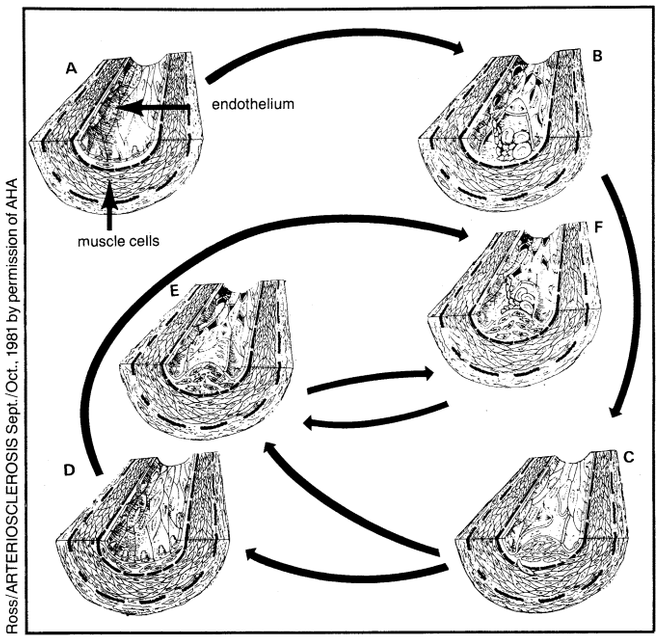
Anatomy of Atherosclerosis

In hardening of the arteries, the body's attempt to heal itself causes problems



Ross/ARTERIOSCLEROSIS Sept./Oct., 1981 by permission of AHA

"Response to injury" hypothesis: In A-D, the normally continuous endothelial layer is disrupted by chemical (e.g. high cholesterol) or mechanical forces, but manages to repair itself. In F, continuous injury has led to progression of atherosclerosis.

By JOANNE SILBERNER

When pipes clog up, it's generally because something gets stuck in them — a hairball in a drain, leaves in a drainpipe. But in atherosclerotic arteries the clogging is not in the inner space, or lumen, of the vessels but in the walls of the vessels themselves, which swell up with new cells and eventually limit or shut down blood flow.

With atherosclerosis a contributing factor in the estimated 1.5 million heart attacks and 500,000 strokes in the United States this year, understanding the process is of more than academic interest. At the recent American Heart Association Science Writers Forum in Monterey, Calif., Russell Ross of the University of Washington in Seattle detailed how cells of the vessel wall enlarge and multiply, and how recent discoveries have complicated the picture, while A. Clifford Barger of Harvard University illustrated how the body grows new blood vessels within the bloated walls of the old vessel. Both areas of investigation are aimed at delineating the exact process of atherosclerosis so that interventions can be found.

Like cancer, atherosclerosis is a disease of proliferating cells, but unlike cancer cells, these cells have not been genetically altered. Rather, Ross hypothesizes that the cells reproduce in response to injury — triggered by such factors as cholesterol, smoking, high blood pressure and diabetes — with unfortunate effects.

Normal arteries have three layers. The inner layer consists of a thin lining of smooth endothelial cells, backed by fibers and support components. Surrounding this is a layer of muscle, which in turn is surrounded by connective tissue cells.

As people age, cells from the muscle layer, along with white blood cells, migrate to just beneath the endothelial layer, where they fill up with fat (mostly cholesterol) and form "fatty streaks." Such streaks have been found during autopsies of hearts from children as young as 10 years of age; in older people, many researchers believe the streaks sometimes progress into advanced atherosclerotic lesions.

To follow what happens during atherosclerosis, Ross and his colleagues have monitored the pattern of cell changes in monkeys on a high-cholesterol diet. On a very high-fat diet, the process of atherosclerosis is swift. "The first thing that we see 12 days after [the high-cholesterol diet is begun] is a modified form of inflammatory response," Ross says. White blood cells called monocytes stick to the smooth inner endothelial lining of the artery, "something they don't normally do," says Ross. "They literally crawl around on the surface, find a junction and slip between."

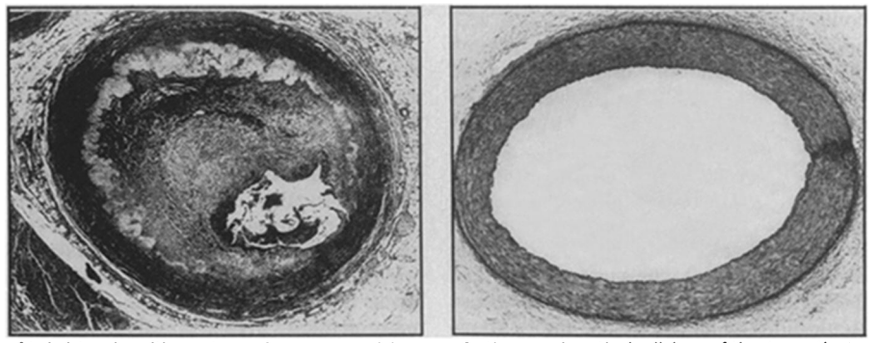
The cells develop into another type of white cell called a macrophage, and pick up fat. More monocytes continue to crawl in and muscle cells accumulate as well. The formerly smooth endothelium becomes irregular and bumpy. Stretched by all the new cells accumulating underneath, the endothelial cells "seem to part at their junctions," says Ross.

The split exposes the inner part of the artery wall to blood flow. Platelets, blood components involved in clotting, can attach to the exposed cells within one or two months. The platelets release factors that promote the division of the muscle cells surrounding the endothelium. The whole mess becomes a "huge lesion," says Ross.

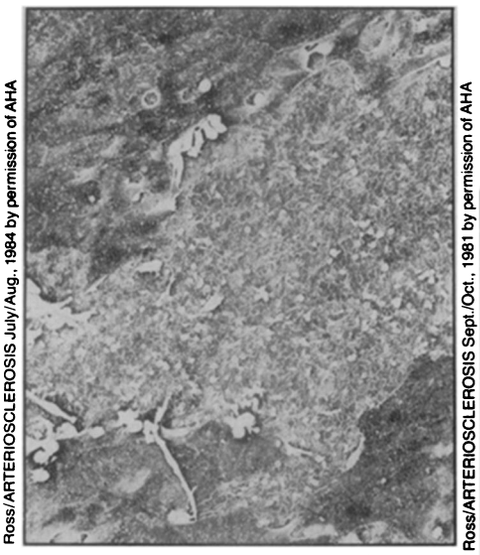
Ten years ago Ross and co-worker John Glomset postulated that atherosclerosis-promoting conditions such as high cholesterol or high blood pressure kick off the process the same way a mechanical injury to isolated arteries in the laboratory does — by disrupting the smooth endothelial lining, allowing the invasion process to begin.

In the search for the agent produced by platelets that induces cell division, Ross's laboratory was able to isolate a protein called platelet-derived growth factor, or PDGF. This protein normally plays a helpful role in the healing process, causing needed cells to multiply. But in atherosclerosis, says Ross, PDGF "turns normal response to injury into an exuberant response, resulting in the narrowing of the lumen of the artery."

Since the discovery of PDGF, nonplatelet sources of the factor have surfaced.



At right, a healthy artery shows no evidence of atherosclerotic buildup of the type that limits blood flow in the artery at left.



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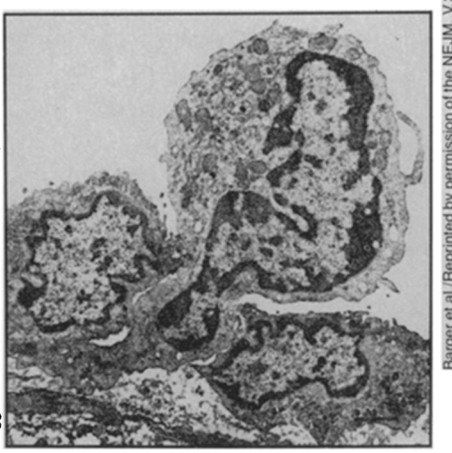
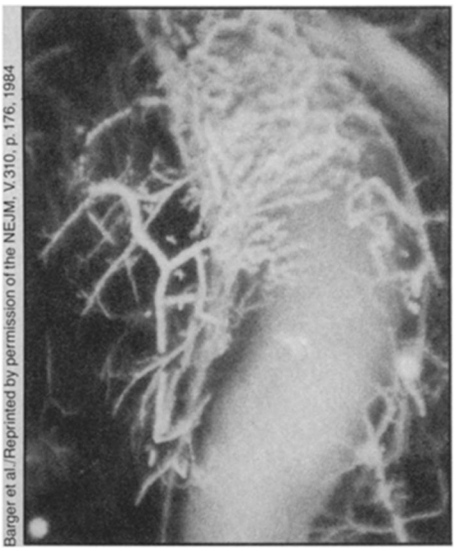
Electron micrograph of an artery from a 2-year-old monkey raised on a high-cholesterol diet. The endothelial layer has split open, and platelets can be seen spread over the exposed tissue in the rough area running across the middle. Platelets release platelet-derived growth factor (PDGF), which stimulates cells to multiply. Magnification ×525.



Faggiotto, Ross/ARTERIOSCLEROSIS Sept./Oct., 1981 by permission of AHA

The arteries of monkeys on high-fat diets show the initial stage of atherosclerosis after only 12 days. This electron micrograph shows a balloonlike white blood cell worming its way into the vessel wall from upper right.



Barger et al./Reprinted by permission of the NEJM, V.310, p.176, 1984

Silicone injected into a coronary artery of an autopsied human heart reveals tiny blood vessels that have developed to nourish an atherosclerotic section of the artery. There are no such vessels in the part of the artery where there is no atherosclerosis. The artery is from a man with a long history of hypertension who died at the age of 79.

Macrophages and endothelial cells have also been found to produce PDGF, and recently Daniel Bowen-Pope in Ross's lab found that muscle cells can be stimulated to secrete this protein. The elevation of macrophages, endothelial cells and muscle cells to leading roles in PDGF production complicates the picture.

"It means we have to look at four different cell types, not just one," explains Ross. An injury could presumably kick off the atherosclerotic process by stimulating any of the four cell types, singly or in combination.

The accumulation of cells will disappear on its own if the stimulus—for example, a high-cholesterol diet—is removed. But eventually calcium collects in the cells of the lesion and makes it hard; once this happens, says Ross, it may be impossible for the body to reverse the process.

While these cellular events were scripted from studies on monkeys and pigs, it's reasonable to assume the same things happen in humans but at a slower pace, Ross says. "We're beginning to understand different forms of injury," he says—the different cells that can be affected by cigarette smoking, diabetes and high blood pressure.

But knowing what is happening isn't of much use unless you can stop it. Ross and his co-workers are experimenting with antibodies that block the effects of PDGF. "We have a specific antibody that can completely abolish its effects," he says. They are using it to see which cells make PDGF and when. The antibody is not a likely option for therapy because it would mean long-term administration of a foreign antibody, something the body is not thought to tolerate well.

The researchers are still investigating ways to interrupt the process, but for now, Ross notes, "at least we understand what the actors are and what some, though not all, of the molecules are."

Many details remain to be worked out. The process is not the same in everyone—some people can eat all the eggs and butter they want, while other people's arteries seem to clog at the mention of butter. It's clearly dependent on a person's environment in combination with many genetic factors, Ross notes.

The "response to injury" hypothesis would explain why very often the grafted vessels in coronary bypass surgery quickly develop atherosclerosis. "Where you tie in the bypass, you're mechanically injuring the artery," says Ross. "That mechanical injury induces atherosclerosis at the site of the connection."

The hypothesis may also explain how agents such as aspirin that block platelet action reduce the incidence of coronary atherosclerosis, since platelet attachment is a key step in the process. Aspirin's protective effect is "a nice application of our basic data," Ross says.

All the thickening in atherosclerosis, however it comes about, results in some of the muscle cells residing far from the vessel lumen. Studies by Harvard's Barger show that the thickened vessel walls develop their own blood vessels—the vaso vasorum, or vessels of the vessel. He and his colleagues washed out autopsied human hearts and injected them with silicone. "In areas of atherosclerotic injury a rich network of capillaries arises from the outer vaso vasorum and penetrates through the muscle layer to the region of the plaque," Barger says.

The formation of new vessels represents the victory of the system that initiates blood flow in areas needing nourishment, a process that enables unwanted cells to flourish. Finding a way to stop new vessel formation might be a key to starving out the atherosclerosis.

"Usually the wall is so thin that oxygen just diffuses through. No blood vessels are needed," says Barger. But the walls of atherosclerotic vessels get so thick that they can no longer depend on nutrients and oxygen diffusion from the lumen; they need their own source of nourishment. The cells send out agents that induce new blood vessels to form.

The thready new blood vessels sometimes rupture—an act, says Barger, that "may also cause a high concentration of agents that cause muscle to contract." The finding could thus explain why coronary artery spasms, which can choke off blood flow to the heart muscle and cause heart attacks, occur primarily in the area of atherosclerotic deposits.

In addition, blood from a ruptured vessel can tear the inner lining of the coronary artery, cause a clot to form and result in a heart attack by blocking the artery, Barger notes.

Barger's lab, like many others, is trying to develop factors to halt new vessel growth, a tactic that could be used to stymie tumors as well. The work hasn't yet led to a treatment for atherosclerosis. "The hope," says Barger, "is that as we learn more about it, we'll learn to prevent it." □