Reprinted from CLINICAL CARDIOPULMONARY PHYSIOLOGY

— 17 —

Pathogenesis of Organic Changes in Chronic Hypertension and Hemodynamic Effects of Antihypertensive Agents

By EDWARD D. FREIS, M.D.

Senior Medical Investigator, Veterans Administration Hospital; Associate Professor of Medicine, Georgetown University School of Medicine, Washington, D. C.

THE characteristic hemodynamic abnormality in hypertension is the increase of total peripheral vascular resistance. All other possible factors such as cardiac output, total blood volume and blood viscosity are normal in uncomplicated essential hypertension, but when unduly elevated might produce a rise of blood pressure. Except in rare instances, as in patients with pheochromocytoma, the cause of the vascular constriction is unknown.

Despite the present ignorance concerning the etiology of chronic hypertension, there is considerable evidence to suggest that the pathogenesis of organic complications is connected directly to the elevation of arterial pressure. The characteristic pathologic lesion is hyperplasia of the intima of the arterioles. It was considered previously that this change, as a primary process, produced the increased peripheral resistance, resulting in hypertension, the impression having been gained from autopsy examination of patients dying in the advanced stages of the disease.

It is known that proliferation and fibrosis of the arterial intima are not found early in the course of benign essential hypertension. Biopsies of muscle and also of kidney as well as autopsies in young hypertensives dying of other causes fail to reveal structural changes in the intima of the arterioles. Arteriolosclerosis, therefore, is a late development. In the early stages, the constriction is functional —a narrowing due to smooth muscle contraction. This functional constriction often can be seen in the optic fundi of patients with significant hypertension of relatively short duration. More interesting, the spasm may subside when the blood pressure is reduced. Byrom has shown this reversal to occur in the meningeal arterioles of hypertensive rats.[1] Relaxation of arteriolar spasm has been seen in the optic fundi in patients with short-lived hypertension such as acute nephritis or toxemia of pregnancy when the blood pressure was reduced with antihypertensive agents or following recovery from the acute hypertensive state. Reversal of fundic arteriolar spasm may also occur in young adults with chronic essential hypertension after their blood pressures have been controlled at normotensive levels with antihypertensive agents.

Since the sclerosis of arterioles follows the hypertension by some years, it seems possible that the condition is produced by the hypertension per se or by the associated arteriolar spasm. Evidence supporting this concept has been supplied by Wilson and Byrom.[1] They induced hypertension in the rat by constricting one renal artery with a partially occluding clamp. As a result, distal to the clamp there occurred not only reduction of blood flow but also of blood pressure. A severe hypertension, however, developed in the remainder of the animal, including the arterial branches of the opposite kidney. In the animals who died of severe hypertension, typical arteriolosclerotic and arteriolonecrotic lesions were found in the vessels of the *opposite* or high-pressure kidney, whereas in the low-pressure kidney distal to the clamp the arterioles appeared quite normal.

Some instances of hypertension associated with narrowing of a renal artery in man suggest that human arterioles react similarly. For example, in patients with hypertension secondary to partial thrombosis or other forms of narrowing of one renal artery, intimal proliferation of arterioles is found in the opposite kidney but seldom in the involved kidney. Bland

described an unusual instance of hypertension apparently due to thrombosis of a main branch of one renal artery. Approximately one-half of the kidney was supplied with low blood flow and pressure, the other with blood under high pressure. Histologic examination revealed hyperplastic arterioles on the hypertensive side and normal-appearing arterioles on the hypotensive side. Since the hypotensive side was not infarcted, it must have received some blood supply even though this was limited. Thus, if there were any unknown circulating or neurogenic toxic substance acting on arteriolar walls to damage them one would expect this factor to act on both portions of the kidney. Indeed, since the side distal to the thrombosed artery was the seat of the disorder, one would expect the arterioles to be, if anything, more diseased in that portion.

There is evidence to suggest that arteriolar smooth muscle, like the smooth muscle of the ureter or gastrointestinal tract, reacts to stretching by further contraction. Many years ago, Baylis made this proposal, and more recently Folkow and others have shown that in vessels entirely freed of neurogenic or humoral influences elevation of pressure produce vascular constriction, while reduction of pressure induces peripheral vascular relaxation.[2] Teleologically, this intrinsic response of vascular smooth muscle provides a second line of defense in case of exhaustion or failure of the moderator (carotid sinus and aortic arch) reflexes. It also is important to note in this connection that the moderator reflexes in hypertensive individuals are set at a higher level. In addition, it is apparent that the constriction of smooth muscle to pressure provides a mechanism for the continuation of increased peripheral resistance even after the initiating cause of the hypertension has been removed. This may explain why hypertension sometimes fails to regress following removal of a pheochromocytoma, or a unilaterally diseased kidney, or following delivery in toxemia of pregnancy. Another important factor in the perpetuation of some hypertensions is the development of nephrosclerosis.

Accelerated Atherosclerosis of Large Arteries

Many of the incapacitating or fatal complications of hypertension are caused by the frequency of atherosclerosis of large arteries particularly in the cerebral and coronary blood vessels. The hypertensive patient is more prone to develop atherosclerosis than the normal individual. The incidence of myocardial infarction has been found to be four to five times higher in hypertensive males than in the general population and twenty times higher in hypertensive than in normotensive females.[8] It is well recognized also that the incidence of cerebrovascular atherosclerosis and thrombosis is unusually high in the hypertensive population.

Some factor must be present in the hypertensives which accelerates the atherosclerotic process. This acceleration may be due to the high pressure existing in the arterial tree or to some other unknown factor present in hypertensive patients. In deciding between these two possibilities, it is pertinent to refer to the changes that may occur in the pulmonary arteries following long-standing and persistent pulmonary hypertension. Pulmonary hypertension of long duration is found in certain forms of congenital heart disease, such as in patent ductus arteriosis with right-to-left shunt or in large interventricular septal defects in which the patients occasionally survive to adult life. The level of pulmonary pressure in such individuals is several fold higher than is normal for that system. At autopsy, it is common to find in such patients extensive atherosclerosis of the pulmonary rather than the systemic arterial system.

It is evident that if the acceleration of atherosclerosis were due to some circulating or neurogenic noxious factor it should affect both sides of the circulation. It would not spare the systemic circulation in pulmonary hypertension and the pulmonary circulation in systemic hypertension. The fact that the atherosclerosis is limited in each case to the areas of elevated pressure suggests strongly that the hypertension is the aggravating factor. These observations are not cited to imply that hypertension

causes atherosclerosis but rather to indicate that the hydraulic effect of an increased pressure head existing within the arterial tree hastens and intensifies the process of lipid deposition.

Congestive Heart Failure

It has been recognized for many years that the left ventricle responds immediately to an increased peripheral resistance by dilation and somewhat later by hypertrophy. The dilatation is purely a mechanical response conditioned by the contractile properties of cardiac muscle. If the peripheral resistance is elevated, the ventricle fails to empty as completely as it had previously. As a result, the volume of residual blood increases in the ventricle producing further stretching of the myocardial fibers. According to Starling's law, cardiac output is proportional to diastolic fiber length; the greater the stretch the greater the subsequent contraction. As a result, the output is restored to normal despite the elevated aortic pressure.

It should be noted, however, that in order to maintain a normal output the contraction of the heart muscle is increased; this requires a greater expenditure of energy (increased work). As with any muscle subjected to prolonged work demands, the fibers hypertrophy and the ventricular wall thickens.

Eventually, if the hypertension becomes more severe, or if the blood supply to the myocardium becomes compromised by atherosclerosis of the coronary arteries, or if the myocardial musculature becomes diseased through other causes, a point is reached in which further diastolic stretching leads to less effective rather than more effective contraction. It was demonstrated by Starling and later amplified by Sarnoff that there are limits to the compensatory powers of cardiac muscle. In every myocardium there is a critical point at which further stretching of the fibers leads to less effective contraction and the cardiac output falls. Once this point is passed, additional increases in arterial pressure evoke progressively poorer contractions with a consequent rapid decline in output. If the heart is damaged from other causes such as coronary artery disease or myocardial fibrosis, this critical point occurs at lower aortic pressures than in an undamaged heart.

It is logical to assume that the left ventricle will fail first and that pulmonary edema will result; and indeed this is often the case. At first, there will be only dyspnea on exertion, then paroxysmal nocturnal dyspnea and finally persistent chronic pulmonary edema or bouts of acute pulmonary edema requiring emergency therapy.

It is possible, however, for right ventricular failure to occur and even predominate with the appearance of peripheral edema, high venous pressure and an enlarged liver. The reasons for this are not completely understood, but there are several possible explanations which probably operate in concert to produce the right ventricular failure. First, it should be recalled that the myocardial musculature is a syncytium involving both ventricles. Damage to the major or left ventricle can compromise the weaker or right ventricle, although the reverse seldom occurs. Second, the reduction of left ventricular output lowers the driving force that keeps the blood circulating and results in a tendency for blood to collect on the venous side of the circulation. Third, reduction of arterial pressure secondary to the fall of cardiac output stimulates the aortic and carotid sinus nerves to produce peripheral vasoconstriction involving postarteriolar as well as arteriolar small vessels. By this means, much of the blood normally distributed in the small vessels is shunted into the central venous system where it tends to accumulate because of the ineffective cardiac output. Finally, the disordered circulation stimulates secondary reactions, possibly involving aldosterone secretion. This may compromise salt and water excretion in the kidney, thus favoring salt retention and edema.

It seems probable, as pointed out a number of years ago on the sequence of events following severe myocardial infarction, that the body has only a limited number of response patterns to stress. Indeed, most important for survival of the species are the reactions following hemorrhage; the wounded animal must fight or flee if he is to survive and propagate. After hemorrhage, as the cardiac output falls, the baroreceptors are stimulated to constrict small

peripheral vessels of all types in order to shunt blood into the central circulation. At the same time, the heart rate increases. In the healthy individual subjected to blood loss, these reactions are advantageous, but with a low output as in heart failure they only add to the burdens of an already overworked myocardium. In addition, the reduction of cardiac output or possibly of arterial blood volume following hemorrhage or low output heart failure stimulates renal salt and water retention with resulting expansion of the extracellular fluid and plasma volumes. Within 48 hours following blood loss there develops a considerable expansion of plasma volume due to this mechanism. Unfortunately, the body does not seem to differentiate between a reduction of cardiac output due to blood loss and a reduction due to cardiac failure. The reaction which is so helpful to the rapid restoration of blood volume following hemorrhage only adds to the burdens of the failing heart producing edema and further venous congestion. The salt and water retention mechanism restores blood volume and cardiac output in the healthy heart, thereby shutting off the stimulus to further salt retention. In the failing heart, however, as these burdens further reduce the cardiac output, the stimulus to salt and water retention increases, thereby setting up a vicious cycle.

Other Complications

Dissecting aneurysm of the aorta which occurs almost exclusively in hypertensive patients may also be a direct consequence of the elevated pressure. The aorta, being made up primarily of elastic tissue rather than smooth muscle, dilates in the presence of hypertension. It seems possible that the distention and stretching of the aortic wall may compromise the patency of the capillaries feeding the media and thus lead to medial necrosis. The resultant weakness of the aortic wall favors tearing or splitting in the presence of a constantly increased distending pressure or in a moment of extreme hypertensive overshoot. Very little is known about the mechanism of cerebral hemorrhage. It is recognized, however, that hypertension contributes to excessive bleeding during brain surgery.

These considerations as to the pathogenesis of the various organic complications of hypertension are of more than academic interest. If it is true that the elevated pressure produces organic damage, then reduction of blood pressure in the *early* stages of the disease would retard or prevent the development of organic damage. The argument that effective antihypertensive therapy should be reserved only for the advanced patients who already have severe organic damage becomes illogical when viewed in the light of the basic considerations.

Pharmacology of Antihypertensive Agents

The basic mechanisms by which arterial pressure may be reduced are: (1) by decreasing cardiac output and (2) by reducing total peripheral resistance. Most of the agents used today probably act on both mechanisms.

Ganglionic Blocking Agents

The hemodynamic effects of the ganglion-blocking drugs can be demonstrated most clearly by substituting a mechanical pump for the left ventricle.[3] In an anesthetized dog, blood is diverted as it enters the left atrium into a reservoir and then is pumped back into the animal via a T tube in the descending thoracic aorta. When hexamethonium is injected intravenously, there is first a fall in arterial pressure, indicating clearly a decrease in peripheral vascular resistance, since the pump is maintained at a constant output. There soon follows, however, a decrease in central venous pressure, pulmonary arterial pressure and a transient decrease in the volume of blood returned from the right heart through the pulmonary circulation to the reservoir. As a result of the temporary disparity between the output of the right heart and the pump's constant flow, the reservoir is depleted of several hundred milliliters of blood. Thus, the vascular volume or capacity of the dog must have increased sufficiently to accommodate the amount of blood transferred from the reservoir to the animal. Since this amount is too great to be explained on the basis of arteriolar dilation alone, it is apparent that the postarteriolar vessels must have dilated as well.

In the intact animal or human,[4] the sequence of events appears to be as follows: As sympathetic vasoconstrictor discharges are inhibited by the blocking agent, some arteriolar dilation occurs which is followed quickly by postarteriolar (capillary and venular) relaxation and pooling of blood in these small vessels. As a result, right heart filling pressure declines due to lack of adequate venous return, and the cardiac output falls. Thus, there is produced a further fall in arterial pressure. Since arteriolar relaxation and reduced cardiac output are present, the calculated total peripheral resistance relative to the cardiac output shows no significant change.

In the presence of congestive heart failure, however, the cardiac output rises rather than falls after ganglion-blocking agents. This paradoxical response results from the combined beneficial effects of arteriolar relaxation (decreased aortic pressure head reducing the work load) and pooling of blood volume peripherally (relief of central venous congestion).

The effects of the inhibition of the sympathetics are aggravated when the patient assumes the erect position (failure of compensatory reflex vasoconstriction) and are counteracted when he assumes the head down position, since gravity facilitates venous return. Similarly, blood loss cannot be compensated for by vasoconstriction, and severe hypotension can result from only moderate depletions of total blood volume.[3] With continued inhibition of the sympathetics, however, some homeostasis seems to return in time. This so-called "autonomous tone" of the muscular blood vessels probably is due to the intrinsic property of smooth muscle to contract under stretch and to relax after the stretching force has been removed. Normally, the sympathetic reflexes rather than autonomous tone provide the quick adjustments required for circulatory homeostasis during changes of body position. When the sympathetics no longer function effectively, as after surgical sympathectomy or ganglion-blocking drugs, the autonomous tone mechanism probably comes into play as a second line of defense.

When the sympathetic tone is released, following ganglion-blocking agents there is also some redistribution of blood flow to the various areas of the body.[4] Renal blood flow is reduced at first, but, due to the remarkable autonomy of the renal vasculature, adjustments are made promptly to restore blood flow to control levels. Essentially, the same adjustment occurs in the brain. The hepatic-portal blood flow decreases whereas the flows of the calf and forearm increase immediately. In the hands and feet, however, if there has been vasoconstriction by, e.g., placing the subject in a cold room, the increase in blood flow is approximately tenfold. The other effects of ganglionic blockade are related to inhibited transmission of nervous impulses through all autonomic ganglia, parasympathetic as well as sympathetic.

Salt-Restricted Diets and Saluretic Agents

Since it is our belief that low sodium diets and saluretic agents such as chlorothiazide produce similar hemodynamic effects, they will be discussed under the same heading. The considerations are limited to the effects of diets, such as the rice diet, which are restricted to 200 mg. of sodium per day or less. It should be mentioned that diets more liberal in sodium content do not produce a degree of salt depletion necessary to induce a reduction of blood pressure.

Salt depletion can be accomplished more effectively and quickly with a saluretic agent, such as chlorothiazide, than with a sodium-restricted diet. If a nonedematous, hypertensive patient is given orally 1.0 to 1.5 Gm. of chlorothiazide per day, there will occur a prompt diuresis of sodium and chloride, and, to a lesser extent, potassium.[5] During the first 48 to 72 hours, approximately 250 to 350 mEq. of sodium and chloride are lost from body stores, i.e., over and above the daily intake. If the chlorothiazide is maintained beyond this period, the depletion of body stores of salt levels off and the patient comes into balance with his intake. However, he does not regain the original losses. If the salt ingestion is increased, the extra amount is excreted unless the intake is pushed to excessive levels (approximately 25 Gm. per day).

The excreted salt appears to be derived primarily from the total extracellular fluid space. The patient characteristically loses 1 to 2 kilos of body weight and 1 to 2 L. of extracellular fluid as measured by thiocyanate, radiosodium or radiosulfate dilution spaces. The serum concentrations of sodium and chloride do not change significantly indicating that the elimination of extracellular salt and water is proportionate. The serum concentration of potassium usually falls slightly, but this reduction frequently is progressive unless potassium supplements are administered.

Included in the extracellular fluid space is the plasma volume which is reduced by about 15 per cent from its original level. All of these effects occur approximately within the first 48 hours, during which time the blood pressure also falls. The reduction in plasma volume and extracellular fluid space usually is maintained for periods of at least one month with the continued administration of chlorothiazide in the dosage of 500 mg. twice daily. The hemodynamic importance of the plasma volume depletion is indicated by the fact that restoration of plasma volume loss alone, without added salt, as by infusion of 500 ml. of 6 per cent dextran in glucose and water, usually returns the blood pressure to the previous or pretreatment level.

Normotensive, nonedematous individuals also exhibit a similar saluretic response and reduction of extracellular fluid and plasma volumes. However, unlike the hypertensive patients, there is no reduction of basal blood pressure. Nevertheless, altered vascular reactivity in that the degree of blood pressure elevation following infusions of pressor agents such as norepinephrine usually is reduced and the hypotensive response to depressor agents is increased. This altered vascular responsiveness can be reversed by restoring the plasma volume with salt-free dextran.

Several important considerations emerge from these observations. First, there is a labile pool of extracellular fluid and plasma volume which can be eliminated either by effective saluretic agents or by severely restricted salt intake. Parenteral mercurials also produce a depletion of plasma volume with an alteration in vascular reactivity.

Second, the reduction of plasma volume alters vascular reactivity in both the normotensive and hypertensive individual but reduces basal blood pressure only in the hypertensive. Our experience indicates that individuals with basal diastolic blood pressures in the region of 90 mm. Hg or above react to chlorothiazide with a fall of basal blood pressure, whereas those with diastolic levels of 85 or lower are not responsive. Since the fall of blood pressure may occur even in patients with only mild elevations of diastolic blood pressure, it is concluded that a basic difference exists between mildly hypertensive and normotensive individuals. We have interpreted our results to indicate that in all hypertensives, including those with only moderate elevations, a pressor mechanism or stimulus of some type is operative. Chlorothiazide reduces the blood pressure in such a group by decreasing the vascular reactivity to this stimulus.

A third implication is that the studies show an important relationship between total blood volume and vascular reactivity. It is probable that when the venous system is well filled a stimulus to vascular contraction produces a greater venous return to the heart than when the venous system is poorly filled. According to Crosley and also Dunstan, the cardiac output in hypertensive patients is reduced by chlorothiazide. It is a general property of muscle cells that the greater the initial tension the greater the contraction. Thus, other things being equal, a decrease in blood volume would reduce vascular tone. This reduction of vascular tone does not occur following hemorrhage, because the baroreceptor reflexes initiate sympathetic vasoconstriction, and the total blood volume is restored rapidly through hemodilution. Following chlorothiazide, however, these compensatory reactions are not prominent. There is no tachycardia or other evidences of compensatory vasoconstriction in the hypertensive as contrasted to the normotensive subject after chlorthiazide.

Finally, the studies of salt restriction and saluretic agents provide no evidence that sodium plays an important etiologic role in hypertension. The effect of sodium seems to be secondary rather than primary, permissive rather than causative. The administration of an *excessive* amount of salt does not elevate the

blood pressure of nonedematous normotensive or hypertensive subjects. It appears that a *depletion* of sodium ion induced either by diet or by potent saluretic agents reduces blood pressure in hypertensive patients. However, the hypotension occurs primarily because the salt loss is associated with a reduction of plasma volume. The unimportance of the sodium ion per se is indicated by the fact that the blood pressure can be restored simply by replenishing the plasma volume with salt-free dextran solutions. The role of salt, therefore, appears to be permissive. Its presence is required to maintain a normal expansion of plasma volume. This expansion permits normal vascular reactivity to the unknown pressor mechanism operative in hypertension. Salt loss and resulting plasma volume depletion reduce this vascular reactivity.

Hydralazine

Hydralazine or Apresoline produce hemodynamic effects which are unique among the antihypertensive agents. Pyrogenic substances produce similar hemodynamic changes, but hydralazine does not induce fever. Either hydralazine or pyrogenic substances produce a marked decrease in total peripheral vascular resistance while at the same time approximately doubling the cardiac output.[6] The heart rate also accelerates. Renal, splanchnic, cerebral and coronary blood flows increase, whereas flow remains essentially unchanged in the extremities.

Teleologically, the increased circulatory rate, particularly through the kidneys, heart and liver, aids in the rapid detoxification and elimination of noxious products associated with febrile infections and with the mobilization of body defenses. This represents another reaction pattern of the body useful for survival of the species which is advantageous in the treatment of hypertensive patients.

The increase in cardiac output counteracts the marked arteriolar relaxation induced by hydralazine, so that the percentage of fall in systolic pressure is not as great as the fall in diastolic. Therefore, when hydralazine is administered alone, the most significant reductions occur in the diastolic pressure. However, it is readily seen that if the venous return to the heart is impaired by the addition of ganglion-blocking agents or chlorothiazide the cardiac output cannot increase effectively, and the peripheral dilating effects of hydralazine then become relatively unopposed. For this reason, hydralazine is far more effective when used in combination with other drugs which reduce cardiac output, particularly chlorothiazide.

The tachycardia and palpitation produced by hydralazine sometimes is disturbing to the patient. If this is troublesome, Rauwolfia, which produces some bradycardia and also dulls apprehension, provides a worthwhile counteragent. In high dosages, hydralazine may produce a syndrome indistinguishable from disseminated lupus erythematosus. This does not occur, however, when dosages are maintained below 200 mg. per day. When properly administered, hydralazine is an extremely useful antihypertensive agent.

Other Antihypertensive Agents

Little is known about the hemodynamic effects of *Rauwolfia serpentina*. When injected parenterally in animals, reserpine, the active alkaloid of Rauwolfia, produces a central depression of sympathetic vasoconstrictor reflexes. When given orally in man, it is doubtful that the drug reduces basal blood pressure. It appears more likely that, following Rauwolfia, the patient becomes less emotionally reactive, and as a result the transient elevations of blood pressure caused by fear and apprehension become less frequent and severe. Since these elevations often occur as the result of subconscious or conscious fears associated with the visit to the doctor's office, Rauwolfia may give a false overestimation of antihypertensive potency when evaluated under such conditions. When evaluated under more critical conditions, notably in hospitalized patients, the drug in customary dosage has little if any antihypertensive effect on basal blood pressure.

The considerations of Rauwolfia are not meant to imply that the drug and its active alkaloid reserpine have no place in the treatment of hypertensive patients. By the parenteral route in dosages of 2 to 5 mg., reserpine is an active antihypertensive drug. By the oral route in far smaller dosages, it may be a useful

adjunct in the total management of the patient. Psychic factors are important; certain emotions, particularly fear (but probably not anger unassociated with fear) and anxiety, tend to oppose the antihypertensive effectiveness of most blood pressure-reducing drugs. Reserpine is a particularly useful sedative in such patients. It should be mentioned, however, that the drug also is potentially harmful, since serious and long-lasting mental depressions as well as other disturbing side effects can occur following prolonged use. Therefore, it is safer to administer other sedative drugs, such as the barbiturates or meprobamate, whenever these will provide the desired psychic effects. In regard to the so-called nonsedative, antihypertensive alkaloids of Rauwolfia, such as rescinnamine, when given orally in the advised dosages, this author has merely found a placebo-like action.

The *Veratrum alkaloids* stimulate still another type of hemodynamic reaction pattern used by the body for survival. This occurs when blood loss poses limitations for violent activity or when fear and other forms of psychic shock become overwhelming in the face of a challenge which cannot be met either by defense or flight. In this situation, a sudden vasodilation occurs with a marked fall of blood pressure, the heart rate slows and the pulse becomes almost imperceptible; a deathly pallor ensues and consciousness is lost as the individual falls to the ground in a faint. This reaction is a prominent protective device of cold-blooded animals who affect all the appearances of death when caught in a position that permits no successful escape. In man, the residual of this reaction is called vagovagal syncope.

The efferent arm of the reflex response as mentioned above travels out over the vagus nerve to produce bradycardia and over unknown pathways to produce peripheral vasodilation. The afferent arm may originate as follows: in the cortex under the impact of some intense emotional shock, in the carotid sinus or in afferent vagal nerve endings distributed to the lungs and myocardium. The Veratrum alkaloids stimulate these afferent nerve endings and so initiate a reflex vasodilation and bradycardia. Syncope, however, rarely occurs, but nausea and vomiting, due to stimulation of the emetic center, is common. Thus, the drug does not entirely reproduce the picture of vagovagal syncope.

Of all known antihypertensive agents, the hemodynamic responses produced by the Veratrum alkaloids are the most physiologic. The cardiac output remains unchanged while the total peripheral resistance falls.[7] Blood flowing to various body areas may fluctuate initially but soon reverts to the pretreatment level. There is no interference with postural and other homeostatic reflex adjustments. Unfortunately, Veratrum has been less satisfactory than other agents in long-term therapy for the following reasons: (1) a narrow spread between the hypotensive and the emetic dose and (2) the developement of tolerance to the antihypertensive effect.

Considerable progress has been made in the control of hypertension during the past 10 years and further advances are to be expected in the future. Careful study of the mechanisms by which blood pressure can be reduced may continue to shed more light on the hypertensive process.

REFERENCES

1. Byrom, F. B.: The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension. Lancet *2:* 201, 1954.
2. Folkow, B.: Intravascular pressure as a factor regulating the tone of the small vessels. Acta. physiol scandinav. *17:* 289, 1949.
3. Freis, E. D., and Rose, J. C.: The sympathetic nervous system, the vascular volume and the venous return in relation to cardiovascular integration. Am. J. Med. *22:* 175, 1957.
4. ——,——, Partenope, E. A., Higgins, T. F., Kelley, R. T., Schnaper, H. W., and Johnson, R. L.: The hemodynamic effects of hypotensive drugs in man. III. Hexamethonium. J. Clin. Invest. *32:* 1285, 1953.
5. ——: The treatment of hypertension with chlorothiazide. Angiology. In Press.
6. ——, Rose, J. C., Higgins, T. F., Finnerty, F. A., Jr., Kelley, R. T., and Partenope, E. A.: The hemodynamic effects of hypotensive drugs in man. IV. 1-hydrazinophthalazine. Circulation *8:* 199, 1953.
7. ——, Stanton, J. R., Culbertson, J. W., Litter, J., Halperin, M. H., Burnett, C. H., and Wilkins, R. W.: The hemodynamic effects of hypotensive drugs in man. I. Veratrum viride. J. Clin. Invest. *28:* 353, 1949.
8. Goldstein, F., Jenson, W. K., Waldron, J. M., and Duncan, G. F.: The relationship between hypertension and coronary occlusion. Ann. Int. Med. *44:* 446, 1956.