[your healthy heart]

BY SHELDON H. GOTTLIEB, MD, FACC

VIPERS, VENOM, *And Life-Saving Snakes*

ARALDO DE LUCA/CORBIS

IMAGINE THIS: Cleopatra VII, soon to be the last Pharaoh of Egypt, is sitting in her throne room, thinking about the chances people take with their politics and their health. Her pet asp lies coiled in a basket at her feet....

"I foresee," muses Cleo, "that viper venom, after much testing and approval by regulatory agencies, will greatly benefit those with diabetes. Those few, thin, young people, with

sweet-urine wasting disease, who pass water like my chariot horses after battle, will live better lives by taking bioengineered viper venom. Those people whose bodies resemble the heavy blocks of the pyramids, whose urine flows sweet from too much rich food and not enough time spent digging in the soil, will be as numerous as reeds on the banks of the Nile. They too will take viper venom with their morning bagel and orange juice. As for me, dear asp, as I put you to my breast, I say, 'Goodbye, Julius Caesar and Mark Antony; hello immortality.'"

Snakes and snake venom have been an important part of medicine since, well, since there were patients and physicians. In the ancient Egyptian religion, the snake was the minister of Amon-Ra, the sun-god. Death by snakebite brought the victim immortality. The first animal that plays an active role in the Bible is a snake, and Moses protected his people against snakebite by carrying a copper snake banner. The wand of Aesculapius, the symbol of medicine and healing, consists of the familiar staff and coiled snake. The Medical Corps of the U.S. Army uses as its symbol the wand of Mercury, the messenger of the gods, which consists of two snakes coiled around a torch. And snake oil has made it to the dictionary as a substance used as a medicine without regard to its worth or properties. In folklore and in practice, snakes are respected, feared, and shunned.

But there is a snake, one of the world's deadliest, which should be near and dear to the heart of every person with diabetes: It is *Bothrops jararaca*, the Brazilian pit viper.

Most snake venoms poison nerves, or trigger massive bleeding and tissue breakdown. But *Bothrops jararaca* venom is unique: It causes blood pressure to plummet. Because of the striking effect of *Bothrops jararaca* venom on blood pressure, its potential medical uses were obvious for many years, but it was not until 1949 that scientists showed that *Bothrops jararaca* venom increased the production of a substance called bradykinin. Bradykinin, a potent chemical, directly dilates (expands) blood vessels, which causes blood pressure to drop.

By the early 1960s, it was known that the venom also inhibits the action of angiotensin converting enzyme, or "ACE," which converts an inactive substance in the blood and body tissues called angiotensin 1, to angiotensin 2. Angiotensin 2 is one of the most intense blood vessel constrictors and it plays an important role in blood pressure regulation. Angiotensin 2, by working in the brain, also regulates the sense of thirst.

VOLKER STEGER/SPL/PHOTO RESEARCHERS

Early attempts to produce a useful drug from *Bothrops jararaca* venom were crude and not very successful. Scientists were able to split the main active molecule of the venom, which is large, into small, active chunks of protein that did lower pressure. However, these protein chunks were expensive to synthesize, and they had to be given by intravenous injection.

By the mid-1960s, scientists knew the size and shape of ACE, and how it worked. They realized that one small part of the venom protein chunks must fit like a key into the ACE lock to block the ACE. Because they understood how ACE

worked, they were able to design a drug that blocked the ACE, could be taken by mouth, and was easy to make. This drug, called Captopril, is considered to be the first "designer drug." At least 10 related drugs have been developed; they are known as "ACE inhibitors."

ACE inhibitors have important protective effects on the heart, blood vessels, and kidneys. Besides effectively controlling high blood pressure, they also keep the heart from enlarging after a heart attack, they protect the inner lining of the blood vessels, and they protect the kidneys from damage caused by high blood pressure and diabetes.

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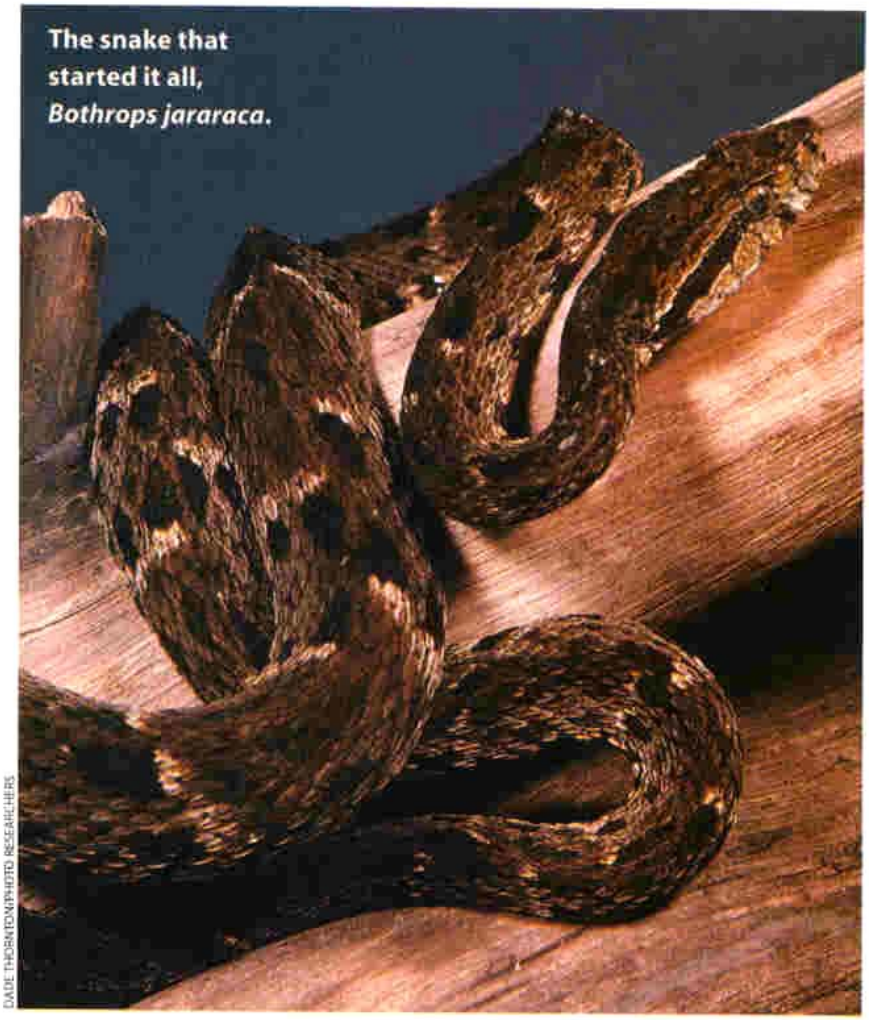
One recent clinical study, called the HOPE trial, was aptly named. In this study, ACE inhibitors protected high-risk patients both from developing diabetes and from dying. ACE inhibitors have been shown to reduce death and improve quality of life in patients with heart failure, and to markedly reduce the amount of protein spilled in the urine of patients with diabetes and kidney damage.

ACE inhibitors appear to have specific protective effects on the heart, blood vessels, and the kidneys, which are unrelated to their effect on blood pressure. They may keep the body from "turning on" certain damaging genes in response to heart disease and diabetes. Because of these protective effects, some studies suggest that ACE inhibitors should even be taken by diabetics who do not have hypertension or known cardiovascular disease.



The snake that started it all, *Bothrops jararaca*.

DAVE THORNTON/PHOTO RESEARCHERS

ACE inhibitors are now considered first-line drugs for use in treating hypertension or heart disease in patients with type 1 and type 2 diabetes. There is, however, one important exception: Because they affect the vascular system in so many ways, ACE inhibitors damage the developing fetus, and thus should not be taken by pregnant women.

So now you know how one of the world's most deadly snakes became a major player in the battle against heart disease and diabetes. Thank you, *Bothrops jararaca*, from the bottom of all four chambers of our hearts!

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