PART ONE

How We Get Clogged

Chapter 1

Death by Inflammation

Inflammation is our body's first line of defense against injury or infection. It's what causes a burn to turn red or a bruise to swell. It's nature's design to help us heal. But if inflammation becomes chronic and goes into constant overdrive, it can cause disease.

In 2000, doctors at Harvard University published the first of a series of landmark research studies revealing the central role of inflammation in cardiovascular disease (CVD). Evidence from the Women's Health Study, a project that monitored the status of twenty-eight thousand initially healthy postmenopausal women, put a new risk factor into the spotlight: C-reactive protein (CRP), a key biochemical substance indicating the presence of vascular inflammation. People with the highest level of CRP had five times the risk of developing CVD and four times the risk of a heart attack or a stroke compared to individuals with the lowest level. CRP predicted risk in women who had none of the standard risk factors and was the best predictor among twelve risk factors studied, including cholesterol. The cardiologist Paul Ridker, who led the study, said that "we have to think of heart disease as an inflammatory disease, just as we think of rheumatoid arthritis as an inflammatory disease."

Ridker estimates that approximately 25 percent of Americans have a normal to low cholesterol level, lulling them into complacency, but at the same time they have an elevated CRP without knowing it. Millions of

Americans are unaware that they have an increased risk for future CVD, heart attack, or stroke.

Ridker's research confirmed what we as clinicians had suspected for years: that low-grade inflammation, like a silent, creeping fire, consumes arterial tissue and causes CVD. It leads to the weakening and eventual rupture of arterial plaques that directly trigger heart attacks and strokes. The CRP–inflammation link helps explain why more than half of heart attack and stroke victims have normal cholesterol levels.

Medical research has introduced us to other far-reaching and complex risk factors that go beyond the solitary threat of high cholesterol. Indeed, we have moved so far forward in recent years that the familiar model of diseased arteries as a network of inanimate pipes clogged by cholesterol-laden plaque seems almost as outmoded as the typewriter.

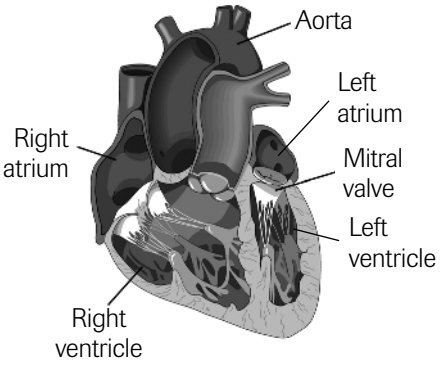
Life-threatening plaque is now regarded as an inflammatory injury—a lesion—that develops, almost like a boil, along the inner surface of the arterial walls where vital biological functions take place as blood rushes by. The walls become damaged by the inflammation—a process influenced by lifestyle, environment, and genetics. In some cases, the process unfolds slowly, stifling arterial wall chemistry and causing vessels to narrow. In other cases, deterioration occurs surprisingly fast, leading to vessel closure, stroke, or sudden death.

Plaque can be of two types. Stable plaque, covered with a fibrous cap, slowly expands inward and shrinks the diameter of blood vessels. Of greater danger is the vulnerable, unstable plaque, which can rupture and spill its noxious contents into the arteries and shut off blood flow. Identifying and combating the latter type of plaque has become the number one priority of today's cutting-edge cardiologists.

Indicative of a turnaround in thinking about the causes of CVD, the American Heart Association and the Centers for Disease Control and Prevention published new recommendations for CVD screening in 2003 that included a test for CRP. Today you may see posters on laboratory walls with information for patients about this new and potentially life-saving blood test. There is more to inflammation than CRP and more to CVD than inflammation, but we see this kind of public awareness effort as a good first step in getting out the message about inflammation and CVD.

Cardiovascular System 101

The heart and its network of blood vessels deliver oxygen and metabolic fuel to the cells. Think of your heart as a fist-sized, cone-shaped muscular



The heart

pump wrapped around four chambers. The chambers are connected by a series of one-way valves that let blood flow in one side and out the other. Oxygen-poor "used" blood returning to the heart collects in the right atrium chamber and is funneled into the right ventricle, which pumps it into the lungs to pick up oxygen. Oxygenated blood returns to the left atrium, passes through the mitral valve into the left ventricle, and is pumped out with great force (in a healthy heart) into the main artery of the body, the aorta. From the aorta, other arteries branch off to feed the body, including the two coronary arteries that supply the heart muscle.

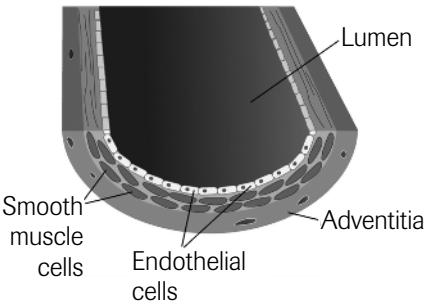
Blood moves through your body's sixty thousand miles of blood vessels known as the circulatory system. Think of this system as the branches of a tree with many offshoots or a river with many tributaries. Large arteries branch off into smaller arterioles. These, in turn, branch off into the smallest vessels, called capillaries, which feed the cells of the body, then carry wastes and deoxygenated blood back out into venules (small veins), then into larger veins, and finally back to the right atrium.

This elaborate system needs to be clear to accommodate the forceful contractions of the heart and permit strong blood flow. The walls of the blood vessels have to be smooth and free of obstruction. We will concentrate on the arteries, since CVD primarily affects arteries rather than veins.

As Goes the Endothelium, So Go You

Artery walls are not hard and firm. Instead, they are composed of smooth muscle that contracts and expands in metronomic response to the rhythm of the heart, accommodating the pulsatile flow of blood. They are a living, breathing, dynamic organ, not a static system of tubes and pipes.

We are most concerned with the innermost layer of the wall known as the endothelium. The blood meets the vessel walls at the endothelium. Though only one cell thick, this permeable lining carries out critical



The endothelial lining

molecular exchanges between the blood-borne contents floating through the lumen and the smooth muscle and adventitial tissues behind it that form the bulk and structure of the arteries. A healthy endothelium produces chemical substances that allow for the normal expansion and relaxation of blood vessels. Endothelial health is critical to cardiovascular health. If you have a 40 to 50 percent narrowing of the arteries and impaired endothelial function, you are at greater risk for an adverse event than if you had an 80 percent narrowing of the arteries with intact endothelial function.

The endothelial lining is extremely delicate and sensitive to injury. It can be damaged by a variety of insults. Of course, you can injure the endothelium, along with the entire artery wall, if you cut yourself and slice an artery. Trauma aside, we are concerned with the steady damage from inflammation that develops over time from a less than healthy lifestyle. Unhealthy habits include overeating refined, packaged, and processed foods with lots of sugar, unnatural fats, and chemical preservatives; not eating enough fresh fruits and vegetables and not drinking enough water; smoking; and not being physically active. Living in an environment where you are regularly exposed to pollution and contaminants is an inflammation risk factor. Stress associated with work, relationships, and financial pressures can compound the problem.

Silent Inflammation Starts Early

A middle-aged person may go to the doctor, perhaps complaining of shortness of breath or maybe just for a checkup, and hear that his cholesterol is too high and he has the beginnings of atherosclerosis, commonly known as hardening of the arteries.

The news comes with a loud jolt. But the process itself has been going on silently for a long time, starting at a surprisingly young age. Studies going back to Korean War and Vietnam War casualties show that even some teenagers have early arterial disease. More recently,

researchers specializing in the study of early-onset atherosclerosis reported in the medical journal *Circulation* that 20 to 25 percent of young people (aged fourteen to thirty-five) autopsied after death from homicide, auto accident, or suicide already had a major lesion in the coronary arteries. The study was performed on three thousand bodies.

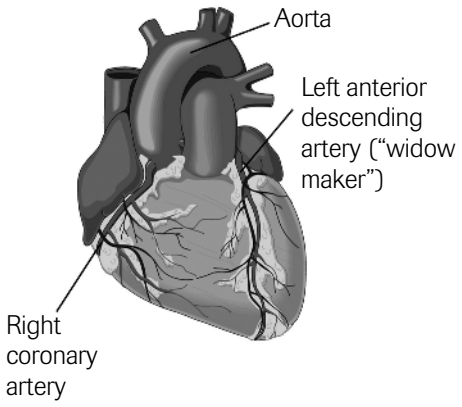
- Just over 3 percent of men aged fifteen to nineteen had 40 percent narrowing or greater in at least one coronary vessel. The prevalence increased to nearly 20 percent in thirty- to thirty-four-year-old men.
- Narrowing of 40 percent or more was not found in women before the age of twenty-five. Occlusions of this magnitude were found in 8 percent of those aged thirty to thirty-four.
- The presence of risk factors (such as smoking and diabetes) increased the likelihood of significant narrowing.

These numbers show that millions already have significant coronary disease at an early age. Most likely, they don't know it.

The message from these statistics is clear: you should not wait to begin a preventive program. Start as early as possible.

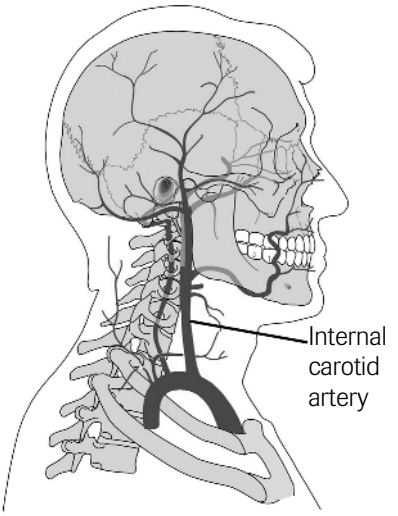
Arterial Hot Spots

The major cardiac hot spots are the left main coronary artery—the "left main" for short—and locations just beyond where it splits into the left anterior descending and left circumflex arteries on the outer surface of the heart. These blood vessels supply the front and side walls of the heart muscle.



The heart and coronary hot spots

The higher up in these vessels that blockages develop, the more damage that occurs "downstream." The left anterior descending artery is the potential site of the most dangerous lesion. We call it the "widow maker." It puts two-thirds of the heart muscle in jeopardy. The



The internal carotid arteries, the most important vessels feeding the brain

right coronary artery feeds the bottom and back portions of the heart muscle.

A blockage compromises the supply of oxygen and other blood-borne nutrients to the cells served by the artery and its branches. Denied their essential raw materials, these cells fail to generate adequate energy to sustain themselves and their multiple functions. If the blockage is incomplete, the cells starve. Pumping function ceases, but the cells remain alive. If the blockage closes the vessel, the cells die, and a myocardial infarct—a heart attack—is the result.

In the neck, the carotid arteries are the hot spots because they feed the front of the brain where you do your thinking. A stroke is like having a heart attack in the brain. There are four major arteries going into the brain: the left and right carotid arteries, which split into the external and internal branches; and the left and right vertebral arteries, which split into vessels serving the back of the brain. If a major blood vessel becomes blocked (especially before the split), a stroke is likely.

If you could take a miniature close-up camera and position it at a site of arterial inflammation, you would see a bulge along the artery wall, making the lumen (the flow area) narrower and less easily passable. The endothelium would look stretched out, like overstressed elastic. The spaces between the endothelial cells would be larger. Under the cap of this endothelial bulge, the plaque lesion forms—a virtual witch's brew of toxicity.

Narrowed arteries place a strain on the cardiovascular system and create all sorts of other health problems, as the heart is overstressed to pump harder and compensate for the partially obstructed blood flow. In turn, this raises blood pressure, leading to further cardiac strain.

The Role of the Immune System

The immune system protects the body from foreign invaders such as bacteria. It fields a variety of cells armed with different weapons to fight the

enemy. Some of these cells are released by the immune system and others by the injured tissue itself. Some are designed to engulf invading organisms, others to gobble them up, others to cart off the debris, and still others to seal off the injury and allow healing to begin.

This internal defense force is constantly challenged as it is involved in battle and repair operations. Without such a robust system, you would be overwhelmed by every germ you encounter and every injury you sustain.

Inflammation takes place when immune cells are summoned to the site of an injury such as an insect bite, a laceration, gum disease, or a broken ankle. The composition of cells depends on the nature and the location of the challenge, but all cause some characteristics of inflammation, namely redness, heat, and sometimes swelling. In the case of a viral or bacterial assault, the system may respond with fever, diarrhea, or nausea in addition to any localized distress.

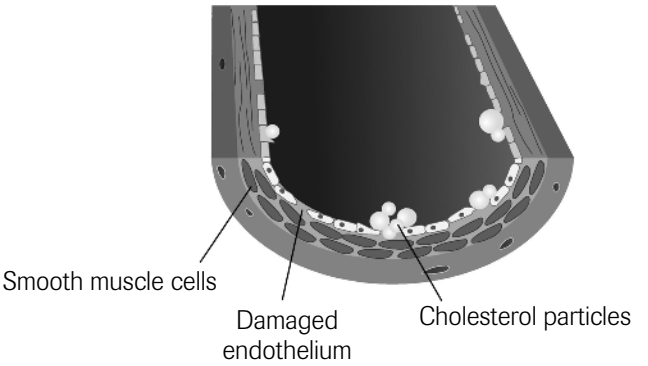
In any case, the inflammatory response stirs up a complex array of chemicals throughout the body. In this alert mode, a normal defensive reaction in one place can contribute to unwanted inflammation elsewhere. An infection in the gums can leak bacteria into the bloodstream. The bacteria may find fertile ground in a weakened arterial wall or a defective heart valve and fan the flames of inflammation there. In rheumatoid arthritis, a highly inflammatory condition, researchers have discovered that a woman's risk for heart attack is doubled.

Inflammation may or may not be obvious. It can take place on a subtle or silent level. From head to toe, your body is always in a process of repairing itself, with countless mini-inflammation dramas going on that you are not aware of as you go about your daily business or sleep. Inflammation in the arteries is an example of this below-the-radar-screen activity.

From Inflammation to Plaque

The delicate endothelium can become damaged from a variety of elements, including cigarette smoke, toxic chemicals and metals, bad fats, poor diet, elevated insulin, bacteria, high blood pressure, and excess stress.

Singly, or in combination, these elements kindle inflammation that can evolve into plaque. Following is a stage-by-stage description of the process.



The start of arterial damage

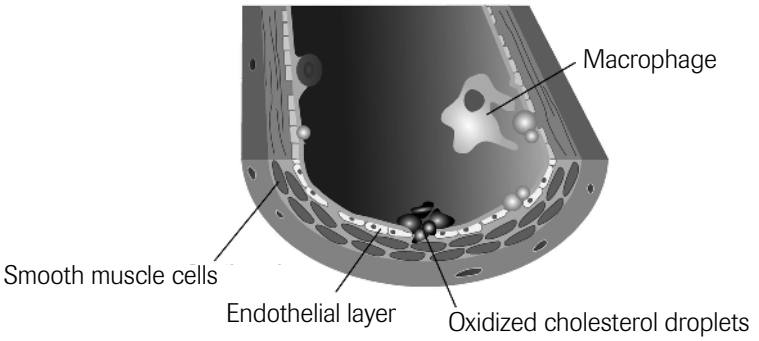
Stage 1

Under siege, the normally smooth endothelium becomes permeable or porous, attracting fatty particles such as circulating cholesterol. These particles wriggle into the lining and disturb biological activities. Usually, though not always, this occurs at locations where the endothelium tends to be under extra pressure. A typical hot spot is where the left main coronary artery splits into the anterior descending and circumflex arteries.

Once cholesterol becomes wedged in the arterial wall, a chemical process may take place in which the fatty molecules are damaged by free radicals to form oxidized LDL (low-density lipoprotein) cholesterol. Soon the ever-vigilant immune system takes notice that something is amiss and needs attention. The system goes into action.

Stage 2

Local cells surrounding a distressed site release immune chemicals that initiate an inflammatory process. The intima, the layer of tissue just behind the endothelium, secretes adhesion molecules to create a sticky endothelial surface like fly paper. Blood cells adhere, including monocytes, circulating immune cells instrumental in the inflammatory response. Meanwhile, the besieged endothelium secretes endothelin and other distress-signaling agents.



The inflammatory damage intensifies

Stage 3

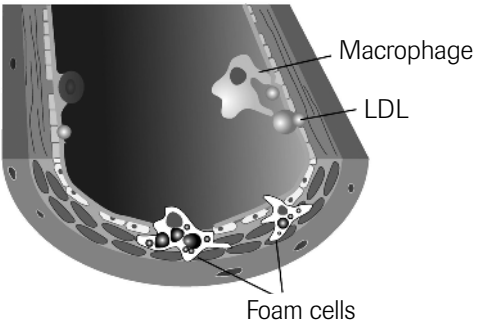
The endothelium and intima now release other chemicals. They cause more circulating monocytes to swarm across the endothelial barrier and mature into full-fledged scavengers called macrophages that are designed to seek and destroy foreign objects. Under ordinary circumstances, macrophages engulf invading cells, consume them, and are eliminated from the body by other specialized immune cells. But the developing situation here is no longer ordinary.

Stage 4

Oxidized LDL is not benign. It is toxic to the macrophage. Oxidized LDL immobilizes the macrophage, preventing it from returning to the bloodstream. The stressed macrophage sends out an SOS—a proinflammatory distress signal that draws other white cells into the area, where they, too, are destroyed by the oxidized LDL. Under the microscope, we see a fatty streak made up of dying macrophages loaded with oxidized LDL layering out from the inner area of the artery wall.

Stage 5

Proinflammatory substances gather in a seething commune of cytokines, enzymes (proteins responsible for stimulating other chemical reactions in



The lesion grows . . .

the body), and growth factors. They go by such names as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), macrophage colony-stimulating factor, and various interferons. These chemicals increase the stickiness of the endothelial wall and make it even more permeable to white blood cells and LDL cholesterol, which continue to enter and burrow inside. The lesion grows and attracts other chemical bedfellows such as CRP and fibrinogen, all produced in the liver and dispatched to sites of injury or infection.

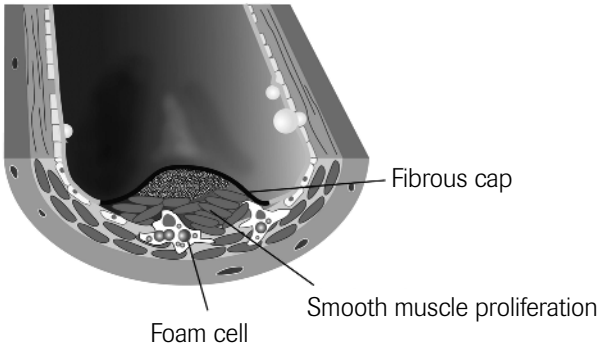
C-reactive protein is probably the most pervasive of these substances, abundantly present in all inflammatory fluids, in the intimal layer of the atherosclerotic artery, and in the foam cells (LDL-engorged macrophages) within the lesions of the forming plaque. CRP stimulates cells to release tissue factor, a protein central to the clotting process.

Remember that the body wants to heal or seal off any injury. That's the purpose of these individual chemicals. But nature's plan backfires. The lesion becomes stickier and keeps attracting dangerous chemicals as it grows—a truly vicious cycle. Bacteria and toxic metals join in.

Think of plaque progression in terms of the body responding to a growing internal infection. The immune system's natural reactions feed on itself, creating a general state of inflammatory alert.

Stage 6

The body now calls in yet another set of chemicals designed to create a hard seal over the roiling inflammation. They team up with white blood cells, collagen and elastin (two important proteins that make up connective tissue), and platelets to form a tough, fibrous cap.

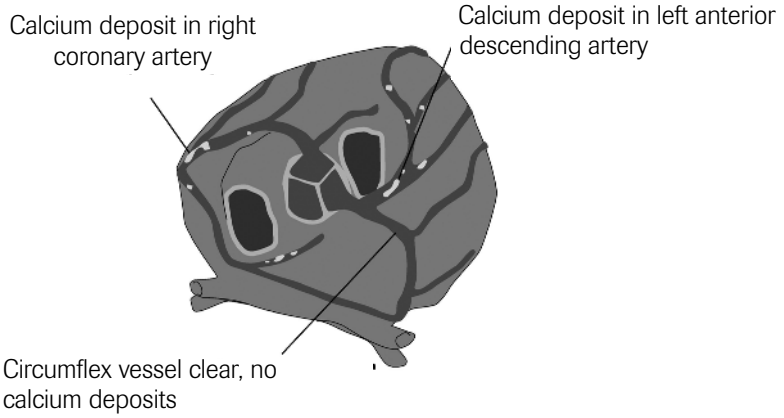


. . . into a potentially dangerous plaque

Under the cap, dead cells pile up and decay. Pus develops. This necrotic core becomes a growing plaque. It's like a boil within the artery wall.

Typically, this drama is not confined to a single location but unfolds at various points along arterial walls throughout the system. Inflammatory mediators released at one vulnerable site can agitate endothelial cells elsewhere, converting stable plaque into vulnerable plaque. Vulnerability and the tendency for plaque rupture increases. Plaque begets plaque. If you have it in your heart arteries, you most likely have it in your carotids and aorta. And elsewhere.

At some advanced point in the inflammatory process, calcium becomes deposited in the struggling arterial cells as part of their effort to produce adequate energy. When they open to calcium, the cells also let in



An example of plaque in the coronary arteries

circulating toxic metals such as lead and cadmium. This is not a clearly understood phenomenon. All we know is that calcium is there—and shouldn't be—making up about a fifth of the volume of the plaque and contributing to its hardness.

Stage 7

The affected arteries reshape themselves to accommodate plaque buildup. As the lesions grow, the arterial wall expands and bulges to accommodate them. This process is called remodeling. Lesions soon begin to obstruct the lumen through which blood is flowing and the arterial walls begin losing elasticity.

Stage 8

At this point, significant plaque deposits exist in various stages, and further developments determine whether a heart attack or a stroke follow. Subsequent events can take two possible scenarios.

Scenario 1: Stable Plaque

In this scenario, the fibrous cap holds firm, withstanding the roiling changes from within and the immune system's siege from outside. There could be a number of reasons for this resiliency under duress:

- Changes in lifestyle that reduce the toxins entering the body—for instance, eating less bad fats and quitting smoking
- Beginning a treatment program designed to quell inflammation and repair the endothelial layer
- A genetic predisposition to a lower-level inflammatory response

Hardened, constricted arteries cause the heart to work harder to pump blood through narrower blood vessels. This can lead to angina—chest pains commonly associated with heart disease.

Stable plaque can cause symptoms if the heart weakens due to chronic oxygen deficiency or if the artery is so narrow that it becomes completely blocked. Surprisingly, this dynamic is responsible for relatively few heart attacks. Many people with plaque-ridden arteries live well into their eighties and nineties—as long as the plaque is stable. Often, with slowly closing arteries, the body forms natural bypasses.

Heart failure occurs if the heart cannot pump sufficient amounts of blood to the rest of the body. Fluid accumulates in the lungs, ankles, or

legs, creating general fatigue and shortness of breath. If leg arteries are affected, numbness, fatigue, or pain may be experienced in the lower extremities, especially upon walking. This situation is called intermittent claudication, a prime symptom of peripheral artery disease.

Scenario 2: Vulnerable (Unstable) Plaque

This scenario carries the most danger. The fibrous cap starts to erode as a result of ongoing inflammatory assault from within the lesion and from outside. In the necrotic core, cellular breakdown and release of inflammatory substances create internal destabilization. Foam cells, for instance, release chemicals that can weaken the protective cap.

New plaque zones form externally, and the inflammatory chemicals they release, together with circulating destructive substances such as free radicals, also lead to destabilization. A leak develops and macrophages enter. They produce enzymes and inflammatory substances, along with clotting factors such as fibrinogen, to reseal the injury. However, the lesion swells and the fibrous cap continues to degrade until suddenly the cap ruptures.

The noxious contents spill into the bloodstream. Platelets and clotting agents converge to plug the leak. A thrombus (blood clot) forms immediately. The clot can obstruct a vessel on the spot, or if it is small enough, can flow downstream until it clogs a smaller vessel. Or a piece of the plaque cap can break off and do the same.

Inflammation causes the plaque to rupture, and the rupture is what kills most of the time. We used to call this event coronary thrombosis. Now we call it plaque rupture. Vulnerable, oxidized, inflamed plaques will rupture. Plaque rupture can lead to three potentially devastating events: acute heart attack, death from arrhythmia (the heart stops or races wildly because of electrical instability due to the sudden loss of oxygen), and, if it occurs in the carotid arteries or the brain, a stroke.

In emergency rooms and coronary care units, we apply clot-busting medication to alleviate the clot component of arterial obstruction. Then we do bypass surgery or dilate the narrowing and place a stent. This saves lives and limits heart muscle damage.

The size of the lesion means far less than its stability. Today, medical science allows us to pinpoint these plaques and stabilize or even reverse them before an event occurs.

If an occluded blood vessel can be expanded by just a fraction, blood flow can be improved considerably. This is what we try to do with medication and, in New Cardiology, with combinations of medication and

nutritional supplements. Getting the blood vessel to relax or just open up slightly—what we call plaque reversal—produces an incredible effect. A mere 10 percent increase in vessel diameter from, say, 90 percent narrowing to 80 percent, will double blood flow.

In the old cardiology, the focus was on percent of blockage of the artery. We did nothing until a 70 percent narrowing was seen on the angiogram, then we did angioplasty or bypass surgery. In New Cardiology, we focus on the integrity and function of the endothelium—that is, the biology of the cells lining the arteries. We never give up because of high-grade narrowing. And we don't hold off treating a patient just because only a moderate narrowing is seen. We know we can always influence the biology of the lining of the cells.

The Speed of Plaque

How fast does plaque develop into a killer? That depends.

We have been shocked many times by people who form plaques within six months. All cardiologists have seen this. That's the nature of coronary artery disease. It can be like a snowball rolling down the hill. It gathers bulk as it increases momentum.

Stress can speed things up. For a cardiac patient, emotional stress is deadly. Blood vessels can spasm and tighten up, creating more deficiency to the heart. There could also be some lesser plaque that our diagnostics don't pick up—for example, 10 or 20 percent blockage—or the plaque can develop inside the wall where it can't be seen.

Plaque is dynamic. Left to its own devices, it will increase in size. If it develops substantially but very slowly, the body's intelligence can form natural bypasses. We call these collaterals. A patient may have a slowly closing coronary artery and not have a heart attack. A narrowed artery does not always require surgery.