On Two Hearts & Other Coronary Reflections

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It is almost 30 years since my father died of heart disease. At that time there was little that could be done for someone who had angina, suffered a series of heart attacks, and ended up with congestive heart failure. Treatment of heart disease has changed radically since then. For several years I've kept a file of articles about the heart, intending eventually to write a column about the latest discoveries as a small memorial to my father whom I still miss very much. But the file kept getting thicker and thicker until the idea of plowing through it became daunting. Finally, I decided it was time to tackle the pile, and this column is the result of that effort, though I can only mention a few of the articles here. What I read taught me not only about how our understanding of heart disease has developed, but also something about how medical science makes progress.

Atherosclerosis

Though the death rate from atherosclerosis—the buildup of fatty deposits in the walls of arteries and the major cause of heart disease—has been decreasing since the late 1960s, it remains the leading cause of death in the United States. One of the best recent reviews of what happens in an artery as atherosclerosis progresses was written by David Hajjar and Andrew Nicholson (1995). The presently held model is based on the idea of response-to-injury: there is an inflammatory response in the inner lining of the artery, the endothelium, and eventually the underlying media also becomes involved; it is this immune response that leads to the damage of the arterial wall. The first step seems to be the movement of monocytes from the circulation, through the endothelium, and into the intima which lies just beneath the endothelium's single layer of cells. But what induces monocytes to enter? It seems that the endothelium has changed, perhaps in response to cholesterol, so that its cells produce an adhesion molecule to which the monocytes attach and then move through the endothelium. Once in the intima, the monocytes become macrophages that ingest lipids, primarily oxidized lipids. As the lipids accumulate, the macrophages take on a foamy appearance, and they become one of the primary components of a fatty streak, the first apparent sign of damage to the artery wall. Also, smooth-muscle cells move up from the medial layer into the intima where they proliferate and accumulate lipid. These cells also produce an extracellular matrix of collagen that makes up the bulk of the developing atherosclerotic lesion or plaque.

One form of progress has come in identifying some of the molecules responsible for this process. Researchers are gaining a better understanding of exactly what is happening at the molecular level, though that understanding is hardly complete. The molecules that have already been found to play a role include several growth factors which promote cell division, cytokines which regulate white blood cell functions and also blood clotting, and nitric oxide which dilates blood vessels. I find nitric oxide to be particularly interesting because its role is so surprising: here is a very small molecule that was originally dismissed as merely a byproduct of other processes and has now been found to have a number of powerful effects. These include vasodilation which is achieved when nitric oxide is released from the endothelium and diffuses into the medial layer where it causes smooth-muscle relaxation (Loscalzo 1995). At the same time, nitric oxide is also released into the blood vessel's lumen where it inactivates platelets (Lüscher 1994). In other words, nitric oxide helps to lower blood pressure and to prevent clots in the arteries. Since reduced synthesis of nitric oxide has been found to be related to hypertension and blood clotting, research is being done on how to maintain its synthesis in the endothelium.

I don't really have the room here to go into more detail on the other molecules implicated in the development of atherosclerosis. As with nitric oxide, the evidence for their role is still being amassed, and efforts at controlling these chemicals are still in the early stages. As research continues, it is becoming more and more apparent that atherosclerosis is an extremely complex process. This has both its negative and positive aspects. The complexity makes research difficult because it requires unraveling extremely intricate processes with dozens of factors involved, but this complexity also means that there are a large number of points at which intervention may be possible, a large number of molecules whose role can be influenced in an effort to slow or even halt and reverse the process.

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Much of the focus on slowing atherosclerosis has been on cholesterol and the triglycerides that both accumulate in the foam cells of the fatty streak. These lipids are carried through the blood attached to lipoproteins. One of these, LDL, is involved in the removal of cholesterol from the bloodstream. Macrophages in the arterial intima bind and ingest LDL particles, but only when the particles are oxidized. In other words, oxidation speeds the formation of foam cells; it can also activate inflammatory processes within the blood vessel wall. The dangers of oxidation may explain why antioxidants such as vitamin E have been found to protect against heart disease (Steinberg 1993). A portion of another lipid-transporting particle called lipoprotein (a) has a structure similar to the precursor of plasmin, a protein that degrades the fibrin in a blood clot; thus lipoprotein (a) competes with this precursor and slows clot degradation and intensifies clot formation. So it is becoming clear that lipids are not just accumulating in the walls of arteries but contributing to the process of atherosclerosis in other ways, from stimulating inflammation to preventing the destruction of clots. This helps to explain how an atherosclerotic plaque progresses through an interaction of processes; lipids don't just build up in the walls of the artery, they are also actively accelerating the damage.

Other Hypotheses

One observation that should be noted here is that of Earl Benditt of the University of Washington who has found evidence that all the smooth-muscle cells in a plaque are derived from one or a small number of cells. I can remember reading about this monoclonal theory back in the late 1970s and being fascinated by it: could there be some link between two big killers—heart disease and cancer? This tidbit of information seemed to sink into oblivion, primarily because it didn't fit; it didn't make sense in terms of the prevailing idea of the day that atherosclerosis is related to cholesterol levels, that it's a result of problems with lipid metabolism. But Benditt argues that the monoclonal original of the smooth-muscle cells found in the intima could be explained by a viral infection that causes cell proliferation. And it turns out that this may be the case in at least some forms of atherosclerosis. Researchers have found cytomeglia virus associated with some atherosclerotic lesions, though there is argument as to whether this is the cause of the lesions or just an aftereffect (Blakeslee 1991).

Another hypothesis that was developed in the 1970s links an amino acid called homocysteine, a product of methionine metabolism, to the development of atherosclerosis. The idea originated with Kilmer McCully who observed atherosclerotic plaques in the arteries of two children who had died of a genetic defect that elevated the homocysteine levels in their blood (Stacey 1997). McCully's research, which was for a long time ignored, has recently received a great deal of attention because several studies have verified the relationship between homocysteine levels and atherosclerosis (Nygård et al. 1997). Since homocysteine levels can usually be reduced by increasing folic acid and vitamin B6 and B12 intake, it is hoped that at least some forms of atherosclerosis may be treatable in this way. All this doesn't mean that cholesterol is not involved in atherosclerosis, but that damage done by homocysteine may allow for the buildup of fatty streaks.

Heart Attacks

As a plaque develops, the endothelium is disrupted and eventually destroyed, and the area of damage is covered with a fibrous cap which pushes out into the lumen of the blood vessel, making it more and more difficult for blood to flow around it. Eventually the plaque may become so large and unstable that the cap can rupture; this can either directly stop the flow of blood or can trigger the formation of a clot that has the same effect (Fuster et al. 1992). If the artery is large enough and the clot big enough, the result can be a myocardial infarction—a heart attack. Just writing the words "heart attack" fills me with terror, as the word "cancer" does, and with good reason. More than half the people who suffer massive heart attacks don't survive, but this statistic belies the fact that great progress has been made in the treatment of myocardial infarctions. Things are very different from the 1960s when my father was battling heart disease, and when little could be done to prevent the damage done to heart muscle by a clogged artery. Now powerful anti-clotting drugs, if used as soon as possible after the start of symptoms, can dissolve clots and restore blood flow quickly enough that muscle damage is minimized (Collins et al. 1997).

There is also a great deal that can be done to prevent the situation from getting this bad, to prevent a heart attack from occurring. If there is evidence for areas of blockage in the coronary arteries, these plaques may be compressed and blood flow restored with balloon angioplasty, in which a catheter is threaded through a coronary artery to the blocked area and then a tiny balloon is inflated at the artery's tip. Many times, this will compress the plaque and allow the blood to flow past the plaque more easily (Landau et al. 1994). Sometimes, this procedure doesn't work, or the plaque redevelops, and then bypass surgery may be done: the saphenous vein in the leg or the internal thoracic artery is sewn into a branch of the coronary artery to bypass a blocked area (Loop 1996). Often three, four, or even five such areas may be bypassed. This procedure requires open-heart surgery in which blood is diverted from the heart and lungs, with blood circulation and oxygenation maintained with a heart-lung machine.

In my review of research on the heart, I read a large number of articles on both these procedures which are now so commonly performed that it is possible to do large-scale studies on their outcomes. Obviously, bypass surgery is more costly and entails greater risk than does angioplasty. For some patients, the long-term outcome is not that different with the two procedures, especially when angioplasty is followed with medications that lower cholesterol levels or control blood pressure (Hillis & Rutherford 1994). A lot depends on how severe and numerous the blockages are. Both procedures carry with them the risk that blockages will recur. To help prevent this after bypass surgery, stents or tubes are inserted into the arteries during angioplasty to keep the artery open. There is also a form of angioplasty called atherectomy in which the plaque is cut away (Bittl 1993) and another in which a laser at the end of the catheter is used to burn away the plaque.

Medical Research

The results of medical studies are often equivocal, and here it is important to note the problems of medical research. Rarely does one study produce truly definitive results in medicine. Research studies published over several years reveal that the picture gradually becomes clearer as to when to use a particular procedure and on which patients. In an ideal study, it would be nice to have a hundred people, all of the same age, sex, and genetic background, and all with exactly the same types of blockages in the coronary arteries, and then to divide this

group in two and perform, for example, angioplasty on one group and atherectomy on the other and compare the outcomes in the two groups. But such an experimental design is impossible with humans. The first issue is the size of the available patient pool. There are two ways of insuring that there are enough patients in the study to make it possible to get statistically valid results. One is to use as many patients as possible at one location, but this usually means enrolling a rather heterogeneous group. The other approach is to have many medical facilities involved, thus providing a much larger patient pool to draw from, so that either a very large group or a smaller group with a narrow range of characteristics can be enrolled. But a large multi-facility study is usually much more costly, economics being one of many factors restraining experimental design.

It is the desire to reduce variables as much as possible that has led to so many studies only enrolling members of one sex, and in the case of research on heart disease, it has usually been males who were chosen. This has created a problem in the treatment of women with heart disease because the evidence is mounting that women often experience different symptoms and have different responses to treatment, so approaches that have been found to work well with male patients may not necessarily be effective with women (Henig 1993). But as Marcia Angell (1993) points out, while this situation is regrettable, there were often valid reasons for focusing on males, such as reduction of variables and the fact that men often develop heart disease at an earlier age.

Another important consideration in how a study is designed is the use of controls. While results on one or two patients are sometimes published because of the rarity or interest of the case, controlled studies are the only way valid comparisons can be made. But no matter how carefully designed a medical study is, it always has some flaws: the patients could have been studied for a longer period of time, a greater variety of treatment options could have been compared, only patients with more clearly defined symptoms or with a narrower range of disease progression could have been enrolled, etc., etc. What all this amounts to is that no one study is definitive; many studies, with differing emphases, have to be carried out before any treatment is considered effective. It is becoming more common now to do a meta-analysis of a particular issue; this is a procedure in which the results from a number of studies are combined and statistical tests are done on the pooled data. This has the advantage of providing results on a large number of patients, and it also tends to even out slight differences between the studies.

Two Hearts

But besides being viewed as an object of medical research, the heart can also be seen in a very different way, as John Stone notes in his book *In the Country of Hearts* (1990) where he tells of his experiences as a cardiologist. In the introduction, he writes that each of us really has two hearts, the one that is beating in our chest and that electrocardiograms and bypass surgery can be done on, and the other, our emotional heart, the heart of Valentines and love poems (A.R. Ammons's poem to his wife on her birthday which just appeared in *The New Yorker* is at the moment one of my favorites). In thinking about atherosclerosis and atherectomy, angioplasty and endothelium, it is easy to lose sight of this other heart, but in many ways it is as real and as important to health as the first heart. This is the main point of Charles Siebert's article, "The Rehumanization of the Heart," that appeared in 1990 in the February (of course!) issue of *Harper's Magazine*. Siebert focuses on the artificial heart that had been implanted in several individuals with very poor results during the 1980s. He argues that part of the problem was that the heart and the way it functioned was very foreign to the body. The heart's power source was a large array of batteries kept in a cart to which the patient was tethered, and a noisy air pump was used to move blood through the body, so the patient was never liberated from physical attachment nor from the sound of the mechanically steady beat of this machine. Thus Siebert argues that the artificial heart only replaced one of the two hearts that Stone referred to and was therefore a most inadequate device.

Though the artificial heart is no longer employed, a number of implantable devices that assist the heart are being used (Wickelgren 1996). Since the left ventricle is the heart's most muscular chamber and the one that has to work the hardest because it pumps blood through the body, it's not surprising that it is the chamber most seriously damaged by heart attacks, infection, and other diseases. There is now a left-ventricle assist device (LVAD), a pump that is implanted in the abdomen and attached to the heart, with a power pack worn externally. The LVAD does the work of the left ventricle, making it possible for many people with failing hearts to function much more normally than in the past. This device is very different from the device Siebert was criticizing; the LVAD is light-weight enough and unobtrusive enough to allow relatively normal activity.

A Material Problem

At the time artificial hearts were being used, I can remember reading that the main problem with the artificial heart was with the material from which it was made. This struck me as odd; surely the major problems must be with the design, with the structure of the organ. But no, most of these difficulties had been ironed out, yet despite all their work and research, the developers were unable to come up with a material that did not cause the rupture of platelets and thus blood clotting. In other words, they couldn't duplicate the endothelium, that layer of sophisticated cells so important in determining what happens in blood vessels. Because the formation of clots couldn't be prevented, those with artificial hearts suffered strokes caused by blood clots that traveled to the brain. So the irony was that while their heart replacements worked reasonably well, it was at the expense of their brains, hardly an attractive bargain.

With all attempts to fix the heart, or any other part of the body for that matter, there is always a price to pay. As I often tell my students, a replacement part is never as good as the real thing—*if* it is working well. An example of this is the story of a physician named John Harrington (1993) who wrote wittily of his experiences with valve replacements in *The New England Journal of Medicine*. As a child—just before penicillin became available—he had rheumatic fever. Though this infection left him with a heart murmur and he knew he would eventually need a new aortic valve, he always managed to convince himself that "such an operation lay 10 years away from whatever day it was" (p. 1345). When he began to have trouble exercising, he knew the day had come. He chose to have a bioprosthetic valve inserted, one made from the pericardium of a cow. The alternative, a mechanical valve, though more likely to last a long time, would have meant that he would have to take anticoagulants because such valves are clot-producers (the material problem again).

Harrington's replacement valve lasted over eight years, but finally went with a bang. One morning at breakfast,

he suddenly experienced intense chest pain because one of the valve's cusps had torn loose. As he describes it:

Remaining true to the code, I didn't say anything. And being brilliant, I walked up a flight of stairs to get away from the kids (p. 1346).

Fortunately, his wife had enough sense to follow him upstairs and call an ambulance. At the end of that ride, he got another valve, a mechanical one. This time, the durability of something called a Saint Jude valve now seemed worth the price of anticoagulants. This story is an interesting example of how risks must be weighed in making treatment decisions, especially ones that will have such long-term consequences, and how the relative weight of risks may change over time and from patient to patient.

Valve replacement is also a good example of the wonderful kinds of treatments that the heart-lung machine made possible. Before its development in the 1950s, there was almost nothing that could be done for someone with a diseased valve like Harrington's. [I *have* to mention *The Scalpel and the Heart* (Richardson 1970), a wonderful book of the early struggles to operate on the heart.] Now the mortality rate from valve surgery is less than 1%. Not only can valves be replaced, but holes in the heart closed, and birth defects repaired. Stone gives a particularly good explanation of how the set of four birth defects called the tetralogy of Fallot is repaired. In fact, Stone's book is filled with interesting essays on various aspects of cardiology, from heart murmurs to the history of the stethoscope. And I should note here that reliance on sophisticated technologies seems to have blunted doctors' expertise with this symbol of the medical profession. A recent study found that heart defects were identified by resident physicians during physical examinations with a stethoscope only about 30% of the time, while that number is over 70% among those who regularly use this instrument (Grady 1997). This creates a problem because despite all the technology now available, many heart malfunctions are first discovered by doctors during physical examinations; the stethoscope still has an important role to play in modern medicine.

Exercising the Heart

When I think of a stethoscope, I think of Dr. Warner, our family doctor, who treated my father's heart condition as best he could. I can remember my father returning home from the hospital after one of his heart attacks, and facing the problem of climbing the stairs to the bedroom. In the 1960s, heart patients were not to overexert themselves, and before leaving the hospital there would be negotiations about how many times a day—and at what pace—my father could climb the stairs. Now heart patients are often enrolled in exercise programs that involve jogging, swimming, and bicycling, a far cry from the leisurely walks I often took with my father. In "Secrets of the Heart" (1996), Mair Zamir (a mathematician no less) explains why the approach to physical exercise has changed so much in the past 30 years.

Researchers have found that the arteries of the heart form a tree, rather than a mesh-like structure. With a mesh, if one branch became clogged, others in the area could grow larger and take up the slack, with a tree, however, little of this happens. But if this is so, why doesn't constriction of the arteries become obvious, that is, result in the pain of angina in oxygen-deprived muscle until an artery is 90% or even 95% occluded? The answer is that the arterial tree in the heart is a very dense one. As Zamir notes:

In some places (such as the walls of the left ventricle, which does the heavy work of pumping blood through the body) the vasculature is so dense that it is hard to see where there was room for the muscle fibers it served (p. 29).

And normally, each artery can widen to provide more blood when the heart muscle is stressed with exercise. With this rich blood supply, it is not surprising that the heart can make do on the blood that reaches it, even when an artery is 90% clogged. It is only when the occlusion is very severe that the remaining blood vessels reach the limit of their capacity to respond during exercise. The advantage of regular exercise is that it keeps the blood vessels flexible so that they are better able to expand and provide the heart with sufficient oxygen during physical exertion. Exercise also triggers the growth of more small arteries, again making the heart more efficient.

When I started to write this column, I wanted to include everything I had learned about the heart as I dipped into the latest research. But it soon became apparent that in a field so active as this all I could do was mention a few items I found particularly interesting. I hope that even this brief survey indicates how exciting and hopeful this field is, and also how much work is still to be done. My father had a very inquisitive mind, and I think he would be fascinated by what is known about the heart today. I wish I could sit down and discuss it with him.

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