Bloodsuckers Reconsidered

Leech saliva inspires a medical quest

By KATHY A. FACKELMANN

The year is 1787. A woman suffering from dropsy lies face-down on the bed as her physician administers a time-honored "cure." He sweetens the woman's skin by rubbing in a sugary solution, then pulls a jar of yellow-striped leeches from his bag. Gingerly, he places the bloodsuckers one by one on her back, where the hungry creatures, enticed by the sugar, extract more than a liter of blood.

For centuries, physicians turned to leeches to counter ailments ranging from heart disease to headaches. By the early 20th century, leeches had lost their grip on medical practice as doctors realized that bloodletting usually did more harm than good. But new scientific findings hint that physicians may once again find value in the lowly leech.

Researchers are now studying a genetically engineered version of hirudin, a powerful blood thinner found in the saliva of the European leech *Hirudo medicinalis*. Their preliminary findings suggest the clot-blocking prowess of the recombinant version may rival that of natural hirudin. If so, the compound may one day provide an alternative to the well-known blood thinner called heparin, and perhaps save lives now claimed by heart attacks.

Cardiologist Valentin Fuster is one of several scientists racing to confirm hirudin's clot-blocking efficacy. He predicts that hirudin may prove "a real miracle" in the treatment of clots that can shut off the heart's blood supply and thus trigger heart attacks. Such clots are particularly lethal when cholesterol clogs the coronary arteries that normally supply the heart with oxygen-rich blood, says Fuster, of the Mount Sinai Medical Center in New York City.

Fuster's quest for a better clot-blocker began with a study designed to explore hirudin's ability to reduce the risk of heart attack after angioplasty, a procedure in which physicians snake a catheter through the coronary arteries and inflate a tiny balloon that compresses the artery-clogging plaque — thus enlarging the narrowed vessels.

Although angioplasty can save lives, the catheter can damage the vessel wall and trigger the very thing doctors are trying to prevent — a blood clot that precipitates a heart attack, says James H. Chesebro at the Mayo Clinic in Rochester, Minn. To reduce that small but lethal risk, physicians now give angioplasty patients the anti-clotting drug heparin. However, heparin sometimes fails to ward off clots, Chesebro says.

Fuster and Chesebro compared heparin and recombinant hirudin's clot-protection power in a study of 50 pigs, whose cardiovascular systems resemble those of humans. Using recombinant hirudin from the Ciba-Geigy Corp. of Ardsley, N.Y., one of a dozen pharmaceutical companies developing hirudin-like drugs, they randomly assigned four-month-old pigs to receive infusions of a placebo, heparin or hirudin at one of three different doses. Then the team performed angioplasties in the left and right carotid arteries. They used brain arteries because the far smaller coronary arteries pose many surgical difficulties. After the procedure, the team administered a lethal dose of a narcotic, then removed and studied sections of the catheter-damaged arteries.

In comparing the arteries, they discovered that the engineered hirudin was about 10 times more effective than heparin at preventing clots, Fuster says.

Photographs of the hirudin-treated arteries revealed a single layer of cell fragments, called platelets, plugging the injured areas of the artery walls. By contrast, photographs of arteries from heparin-treated pigs showed multiple layers of platelets — a snapshot of a clot in progress, says Lina Badimon, a physiologist at Mount Sinai and a coauthor of the study, reported in the October 1990 CIRCULATION.

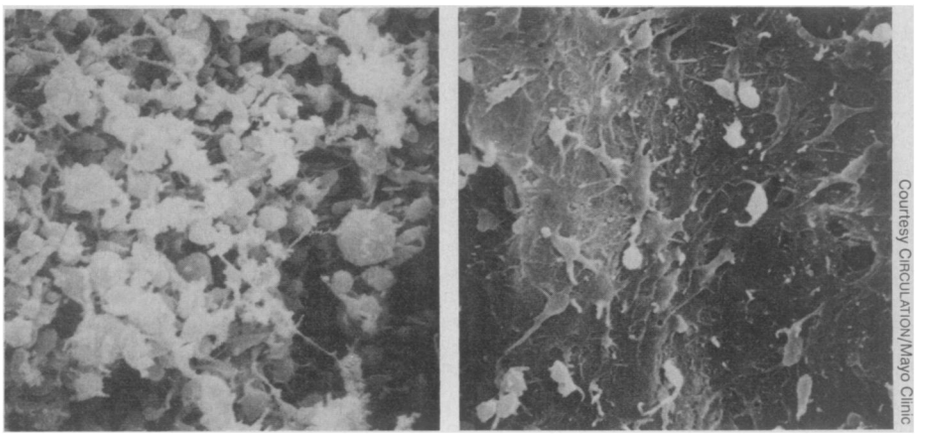
Indeed, the team found potentially deadly blood clots in 76 percent of the placebo-treated arteries and 57 percent of the heparin arteries. By contrast, pigs receiving hirudin at the two higher doses showed no evidence of clotting, a finding that suggests the experimental drug may one day ward off clots in people recovering from angioplasty, Chesebro says.

The researchers believe hirudin's effectiveness results in part from its ability to bind directly to an enzyme known as thrombin, which the body uses to produce fibrin, the "glue" that holds platelets and red blood cells together in a gelatinous clot. More important, hirudin appears to keep thrombin from initiating platelet clumping, a process that can end in a full-blown clot, Fuster says.

Because heparin cannot bind directly to thrombin, it must bind to another substance, antithrombin III, which in turn inhibits thrombin. This indirect mechanism sometimes fails to block clotting, Fuster says.

Clot-blocking may represent just one of hirudin's pharmaceutical talents. The researchers suspect this drug may also enhance the clot-dissolving power of other drugs, such as streptokinase or tissue plasminogen activator (tPA). Physicians inject such drugs during a heart attack to disintegrate clots blocking blood flow to the heart. This strategy can provide dramatic relief if the drug busts the clot in time.

Fuster and Chesebro's group decided to test hirudin's potential for dissolving the clots that invariably form following atherectomy, the surgical scraping of



Courtesy CIRCULATION/Mayo Clinic

Left: Scanning electron micrograph shows platelets clustering at injured site in the carotid artery of a pig treated with placebo. Right: Carotid artery from hirudin-treated pig shows only a few platelets sticking to the damaged area.

plaque and healthy cells from the inside of vessel walls. Again using pigs, they reamed out the carotid arteries of 16 animals. Then they injected three pigs with a placebo, six with tPA and seven with a dual regimen of tPA and recombinant hirudin.

The double-drug infusion unclogged all seven arteries within about 30 minutes, the team reported last November at the American Heart Association's scientific sessions in Dallas. By contrast, tPA cleared just two of six arteries and took longer to bust the clots – up to two hours in one case. Arteries from the three pigs receiving the placebo remained completely blocked with the clots that had formed after the invasive scraping procedure, Chesebro adds.

But pigs aren't people, and the investigators say they have a long way to go before hirudin gets Food and Drug Administration approval.

First, they must demonstrate the drug's safety. The team has already taken a step in that direction with the initiation of a small trial of recombinant hirudin in people with coronary artery disease. Unpublished results from that pilot study indicate the drug does not cause excessive bleeding, the researchers say, but they decline to offer further details.

If the safety study continues to go well, the researchers hope to begin a larger trial involving about 100 people with unstable angina, a risky type of chest pain caused by a blood clot. If hirudin can keep these clots from growing, the drug may short-circuit the lethal trend toward heart attacks in this vulnerable group, Fuster says.

Finally, the team wants to learn whether recombinant hirudin can boost the clot-busting power of drugs such as tPA when administered to people in the throes of a heart attack. However, Fuster adds, those trials may carry the biggest risks of excessive bleeding, and the researchers intend to proceed cautiously. □