deficient/ Defect	Abnormal Accumulation Of
Sudden Infant Death Syndrome (SIDS)	**Acyl CoA Dehydrogenase**	Acyl CoAs
Refsums Disease	**α-Phytanic Acid Oxidase**	Phytanic Acid
Zellwegers Syndrome	**Peroxisomal β Oxidation**	VLCFAs in Peroxisomes

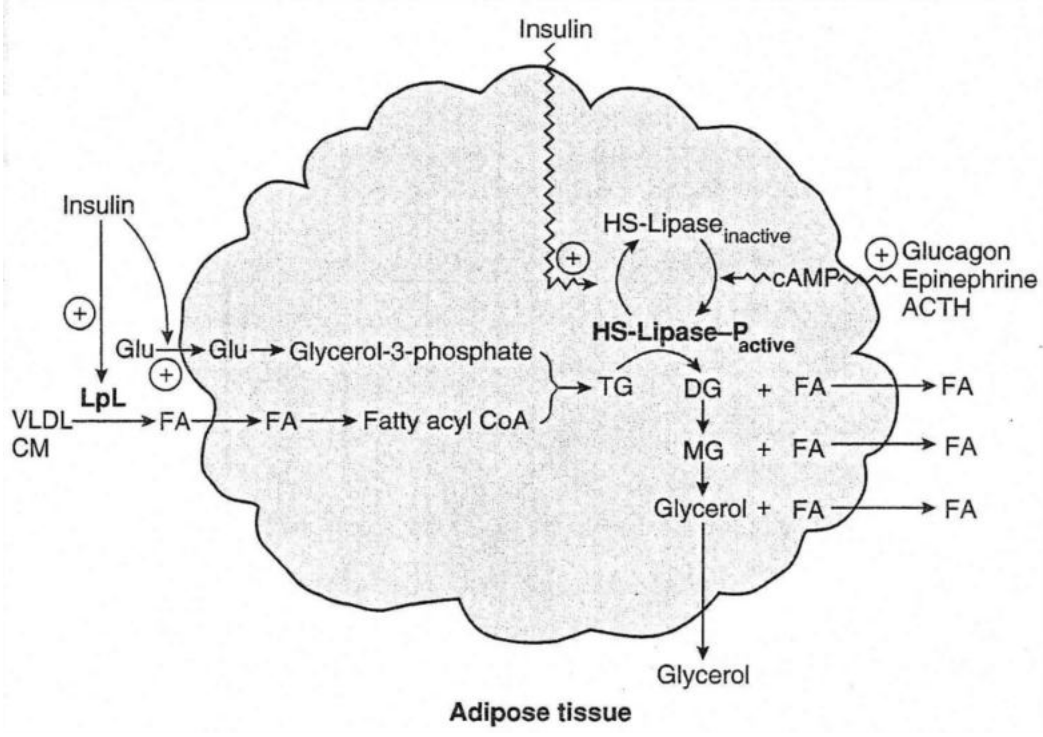
Inborn Error Lipid Storage Disorders	Enzyme Defect	Abnormal Accumulation Of
Niemann Picks Disease	**Sphingomyelinase**	Sphingomyelin in Liver and Spleen
Tay Sachs Disease	**Hexoseaminidase Defect**	**Gangliosides in Tissues**
Gaucher's Disease	**Beta Glucosidase**	**Glucosides in Tissues**

Inborn Error	Enzyme Defect	Abnormal Accumulation Of
Krabbe's Disease	**Beta Galactosidase**	Galactocerebroside
Farbers Disease	**Ceramidase**	Ceramides

Disease	Defective Enzyme[a]	Accumulated Intermediate
GM_1 gangliosidosis	1 β-Galactosidase	GM_1 ganglioside
Tay–Sachs disease	2 β-*N*-Acetylhexosaminidase A	GM_2 (Tay–Sachs) ganglioside
Fabry's disease	3 α-Galactosidase A	Trihexosylceramide
Gaucher's disease	4 β-Glucosidase	Glucosylceramide
Niemann–Pick disease	5 Sphingomyelinase	Sphingomyelin
Farber's lipogranulomatosis	6 Ceramidase	Ceramide
Globoid cell leukodystrophy (Krabbe's disease)	7 β-Galactosidase	Galactosylceramide
Metachromatic leukodystrophy	8 Arylsulfatase A	3-Sulfogalactosyl-ceramide
Sandhoff disease	9 *N*-Acetylhexosaminidases A and B	GM_1 ganglioside and globoside

Role Of Insulin In Lipid Metabolism

- **Insulin**
- **Stimulates LPL**
  - increased uptake of FA from Chylomicrons and VLDL
- **Stimulates Glycolysis**
  - increased glycerol phosphate synthesis
  - increases esterification
- **Induces HSL-phosphatase**
  - inactivates HSL
  - Inhibits Lipolysis
- **Net effect: TG storage**

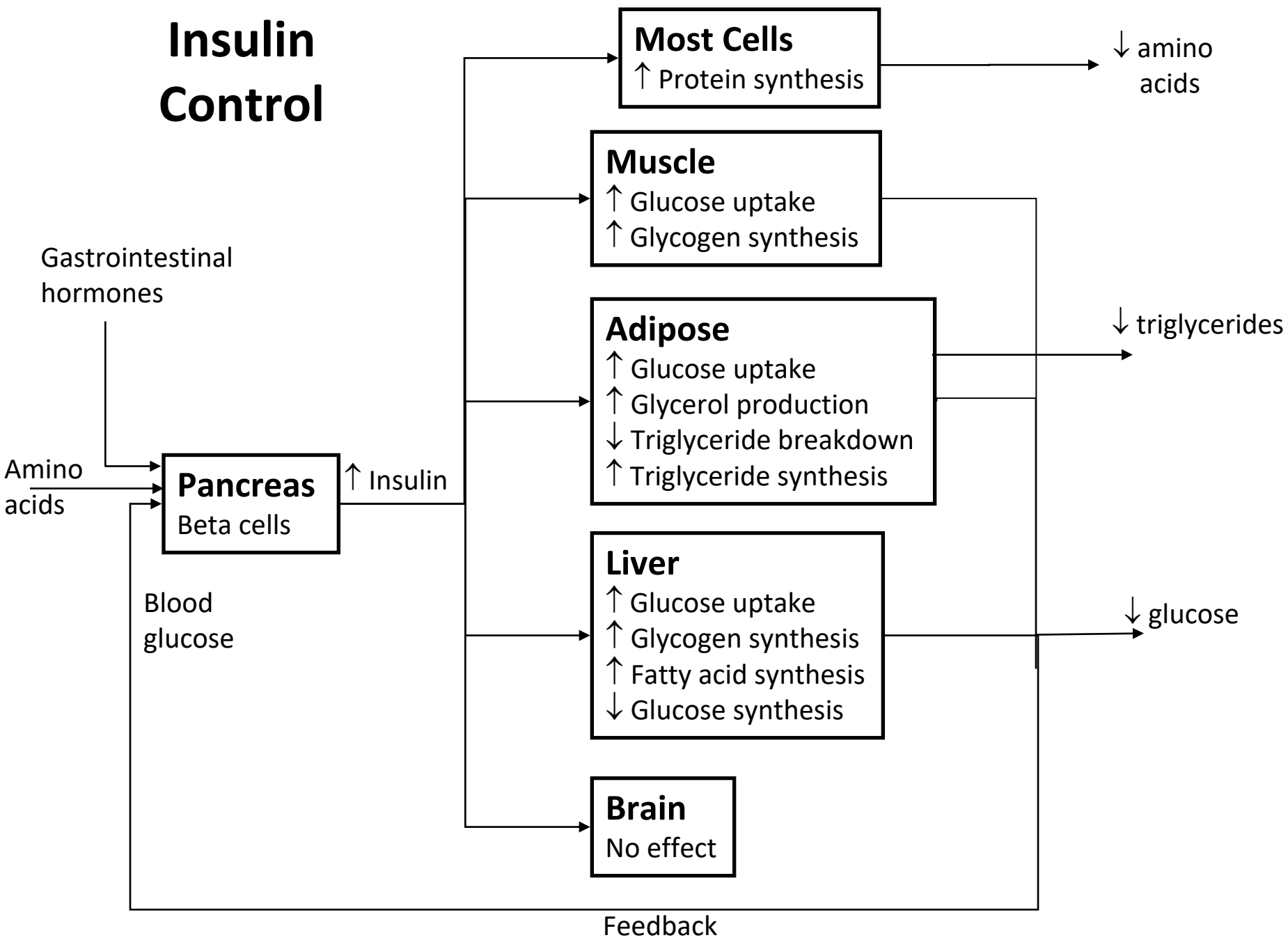


- **Lack of Insulin**

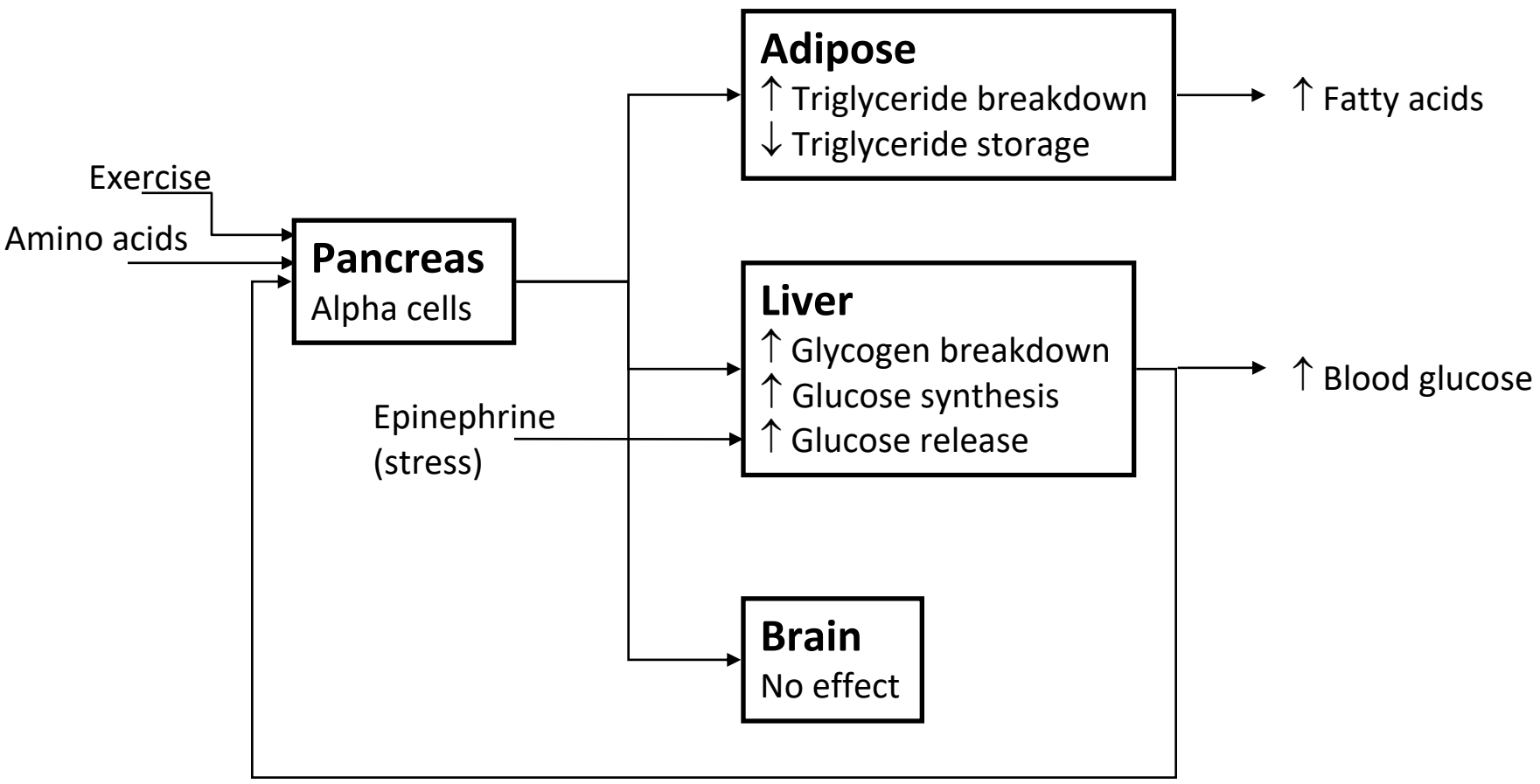
–Free Fatty acids build up in blood

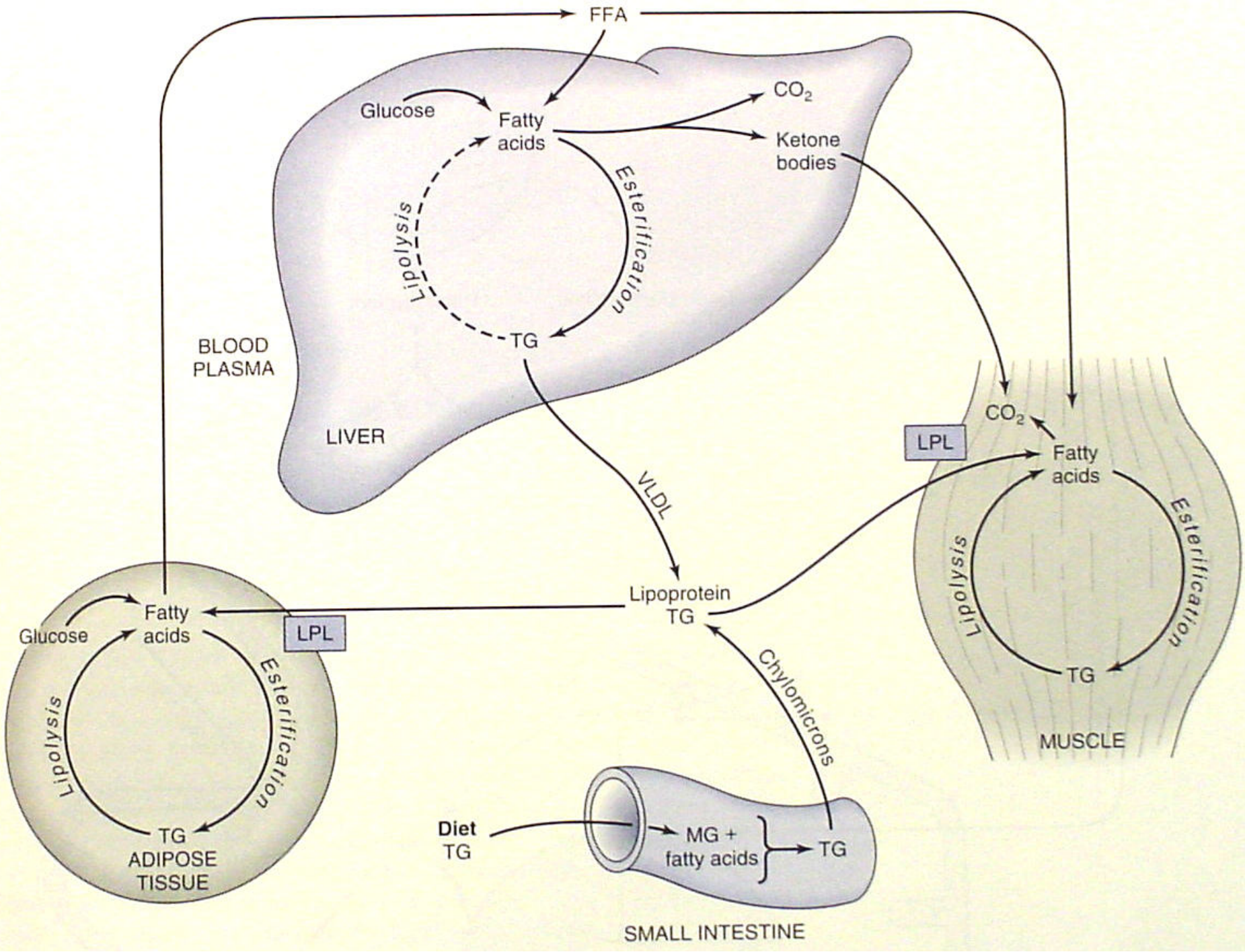
–Can lead to excess Acetoacetic acid production and buildup of acetone (acidosis, which can lead to blindness and coma)

Insulin Control



Glucagon Control





Types Of Lipases

S. No	Type Of Lipase	Location Action Upon
1	Lingual Lipase	**Mouth** Dietary TAG (Insignificant Action)
2	Gastric Lipase	**Stomach** Dietary TAG (Insignificant Action)
3	Pancreatic Lipase	**Small Intestine** Dietary TAG (Significant Action)

S. No	Type Of Lipase	Location Action
4	Lipoprotein Lipase	**Endothelial Lining** Of Blood Vessels Lipoprotein TAG
5	Hormone Sensitive Lipase	**Adiposecytes** Hydrolyzes Stored TAG
6	Hepatic Lipase	Liver TAG
7	~~Phopshpholipase A2~~	~~Small Intestine~~ Phospholipids

Questions

Q.1. Describe in details the **digestion & absorption of dietary** form of lipids & add a note on Steatorrhoea

OR

Q.1.What are **different forms of dietary lipids**? How the **dietary lipids** are **digested & absorbed in G.I.T** ?

Q.2. What are the different modes of oxidation of fatty acids in the body? Give **β-oxidation of even chain fatty acid.**

OR

Q.2. Define β -oxidation of fatty acid. Explain the **oxidation of Palmitate and calculate** its energetics./Fate of fatty acids in human body?

OR

Q.2. Explain **β -oxidation of odd chain fatty acids.**

Q.3. **What is Lipogenesis**? Describe in details the **De-novo synthesis of fatty acid.**

OR

Q.3. Explain the **Extra mitochondrial synthesis of Palmitate.**

Q.4. What is **ketoacidosis? Give fate & formation ketone bodies**.

- **Short Notes**

- **Transport & storage of lipids** / Role lipoproteins.
- **Emulsification & its significance** / Role of Bile salts in digestion & absorption of lipid.
- Lipolysis **/ Role of Hormone Sensitive Lipase**/Adipose tissue metabolism.

- Clearing factor / **Lipoprotein lipase.**
- **Multi-enzyme complex** of Fatty acid biosynthesis / **Fatty acid synthesis complex.**
- Microsomal synthesis of fatty acid.
- **Fatty liver /Lipotropic factors.**

- **Cholesterol-outline of Biosynthesis**.
- **Hypercholesterolemia** – causes & consequences
- Atherosclerosis
- Myocardial Infarction
- Enumerate the Inborn errors related to lipid metabolism.
- Transport & Excretion of Cholesterol/ Reverse transport of cholesterol.

- Fate & formation of Acetyl–CoA
- Fate of Propionyl-CoA
- Role of Carnitine in Lipid metabolism
- Role of Liver in Lipid metabolism.
- TAG metabolism.

- Ketonemia & Ketonuria
- Represent the schematic structure of lipoprotein.
- Role of Citrate in lipid metabolism.
- Role of Carnitine in lipid metabolism.
- Hormonal Influence in Lipid Metabolism

- Catabolism of Cholesterol.
- CETP activity
- HDL2 and HDL 3
- Zellweger & Refsum’s disease.
- Mixed Micelle
- Four types of Lipoproteins & their role
- Hyperlipoproteinemias
- Hypolipoproteinemia's
- Different types of Lipases & their action.

Biochemistry Department