Breakthroughs in Bioscience

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FROM VIPER’S VENOM TO DRUG DESIGN:
TREATING HYPERTENSION

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COVER IMAGE: Isolation of compounds from the venom of the deadly Brazilian pit viper (Bothrops jararaca) was critical in development of certain drugs to treat hypertension. Snake photo courtesy of Dr. Ivan Sazima, Universidade Estadual de Campinas; graphic design by Corporate Press.
From Viper’s Venom to Drug Design:
Treating Hypertension
By Margie Patlak

During the dozen years that he was president, Franklin D. Roosevelt’s blood pressure steadily climbed. By the start of World War II, his consistently high blood pressure began to take its toll. It made him excessively tired, and plagued him with severe headaches. In his radio addresses at the time of the Yalta Conference, FDR was having such trouble breathing he was unable to complete sentences (Figure 1). Some historians believe Roosevelt’s weakened condition gave Stalin the advantage during the negotiations over post-war Europe—an advantage that put the fate of Eastern Europe in Stalin’s hands and changed the course of the 20th century.

There were no effective drugs for high blood pressure during the 1940s. Consequently, Roosevelt’s cardiologist was unable to control the condition and it eventually led FDR to his death at age 63 from a stroke. Writing about his experiences treating the president’s high blood pressure, (which he terms “hypertension”), Howard Bruenn lamented in the Annals of Internal Medicine, “I have often wondered what turn the subsequent course of history might have taken if the modern methods for the control of hypertension had been available.”

In the last 50 years, an impressive arsenal of medications that bring blood pressure down to normal levels in more than 95 percent of all patients has been developed. These drugs include dozens of medicines whose names are based on the different ways they work in the body. Diuretics, calcium channel and beta blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II-receptor blockers (ARBs) have extended the lives of millions of Americans and contributed to the more than 50 percent drop in heart attacks and strokes that has occurred in the last two decades within the United States.

Surprisingly, the successful development of such blood pressure medications hinged not just on the efforts of pharmacologists.
whose sole objective was to create them, but rather on a diverse array of scientists including biochemists, pathologists, physiologists and chemists. Many of these curious investigators were not directly involved in hypertension research, but instead were receiving government funding to pursue answers to such basic questions as how does a digestive enzyme do its job?, what role does the kidney play in salt and water excretion?, and why is snake venom so deadly? Thanks to their efforts, high blood pressure has been transformed from an untreatable, often fatal disease to a manageable condition that does not hamper the daily functioning of the two-thirds of older adults who have it in this country.

**Hazards of High Blood Pressure**

A major step on the way to controlling hypertension was the discovery, in the middle of the 20th century, that elevated blood pressure is a serious health problem and not a benign consequence of aging. By tracking the long-term health of thousands of individuals, government-funded studies, including the well-known Framingham Heart Study, uncovered that hypertension often fosters heart attacks, strokes, heart and kidney failure, and a deadly rupture of blood vessels (aneurysm). The risk of death from these conditions rises consistently as blood pressure increases into the abnormal range (Figure 2). These findings highlighted the need for medicines that adequately treated

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**Figure 2**: The damage chronic hypertension wreaks on arteries can be seen in these photographs of the internal surface of the aorta from a normal young adult, (left panel) and that from a patient with long-standing hypertension (right panel). Unlike the smooth surface of the artery in the left panel, the one on the right is studded with plaque deposits comprised of cholesterol and lipoproteins (irregular shaped yellow and brown areas indicated by the arrows). Hypertension injures the cells that line the inner surfaces of arteries such that blood cholesterol, lipoproteins and calcium are deposited in the vessel walls. Over years the vessels become narrow and rigid thereby impeding the flow of blood to vital organs. The end result is a greater likelihood of suffering a heart attack or stroke. *Courtesy of Dr. Richard Lynch, University of Iowa College of Medicine.*
hypertension. But progress in this regard could not be made until scientists gained a better understanding of how the body controls blood pressure.

Because blood pressure is so vital to maintaining normal function (see box – “Blood Pressure Basics”), the body has many overlapping systems for controlling blood pressure that involve the heart, kidneys, nervous system and other organs or tissues. When one means for changing blood pressure is ineffective, another backup system kicks in, thereby ensuring that the body continues to function properly. Although it is reassuring that these backup systems exist, making sense of the many facets of blood pressure control was difficult, to say the least.

It took more than two centuries from the time when blood pressure was first measured in 1733 (in the horse) by Steven Hales to when doctors began to use the first effective blood pressure medicines after World War II. Discovery and development of drugs that effectively took the reins of blood pressure were not possible until scientists painstakingly teased out the strings controlling blood pressure one by one. The end result is a fascinating story of discovery that stars deadly snakes in the tropical rainforests of Brazil, a researcher trying to find a cure for menstrual cramps, and four major organs, including a hardworking pair known as the kidneys.

### Blood Pressure Basics

Not much bigger than a fist, the human heart beats 100,000 times each day, sending about 2,000 gallons of blood coursing through vessels, which, laid end-to-end, would be long enough to circle the earth more than twice. Adequate blood pressure is key to ensuring that all parts of the body are supplied with the vital fluid that sustains them. To be adequate, not only does blood pressure have to be high enough to flow rapidly throughout the body, but it needs to change quickly to accommodate the body’s needs. For example, rising in the morning after sleep requires a rapid rise in blood pressure so that a person’s boosted activity is supported by the increased supply of energy that the blood provides. A major loss of blood or water from the body also requires a compensatory rise in blood pressure.

The body has three main ways to raise blood pressure:

- Increase how frequently the heart contracts or make each contraction stronger so a greater volume of blood is propelled through vessels;
- Constrict blood vessels so that blood flows more quickly through them; and
- Retain more salt and water in the blood to boost its volume.

High blood pressure (hypertension) is currently defined as being above 140/90 mmHg (millimeters of mercury; a way to measure pressure). Stress often causes blood pressure to rise above this level as the body gears up for the “fight or flight” response that was needed in prehistoric times, when the major stressors were carnivorous animals and not overbearing bosses! Blood pressure is thought to stay elevated due to chronic stress and/or many other factors. These might include a high salt diet that causes water retention, kidney disease and excessive weight gain. Most people with hypertension inherit a tendency to be particularly sensitive to environmental factors, such as dietary salt, that can raise blood pressure.

More than 50 million adults in this country have high blood pressure. Many do not know it because early stages of the condition have no symptoms other than frequent headaches. Nine out of every 10 people will develop hypertension during their lifetimes, and more than half of all middle-aged and elderly adults need to take blood pressure medication.

### The Search for a Diuretic

Basic research done in the early 20th century revealed that the kidneys filter one quarter of all the blood that leaves the heart each minute. Part of that filtering process determines how much salt is left in the blood. The more salt, the more fluid the body retains to dilute it. Excessive fluid retention to dilute salt raises blood pressure and can eventually cause congestive heart failure. In patients with this condition, the excess fluid in the blood leaks out into the spaces between cells, causing swelling and fluid in the lungs that can disrupt breathing. During Roosevelt’s time, the only treatment for hypertension and congestive heart failure was a
stringently low-salt diet to which few patients were able to adhere.

Building on this knowledge, physiologist Karl Beyer, Jr. and his pharmacologist and chemist colleagues at Merck Sharp and Dohme Research Laboratories reasoned that rather than require high blood pressure patients to restrict the salt in their diets, why not give them a drug that makes their kidneys expel more salt into their urine? A way of doing this surfaced with the serendipitous observations of clinical researchers. They noticed that when they gave patients a new antibiotic called sulfanilamide, their urine became more acidic and had greater than normal concentrations of various salt components. Intrigued by this finding, British physiologists T. Mann and David Keilin set out to discover why. They uncovered that such boosted salt excretion stemmed from the antibiotic disrupting the work of a particular enzyme called carbonic anhydrase.

This finding led Beyer and his colleagues to try creating a drug that blocked carbonic anhydrase in the kidney. Fortunately, university-based researchers, interested in exactly how certain enzymes work, had already learned quite a bit about carbonic anhydrase, thanks to federal government support of their endeavors. These researchers showed, in papers published in scientific journals, that the enzyme-inhibiting actions of sulfanilamide stemmed from a specific chemical constituent. With this target in mind, the Merck researchers made a number of chemical changes to a sulfanilamide drug they had in hand. Because of the complexity of the physical changes they needed to measure and the precision required, they chose to test their new drug on dogs, rather than on rats or other smaller animals. Their first experiment on a dog showed, to the researchers’ delight, that their compound selectively boosted the amount of salt components expelled into the animal’s urine.

This compound was the diuretic known as chlorothiazide (Diuril). In 1957, investigators demonstrated diuril dramatically lowered blood pressure in patients, making it the first highly effective oral drug for hypertension. Since then, over a dozen additional diuretics have been developed. These drugs have become mainstay treatments for hypertension, and slash the risk of suffering a stroke, congestive heart failure or heart attack by about a third. But diuretics boost the levels of sugar and artery-clogging fats in the blood, which could be life-threatening in the long term. They also frequently cause impotence, a major deterrent to their use by men. So the quest for better blood-pressure-lowering drugs continued after the debut of diuretics.

**Beta and Calcium Channel Blockers**

The next two groups of drugs to enter the market for the treatment of hypertension were actually developed to treat chest pain, or angina. This pain comes from a lack of oxygen reaching heart tissue, often because of partially blocked arteries. To stem the oxygen needs of the heart and thus the angina, researchers strived to create a drug that could lower the frequency of heart contractions (heart rate). That way, the heart would not work as hard and need as much oxygen.

To accomplish this feat, drug developers relied on a century’s worth of basic research showing that the hormone epinephrine affected how frequently the heart beats. But this hormone controls a number of vital functions in the body so attempts to block its actions in the heart could not be accomplished without causing serious side effects. A breakthrough came in 1948, when pharmacologist Raymond Ahlquist (Figure 3) of the Medical College of Georgia, who was searching for a drug to relieve menstrual cramps, accidentally discovered that the actions of epinephrine in the body varied depending on the type of cell receptor the hormone used to affect tissues. The heart rate was largely controlled by the actions of epinephrine on “beta” adrenergic receptors, Ahlquist discovered.

This discovery opened up the possibility of selectively slowing heart rate without hampering other vital functions that involved “alpha” receptors, and eventually led to a hunt for drugs that would
break beta receptors. In 1964, the first beta blocker drug to be marketed, propranolol (Inderal) was shown to be effective at relieving angina. Clinical researchers also noticed that propranolol lowered the blood pressure of many of their patients, and the drug was subsequently approved for the treatment of hypertension in the early 1970s.

The success of propranolol at relieving angina triggered a quest for similar drugs and led to the development of the drug verapamil. Later studies revealed that verapamil was not actually a beta blocker at all, but rather lowered the heart rate by hindering the entry of calcium into heart cells. This observation rang bells in the research community, because a century’s worth of bench work had revealed that the flow of calcium into heart muscle cells and blood vessels prompts them to contract. The discovery that verapamil hindered such calcium flow led to efforts to create similar calcium channel blockers, of which eight are now used to treat angina. Studies in the 1970s revealed that calcium channel blockers also effectively lowered blood pressure by relaxing blood vessels and led to their use to treat this condition by the 1980s.

Clinical research reveals that calcium channel and beta blockers reduce the risk of heart attack and stroke by about one-third. But their effectiveness is often marred by their frequent side effects because their actions are not specific enough in the body. Beta blockers often cause fatigue, dizziness, insomnia and impotence. Calcium channel blockers frequently cause constipation, headaches and a swelling of the ankles.

By the late 1980s, despite the array of drugs available to treat hypertension, this condition still could not be adequately overcome in many patients who had to discontinue their blood pressure medicines because of side effects. In patients with extremely high blood pressures, even a combination of diuretic, beta and calcium channel blockers was not enough to lower their blood pressure levels to normal.
Help came once more from basic research on the kidney. These explorations led to the discovery of an amazingly powerful and highly specific control system for blood pressure that went far beyond the kidney’s effect on salt excretion.

The Kidney Connection

Scientists began to suspect that the kidney acts a major guardian of blood pressure in the mid 19th century. Several doctors noted that their patients with kidney disease also had the enlarged hearts that are seen in people who have experienced high blood pressure for long periods of time. At that time, an easy and accurate way of determining blood pressure wasn’t available. But in 1872, an Indian doctor Frederick Akbar Mahomed, who was working in London, was able to make crude blood pressure measurements to show that his patients had high blood pressure in addition to kidney disease and enlarged hearts.

How the kidney might affect blood pressure remained a mystery until the Scandinavian physiologist, Robert Tigerstedt (Figure 4), of the Karolinska Institute, ground up the kidneys of rabbits. He tested various components of this rabbit kidney mash to see if they triggered a rise in blood pressure when they were injected back into rabbits. After dozens of experiments, he found a kidney extract that made the animals’ blood pressure shoot up. Tigerstedt also established that blood taken from the vein leading out of the kidney raised the blood pressure of rabbits whose kidneys have been removed. From this evidence, he concluded, in 1897, that the kidney released into the bloodstream a substance that raised blood pressure. He called that elusive substance renin, in honor of its kidney (renal) origins.

Unfortunately, because few other scientists were able to duplicate his results, Tigerstedt’s findings were essentially shelved for years. One of the scientists to next pursue how the kidney affected blood pressure was Harry Goldblatt (Figure 5) of Case Western Reserve University in Cleveland. As a pathologist who frequently conducted autopsies, Goldblatt noticed that the kidney blood vessels in many patients with hypertension were often abnormally narrowed. Such narrowing was rarely seen in patients without high blood pressure.

Intrigued, Goldblatt wanted to better understand this link between high blood pressure and the constriction of blood vessels in the kidney. Did one cause the other?, he wondered. To seek an answer to this question, in 1934 Goldblatt conducted a simple experiment that some say unleashed more research than...
Using an adjustable silver clamp that he had fashioned himself, he partially constricted the artery to the kidney of a dog. He then monitored the dog’s blood pressure and was surprised to see that even though the artery to the other kidney was unimpeded, the dog’s blood pressure rose in response to the clamping. (He didn’t clamp both kidney arteries because he was afraid that would have killed the dog.) For the first time, researchers now had a hypertension animal model—a highly useful tool with which to further explore blood pressure control. Large animals, such as dogs, have proven invaluable to biomedical research because their physiology often closely mimics that of humans.

Goldblatt suspected that the constriction of the kidney artery triggered excess production of renin, which not only caused high blood pressure in the experimental dogs, but also might be responsible for the hypertension that commonly afflicts patients without kidney disease. Researchers couldn’t clarify the role of renin in causing high blood pressure, however, until they pinpointed the biochemical nature of renin.

The Hunt for Renin

Goldblatt’s animal model of hypertension fostered an international hunt for this mythical substance called renin that Tigerstedt had hypothesized but no one had yet identified. But researchers kept hitting a puzzling impasse—the purer they made their renin-containing extracts, the less these extracts raised blood pressure. However, if blood was added to the purified extracts, they regained their potency and caused blood pressure to rapidly elevate.

By 1940, two research labs working independently—one based in Buenos Aires, Argentina, led by Eduardo Braun-Menendez, and one in Indianapolis, led by Irvine Page—discovered why these confusing findings reoccurred. These scientists uncovered that renin was an enzyme that forms a blood pressure-raising peptide.
(a chain of amino acids, the building blocks of proteins) called angiotensin from a large peptide (angiotensinogen) that circulates in blood. The purified renin extracts didn’t raise blood pressure because they lacked the precursor, angiotensinogen, that renin makes into angiotensin. Later studies revealed that this precursor peptide is made by the liver, adding yet another organ to the control of blood pressure.

Serendipity then played a role in uncovering an additional missing piece to the puzzle of how the kidney affects blood pressure. In 1956, while trying to purify angiotensin, biochemist Leonard Skeggs, Jr. of Case Western Reserve University and his colleagues discovered that not one, but two substances in their extracts raised blood pressure. This led them to hypothesize that the fashioning of angiotensin is a two-step process and renin can only accomplish the first step. The second step is triggered by a different enzyme, which was christened angiotensin-converting enzyme (ACE), fully described in 1955 by Ervine Erdos. Renin makes angiotensin I, a compound which has no effect on blood pressure until it makes contact with ACE. This enzyme snips off two amino acids of angiotensin I to convert it to

Figure 6: The Renin–Angiotensin–Aldosterone System. Angiotensinogen (44 amino acids), the precursor of all angiotensin peptides, is synthesized by the liver. In the circulation, it is cleaved by renin, forming angiotensin I. In turn, angiotensin I (10 amino acids) is cleaved by angiotensin-converting enzyme (ACE), which is bound to the cells lining the blood vessel, to form angiotensin II (8 amino acids). In the adrenal glands, angiotensin II stimulates the production of aldosterone. Aldosterone raises blood pressure by prompting the kidneys to retain more salt. Used with permission from the New England Journal of Medicine (2001; 345:1690).
angiotensin II, which researchers later found was a powerful blood-pressure raising peptide hormone in animals.

Despite all these exciting laboratory discoveries, many were skeptical that renin played any role in governing the blood pressure of people in the clinic. Feeding that skepticism were conflicting findings on whether people with hypertension also had high renin levels. Progress would not be made until researchers working in a totally unrelated area—the study of hormones released by tiny organs called adrenal glands—unveiled yet another renin-related trick the body uses to control blood pressure.

During the first half of the 20th century, fundamental research on the adrenal glands (sometimes called adrenals), which rest atop the kidneys, revealed that these organs release a hormone called aldosterone. This hormone raises blood pressure by prompting the kidneys to retain more salt. In 1960, James Davis and other researchers at the National Heart Institute (now the National Heart, Lung and Blood Institute), discovered that the kidneys secrete a substance into the blood that triggers the adrenals to release aldosterone. Investigators soon discovered that the aldosterone-prompting substance was angiotensin II, suggesting once more that the renin-angiotensin-aldosterone system played a key role in high blood pressure (Figure 6.) The proof of the pudding, though, came from an unusual and unexpected source—the Brazilian pit viper.

Workers in the banana plantations of southwestern Brazil were known to collapse suddenly after being bitten by a pit viper due to a drastic drop in blood pressure. Curious about what exactly this venom does to the body, biochemist Mauricio Rocha e Silva of a Brazilian research institute made extracts of the venom and began to study their effects in dogs and guinea pigs. In the mid 1960s, one of Silva’s postdoctoral students, Sergio Ferreira, traveled to London to work in the lab of pharmacologist, Sir John Vane (Figure 8) of the Royal College of Surgeons. In Ferreira’s pocket was a vial full of the venom of the notorious Brazilian pit viper (Figure 7).

Although Vane eventually won the Nobel Prize for basic research...
explaining how aspirin works, at the time Ferreira arrived, Vane was heavily immersed in studies of angiotensin I and II, and ACE. He had recently shown that much of ACE is generated by the blood vessels in the lungs, and was curious to see if the snake venom’s blood pressure-lowering effect could be due to an effect on ACE.

Unable to interest Ferreira into studying this further, Vane convinced one of his colleagues, Mick Bakhle to pursue it. The researchers were thrilled to discover, in 1970, that something in the snake venom was a potent inhibitor of ACE’s ability to generate angiotensin II. Vane was quick to realize that with such an inhibitor in hand, researchers could easily show exactly what effect angiotensin II has on blood pressure and put to rest the uncertainty over whether renin and angiotensin were relevant to blood pressure control.

During this period, Vane became a consultant of the pharmaceutical company Squibb in New Jersey. He suggested to researchers there that they study the snake venom and use it to show whether angiotensin II was important in regulating blood pressure. If it was, then they had a starting point for a new hypertension drug, Vane argued. But it wasn’t easy convincing management at the company that researchers might be able to dish up a useful drug from an extract of poisonous snake venom. Any drugs that might evolve from these studies would have to be injected, the Squibb marketing people argued, and only oral drugs are practical to control high blood pressure.

But eventually an enzymologist and peptide chemist at Squibb—David Cushman and Miguel Ondetti—were put to work identifying, purifying and testing the blood-pressure lowering substance in the snake venom. After making a synthetic version of the substance, they then passed it on to Vane. He injected it into human volunteers and showed that it inhibited their conversion of angiotensin I to angiotensin II. Squibb also sent the substance to John Laragh, a hypertension expert at Cornell Medical Center in New York. When he injected it into some of his patients with high blood pressure, he was delighted to find their blood pressure dropped significantly (but not as dramatically as in those bitten by the Brazilian pit viper!) At this point, few people doubted that renin and angiotensin II played an important role in regulating blood pressure, and that an ACE inhibitor would have some value in treating hypertension.

But there was one major problem—the ACE inhibitor Cushman and Ondetti had created could not be taken orally, but such tinkering failed abysmally and frustrated the scientists, not to mention the higher-ups in Squibb who predicted this would be a problem. In the meantime, Cushman and Ondetti screened thousands of chemicals on Squibb’s laboratory shelves to see if they too might inhibit ACE, but came up empty-handed.

At this point, attempts to create an ACE inhibitor were abandoned at Squibb for a few years and the Cushman-Ondetti research team split up. But in their spare time, these men still continued their discussions on how they could convert the venom-based ACE inhibitor into a compound that could be taken orally. A breakthrough in their thinking arose after publication of basic research results from biochemists at the University of North Carolina, Chapel Hill and Harvard University pursuing a totally unrelated topic—a digestive enzyme made in the pancreas called carboxypeptidase A.

Enzyme Research Shows the Way

To figure out how this digestive enzyme worked, William Lipscomb of Harvard University used X-ray crystallography, an imaging technique, to visualize the three-dimensional structure of the enzyme. To gain further insight into how carboxypeptidase A worked in the body, Larry Byers and Richard Wolfenden of the University of
North Carolina used Lipscomb’s findings to create a simple yet highly potent chemical inhibitor of the enzyme by mimicking the structure of the portion of the compound to which the enzyme usually attaches. They published the structure of the inhibitor in a May 1973 issue of the scientific journal *Biochemistry*. Cushman had previously noticed how remarkably similar in structure ACE was to the pancreatic enzyme. So the discovery of a small yet powerful inhibitor of carboxypeptidase A ignited a whole new approach to creating an inhibitor to ACE.

Designing an Enzyme Inhibitor

A key workhorse for raising blood pressure is angiotensin-converting enzyme (ACE). Angiotensin I is a peptide—a chain of eight protein building blocks called amino acids—and acts as a substrate for this enzyme. A portion of angiotensin I has just the right shape, and positive or negative charges at just the right spots, to slip into the crevices of ACE. Like a hand into a glove, it can bind tightly to the enzyme. (See top drawing.) ACE then snips off two of angiotensin I’s amino acids to form the peptide angiotensin II, a powerful blood-pressure raising agent. *Image design by Corporate Press.*

To design a drug that could block ACE’s actions, researchers had to create an angiotensin I mimic—a molecule that also was the right shape, with positive or negative charges in the right places, to bind to ACE. But this mimic cannot be converted into angiotensin II. Instead, by binding to ACE, it blocks the enzyme from making contact with its real target, angiotensin I. The bottom drawing shows one of the first “ACE inhibitors,” the drug Captopril, binding to ACE. It is remarkably similar to a portion of angiotensin I that binds to ACE. This approach to making drugs has been called rational or structure-based drug design. *Bottom image courtesy of Dr. Cherie Koch, Merck & Co., Inc.; adapted by Corporate Press.*
In the spring of 1974, Cushman and Ondetti began manipulating the pancreatic enzyme inhibitor so that it more closely resembled the snake venom-ACE inhibitor prototype that they had created. After trying out nearly 60 different changes to the molecule, they finally struck pay dirt—a compound that was amazingly effective at inhibiting ACE, but unlike their previous synthetic inhibitor, this one was small enough to be absorbed by the gut. They then modified this compound so that it wouldn’t be torn apart by enzymes in the stomach and bloodstream. The end result, in the autumn of 1975, was the drug we now know as captopril—the first ACE inhibitor that could be taken by mouth. (See Side Bar—“Designing an Enzyme Inhibitor.”)

Captopril was also one of the first drugs created with an innovative “structure-based design” approach. Prior to this technique of designing new drugs based on a specific desired chemical structure, drug companies relied on luck to find new medicines. They typically screened thousands of natural and synthetic compounds until they found one that had the effect they desired. This process is extremely laborious and time-consuming, and often can be fruitless, as was Squibb’s initial screening search for an ACE inhibitor.

Structure-based drug design is much more efficient and has been used successfully to make drugs for AIDS, cancer, and other disorders. This technique often relies heavily on the findings of government-supported basic researchers, who use X-ray crystallography and other techniques to pinpoint the portions of enzymes and other compounds that are responsible for their actions in the body. Researchers have used structure-based design to make other versions of captopril, ten of which are now on the market. Scientists also used this technique in the 1990s to make five effective angiotensin II-receptor blockers (ARBs). These drugs lower blood pressure by preventing angiotensin II from reaching its target (receptor) in the body.

ACE inhibitors and ARBs are remarkably effective at lowering blood pressure because they offer a two-punch impact—not only do they prevent the blood pressure-raising constriction of blood vessels, but they also lower blood pressure by restricting water retention in the blood. Recent studies have also found that ACE inhibitors and ARBs have additional benefits.

Laboratory research has revealed that angiotensin II appears to foster a number of processes that underlie cardiovascular disease, including the build-up of plaque on blood vessel walls, and the excessive growth of heart tissue that often occurs in response to a heart attack, leading to congestive heart failure. ACE inhibitors and ARBs appear to counter those effects. The end result, clinical studies show, is not only do these drugs decrease the risk of developing a heart attack by more than 20 percent, but they also boost the heart attack survival rate by nearly the same amount, as well as significantly preventing a dangerous buildup of fluid in the lungs and elsewhere caused by congestive heart failure. ACE inhibitors have also been shown to cut the risk of stroke by about a third.

Surprisingly, ACE inhibitors and ARBs may alleviate conditions beyond cardiovascular disease. By lessening inflammation and the buildup of fibrous tissues, these drugs are thought to stall the progress of kidney disease. One study found that an ACE inhibitor cut in half the number of patients with hypertension who progressed to serious kidney disease during a three-year period. Another ACE inhibitor reduced by one-third the number of patients over age 55 who developed diabetes during a nearly 5-year period. It is not known how exactly the ACE inhibitors and ARBs prevent diabetes, although it could be by hampering inflammation and increasing blood flow to the pancreas. Diabetics are particularly prone to kidney disease, but ACE inhibitors and ARBs significantly stem the decline of their kidney function, as well.

Although ACE inhibitors and ARBs are more expensive than diuretics and other blood pressure-lowering drugs, none of these other drugs have been
shown to possess their added, far-flung benefits. In addition, because they are highly specific in the way they act in the body, ACE inhibitors and ARBs cause the fewest side effects of any blood pressure medication. The most common side effect of an ACE inhibitor is a benign dry cough, tolerated by most patients. ARBs rarely cause side effects. Without a doubt, these drugs, along with diuretics, beta and calcium channel blockers, have helped extend the lives of millions, allowing parents to become grandparents, and presidents to serve out their terms. None of these drugs would have been possible if it weren’t for the curiosity and diligence of a number of government-supported scientists, from biochemists to physicians, who were bent on figuring out the basic mechanisms of the body, including the exquisitely intricate maneuvers it uses to control blood pressure.