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Unusual Clinical And Laboratory Manifestations Of Disease

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Essential Hypertension

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The *usual* manifestations of essential hypertension deserve perennial review by the practicing physician, because high blood pressure without recognizable cause is not thoroughly understood. Many denounce the word "disease" when applied to essential hypertension without organic cardiovascular sequelae.

Our interest is clinical, and so our attention is turned mainly to hypertensive cardiovascular disease (HCVD) or what we might call "severe hypertension". Even so, constant review and re-evaluation of the "facts" of these conditions are necessary, for these "facts" bearing on etiology, natural history, and treatment have not been absolutely settled.

For the sake of truth and research, our ignorances must be borne constantly in mind. For the sake of our patients, present statistics of the natural history of essential hypertension and of hypertensive cardiovascular disease must be ever in mind lest one mistreat, undertreat, or overtreat.

We are provided with a large and new armamentarium of medicines. Sadly, the mechanism of action of many of these drugs remains as obscure as does the cause of the condition itself.

Side reactions are seldom so resplendent as when reviewed from reports of treated hypertensive populations. These reactions range from the interestingly annoying to the morbid and even fatal. They constitute, for the demands of this topic, a main source of "unusual manifestations" of essential hypertension.

Indeed, the only other source from which one can draw for unusual manifestations is hypertension with known cause. Essential hypertension can mimic this type and pheochromocytoma, aldosteronism, and renal hypertension can mask as essential hypertension.

Systolic hypertension due to arteriosclerosis, the mild hypertension of hyperthyroidism (and other hyperactive states), and the hypertension due to arterial venous shunts and coarctation of the aorta may for a time be confused with essential hypertension. Hypertension may be produced by Cushing's disease and lesions of the central nervous system. The hypertension of pseudoxanthoma elasticum and Ehlers-Danlos syndrome, studied further, may some day yield knowledge of the pathogenesis of hypertension relating to the arterial wall itself.

The practitioner is interested in patients. It is therefore important to know all one can about hypertension, hypertensive cardiovascular disease, the action of drugs, and paradoxes that sometimes arise during the treatment.

Natural History

The onset of hypertension is usually insidious. Intermittent diastolic hypertension may precede constant elevation by months or years. The average duration of survival of the patient

with hypertension from onset until death is 20 years, the hypertension being uncomplicated for three-fourths of this time. The blood pressures recorded under casual circumstances show little correlation with symptoms, rate of progression, or development of complications. About one-third of patients have no symptoms in the uncomplicated phase. Most patients complain intermittently of fatigue, nervousness, dizziness, weakness, insomnia, palpitation, or headaches, more often to a minor rather than a major degree. Headaches are mainly occipital or over the vertex. They are more apt to be present on awakening and rarely resemble migraine. Restlessness, emotional irritability, tachycardia, and flushing are fairly common, and elevated metabolic rate without true hyperthyroidism may be encountered. Lability of blood pressure is evident in most persons during this phase.

Complications

It is said that concentric hypertrophy produces a relatively inadequate blood supply. Congestive heart failure is responsible for about 25 per cent of cases of hypertension with cardiac complications. About 10 per cent of patients get angina or die from myocardial infarction. Approximately 10 per cent suffer cerebral thrombosis or die from cerebral hemorrhage. In about one-half of hypertensive patients nephrosclerosis develops and is manifested clinically by polyuria and nocturia, diminished concentrating power, or proteinuria with or without the presence of red blood cells in the urine. In an occasional patient azotemia develops, resulting in death from uremia. Aneurysmal formation and rupture of the heart in myocardial infarction are more common in patients with hypertension.

In malignant hypertension pathologic alterations occur more rapidly with progressive renal damage, sometimes accompanied by retinal hemorrhages, encephalopathy, and papilledema. The clinical picture may be similar in occasional patients with severe nephrosclerosis as a result of progressive end-organ damage. The onset is abrupt whether or not preceded by established diastolic hypertension. Severe headache, blurring of vision, nausea, and loss of weight are common. Convulsions may occur. This hypertensive encephalopathy is *rarely*, if ever, encountered in other phases of primary hypertension or hypertension without retinopathy. The sedimentation rate is elevated frequently. Slight alkalosis, hypokalemia, high aldosterone secretion, and high exchangeable sodium concentration are often found, probably related to *secondary* hyperaldosteronism. Cerebrospinal fluid pressure may be high unless the course is terminated along the way by complicating cerebral or cardiac damage. Renal damage progresses to azotemia, and death from uremia occurs in a considerable percentage of patients within two years.

A large number of hypertensive subjects will escape cardiovascular disease. Also, of those with organic changes, many will retain their physical and intellectual capacities for many years, unless disabled iatrogenically by cardiac neurosis. In terms of prognosis, the absolute value of keeping the blood pressure at a near-normal level has not been definitely settled.

Treatment

One need only read the succinct paragraphs of George A. Perera in Cecil's *Textbook of Medicine* to appreciate the best present attitude in treatment of hypertension. He reminds us that the cause cannot be removed, since it not yet known, and that there is no convincing

evidence that most of the pathologic changes can be blocked. Life can be prolonged in patients with malignant hypertension by appropriate management. One should remember, however, that many patients have hypertension; malignant hypertension, which to many modern writers is a different disease, is relatively rare. Counseling the patient is a vital duty. Relief of anxiety can substitute for much drug therapy. Patients can be taught to live with their disease. Interaction of personality, environment, and disease must be given attention. The action of drugs must be thoroughly appreciated.

Etiologic Aspects

Essential hypertension is more common in women than in men. It occurs in 5 per cent of the population of the USA. It is found in 10 per cent of patients with diabetes. The average age at which it can be detected is about 32, and some cases have been reported in childhood. Onset after 50 years of age is most unusual. The malignant form is more common in men. In the USA it is more common among Negroes. Women in whom malignant hypertension develops are lean, whereas most women with hypertension are obese. In only about 1 per cent of patients with essential hypertension does the malignant form develop. One-third of patients with the malignant form get the disease between the ages of 37 and 42 years.

Primary hypertension has been proved clearly to have a familial concentration, and there *is* justification for thinking along the lines of biochemical aberration or inborn error in metabolism.

Hypertension is often transient before it becomes permanent. When it becomes permanent it may or may not produce disease. The specific pathologic alterations produced by hypertension are changes in the arteriolar wall and hypertrophy of the left side of the heart.

The blood pressure is determined by blood volume, cardiac output, blood viscosity, and peripheral resistance. Only peripheral resistance appears to be an important factor in hypertension and hypertensive cardiovascular disease. Major changes of these other factors are required to alter the blood pressure. Only minor changes in the caliber of the arterioles, however, are necessary to produce changes in the blood pressure.

However convincing the theories relating to mental, emotional, or personality changes as the cause of hypertension, it is generally agreed that overaction of sympathetic tone does not play a part in production of hypertension or hypertensive disease. This general line of investigation is not exhausted, however. Studies are now in progress attempting to relate changes in receptor and activator sites of the sympathetic system to pathogenesis.

No significant biochemical differences have been found in patients with essential hypertension and in persons with normal blood pressure. Although we have considerable knowledge regarding catecholamine metabolism, a specific abnormality in this regard is not found in patients with essential hypertension; yet an inborn error of metabolism is not excluded as the possible pathogenesis.

Mechanisms of control of the blood pressure stem largely from adrenergic enervation of blood vessels through such controls as carotid sinus moderator nerves, central and peripheral reflex centers, and chemical mediators such as epinephrine or norepinephrine.

Respiration and venous return affect the blood pressure. Diastolic pressure is higher in the sitting or standing subject. The systolic pressure shows a transitory drop when the erect position is assumed. Pressure is lower during sleep. Exercise raises the systolic pressure. Emotional reactions, discomfort and pain, Valsalva's maneuver, and distended bladder affect the systolic pressure. Some persons have blood pressures of 170/100 with excitement or apprehension for years without ever showing objective signs of disease. The obese arm produces readings, when recorded by the sphygmomanometer, of 10 to 15 mm above the true intra-arterial pressure. Rest, fever, and syncope reduce the blood pressure.

Vascular accidents, coronary or cerebral, may reduce to normal the established diastolic hypertension which the patient had before the attack for periods up to two years. The cause in most cases is obscure.

Most patients with diastolic hypertension show no appreciable change in cardiac output, blood volume or viscosity, pulse rate, circulation time, or venous pressure. Blood flows through the limbs, brain, and other areas at comparatively normal rates contrary to flow observed after epinephrine administration. Muscle blood flow may be increased however, Pressure in the pulmonary artery is usually normal. Patients with established diastolic hypertension excrete a greater proportion of a sodium load than do normal persons.

Problems Relating to Hypertensive Disease Apart From Essential Hypertension

A patient with essential hypertension may have increased systolic pressure produced by severe anemia, thyrotoxicosis, beriberi, arteriovenous fistula, complete heart block, aortic insufficiency, or coarctation of the thoracic aorta.

Toxemia of Pregnancy

Toxemia of pregnancy is accompanied by hypertension. Its cause remains as obscure as that of essential hypertension. In this obscurity they may have more in common than we know. In toxemia of pregnancy retention of sodium and water develops followed by severe generalized vasoconstriction but no cause-and-effect relationship has been demonstrated. The diastolic pressure is usually increased comparatively more than the systolic pressure, and this may be responsible for a number of the cerebral and renal signs and symptoms which are characteristic of the condition. Treatment with the thiazide diuretics, if begun before development of vasoconstriction appears to decrease the likelihood of progression. For emergency situations in the patient whose blood pressure is high and in whom eclampsia is threatening, trimethaphan (Arfonad), which is always given intravenously, is probably the most generally effective single agent available for use. The onset of action is rapid, and its combined effects of ganglionic blockade and direct peripheral vasodilation can almost always lower the blood pressure. Its action is brief, and reliable control of the blood pressure requires minute-to-minute regulation of the rate of infusion.

Diazoxide, which produces fluid retention if used for extended periods, is effective in acute emergencies in pregnancy, and if used only for a short time, does not contribute to salt and water retention.

Coarctation of the Aorta

Coarctation of the aorta produces chiefly high systolic blood pressure. The diastolic pressure may be elevated to a variable degree. The mechanism of hypertension and coarctation is not clear. Experiments on animals suggest that it is not simply an obstructive phenomenon. Humoral and renal theories have been proposed for the cause of this hypertension.

Pheochromocytoma

Pheochromocytoma accounts for less than 0.1 per cent of cases of hypertension. It should be suspected if neurofibromatosis is present. In only half the cases is the hypertension truly intermittent or paroxysmal. When such is the case, however, the episodes complained of are pounding headaches, sweating, palpitation, apprehension, tremulousness, pallor, or flushing of the face, nausea and vomiting, pain in the chest and abdomen, and paresthesias in the extremities. Usually the pupils are dilated, and the limbs are cold. The patient is drenched with perspiration. Hyperpyrexia may be present. These patients give paradoxical response to autonomic blocking agents; that is, to agents which block nerves at locations which result in receptors being oversensitive to norepinephrine. Phentolamine is an adrenergic blocking agent, and, of course, is an exception to this rule.

There are many histamine hyper-reactors in the essential hypertension population. The cold pressor test helps eliminate these. If a patient does have pheochromocytoma and histamine is given and produces an alarming response, 5 mg of phentolamine (Regitine) should be administered intravenously. This is the same dose that is used for the Regitine test.

In essential hypertensives who have had myocardial infarction, catecholamine levels in the urine may be elevated. The same applies to patients with extensive burns.

The internist interested in hypertension who is consulted by surgeons should remember that after surgical removal of a pheochromocytoma the blood pressure may fall precipitously to shock levels. Presurgical control of hypertension with phentolamine orally may obviate many such difficulties. Norepinephrine is a nearly specific drug; however, the extreme hypertension and vasoconstriction produced by the circulating catecholamines and stimulated to greater excess by the surgical procedure cause loss of fluid volume from the blood. Loss in the blood volume with accumulation of fluid in the tissues may require replacement of intravascular fluid to bring about a response from shock. In hypertensive patients who are admitted in a state of shock the possibility of a pheochromocytoma must be considered. The treatment would be as described. Patients with pheochromocytoma may have severe retinal changes. Some have orthostatic hypotension. Glycosuria may be intermittent. The basal metabolic rate is elevated in about half the patients. Pheochromocytomas should be suspected in all hypertensive and hypotensive reactions during anesthetization or pregnancy, in unexpected hypertensive and hypotensive reactions to antihypertensive agents, and in hypotension after administration of phenothiazine tranquilizers. These drugs cause a paradoxical response to circulating catecholamines. Among the commonly used phenothiazine tranquilizers are chlorpromazine (Thorazine) and thioridazine (Melleril). Chlorpromazine has been shown to be an effective sympathetic blocking agent capable of producing vasodilation.

Sometimes the phentolamine test produces shock. Specific treatment is norepinephrine. Bananas and other fruits contain catecholamines and can spoil a urine collection for catecholamine content. Drugs such as reserpine and guanethidine, the antibiotics of wide application, methyldopa, and phenothiazine also interfere. The same is true of monamine oxidase inhibitors, disulfiram (Antabuse), coffee, and vanillin.

False-positive urine catecholamine collections are obtained in conditions other than pheochromocytoma, which increase secretion of catecholamines and their metabolites, A partial listing is hypoglycemia, thyrotoxicosis, angina pectoris, myocardial infarction, renal disease, jaundice, lymphoma and brain tumor. Nose drops containing non-catecholamine derivatives may cause false-positive collections.

There is evidence that false-negative reactions with phentolamine are common in subjects who have been taking antihypertensive drugs during the preceding two weeks.

Hyperaldosteronism

Primary hyperaldosteronism results in hypertension, renal wasting of potassium, hypokalemia, and alkalosis. The common age of occurrence is between 40 and 50 years. The hypertension is usually mild, but there may be cardiomegaly and congestive heart failure, headache, vascular accidents, and occasional retinal changes - indeed, nearly all the signs associated with hypertension from any other cause.

The hypokalemia results in muscle weakness, even paralysis. Electrocardiographic changes associated with hypokalemia and rhythm disturbances are common. Nephropathy may be produced by hypokalemia.

The definitive diagnosis is made by demonstration of excessive adrenal secretion of aldosterone under physiologic conditions that normally do not invoke aldosterone secretion. Remember, normally, sodium depletion stimulates volume receptors that in turn stimulate the adrenal to secrete aldosterone and to conserve sodium. These volume receptors may be in the kidney, heart or major blood vessels, and cervical vessels. Also, renin, angiotensin, or both, may directly augment adrenal aldosterone production independently of the central nervous system.

To demonstrate pathologic elaboration of aldosterone, one must insure that there are optimal expansion of the body fluid and no sodium depletion. The patient is given adequate sodium intake, and diuretic agents are avoided. If there has been previous sodium depletion or diuretic therapy, a patient may be expected to exhibit elevated secretion of aldosterone. In addition, prolonged sodium depletion may correct all the secondary biochemical anomalies, including return of the low levels of serum potassium to normal, lowering of the serum pH and bicarbonate, and expansion of the body stores of potassium.

Patients with essential hypertension who have been treated with diuretics, especially orally, may have low serum potassium concentration and appear to have hyperaldosteronism. Patients with essential hypertension may have renal damage which, in fact, may cause secondary hyperaldosteronism. Unilateral renal ischemia, which produces hypertension, may mimic hyperaldosteronism.

Patients with essential hypertension who have been treated with diuretics and exhibit low serum potassium and elevated urinary potassium concentrations will show slow return to these values to normal if 150 mEq of sodium is allowed daily. In primary hyperaldosteronism, however, the serum potassium concentration will drop further as urinary potassium increases. Patients with hyperaldosteronism seldom have edema. Edema in a given patient would suggest either that the patient has complicating heart failure or that the aldosteronism is due to the disease causing the edema; that is, that secondary hyperaldosteronism is present.

The most frequent initial complaints of hyperaldosteronism are muscle weakness and polyuria. The muscle weakness may be chronic or episodic, and in most cases the weakness appears only after administration of a thiazide-type diuretic. The polyuria is believed to be due to nephropathy produced by potassium depletion. The nephropathy, however, is not specific for primary aldosteronism and may occur in association with any disease attended by significant total body potassium depletion. Elevation of the blood pressure is mild to moderate (160/100 to 200/120). Malignant progression is not characteristic. Retinopathy is usually mild. Cardiomegaly is reported in 40 per cent of cases, but usually congestive heart failure does not develop. The average serum potassium value is below 3 mEq/L; however, some patients have these low levels only episodically. Alkalosis is manifested by elevated bicarbonate concentration of plasma and normal or elevated blood pH.

Hypernatremia is frequent but not consistent, and hyponatremia is virtually never present. Thiazide diuresis may deplete the extracellular fluid volume, and this depletion may stimulate increased urinary aldosterone secretion rate. This may give a false picture of hyperaldosteronism.

Patients for study should not have taken thiazide diuretics for several weeks before appropriate testing. In some patients, 15 mEq/L of potassium chloride three times daily for several days should be given before the testing. On the other hand, as mentioned earlier, sodium depletion resulting from either diuretic therapy or dietary restriction may mask the electrolyte abnormalities of primary aldosteronism, and an adequate sodium allowance should be given when studying these patients.

Mentioned are formidable conceptual, as well as diagnostic, difficulties which may be encountered in the patient with malignant hypertension and secondary aldosteronism. The presence of malignant hypertension is, however, itself strongly suggestive evidence that the patient does not have an aldosteronoma. Patients with malignant hypertension generally have less pronounced hypokalemia, 3.2 to 3.8 mEq/L. These patients usually have hyponatremia, a rare finding indeed in the patient with an adenoma. Reports of muscle weakness and polyuria are scant in the secondary group. Juvenile primary hyperaldosteronism, however, is more frequently accompanied by malignant hypertension. Potassium wasting renal disease in patients with hypertension rarely may serve as a source of confusion, but since most cases represent aberrant forms of Fanconi's syndrome or instances of primary renal tubular acidosis, evidence for other tubular defects, hyperchloremic acidosis, hypophosphatemia, hypouricemia, and renal glycosuria will be demonstrable. Patients with other forms of hyperadrenalism, Cushing's disease, or neoplasms with ACTH production will exhibit increased urinary 17-hydroxysteroids and 17-ketosteroid excretion rates. Ingestion of large amounts of licorice for a long period of time has been incriminated in the production of hypokalemic alkalosis and hypertension, with low aldosterone secretion.

More on Etiologic and Pathophysiologic Considerations

The clinician meeting problems in a disease whose cause is obscure and whose therapeutic rationale is also uncertain may profit by the following knowledge:

Section of the carotid sinus and depressor nerves will elevate the blood pressure and produce tachycardia and an increase in cardiac output. Local application of epinephrine and norepinephrine to these vessels will induce a fall in pressure. Infusions of epinephrine and norepinephrine produce elevation of blood pressure but only for a few days. Cortisone usually produces elevation of the blood pressure only if sodium is allowed.

Some Aspects of Pathophysiology of Abnormal Blood Pressure

The Goldblatt kidney produces renin, which, with hypertensinogen, forms angiotensin, which, in turn, produces high blood pressure through peripheral vasoconstriction. Angiotensin also increases the secretory rate of aldosterone from the adrenals. By this action, it produces sodium retention and antidiuresis in normal persons. In hypertensives, however, it produces a diuretic and natriuretic response. The kidney is said to excrete angiotensin, and some forms of renal disease may produce hypertension as a result of failure of excretion of this material.

Most of these statements apply only to renal hypertension in its early phases. No clinically useful antidotes to increased renin formation have been developed. Continued elevation of serum angiotensin beyond the early phases of renal hypertension is not established.

The total cross-sectional area of all the arterioles of the body is not much greater than that of the aorta, but the surface area in contact with the blood which enhances the resistance to flow is enormous in comparison. The surface area and cross-sectional area of the systemic capillary bed are several hundred times that of the aorta.

Arterioles are normally in a state of partial constriction due to tonic activity of sympathetic vasoconstricting nerves which supply them. In mild bleeding, arterioles reflexly contract and maintain a steady systemic blood pressure, and this causes a decrease in capillary flow.

If a body is heated, the arterioles relax, offering less resistance to flow; and, at this time mean capillary pressure is raised as blood flows through the capillaries more quickly, and as such facilitates heat loss from the skin. The arterioles are also susceptible to chemical influence; thus in exercise local accumulation of metabolites causes severe arteriolar vasodilatation in the muscle, and blood pressure may be kept constant despite a fivefold increase in the cardiac output during the exercise.

Here are some figures for the distribution of cardiac output:

1. 1.300 cc of blood flows through the kidneys per minute, 800 cc flows through the brain, and perhaps 1.500 cc through the liver.

2. The skeletal muscle and resting limbs receive 2 to 3 mL/100 mL of muscle, and as there are about 30 kg of muscle, 40 per cent of the body weight in a man of 70 kg of muscle receives a total flow of 600 to 900 mL. Thus, 4.200 to 4.500 cc of blood flow is accounted for; the remainder supplies the skin, bones, and intestine.

3. Skin flow depends largely on temperature. It may become high when the body temperature has risen. Most people are aware of the danger of taking a hot bath after a large meal, when vasodilatation of splanchnic and cutaneous beds may result in hypotension and syncope.

Hyperventilation causes fall in blood pressure, because the vasomotor center requires a certain CO₂ tension for normal function. CO₂ tension has opposite effects, however, when it is considered in terms of its action directly on the arterial wall. In man, then, hyperventilation seldom produces severe drop in blood pressure. The cutaneous vessels are constricted and the skin becomes cold and pale.

Reflexes

Reflex vasodilatation is occasioned by rises in blood pressure. When blood pressure falls, the tonic activity of the nerve endings is reduced and the vasomotor center escapes from afferent inhibition and thus causes increased sympathetic vasoconstrictor discharge. Reflex nerves then are best called "buffer nerves". Baroreceptors of the cardiovascular system exist in the carotid arteries, the aortic arch, and the root of the right subclavian artery, the right and left atria, the pulmonary artery, and the right and left ventricles.

Effects of Hemorrhage

Haemorrhage reduces the blood volume and causes a fall in the cardiac output, but reflex vasoconstriction secures an increase in peripheral resistance and a sequential reduction in the venous capacity. Since 70 per cent of the blood volume at any one moment is in the venous side of the circulation, reflex vasoconstriction provides a valuable reserve of blood for venous return. Similarly, organs with a reservoir (skin, liver, and spleen) are affected by venous constriction which expresses blood from them toward the heart. The flow of blood is reduced by arteriolar resistance in the skin, splanchnic bed, and muscle, the less vital organs. Because of diminution in capillary pressure at this time, it is more likely that fluid will enter the circulation rather than leave it, and this accounts for increase in blood dilution due to haemorrhage. Hemodilution due to this mechanism is a reflex change and depends neither on the amount of blood lost nor on a fall in the mean blood pressure.

Grayish pallor of more severe shock is due to this sympathetic vasoconstriction, and hence reduced blood flow through the skin. The blood suffers excessive deoxygenation as its flow is so slow, and the graying appearance may be attributed to the content of reduced hemoglobin in the blood contained in the capillaries and subpapillary venous plexus.

Cold sweat is due to sympathetic discharge affecting the sweat glands. Cold skin is due to vasoconstriction. "Goose pimples" are also the result of sympathetic discharge.

The thin, thready pulse is due to the reduced stroke volume of the rapidly beating heart supplied with only a small venous return. Renal flow in hemorrhage is severely reduced as a result of decreased cardiac output and lowered arterial blood pressure combined with renal vasoconstriction. When the patient finally faints, it is because of unexplained sympathetic dilatation of the vessels in the skeletal muscles leading to collapse of the blood pressure. Also, unexplained slowing of the heart beat occurs at this point.

Shock

The clinical picture of inadequate circulation may be produced in many ways: inability of the heart to pump; failure of the heart to fill (because of pericardial tamponade or reduced venous return); obstruction of main arterial pathways, such as pulmonary arteries; widespread failure of cellular metabolism; and loss of vasoconstrictor tone, for example, endotoxin shock. In patients with small blood volume, the low blood pressure is produced by decrease in cardiac output, and arteriolar dilatation is *not* present. The pallor of the skin, coldness of the limbs, sweating, weak and thready pulse, narrowing of the field of consciousness, and restlessness are secondary to the diminished cardiac output and arteriolar reflex vasoconstriction. Thus arises the theory that vasodilators might help correct, in part, in pathophysiology of shock.

Nitroglycerin may produce hypotension due to pooling of blood in the peripheral veins, and syncope may occur in susceptible patients.

In essential hypertension, the cardiac output, capillary and venous pressures, and blood viscosity are all normal. This and other observations tend to show that hypertension is the result of arteriolar narrowing. Circulatory response to carotid sinus compression and carotid occlusion appears to be normal. Adaptation occurs so that the sinoartical baroreceptor reflexes work normally but at a higher arterial pressure "setting." The vascular changes to pressure changes and posture, to painful stimuli, and to psychologic stresses are proportionately similar in hypotensive and normal subjects. On the other hand, fever produces a greater fall in arterial pressure in patients with essential hypertension than in normal persons. The reason for this difference is not known. It has been demonstrated in general that blood flow to the skin, brain, and splanchnic area remains the same; however, in hypertensives blood flow through the muscle is increased but diminished through the kidneys.

In the early stages of essential hypertension, the increase in peripheral resistance is due to reversible contraction of arterioles. This vasoconstriction might be due to sympathetic overaction in the presence of a circulating pressor agent or to intrinsic changes in the contractile properties of arteriolar smooth muscles.

Pheochromocytoma produces hypertension by secretion from the adrenal medullary tissue to large amounts of norepinephrine and epinephrine.

Autonomic Nervous System and Biochemistry

There is a group of hormones which cause smooth muscles to contract. Each of these, serotonin, epinephrine, norepinephrine, acetylcholine, and histamine, has been implicated in normal functioning of the nervous system. There are probably others still unknown.

These neurohormones are formed by specific enzymic reactions and stored away in some cellular particle, in which form they are pharmacologically inactive. On stimulation, they are released to become pharmacologically active. Serotonin, for example, is stored in part in platelets of the blood.

Monamine oxidase, which is found in smooth muscles and in nerves, is an enzyme which destroys these hormones when they meet, serotonin, norepinephrine and epinephrine being monamines. Cholinesterase destroys acetylcholine in a similar fashion.

Work with monamine oxidase inhibitors arose largely from a suggestion that certain psychic abnormalities appear to arise from a deficiency of serotonin content of the brain. Now there are methods of increasing production of the hormone apart from blocking its destruction.

Norepinephrine has been found to be active in the normal transmission of nerve impulses, and it occurs in the hypothalamus. A tranquilizing drug, reserpine, displaces this hormone from the brain, especially from the hypothalamus. Reserpine is a potent releasing agent of such endogenous monamines as serotonin, epinephrine, and norepinephrine from their binding sites; upon release, the monamines are rapidly metabolized.

In the presence of a monoamine oxidase (MOA) inhibitor, these enzymes are not metabolized. MOA inhibitors can therefore reverse the sedative action of reserpine, provided the enzyme inhibitors are given before administration of reserpine. Although the MOA inhibitors afford an increase in the brain levels of a variety of endogenous monamines, their central stimulant effects appear to be due, at least in part, to the action of dopamine. It would be helpful indeed if these interactions could be quantitated.

A well known center of integration of reflex response and control of blood pressure is located in the medulla oblongata. Direct stimulation of hypothalamic nuclei results in massive discharge of the sympathetico-adrenal system.

The sympathetic excitation for vasoconstriction is transmitted through epinephrine at peripheral synapses, although acetylcholine is necessary at the ganglionic level. The parasympathetic system has its impulses transmitted through acetylcholine, both at the ganglionic level, as well as at the neuromuscular or neuroglandular level.

The adrenal medulla is embryologically, anatomically, and functionally homologous to the sympathetic ganglia and is stimulated by acetylcholine. Furthermore, chromophobe cells are innervated by typical preganglionic fibers.

Let us now review responses of effector organs to organic nerve impulses. Adrenergic impulses (sympathetic stimulation) act on the heart at the sinoatrial node to increase heart rate; on the atria to increase contractility and conduction velocity; on the atrioventricular node and conduction system to increase conduction velocity; on the ventricles to increase contractility, conduction velocity, automaticity, and rate of idiopathic pacemakers. All of these responses are mediated through beta receptor types.

The cholinergic response in the heart is, in the sinoatrial node, decreased heart rate (vagal effect); in the atria, decrease in contractility and increase in conduction velocity; and in the atrioventricular node, decrease in conduction velocity, atrioventricular block.

Coronary blood vessels undergo dilatation by adrenergic or cholinergic impulses. The dilatation of adrenergic impulses, however, may be due to multiple indirect causes. Skin and mucosal blood vessels have predominantly an alpha receptor and undergo constriction due to adrenergic impulses and dilatation due to cholinergic impulses. In this area, the data are uncertain. Skeletal muscle has alpha and beta receptors, and these blood vessels undergo constriction and dilatation; however, dilatation is the most common response to physiologically released circulating epinephrine. There are instances in which cholinergic stimulation causes dilatation and cholinergic response is elicited by sympathetic stimulation.

The transmitters of the nerve impulses, acetylcholine, and norepinephrine with adenosine triphosphate (ATP) are stored in the region of the axonal terminals, probably within the synaptic vesicles. The calcium ion perhaps plays a part in elaborating large quantities of this for service in transmission during overstimulation. A certain quantity of these transmitters is always released during the resting state. The quantity is increased, of course, during stimulation. Acetylcholine is destroyed and dissipated by the action of cholinesterase. Whether a chemical destruction is responsible for disappearance of the adrenergic transmitter (norepinephrine) is not known. Diffusion alone may account for termination of the action of the norepinephrine, and it has been shown that diffusion accounts for disappearance of acetylcholine at some synapses.

An oversimplified chemical mechanism for the sympathetic adrenal hormones is as follows:

The amino acid tyrosine becomes dopamine. Dopamine becomes norepinephrine which can become epinephrine. These end products are classified as catecholamines, that is, dopamine, norepinephrine, and epinephrine.

In sympathetic nerves and ganglia, synthesis terminates with norepinephrine, which is stored in amounts of 5 to 10 mcg per gram of tissue. Human adrenal glands contain much more, of course, of which 70 to 80 per cent is epinephrine and the remainder norepinephrine. The hormones are stored in intracellular granules in combination with adenosine phosphate and protein. The concentration of free norepinephrine and epinephrine in plasma are extremely low, being less than 1 mcg per liter.

Inactivation of catecholamines occurs through a combination of physiochemical mechanisms and metabolism by enzymes. In normal persons, as well as those with essential hypertension, the daily urinary excretion of free catecholamines is less than 100 mcg, of which 10 to 80 mcg is norepinephrine and 0 to 20 mcg is epinephrine.

After adrenalectomy, excretion of epinephrine decreases, whereas that of norepinephrine shows little change. Though a potent direct vasoconstrictor, epinephrine infused in man produces generalized vasodilatation and increase in peripheral resistance, as well as striking increase in cardiac output and increase in heart rate. As a result, the systolic pressure is elevated, but the diastolic pressure remains unchanged or falls. In contrast,

norepinephrine causes an increase of both systolic and diastolic pressure due to generalized vasoconstriction. Although norepinephrine is also a potent cardiostimulant agent, the considerable rise in blood pressure leads to reflex slowing of the heart by the carotid sinus mechanism, and, as a consequence, cardiac output is usually unchanged. Large doses of epinephrine produce significant pressor effects, since vasodilatation secondary to accumulation of lactic acid in vascular beds, such as that of muscle, is overcome by the potent direct vasoconstrictor action of the agent.

Monamine Oxidase and Inhibitors

Monamine oxidase is one of the enzymes involved in the metabolism (and destruction) of epinephrine, norepinephrine, serotonin, tyramine, and dopamine. When iproniazide was observed to counteract the apathy and depression in mental patients, many assumed that it acts by inhibition of monamine oxidase activity in the body allowing accumulation of catecholamines. This concept can be questioned, however. Reserpine depletes the body stores of catecholamines and produces mental depression. Monamine oxidase inhibitors can block the sedative action of this drug. The low blood pressure produced by MAO inhibitors is a postural hypotension, and the exact mechanism of this action is unknown. Some of the effects resemble those seen after surgical sympathectomy. It seems paradoxical that hypotension could be due to blocking the metabolism of pressor amines. It is of interest in this connection that some patients with norepinephrine-producing tumors (pheochromocytomas) have supine hypertension but severe postural hypotension. Hypotensive episodes also occur in patients with hyperserotonemia due to malignant carcinoid.

Nearly all norepinephrine in the body is stored in the postganglionic sympathetic fibers and disappears within a few days after section of the nerves. The small amount of residual catecholamine is largely epinephrine, which is presumably localized in chromaffin cells.

Adrenergic fibers can sustain the output of norepinephrine during prolonged periods of stimulation without exhausting their reserve supply. Reserpine causes slow release and nearly complete depletion of the entire catecholamine depots of adrenergic fibers. It reduces their uptake of injected norepinephrine for a considerable period, presumably by blocking the transport mechanism. As norepinephrine is lost, that remaining in the fiber redistributes by equilibrium causing exhaustion of both the mobile and the reserve pools.

Guanethidine produces essentially the same result but by a different mechanism. This is indicated by the observations that another antihypertensive agent, Bretylium, which prevents release of norepinephrine by adrenergic fibers in response to nerve impulses, blocks almost completely the catecholamine-depleting action of guanethidine but to a much lesser extent than that of reserpine.

In addition to reserpine, drugs that inhibit the granular transport mechanism include the psychotropic agents, chlorpromazine, and imipramine, and the adrenergic blocking agent, phenoxybenzamine. Prevention by reserpine of the uptake of catecholamines by the granules with the consequent depletion of norepinephrine from the postganglionic sympathetic fibers is probably the primary basis of its action on the cardiovascular system. Nevertheless, the uptake of 5-HT is also prevented, and many of the effects of reserpine at other sites have been ascribed to this action.

Several drugs that promote release of the adrenergic mediator have already been studied. Tyramine, ephedrine, and amphetamine and related drugs cause relatively rapid, brief liberation of the transmitter and hence produce a sympathomimetic effect. On the other hand, reserpine and guanethidine bring about slow, prolonged depletion of the transmitter, which is largely metabolized as rapidly as it is released. Consequently, their sympathomimetic effects are slight, and their major effects are equivalent to adrenergic blockade.

Alpha and Beta Receptors

One of the more important factors in determining the effects of the sympathomimetic drugs is that there are two types of receptor sites with which it can react to elicit a response in sympathetic effector cells. These receptor cells differ in their physical and chemical properties in such a way as to differ in their affinity for various sympathomimetic amines. In general, the effect on alpha receptors is excitatory and that on beta receptors is inhibitory, although this is by no means an absolute rule. Certain blocking agents are selective for either alpha or beta receptors.

The smooth muscle of blood vessels supplying skeletal muscle has a preponderance of beta receptors by means of which epinephrine causes vasodilatation. It has a smaller number of alpha receptors that allows norepinephrine to constrict these vessels, since this amine has little effect on the beta receptors of smooth muscle. Isoproterenol, which acts on beta receptors and has little or no action on alpha receptors, increases the heart rate, dilates skeletal muscle vascular beds to lower blood pressure, and relaxes bronchial muscle. On the other hand, phenylephrine (Neo-synephrine), which acts on alpha receptors but has little action on beta receptors, has little cardioaccelerator action and does not relax bronchial muscle, but it raises the blood pressure by contracting cutaneous and splanchnic vascular beds. In a number of cases it is not possible, however, to predict the intensity of action of a sympathomimetic amine on any organ even though its activity on the same category of receptor in a different tissue is known. Norepinephrine, for example, elicits little effect by means of its action on beta receptors in the smooth muscle of the bronchial tree, and in blood vessels of skeletal muscle. Nevertheless, it has considerable direct inotropic and chronotropic effects that increase the force of contraction and the rate of the denervated heart by its action on cardiac beta receptors.

Mechanism of Action of Sympathomimetic Drugs

Many sympathomimetic drugs act indirectly by releasing norepinephrine from storage site in the effector organ. Examples are amphetamine and ephedrine, which in general produce a response that is slower in onset and longer lasting than a single equipressure dose of norepinephrine. Repeated injections or continuous infusions of these indirectly acting drugs become less effective as the norepinephrine stores are diminished by continuous release. Other drugs have a dual action, and act directly as does norepinephrine. Continued use of these drugs produces a response that is not abolished.

Intravenous administration of tyramine increases the amount of norepinephrine in the venous outflow of several organs *in vivo*, and at the same times reduces the organ content of norepinephrine. These effects are limited in organs pretreated with reserpine or denervated.

Catecholamines, Noncatecholamines, Autonomic Blocking Agents, and Antihypertensive Drugs

Catecholamines and Noncatecholamines

Epinephrine

Epinephrine is one of the most potent vasopressor drugs known. It can be given intravenously many times, and the response is the same, unlike ephedrine, tyramine, and other amines that owe at least part of their effect to release of norepinephrine. The effect of hypertension is produced by increased ventricular contraction, increased heart rate, and, most important, constriction of arterioles in many vascular beds especially in the cutaneous mucosa and splanchnic regions. Minute doses of epinephrine may cause hypotension, and this depressor effect is due to greater sensitivity to epinephrine of beta receptors in vascular beds dilated by the drug than of alpha receptors in vascular beds constricted by it. Therefore, subcutaneous doses of 0.5 to 1.5 mg usually cause a widened pulse pressure, a lower diastolic pressure, an increased heart rate, cardiac output stroke volume, and left ventricular work per minute, per beat. Therapeutic doses in man increase blood flow to skeletal muscles. Arterial and venous pulmonary pressures are raised, although direct pulmonary vasoconstriction can be shown under suitable conditions. The increase in pulmonary pressure in man is predominantly, if not entirely secondary to an increase in left atrial pressure. Overdosage may cause death by pulmonary edema precipitated by elevated pulmonary capillary filtration pressure. Coronary circulation is enhanced by epinephrine or by cardiac sympathetic stimulation in man as well as in animals. This increase may occur without elevation in aortic blood pressure. The action on the coronary vessels themselves has been alternately reported as constrictor or dilator; however, the flow is increased. Because of the increased work, the requirement for oxygen is greater. Action of epinephrine on the heart is complicated. The cardiac arrest induced by vagal discharge from carotid sinus pressure can be abolished by an epinephrine-induced focus of impulse formation in the ventricles. The action of epinephrine in inducing cardiac automaticity and to some extent its action in causing arrhythmias are antagonized by beta blocking agents that inhibit its chronotropic and inotropic effects; however, alpha blocking agents, such as phenoxybenzamine, are strikingly effective in protecting against epinephrine-induced cardiac irregularities during induction of anesthesia with cyclopropane.

Cardiac arrhythmias have been recorded in man after accidental intravenous administration of conventional subcutaneous doses of epinephrine. Epinephrine is not indicated in shock, and the drug may accentuate the underlying disorder. Its cardiac effects may be of use in restoring cardiac rhythm in cardiac arrests due to various causes, but it is not used in cardiac failure or in hemorrhagic, traumatic, or cardiogenic shock.

Norepinephrine

Norepinephrine increases the peripheral vascular resistance in most vascular beds, and the blood flow through the kidneys, brain, liver, and usually skeletal muscle is reduced. Glomerular filtration rate is maintained unless the decrease in renal blood flow is considerable. Coronary blood flow is substantially increased, probably because of coronary

dilatation and elevated blood pressure. The blood pressure effect of levarterenol, of course, is well known.

Unlike epinephrine, small doses do not cause vasodilatation or lower the blood pressure. The circulating blood volume is reduced by loss of protein-free fluid to the extracellular space, probably because of postcapillary vasoconstriction. This drug has been known to cause sinus bradycardia owing to a reflex increase in vagal tone with or without prolongation of the PR interval. Nodal rhythm, atrioventricular dissociation, bigeminal rhythm, ventricular tachycardia, and fibrillation have been observed. Respiratory minute volume is slightly increased. The drug should not be given to pregnant women, because of its contractile action on the pregnant uterus.

Phenylephrine

Phenylephrine (Neo-synephrine) is related to epinephrine, lacking in OH in the four position of the benzene ring. It is a powerful alpha receptor stimulant with little effect on the beta receptors of the heart. You will recall that the beta receptors of the heart cause an increase in heart rate, increase in contractility and conduction velocity, automaticity, and rate of idiopathic pathmakers. Its action is directly on the receptors primarily, only a small part being due to its ability to release norepinephrine. Central stimulation is minimal. Systolic and diastolic pressures are raised. Effects last 20 minutes after an intravenous dose, or 50 minutes after a subcutaneous dose. There is usually reflex bradycardia, which can be blocked by atropine. Blood flow in the kidneys and skin is reduced. The circulation time is slightly prolonged, and venous pressure is slightly increased. Venous constriction is not pronounced. Phenylephrine is almost completely lacking in chronotropic and inotropic actions on the heart.

Cardiac irregularities occur only rarely, even with large doses, and the reflex slowing is sufficient to permit use of the drug to end attacks of paroxysmal atrial tachycardia.

Roughly, equipressor doses are 0.8 mg intravenously, 5 mg subcutaneously or intramuscularly, and 250 mg orally. Five to 10 mg intramuscularly is the usual dosage. Use of this drug has a rational basis for relieving hypotension occurring during induction of spinal anesthesia and after sympathectomy, or from overdosage of ganglionic blocking agents, anti-adrenergic agents, or veratrum alkaloids, in temporarily constricting resistance vessels relaxed by relief from adrenergic vasoconstriction.

Amphetamine

Amphetamine raises the systolic and diastolic blood pressure. Heart rate is often reflexly slowed. With large doses cardiac arrhythmias may occur.

Noncatecholamines should not be given to patients receiving MAO inhibitors because they are destroyed by monamine oxidase, and if the monamine oxidase is inhibited, high blood pressure may be produced.

Metaraminol (Aramine)

The action of metaraminol is similar to that of norepinephrine, but it is less potent. It does not stimulate the central nervous system. Cardiac output increases strikingly when slowing of the heart is prevented by atropine. Renal and cerebral blood flow is decreased. Pulmonary blood pressure is elevated.

Methoxamine (Vasoxyl)

Methoxamine is another drug in this family which causes peripheral vasoconstriction and has little action on the heart. Sympathomimetic drugs given orally for nasal decongestion must, in general, be given in doses that do increase the blood pressure.

All of these sympathomimetic drugs are useful in shock due to spinal anesthesia. If hypotension persists in spite of administration of the drug, hypovolemia should be suspected. Also, all agents correcting hypotension cause loss of fluid from the vascular compartment. Thus, complications of pheochromocytoma leading to shock are often due to loss of circulating blood volume. Therefore, use of a sympathomimetic drug should be considered a temporary measure only, and volume replacement the specific treatment. In general, the renal and splanchnic blood flows are already decreased in shock, and shock treated by these sympathomimetic drugs can cause further reduction in renal and splanchnic blood flow. Sympathomimetic vasoconstriction can itself produce decreased circulating blood volume. Therefore, shock that follows use of these sympathomimetic drugs usually should be combatted by careful restoration of adequate circulation and blood volume. An alpha adrenergic blocking agent may supplement fluid therapy in some of these patients by further reducing adrenergic vasoconstriction.

The shock complicating myocardial infarction differs in that reduced cardiac output is probably primary and not, as in other types of shock, secondary to inadequate venous return. Elevated blood pressure increases coronary blood flow and, presumably, the nutrition of the uninvolved myocardium, and myocardium of marginal viability; however, it also increased the myocardial work required for any given level of cardiac output, and the effect of sympathomimetic vasopressor agents on the balance between these two opposing factors has never been satisfactorily determined. Myocardial infarction predisposes to the arrhythmic action of cardio-active sympathomimetic amines.

Levarterenol, mephenteramine, and metaraminol produce varying degrees of vasoconstriction and cardiac stimulation, whereas methoxamine (Vasoxyl), phenylephrine (Neo-synephrine), and the polypeptide vasopressor agent, angiotensin, have little myocardial action.

Anti-Adrenergic Agents

Guanethidine

Guanethidine blocks the effect of adrenergic nerve activity. It slowly depletes tissues of catecholamines, and, at the same time, makes end-organs more responsive to catecholamines as much as one hundred fold. The most important complication of

guanethidine therapy is postural hypotension, which is most pronounced shortly after the patient arises from sleep, and may be accentuated by hot weather, alcohol, or exercise. Fluid retention sometimes occur. Ejaculation may be inhibited and associated with impotence. Guanethidine is contraindicated in patients with known or suspected pheochromocytoma because of the pronounced sensitization to circulating catecholamines that it can produce. Likewise, one might expect an over-reaction to administered catecholamines.

The Rauwolfia Alkaloids

With use of these derivatives, inhibition of the effects of peripheral adrenergic nerve activity is obviously due to depletion of norepinephrine. The once widely accepted central mechanism of suppression of the sympathetic nervous system now appears to be untenable. Reduced concentrations of catecholamines can be measured within an hour of administration of reserpine, and depletion is maximal by 24 hours. The doses used in most laboratory experiments reduce tissue catecholamines to negligible levels. Impairment of the adrenergic nerve function usually begins at levels below 30 per cent of normal. Repeated doses have a cumulative action because *tissue catecholamines are restored slowly*. It is not clear that the usual antihypertensive doses in humans regularly reduce tissue catecholamines to levels associated with depressed adrenergic nerve function. There has been some evidence that reserpine disfavors the uptake of catecholamines by certain tissues. It does cause supersensitivity to catecholamines, just as does guanethidine. Even daily doses as small as 0.25 mg can produce nightmares and psychic depression - sometimes severe enough to require hospitalization. Gastrointestinal motility is stimulated, diarrhea sometimes occurs, and gastric hyperacidity is present.

In common with most other antihypertensive agents, the Rauwolfia alkaloids sometimes induce sodium and water retention which can progress to frank congestive heart failure. Cardiac slowing by reserpine and digitalis can be additive. Rauwolfia therapy has been accused of producing cardiovascular lability observed particularly during anesthesia; however, studies designed to confirm this have provided negative results, and routine discontinuance of use of these agents for a period before induction of anesthesia and operation appears to be unnecessary. Congestive heart failure has been aggravated apparently by virtue of cardiac depletion of catecholamines necessary to normal contractile power.

Methyldopa (Aldomet)

Methyldopa is an effective inhibitor of dopamine. It depletes tissue stores of biogenic amines, particularly norepinephrine, including cardiac tissue. Its hypotensive action, however, is not likely related to displacement of norepinephrine from its usual site.

The role of catecholamine depletion or, indeed, of any action on catecholamine metabolism in the antihypertensive effect of methyldopa requires thorough re-evaluation. This hypothesis is questioned because: (1) Excretion of catecholamine metabolites is altered little by hypotensive doses of methyldopa. (2) Normal function of adrenergic nerves can be demonstrated even when the pressure lowering effect is minimal. (3) Other drugs deplete tissue catecholamines even more effectively than does methyldopa, but they do not lower the blood pressure of experimental animals under conditions in which methyldopa is clearly effective. The pharmacologic action is progressive reduction in blood pressure and heart rate

that is maximal in four to six hours and persists for approximately 24 hours after a single dose. The fall in blood pressure is greater in hypertensives than in normotensives. It has been variously reported to be due to decreases in cardiac output, peripheral resistance, or both; postural hypotension can occur and be severe. The hypotension induced by methyldopa has not been shown to involve any major changes in distribution of blood flow. *Renal blood flow and glomerular filtration are well maintained* in both normotensive and hypotensive subjects, and it is considered one of the safest drugs for patients with renal disease.

Sedation is common. Vertigo and psychic depression have been reported. Retention of salt and water with development of edema and congestive heart failure may be somewhat more common with methyldopa than with most other antihypertensive agents. Other side effects are granulocytopenia, drug fever, and impairment of hepatic function. Methyldopa and its metabolites react in chemical tests for catecholamines, and their presence in blood and urine can cause false positive results of tests for pheochromocytoma. This drug has been used in patients with carcinoid disease or nonresectable pheochromocytomas.

Diuretics greatly enhance the hypotensive effects of methyldopa. Untoward reactions include dry mouth, sedation, gastrointestinal irritation, weakness, depression, headache, arthralgia, gain in weight, and acute febrile episodes with chills and aching. Alterations in results of liver function tests, including bromsulphalein, lactic dehydrogenase, and serum glutamic oxalacetic transaminase, have been observed. The drug must be given with extreme caution to patients with depressions or hepatic disease.

Other Antihypertensive Agents

Chlorothiazide (Diuril)

In addition to reducing fluid volume, chlorothiazide has an antihypertensive effect. Normotensive blood pressure is not affected, however. The stronger antihypertensive agent, diazoxide, a cousin, causes salt and water accumulation. Available evidence indicates that the major hypertensive effect of the thiazides is due to direct relaxation of the smooth muscle of resistance vessels, namely arterioles. The mechanism of this effect is not clear. Absence of a significant effect on capacitance vessels allows adequate venous return even in the presence of the gravitational stress of an erect posture, and, therefore, venous pooling and postural hypotension do not occur. By reducing blood volume, however, the thiazides often cause postural hypotension when given with other antihypertensive agents. Norepinephrine, but not angiotensin, affects these capacitance vessels.

Monamine Oxidase Inhibitors

Of the monamine oxidase inhibitors, paragyline (Eutonyl) remains most popular. It is used also as an antidepressant. It has been suggested, on the basis of indirect evidence, that inhibition of MAO might inhibit transmission in ganglia by allowing local accumulation of norepinephrine. The effect of MAO inhibitors is postural hypotension without associated tachycardia. Hepatocellular degeneration, blood dyscrasias, and optic atrophy have been reported. A MAO inhibitor and methyldopa should not be combined in antihypertensive therapy, because this combination can produce severe central nervous system stimulation and a hypertensive reaction under certain circumstances. Pargyline promotes fluid retention and

nonfluid gain in weight, both of which present problems in medical management. Insomnia, nightmares, psychotic reactions, muscle cramps, and other reactions have been reported. With other drugs and unsuspected constituents of diet, extremely severe hypertensive and hyperthermic crises can develop. Cheddar cheese and drugs such as amphetamines have caused hypertensive crises. Demerol may induce *hypotensive* crises. Hyperthermic crises may occur when imipramine hydrochloride (Tofranil) is used.

Veratrum Alkaloids

Veratrum is mentioned to exemplify the effects of the ester alkaloids which have been studied in connection with hypertension and hypotensive effects. The cardiovascular and respiratory systems are profoundly affected by low doses of the active alkaloid. The major cardiovascular effects are reflexive. The terminations of central afferent fibers from pressor or stretch-sensitive areas of the circulatory system are susceptible, and, in the presence of the ester alkaloid, initiate more impulses at any given level of stimulation than under normal conditions. This higher impulse traffic in afferent fibers is interpreted by coordinating areas in the brain stem as denoting a pressure higher than that actually present. As a result, the negative feedback mechanism that normally subserves blood pressure homeostasis is activated, sympathetic tone is decreased, vagal tone is increased, and the pressure is thereby reduced. Blood pressure is decreased, and the heart is moderately slowed. Atropine abolishes the bradycardia but only partially reverses the hypotension.

Because the compensatory mechanisms are reset rather than blocked, the fall in blood pressure does not have a major postural component, cardiac output is only moderately decreased, and cardiovascular reflexes, such as those induced by cold pressor tests of Valsalva's maneuver, are not blocked. Total peripheral resistance is decreased; circulation blood flow to the limbs, kidneys, and liver is slow initially and then becomes almost normal, although the hypotension persists. Venous distensibility is increased. Antidiuresis occurs initially but tends to disappear if the hypotension is prolonged. The action apparently is due to release of the antidiuretic hormone.

Large intravenous doses may cause transient cardiac arrhythmias, heart bloc, and ventricular premature contractions, most of which are accentuated by administration of digitalis and abolished by use of atropine. The margin between the therapeutic and toxic doses is narrow, and this margin is even narrower when continued medication is required. Nausea and vomiting are major complications. Substernal burning, unpleasant taste, salivation, sweating, and hiccough are common. Blurring of vision and mental confusion may appear. Cardiac arrhythmias are more likely to occur in patients receiving digitalis. These arrhythmias are relieved sometimes by administration of atropine. Veratrum is indicated chiefly in patients whose treatment is to be of limited duration and in certain hypertensive emergency conditions, particularly toxemias of pregnancy.

Hydralazine

Hydralazine (Apresoline) reduces the diastolic pressure. The heart rate, stroke volume, and cardiac output are increased. Splanchnic, coronary, cerebral, and renal blood flows are increased unless the blood pressure drops precipitously. Sometimes sodium retention occurs. The general hemodynamic state produced by hydralazine may accentuate specific

inadequacies; for example, hydralazine may considerably increase the pulmonary artery pressure in patients with mitral valve disease. Large doses may reduce the pressor response to epinephrine and impair ganglionic transmission. The exact mode of action is not understood. Continued administration in doses greater than 400 mg a day has produced an acute rheumatoid state indistinguishable from disseminated lupus erythematosus in a small percentage of patients.

Autonomic Blocking Agents

Sympathectomy

Sympathectomy produces predominant orthostatic reduction in blood pressure which may be temporarily disabling, while recumbent pressure is little affected. Side effects are postural hypotension, neuritic pain, patchy sweating in undenervated areas, impaired ejaculation in the male, and nasal congestion.

Hexamethonium

The effects of ganglionic blockade cause vasodilatation of the arterioles with increased peripheral flow and hypotension, pooling of blood, decreased venous return, decreased cardiac output, tachycardia, reduced tone and motility of the gastrointestinal tract, constipation, urinary retention, dry mouth, and anhidrosis. The importance of existing sympathetic tone in determining the degree to which blood pressure is lowered by ganglionic blockade is illustrated by the fact that blood pressure may be decreased only minimally in recumbent normotensive subjects but may fall sharply in sitting or standing subjects. Postural hypotension is common. The cold pressor response is reduced. These blocking agents reduce blood pressure even in patients who have undergone sympathectomy, because ganglionic vasoconstrictive pathways are sometimes not removed surgically. Blood pressure is further reduced by sympathectomy, sodium depletion, and administration of hydralazine.

Usually, mild tachycardia accompanies the induced hypotension. Cardiac output often is reduced; however, in patients with cardiac failure, these blocking agents frequently cause increased cardiac output because of reduction in peripheral resistance and decreased pressure in the right side of the heart resulting from decrease in venous return. A direct positive inotropic effect of hexamethonium on the myocardium has been demonstrated and may contribute to the increased cardiac output of the decompensated heart. In ganglionic blockade, the skin receives more blood. Skeletal blood flow is unaltered, and splanchnic blood flow is usually decreased. There is usually a reduction in cerebral blood flow. However, in hypertensive patients with retinopathy, hexamethonium has been shown to reduce equally cerebral vascular resistance and mean arterial pressure without producing a significant alteration in cerebral blood flow, changes that are favorable for cerebral hemodynamic in hypertension. It reduces coronary vascular resistance and has variable effects on coronary blood flow in hypertensive patients.

In normal subjects, hexamethonium reduces glomerular filtration and renal blood flow; however, in some hypertensive patients, this reduction does not occur. In patients with malignant hypertension, continued use of hexamethonium may cause progressive renal insufficiency and uremia, terminating in death. Gastric secretions are decreased. Achlorhydria

may be produced. Pancreatic secretions are reduced. Biliary secretions are reported to be either unaffected or slightly enhanced. Diminished salivary secretion is another consequence of ganglionic blockade. Constipation has already been mentioned.

The more severe reactions include pronounced hypotension, constipation, paralytic ileus, and urinary retention. Angina may be precipitated. Syncope may occur without warning. The effects of hexamethonium are enhanced when hydralazine is used concurrently. During hexamethonium therapy in a severely hypertensive patient, unexpected pulmonary dyspnea associated with radiologic changes in the lungs may occur and death may ensue. The pulmonary lesion, organized fibrinous edema, is thought to be due to attacks of left heart failure modified by intermittent hypotension. Fatalities from uremia have been reported in patients with malignant hypertension. Therefore, caution must be exercised in the use of ganglionic blocking drugs in patients with cerebrovascular, coronary, cardiac, or renal insufficiency. Gastric retention of food and secretions is sometimes hazardous. Since the catecholamine action is enhanced by ganglionic blockade, the conventional doses for a patient receiving hexamethonium should be reduced accordingly. Intestinal absorption of hexamethonium is unpredictable. Elimination is chiefly through the kidneys. Dosage must be highly individualized, and the patient must be closely supervised. Other agents in this group include mecamlamine (Inversine); pentolinium tartarate (Ansolysen); and trimethaphan (Arfonad).

Parasympathetic Block

Prominent side effects of parasympathetic ganglion blocking agents are common and potentially serious, principally paralysis of the bladder and intestines.

Atropine

Average clinical doses of atropine are 0.4 to 0.6 mg (150 to 300 gr); larger doses cause progressively increasing tachycardia by blocking vagal effects on the sinoatrial pacemaker. Maximal heart rate (response to exercise), however, is unaltered by use of atropine. The influence of atropine is most noticeable in healthy young adults, in whom vagal tone is at its height. In infancy and old age, even large doses of atropine may fail to accelerate the heart rate. Atropine blocks the heart-slowng action of carotid sinus stimulation, pressure on the eyeballs, and the normal afferent impulses causing respiratory arrhythmias; it abolishes bradycardia or asystole from injection of cholinesters, anticholinesterase agents, or other parasympathomimetic drugs. Atropine given as 1.2 mg subcutaneously, has a constant effect on the electrocardiogram in human beings in significantly lowering the T waves usually in all three limb leads. Atropine will correct the shock which is produced by peripheral dilatation caused by cholinesters; however, it has little effect on the blood pressure when given alone. It is a specific drug for the shock due to improper use of cholinesters, such as acetylcholine and methacholine. Methacholine has been used in the treatment of paroxysmal atrial tachycardia, because it acts as a vagomimetic drug; however, atropine is sometimes necessary to counteract the shocklike condition which it produces.

Adrenergic Blocking Agents

Adrenergic blocking agents inhibit responses to adrenergic nerve activity and to epinephrine and other sympathomimetic amines. The locus of action is the effector cell, which distinguishes such agents from substances that prevent sympatho-adrenal discharge by blocking nerve impulse transmission within the cerebrospinal axis, in autonomic ganglia, or along peripheral neurons, or that interfere with release of adrenergic mediator-like norepinephrine. Alpha receptors produce increased blood pressure to norepinephrine; beta receptors respond to isoproterenol.

Before 1958, all known adrenergic blocking agents affected mainly the alpha adrenergic receptors and were unable to prevent myocardial stimulation, bronchial smooth muscle relaxation, and vasodilatation of the skeletal muscle, which are beta receptor functions. The blocking agents are almost entirely specific for one or another of these functions. These alpha adrenergic blocking agents have little effect on the blood pressure of normotensive subjects unless they are hypovolemic. In hypertensive subjects, they produce orthostatic hypotension.

One drug in this series, phenoxybenzamine (Dibenzylamine), has been used to treat patients with Raynaud's disease, acrocyanosis, causalgia, and chronic ulceration of the limbs. The ergot alkaloids were the first adrenergic blocking agents to be discovered; however, they have important pharmacologic properties concerning direct stimulation of the smooth muscle, and complex excitation and depression of the central nervous system.

Phentolamine produces a moderately effective, competitive alpha adrenergic blockade that is relatively transient. Five milligrams of phentolamine effectively reduces the blood pressure if it is elevated by action of pheochromocytoma. False positive and false negative responses are more common in patients who are azotemic or receiving sedatives or narcotics. Tachycardia and dizziness usually develop. The drug has been used in treatment of shock to counteract vasoconstriction.

Protection can be attributed to three specific antishock effects: (1) increased total blood flow, particularly in the abdominal viscera; (2) local redistribution of blood flow so that a larger percentage passes through channels that readily exchange metabolites with tissue cells, presumably true capillaries, and (3) reversal of the vasoconstriction-induced shift of fluid from the vascular to the interstitial compartment. Thus, phenoxybenzamine is under investigation for treatment of patients in shock; results have been encouraging.

In addition to its specific antishock effects seen sometimes in patients operated on for pheochromocytoma, two other effects of phenoxybenzamine might contribute to the practical clinical management of certain conditions in the future:

1. The fall in blood pressure induced only when it is administered to hypovolemic patients provides a quick and reliable indication of the inadequacy of intravascular fluid volume replacement, a point often difficult to assess.

2. The shift of blood from the pulmonary to the systemic vascular bed associated with blockade of sympathetic vasomotor tone allows administration of larger volumes of fluid more

rapidly than would otherwise be possible, particularly with patients with some myocardial inadequacy.

Isoproterenol

Isoproterenol has a powerful action on beta receptors and almost no action on alpha receptors. Its main actions are therefore on the heart, smooth muscle of the bronchi, skeletal muscle vasculature, and alimentary tract. On the cardiovascular system it lowers the peripheral vascular resistance mainly in skeletal muscle but also in renal and mesenteric vascular beds, and the diastolic pressure falls.

An Important Pressor Agent

Angiotensin

Angiotensin is physiologically produced when the enzyme, renin, liberated from storage sites in the kidney, acts on the substrate angiotensinogen, a plasma globulin. The first product is angiotensin I, which is pharmacologically inert; however, through the action of a further enzyme system present in the plasma and many tissues, it is rapidly converted to the active octapeptide, angiotensin II. Angiotensin produces intense vasoconstrictor and pressor reactions. It is a powerful stimulant to the secretion of aldosterone. The blood pressure is increased as a direct stimulant action on vascular smooth muscle. The precapillary region is most affected. Postcapillary vessels and veins are only feebly constricted. The effect is strongest in the vessels of the skin, splanchnic region, and kidney, and the blood flow in these organs falls sharply. The effect is less in the vessels of skeletal muscle and in cerebral and coronary vessels, and blood flow in these beds is maintained or increased as the relatively weak vasoconstrictor response is opposed by the elevated systemic blood pressure.

In vivo, positive inotropic effects are inconstant and fleeting, and there is no sustained increase in myocardial contractility. Usually, the heart rate is slowed by reflex action. Cardiac output may fall slightly. There is an increase in the work done by the heart, but this is usually unaccompanied by evidence of coronary insufficiency, presumably because the raised systemic blood pressure insures an adequate coronary blood supply despite the coronary constrictor action of angiotensin.

For blood pressure angiotensin is the most powerful stimulant known, molecule for molecule. It is about forty times as active as norepinephrine. Systemic blood pressure in man has been raised by infusing as little as 0.002 micrograms per kilogram of body weight each minute. The response occurs in one minute, and blood pressure returns to normal in about five minutes. It is less likely to be followed by hypotension. It has little or no tendency to set up disturbing arrhythmias. It can be combined with anesthetics, such as cyclopropane and other halogenated hydrocarbon agents. There is no tissue necrosis or sloughing; however, it shares the disadvantage that it diminishes blood volume by prompting loss of protein-free fluid from the circulation to tissue spaces. It does not reduce the venous reservoir as effectively as does norepinephrine.

Summary

The common clinical course of essential hypertension is fairly well known, but the cause and results of treatment are not fully appreciated even in the light of an abundant new body of information regarding the etiologic influence of the autonomic nervous system, and on the mechanism of drug action. It is, therefore, not practical to discuss unusual "laboratory" manifestations of essential hypertension.

Essential hypertension is unusual when it mimics hypertension which has a cause. Likewise, these diseases masking as essential hypertension may be considered under "unusual manifestations." Many "unusual manifestations" occur clinically during treatment of hypertension with old and new agents. These range from interesting nuisances to life-threatening reactions. Many such reactions are unavoidable, justifiable, and sometimes *necessary*. Some are absolutely unnecessary and inexcusable. This is true when powerful agents whose total action is not appreciated, are used to treat a sign only and not specifically to correct a pathophysiologic process. Herein is presented information which must bear an intelligent recognition, appreciation, and management of unusual manifestations of essential hypertension. This information has been gathered from standard reference sources and arranged in an attempt to fit the practitioner's needs.