BY DEBORAH FRANKLIN

Putting the Squeeze on Hypertension

Researchers believe that brain chemical activity centers called alpha-adrenoceptors may play a key role in certain types of high blood pressure problems

"Forty years ago, hypertension couldn't be treated at all," says P. A. van Zwieten, a researcher at the University of Amsterdam currently probing receptors in the brain for clues to the regulation of blood pressure. "Tremendous progress has been made," van Zwieten says, though the roots of the condition plaguing more than 30 million Americans still are unknown and probably quite complex.

Pinpointing a "cause" of chronically high blood pressure for 90 percent of the sufferers is like stumbling around furniture in a pitch-black room, says another researcher. Only after you've stubbed your toe a few times and finally flicked on the light switch in the corner, does the path around the furniture become clear. Four decades of research have produced four or five families of drugs, each with its own batch of unpleasant but tolerable side effects, capable of reducing blood pressure relatively safely. But despite advances in drug therapy, scientists still are seeking the "light switch" to illuminate the underlying causes of the condition that, if left untreated, can lead to stroke, heart attack or kidney failure.

In search of illumination, 300 researchers from around the world gathered in Palm Springs, Calif., in March to pool information on "alpha-adrenoceptors" — sites of chemical activity in the brain, kidney and nervous system that, among other functions, seem to play a leading role in the regulation of blood pressure. Some of the scientists, like William Pettinger, director of clinical pharmacology at the University of Texas Health Sciences Center in Dallas, theorize that a genetically determined abnormality in the receptors might interact with the salt intake of some patients to trigger hypertension. Others are skeptical that any simple explanation for hypertension exists.

Maintaining a steady flow of blood from head to toes throughout daily activities is vital for proper functioning of the body's organs. But making certain that the exuberant person who jumps out of bed in the morning doesn't keel over from a misdistribution of blood takes the finely tuned cooperation of several regulating organs. The heart, the blood vessels and the kidneys, under close supervision of various parts of the brain, work together to make sure that as a person runs faster and jumps higher, a steady flow of blood reaches every tissue.

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Each organ accomplishes its task in a different way. The heart can raise blood pressure by beating faster or with more force; arteries and arterioles — tiny vessels encased in muscle — can constrict like the nozzle on a garden hose, increasing the pressure by forcing the blood through tinier openings. By releasing chemicals that prompt the retention of salt and water, the kidney increases the body's water volume. Tissues heavy with water stiffen, forcing the heart to exert extra pressure to move blood through them.

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In a healthy body, the organs are synchronized so that any increase in the blood pressure at one site can be compensated for at another. In order to achieve the synchrony, the brain and central nervous system act as a communications network, to make certain that the blood pressure regulators work together smoothly.

But for hypertension victims, some part of the regulation system has faltered, and the blood pressure shoots up and stays up. In about 10 percent of these cases, physicians can trace the problem to disease or a blockage in some part of the renal or cardiovascular system. The cause of hypertension in the other 90 percent remains a mystery.

Sometimes a sharp reduction of salt in the diet and loss of extra pounds is enough to bring dangerously high blood pressure down to normal. If this doesn't work, physicians treating high blood pressure choose from drugs that act on different parts of the cardiovascular or kidney systems to reduce the pressure. Diuretics act on the kidneys to reduce pressure by getting rid of excess body fluids. Muscle relaxers, like hydralazine, act by relaxing the smooth muscle cells surrounding arterioles, thereby permitting the vessels to dilate. Other drugs act on various sites of the involuntary nervous system to reduce blood pressure. Reserpine, for instance, depletes neurotransmitters at the end of involuntary nerves. Beta-blocking drugs lower blood pressure by interfering with the ability of neurotransmitters to bind to receptors at the end of involuntary nerves called beta receptors.

But it is the drugs that work on the alpha-adrenoceptors that excited many of the scientists at this meeting. Drugs such as clonidine and alpha methyldopa, first thought to act in the body's periphery, now are thought to reduce blood pressure primarily by stimulating alpha receptors in the brain to slow down the release of the chemical messenger norepinephrine. Effects in the brain ultimately slow the heart rate and "decrease sympathetic tone" in some nerves that control peripheral vessel constriction.

'No drug is a wonder drug.'

"No drug is a wonder drug," says Mohinder P. Sambhi of the Veterans Administration Hospital in Sepulveda, Calif., who co-directed the conference sponsored by the International Society of Hypertension and the American College of Chest Physicians. "All drugs are foreign agents to the body; all drugs have side effects. What we are saying is that this type of drug [one that acts on central alpha receptors] should get its share of attention in certain kinds of hypertension."

By acting primarily in the brain, drugs that activate the alpha receptors can reduce blood pressure without instigating long-term metabolic changes in the heart, kidney or blood — effects often associated with other antihypertensive agents, Sambhi explains. Most inhibitors and muscle relaxers can cause salt and fluid retention, and therefore must be taken along with a diuretic to be effective. In contrast, medications that act on the alpha-adrenoceptors can be effective when taken alone.

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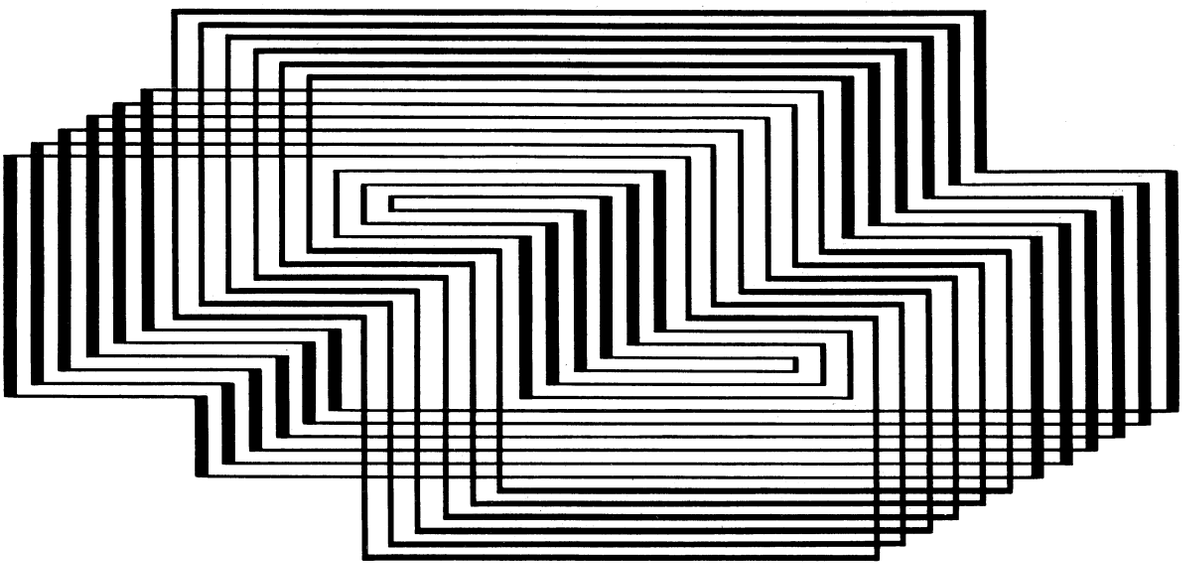
Despite some advantages, these centrally acting drugs have formidable drawbacks, according to some clinicians. The dry mouth and drowsiness suffered by some patients taking the drugs can make the cure feel worse than hypertension, often called the "silent killer" because of its lack of painful symptoms. Coaxing patients to continue taking a medication with unsavory side effects is a common problem for physicians, but a sudden halt in treatment can be life-threatening for persons taking clonidine, which has been known to trigger an "overshoot" of pres-



Ascension, Josef Albers, National Gallery of Art, Washington, Gift of the Artist

sure to dangerously high levels if daily doses are missed.

Several researchers at the Palm Springs conference presented data indicating that the side effects of clonidine seem to be related to larger doses. Patients whose hypertension could be curbed with small doses of the drug suffered little or no discomfort, they said.

"We don't have that many antihypertensive drugs, so the good doctor has to pick from among the seven or eight or nine drugs that are available," Walter Kobinger, a researcher at the Ernest Boehringer Institute for Pharmacological Research in Vienna, Austria, told SCIENCE NEWS. The "alpha drugs" aren't appropriate for every patient, he said, but have an important place in a good physician's treatment schedule.

'The hypertensive patient might lack an adequate sensitivity to alpha-adrenoceptors.'

Although the value of alpha drugs in the treatment of high blood pressure is still debated, they do appear to be important research tools toward understanding the contribution that the brain and nervous system make to high blood pressure. Twenty years ago, for instance, researchers hoped that newly discovered clonidine would be an effective nasal decongestant because it caused blood vessels lining nasal passages to constrict. But then it was found to have an even more valuable clinical potential — the lowering of high blood pressure. Then during the late 1960s and early 1970s clonidine was found to lower high blood pressure by two seemingly contradictory routes — the stimulation of, and blocking of, alpha receptors. This paradox then seemed to be explained, at least partially, by the discovery in 1974 of two classes of alpha receptors — $alpha_1$ and $alpha_2$.

And now scientists are using clonidine, among other tools, to try to learn what role $alpha_1$ and $alpha_2$ receptors might play in high blood pressure. Detailed mapping of the receptors and exploration of their function in cardiovascular regulation is still going on, but the most recent studies indicate that some $alpha_2$ receptors located on the ends of sympathetic nerves reduce transmitter release when stimulated by a drug like clonidine. Other $alpha_2$ receptors seem to prompt a sensitization of "baroreceptors" — receptors responsive to changes in the pressure inside blood vessels.

Although $alpha_1$ receptors in smooth muscle are known to cause constriction of peripheral blood vessels when stimulated, their roles in the central nervous system and in blood platelets, where they are also found, have yet to be determined.

"Ten years ago it was thought that only one class of alpha-adrenoceptors existed," says Solomon Z. Langer, a researcher from the Laboratoires d'Etudes et de Recherche Synthélabo in Paris, France, who in 1974 published some pioneering research distinguishing between the two receptor subtypes. The differences between the two are "not only an academic distinction," Langer emphasized in an interview with SCIENCE NEWS. The practical consequences of the distinctions are illustrated by the actions of "phentolamine," a chemical tested as an antihypertensive drug because it was known to act at alpha receptors. The drug was discarded for that purpose before it ever reached the market, Langer says, because it produced too many side effects. Later research showed that phentolamine activates both $alpha_1$ and $alpha_2$ receptors, producing the side effects of both while diluting the main effect of lowering blood pressure.

Drugs that selectively stimulate $alpha_2$ receptors "may be more fruitful," Langer says, in light of recent animal studies indicating that hypertensive rats seem to show a higher number of $alpha_2$ receptors in the kidney and brain when fed a diet high in sodium. Whether the finding in animals can be translated into a biochemical marker for an inherited vulnerability to hypertension in humans remains to be tested. "The hypertensive patient might lack an adequate sensitivity to alpha-adrenoceptors," Sambhi said after preliminary results of several studies were presented at the meeting. "But at this point, this is pure speculation."

Says Austin Doyle, a long-time investigator of hypertension at the University of Melbourne in Heidelberg, Australia, "Until you know what causes hypertension in the individual, you can't talk about the ideal hypertensive drug." □