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## The role of adrenergic drugs in antihypertensive therapy

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■ Abnormalities in the adrenergic system are believed by some to be a major contributing factor to primary hypertension, which may explain the increasing clinical usefulness of drugs that affect the adrenergic system. The clinical effects of drugs in this class can be predicted by the location of the alpha or beta receptors that are activated or inhibited by the drug. With the wide range of antihypertensive drugs now available, including diuretics and vasodilators as well as adrenergic agents, it is possible to individualize treatment in ways more appropriate than the traditional stepped-care approach.

□ INDEX TERMS: ADRENERGIC DRUGS; HYPERTENSION □ CLEVE CLIN J MED 1991; 57:79-93

**I**N PROPOSING the "Mosaic Theory of Hypertension," Irvine Page<sup>1</sup> called attention to the many interrelated factors that influence the level of blood pressure (*Figure 1*). Generally, patients with secondary hypertension, as may occur with pheochromocytoma or renovascular disease, demonstrate a gross aberration of a single factor, such as excessive catecholamines or renin which, if recognized and corrected, can result in cure of the hypertensive state.

The situation is less simple in most individuals with primary or essential hypertension where the changes are more subtle. Smaller aberrations of a pro-hypertensive mechanism, usually combined with inadequate

compensatory hypotensive responses,<sup>2</sup> may be responsible for the elevated blood pressure. Frequently, a pathophysiologic mechanism cannot be found, and the situation is not amenable to cure. Nevertheless, the blood pressure of patients with primary hypertension can be controlled by appropriate changes in lifestyle or the use of antihypertensive agents. The therapeutic measures used for these patients have not usually been directed against a specific aberration that caused the elevated blood pressure; instead, treatment measures have been designed to diminish one of the many pro-hypertensive factors, or to enhance various hypotensive influences included in Page's mosaic.

In recent years, we have learned a great deal about circulatory control mechanisms, developed a bank of epidemiologic data, and improved our diagnostic procedures. We have become more adept at recognizing important contributory factors to the elevation of blood pressure among individual patients, even among those with primary hypertension. We have learned to assess better the pathologic processes and target organ damage suffered by hypertensive individuals.

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This article was produced by Consultants in Medical Education, Inc, Manhasset, New York, under an educational grant from Schering-Plough International.

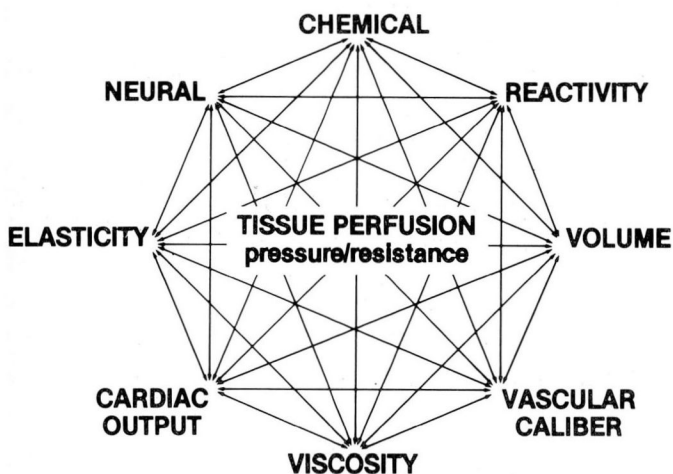


FIGURE 1. Depiction of the mosaic theory of hypertension, proposed by Irvine Page, MD. The mosaic theory recognizes that essential hypertension may not represent a disturbance in a single regulatory mechanism of tissue perfusion but may, in fact, be the end result of the interplay of many factors in an interlocking, dynamic system that controls arterial pressure.

In conjunction, many new antihypertensive agents have become available that can affect a variety of specific circulatory control mechanisms. These advances have led us to reconsider the way we treat patients with primary hypertension. Our previous goal was simply to lower blood pressure. This benefitted most hypertensive patients, but there were many side effects associated with antihypertensive therapy and, although the death rate improved, it remained greater than normal. Thus, we have had to develop a new approach, and we now attempt to target our therapy to the individual patient.<sup>3</sup> By so doing, we can design a treatment regimen that will counter specific physiologic alterations and prevent specific pathologic consequences in that particular patient. Targeted therapy offers the possibility of lowering blood pressure with smaller doses of medication and fewer side effects. It is hoped that this approach will be associated with improved morbidity and mortality statistics.

The mosaic theory of hypertension illustrates Poiseuille's Law, as shown in Figure 2. Those factors which influence blood pressure ultimately affect the cardiac output and peripheral vascular resistance.

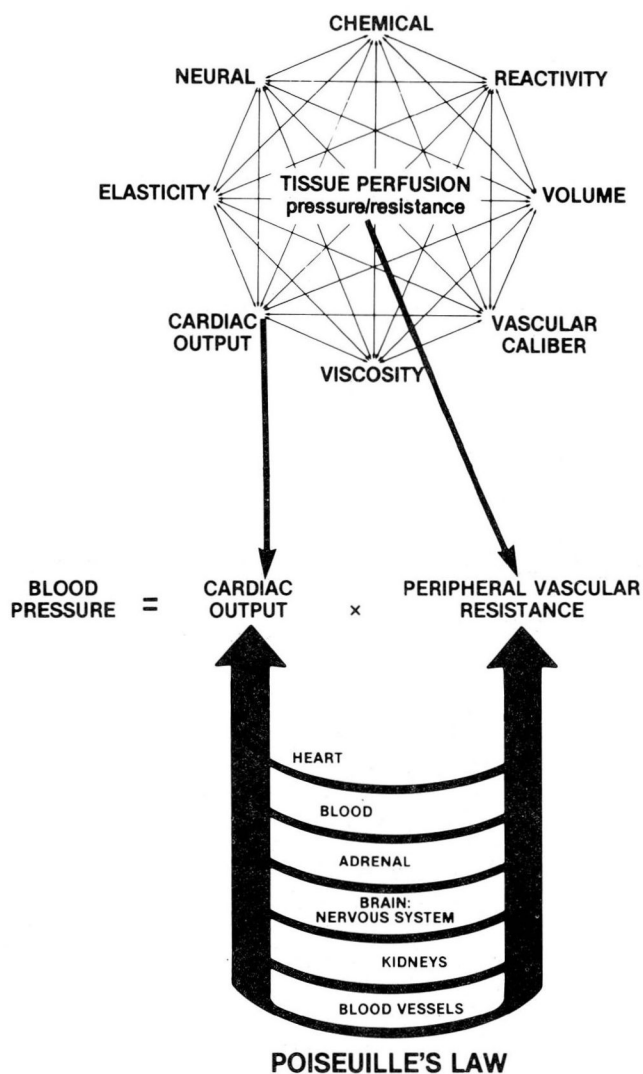


FIGURE 2. Poiseuille's law illustrated by the mosaic theory. Factors that influence blood pressure ultimately affect the cardiac output and peripheral vascular resistance; conversely, effects on cardiac output and peripheral vascular resistance can give rise to elevated blood pressure.

Measurements of hemodynamics in patients with hypertension typically demonstrate some combination of an elevated cardiac output and elevated peripheral vascular resistance. Antihypertensive drugs lower blood pressure by decreasing the cardiac output and peripheral vascular resistance.<sup>4</sup>

### HYPERTENSION AND THE ADRENERGIC SYSTEM

The adrenergic system (referring here to the adrenergic or sympathetic nervous system and the adrenergic hormones, epinephrine and norepinephrine) can be included among the neural and chemical components of the mosaic. A closer analysis of Poiseuille's Law indicates that the adrenergic system plays an especially important role since it affects the cardiac output and peripheral vascular resistance in multiple ways (Figure 3). The adrenergic nervous system and adrenergic hormones have direct and reflex actions on the heart to alter myocardial contractility and heart rate. By more indirect means, the adrenergic system can influence the cardiac output by affecting other hormonal systems which act on the heart, or by helping to determine the effective blood volume and venous return as a result of actions on the veins and kidney.

The adrenergic nervous system, circulating adrenergic hormones, and their many interactions with other vasoactive systems (renin-angiotensin, prostaglandins, atrial natriuretic factor, kinins) are also prime determinants of peripheral vascular resistance. The influences of the adrenergic system on the circulation are so pervasive that some investigators believe that the major cause of primary hypertension may derive from an abnormality of this system.<sup>5</sup> Their reasoning finds support in the observation that many of our most useful drugs for treatment of hypertension act via the adrenergic system.

As we move from less specific application of antihypertensive agents to targeted modes of therapy, the drugs that affect the adrenergic system are becoming ever more useful. These drugs can interfere with the

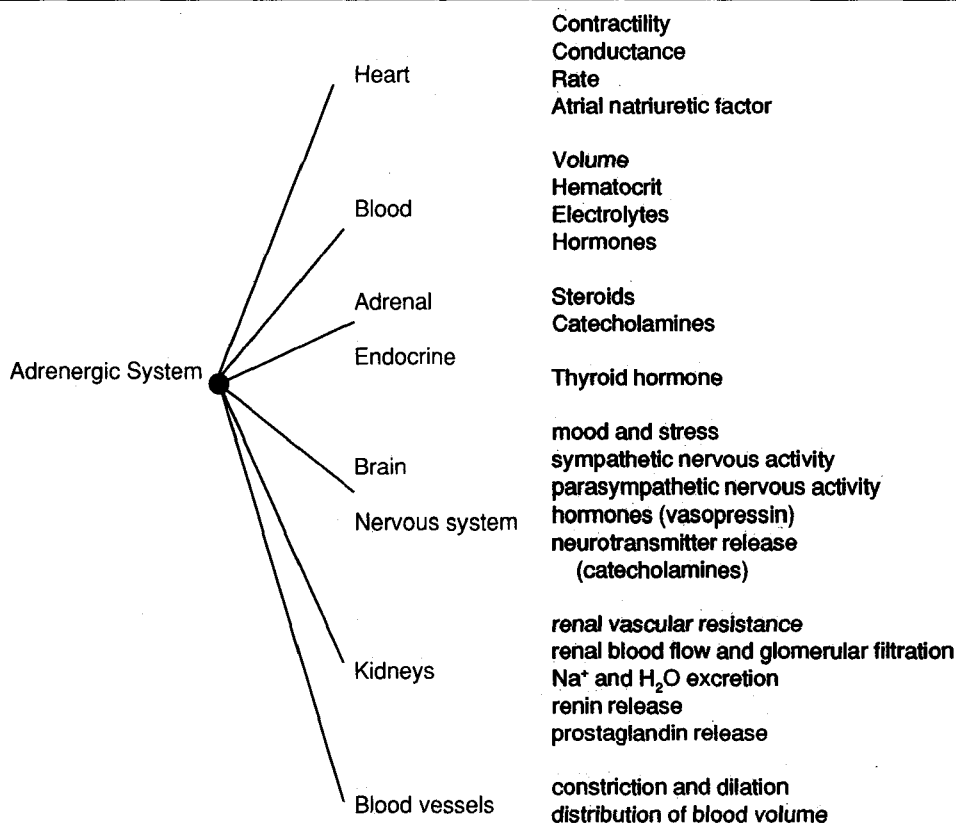


FIGURE 3. The adrenergic system, which is included in the neural and chemical components of the hypertension mosaic, has multiple direct and indirect effects on the cardiac output and peripheral vascular resistance.

autonomic nervous system at a particular desired level, affect selected hormonal release mechanisms and hormonal actions, alter metabolism and organ function, help protect the heart, modify the atherosclerotic process and, in general, provide multiple possibilities to individualize treatment for the needs of the individual patient.

### ANTIHYPERTENSIVE DRUG THERAPY

In the past, antihypertensive agents could be divided into three categories, depending upon whether they act primarily as diuretic agents, direct vasodilators, or adrenergic agonists and antagonists (Table 1). Today any such categorization cannot be precise, since many antihypertensive agents have additional secondary actions and indirect metabolic or compensatory hemodynamic effects that also affect blood pressure. In several instances,

TABLE 1  
CATEGORIES OF ANTIHYPERTENSIVE DRUGS

Categories:	I Diuretics	II Vasodilators	III Adrenergic Agents
A.	Thiazides and related compounds (early distal tubule) Hydrochlorothiazide Chlorothalidone Indapamide	A. Direct Vasodilators Hydralazine Minoxidil Diazoxide Nitroprusside Nitrates	Central Nervous System (CNS) A. Reserpine Propranolol B. Alpha-2 Agonists Clonidine Methyldopa Guanabenz Guanfacine
B.	Loop Diuretics Furosemide Ethacrynic Acid Bumetanide	B. Calcium Channel Blockade Nifedipine Nitrendipine Nicardipine Verapamil Diltiazem	Peripheral Sites A. Ganglionic Blockade Trimethaphan Pentolinium Mecamylamine
C.	K-Sparing Triamterene Amiloride Spironolactone	C. ACE Inhibitors Captopril Enalapril Lisinopril D. Alpha Blockade 1. Non-Selective $\alpha$ -1, $\alpha$ -2 Phentolamine Phenoxybenzamine 2. Selective $\alpha$ -1 Prazosin Terazosin Doxazosin Amusolol 3. Selective $\alpha$ -1, $\beta$ -1, $\beta$ -2 Labetalol	B. Adrenergic Blockade Reserpine Guanethidine Guanadrel C. Alpha-2 Agonists Clonidine Methyldopa Guanabenz Guanfacine D. Alpha Blockade (see Vasodilators II D) E. Beta Blockade 1. Non-Selective $\beta$ -1, $\beta$ -2 Propranolol Nadolol Timolol 2. Selective $\beta$ -1 Metoprolol Atenolol 3. Intrinsic Sympathomimetic Activity Pindolol Acebutolol F. $\beta$ -1, $\beta$ -2 and $\alpha$ -1 blockade Labetalol

these additional effects have been recognized in *Table 1*, where some antihypertensive drugs have been listed in more than one category.

### Diuretics

Diuretics lower blood pressure by enhancing salt and water excretion, thus reducing the plasma volume and cardiac output. These hemodynamic effects are most pronounced during the early stages of diuretic therapy, before compensatory homeostatic adjustments have been made.<sup>6</sup> Additionally, diuretics may diminish peripheral vascular resistance either by slight vasodilatory actions or by reducing vascular reactivity, perhaps as a consequence of metabolic alterations. The vascular effects of the diuretics tend to become manifest after longer-term therapy.

The antihypertensive efficacy of the diuretics is

equivalent to that of the other categories of antihypertensive drugs, although certain patients may be particularly sensitive or insensitive to their actions. The potassium-sparing group (especially triamterene and amiloride) appears to have a smaller antihypertensive effect than the other diuretic agents. In terms of their metabolic effects, important differences may be observed depending to some extent on their renal tubular sites of action. Generally, agents (such as the thiazides and related compounds) that act at the diluting segment of the early distal tubule have a longer antihypertensive duration of action. These agents may have a somewhat greater vascular effect but lesser diuretic action than agents such as furosemide, which act primarily at the loop of Henle.

The choice of diuretic in a given patient may depend upon the degree of diuresis and type of metabolic alteration deemed most appropriate to that patient's condition. The ability of diuretics to act synergistically with many other antihypertensive drugs led to their past popularity. In recent years, a greater recognition of their potential to cause undesirable metabolic effects, such as hypokalemia, glucose intolerance, and lipid abnormalities, has diminished their favor. Furthermore, unlike the adrenergic agents, the diuretics are not believed to be cardioprotective,<sup>7-9</sup> and they have not been shown to improve left ventricular hypertrophy secondary to hypertension.<sup>10,11</sup> As a result, morbidity and mortality statistics for cardiovascular disease associated with the use of diuretics for hypertension have not improved to the extent anticipated, except for the reduced incidence of stroke.

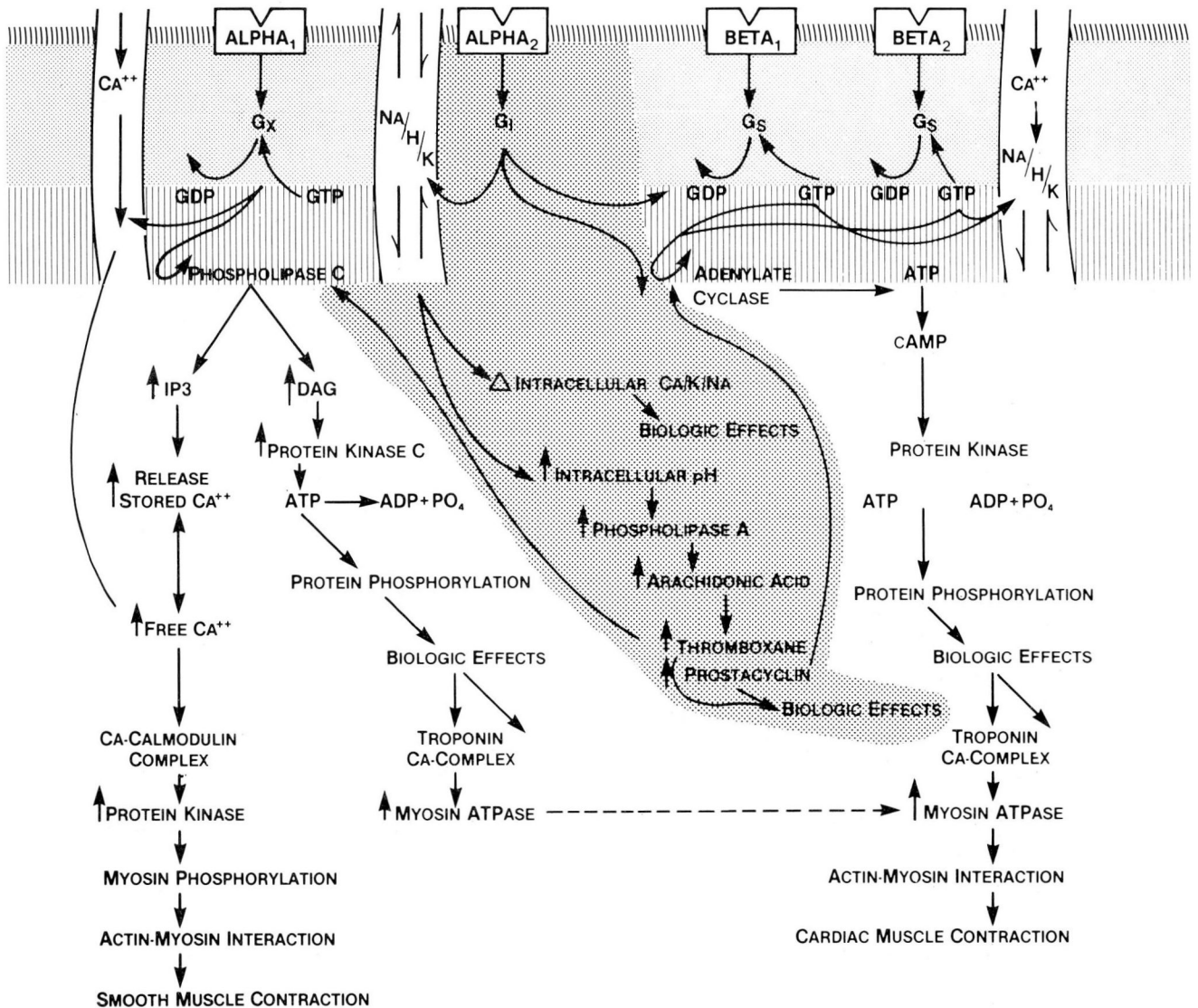


FIGURE 4.  $G_x$ ,  $G_i$ , and  $G_s$  represent guanine nucleotide binding proteins (G proteins) specific to each receptor. Conversion of guanine diphosphate (GDP) to guanine triphosphate (GTP) G-protein complex activates membrane channels and membrane enzymes resulting in formation of second messengers inositol 1,4,5 triphosphate (IP3), diacylglycerol (DAG), and cyclic AMP (cAMP). Resulting changes of intracellular free calcium and activation of protein kinases produce biochemical events leading to muscle contraction and other biologic events associated with the specific receptor at different tissue sites. Note: alpha-2 receptor activation tends to inhibit effects of beta-receptor stimulation and may increase prostanoid activity.

### Vasodilators

Vasodilators reduce blood pressure by direct effects on blood vessels to decrease vascular resistance. Verapamil has negative inotropic and chronotropic effects and, under certain circumstances, may reduce cardiac output. In general, the vasodilators do not have

major direct effects on the heart that alter the cardiac output to any significant degree. Indirectly, as a consequence of lower blood pressure, which diminishes baroreceptor inhibitory activity of the sympathetic nervous system, several vasodilators may cause undesirable reflex tachycardia (hydralazine, minoxidil,

TABLE 2  
EFFECTS OF ALPHA ADRENORECEPTOR SUBTYPES

Alpha <sub>1</sub>		Alpha <sub>2</sub>	
Location	Effect	Location	Effect
CNS	Stimulation	Neurons: CNS (postsynaptic)	Sedation
Heart	↑ Contractility		↓ Sympathetic outflow
Vascular smooth muscle	Contraction		↑ Vagal activity
Non-vascular smooth muscle: uterus, trigone, ureters sphincters (GI, bladder) GI tract	Contraction	Sympathetic nerve terminals (presynaptic)	↑ Baroreceptor reflexes
Liver	↑ glycogenolysis	Sympathetic ganglia	↓ Norepinephrine release
Kidney	↑ Na <sup>+</sup> absorption	Cholinergic (peripheral)	Hyperpolarization
		Serotonergic	↓ Acetylcholine release
		Vascular smooth muscle	↓ Firing
			↓ Serotonin release
			Contraction
			↑ Endothelial derived relaxing factor
		Platelets	Aggregation
		Kidneys	↓ Renin release
		Pancreas	↓ Insulin release
		Adenohypophysis	↑ Growth hormone
		Fat cells	↓ Lipolysis
		Intestine	↑ H <sub>2</sub> O and electrolyte absorption

nifedipine) and compensatory increases in cardiac output (hydralazine, minoxidil).

The vasodilators reduce vascular resistance by a variety of mechanisms. Agents such as hydralazine and minoxidil have direct actions on vascular smooth muscle that are not fully understood. The various calcium channel blockers interfere with the slow voltage-dependent channels by which calcium enters cells, leading to a relaxation of vascular smooth muscle.<sup>12</sup> The angiotensin-converting enzyme (ACE) inhibitors prevent the vasoconstrictor effects of angiotensin-II by blocking its synthesis, and the alpha-receptor antagonists function as vasodilators by diminishing adrenergic nervous vasoconstrictor influences.

The various vasodilators can effect a multiplicity of hemodynamic responses because of their different modes of action. There may be (as with hydralazine) compensatory increases in cardiac output or there may not be (as

with nifedipine). Diverse effects on regional circulations can redistribute blood flow, and the different agents have individual propensities to dilate arteries or veins selectively (hydralazine and minoxidil v nitrates) or arteries plus veins (prazosin and nifedipine).<sup>13</sup>

Undesirable side effects, such as tachycardia, flushing, headache, peripheral edema, and orthostatic hypotension can result. These can be particularly relevant in patients with congestive heart failure, atherosclerotic heart disease, cerebrovascular insufficiency, migraine, and renal disease. Thus, it is important to tailor the vasodilator to the patient.

As newer vasodilators with fewer side effects are developed these agents are becoming increasingly popular for treatment of hypertension. Most hypertensive individuals demonstrate increased peripheral

vascular resistance. In particular, vasodilators may be useful for elderly hypertensive patients and for individuals with diseases that make it essential to maintain good blood flow to the limbs and vital organs.

### Adrenergic drugs

To understand the mechanisms by which the individual adrenergic agents lower blood pressure, and the potential advantages and disadvantages of each, it is appropriate to consider these agents in terms of their receptor activities. *Figure 4* summarizes the cascade of events involved in the activities of the alpha-1 and alpha-2 and beta-1 and beta-2 adrenergic receptors.

There is evidence for further subdivision of the adrenergic receptors than shown here, but it is not possible, at this time, to incorporate this information into our concepts of how the adrenergic hypotensive agents lower blood pressure. More detailed descriptions of the

biochemistry and physiology of adrenergic receptors have been published.<sup>14</sup>

**Receptor activities.** When an agonist binds the alpha-1 receptor (Figure 4), a transmembrane-signaling process is induced via a specific regulatory guanine nucleotide-binding protein (G<sub>x</sub> protein) present in the cell membrane.<sup>14-19</sup> This catalyzes the dissociation of guanine diphosphate (GDP) from a subunit (alpha-1) of the G protein and promotes in its place the subsequent binding of the active ligand guanine triphosphate (GTP).

The resulting GTP-alpha-1 subunit complex splits off from the parent G protein and effects several responses. For one, it may modulate membrane ion channels to increase calcium movement into the cell. In addition, the GTP-alpha-1 complex can activate membrane enzymes such as phospholipase C. Phospholipase C catalyzes the hydrolysis of a membrane phospholipid, resulting in the generation of second messengers, inositol-1, 5-triphosphate (IP<sub>3</sub>), and diacylglycerol (DAG).

IP<sub>3</sub> causes a further increase of intracellular free calcium via the release of calcium from intracellular stores. When intracellular free calcium reaches a critical concentration, a calcium calmodulin complex is formed.<sup>20</sup> This, in turn, activates a protein kinase that generates the

TABLE 3  
EFFECTS OF BETA ADRENORECEPTOR SUBTYPES

Beta <sub>1</sub>		Beta <sub>2</sub>	
Location	Effect	Location	Effect
Sympathetic nerve terminals (presynaptic)	↑ Norepinephrine release	Vascular smooth muscle	Relaxation
Heart: myocardium	↑ Contractility	Non-vascular smooth muscle: uterus, bladder, lung, GI	Relaxation
	↑ Conduction velocity	Skeletal muscle	↑ Contractility
SA, AV nodes conduction system	↑ Automaticity	Liver	↑ K <sup>+</sup> uptake
	↑ Rate Conduction velocity		↑ Glycogenolysis
Kidney	↑ Automaticity	Pancreas	↑ Glycogenolysis
	↑ Renin release		↑ Insulin release
Posterior pituitary	ADH secretion		
Fat cells	↑ Lipolysis		

TABLE 4  
BETA ADRENERGIC RECEPTOR AGONISTS AND ANTAGONISTS

	Alpha <sub>1</sub>	Alpha <sub>2</sub>	Beta <sub>1</sub>	Beta <sub>2</sub>
Agonists	Epinephrine*	Epinephrine*	Epinephrine*	Epinephrine*
	Norepinephrine*	Norepinephrine*	Norepinephrine*	
	Methoxamine	CLONIDINE	Dopamine	Albuterol
	Phenylephrine	α-methyl NE (METHYLDOPA) GUANABENZ GUANFACINE	Isoproterenol* Prenalterol	Isoproterenol* Metaproterenol Pirbuterol Terbutaline
Antagonists	PHENTOLAMINE*	Phentolamine*	PROPRANOLOL*	Propranolol*
	PHENOXYBENZAMINE*	Phenoxbenzamine*	NADOLOL*	Nadolol*
	Tolazoline*	Tolazoline*	TIMOLOL*	Timolol* Labetalol*
	PRAZOSIN <sup>+</sup>	Yohimbine	METOPROLOL <sup>+</sup>	
	TERAZOSIN <sup>+</sup>		ATENOLOL <sup>+</sup>	
	DOXAZOSIN <sup>+</sup>		ACEBUTOLOL▲	
	TRIMAZOSIN <sup>+</sup>		PINDOLOL▲	
	LABETALOL* <sup>+</sup>		Labetalol*	

Agents that have found use in the treatment of hypertension are shown in capital letters at the receptor site of antihypertensive activity.

\* Drugs with significant effect at more than one adrenergic receptor

+ Drugs considered to have selective alpha-1 or beta-1-blocking effects

▲ Beta blockers with intrinsic sympathomimetic activity

biochemical reactions which result in the actin-myosin interaction, vascular smooth-muscle contraction, and increased blood pressure. DAG also activates a protein kinase (protein-kinase C) that initiates the series of events outlined in Figure 4 and a host of biologic effects, depending on the tissue location of the alpha-1 receptor (Table 2).

In the circulatory system, a troponin-calcium complex is formed (also enhanced by increased intracellular free calcium) which diminishes the inhibitory effect of troponin on myosin ATPase and allows the actin-myosin interaction to occur.<sup>20</sup> When this takes place in the heart, there is an increased contractility of cardiac muscle and increased cardiac output.

A similar series of events to increase cardiac output also occurs via the beta-1 receptors, which are especially prominent in the heart. Figure 4 illustrates the membrane and intracellular processes that follow activation of the beta-1 and beta-2 adrenergic receptors. In this case, the G protein has been specified GS (actually there is a heterogeneous group of GS proteins). The active GTP-alpha-1 subunit formed in association with beta receptor stimulation may act directly on membrane ion channels to enhance calcium influx and alter sodium/hydrogen/potassium exchange mechanisms. Adenylate cyclase is also activated, resulting in the hydrolysis of adenosine triphosphate (ATP) and formation of cyclic AMP as the second messenger.

There follows an increase in protein kinase activity, phosphorylation of effector proteins, and biologic ef-

TABLE 5  
SELECTION CRITERIA FOR ANTIHYPERTENSIVE DRUG THERAPY

Patient Characteristics	Considerations	Choice*	Possible Disadvantage*
Non-Compliant	Avoid drugs with prominent side effects - lassitude, impotence; avoid drugs with rebound effects Prefer one dose/day.	ACE inhibitors (II C) Ca channel bl. (II B)	Alpha-2 agonists (III B, CNS) Adrenergic bl. (III B, Periph)
Black: Salt-Sensitive	Tendency for hypervolemia and low renin state Need for drugs which maintain renal hemodynamics and enhance Na <sup>+</sup> and H <sub>2</sub> O excretion	Diuretic (I A, B) Ca channel bl. (II B)	Beta bl. (III E 1, 2) Adrenergic bl. (III B, Periph)
Young:	Need to maintain vigorous mental and physical life style		
High Pulse Rate High Cardiac Output	Often have elevated catecholamines and renin Need to reduce hyperdynamic circulation	Beta bl. (III E) Labetalol	Diuretics (I) Alpha-2 agonists (III B, CNS) Hydralazine Nifedipine, Nitrendipine, Nicardipine
Slow Pulse Rate Normal Cardiac Output	Need to maintain appropriate pulse and cardiac output	Vasodilators (II)	Beta bl. (III E 1, 2) Alpha-2 agonists (III B, CNS) Adrenergic bl. (III B, Periph), Verapamil
Elderly:	Tendency for increased peripheral vascular resistance; diminished cardiac output and renal function Frequent presence of multiple medical problems and medication	Ca channel bl. (II B) Alpha bl. (II D 2, 3)	Alpha-2 agonists (III B, CNS) Adrenergic bl. (III B, Periph) Beta-1, beta-2 bl. (III E 1) Diuretics (I)
Ischemic Heart Disease	Need for cardiac protection: Avoid arrhythmias Dilate coronary arteries Decrease oxygen demand	Beta bl. (III E) Ca channel bl. Nitrates	Diuretics (I) Hydralazine Minoxidil
Left Ventricular Hypertrophy	Potential benefits of reversal	Adrenergic drugs (III) ACE inhibitors (II C) Ca channel bl. (II B)	Diuretics (I) Hydralazine Minoxidil
Congestive Heart Failure	Need to decrease preload and afterload Avoid negative inotropism	ACE inhibitors (II C) Hydralazine plus nitrates Diuretics (I)	Beta bl. (III E, F) Ca channel bl. (II B)

\*Parenthetical data - (roman numeral, letter and number) refer to antihypertensive drug categories in Table 1

fects determined by the tissue location of the beta receptors (Table 3). Thus, activation of beta-1 receptors in the heart can cause increased blood pressure by increasing the cardiac output, whereas activation of beta-2 receptors in vascular smooth muscle can decrease blood pressure by vasodilation.

Finally, Figure 4 illustrates the events that follow alpha-2-receptor occupancy. The G protein for the alpha-2 receptor has been termed G<sub>1</sub>. The activated G<sub>1</sub> protein may affect membrane ion channels to alter intracellular concentrations of calcium, potassium, and



TABLE 6  
SELECTING ANTIHYPERTENSIVE DRUG THERAPY

Patient Characteristics	Considerations	Choice*	Possible Disadvantage*
Cardiac Arrhythmias:	Need to maintain electrolyte and metabolic balance; avoid drugs which increase arrhythmic potential		
Rapid Heart Rate	Need to reduce heart rate, aberrant impulses and conduction disturbances	Beta blockers (III E) Adrenergic bl. (III B, periph.) Labetalol Verapamil	Diuretics (I) Hydralazine Minoxidil
Slow Heart Rate	Need to enhance pulse rate and normal conduction pathways	Ca channel bl. (II) (except Verapamil)  Alpha-1 bl. (II D 2)	Verapamil Diltiazem Beta bl. (III E, F)  Adrenergic bl. (III B, Periph)
Peripheral Vascular Disease	Need to decrease peripheral vascular resistance and maintain cardiac output	Vasodilators (II)	Non-selective beta bl. (III E 1) Adrenergic bl. (III B, Periph) Diuretics (I)
Renal Disease	Need to maintain RBF and glomerular filtration rate, avoid metabolic and electrolyte abnormalities	Vasodilators (II B, C, D 2) Alpha-2 agonists (III B, CNS) Loop diuretic if necessary (I B)	Beta bl. (III E 1, 2) Adrenergic bl. (III B, Periph) Thiazide and K-sparing diuretics (I A, C) ACE inhibitors with renal vascular disease (II C)
Broncho-Pulmonary Disease	Need to promote bronchial and pulmonary vascular dilation	Ca channel bl. (II B) Alpha-1 antagonists (II D 2)	ACE inhibitor (cough) (II C) Beta bl. (III E 1, 2)
Metabolic Problems: Diabetes Lipid Abnormalities	Avoid agents which interfere with insulin and glucose metabolism, avoid hypokalemia Need for lipid-favorable drugs	ACE inhibitors (II C) Alpha-1 antagonists (II D 2) Ca channel bl. (II B)	Diuretics (I) Non-selective beta bl. (III E 1)
Thyroid Disease: Hypothyroidism Hyperthyroidism	Interactions with adrenergic system	Adrenergic drugs (III)	Adrenergic drugs (III)

\*Parenthetical data - (roman numeral, letter and number) refer to antihypertensive drug categories in Table 1

sodium, and to increase intracellular pH. Also, the G<sub>i</sub> protein may act directly to inhibit adenylate cyclase, as well as indirectly, by diminishing the concentration of GTP available to the G<sub>s</sub> protein. Thus, one result of alpha-2-receptor stimulation is to inhibit the series of events associated with beta-receptor stimulation.

Additionally, the increased intracellular pH following alpha-2 stimulation is believed to enhance the enzyme phospholipase A. This increases the availability of free arachidonic acid, which can result in the formation of prostanoids, such as thromboxane and prostacyclin, at specific tissue sites. Thromboxane enhances platelet aggregation and can increase blood pressure by stimulating phospholipase C, as shown in Figure 4, whereas pros-

tacyclin diminishes platelet aggregation and, in vascular smooth muscle, can diminish peripheral vascular resistance by increasing adenylate cyclase.

*Predicting clinical effect.*

The biologic effects of adrenergic receptor stimulation depend on the location of the activated receptor. Tables 2 and 3 summarize events associated with the alpha and beta receptors at different tissue sites, and Table 4 lists various endogenous and clinically available agonists and antagonists of these receptors.<sup>14,21-26</sup> Analysis of these tables makes it possible to predict cardiovascular and other effects associated with the use of pharmacologic agents that act at these adrenergic receptors. Apparently, agonists of the alpha-1 and beta-1 receptors, and antagonists of the alpha-2 and beta-2 receptors tend to increase blood pressure, whereas alpha-1 and beta-1 antagonists and alpha-2 and beta-2 agonists may find use as antihypertensive agents.

Drugs that act at several receptors may have a combination of effects on hemodynamics and blood pressure. A nonselective beta-blocking agent such as propranolol lowers blood pressure primarily by its beta-1-blocking effect (decreased cardiac output, decreased renin), whereas its beta-2-blocking effect (increased peripheral vascular resistance) tends to diminish its antihypertensive efficacy.

Antihypertensive beta-receptor antagonists with intrinsic sympathomimetic activity, such as pindolol, have partial agonist activity at beta receptors and present a different hemodynamic picture: These tend to lower cardiac output with little effect on renin release and do not increase peripheral vascular resis-

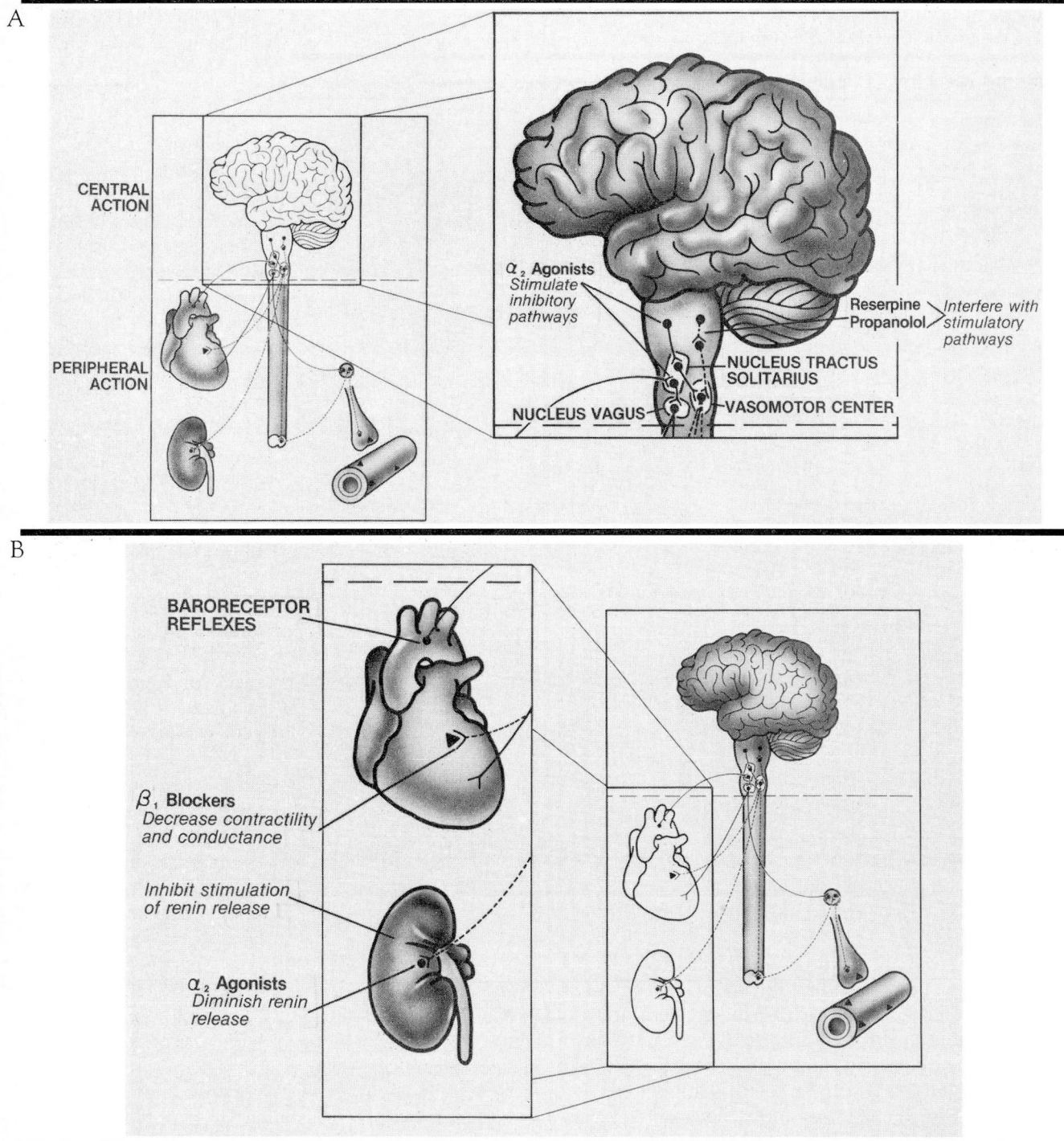
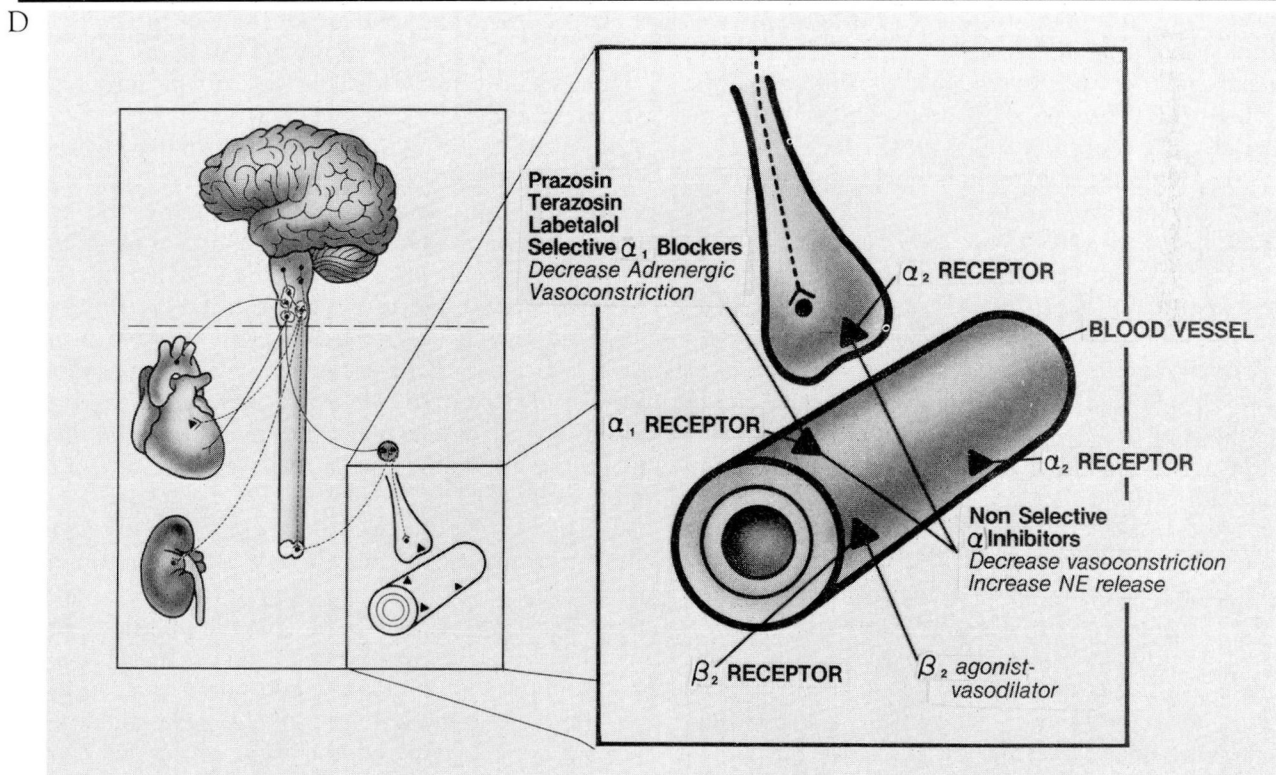
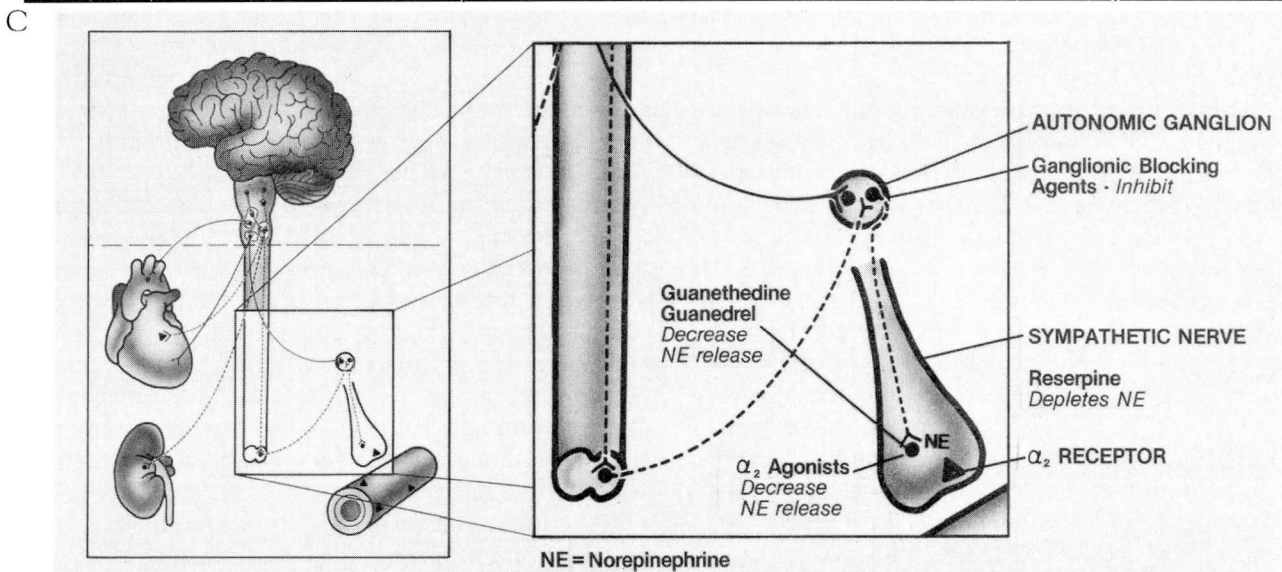


FIGURE 5. Peripheral and central sites of action of adrenergic drugs.

tance. Labetalol has receptor-blocking actions at the alpha-1 and beta-1 and beta-2 receptors. Thus, labetalol lowers blood pressure in association with a

lower heart rate and decreased renin release with a decreasing peripheral vascular resistance.

The effects of different adrenergic hypotensive



agents on mood, heart rate, postural changes, endocrine activities, renin release, glucose and fat metabolism, and gastrointestinal and genitourinary function can also be derived from *Tables 2, 3 and 4* (these tables do not take into account other effects which

may be unique to the drug, independent of their receptor activities). This information may be useful in predicting their special attributes, side effects and problems, and help in the selection of an appropriate hypotensive agent or combination of agents for the

individual patient. The therapeutic recommendations summarized in *Tables 5* and *6* were based such analyses as well as clinical experiences.

*Central v peripheral sites of action.* To enhance our understanding of the actions of the adrenergic hypotensive agents, it is useful to consider these agents in terms of central nervous system (CNS) v peripheral sites of action and, further, to target the specific tissue sites where they are likely to have major effects. These are illustrated for the most commonly used drugs in *Figure 5*.

Additional influences may affect hypotensive efficacy and modulate the mechanisms by which various adrenergic agents lower blood pressure. These include patient factors, such as the state of the receptors (upregulation v downregulation), activity of local enhancers or inhibitors (ie, trace metals, prostaglandins), and the use of complicating pharmacologic agents such as nonsteroidal anti-inflammatory drugs. Finally, the concentration of pharmacologic agent available to the receptors plays an important role. Contributing to this are the dose of drug; its absorption, excretion and metabolism; binding and storage; and its ability to cross the blood-brain barrier. The drug's ability to reach potential target receptors at different tissue sites determines the hemodynamic, metabolic, and possible side effects of the agent.

Thus, beta-1 receptors have been described in the CNS and heart, as well as other tissues. When beta-1 receptors are stimulated in the CNS, the blood pressure tends to increase, because of enhanced medullary sympathetic nervous activity<sup>24</sup>; stimulation of beta-1 receptors in the heart increases blood pressure by a direct effect that increases cardiac output. A lipid-soluble beta-blocking agent, such as propranolol, readily crosses the blood-brain barrier, and subsequent inhibition of both CNS beta-1 receptors and cardiac beta-1 receptors contributes to its antihypertensive efficacy. Atenolol, which is a water-soluble beta-1-blocking agent, is less likely to cross the blood-brain barrier, and its antihypertensive effects depend to a greater extent on cardiac beta-1-receptor blockade. On the other hand, by acting at a CNS site, propranolol is more likely to cause fatigue and depression than atenolol, which has limited access to the brain.

Generally, the adrenergic drugs that work centrally (*Figure 5A*) act at the hypothalamic or midbrain level, or at the autonomic nervous center in the medulla, which controls the circulation.<sup>6,22,25</sup> The hypothalamus and midbrain exert modulating influences that enhance or diminish medullary adrenergic nervous activity.

Reserpine and propranolol are examples of drugs that have small central inhibitory effects at the midbrain level

and decrease enhancement of medullary adrenergic impulses. The alpha-2-receptor agonists such as clonidine, methyldopa, guanabenz, and guanfacine also have midbrain effects. These drugs stimulate postsynaptic alpha-2 receptors which in turn activate inhibitory pathways of medullary adrenergic outflow.

These same alpha-2 agonists stimulate additional postsynaptic alpha-2 receptors located in the medulla in neurons of the nucleus tractus solitarius, which results in a further reduction of medullary adrenergic efferent activity. The nucleus tractus solitarius is the medullary site through which reflex baroreceptor mechanisms located in the aortic arch and the carotid sinus accomplish inhibitory actions of adrenergic neurons in the medullary circulatory control center (*Figure 5B*). Thus, alpha-2 receptor antagonists reduce blood pressure in part by increasing the sensitivity of the baroreceptor reflex control mechanism.

In terms of Poiseuille's law, the antihypertensive effects of drugs that act centrally may be attributed to reductions of efferent adrenergic nervous impulses which would otherwise increase cardiac output and peripheral vascular resistance. Further, by diminishing renal sympathetic activity and by stimulating renal alpha-2 receptors, these drugs decrease that component of renin release that depends on the sympathetic nervous system (*Table 2*) and, thus, further reduce peripheral vascular resistance. Despite their desirable antihypertensive mode of action, the centrally acting adrenergic antihypertensive agents have limited usefulness since they tend to cause a number of unwanted side effects, including tiredness, malaise, and occasionally depression. Also, these agents are associated with a relatively high incidence of impotence.

In the periphery, one site at which adrenergic antihypertensive agents may act is at the autonomic ganglia (*Figure 5C*)<sup>26</sup>. At the present time, these drugs, including mecamylamine and trimethaphan) are used infrequently. Their hypotensive effects depend upon the inhibition of postganglionic adrenergic outflow, but they also inhibit the peripheral parasympathetic nervous system. This combination of actions causes many undesirable side effects, such as orthostatic hypotension, dry mouth, constipation, and impotence, which have diminished their popularity.

Other peripheral sites of action are at the adrenergic nerve endings in the heart, blood vessels, and various organs.<sup>6,22,26</sup> These sites provide an effective means for lowering high blood pressure. Reserpine (which was mentioned previously for its action in the CNS),

guanethidine, and guanadrel are the three pharmacologic agents used most frequently for their effects at peripheral adrenergic nerve endings (Figure 5C). Reserpine interferes with the synthesis and storage of the neurotransmitter norepinephrine within the chromaffin granule of the nerve ending. Guanethidine and guanadrel inhibit the release of norepinephrine from the nerve ending in response to sympathetic nervous impulses.

Although these drugs do not block adrenergic receptors per se, their pharmacologic action can be likened to simultaneous inhibition of both alpha and beta receptors, since they deprive each of these receptors of their neurotransmitters. They have no counterbalancing effect on the parasympathetic nervous system and allow a preponderance of vagal and parasympathetic nervous activity in general. Their hemodynamic effects are predictable on the basis of alpha-1 and alpha-2 and beta-1 and beta-2 blockade, as outlined in Table 2 and 3. Thus, they lower blood pressure by decreasing cardiac output secondary to increased vagal and decreased beta-1 adrenergic effects, and by reducing peripheral vascular resistance secondary to decreased alpha-1 adrenergic effects and decreased renin release.

Their hemodynamic actions result in diminished blood flow to vital organs, including the brain, adding further to their major side effects of tiredness and lassitude. They reduce renal blood flow, glomerular filtration rate, and secondarily decrease salt and water excretion. Postural hypotension may be a consequence of alpha-1-receptor inhibition and loss of compensatory reflex mechanisms may occur secondary to sympathetic paralysis. Unopposed parasympathetic activity and increased vagal effects may lead to other complications, including gastric hyperacidity, increased gastric and intestinal motility, and diarrhea. Because of their many side effects, these agents have lost favor since the introduction of better tolerated antihypertensive medications.

Each of the other peripheral adrenergic agents stimulate or inhibit various adrenergic receptors. The centrally acting alpha-2 agonists clonidine, methyl-dopa, guanabenz, and guanfacine have a secondary peripheral site of action to stimulate additional alpha-2 receptors (Figure 5D), this time at a presynaptic level.<sup>25</sup> The result of such presynaptic alpha-2-receptor stimulation is a reduction of norepinephrine release and, thus, diminished adrenergic nervous vascular constriction (Tables 2 and 3).

Since these drugs may inhibit cholinergic neuronal firing and acetylcholine release, their side effects in-

clude dry mouth and constipation. Phentolamine and phenoxybenzamine are not alpha agonists but are non-selective alpha-1 and alpha-2 receptor antagonists.<sup>26</sup> Whereas alpha-1 receptor blockade has the desirable hemodynamic effect of reduced peripheral vascular resistance, alpha-2 blockade allows increased norepinephrine release from the nerve ending (in contrast to the alpha-2 agonists).

The resulting increased norepinephrine cannot affect the blocked alpha-1 receptors but can circulate in the blood to the heart. Since norepinephrine has beta agonist activity it can stimulate the cardiac beta receptors that are not blocked. As a result, phentolamine and phenoxybenzamine can cause tachycardia and increased cardiac work which can be detrimental to the patient. Thus, the routine use of nonselective alpha-1, alpha-2-blocking agents is not generally recommended for treatment of primary hypertension. In contrast to the nonselective alpha-receptor antagonists, selective alpha-1-receptor inhibitors (prazosin, terazosin, doxazosin, and labetalol) can diminish peripheral vascular resistance without a marked increase in norepinephrine release, since they do not interfere with the presynaptic alpha-2 receptors. As a result, the selective alpha-1-receptor blockers do not increase cardiac activity to the same degree as phentolamine and phenoxybenzamine, although prazosin, terazosin and doxazosin may be associated with a slight increase in heart rate, orthostatic hypotension, and alterations in cardiac output. This is not observed with labetalol which has an additional action to antagonize the cardiac beta receptor, thus preventing an increased heart rate or cardiac output in association with alpha-1-receptor blockade. Also, by blocking beta receptors, labetalol can diminish renin release, whereas the other alpha-1-receptor blockers do not affect renin metabolism.

*Beta-blocking agents.* The beta blocking agents, even without alpha-receptor effects, have been useful antihypertensive drugs for many years (Table 4).<sup>6,22</sup> Among these are the nonselective beta blockers propranolol, nadolol, and timolol, which inhibit both cardiac beta-1 receptors and the beta-2 receptors located on blood vessels. The nonselective beta blockers, by inhibiting cardiac beta-1 receptors, reduce blood pressure primarily by diminishing cardiac output. However, they can increase peripheral vascular resistance and diminish blood flow to vital organs and skeletal muscle by inhibiting the vasodilator beta-2 vascular receptors.

Metoprolol and atenolol are selective beta-blocking drugs; at low doses, these agents preferentially inhibit the cardiac beta-1 receptor with little effect on vascular beta-2 receptors. In this case, their antihypertensive effects

depend primarily on reductions of cardiac output.

Pindolol and acebutolol are beta blockers with intrinsic sympathomimetic activity, which diminishes beta-blocking effects on the heart and vasculature. The metabolic effects of the different beta-blocking agents, relevant to their activities at different receptor sites, can be derived from *Tables 2 and 3*.

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#### CHOICE OF THERAPY

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Once it is determined that antihypertensive medication may benefit the patient, a wide range of drugs is available to the physician. The current strategy for selecting the most appropriate agent recognizes that our task is to treat the whole patient and not just blood pressure. Thus, our choice of therapy is based on the probable pathophysiologic mechanism for hypertension, risk factors, and type of pathologic damage suffered by the patient. We consider the patient's age, work, and physical and mental requirements. We also consider his overall medical condition, and the presence of other disease states and medications that may be required for those diseases.

*Tables 5 and 6* present a scheme that accounts for many factors in the decision concerning choice of therapy. The information required for this scheme is easily obtainable via routine history, physical examination and standard laboratory examinations. By such analyses and a working knowledge of the mechanisms of action and effects of the various antihypertensive drugs (*Tables 2, 3 and 4*), logical choices for initial or combination therapy can be made.

In more complicated cases, the choice of therapy rests upon the selection of an agent which is most appropriate for the combination of factors. Thus, in a young black male with uncomplicated hypertension, the prime factor to be considered may be salt sensitivity, and diuretic therapy would be a logical choice. In a middle-age male with hypertension complicated by left ventricular hypertrophy and peripheral vascular

disease, an agent such as an alpha-1 receptor blocking agent, an ACE inhibitor, or verapamil may offer the greatest benefit for his multiple problems.

Several points emerge from the scheme outlined in *Tables 5 and 6* that reflect current medical practice.

A case can no longer be made for the routine stepped-care approach in the treatment of hypertension, since this focuses primarily on a pharmacologic means to lower blood pressure rather than treatment of the whole patient. Accordingly, the stepped-care approach does not consider reversal of left ventricular hypertrophy or cardioprotection as important goals of therapy, nor does it take into account the presence of other medical problems, such as diabetes or asthma, or the potential for drug interactions.

There is greater reliance on vasodilator therapy since this is beneficial, but has fewer metabolic problems for most forms of hypertension and associated medical complications. The adrenergic drugs are particularly useful to obtain targeted effects, especially in the heart.

Combinations of desirable hemodynamic effects, which in the past required several different agents or the use of diuretics, can now be accomplished with single drugs which have fewer adverse metabolic consequences. Thus, calcium channel blockers, such as verapamil or sustained-release nifedipine, diminish vascular resistance without producing tachycardia and they have slight diuretic effects themselves; labetalol functions as a beta blocker and also as a vasodilator since it blocks alpha-1 receptors.

We continue to progress in our ability to treat hypertension with the development of effective and better tolerated drugs. It is now possible to employ more rational therapy in most patients with hypertension, and it is anticipated that our present approach will provide the treated hypertensive patient with a more normal prognosis than has been possible in the past. The adrenergic drugs will play an important role in reaching this goal.

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