

It's ALIVE: Atherogenesis, a Dynamic Inflammatory Process

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Clogged pipe

www.culligan.com



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Concepts to Remember

- Inflammatory/Immune response
- Endothelium
- Cytokines
- Functions of "Good" Cholesterol
- Renin Angiotensin Aldosterone System (RAAS)

INFLAMMATORY/IMMUNE RESPONSES

- Inflammatory response:
 - Generalized
 - Can be triggered by:
 - Microbial invaders
 - Mechanical stress
 - Chemical stress
 - Oxidative stress
 - Other

Inflammatory Response

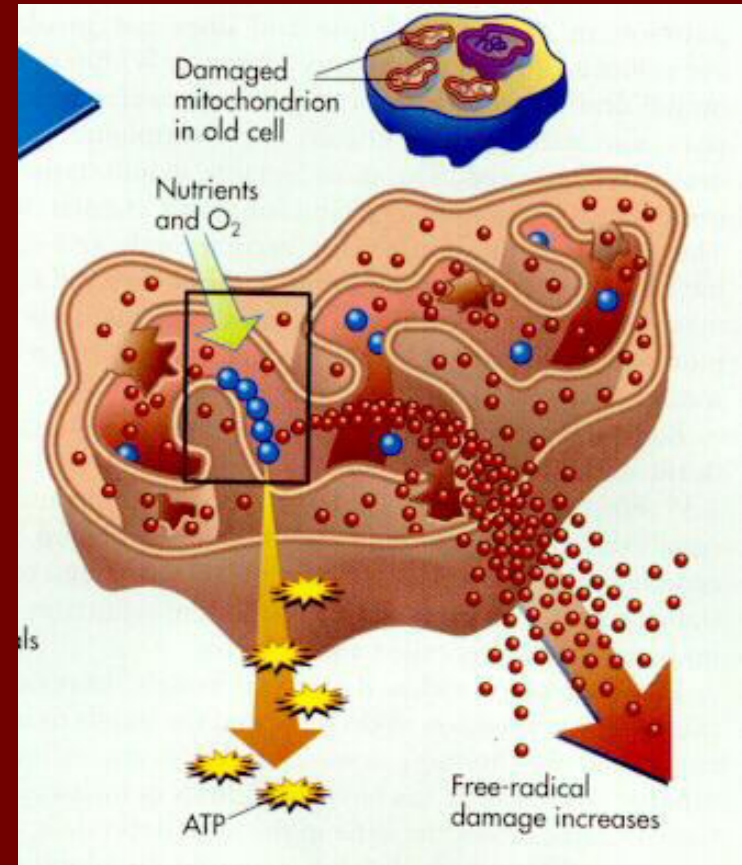
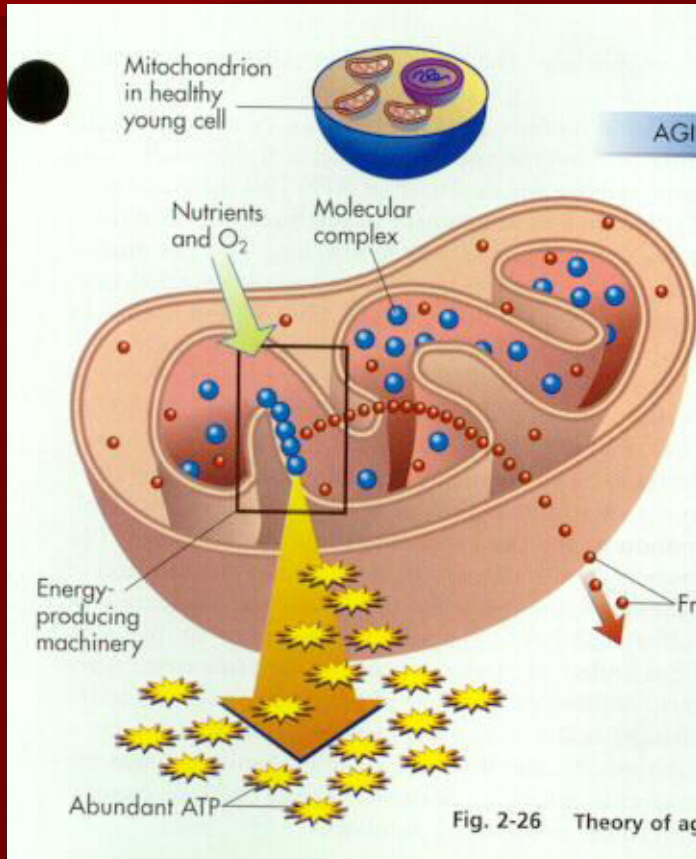
■ Four Basic Phenomena

- Changes in vascular tone of blood vessels
- Increased oxygen utilization by cells facilitating the response
- Changes in blood vessel walls (short term: inc. capillary permeability; long term: smooth muscle proliferation)
- Changes in coagulation

Origination of Free Radicals/ ROS

- absorption of extreme energy sources
 - ultraviolet light
 - x-rays
 - Star Trek Phaser
- Endogenous (oxidative) reactions
- Enzymatic metabolism of exogenous chemical or drugs

Oxidative Stress

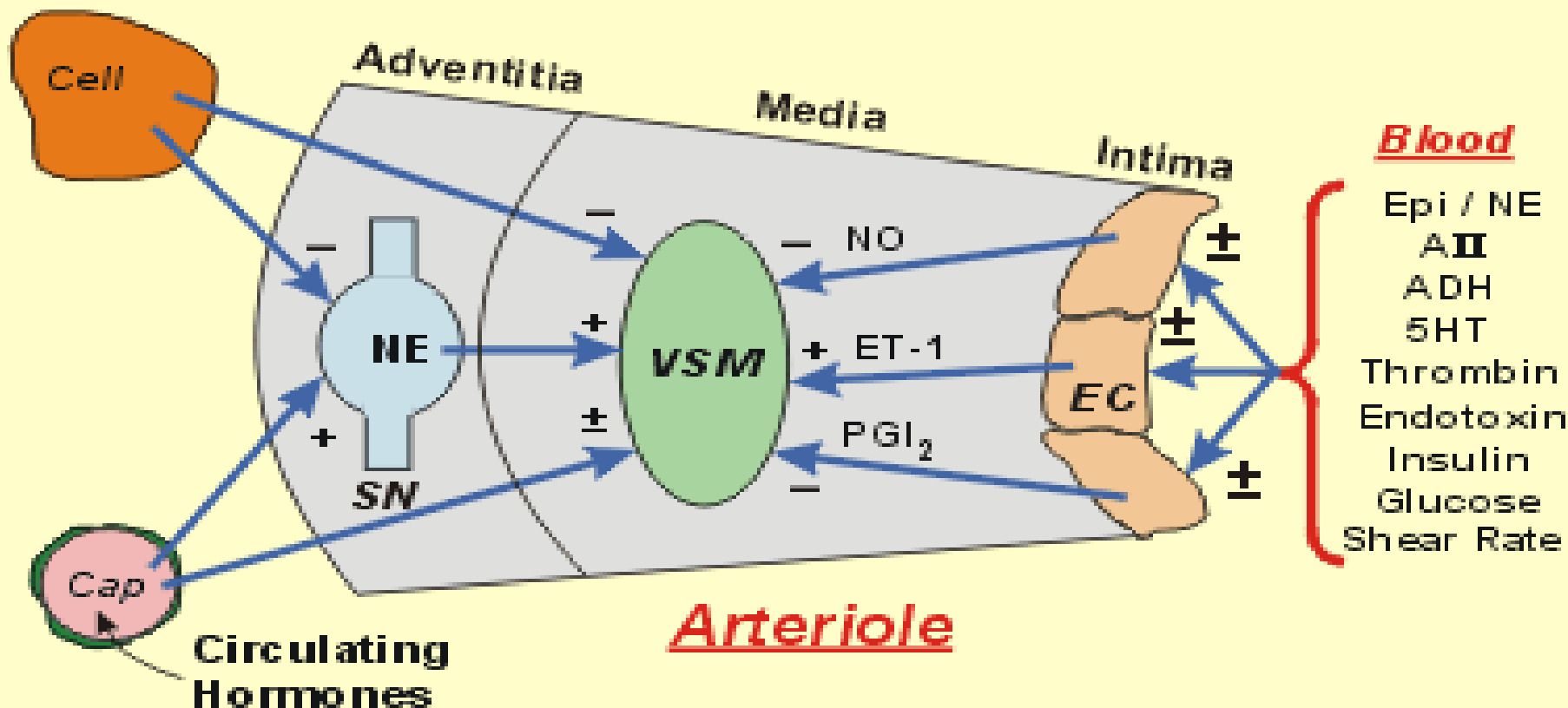


Immune Response

- Much more specific than the inflammatory response
- Involves memory and specificity
- Antigen/Antibody response
- Can sustain inflammatory response

Endothelium

- More than a plasma barrier
- Produces:
 - Vasoconstrictors (endothelin [Et-1]) and vasodilators (nitric oxide [NO], prostacyclin [PGI₂])
 - Pro-thrombotic, anti-thrombotic and fibrinolytic substances
 - Adhesion molecules (platelets, monocytes, lymphocytes)



Endothelial and non-endothelial factors acting upon vascular smooth muscle in arterioles. *Abbreviations:* Cap, capillary; SN, sympathetic nerve; NE, norepinephrine; VSM, vascular smooth muscle; NO, nitric oxide; ET-1, endothelin-1; PGI₂, prostacyclin; EC, endothelial cell; Epi, epinephrine; Angiotensin II, ADH, antidiuretic hormone; 5HT, serotonin; + and -, contraction and dilation, respectively.

Key Point

All atherogenesis is related to an inflammatory response to endothelial damage

Cytokine

- “Any of several regulatory proteins, such as the interleukins and lymphokines, that are released by cells of the immune system and act as intercellular mediators in the generation of an immune response.”

<http://www.answers.com/topic/cytokine>

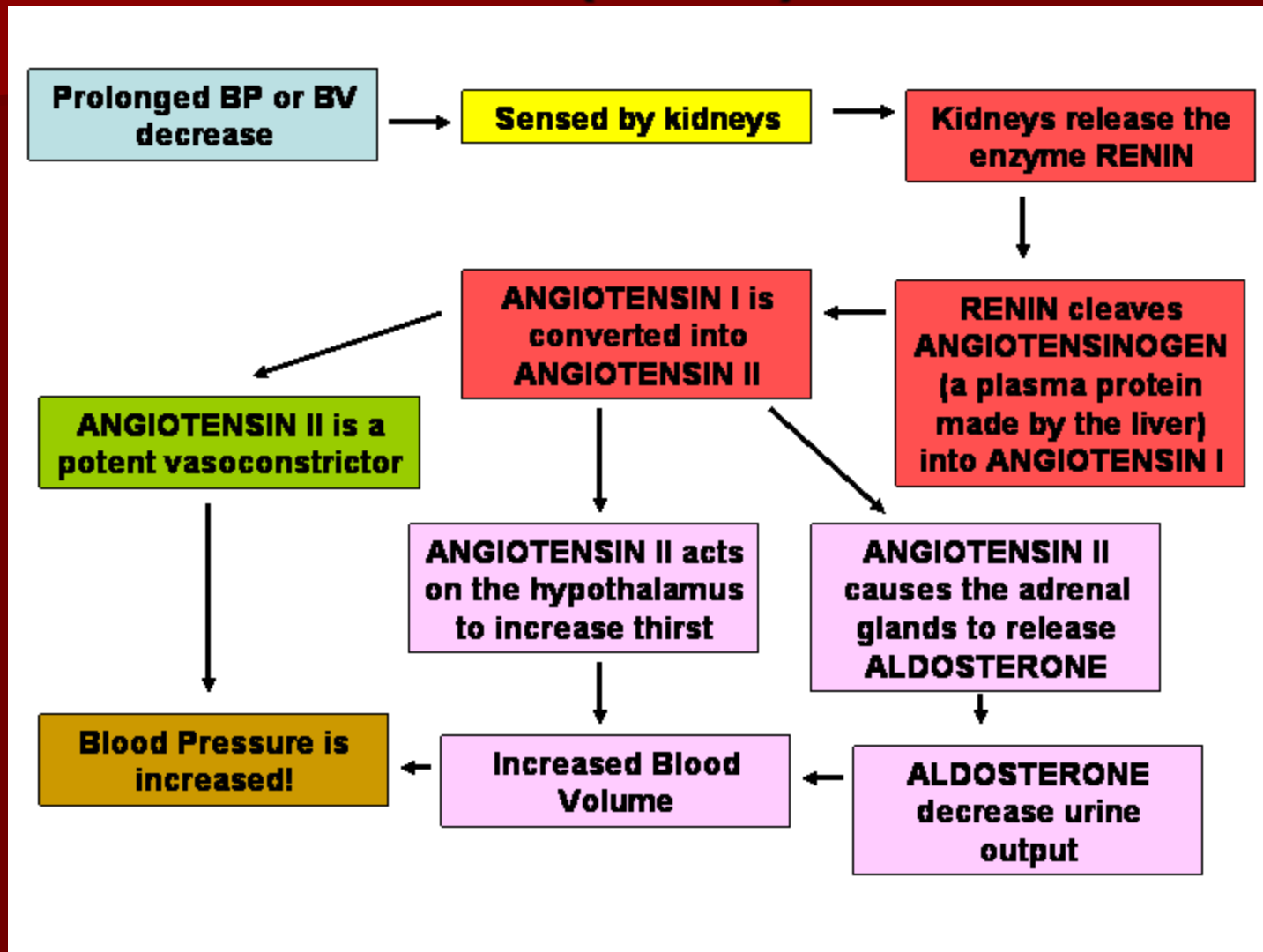
Bradykinin

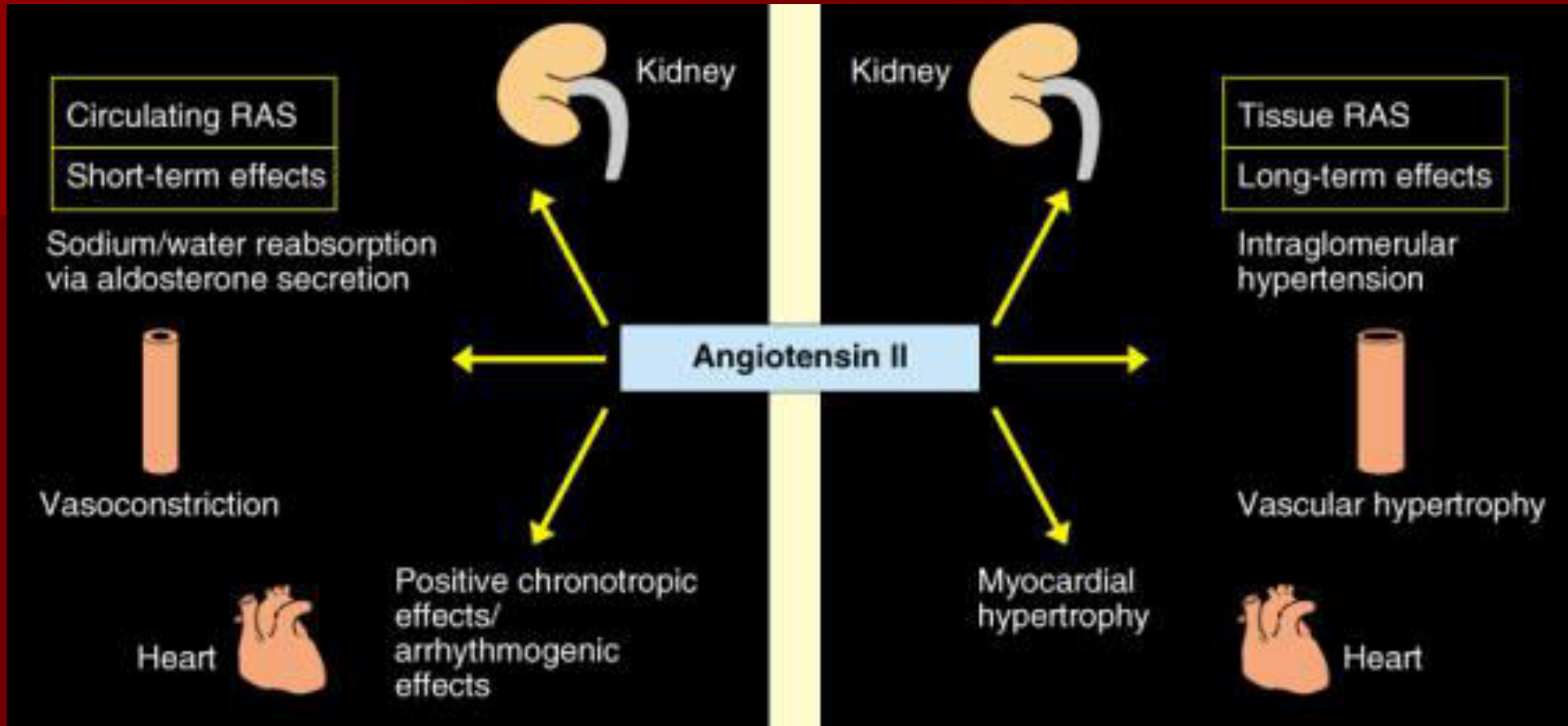
- **bradykinin** - : bradykinin \bra`dy*ki"nin\
n. a hypotensive tissue hormone which acts on smooth muscle, dilates peripheral vessels and increases capillary permeability. It is formed locally in injured tissue and is believed to play a role in the inflammatory process.

TNF

- Tumor Necrosis Factor
 - One of a family of cytokines that has both anti-neoplastic and pro-inflammatory effects.

The Renin Angiotensin Aldosterone System (RAAS)





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<http://medinfo.ufl.edu/cme/grounds/cv/gibbons/slide21.html>

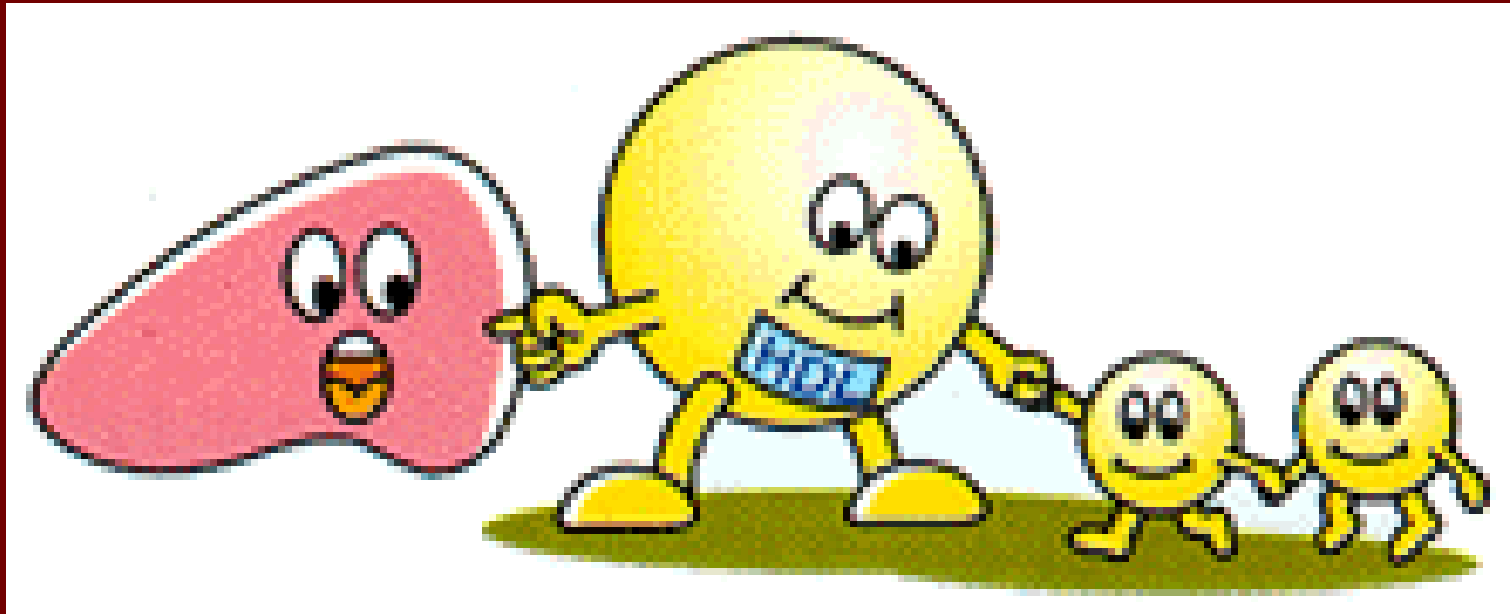
Pro-Inflammatory Effects of Angiotensin II

- Production of ROS
- Production of Cytokines
- Adhesion molecules

Sources of Angiotensin II

- Conversion of Angiotensin I to Angiotensin II via ACE
- Up to 50% of all Angiotensin II is produced in the tissue, independent of the ACE pathway.

Function of “Good” Cholesterol



www.ha.org.hk/org/antitb/images/hdl.gif

Other than Transport.....

- Anti-inflammatory
- Anti-oxidative
- Anti-aggregatory
- Anti-coagulant
- Pro-fibrinolytic

■ Jerzy-Roch Nofer, et al. (2001)

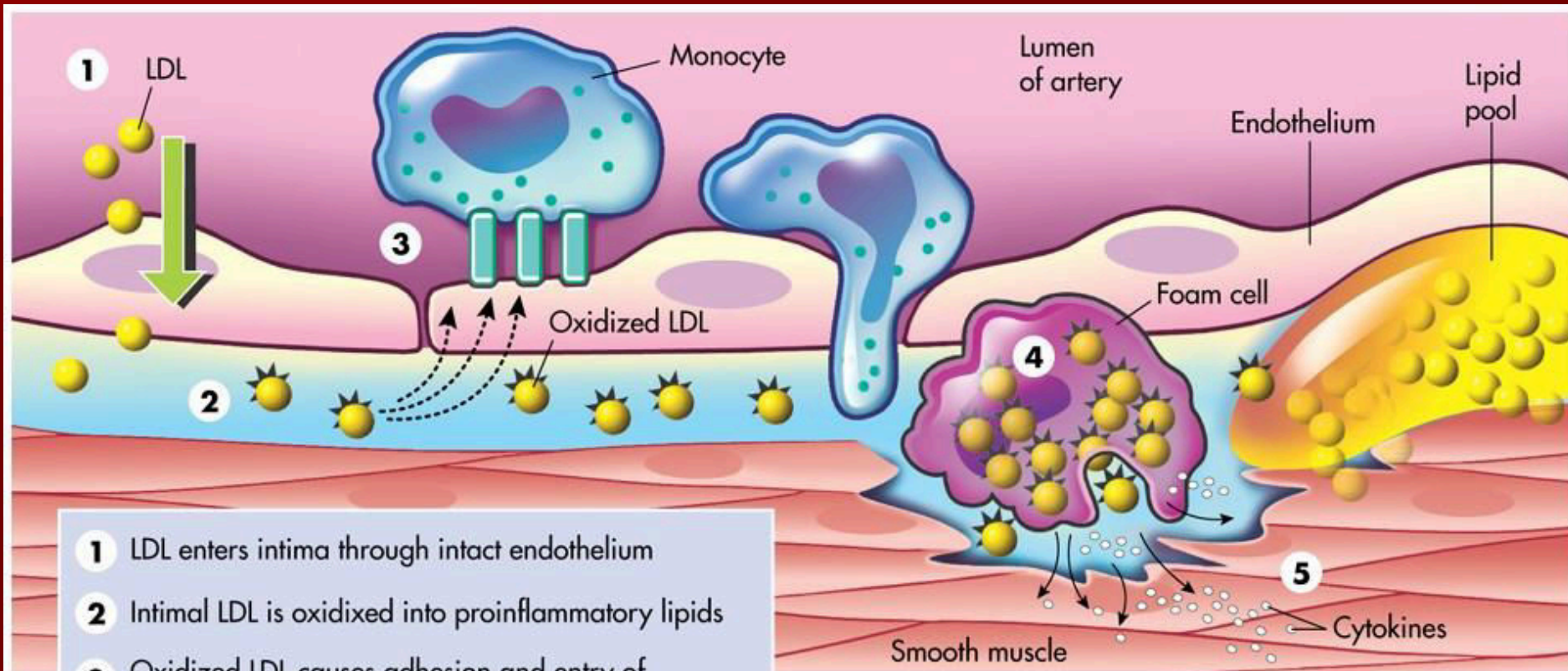
Other than Transport.....

- HDL Inhibits:
 - Chemotaxis of monocytes
 - Adhesion of leukocytes
 - Endothelial dysfunction
 - Apoptosis
 - LDL Oxidation
 - Complement activation
 - Platelet activation
 - Factor X activation

Other than Transport.....

- HDL promotes
 - Endothelial cell repair/regeneration
 - Smooth muscle proliferation
 - Synthesis of prostacyclin
 - Synthesis of natriuretic peptide
 - Activation of Protein C and Protein S

The Basic Process of Atheroma Formation



- 1** LDL enters intima through intact endothelium
- 2** Intimal LDL is oxidized into proinflammatory lipids
- 3** Oxidized LDL causes adhesion and entry of monocytes and T lymphocytes across endothelium
- 4** Monocytes differentiate into macrophages and then consume large amounts of LDL, transforming into foam cells
- 5** Foam cells release growth factors (cytokines) that encourage atherosclerosis

Modified from Crawford MH, DiMarco JP, editors: *Cardiology*, London, 2001, Mosby.

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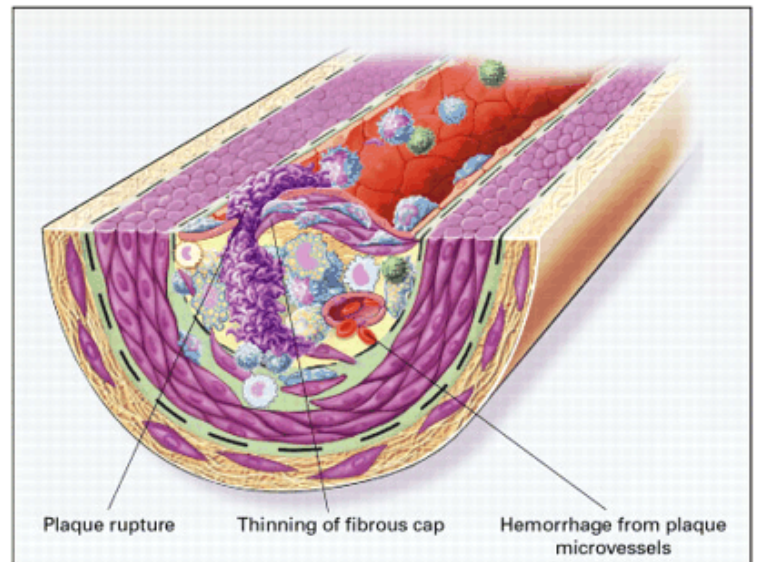
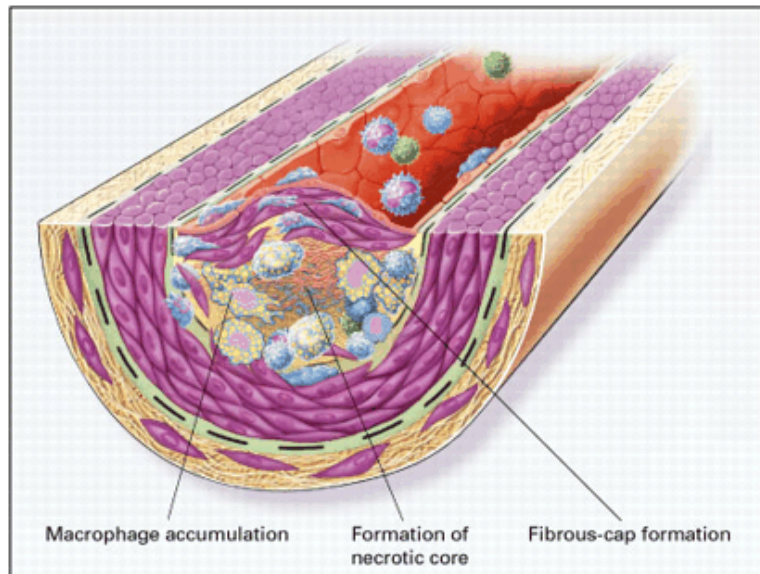
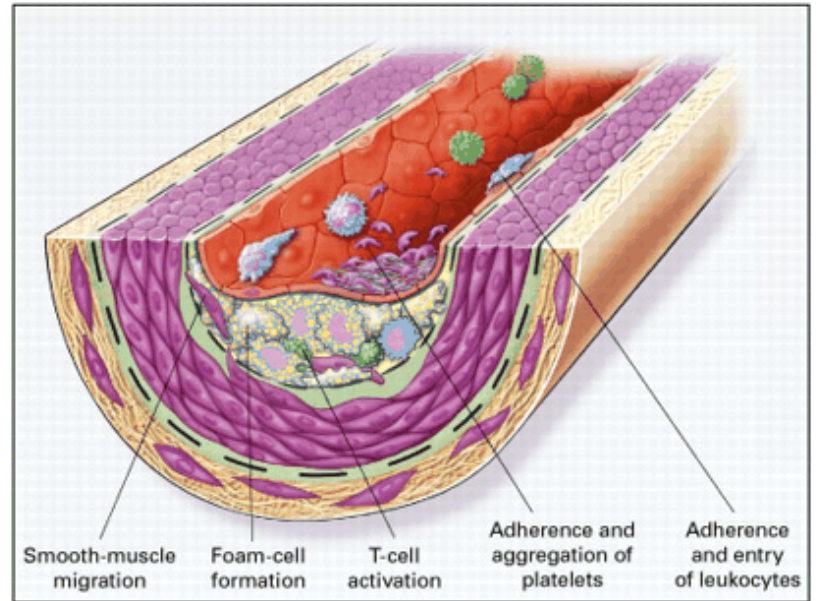
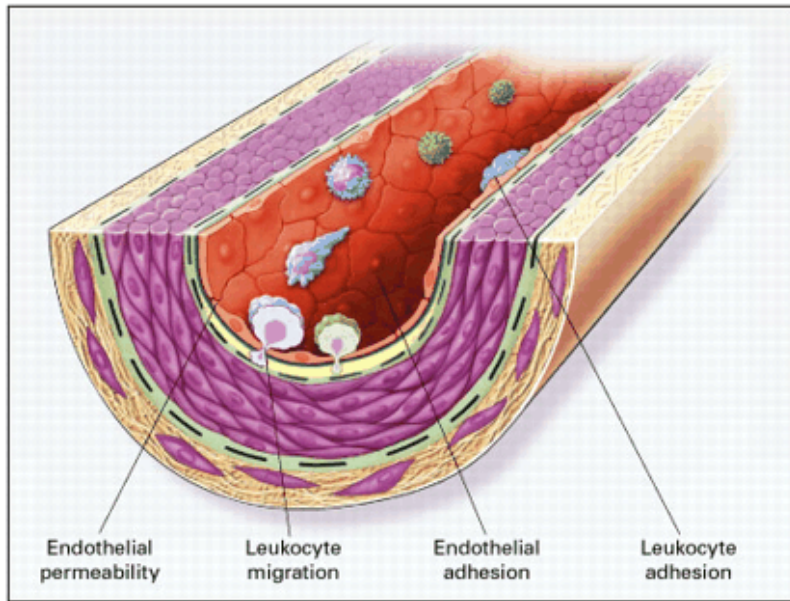


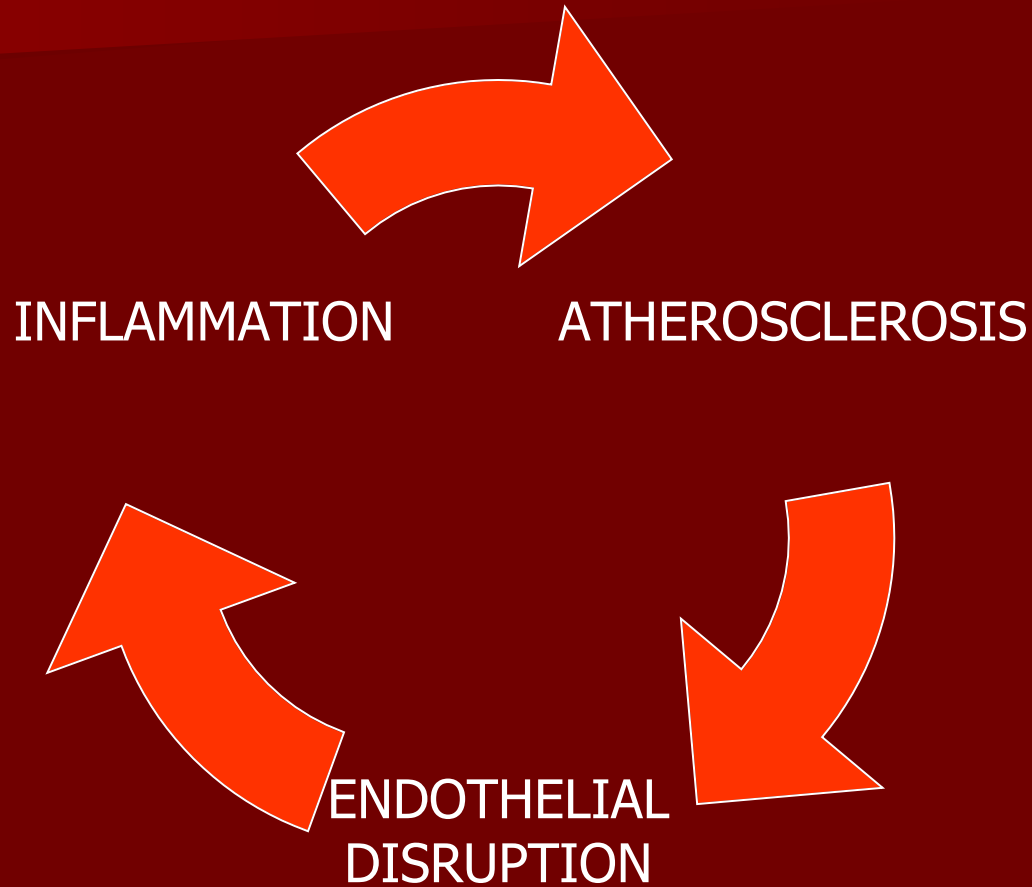


Figure 17-3 ■ ■ ■

Fatty streak of atherosclerosis. The aorta of the young man shows numerous fatty streaks on the luminal surface when stained with Sudan red. The unstained specimen is shown on the right.



A Vicious Cycle is Born!!



KEY POINT

Atherogenesis is the result of AND results in sustained chronic inflammation

Treatment Strategies

- Aspirin
 - Anti-inflammatory effects even at low doses
 - Anti-platelet activity
- ACE Inhibitors/ARBs
 - ACE Inhibitors block conversion of Angiotensin I to Angiotensin II; also interferes with bradykinin production
 - ARBs block effects of Angiotensin II at receptor sites; preserves bradykinin function
- Carvedilol
 - Suppresses inflammatory cytokines
 - Anti-oxidant
- Aldosterone blockade

Treatment Strategies

- Drug eluting stents:
 - Slowly releases sirolimus
 - Drug absorbed by arterial wall
 - Prevents endothelial proliferation
- Next Generation:
 - Drugs to enhance endothelial repair



**PULLING IT ALL
TOGETHER**

Insults to Endothelium

- AGEs: Advanced glycosylation endproducts
- Reactive Oxygen Species
- Hyperinsulinemia
- Hypertension
- Homocysteine
- Activated T-Cells/Lymphocytes
- Small dense LDL

Relationship to Risk Factors

Central Adiposity



Smoking

- Causes intimal injury
- Promotes oxidation
- Promotes inflammatory response in respiratory tract
- Enhances platelet aggregation
- Promotes vasoconstriction

Diabetes Mellitus

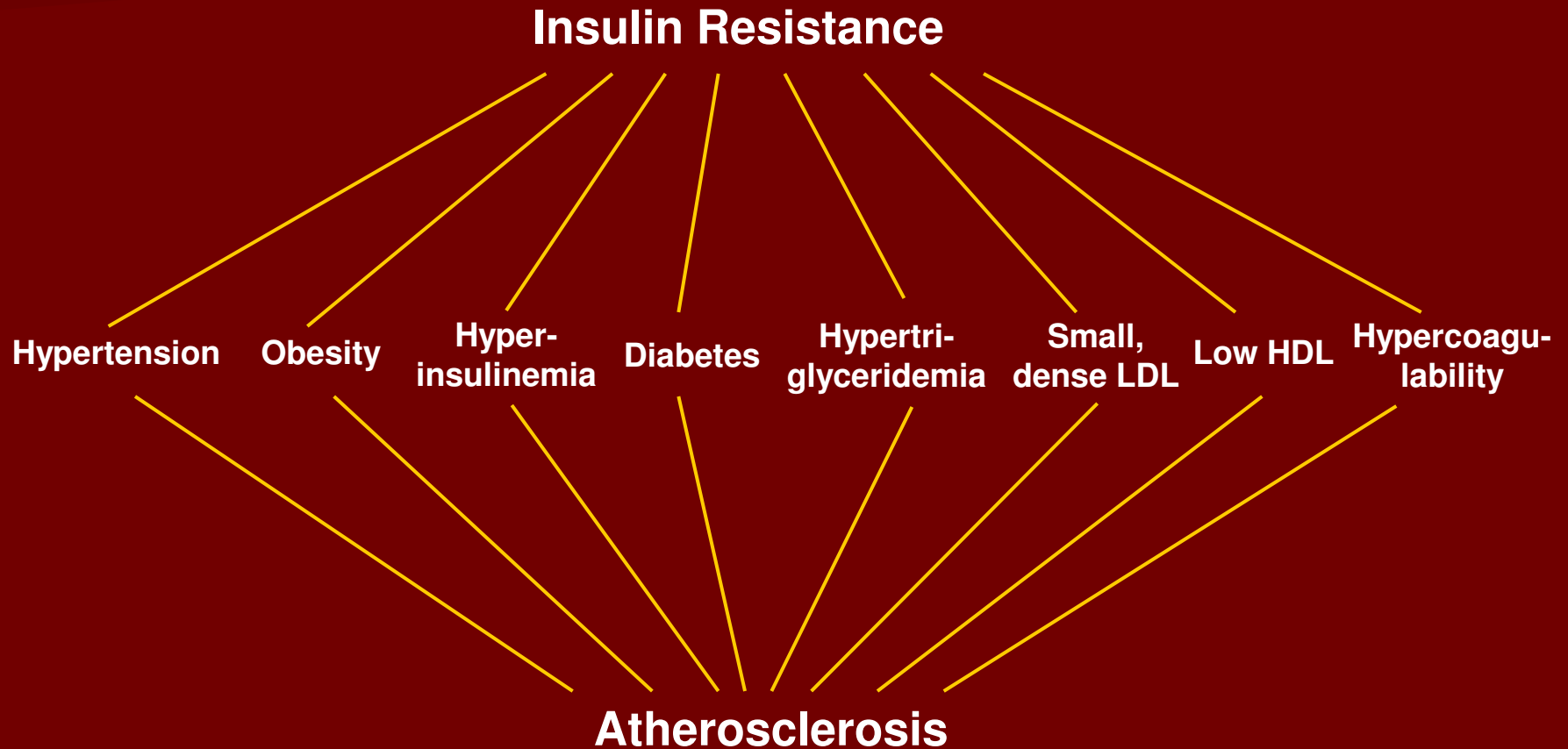
- Production of AGEs
- Hyperglycemia induces inflammatory response
- Frequently co-exists with small dense LDL
- Insulin growth factor promotes smooth muscle proliferation

Interrelation Between Atherosclerosis and Insulin Resistance

Insulin Resistance

Hypertension Obesity Hyperinsulinemia Diabetes Hypertriglyceridemia Small, dense LDL Low HDL Hypercoagulability

Atherosclerosis



Chronic Infection

- How is chronic infection relation to atherogenesis?
- Possible Agents:
 - Peridontal disease
 - Chlamydia pneumoniae
 - Helicobacter pylori
 - Herpes simplex virus
 - Cytomegalovirus

Inflammatory Markers

- Homocysteine levels
- IL6
- Chlamydia titers
- Serum amyloids
- CRP

Future Treatment Strategies

- Genomic therapy
- Synthetic HDL
- Antibiotics?
- Renin/Aldosterone Blockade
- pFOX (partial fatty oxidation)

- This presentation will be available at <http://www.unf.edu/~krobinso/nti.html> from May 16, 2005 until June 1, 2005.