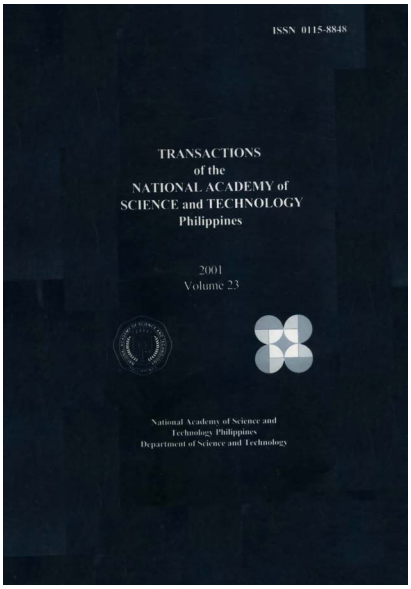
TRANSACTIONSNASTPHL
ISSN 0115-8848 (print)
ISSN 2815-2042 (online)
https://transactions.nast.ph
Vol. 23 Issue No. 2 (2001)
doi.org/10.57043/transnastphl.2001.5131



On Atherosclerosis and Diseases of "Degeneration"

Acd. Conrado S. Dayrit

Past President of NAST,
Philippine College of Physicians and
Philippine Heart Association; Emeritus Professor,
College of Medicine, UP

Citation
Dayrit CS. 2001. On atherosclerosis and diseases of "degeneration". Transactions NAST PHL 23(2): 163-177. doi.org/10.57043/transnastphl.2001.5131

Trans. Natl. Acad. Sci. & Tech., Philippines (2001) **23:** 163-177

ON ATHEROSCLEROSIS AND DISEASES OF "DEGENERATION"

ACADEMICIAN CONRADO S. DAYRIT
Past President of NAST,
Philippine College of Physicians and
Philippine Heart Association; Emeritus Professor,
College of Medicine, UP

ABSTRACT

Twenty-five years ago, in 1876, when this Academy was formed, atherosclerosis or hardening of the arteries was believed to be caused principally by saturated animal fats. This came to be known as the Lipid Theory of Anitzkov who produced atherosclerotic lesions in rabbit aortas by loading their diet with fat and cholesterol. Today, 25 years later, while cholesterol and saturated fats are still of causative importance, we know so very much more about this disease – its predisposing, exciting exacerbating and propelling causes, its mechanisms of progression and termination – that even if we may not have yet succeeded in completely controlling it, we have an armamentarium of remedies now available to slow its progress with even more promising remedies soon, we hope, to be available. These advances in knowledge of atherogenesis and "degenerative" conditions like arthritis and diabetic complications will be recounted in this paper. The basic underlying processes are genetic (Inheritance), Infection, Immunology, and Inflammation – the I's of Human Diseases.

INTRODUCTION

The topic assigned to me is "Cardiovascular and Degenerative Diseases". Let me limit this paper to atherosclerotic and degenerative disease mechanisms (pathogenesis). The topic I propose to dwell on is the recent realization that the underlying pathologic processes of so-called "degenerative diseases" including atherosclerosis, are our own defense and restorative mechanisms – the Inherited mechanisms, Immunologic and Inflammatory processes. When led astray, these processes that are meant to defend and help us, become the cause of our ailments. "Auto-immune Disease" is a term long applied to arthritis and allergies – but not to atherosclerosis. I propose that the atherogenesis be reclassified from a lipid

disorder to a heredo – inflammatory process, with the lipid metabolic derangement playing a distinctly secondary role. Inheritance (genes), Immunologic and Inflammatory processes (gone astray), plus Infection, thus underlay much of human disease (Fig. 1) – given that the infinity of diversity and variation must await elucidation by the new science of genomics.

Inflammation

Inflammation has been described classically as redness, swelling, warmth, pain and loss of function (rubor, tumor, calor, dolor, functio laesa). Now we view it more accurately, (from its microscopic-bio-molecular nature) as an invasion of macrophages, polymorphonuclears (PMNs) and T and B lymphocytes – all inflammatory cells for body defense. All these cells secrete various cytokines – chemicals for (a) mobilization and activation of more defensive cells (chemotactic and growth factors), (b) toxins and free radicals to kill "enemy" cells, and (c) digestive enzymes to clean up the debris.

Unfortunately, as just mentioned, this inflammation instead of being for defense, could be destructive. In the crippling condition of rheumatoid arthritis there is, first, swelling of the synovial membrane and increase in synovial fluid, later, erosion of the cartilage of the bone ends; ultimately fusion of the bones and join immobilization.

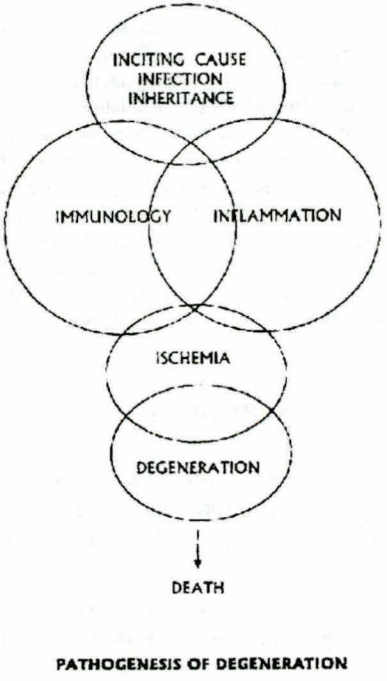


Figure 1. Pathogenesis of Degeneration

Bronchial asthma was thought to be only bronchoconstriction from histamine released from mast cells (Fig. 2). It now is considered more as an inflammatory disease caused by activation of prostaglandins (PGE_2), leukotrienes ($LTB_4/C_4/D_4$) and lipoxin released by phospholipase A_2 (PLA_2) acting on cell membrane phospholipids (Fig. 3).

The involment of inflammatory leukotrienes is widespread. Besides asthma and rheumatoid arthritis (Fig. 4), LTB_4, LTC_4, and LTD_4 have also been found to be present in inflammatory bowel disease, psoriasis and in so-called allergic rhinitis - all known for their persistence and chronicity.

Of what importance is this knowledge? Specific drug therapy is not possible unless we know what we are dealing with. The treatment of asthma, for one, has become so much more effective when the role of inflammation was recognized and anti-inflammatory were added. Recent use of anti leukotriene drugs promises even better results.

Atherogenesis

The lipid theory of atherogenesis first proposed by Anitzkov (1925) and strongly supported in the 50s by the Seven Country Studies of Ancel Keys *et al.* and by many later studies, has been the unquestioned etiology of atherogenesis,

IMMUNO-PATHOLOGIC PROCESSES

Type of Inflammation	Immune recognition component	Mediators	Inflammatory Response	Diseases
Allergic	IgE	Basophil and mast cell products: histamine arachidonate derivs	Immediate flare and wheal; Smooth muscle constriction	Atopy/Anaphylaxis Asthma
Cytotoxic antibody	IgG, IgM	Complement	Lysis /Phagocytosis of antigens; acute tissue inflammation	Autoimmune Hemolytic anemia; Thrombocytopenia
Immune complex	IgG, IgM	Complement	Migration of PMNs macrophages	Rheumatoid arthritis; Lupus erythematosus (SLE)
Delayed hypersensitivity	T-lymphocytes	Cytokines	Mononuclear cell migration	Tuberculosis Sarcoidosis Polymyositis Granulomatosis Vasculitis ? Atherosclerosis

Figure 2.

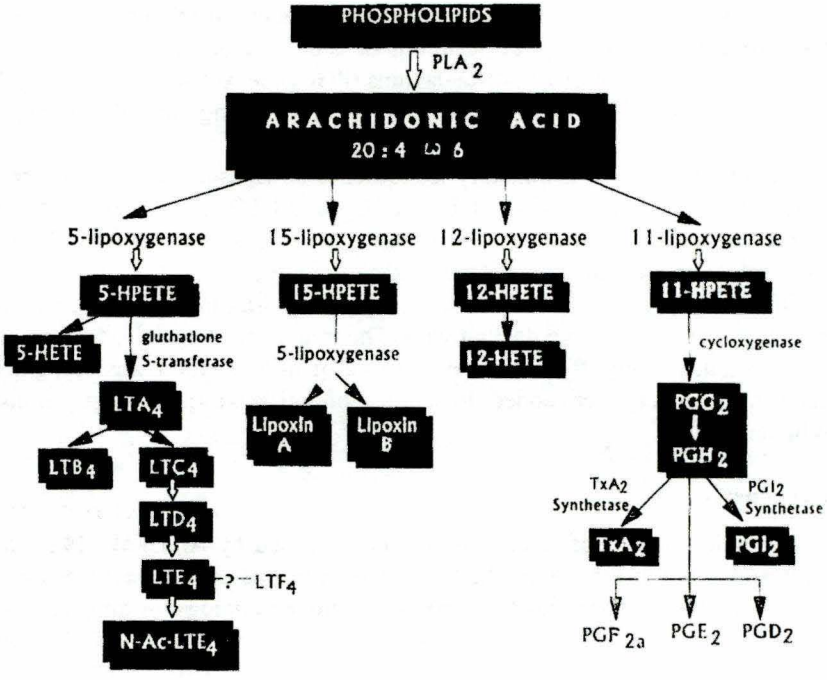


Figure 3

POSSIBLE INVOLVEMENT OF 5-LIPOXYGENASE COMPOUNDS IN VARIOUS DISEASES

Disease	5-lipoxygenase Compounds Found
Asthma	**LTD_4, LTE_4, and 20-OH-LTB_4 in serum and/or urine of patients with asthma and airway hyperresponsiveness**
Inflammatory bowel disease	**LTB_4 in rectal secretions**
Rheumatoid arthritis	**LTB_4 in joint fluid**
Psoriasis	**LTB_4, LTC_4, and LTD_4 in lesions**
Allergic rhinitis	**LTC_4 and LTB_4 in nasal fluid**

Figure 4

particularly of coronary artery disease. And up to the present time, treatment has been directed predominantly to the lowering of blood lipids. True, there have been many doubts raised but these have largely been muted and drowned out by the overwhelming acceptance of the evils of animal fats - and of coconut and tropical oils. In the case of coconut and tropical oils, it is now evident that the objection to these oils is neither scientific nor medical but political and economic.

> "80% of individuals who developed Coronary Artery Disease (CAD) have a total plasma cholesterol value of within the same range as those who do not developed CAD" – Kannel *et al.*, 1979 *Annals of Internal Medicine,* 90:85.

With atherosclerosis, the progress in the molecular biology aspects of immunology and inflammation has revealed what happens in atherogenesis.

The 10 year Pathological Determinants of Atherosclerosis in Youth (PDAY) research program led by Wissler as well as other studies achieved a more meaningful classification of atherosclerotic lesion and in identifying the atherosclerotic-prone and atherosclerotic resistant regions of the circulatory system, These studies of atherosclerotic plaques have also determined why some plaques are benign and innocuous, and why others are malignant or vulnerable.

Fatty streaks are the first to form (Fig. 5). These have been found at autopsy even in children. They are deposits of fat and cholesterol. How or why they are formed to one knows. They are innocuous but appear to be the seat of future plaques. They occur in vulnerable areas of blood vessels where they are more stress and turbulence.

The fibrotic plaques are flat, have smooth surfaces, are free of thrombi and are also benign. Their presence cause no disturbance in the blood flow and pose no danger to the organs supplied. We see them in the vessels of many elderly, with no history of circulatory problem who die from other causes.

The malignant plaques, on the other hand, are soft and swollen, loaded with inflammatory cells and cholesterol; they are called "vulnerable" as they are prone to hemorrhage and to fissure and rupture, discharging their gruelly contents and exposing their internal collagenous material. To this collagenous material platelets love to adhere and become activated to form platelet plugs (aggregated platelets) which in turn stimulate the coagulation cascade. In the presence of a clot-prone environment (hyperfibrinogenemia and a dysfunctional endothelium that secrets more pro-coagulants (instead of anti-coagulants) more clotting and thrombus formation occurs. The vulnerable plaque therefore is one that promotes clotting and thrombus formation over itself so that the occlusion of the arterial lumen is just a matter of time. Furthermore, at any time during this process, bits of thrombi can break off as emboli, a process most common in the larger vessels aorta, carotids and iliac arteries) where the blood pressure also is highest. A most important addition to our knowledge is this identification of the vulnerable malignant plaque vs. the fibrous innocuous one.

ATHEROSCLEROSIS

	Risk	Rx Effectiveness
Fatty Streak	0	0
Plaque	±	?
Soft Plaque w/ Thrombus	+ + +	+

Figure 5.

Endothelial Dysfunction

The endothelial lining of blood vessels was thought to function only as a physical barrier between the blood and the vessel wall. Actually, these simple looking single layer of cells is a mighty organ producing no fewer that 15 biologic chemicals or cytokines that control various processes: pro or anti-inflammation, vasoconstriction or vasodilation, pro-clothing or anticlothing, pro or anti-aggregation of platelets (Fig. 6). These factors are kept in "physiologic balance" and served to preserved the internal milieu. In some persons, at sometime later in life, earlier in males, something disturbs this balance and plaques form in their arteries. The imbalance, called endothelial dysfunction, is promotive of inflammation, vasoconstriction and coagulation.

Benditt was the first to call attention to the migration of smooth muscle cells of the arterial wall to the subintimal layer where the plaque forms. It is not clear whether the site of monoclonal migration. Both platelets and endothelial cells are known to secrete a growth factor – the PDGF or platelet-derived growth factor. The dysfunctional endothelium could be the source of this PDGF.

Another important endothelial secretion is Nitric Oxide (NO), a free radical, which possesses many important actions (Fig. 7) including a potent vasodilating action and inhibition of inflammatory and oxidative processes. A dysfunctional endothelium secretes less NO which results in vasoconstriction, expression of more adhesion molecules (e.g. VCAM-1, ICAM-1), migration of platelets, leukocytes, smooth muscles, and macrophages, i.e. an inflammatory situation.

Fig. 8 illustrates a curious change in the action of acetycholine. Normally, intra arterial Ach by acting on NO synthase, causes NO synthesis and vasodilatation. When endothelial dysfunction is present, Ach injected intra arterially causes vasoconstriction instead. This is now used as a test of E.D.

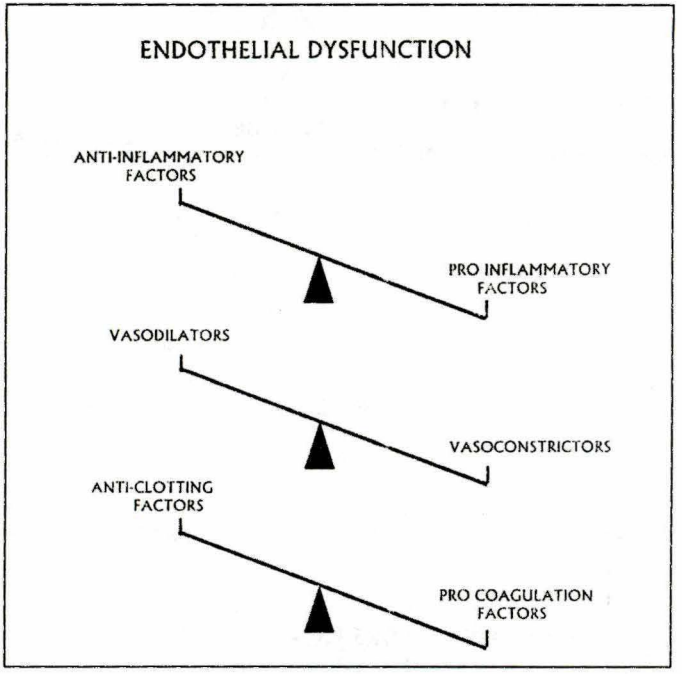


Figure 6.

VASCULAR ACTIONS OF NO (EDRF)

1. **Potent vasodilator**
2. **Inhibit plately adhesion and aggregation**
3. **Inhibit leucocyte (PMN) adhesion to activated endothelium**
4. **Inhibit vascular smooth muscle migration and proliferation**
5. **Inhibit expression by vascular endothelium of endothelin and PDGF**
6. **Reduce LDL oxidation by macrophage free radicals.**

Figure 7

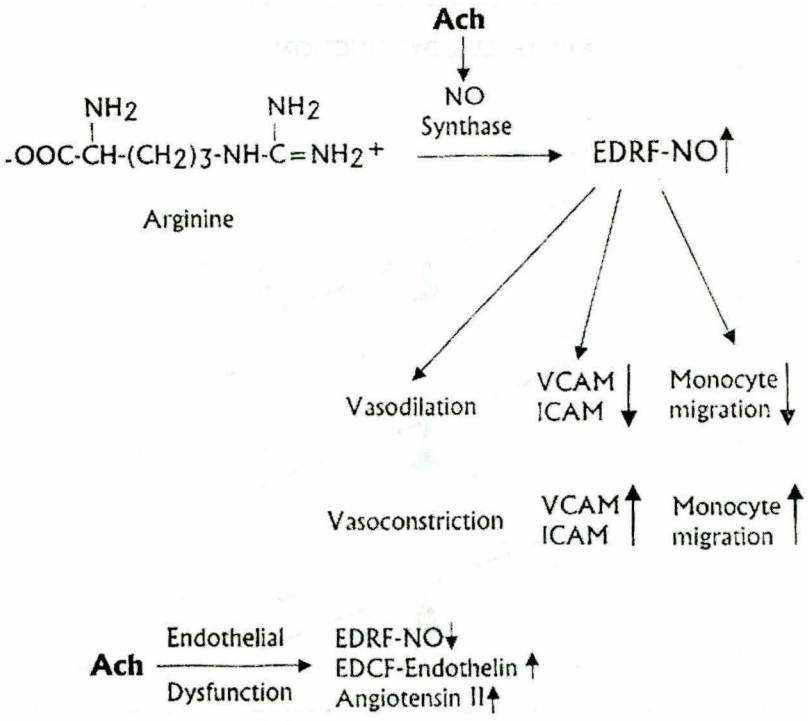


Figure 8

Atherogenic Profile

Heredity has long been known to play an important role in atherogenesis. Lipoproteins, the carriers of fats (cholesterol and triglycerides) in the aqueous-natured blood, are diet controlled but also gene-related . The predominantly gene-controlled are the levels of lipoprotein (a), small dense LDL and low HDL numbers predispose to atherosclerosis (Fig. 9). The other gene-related predisposing factors are diabetes, hypertension, PAI-1 expression (sign of endothelial dysfunction) hyperfibrinogenemia and the male hormone (or absence of the female hormone?). Among the atherogenic factors, only hyperhomocysteinemia appears to be due to vitamin deficiency rather than to hereditary enzyme abnormality.

Are Fats the Culprit or the Proteins?

When the high mortality rate was blamed on high animal fat intake, the studies were focused on the dietary fat of the subject peoples. The animal protein that was ingested along side the fats was ignored completely. Now homocysteinemia derived from methionine is looked upon as toxic to the arterial endothelium.

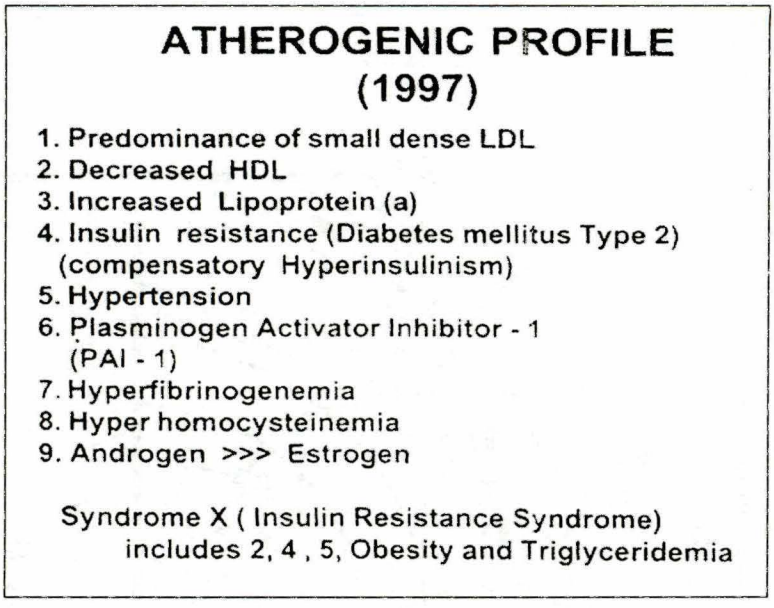


Figure 9

Hyperhomocysteinemia can develop from too much protein in the diet or a lack of the vitamins folic acid, B6 and B12. Was it only the fats that was responsible for the coronary heart mortality or could it have been the protein or the two acting in tandem?

Free Radicals and Lipid Peroxidation

Free radicals are generated by leukocytes and macrophages for defense against pathogens. They are also generated during metabolism of various foods. Among the most vulnerable structures to oxidation are the unsaturated fatty acids which abound in the phospholipids. The circulating cholesterol laden LDL is a harmless body until it enters the subintimal vascular space and is oxidized by free radicals to oxidized LDL (LDLox) – a toxic body and a probable cause of endothelial dysfunction (Fig. 10). Macrophages then engulf the LDLox and are converted to foam cells. Only after these foam cells burst is the cholesterol released into the simply a passenger and its release serves only to make the plaque more lipid laden and softer. Rupture of the soft plaque does not occur in the area of the fibrous cap but rather at the junction of the normal wall and the plaque where the fibrous cap is thinnest. The rupture is aided by the metalloproteinases secreted by macrophages and leukocytes.

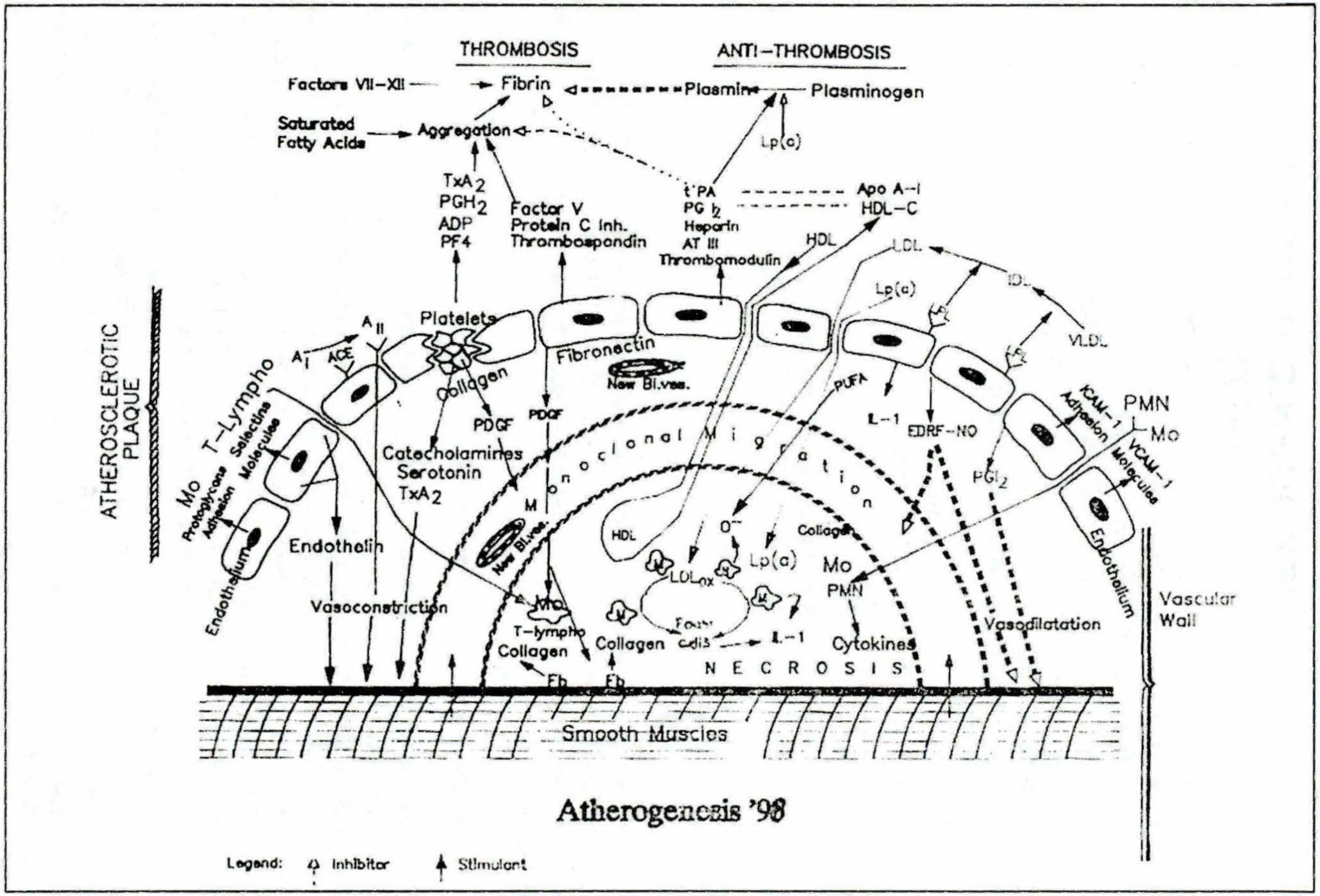

THROMBOSIS
ANTI-THROMBOSIS
Factors VII-XII
Fibrin
Plasmin
Plasminogen
Saturated Fatty Acids
Aggregation
Lp(a)
TxA2
PGH2
ADP
PF4
Factor V
Protein C Inh.
Thrombospondin
t PA
PG I2
Heparin
AT III
Thrombomodulin
Apo A-I
HDL-C
HDL
LDL
IDL
VLDL
Platelets
Fibronectin
Collagen
New Bl.ves.
PUFA
IL-1
EDRF-NO
PGI2
PMN
Mo
ICAM-1
Adhesion
VCAM-1
Molecules
T-Lympho
Selectins
Molecules
Proteoglycans
Adhesion
Endothelium
Endothelin
Vasoconstriction
PDGF
Catecholamines
Serotonin
TxA2
Monoclonal Migration
HDL
Lp(a)
LDLox
Foam cells
Cytokines
T-lympho
Collagen
Fb
NECROSIS
Vasodilatation
Smooth Muscles
Vascular Wall
ATHEROSCLEROTIC PLAQUE
Atherogenesis '98
Legend: Inhibitor Stimulant

Figure 10

Atherogenesis 2001

Figures 10 and 11 depicts graphically and pictorially much of what has been previously discussed.

Fig. 10 is the drawing of a plaque bounded by endothelial cells above and smooth muscles below. There is a layer of monoclonal (smooth muscle) cells under the endothelium – the fibrous cap. There is rapture of the endothelium plugged by aggregated platelets. Both the endothelium and the platelets are shown to secrete PDGF that simulate monoclonal migration. The endothelium also possesses lipoprotein lipase (LDL) molecules that project into the blood stream to reduce VLDLs to IDLs and to LDLs which enter the plaque, encounter oxygen radicals (O^-) and become oxidized to LDLox. Macrophages (M) engulf the LDLox and are transformed to foam cells. The plaque is full of other cells beside macrophages; these are polymorphonuclears (PMN) and T-lymphocytes. These are able to enter after they are showed down by adhesion molecules (VCAM-1, ICAM-1, proteoglycans and selectins) at the endothelial surface. The endothelium possesses another metabolizing enzyme sticking out in the blood stream - angiotensin converting enzyme (ACE) which converts angiotensin I to angiotensin II (AnII), a powerful vasoconstrictor. Other potent vasoconstrictors are endothelin, also secreted by the endothelium, and platelet factors (catecholamines, seretonin and thromboxane A_2 (TxA_2). TxA_2 is also a strong platelet aggregator. To counteract these vasodilators are two potent vasodilators also endothelium-derived, namely NO and prostacylin (PGI_2). At the top of the sketch are the thrombotic and antithrombotic factors. The pro-thrombotic factors secreted by the endothelium are Factor V, protein C inhibitor, thrombospondin and plasminogen activator inhibitor (PAI-1). The anti thrombotic factor of the (PGI_2) and tissue plasminogen activator which activates plasminogen to plasmin (fibrinolysin). This activation is inhibited by Lipoprotein (a) which is why Lp(A) is atherogenic.

Fig. 11 attempts to correlate the various etiologic factors (heredity, B.P., endothelial dysfunction, diabetes, hypertension, smoking, platelets) with the various stages of plaque development discussed earlier. And on the left side of the chart are the pathologic events that are overwhelming inflammatory in nature. Cholesterol deposition may feature prominently in the fatty streaks, which are innocuous, and in changing fibrous plaque into soft plaque that are liable to rupture. But the end belongs to coagulation and thrombus formation. This is what finally occludes the vessel and cause infarction.

Diabetes and Atherogenesis

The most common causes of morbidity and mortality in diabetics are the extensive atherosclerotic changes, micro and macro, of the blood vessels of the heart, brain and kidneys. Hence, diabetes is considered not just a risk factor like smoking and hypertension, but a "coronary heart diseases equivalent". A listing of the effects of hyperglycemic will reveal why this is so:

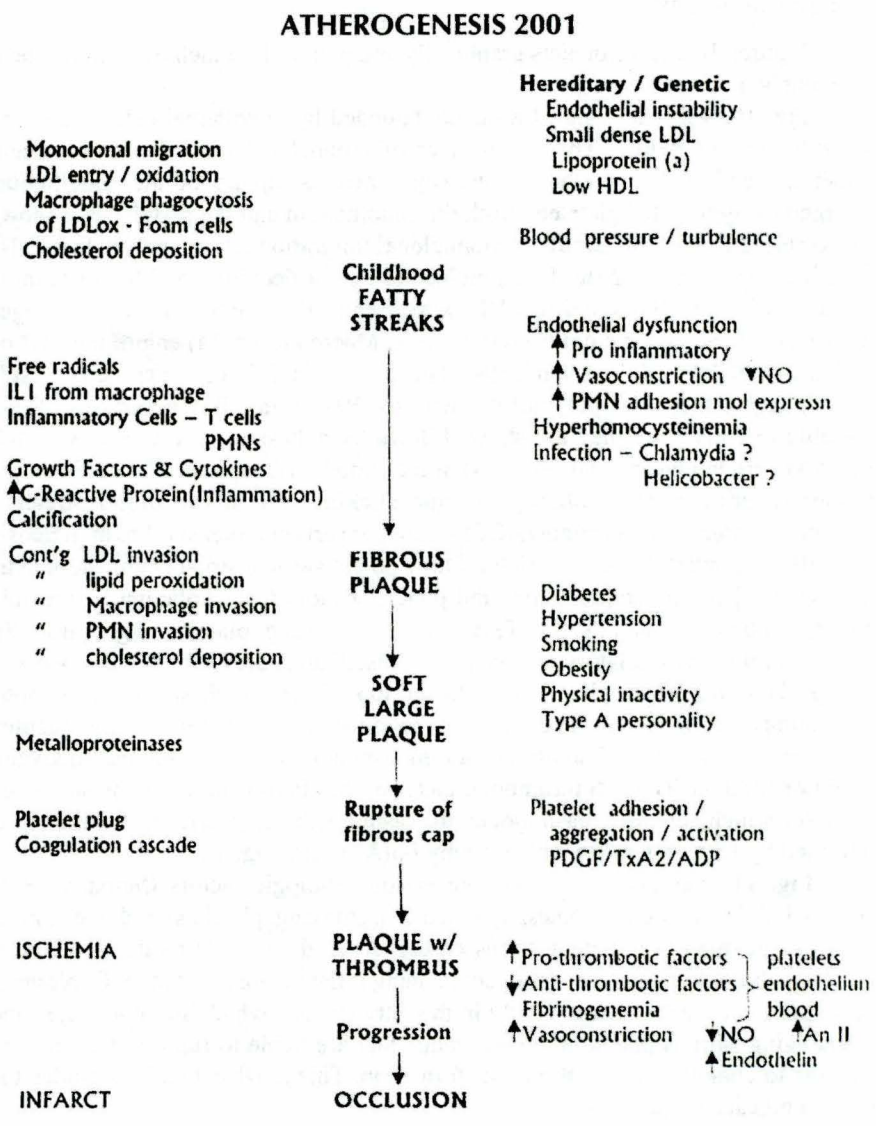

ATHEROGENESIS 2001
Hereditary / Genetic
Endothelial instability
Small dense LDL
Lipoprotein (a)
Low HDL
Monoclonal migration
LDL entry / oxidation
Macrophage phagocytosis
of LDLox - Foam cells
Cholesterol deposition
Blood pressure / turbulence
Childhood
FATTY
STREAKS
Endothelial dysfunction
↑ Pro inflammatory
↑ Vasoconstriction ↓NO
↑ PMN adhesion mol expressn
Hyperhomocysteinemia
Infection – Chlamydia ?
Helicobacter ?
Free radicals
IL1 from macrophage
Inflammatory Cells – T cells
PMNs
Growth Factors & Cytokines
↑C-Reactive Protein(Inflammation)
Calcification
Cont'g LDL invasion
" lipid peroxidation
" Macrophage invasion
" PMN invasion
" cholesterol deposition
FIBROUS
PLAQUE
Diabetes
Hypertension
Smoking
Obesity
Physical inactivity
Type A personality
SOFT
LARGE
PLAQUE
Metalloproteinases
Rupture of
fibrous cap
Platelet adhesion /
aggregation / activation
PDGF/TxA2/ADP
Platelet plug
Coagulation cascade
ISCHEMIA
PLAQUE w/
THROMBUS
↑Pro-thrombotic factors
↓Anti-thrombotic factors
Fibrinogenemia
platelets
endothelium
blood
Progression
↑Vasoconstriction
↓NO
↑An II
↑Endothelin
INFARCT
OCCLUSION

Figure 11

1. Lipid peroxidation by superoxide-dependent pathway
2. Activation of the Protein Kinase C (PKC) pathway induces:
   a. Insulin resistance by desensitization of insulin receptors
   b. Hyperinsulism causing endothelial dysfunstion, decr. NO
   c. Increase activation of phospholipase A2 causing inflammatory PGs and LTs.
   d. Increase cytokine release causing inflammatory changes
   e. Increase vascular cell proliferation (angiogenesis)
3. Activation of Polyol /Sorbitol pathway

$$\text{Excess glucose} \xrightarrow[\text{Reductase}]{\text{Aldose}} \text{Sorbitol (osmotic dysregulation)}$$

4. Formation of Advanced Glycosylated End products (AGE)
5. Dyslipoproteinemia

Why the Female Gender Is Protected?

Estrogen are the female hormones that make a woman a woman. It has long been noted that coronary heart disease spares women as long as they are menstruating and that CAD catches up on the male morbidity/mortality incidence only after her menopause). Unfortunately, estrogen therapy in males, besides being feminizing has not shown much success. Nature however has provided plants that containing estrogen-like substances appropriately called phytoestrogens. A list of the effects of phytoestrogens makes very evident the reasons why these female-hormone substances are protective against atheroclerosis.

Effects of Phytoestrogens

Preclinical Studies

Lower cholesterol
Decreased. LDL oxidation
Increased antioxidant enzymes
Decreased atherosclerotic lesions
Increased vascular reactivity
Decreased platelet aggregation
Decreased expression of ICAM –1 and VCAM-1 (intracellular & vascular cell adhesion molecules)
Decreased angiogenesis
Decreased neoplastic proliferation
Decreased bone loss

Clinical Studies
- Beneficial
  - Decreased cholesterol
  - Decreased LDL oxidation
  - Decreased perimenopausal hot flashes
  - Decreased cancer incidence
  - Increased bone mineral density
- ?Detrimental
  - Increased breast secretions
  - Increased proliferation of breast

Therapy

Figures 12 and 13 show how wide and varied are the approaches to the prevention, control and even reversion of the atherogenetic process.

The most promising new approaches for control or reversal are the new antiplatelet aggregators, the use of anti-inflammatory agents and newest of all, angiogenesis (growth factors to induce new blood vessel formation). And looming large as preventives are the antioxidants.

Meanwhile, the surgical approaches are become more and more "high-tech", simple, faster, event for out-patient use.

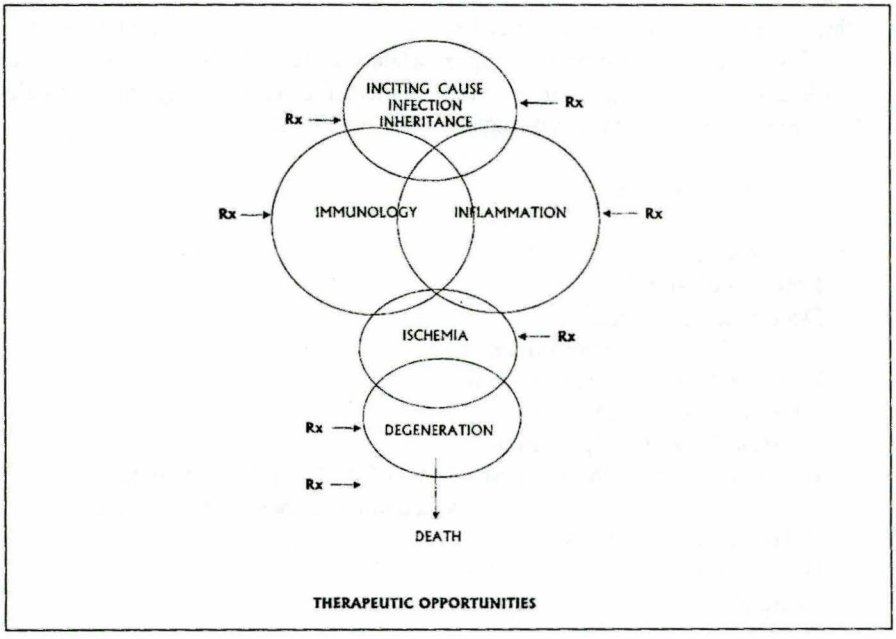


Figure 12

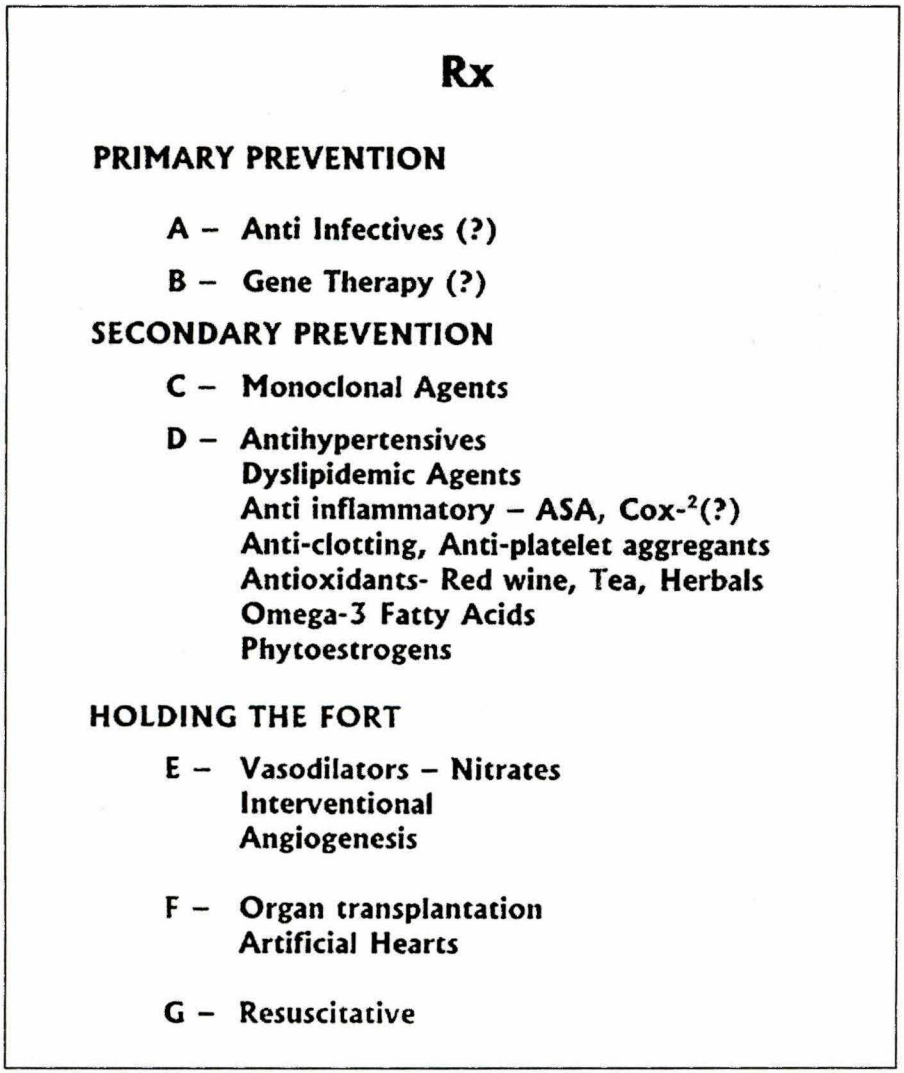

Rx
PRIMARY PREVENTION
A – Anti Infectives (?)
B – Gene Therapy (?)
SECONDARY PREVENTION
C – Monoclonal Agents
D – Antihypertensives
Dyslipidemic Agents
Anti inflammatory – ASA, Cox-2(?)
Anti-clotting, Anti-platelet aggregants
Antioxidants- Red wine, Tea, Herbals
Omega-3 Fatty Acids
Phytoestrogens
HOLDING THE FORT
E – Vasodilators – Nitrates
Interventional
Angiogenesis
F – Organ transplantation
Artificial Hearts
G – Resuscitative

Figure 13