Coronary Artery Spasms and Heart Disease

Brief, periodic constrictions of the coronary arteries may cause angina and even heart attacks in some people

The woman lying in the catheterization laboratory of the Clinical Center at the National Institutes of Health (NIH) was about to undergo an experimental treatment for relief of her steadily worsening chest pains. Only 54 years old, she had suffered for several years from angina pectoris, a painful and sometimes incapacitating condition caused by an insufficient flow of blood to the heart.

Coronary angiography, a diagnostic technique that allows physicians to visualize the arteries carrying blood to the heart muscle, had shown that one of the woman's coronary arteries was almost completely blocked by atherosclerotic plaques—or so her doctors thought. To open up the blood vessel, cardiologists at the National Heart, Lung, and Blood Institute (NHLBI) were going to insert a balloon-tipped catheter through an artery in the groin. After carefully threading the catheter tip to the blocked segment of coronary artery, they would inflate the balloon, thus compressing the atherosclerotic plaques against the arterial wall and allowing the blood to flow freely once again. "But before inflating the balloon," explains the NHLBI's Kenneth Kent, "we first inject nitroglycerin [a drug commonly used to treat angina] into the coronary artery to relax it and prevent it from constricting around the balloon." What the physicians subsequently saw on the monitor used to follow the catheterization procedure came as a surprise. Immediately after the nitroglycerin injection, the artery opened up. "And then," says Kent, "we stopped what we were doing."

The woman's coronary artery had not been blocked by atherosclerosis after all. The arterial constriction and her angina were caused instead by spasms of the blood vessel wall that almost closed off the artery. Such spasms can be treated with drugs and, according to Kent, the woman is doing well, as is another who had a similar experience.

Coronary artery spasms, like those suffered by the NIH patients, are now becoming a hot topic among cardiologists, who are increasingly recognizing the spasms as a cause of angina and even of heart attacks themselves. Kent says, "Lately, they are the most common thing talked about at meetings."

It seems that the more cardiologists look for the spasms, the more readily they are finding them. Eugene Braunwald of Harvard Medical School estimates that "they are pretty important for perhaps 25 to 30 percent of coronary patients." Most of these patients also have atherosclerotic disease but, he points out, "Like so many other areas in clinical medicine, there may be a combination of two factors causing a patient's problems. If you can solve one, you can improve the patient's condition." Although coronary atherosclerosis may not be readily reversible, a group of new drugs, sometimes called calcium antagonists, appears to hold a great deal of promise for controlling the arterial spasms and thus helping the patient.

The idea that coronary vasospasms might cause heart disorders is not new. Clinicians such as William Osler considered the possibility in the early 20th century. But the dominant view, especially during the past 30 to 40 years, has put all the blame for angina and heart attacks on atherosclerotic plaques that build up in the coronary arteries and cut down blood flow to the heart muscle.

Although the blockage might not cause problems for the person at rest, the theory goes, when the heart works harder for any reason, the coronary blood flow may not be adequate to meet the increased demand for oxygen and the individual may suffer the pain of angina. In the case of total blockage of the coronary arteries, a heart attack—actual death of a portion of the heart muscle—might occur.

There were always a few observations that did not quite fit this neat picture, however. Occasionally, little or no atherosclerosis would be found in the coronary arteries of a person who had angina or who had had a heart attack. In addition, some angina patients experienced most of their chest pains while they were at rest and not while engaged in an activity that would increase the heart's demand for oxygen.

In 1959, Myron Prinzmetal, who was then at Cedars of Lebanon Hospital in Los Angeles, renewed interest in coronary artery spasms when he described a form of angina that he labeled variant be-

Heart Research Revisited

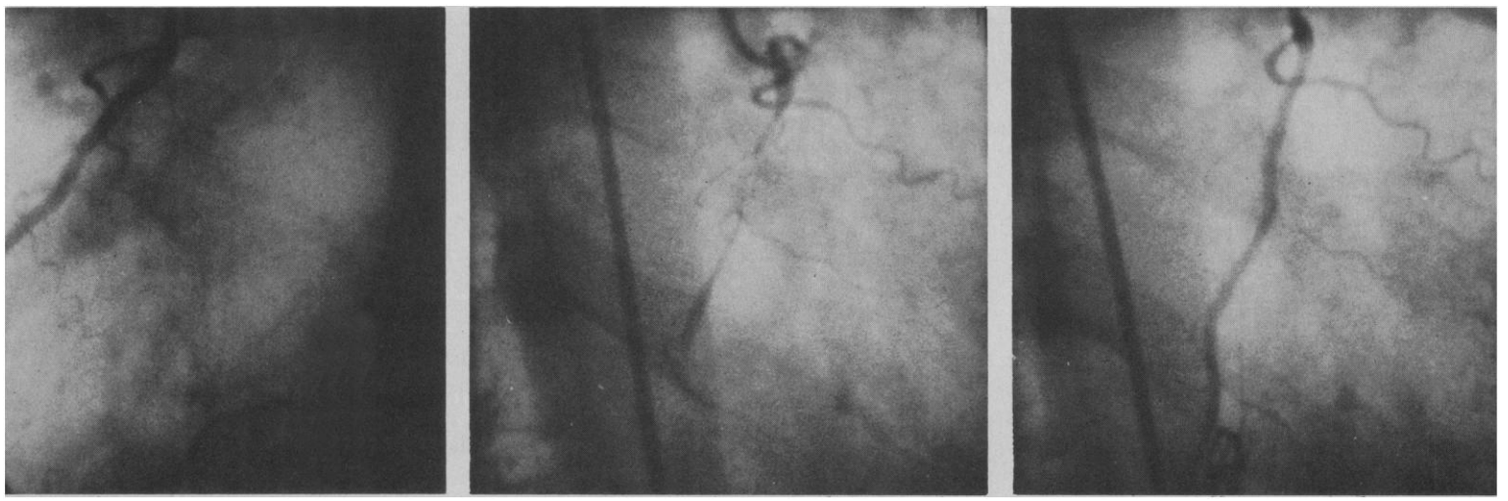
Cutting the toll taken by heart attacks, this nation's number one killer, continues to be a prime goal of health researchers. Two recent developments have, on the one hand, opened up a promising new avenue of investigation that may lead to more effective therapies for some coronary disease patients, and, on the other hand, added more confusion to an already muddled issue.

The promising development is the discovery that spasms of the coronary arteries may be more important as a cause of angina and heart attacks than had been previously recognized. The research also suggests that the spasms may be very amenable to treatment by a new class of experimental drugs.

Meanwhile, the Food and Drug Administration added new controversy to that already surrounding the use of anti-platelet drugs for the prevention of cardiac deaths (*Science*, 22 February, p. 859) when it failed to approve one of these drugs, called Anturane, for use during the first 7 months after a heart attack. Anturane had been highly touted for reducing "sudden death" during that period.

This issue of *Science* will take a look at both of these recent developments in heart research.

0036-8075/80/0606-1127$01.00/0



Angiograms showing a coronary artery spasm. On the right is an angiogram of an essentially normal right coronary artery. The middle figure shows a different view of the same artery, now almost completely occluded by a spasm. Approximately 5 minutes later, the spasm is over and the artery appears almost normal again, although some slight irregularities remain. [Reprinted with permission from Chest *65, 573 (1974)]*

cause it differs from the usual sort in several respects, including the frequent occurrence of chest pains in patients at rest. Often the patients experience the pains at about the same time of day, frequently in the early morning hours. They also have a characteristic change in their electrocardiograms (ECG's), an elevation of a portion of the tracing—the ST-segment—that is not usually found in other angina patients. Prinzmetal suggested that variant angina might be caused by coronary artery spasms that temporarily restrict blood flow to the heart. In this situation, as Braunwald describes it, "the supply problem gets worse, not the demand problem." In the past few years, several investigators, including Philip Oliva of the University of Colorado Medical Center and Atillio Maseri, who recently moved from the Medical University of Pisa, Italy, to London University Medical School, confirmed Prinzmetal's suggestion that coronary artery spasms are the principal cause of the pain of variant angina.

Beginning in the early 1970's, Maseri and his colleagues performed an especially extensive series of investigations on more than 200 patients hospitalized for angina at rest. They found no indications that the angina attacks occurring at rest in these patients were ever preceded by increased demand of the heart for oxygen. For example, neither the heart rate nor the blood pressure of the patients increased before the attacks.

But the investigators did observe spasms in the coronary arteries of patients who underwent angiography during an attack. Moreover, using a new technique that permits the measurement of blood flow to the heart muscle, they were able to demonstrate reductions in that flow during the attacks. The portion of the heart receiving the reduced flow generally corresponded to the region thought to be oxygen-deficient (ischemic) on the basis of the ECG readings. All in all, Maseri concluded that restricted blood flow caused by coronary artery spasms, and not increased demand by the heart, caused the resting angina of his patients.

Just how many people have the spasms is unclear. There is general agreement about their role in Prinzmetal's variant angina, but individuals with this condition constitute only a small proportion—less than 5 percent—of all angina patients. But the spasms are apparently not limited to variant angina, and Maseri, for one, thinks their importance has been generally underestimated. He has observed them in patients who have the more typical type of angina.

There is also evidence that coronary artery spasms may initiate a heart attack. Eight of the patients studied by Maseri, and in whom he had observed spasms, had heart attacks. In all cases the dead heart muscle was located in the region that became ischemic during the spasms. Maseri's findings suggest that heart attacks may have occurred in some of these patients as a result of more permanent blockage of the constricted arteries, possibly caused by clot formation at that site.

Further support for a role for coronary artery spasms in heart attacks comes from Oliva. He has detected the spasms in about 40 percent of a group of heart attack patients studied within 6 hours of their attacks. Although these spasms may have been the result rather than the cause of the heart attacks, the demonstration that the arteries supplying the dead heart tissue may not be completely blocked after the event supports the idea that a transient constriction in a partially occluded vessel can cause a heart attack.

The cause of the coronary artery spasms is not completely understood, although they may be triggered by the nervous stimulation of certain receptors, called α-adrenergic receptors, located in the coronary arteries. Certain chemicals, when released from nerve endings, bind to these receptors and elicit constriction of the arterial walls. Such constriction is part of the normal controls regulating arterial blood flow, but if it is excessive or occurs at the wrong time, spasms and angina pains might occur.

Evidence involving the α-adrenergic receptors in spasms comes from the laboratory of Hirofumi Yasue and his colleagues at the Shizuoka City Hospital in Japan. They have shown that two drugs, which are known to bind specifically to α-adrenergic receptors and prevent their activation, suppress the angina attacks of patients with Prinzmetal's angina.

There is also evidence that atherosclerotic blood vessels are more susceptible to the spasms than normal ones. For example, Braunwald found that patients known to have coronary atherosclerosis undergo greater constriction of the coronary arteries when exposed to a cold stress (immersion of the hand in a bucket of ice water) than do people with more normal coronary arteries. Here, too, a drug that blocks the α-adrenergic receptors prevented the coronary vasoconstriction, again suggesting that the receptors play some role in triggering the spasms.

In addition, Philip Henry of the Washington University School of Medicine

has shown that vasoconstricting agents induce spasms much more readily in the atherosclerotic coronary arteries of experimental animals fed a high cholesterol diet than they do in normal arteries. According to Henry, normal arteries, when incubated with cholesterol, also show increased constrictor responses. He hypothesizes that the increase is caused by incorporation of some of the added cholesterol into the membranes of the arterial smooth muscle cells, similar to the cholesterol incorporation that occurs in the early stages of atherosclerosis. The added cholesterol might alter the membrane properties with the result that the cells become more susceptible to contractile stimulation.

Not only may nervous impulses acting through the α-adrenergic receptors evoke coronary vasoconstriction, but certain chemicals may also do so. The blood platelets, which are small cells needed for blood clotting, release at least two such chemicals. One is thromboxane A_2, an extremely potent local vasoconstrictor. The other is serotonin, which also serves as a transmitter for some nerve cells. Serotonin acts by binding to receptors, and work in Henry's laboratory suggests that the increased sensitivity of atherosclerotic arteries to vasoconstriction may involve enhanced responsiveness of the receptors for serotonin. Release of serotonin and the thromboxane by platelets is more likely at regions of blood vessels that have been damaged—by atherosclerosis, for example.

Although atherosclerotic plaques may foster spasms, they are not absolutely required, as Maseri has shown. The spasms of many of the patients he studied occurred at the site of existing plaques, but in others—perhaps in 10 percent of the individuals—the constricting arteries were free of plaque buildup. In fact, Maseri tells of a 24-year-old woman who had angina and who suffered a heart attack 2 weeks after tests identified severe spasms in an otherwise normal coronary artery. The damaged area of her heart was supplied by the artery in question. These results suggest that spasms alone may cause the coronary problems of some patients.

The presence of the spasms has definite therapeutic implications for the patients, especially those who do not have atherosclerotic coronary arteries. For example, Yasue found that propranolol, a drug often used to treat angina, abnormal heart rhythms, and high blood pressure, may exacerbate the symptoms of spasm-induced angina. Propranolol is a β-blocker—that is, it combines with β-adrenergic receptors to prevent the binding of the neurotransmitters or hormones that would otherwise activate these receptors. Activation of the β-adrenergic receptors in blood vessels causes their dilatation, an effect opposing the constriction induced by activation of the α-adrenergic receptors. With the β-adrenergic receptors blocked by propranolol, the effects of the α-adrenergic receptors may dominate and spasms may be more readily produced.

Moreover, the coronary bypass operation, which is often used to treat severe angina, may not benefit individuals for whom spasms are the major problem. In any event, the operation may be unnecessary for these patients because the calcium antagonist drugs currently under development appear effective for controlling spasms. They are "almost miracle drugs for this problem," says John Schroeder of the Stanford University Medical School. The drugs apparently prevent constriction of the coronary arteries by inhibiting contraction of the smooth muscle of the vessel walls.

The term calcium antagonist was coined about 13 years ago by Albrecht Fleckenstein of the University of Freiburg, Germany. At the time he was studying the drug verapamil, which is now widely used in Europe for treating certain abnormal heart rhythms. Fleckenstein proposed that verapamil depressed contraction of heart muscle by preventing calcium's action as the signal for coupling excitation of the muscle cells to contraction. Diltiazem and nifedipine are two additional drugs that have calcium blocking effects.

The three drugs primarily affect cardiac and smooth muscle contraction by blocking the movement of calcium ions into the cells from the outside—an influx that occurs when the cells are stimulated to contract. Once inside, the calcium ions turn on the contractile apparatus. Calcium ions also serve as the excitation-contraction coupler in skeletal muscle, but here the ions are released from internal storage sites rather than flowing in from outside. The calcium antagonists have little effect on the internal calcium release of skeletal muscle.

Although verapamil, diltiazem, and nifedipine all block inward movement of calcium ions, each has a somewhat different range of effects both in laboratory test systems and in human patients. Investigators are not yet sure whether all the drug actions can be attributed to their calcium antagonism. Says Arnold Schwartz of the University of Cincinnati College of Medicine, "We are still in a state of flux about how and where the agents act."

Clinical experience with the calcium antagonists has been more extensive in Europe and Japan than in this country, where none of the agents has been approved for use by the Food and Drug Administration. Clinical trials are proceeding here, however, and producing promising results. In one cooperative study, the results of which were described by Elliott Antman of Peter Bent Brigham Hospital at last fall's meeting of the American Heart Association, the effectiveness of nifedipine was tested in 100 patients with variant angina or proved coronary artery spasms. Almost 80 percent of the patients taking nifedipine had at least a 75 percent reduction in the frequency of their angina attacks; the attacks were abolished in about 60 percent of the patients. In another, smaller study, Schroeder found that diltiazem gave complete or almost complete relief of angina attacks in six of seven variant angina patients. The seventh patient responded partially.

The presence of the spasms has definite therapeutic implications for the patients, especially for those who do not have atherosclerotic coronary arteries.

Schroeder and Braunwald agree that the side effects of the calcium antagonists are relatively mild compared to those of other long-acting drugs, principally nitrates, given to treat variant angina. There have been gastrointestinal disturbances and lowered blood pressure, which is probably the result of the drugs dilating peripheral blood vessels, but "no major league problems," according to Braunwald.

With an effective method for treating coronary artery spasms at hand, their diagnosis has become more important. It is not always possible to catch an artery in

spasm on its own, but Schroeder has devised a test that can pick up the problem more readily. It requires the administration of a drug called ergonovine maleate, a known vasoconstrictor, to patients who are undergoing coronary angiography. This drug induces spasms in coronary arteries that are susceptible to them. Although the test sounds dangerous, Schroeder says that the spasms are easily relieved by nitroglycerin and that coronary angiography with ergonovine maleate administration is no more dangerous than the angiography without it. He concludes that it is a safe test for coronary spasms in patients whose symptoms cannot be explained by atherosclerotic blockage of their coronary arteries.

The calcium antagonists may be useful for treating other heart problems in addition to coronary artery spasms. Researchers, including Robert Jennings of the Duke University Medical School, have shown that one of the earliest changes produced during ischemic damage of the heart is accumulation of calcium ions by the cells of the affected region. This has prompted suggestions that the calcium antagonists may be valuable for limiting the damage caused by a heart attack. Henry and his colleagues have shown that nifedipine prevents calcium accumulation in isolated rabbit hearts subjected to oxygen deprivation and also prevents the rigid contraction that usually occurs in such oxygen-deprived hearts.

Rigid contraction is one of the hallmarks of a condition called stone heart that sometimes occurs in patients who have been put on a heart-lung machine for cardiac surgery. The surgeon occasionally finds that the heart, which is in this state as a result of oxygen deprivation, does not beat properly, if it beats at all, when it is reconnected to the body's circulatory system. Henry has shown that nifedipine prevents this form of heart failure in dogs put on cardiopulmonary bypass for 2 hours—enough time to kill the control dogs who were not treated with the drug. The Washington University group is now testing the drug for prevention of stone heart in human patients.

Another way in which the calcium antagonists may help to limit damage to heart muscle is by dilating, and thus increasing the flow of blood through whatever vessels remain open after a heart attack. Schwartz, with Ronald Millard, who is also at Cincinnati, showed that diltiazem has this effect on both pigs and dogs in which they induced artificial heart attacks. Henry found a similar effect of nifedipine in dogs.

Currently, then, the calcium antagonists are being tested as therapies for coronary artery spasms, cardiac arrhythmias, stone heart, and heart attacks. If they continue to work out, cardiologists will have a potent new weapon for combating a wide range of coronary problems.—JEAN L. MARX

FDA Says No to Anturane

Controversial study of Anturane fails to show that the drug prevents "sudden death," FDA says

Each year, 1 million people suffer heart attacks and of them 400,000 survive. But the survivors are still at a high risk of dying—one out of eight will succumb within the year, many from "sudden death," a somewhat poorly defined term meant to connote a death caused by abnormal heart rhythms.

Since sudden deaths in the first year after a heart attack are such a formidable public health problem, the medical community was elated by reports that Anturane, a drug widely used for the treatment of gout, might prevent them. The evidence was from a clinical trial funded and designed by Ciba-Geigy (which makes Anturane) but conducted by independent members of the medical community.

In January, the final report from the trial was released. Anturane, it said, reduced the sudden death rate by 74 percent from the second through the seventh month following a heart attack. The total mortality rate was also reduced, but by an amount just short of statistical significance. Interest in the report was great and it received much favorable publicity.

On the basis of the reports from the Anturane study, an advisory committee to the Food and Drug Administration (FDA) recommended that the agency approve Anturane for the prevention of sudden death. But on 25 April, the FDA said no on the grounds that the case for Anturane is not persuasive.

Ciba-Geigy disagrees with the FDA and in a prepared statement says it "is confident that in cooperation with the FDA the differences will be resolved and Anturane will be found to be useful in preventing sudden death following a heart attack."

Ironically, the Anturane trial was never expected to show that the drug prevents sudden death, and there are no good explanations for how it may do so. The working hypothesis was that the drug might prevent heart attacks in patients who had already survived one. A heart attack is caused by an obstruction in a coronary artery that, by preventing the heart from getting an adequate supply of blood, actually causes the death of a portion of heart muscle. Usually it is accompanied by chest pains and characteristic electrocardiogram tracings. One of the possible causes of a heart attack is the formation of blood clots in the coronary arteries. Anturane inhibits blood clot formation by stopping platelets from clumping. So, the theory went, Anturane might prevent heart attacks.

While Ciba-Geigy was testing Anturane, the National Heart, Lung, and Blood Institute (NHLBI) was also testing the hypothesis that drugs that inhibit clotting could prevent subsequent heart attacks in patients who already had survived one. The heart institute's trial compared aspirin (well known for its effects on platelets) and a placebo. The NHLBI trial showed no effect of aspirin in decreasing the mortality rate of heart attack victims, but most of the study participants began taking aspirin at least 6 months after their heart attacks. It remains possible that the drug might be effective if given earlier.

The Anturane study and the NHLBI study were concluded at about the same time and the Anturane results were released just before those of the NHLBI. But despite the apparently dramatic decrease in the sudden death rate among Anturane users, there was some feeling

0036-8075/80/0606-1130$00.75/0