

Cardiovascular Disease and the Endothelium

by Jeffrey Porro

This series of essays was developed as part of FASEB's efforts to educate the general public, and the legislators whom it elects, about the benefits of fundamental biomedical research—particularly how investment in such research leads to scientific progress, improved health, and economic well-being.

Millions of Americans are counting cholesterol, spending more time on the stairmaster and less in front of TV, and trading their burgers for broiled fish—all in an effort to prevent heart attacks and strokes. Doctors and scientists are doing their part, too. Their biomedical research is unraveling the complex causes of these deadly disorders, which kill almost half the people who die every year in the United States, Japan, and Europe.

Some of the most important progress has been in research on a disease called atherosclerosis. Doctors know atherosclerosis all too well as the main cause of heart attacks and strokes. In the last decade, researchers investigating what causes the disease have discovered that the endothelium, an extremely thin lining of the walls of the body's arteries, plays a crucial role. Recent discov-

eries about how that lining operates are providing doctors new tools for preventing atherosclerosis, diagnosing it if it occurs, and treating it effectively.

Atherosclerosis

From Fatty Streaks to Strokes. In a healthy person, blood flows freely from the heart to all parts of the body through miles of arteries. But disease sometimes damages the arteries, slowing the flow of blood or even stopping it. When that happens, the result can be extremely dangerous, resulting in a stroke or heart attack. The most important artery-damaging disease is atherosclerosis ('athero' means fatty; 'sclerosis' means scarring or hardening).

Atherosclerosis clogs the blood's pathways with an outgrowth called fibrous plaque, which narrows the arteries, developing gradually over years and even decades.

Fibrous plaque begins as changes in the structure of the artery or fatty streaks. These

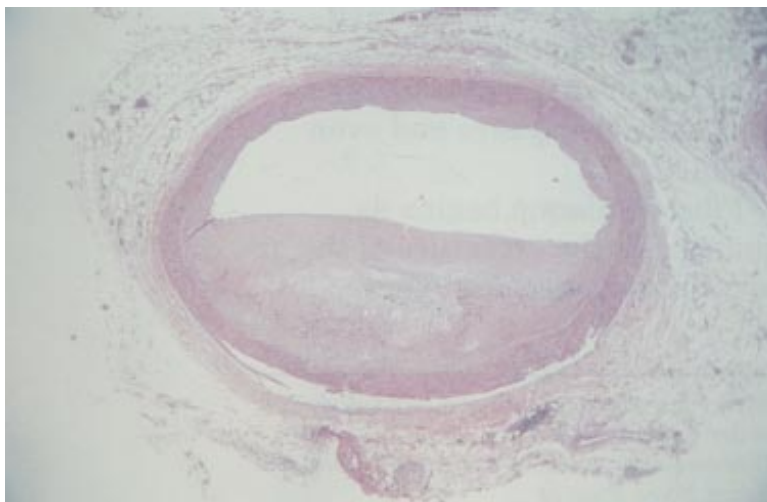
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streaks, one of the first signs of atherosclerosis, are composed of fat-laden blood cells and other material that build up in the artery wall. As atherosclerosis progresses, the streaks gradually change, becoming larger and more complex, turning into intermediate lesions. These lesions, in turn, evolve into fibrous plaque—the still larger, more complicated, and more dangerous advanced form of atherosclerosis.

Fibrous plaque can be a serious health problem, not only because it can narrow the arteries, but also because it can be a source of thrombosis (blood clots.) When a fibrous plaque becomes unstable and breaks or tears, thrombi can form on the surface of the plaque. If these clots are large enough, they can block the artery that has already been narrowed by the fibrous plaque. If such a clot forms in an artery leading to the heart, the blockage that results can cause a heart attack. When a clot cuts off blood to the brain, the result is a stroke.



Microscopic image of an advanced lesion from a coronary artery.
(Courtesy: Russell Ross)

What Causes the Disease? Scientists have been searching for the causes of atherosclerosis for a long time. They have known for more than a century that people who eat diets high in animal fat tend to have high levels of cholesterol in their bloodstream. And it has been well established that elevated cholesterol in the bloodstream is very likely to lead to atherosclerosis and the health dangers that come with it. But only in the last two decades have scientists begun to unravel exactly how the cholesterol traveling around in the blood leads to the development of a fibrous plaque and blood clots that block the artery.

The Role of the Endothelium.

Cholesterol in the Blood. Blood consists of a liquid (plasma) and several kinds of blood cells, including red cells, white cells, and platelets. Blood plasma also carries a huge variety of different substances from one part of the body to another. One key substance is cholesterol, one of the many lipids found in plasma.

Scientists have discovered that when people digest fat it goes into the bloodstream, but does not just float around freely. Cholesterol is carried in the blood from place to place on special particles called lipoproteins. One kind of lipoprotein particle, low-density lipoprotein or LDL, carries cholesterol to different parts of the body, including the walls of arteries, and can lead to problems when it carries more cholesterol than cells require to function normally. Another kind, high-density lipoprotein or HDL, carries cholest-

terol away from the artery walls and eventually out of the body. There is a direct link between elevated levels of LDL and atherosclerosis and decreased levels of HDL, which are protective.

Two Breakthroughs. Two major, closely related breakthroughs in research have helped scientists understand how the risk of developing atherosclerosis is linked to LDL. The first was the discovery that a part of the artery called the endothelium plays a major role. Arteries consist of three distinct layers. The innermost layer is called the intima. The endothelium, which is only a single cell thick, comprises the lining of that innermost layer and acts as an interface between blood and arterial wall.

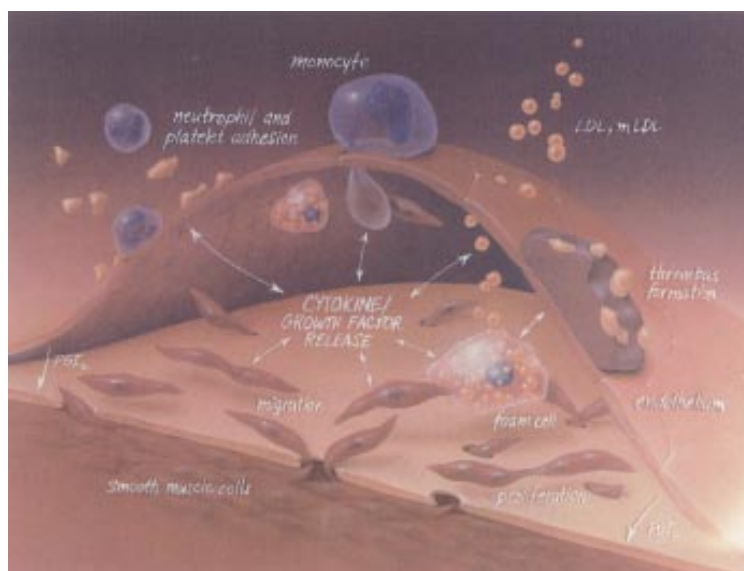
The second breakthrough was that atherosclerosis appears to be a healing response by the body that goes haywire. When any part of the body is damaged—whether by infection with bacteria, sports injury, a burn, etc.—the body increases the flow of blood to the injured area and puts white blood cells to work there. White blood cells surround the bacteria or the damaged tissue. Then, together with other cells in the damaged tissue, the white blood cells neutralize and remove whatever is causing the injury and repair the damage. Researchers now believe that a similar process occurs in atherosclerosis. But the process of inflammation and healing the injury may be slow and excessive, and the result can be increased risk of stroke and heart attack.

Endothelial Activation: From LDL to Oxidized LDL to Adhesion Molecules. Until about 10

years ago, scientists thought that the endothelium was just a kind of sieve: When people had high levels of cholesterol in their blood, LDL particles would leak into the artery wall and become trapped there. Now it appears that the endothelium does much more.

When high levels of LDL are in the blood, a small amount of the LDL that builds up in the artery wall becomes oxidized. This occurs through chemical reactions in the endothelium that change the LDL by adding extra oxygen atoms to it. This change is important because oxidized LDL is one of the triggers that can set off a chain reaction.

It appears that the more LDL there is in the blood, the more oxidized LDL will be produced. Oxidized LDL injures the endothelium and causes the surface of the endothelium to express a special kind of molecular 'glue' called ELAMS (endothelial-leukocyte adhesion molecules). These cause certain kinds of white blood cells (monocytes and T lymphocytes),

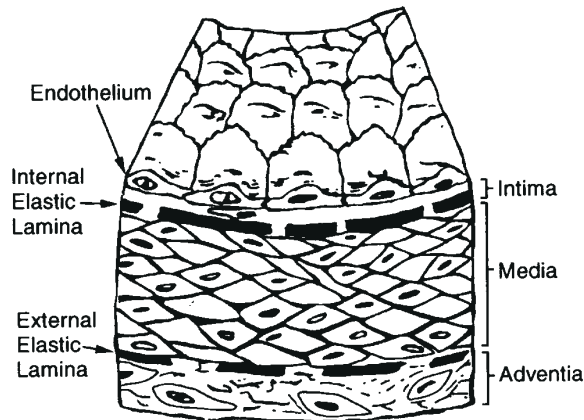


Signal transduction — the complex processes at work in atherosclerosis. (FASEB J. 1992, 6, cover; reprinted with permission.)

which are floating by in the bloodstream, to adhere to the endothelium.

A Healing Process Gone Haywire. Scientists now believe that this phase of atherosclerosis (oxidized LDL leading to adhesion molecules, which attract certain white blood cells to the endothe-

Structure of normal muscular artery.



Redrawn from R. Ross and J.A. Glomset (1976), The pathogenesis of atherosclerosis. *NEJM* 295

lium) is a form of the body's normal healing process. What the endothelium does during atherosclerosis is what all injured tissue does—up to a point.

As mentioned above, when any part of the body is hurt, white blood cells help neutralize bacteria or other agents that are causing injury and thus help in the process of repairing damaged tissue. It turns out that most injured tissue uses adhesion molecules to make white blood cells adhere to the spots where they are needed. The problem in atherosclerosis is that after the white blood cells (the monocytes and T lymphocytes) stick to the endothelium, what should be a healing process goes off track.

Specifically, the white cells move between and below the endothelium and start to do real damage in two major ways. In a complex chemical reaction, the white cells cause some of the muscle cells in the artery wall to grow. The white cells also incorporate the particles into the artery wall, consuming oxidized LDL particles.

The result is a fatty streak, which can progress to become a fibrous plaque. These intricate processes occur in the tissues beneath the endothelium and are enhanced by molecules secreted by the blood platelets, macrophages, and smooth muscle cells. Some of these molecules are called cytokines; others are called growth factors. The effects of these and other growth-regulatory cell products are now being studied and analyzed by medical researchers worldwide.

Future Implications

As scientists learn more about how each stage of atherosclerosis occurs, they are making it easier to detect and treat the disease.

For example, doctors now must rely on indirect methods, i.e., imaging techniques, to detect atherosclerosis. One of these methods is a stress test, an imaging technique that helps determine whether a patient's arteries are becoming clogged. Moreover, it is especially difficult to detect atherosclerosis in its early stages, when fatty streaks or intermediate lesions are just forming.

Medical research has, however, identified risk factors for atherosclerosis. These include:

- **cholesterol levels**—total serum cholesterol higher than 200 mg¹ per dL, with HDL cholesterol lower than 35 mg per dL
- **age**—men 45+, women 55+
- **diabetes mellitus**
- **family history**—myocardial infarction or sudden death before age 55 in male first-degree relative or before age 65 in female first-degree relative
- **hypertension**—blood pressure greater than 140/90 mm Hg, or the taking of medicine for hypertension
- **smoking**—smokers are at higher risk.

In the future, it may be possible to devise new diagnostic tools. For example, current research may well lead to sophisticated blood tests that will detect the molecules—such as adhesion molecules—that are produced at each stage of the disease. Such tests could be an even more effective early warning system for atherosclerosis.

Meanwhile, several therapies are being used to treat atherosclerosis. One of them is having the patient make lifestyle changes. Although scientists have not identified the direct physiological link between smoking and atherosclerosis, stopping smoking lowers the risk of the disease dramatically. For at-risk patients with moderately high levels of serum cholesterol, dietary inter-

vention and increased exercise also have proved effective.

When lifestyle changes alone are insufficient to bring about change, the most effective drugs now available are those that lower the amount of lipids in a patient's blood. Surgical approaches include angioplasty, in which a clogged section of the artery is stretched by introducing a balloon into the artery; bypass grafting, in which a section of healthy vein or artery is used to bypass a clogged artery; and endarterectomy, in which the inner part of the affected artery and the blood clot are surgically removed.

In the future, doctors may acquire more weapons against the disease, thanks to ongoing research on the endothelium's role in atherosclerosis. It may be possible to develop new drugs that will target each stage of the disease, preventing atherosclerosis from occurring, or even reversing the growth of fatty streaks, lesions, and fibrous plaque.

Classification of Cholesterol Levels

Total serum cholesterol
Desirable: <200 mg per dL (5.20 mmol per L)
Borderline high: 200 to 239 mg per dL (5.20 to 6.20 mmol per L)
High risk: >240 mg per dL (6.20 mmol per L)
Low-density lipoprotein cholesterol
Desirable: <130 mg per dL (3.35 mmol per L)
Borderline high: 130 to 159 mg per dL (3.35 to 4.10 mmol per L)
High risk: >160 mg per dL (4.15 mmol per L)
High-density lipoprotein cholesterol
High risk: <35 mg per dL (0.90 mmol per L)
Desirable: 35 to 59 mg per dL (0.90 to 1.55 mmol per L)
Low risk: >60 mg per dL (1.55 mmol per L)

Adapted from Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA 1993; 269: 3015-23.

¹mg=milligrams; dL=100 millimeters; 100 milliliters is about 1.6 fluid ounces

Suggested Readings

For a good sense of the progress that has been made over the last two decades in understanding the causes and pathogenesis of atherosclerosis read two articles, written almost 20 years apart, by Russell Ross, one of the major researchers on the disease (with John A. Glomset, M.D.): "The pathogenesis of atherosclerosis," *New England Journal of Medicine*, 295, 369-377, 420-425, 1976; and "The pathogenesis of atherosclerosis: a perspective for the 1990s," *Nature*, 362, 29 April 1993, 801-807.

Michael A. Gimbrone, Jr., M.D., provides a detailed overview of the role of the vascular endothelium in atherosclerosis in "Vascular endothelium in health and dis-

ease," in *Molecular Cardiovascular Disease*, edited by Edgar Haber, M.D., Scientific American Medicine (1995) New York, 49-61; and Michael A. Gimbrone, Jr., et al. in Hemodynamics, endothelial glue expression and atherogenesis (1997) *Annals NY Academy of Sciences*, Vol. 811, 1-11.

A lot has been written about controlling cholesterol in the last few years. You can find a readable summary of some of the latest findings in "Management of hypercholesterolemia," by Gregory H. Blake, M.D. M.P.H. and Laramie C. Triplett, M.D., *American Family Physician*, Vol. 51, No. 5, April 1995, 1157-1166.