INTERNAL MEDICINE GRAND ROUNDS

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Norman M. Kaplan, M.D.

ALPHA AND BETA RECEPTOR BLOCKING DRUGS IN THE TREATMENT OF HYPERTENSION

The primary purpose of this presentation is to provide information for the proper use of recently introduced alpha and beta adrenergic-receptor blocking drugs in the treatment of hypertension. The term "adrenergic neuronal blocking drugs" is appropriate for drugs such as guanethidine, reserpine, methyldopa and clonidine which act primarily by inhibiting activity within the central or peripheral portions of the sympathetic system. They do not directly affect the adrenergic receptors. To provide the appropriate background, the possible pathogenetic role of the sympathetic nervous system in essential hypertension will be considered first. Then a review of current knowledge about the receptors which these new drugs block will be provided. Hopefully these will set the stage for better understanding of how these drugs work, their advantages and side effects.

I. The Sympathetic Nervous System and Essential Hypertension:

Though drugs which block the sympathetic nerves are effective in lowering high blood pressure, the sympathetic nervous system may not be directly responsible for the hypertension. However, some believe it plays a pivotal role.

A. The Hemodynamic Alterations of Essential Hypertension:

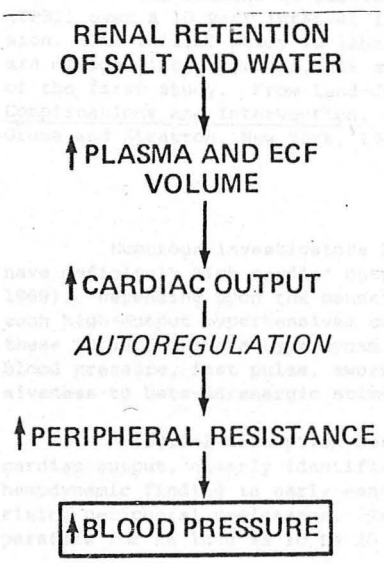


Figure 1. The hemodynamic pattern of essential hypertension.

The blood pressure is determined primarily by the product of the amount of blood pumped by the heart (cardiac output) and the resistance to the flow of this blood by the vascular bed (peripheral resistance). In the final analysis, either cardiac output or peripheral resistance must be increased if the pressure is elevated. In hypertensive people and experimental animals, both have been found to be high. As diagramed in Figure 1, a changing pattern of initially high cardiac output giving way to a persistently elevated peripheral resistance has been observed in a few people (Figure 2) and many animals with experimental hypertension and this is likely the hemodynamic pattern of essential hypertension.

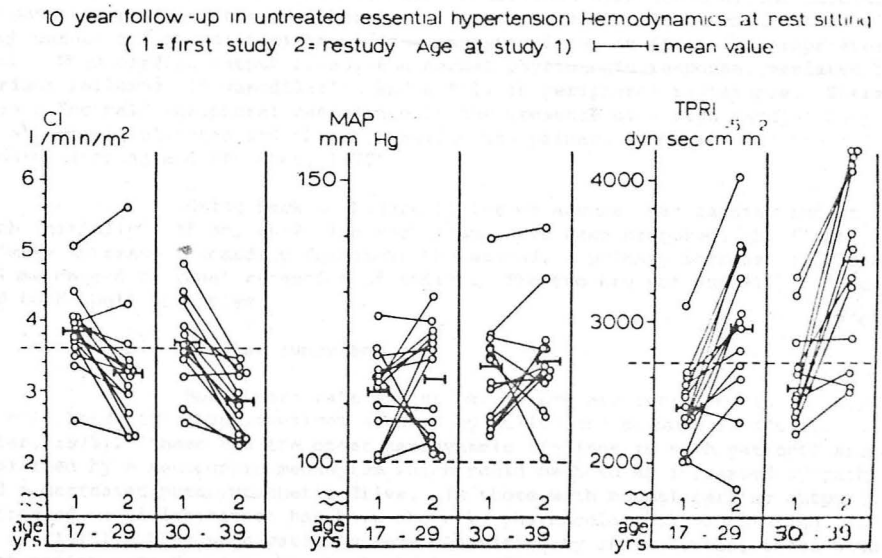


Figure 2. The changes in cardiac output (CI) and total peripheral resistance (TPRI) over a 10 year interval in 28 untreated patients with essential hypertension. The initial study is labeled 1, the one 10 years later is 2. The patients are divided into 2 groups, one aged 17 to 29, the other aged 30 to 39 at the time of the first study. From Lund-Johansen, P. in Hypertension: Determinants, Complications and Intervention, ed. G. Onesti, R. Klint and R.J. Schaefer. Grune and Stratton, New York, 1977.

Numerous investigators have described hypertensives, mostly young, who have definitely high cardiac outputs (Werko & Lagerlof, 1949; Frohlich et al, 1969). Depending upon the manner in which patients were selected for study, such high-output hypertensives comprise from 10 to 70% of the series. Some of these patients have a hyperdynamic or hyperkinetic circulation with labile blood pressure, fast pulse, awareness of the heartbeat and an increased responsiveness to beta-adrenergic stimulation.

A logical assumption has been widely made that this pattern of high cardiac output, clearly identifiable in some young hypertensives, is the usual hemodynamic finding in early essential hypertension, giving way gradually to a rising peripheral resistance. In some, the hyperkinetic, high-output state persists for as long as 10 to 20 years (Ibrahim et al, 1975).

1. Increased Peripheral Resistance:

In most patients with established hypertension, the cardiac output is normal and the peripheral resistance is high. But even in those with high output and normal resistance, the resistance is, in fact, inappropriately high. When cardiac output rises, the normal physiologic response, mediated by various reflexes, is vasodilation and a fall in peripheral resistance. Therefore a "normal" peripheral resistance in the presence of a high cardiac output is abnormally elevated and thereby remains the primary mechanism for the hypertension (Korner and Fletcher, 1977).

Going back to Figure 1, let us assume that cardiac output is high initially. If so, why? Two mechanisms have been proposed: the first, a primary increase in cardiac function; the second, a primary increase in blood volume caused by renal retention of sodium. The two are not mutually exclusive, and both could be active.

2. Cardiac Function:

Both heart rate and stroke volume are increased in the hyperkinetic borderline hypertensives studied by Julius and co-workers (Julius and Esler, 1975). These and the other hemodynamic findings in such patients are explained by a neurogenic mechanism which could be both an increased sympathetic and a decreased parasympathetic drive. In those with normal cardiac output, decreased vagal inhibition has been shown by pharmacological maneuvering (Julius et al, 1975). When such patients were classified by renin levels, those with high renins were found to be particularly influenced by increased sympathetic nervous activity (Esler et al, 1975).

B. Stress and Autonomic Nervous Activity:

An enhanced degree of sympathetic nervous activity has been postulated to be responsible for various parts of the pathogenetic cascade of essential hypertension. And a decreased level of vagal inhibition has been invoked by some to explain the cardiac dysfunction (Julius et al, 1975). Moreover, the literature increasingly incriminates psychogenic factors in human hypertension which presumably act through the sympathetic nerves. The following summarizes the evidence.

1. Hypertension and Stress:

People exposed to repeated psychogenic stresses may develop hypertension more frequently than otherwise similar people not so stressed.

a. Air traffic controllers, who work under tremendous psychological stress, develop hypertension at an annual rate 5.6 times greater than do non-professional pilots who were initially comparable in physical characteristics (Cobb and Rose, 1973).

b. Men repeatedly stressed by high levels of noise have significantly higher blood pressures and more hypertension (Jonsson and Hansson, 1977).

c. In at least 22 instances, populations living in small, cohesive, protected societies have been found to have low blood pressures which do not rise with aging; those who abandon such an environment and migrate to more urbanized, modern, disorganized societies have high blood pressures which rise with aging (Cassel, 1974). Obviously other environmental factors may be responsible, but in some of these groups the association between hypertension and social disorganization seems strong.

Animals may also develop hypertension when repeatedly stressed (Henry et al, 1975). Rats with a genetic predisposition to hypertension, the Dahl salt-sensitive animal, develop more hypertension when chronically exposed to stress, whereas the salt-resistant strain does not (Friedman and Iwai, 1976).

Among people, various personality traits such as a tendency to suppress emotions (Pilowsky et al, 1973), free-floating and phobic anxiety and depression (Bulpitt et al, 1976), have been found to be more prevalent in hypertensives. The higher prevalence of hypertension among blacks has been laid to their increased level of discontent (Naditch, 1974) and other social stresses (Harburg et al, 1973). But the black may not be peculiar in this regard: whites in the lower social class (Syme et al, 1974) and with less formal education (Dyer et al, 1976) also have more hypertension.

2. Sympathetic Nervous Overactivity:

Psychogenic stress presumably raises blood pressure by activation of the sympathetic nervous system by one or more neurogenic pathways. Evidence for such increased activity is particularly prominent in those with borderline hypertension who have high cardiac output, heart rate and stroke volume, decreased plasma volume, and enhanced pressor responsiveness (Julius and Esler, 1975). The evidence includes these observations:

a. Plasma catecholamine levels have been reported to be elevated in some hypertensives (de Champlain et al, 1976) and positive correlation between plasma norepinephrine and the diastolic blood pressure has been found (Louis et al, 1973). Elevated plasma catecholamines have been noted more commonly in those with high plasma renin levels (De Quattro et al, 1976; Esler et al, 1977); presumably the hyperactive sympathetic system stimulates renin release. However, when adjustment for age is made, the plasma norepinephrine levels have been found to be similar in normotensive and hypertensive subjects (Weidmann et al, 1977), the higher levels noted in other studies being attributed to the older age of the hypertensive populations (Lake et al, 1977) since plasma norepinephrine levels increase with age.

Another, less direct index of sympathetic activity -- plasma levels of dopamine-beta-hydroxylase was claimed to be higher in patients with essential hypertension (Stone et al, 1974). Subsequently, the levels of this enzyme have been shown to be normal in such hypertensives, though high in patients with pheochromocytoma (Kopin et al, 1976).

b. Mendlowitz and co-workers (1965) have long argued for a role for decreased tissue storage of norepinephrine, thereby releasing more into the circulation. A possible connection between such a decrease in tissue storage and increased dietary sodium intake has been demonstrated in rats (de Champlain et al, 1968).

c. The levels of enzymes involved in the biosynthesis of norepinephrine were higher in tissue from hypertensive men than from normotensives of similar age (De Quattro et al, 1975).

d. Urinary excretion of catecholamines was increased after mental stress in a group of early hypertensives (Nestel, 1969).

e. Pharmacologic blockage (Drayer et al, 1977) or surgical removal of the sympathetic nervous system almost always lowers blood pressure. This may, of course, mean nothing more than that sympathetic nervous tone is important in the maintenance of normal blood pressure and does not necessarily support its role in the causation of hypertension.

f. Hypertension can be induced in animals by various manipulations of central neural mechanisms (Reis and Doba, 1974), particularly those impairing central adrenergic function or leading to an imbalance of the hypothalamic excitatory and bulbar inhibitory systems (Haeusler, 1975).

g. The baroreceptor reflex, arising in the carotid sinus, normally relaxes the heart and dilates peripheral vessels when the blood pressure rises. In experimental animals, the blood pressure rises when this reflex is interrupted. When the carotid sinus is stimulated in humans with hypertension, the blood pressure falls. The suggestion has been made that resetting or attenuation of this baroreceptor mechanism, so that higher pressures are tolerated and not counteracted, could be responsible for the maintenance of hypertension (Takeshita et al, 1975).

h. Using a strain of rat which spontaneously becomes progressively more hypertensive, Folkow et al (1973) have shown that, even before the pressure rises, psychological stimuli evoke an enhanced central autonomic discharge which leads to an exaggerated cardiovascular response. These investigators propose this sequence: stress ⟶ a genetically determined autonomic hyperactivity ⟶ intermittent rise in blood pressure ⟶ structural changes in resistance vessels ⟶ permanent hypertension.

Obviously, sympathetic nervous hyperactivity, even if partially responsible, is not the only mechanism for essential hypertension. Looking for a single cause is likely fruitless. As stated by an editor of Lancet (Editorial, 1977):

> "Blood pressure is a measurable end-product of an exceedingly complex series of factors including those which control blood-vessel calibre and responsiveness, those which control fluid volume within and outside the vascular bed, and those which control cardiac output. None of these factors is independent: they interact with each other and respond to changes in blood-pressure. It is not easy, therefore, to dissect out cause and effect. Few factors which play a role in cardiovascular control are completely normal in hypertension: indeed, normality would require explanation since it would suggest a lack of responsiveness to increased pressure."

Figure 3 is an attempt to put all of these fragments into a single hypothesis. Some of the components are unproved; others, more importantly, may be omitted. But at least it fits with much of what is known today.

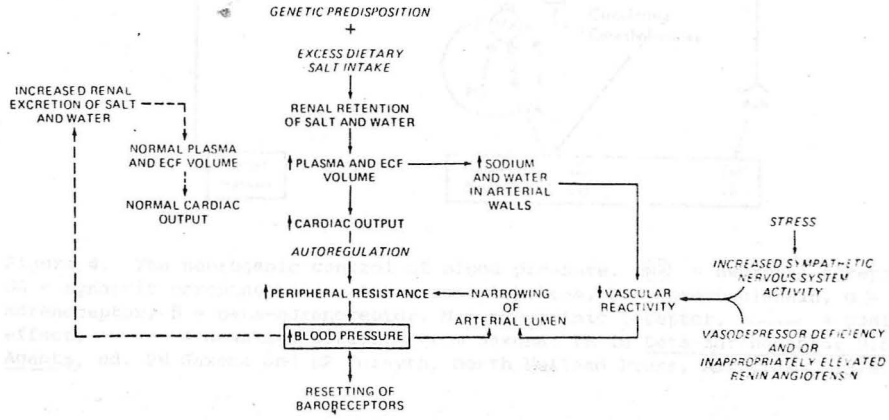


Figure 3. The hemodynamic pattern of established hypertension. From Kaplan, N.M., Clinical Hypertension, 2nd edition. Williams & Wilkins, Baltimore, 1978.

Whatever its role in hypertension, the autonomic nervous system obviously is important in the control of blood pressure and drugs which work upon the sympathetic portion are mainstay of antihypertensive therapy. Figure 4 provides an overview of the neurogenic control of blood pressure.

In order to understand better the workings of the sympathetic system and the manner in which antihypertensive drugs affect it, the role of the adrenergic receptors must be recognized.

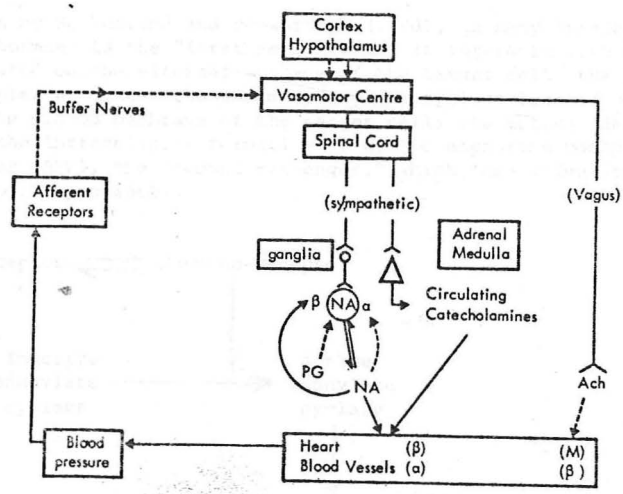


Figure 4. The neurogenic control of blood pressure. (NA) = neuronal norepinephrine, NA = synaptic norepinephrine, Ach = acetylcholine, PG = prostaglandin, α = alpha-adrenoceptor, β = beta-adrenoceptor, M = muscarinic receptor, ——— = positive effect, ----- = negative effect. From Saxena, PR in Beta-adrenoceptor Blocking Agents, ed. PR Saxena and RP Forsyth, North Holland Press, Amsterdam, 1976.

II. Adrenergic Receptors:

A. Background:

The effects of an endogenous hormone or an exogenous drug ultimately depend upon physiochemical interactions between the hormone or drug and functionally important molecules in the organism. In most cases, the interactions initially involve the combination of the drug or hormone with macromolecular components of cells called *receptors*. *Agonists* are agents which interact with a receptor and elicit a response; *antagonists* interact with receptors and prevent the action of agonists. Often the drug/hormone-receptor interaction provides the initial stimulus for amplification through enzymatic or other metabolic changes which in turn produce the final response (Figure 5).

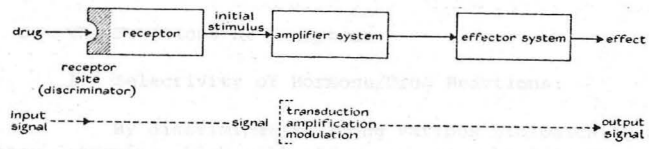
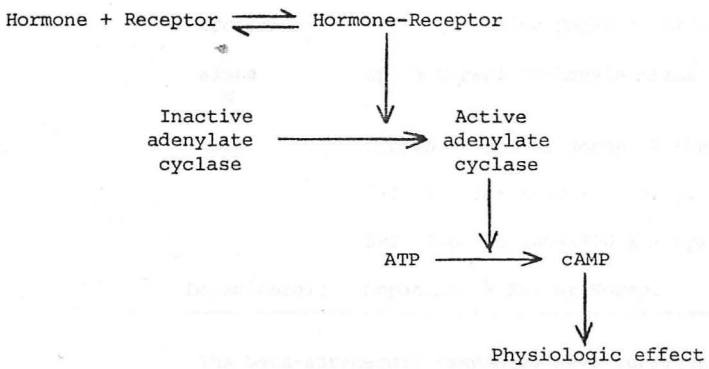


Figure 5. The general scheme of drug interaction with receptor, acting as the initial stimulus, with amplification to produce the physiological effect.

As shown by Sutherland and co-workers (1968), in many interactions the circulating hormone is the "first messenger." It interacts with its specific receptor located on the external surface of the target cell; the hormone-receptor complex activates the enzyme adenylate cyclase located on the internal surface of the plasma membrane of the target cell; the active adenylate cyclase accelerates the intracellular formation of cyclic adenosine monophosphate (cyclic AMP or cAMP), the "second messenger," which then stimulates or inhibits various metabolic processes.



Until recently, most research on receptor action bypassed the initial binding step and the intermediate steps and examined the accumulation of cAMP or the end step, the physiologic effect. However in the past few years, techniques have become available to study the initial binding to the receptor. Many of these involve the use of radioactive agonists or antagonists (radioligand) which attach to and label the receptors (Aurbach et al, 1974; Lefkowitz et al, 1976).

A great deal of information about receptors has been obtained with these techniques, which help to explain drug and hormone actions. One of the interesting sidelights: a clone of mouse lymphoma cells has been isolated which has normal beta-adrenergic receptor binding activity but which has no adenylate cyclase activity (Insel et al, 1976). This suggests that the receptor site is a product of a gene different from that coding for the adenylate cyclase.

B. The Functions of Receptors:

1. Selectivity of Hormone/Drug Reactions:

By discriminating among various biologically active molecules, they determine which will affect target cell function. Only those molecules which can bind to a receptor will be active. Subtle differences in molecular structure determine the distinct specificity of each receptor.

2. As previously described, they transmit and amplify a signal that results in desired physiological effects. Therefore minute quantities of hormones or drugs may induce a response.

C. Classification of Adrenergic Receptors:

Ahlquist (1948) used the differences in the ability of various catecholamines to stimulate a number of physiologic processes to separate adrenergic effects into two main types, alpha and beta (Table 1).

Table 1. Classification of Adrenergic Receptors

Receptor	*Catecholamine Order of Stimulation*
alpha α	Epi ⩾ Norepi > Phenylephrine > Isoprot
beta β	Isoprot > Epi or Norepi > Phenylephrine
	β-1 Isoprot 5-10 X > Norepi = Epi
	β-2 Isoprot 100-1000 X > Epi > Norepi
Dopaminergic	Dopamine >> Epi or Norepi

The beta-adrenergic responses have subsequently been further subdivided into $beta_1$ and $beta_2$ subtypes (Lands et al, 1967). The $beta_1$ responses include the cardiac stimulation and lipolytic effects of catecholamines, the $beta_2$ responses include bronchodilation and vasodilation. The division between β_1 and β_2 receptors, though not physiologically complete, can be taken advantage of by the use of agonists or antagonists which are relatively selective for one or another subtype. Examples include the $beta_2$-selective agonists orciprenaline (Alupent^R) and terbutaline (Brethine^R) which cause significant bronchodilation with little cardiac stimulation. Selective β_2-antagonists have also been sought to decrease the side effects (bronchospasm, vasospasm) of non-selective (β_1 and β_2) antagonists such as propranolol. A third type of adrenergic response, stimulated most by the norepinephrine precursor dopamine and therefore called dopaminergic, has recently been defined (Goldberg, 1975). These receptors are found in certain areas of the brain and in renal vessels, where they cause vasodilation.

The structure of several catecholamines (agonists), the receptor to which they primarily bind and a typical antagonist for each is shown in Figure 6.

Some of the physiological effects of alpha and beta stimulation are listed in Table 2. The β-adrenergic effects of catecholamines are almost all associated with an activation of the adenylate cyclase-cyclic AMP system. The mechanism for alpha-adrenergic responses is not yet known. Some believe it involves the activation of another cyclic nucleotide, cyclic guanosine monophosphate (cyclic GMP). Others believe it involves movement of calcium ions.

Not only has it been easier to identify the physiologic responses of stimulation of β-adrenergic receptors, but also radioactively labeled β-adrenergic antagonists with high specific activity have been more readily available.

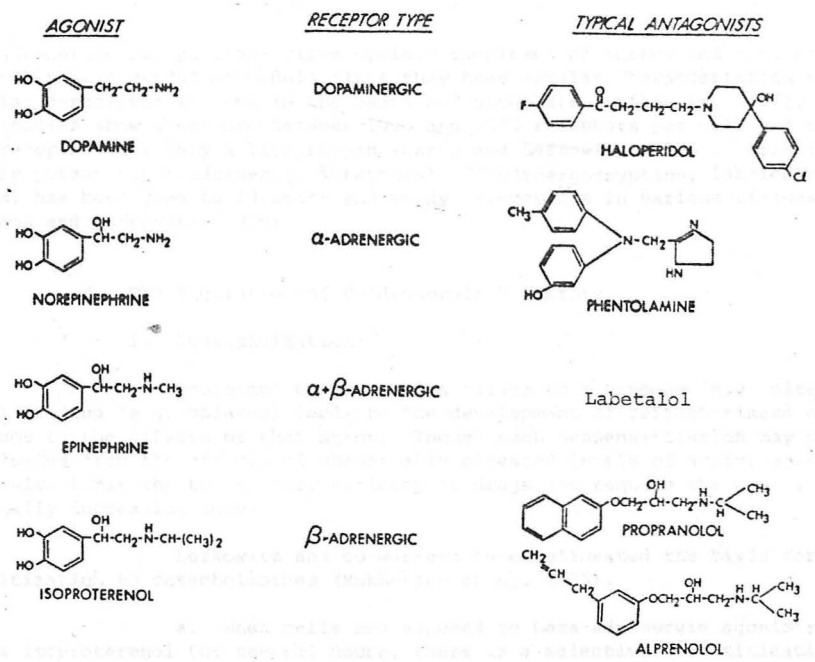


Figure 6. The structures of some adrenergic agonists and antagonists. From Lefkowitz R.J., N Engl J Med 295:323, 1976.

Table 2. Effects of Stimulation of Adrenergic Receptors

	α	β
Heart		Increase heart rate (β_1) Increase contractility (β_1) Increase conduction velocity (β_1) Shorten refractory period at AV node (β_1)
Blood vessels	Constrict	Dilate (β_2)
Bronchi		Dilate (β_2)
Stomach	Contract sphincter	Decrease motility and tone
Urinary bladder	Contract sphincter	Relax detrusor
Uterine smooth muscle	Contract	Relax
Renin release	Decrease ?	Increase

The β-adrenergic receptor-adenylate cyclase complexes of turkey and frog red blood cells have served as models since they have similar characteristics to mammalian β-receptor systems in the heart and elsewhere (Lefkowitz, 1977). These studies show there are between 1000 and 2000 receptors per cell and that the β-receptor is likely a lipoprotein (Caron and Lefkowitz, 1976). Recently a highly potent alpha-adrenergic antagonist, dihydroergocryptine, labeled with tritium, has been used to identify and study α-receptors in various tissues (Williams and Lefkowitz, 1976).

D. The Regulation of β-Adrenergic Receptors:

1. Desensitization:

Prolonged exposure of a tissue to a hormone (e.g. catecholamines) or drug (e.g. opiates) leads to the development of refractoriness or tolerance to the effects of that agent. Though such densensitization may protect tissues from the effects of chronically elevated levels of active agents, it may also limit the therapeutic efficacy of drugs and require the use of continually increasing doses.

Lefkowitz and co-workers have delineated the basis for desensitization to catecholamines (Mukherjee et al, 1975).

a. When cells are exposed to beta-adrenergic agonists such as isoproterenol for several hours, there is a selective desensitization of the membrane-bound adenylate cyclase to the stimulatory effects of catecholamines by 50 to 70% (Figure 7).

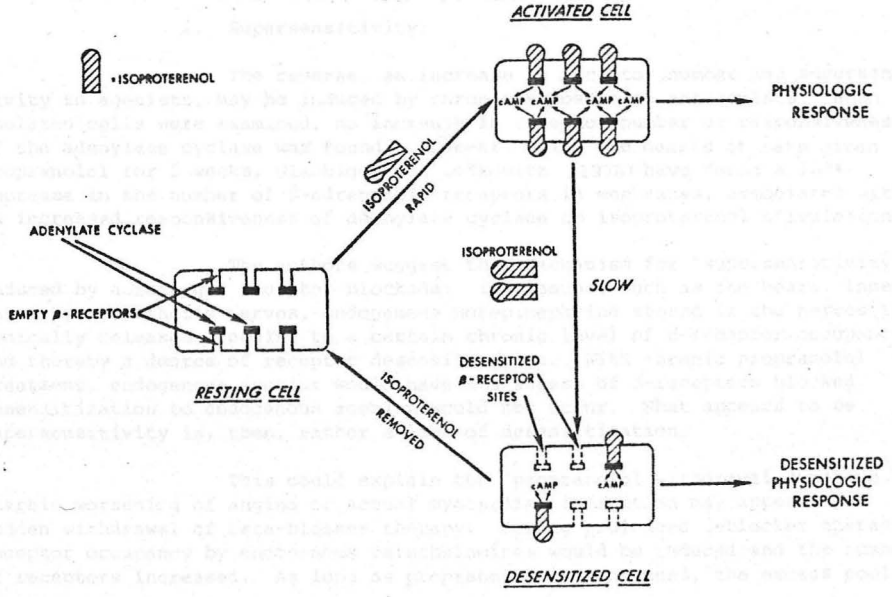


Figure 7. The activation and inactivation (desensitization) of β-adrenergic receptors. "Rapid" refers to processes occurring within seconds, "slow" refers to processes requiring minutes to hours for completion. From Lefkowitz, R.J., N Engl J Med 295:323, 1976.

b. This desensitization is quite specific, so that other hormones such as prostaglandin E, can still stimulate the enzyme normally (Mickey et al, 1976).

c. Desensitization is associated with about a 50% decrease in the apparent number of functional beta-adrenergic receptor binding sites. The binding affinity of the remaining receptors is unaltered.

d. The fall in receptor number is not caused by a change in the rate of receptor formation or degradation but rather to catecholamine-induced changes in the conformation of the receptors which render many of them inactive. The agonist-induced fall in receptor number requires coupling of the receptors with adenylate cyclase (Mukherjee and Lefkowitz, 1977). Presumably, the coupled adenylate cyclase induces the conformational changes in the beta receptors which render them inactive or desensitized. This implies a function for the adenylate cyclase enzyme independent of its role in cAMP generation. Desensitization may involve other mechanisms in other tissues with other hormones.

These conformational changes are reversible, providing a rapid, dynamic regulatory mechanism for dampening the cell's response to excess catecholamines. The reversibility of desensitization enables the clinician to preserve the desired effect of adrenergic agonists by intermittent therapy.

e. Beta-adrenergic antagonists (e.g. propranolol) do not induce desensitization or changes in the conformation of the receptors. They do block the ability of the agonist catecholamines to desensitize in a pattern identical to their *in vivo* selectivity.

2. Supersensitivity:

The reverse, an increase in receptor number and supersensitivity to agonists, may be induced by chronic exposure to antagonists. When isolated cells were examined, no increase in receptor number or responsiveness of the adenylate cyclase was found. However, using the hearts of rats given propranolol for 2 weeks, Glaubiger and Lefkowitz (1978) have found a 100% increase in the number of β-adrenergic receptors in membranes, associated with an increased responsiveness of adenylate cyclase to isoproterenol stimulation.

The authors suggest this mechanism for "supersensitivity" induced by adrenergic receptor blockade: in tissues, such as the heart, innervated by sympathetic nerves, endogenous norepinephrine stored in the nerves is tonically released, leading to a certain chronic level of β-receptor occupancy and thereby a degree of receptor desensitization. With chronic propranolol treatment, endogenous agonist would have its access of β-receptors blocked. Desensitization to endogenous agonist would not occur. What appears to be supersensitivity is, then, rather a lack of desensitization.

This could explain the "propranolol withdrawal syndrome," wherein worsening of angina or actual myocardial infarction may appear upon sudden withdrawal of beta-blocker therapy. During prolonged β-blocker therapy, receptor occupancy by endogenous catecholamines would be reduced and the number of receptors increased. As long as propranolol is continued, the excess pool

of β-receptors would be blocked by occupany by propranolol and would be of no physiological significance. However when the β-blocker is suddenly withdrawn, an increased pool of receptors would become available for occupancy by catecholamines, leading to all of the ill effects of increased beta-adrenergic stimulation.

3. Reduced β-Receptors With Aging:

The concentration of β-adrenergic receptors in membranes of mononuclear cells significantly decrease with age (Schocken and Roth, 1977) (Figure 8).

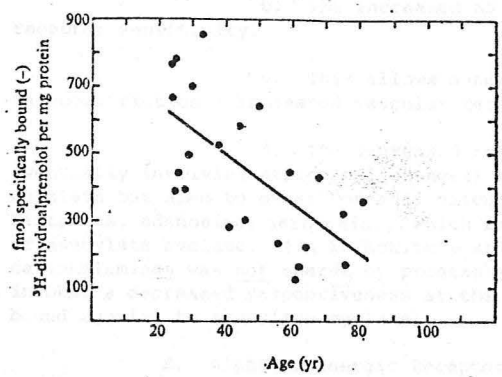


Figure 8. The fall in maximal specific binding of the β-antagonist, ^{3}H-dihydroalprenolol, to crude mononuclear cell membranes with increasing age of subjects from age 24 to 81. From Shocken D.D. and Roth G.S. Nature 267:856, 1977.

Though similar declines with age have been found in steroid receptor concentration of rats, this is the first demonstration of age-associated changes of surface hormone receptors in cells taken directly from man.

The mechanism is unknown. Plasma norepinephrine levels increase with age (Lake et al, 1977) so perhaps desensitization from chronic exposure is involved. Whatever the mechanism, the decrease in receptors could explain the progressive fall in response to β-adrenergic blocker therapy with increasing age of the hypertensive population (Buhler et al, 1975).

4. Changes by Hormones:

a. Experimental hyperthyroidism increases the number of beta-adrenergic receptors in the heart (Williams et al, 1977a). The increased number of receptors would provide an entry for additional catecholamines, inducing a hyper-beta-adrenergic state. This may explain many of the signs and symptoms of thyrotoxicosis: tachycardia, hyperdynamic circulation, tremor, stare, sweating, etc. This would provide an explanation for the known effects of propranolol in relieving these symptoms, without decreasing the hyperfunction of the thyroid gland.

b. Ectopic tumor secretion may involve the presence of ectopic hormone receptors in the malignant cells (Williams et al, 1977b).

5. Abnormalities in receptor number or function have been postulated in asthma (Parker and Smith, 1973) with the idea that bronchospasm develops because endogenous catecholamines are thereby rendered incapable of maintaining airway patency.

6. Decreased sensitivity of β-adrenergic receptors in the heart and blood vessels of animals with hypertension has been described. Amer (1977) has formulated this hypothesis:

a. Early in the development of hypertension, during periods of stress, increased sympathetic activity → increased norepinephrine.

b. The increased NE levels → decreased β-adrenergic receptor sensitivity.

c. This allows α-adrenergic activity to predominate → vasoconstriction → increased vascular resistance.

d. The decreased responsiveness of the vasculature (perhaps eventually involving structural changes) would apply not only to β-adrenergic agonists but also to other hormonal vascular smooth muscle relaxants (Prostaglandin, histamine, adenosine, serotonin), which result in vasodilation through activation of adenylate cyclase. (In Lefkowitz's studies, the loss of responsiveness to catecholamines was not shared by prostaglandin E. Amer disregards these data and invokes a decreased responsiveness at the level of the coupling of receptor-bound agonist to adenylate cyclase).

E. Alpha-Adrenergic Receptors:

Less is known about the properties and functions of alpha-adrenergic receptors but the availability of a radioactive α-receptor antagonist, dihydroergocryptine, should lead to more knowledge. Williams and Lefkowitz (1977) have reported a decrease in uterine alpha-adrenergic receptors by treatment of rabbits with progesterone. There is strong evidence that alpha receptors exist both on the sympathetic nerve ending (presynaptic) as well as on the effector cells (postsynaptic) (Langer, 1974). The postsynaptic α-receptors have been called "α_1," the presynaptic "α_2" (Berthelsen and Pettinger, 1977). Moreover, there is functional evidence that β-receptors also exist on the neuronal surface (Yamaguchi et al, 1977). As elsewhere, stimulation blockade of the alpha and beta receptors appear to induce opposite effects (Figure 9). The α_2-receptor serves as a negative feedback mechanism regulating norepinephrine release during nerve stimulation (Langer et al, 1977).

The existence and function of these presynaptic alpha and beta receptors may explain part of the action of various antihypertensive drugs, in this manner:

α_2 receptor	Drug
agonist → ↓ NE release	Clonidine
antagonist → ↑ NE release	Phenoxybenzamine
β receptor	
agonist → ↑ NE release	Isoproterenol
antagonist → ↓ NE release	Propranolol

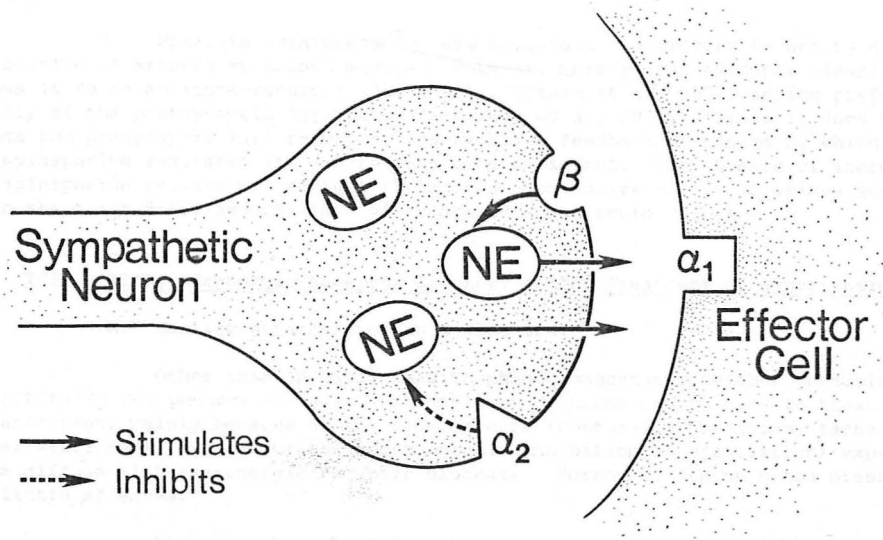
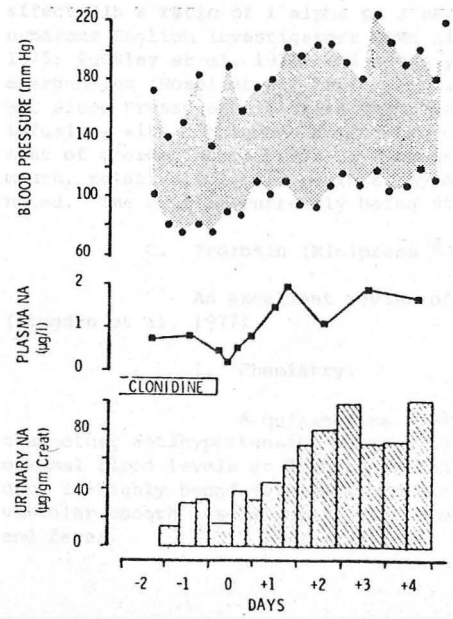


Figure 9. A schematic representation of presynaptic α and β receptors. Stimulation of the α-receptor inhibits norepinephrine release, stimulation of the β-receptor increases norepinephrine release.



Clonidine chronically lowers the blood pressure by its primary action as an alpha-agonist in the central nervous system, thereby reducing sympathetic outflow. However, with large doses I.V., an initial pressor response reflects its peripheral α-agonist action. But clonidine acts predominately on the presynaptic α-receptors, thereby inhibiting the release of norepinephrine and reducing circulating levels. This may contribute to its antihypertensive action but may also be responsible for the rapid rebound of the blood pressure which may develop when the drug is abruptly stopped (Reid et al, 1977) (Figure 10).

Figure 10. The changes in blood pressure, plasma and urinary norepinephrine (NA) in a patient after abrupt withdrawal of clonidine. From Reid J.L., Dargie H.J., Davies, D.S., et al. Lancet 1:1171, 1977.

Propranolol reduces the release of norepinephrine from adrenergic nerve endings (Saelens et al, 1977), which may be yet another mechanism for its action.

Prazosin (Minipress®) was originally considered to act by direct relaxation of arteriolar smooth muscle. However, more recent evidence clearly shows it to be an alpha-receptor antagonist, (Graham et al, 1977) acting preferentially at the postsynaptic (α_1) site (Cambridge et al, 1977). Since it does not block the presynaptic (α_2) receptor, the negative feedback mechanism by which norepinephrine regulates its own release remains intact. The absence of increased norepinephrine release may explain the marked hypotensive effect sometimes seen with the first dose, and the lack of tachycardia and renin release.

III. Alpha-adrenergic Receptor Blockers in the Treatment of Hypertension:

A. Earlier Attempts to Use α-Blockers:

Other than in patients with pheochromocytoma, neither phentolamine (Regitine®) nor phenoxybenzamine (Dibenzyline®) alone can be used to treat hypertension, mainly because of the side effects (postural hypotension, tachycardia, nasal stuffiness, dryness of the mouth, miosis, inhibition of ejaculation) expected from diffuse alpha-adrenergic receptor blockade. Moreover, supine blood pressure is little affected.

Alpha-blockers have been tried in combination with β-blockers. Some still observed too many serious side effects (Beilin and Juel-Jensen, 1972), but others find the combination plus a diuretic to be successful (Majid et al, 1974; Vlachakis and Mendlowitz, 1976).

B. Labetalol (AH 5158):

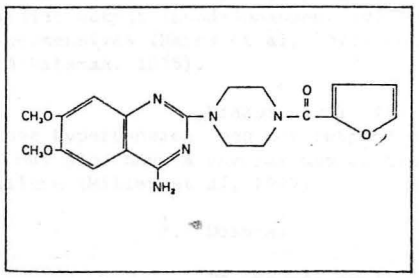
This drug has both alpha- and beta-adrenergic receptor blocking effects in a ratio of 1 alpha to 3 beta. It has been found to be effective by numerous English investigators when given chronically by mouth (Prichard et al, 1975; Pugsley et al, 1976) and acutely I.V. for the treatment of hypertensive emergencies (Rosei et al, 1977). In a recent letter in Lancet, members of the MRC Blood Pressure Unit state that "labetalol, given slowly by graded intravenous infusion, with continuous monitoring of arterial pressure, is our current treatment of choice in hypertensive emergencies" (Brown et al, 1977). When given by mouth, relatively little postural hypotension or other side effects have been noted. The drug is currently being studied in the US.

C. Prazosin (Minipress®):

An excellent review of this drug has recently been published (Brogden et al, 1977).

1. Chemistry:

A quinazoline derivative, prazosin is chemically different than other antihypertensive drugs (Figure 11). It is rapidly absorbed, reaching maximal blood levels at 2 hours and has a plasma half-life of 2-3 hours. The drug is highly bound to plasma proteins but, in dogs, is rapidly taken into vascular smooth muscle cells. It is metabolized and excreted largely via bile and feces.



Structural formula of prazosin.

Figure 11. The structure of prazosin.

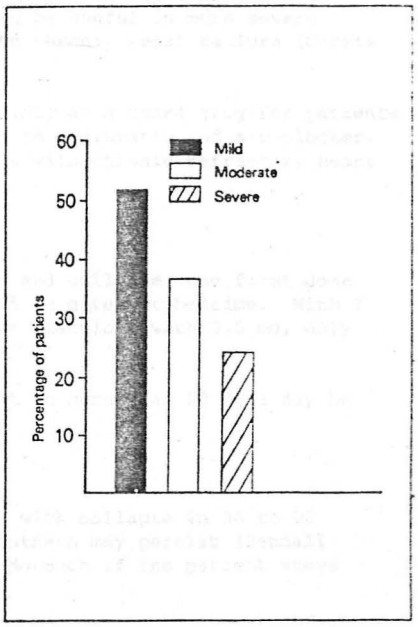


Figure 12. The percentage of patients with mild, moderate or severe hypertension whose supine diastolic blood pressure was reduced to 90 mm Hg or below during treatment with prazosin. From Brogden R.N., Heel R.C., Spreight, T.M., et al. Drugs 14:163, 1977.

2. Actions:

Prazosin, though originally considered to be a vasodilator, acts as an alpha-adrenergic blocker. The hemodynamic effects in man are a fall in peripheral resistance, no change in cardiac output, renal plasma flow or glomerular filtration rate or plasma renin levels and an increase in plasma volume (Koshy et al, 1977). Renin levels tend to fall with prolonged therapy (Hayes et al, 1976). In animals, impressive data support the primary action of prazosin as an alpha-adrenoreceptor blocker (Scivoletto et al, 1976; Oates et al, 1976; Graham et al, 1977). It differs from the alpha-blocker phenoxybenzamine which has an affinity for both pre- and post-synaptic receptors. Prazosin's specificity for post-synaptic alpha-adrenoreceptors (Cambridge et al, 1977) may explain the lack of tachycardia, tolerance and renin release as noted with other alpha-blockers, since the pre-synaptic α_2-receptor remains active to inhibit norepinephrine release. Moreover, it seems to affect the visceral vascular bed more than the peripheral vascular bed; the subsequent pooling of blood in the viscera along with the absence of increased norepinephrine release may explain the propensity to first-dose hypotension (Moulds and Jauernig, 1977).

Regardless of how it works, prazosin is modestly effective in lowering the blood pressure of hypertensive people (Figure 12). In various trials, the drug seems equivalent to methyldopa, both in antihypertensive potency and side effects (Mroczek et al, 1974; Stokes and Weber, 1974). One mg of prazosin is equipotent to 30 mg of hydralazine (Rasmussen and Jensen, 1976). New Zealanders and Australians, in particular, seem to prefer prazosin (Kincaid-Smith et al, 1976; Stokes et al, 1977; Turner et al, 1977).

Prazosin can be effectively combined with beta-blockers (Stokes and Weber, 1974; Marshall et al, 1977). In combination, the reduction in blood pressure is caused by a combination of a fall in peripheral resistance and in cardiac output (Lund-Johansen, 1977). Prazosin can be useful in more severe hypertensives (Hayes et al, 1976) and in those with chronic renal failure (Curtis and Bateman, 1975).

Prazosin will likely be used mainly as a third drug for patients whose hypertension does not respond satisfactorily to a diuretic and a β-blocker. It may also have a special use in treating patients with chronic refractory heart failure (Miller et al, 1977).

3. Dosage:

To prevent profound hypotension and collapse, the first dose should be no more than 1 mg, preferably 0.25 to 0.5 mg given at bedtime. With 2 mg as a first dose, 16% of 74 patients had a severe reaction; with 0.5 mg, only 5% had mild dizziness (Rosendorff, 1976).

The manufacturer recommends that no more than 20 mg a day be given divided into 3 doses a day.

4. Complications:

Beyond the first-dose response, with collapse in 30 to 90 minutes, marked hypotension with dizziness and faintness may persist (Bendall et al, 1975). But even massive overdoses may not do much if the patient stays supine (McClean, 1976).

Other side effects observed in 934 patients who took prazosin for a mean duration of 4.7 months were (Pitts, 1975): edema in 5%, anticholinergic effects in 16%, lassitude in 14%, other CNS symptoms in 26%.

D. Indoramin:

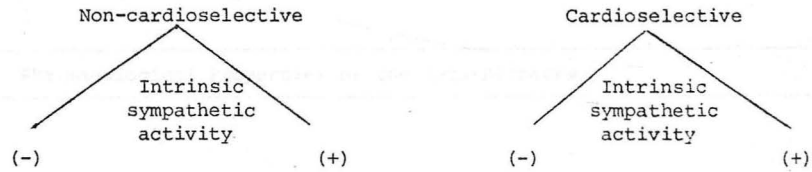
This is another α-blocker with moderate cardio-inhibitory effects which is currently being investigated (Klahr et al, 1976).

IV. Beta-adrenergic Receptor Blockers in the Treatment of Hypertension:

A. Differences Between β-Blockers:

A number of beta-blockers are available though, as of early 1978, only propranolol has been approved for use in the United States. These drugs can be broadly divided into the "first generation" which block both $beta_1$-receptors in the heart and $beta_2$-receptors in the bronchi and peripheral blood vessels and the "second generation" which specifically block $beta_1$-receptors and can be characterized as cardioselective (Table 3). Their cardioselectivity is not absolute but their affinity for blocking $beta_1$-receptors is at least 50 times greater than their effect on $beta_2$-receptors. Clinically, this means they may

Table 3: A Classification of Beta-Blockers



Propranolol	Oxprenolol	Metoprolol	Practolol
Sotalol	Alprenolol	Atenolol	Para-oxprenolol
Timolol	Pindolol	Tolamolol	Acebutolol
Bupranolol	Toliprolol		
Bunolol	Nifenalol		
Labetalol			

be antihypertensive without precipitating as much bronchospasm or peripheral vasospasm. Insulin-taking diabetics may also benefit by not having their adrenergic responses to a falling blood sugar blunted. In England, Australia and Scandinavia where all of these are available, the "second generation" drugs are finding increasing acceptance. But their antihypertensive potency, in equivalent doses, is almost identical (Davidson et al, 1976).

In addition to their different cardioselectivities, these drugs have varying degrees of intrinsic sympathomimetic agonist, membrane-stabilizing and renin-suppressive actions (Hansson and Werkö, 1977) (Table 4). Practically, these seem to be largely irrelevant to their antihypertensive efficacy. The intrinsic sympathomimetic agonist action is invariably weak in relation to the antagonist effect but those with agonist action might cause a lesser reduction of heart rate and myocardial performance. Those without intrinsic sympathomimetic activity continue to produce additional beta-blockade at progressively higher doses; those with such activity have less response at higher doses, presumably because of increasing prominence of the agonist activity (McDevitt et al, 1977). The membrane-stabilizing effect is of no clinical import since its expression requires a dosage approximately 100 times that used in the treatment of hypertension.

Beyond those shown in Table 4, the other two important practical differences between beta-blockers are their side effects and their duration of action.

1. Side Effects:

Most of their side effects are predictable from their mode of action including bradycardia, heart failure, bronchospasm and cold extremities. Patients with cardiac, pulmonary, metabolic or other diseases which make them dependent on adrenergic support are particularly susceptible to serious troubles.

As shown in Table 5, fewer side effects are seen with more cardioselective drugs but those related to β_2-blockade still occur.

Table 4. Pharmacological Properties of the Beta-Blockers

Drug	Other Name	Beta-blocking potency ratio (propranolol=1)	Cardio-Selectivity	Sympatho-mimetic agonist activity	Membrane Stabilizing Activity
Acebutolol	Sectral	0.3	+	+	+
Alprenolol	Aptin	0.3	0	++	+
Atenolol	Tenormin	1	+	0	0
Bunolol	--	0.1	0	0	±
Metoprolol	Lopressor	1	+	0	±
Oxprenolol	Trasicor	0.5 - 1.0	0	++	+
Penbutolol	--	4	0	0	+
Pindolol	Visken	6	0	+++	+
Propranolol	Inderal	1	0	0	++
Sotalol	Sotacor	0.3	0	0	0
Timolol	Blocadren	6	0	0	0
Tolamolol	--	0.8	+	0	0

from Kaplan NM: Clinical Hypertension. 2nd ed. Williams and Wilkins, Baltimore, 1978.

Table 5. Adverse Effects With Propranolol (390 patients, 10 years) and Atenolol (543 patients, 4 years).

	Propranolol	Atenolol
Cardiac: Heart failure	0.8%	0.4%
Peripheral vascular: Cold extremeties	2.5%	2.8%
Worsening claudication	2.8%	1.3%
Bronchial: Bronchospasm	5.1%	3.3%
Central nervous: Vivid dreams, hallucinations	2.5%	0.9%
Dizziness, ataxia	0.4%	1.1%
Depression	0.8%	0.7%
Fatigue	3.9%	3.9%
Impotence	0.2%	0.2%
Total adverse effects	24.1%	16.9%

from Zacharias et al: Postgrad. Med. J. 53, Suppl. 3:102, 1977.

One of the most serious side effects was unexpected--a progressive oculomucocutaneous syndrome seen with practolol. This syndrome, characterized by rash, eye lesions, sclerosing peritonitis and pericarditis, was recognized only after the cumulative experience with the drug had totalled one million patient years (British Medical Journal, 1977) at a time when it had become the most popular beta-blocker in England.

The reaction, which may be life-threatening (Marshall et al, 1977a), may be peculiar to practolol--which of all the beta-blockers is the only one to possess an acetanilide structure--and to certain people made susceptible by altered immune responses (Behan et al, 1976). The syndrome has not been seen with propranolol after 12 years of use nor with other beta-blockers. Nonetheless, the caution being shown by the FDA in approving other beta-blockers seems warranted.

2. Duration of Action:

As to the duration of action, the various beta-blockers have varying pharmacokinetic characteristics (Taylor, 1976) but these seem not to matter since their physiological effects substantially outlast the survival of unchanged drug in the circulation. Most can be used in twice daily dosage; some such as atenolol may be used once daily; long-acting, slow-release forms of oxprenolol are also available (O'Brien and Stephens, 1976). But even with propranolol, which has a short plasma half-life of 3.5 to 6 hours, two (Berglund et al, 1973) or even one (Wilson et al, 1976) dose a day will work. Moreover, neither the dose nor the plasma concentration of propranolol is closely correlated to its antihypertensive effect (Lehtonen et al, 1977).

We are left with a basket-full of drugs with varying actions and doses, but with very little to choose from as to what counts--the blood pressure lowering effect and the propensity toward side effects (Davidson et al, 1976). For now, propranolol does quite well. For the future, a cardioselective beta-blocker or a combined alpha and beta blocker may be more acceptable.

Little further consideration will be given other beta-blockers than propranolol. Reviews of all of them are available (Hansson and Werkö, 1977; Waal-Manning, 1976). Most of what's important about beta-blocker therapy of hypertension can be gained from knowing about the drug which has been around longest, propranolol.

B. Propranolol (Inderal®):

1. Chemistry:

Propranolol has a close structural similarity to the beta receptor stimulant isoproterenol. The identical side chain apparently allows propranolol to interact with the beta receptors and thereby block the effects of adrenergic stimulation mediated through them.

2. Actions (Figure 13, page 23):

a. blockade of the *cardiac* beta receptors, both the chronotropic and inotropic, resulting in a decrease in heart rate and myocardial contractility with about an 18% decrease in cardiac output (Tarazi and Dustan, 1972).

This effect may be an important part of the antihypertensive action of propranolol but a fall in cardiac output is seen even when the blood pressure doesn't fall. In rabbits, chronic β-blockade induces structural changes in the myocardium which produce a relative increase in capillaries and a shorter diffusion pathway for oxygen (Vaughan Williams et al, 1977). Moreover, both the dry weight of the ventricle and the rate of growth of the heart in young rabbits were reduced. The possible relevance of these findings to the effects of β-blockers in treatment of hypertension, angina and hypertrophic obstructive cardiomyopathy is unknown but intriguing.

b. blockade of *peripheral* vascular beta receptors preventing the vasodilatory effects of circulating beta agonists (epinephrine), leaving alpha receptor-mediated vasoconstriction unopposed and thereby increasing peripheral vascular resistance. This initially causes peripheral resistance to rise; with time, resistance falls back to normal or below (Figure 13) and this may be the crucial effect of chronic beta-blocker therapy (Ablad et al, 1976). Vasodepressor prostaglandins might be involved; the anti-hypertensive effect of propranolol was prevented by simultaneous intake of the prostaglandin inhibitor indomethacin (Durao et al, 1977). Caution should be taken in giving aspirin, indomethacin or other PG-inhibitors to patients on β-blockers.

c. blockade of *central* beta-adrenergic receptors, probably in the floor of the fourth ventricle (Srivastava et al, 1973), thereby producing bradycardia and vasodepression. This is likely the prime action of high doses.

d. blockade of *renal* beta receptors, inhibiting the release of renin in response to various stimuli (Winer et al, 1969). Renin supression occurs despite renal vasoconstriction (Sullivan et al, 1976) and may be the prime action of low doses.

e. Lewis (1976) has proposed that the essential action is to blunt cardiac impulses to the brain, thereby reducing sympathetic nerve output.

f. Amer (1977) has proposed an attractive hypothesis which explains many of the properties of β-blocker action. He begins with the evidence that, in early hypertension, excess sympathetic tone reduces vascular β-receptor sensitivity so that β-stimulated vasodilation is impaired. Since the mode of β-receptor action, involving the adenylate cyclase complex, is shared by the other vasodilatory systems, e.g. prostaglandins, histamine, etc., vasoconstriction is unopposed and the blood pressures rises. β-blockers protect the vascular β-receptors from the catecholamine-induced loss of sensitivity. Thereby the vasodilatory mechanism slowly regains its responsiveness and the blood pressure falls. As noted on page 14, the hypothesis suffers from a basic defect.

g. Beta-blockers interact with brain receptors for 5-hydroxytryptamine (5-HT), one of the central nervous system neurotransmitters (Middlemiss et al, 1977). Long-term therapy with various beta-blockers produces a slow-onset reduction in the activity of the enzymes, tyrosine hydroxylase and dopamine beta-hydroxylase, in sympathetic ganglia (Raine and Chubb, 1977). Whether this is clinically important is questionable: after 3 months of therapy with the cardioselective beta-blocker, metoprolol, basal and stimulated plasma catecholamine levels were normal (Hansson et al, 1977a,b). The suppressive effect on sympathetic activity might involve blockade of the presynaptic β-receptors which, if unblocked, stimulate the release of norepinephrine via a positive feedback mechanism. A reduction in sympathetic and other nervous system activity may play an important role in the action of beta-blockers.

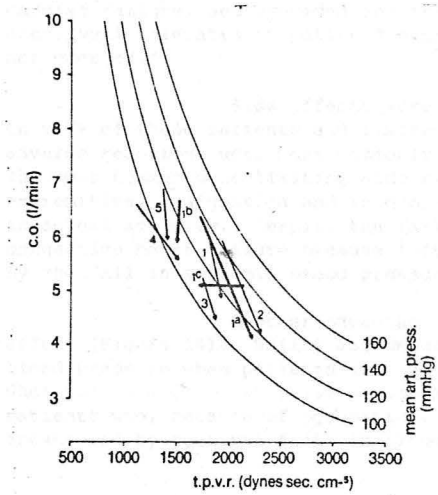


Figure 13a. Hemodynamic changes during beta-adrenergic blockade as observed by 1) Birkenhäger et al, 1976; 2) Frohlich et al, 1968; 3) Hansson, 1973; 4) Julius et al, 1971 and 5) Lund-Johansen, 1974. From Birkenhäger W.H., Wester A., Kho T.L. et al. in Beta-adrenoceptor Blocking Agents, ed. P.R. Saxena and R.P. Forsyth, North-Holland Press, Amsterdam, 1976.

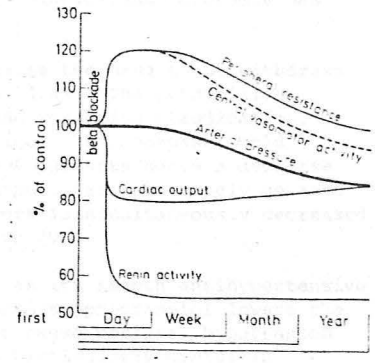


Figure 13b. A scheme of the various changes, with time, induced by propranolol therapy. The dotted line, for central vasomotor activity, represents a variable which cannot be measured in patients. From Birkenhäger W.H., DeLeeuw P.W., Wester A. et al, in Advances in Internal Medicine and Pediatrics, Vol. 39, ed. P. Frisk, G.A. von Harnack, G.A. Martini, et al. Springer-Verlag, Berlin, 1977.

3. Clinical Effects:

Though considerable doubt remains about the mechanism, little doubt remains about the ability of propranolol to lower the blood pressure. Its hypertensive effect was first reported by Prichard and Gillam (1964). Of numerous subsequent reports, those of Zacharias et al (1972, 1977a) are representative and especially useful in that 480 patients were followed for up to 10 years. The average systolic and diastolic pressure in a group of 221 patients fell from 192/113 to 143/88 after an average of 510 mg of propranolol daily for 62 months. The doses of propranolol were often large: 50% responded to doses less than 500 mg per day; 30% needed 500 to 1000 mg, 10% 1000 to 1500 mg and the final 10% 1500 to 2000 mg. In England, 160 mg tablets are available.

Of these 221 patients given propranolol plus a diuretic, 86% had a diastolic blood pressure below 100 mm Hg. Another 103 patients needed additional drugs; 79% of them were also well controlled. The following conclusions, made by these authors after 5 years, were reiterated after 10 years of use:

"Provided that it is not used in the presence of obstructive airways disease or cardiac failure, and provided one starts with small doses, propranolol is a safe drug, well tolerated by patients over long periods. Significant tolerance has not emerged."

Side effects were so bad as to cause the drug to be withdrawn in 9.7% of these patients and limited the dosage in 14.4%. The prohibitive adverse reactions were most commonly bronchospasm and worsening claudication. The most common dose-limiting side effects were fatigue, bronchospasm, cold extremities, indigestion and insommia. Only 3 of 390 patients noted a decrease in sexual activity. Despite the fall in cardiac output, patients rarely go into congestive heart failure because left ventricular work is simultaneously decreased by the fall in systemic blood pressure (Table 5, page 20).

Another advantage of propranolol is its smooth antihypertensive effect (Figure 14). Unlike adrenergic neuronal blockers, propranolol lowers the blood pressure when patients are supine and does not cause postural hypotension when they stand up, exercise or become warm. It is particularly useful in patients who, because of occupation, age or ischemic vascular disease, are endangered by postural falls in blood pressure.

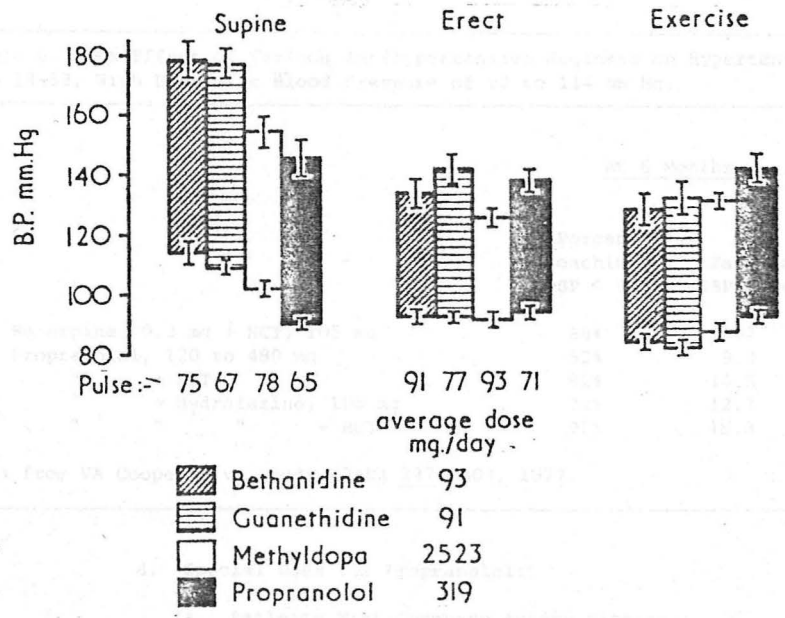


Figure 14. The average blood pressures, supine, erect and after exercise (up and down 18 stairs) in patients treated with one of 4 drugs. Each group included 13 patients. From Prichard, B.N.C. and Gillam P.M.S. Br. Med. J. 1:7, 1969.

The enthusiasm shown by Zacharias et al is generally shared (Holland and Kaplan, 1976). As in the Zacharias study, all find the drug to be more effective with concomitant diuretic therapy. Of all the antihypertensive drugs, beta-blockers give less tendency to fluid retention perhaps because they lower renin and induce less secondary aldosteronism. Therefore, the rare patients for whom diuretics are contraindicated can probably best be treated with propranolol alone. But fluid retension may appear with beta-blockers alone (Sederberg-Olson and Ibsen, 1972), endangering the patient and blunting their antihypertensive efficacy.

Some advocate beta-blockers alone to simplify therapy and prevent the real and imagined side effects of diuretic drugs. However, only half of hypertensives given up to 480 mg daily of propranolol alone achieved adequate control (VA Cooperative Study, 1977) (Table 6) and the majority of hypertensives over age 40 given a similar dose failed to bring their diastolics below 95 mm Hg (Bühler et al, 1975)(Figure 15). The lesser responses in the older hypertensives were related to their higher frequency of the low renin state, wherein the effects of beta-blockers are blunted. However, it may reflect an age-related decrease in the number of beta-receptors (Shocken and Roth, 1977).

Table 6. The Effect of Various Antihypertensive Regimens on Hypertensive Men, Age 18-59, With Diastolic Blood Pressure of 90 to 114 mm Hg.

	At 6 Months	
	Percent Reaching DBP < 90	Mean Fall In DBP(mmHg)
Reserpine, 0.3 mg + HCT, 105 mg	88%	16.7
Propranolol, 120 to 480 mg	52%	9.0
" + HCT	81%	14.5
" + Hydralazine, 105 mg	72%	12.7
" " " + HCT	92%	18.3

data from VA Cooperative Study, JAMA 237:2303, 1977.

4. Special Uses for Propranolol:

a. Patients With Coronary Artery Disease:

Not only may the drug be useful in treating angina pectoris, it may also protect against initial (Stewart, 1976) and recurrent myocardial infarction. This protection has been shown for other beta-blockers (Ross, 1976; Multicentre Study, 1977) but likely holds for propranolol as well.

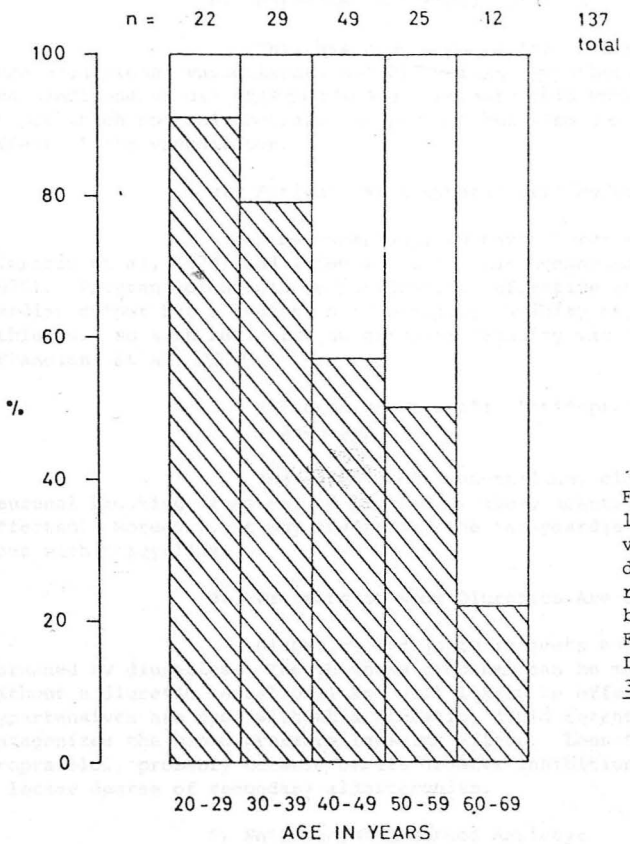


Figure 15. The percent of 137 hypertensive patients in various age groups whose diastolic blood pressure was reduced to 95 mm Hg or less by therapy with beta-blockers. From Bühler, F.R., Burkart F., Lütold B.E. et al. Am. J. Cardiol. 36:653, 1975.

Propranolol may also be useful in reducing the signs of myocardial ischemic injury in patients having just had a myocardial infarct (Mueller and Ayres, 1977). On the other hand, patients on chronic propranolol therapy at the time of myocardial infarction may be more vulnerable to the development of heart failure (Bloch et al, 1976).

Abrupt withdrawal of propranolol from patients with coronary disease may precipitate an acute myocardial infarction (Alderman et al, 1974) perhaps because of the sudden opening of a relatively large number of β-receptors to circulating catecholamines. Therefore, if it is to be stopped, it should be slowly withdrawn over 2 days or longer; for most emergencies such as surgery, it should be continued and the anesthesiologist advised.

b. Patients on Vasodilators:

This has proved to be one of the best uses for propranolol. When used alone, vasodilators set off reflex sympathetic stimulation of the heart. The simultaneous use of beta-blockers prevents this undesired increase in cardiac output which not only bothers the patient but also dampens the antihypertensive effect of the vasodilator.

c. Patients With Hyperkinetic Hypertension:

Some hypertensives have increased cardiac output early (Ibrahim et al, 1974) and a few maintain this hemodynamic pattern (Ibrahim et al, 1975). Propranolol should be particularly effective in such patients with high cardiac output but a reduction in exercise capacity may restrict its use in young athletes. No such reduction in exercise capacity was observed with oxprenolol (Franciosa et al, 1977).

d. Patients on Tricyclic Antidepressants and Antipsychotic Agents:

The effects of guanethidine, clonidine and other adrenergic neuronal blocking drugs may be blunted by these agents. Propranolol should not be affected. Moreover, it may counteract the tachycardia and arrythmias sometimes seen with tricyclics.

e. Patients in Whom Diuretics Are Contraindicated:

Diabetics and gouty subjects may have their diseases worsened by diuretics. Though these problems can be managed, the use of propranolol without a diuretic is rational and will likely be effective. When most other antihypertensives are used without a diuretic, fluid retention frequently appears and antagonizes the blood pressure lowering effect. Less fluid retention occurs with propranolol, probably because of its greater inhibition of renin release and thereby a lesser degree of secondary aldosteronism.

f. Patients With Marked Anxiety:

The somatic manifestations of anxiety --- tremor, sweating, tachycardia --- can be helped. In a controlled study, the performance of 24 musicians was found to improve when they took 40 mg of oxprenolol before the concert (James et al, 1977). The undesirable effects of methods commonly used to control anxiety, alcohol and tranquilizers, were not observed.

5. Dosage:

Propranolol is almost completely absorbed from the gut, with the peak plasma concentration reached in about 90 minutes. However, 50 to 70% of the dose is extracted and metabolized on the first pass through the liver so that the plasma concentration of active drug after repeated oral doses is quite variable (Nies and Shand, 1975). The drug and its metabolites remain active in blocking the response to the beta agonist, isoproterenol, for over 24 hours with excretion continuing beyond that interval. The prolonged effect of chronic therapy is explained by saturation of both hepatic binding and systemic clearance (Nies and Shand, 1975).

Patients should be asked to take their medication in a set manner, preferably with breakfast and dinner since food enhances the bioavailability of propranolol and metoprolol (Melander et al, 1977). Other drugs should be avoided, if possible. Aluminum hydroxide reduces the absorption of propranolol (Dobbs et al, 1977); pentobarbital increases the hepatic elimination of alprenolol (Alvan et al, 1977); prostaglandin-inhibitors decrease the effectiveness of propranolol (Durao et al, 1977).

For mild and moderate hypertension the initial dosage is 40 mg twice a day, increased every 2 or 3 weeks. For more severe disease the dose can be raised more rapidly. The maximum daily dose reported is over 2,000 mg, though most patients respond to 160 to 480 mg. Though some may need more frequent doses, two doses a day were as effective as four (Hansson et al, 1971) and one as effective as two (Wilson et al, 1976).

The metabolism of the drug is altered little in patients with renal insufficiency (Lowenthal, 1977) and the drug can be given with good effect to such patients (Briggs et al, 1976). Its safety in pregnancy is unknown; isolated examples of fetal trouble have been reported (Gladstone et al, 1975). The drug enters breat milk (Levitan and Manion, 1973) so lactating mothers should not take propranolol.

6. Complications (Table 5, page 20):

Most of the complications are related to the known effects of beta blockade: decreased cardiac function, bradycardia, and bronchospasm. The drug therefore should be used with caution in patients with congestive heart failure, atrio-ventricular conduction blocks, or bronchial asthma. Hypoglycemia may be more serious in diabetics on insulin presumably by interference with the normal compensatory responses to a rapidly falling blood glucose. Fatigue may be a nonspecific response to lowering of the blood pressure caused by a fall in cerebral blood flow. Nonspecific and rare side effects include bad dreams and fitful sleep, gastrointestinal distress, diarrhea, and purpura.

Rarely skin rashes have appeared (Aerenlund-Jensen et al, 1976) and one patient developed an ocular reaction (Cubey and Taylor, 1975). But the great rarity of oculomucocutaneous reactions after so long and extensive usage makes it very unlikely that propranolol will be accompanied by the problems seen with practolol.

Cold extremities, intermittent claudication and Raynaud's phenomenon may be the most common symptomatic but not immediately serious side effect. The reported frequency varies from 3 to 8% (Marsden and Bayliss, 1976) but when specifically sought the symptom was found in 50% of 102 patients (Marshall et al, 1976). The decrease in blood flow to the extremities likely reflects unopposed alpha-adrenergic vasoconstriction but the symptoms may also appear when cardioselective beta-blockers are used. Therefore, the desired fall in blood pressure may also be responsible. Whatever the mechanism, the problem is more common with beta-blockers and, among them, with the non-cardioselective ones such as propranolol.

The first β-blocker studied, pronethalol, was withdrawn from the market because it caused tumors in mice. Though no reports have appeared concerning tumors with any other β-blocker, propranolol has been found to increase the incidence of liver tumors in rats given a known carcinogen (Boyd and Martin, 1977).

C. The Probable Use of Other β-blockers:

It is likely that one or more of the multitude of other β-blockers will soon be introduced in the US, probably from the cardioselective group (atenolol, acebutolol, metoprolol). A recent series of papers on atenolol attest to its effectiveness and acceptability to patients (Postgrad. Med. J. 53, Suppl. 3: 52-175, 1977). Zacharias, (1977b) concludes, on the basis of 4 years of experience in 543 patients, that "atenolol is at least as effective as propranolol --- and for some patients marginally better. In patients with airways obstruction or reduced respiratory reserve it is considerably more useful than propranolol.... There is clear evidence of a difference in the antihypertensive dose response curve of atenolol --- resulting in a smaller range of effective dosage and possibly greater economy of use." Other papers in this supplement document the effectiveness of a single 100 mg atenolol tablet a day for most patients with mild to moderate hypertension.

V. The Relevance of Renin:

A. The Laragh Concept:

In 1972, Buhler et al reported a close correlation between the antihypertensive effectiveness of propranolol and renin levels, both the pre-existing level and the degree of suppression post-therapy (Figure 16).

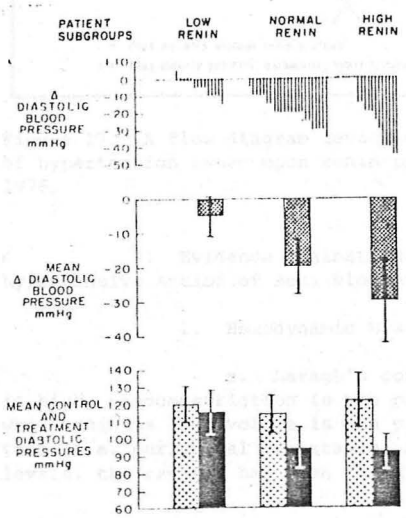


Figure 16a. The change in diastolic blood pressure after propranolol therapy among hypertensives with low, normal or high renin state, determined prior to therapy. From Bühler, F.R., Laragh J.H., Baer, L. et al. N. Engl. J. Med. 287:1209, 1972.

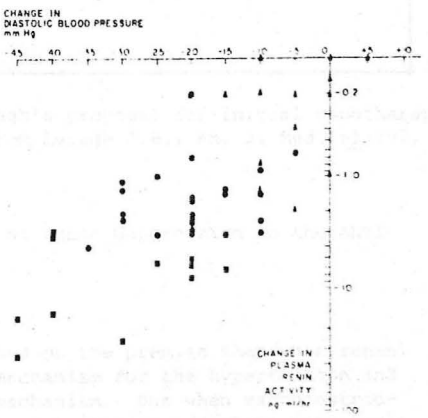


Figure 16b. The changes in diastolic blood pressure in relation to changes in plasma renin activity in patients with initially low (triangles), normal (circles) and high renin (squares). From Bühler F.R., Laragh J.H., Baer L. et al. N. Engl. J. Med. 287:1209, 1972.

Subsequently John Laragh has popularized the concept that knowledge of renin status is critical to proper use of Beta-blocker therapy and has offered the charm and simplicity of "monotherapy" based upon renin profiling (Laragh, 1976; Laragh, 1977) (Figure 17). Despite the attractiveness of the scheme, I do not believe it is valid either on experimental or clinical grounds.

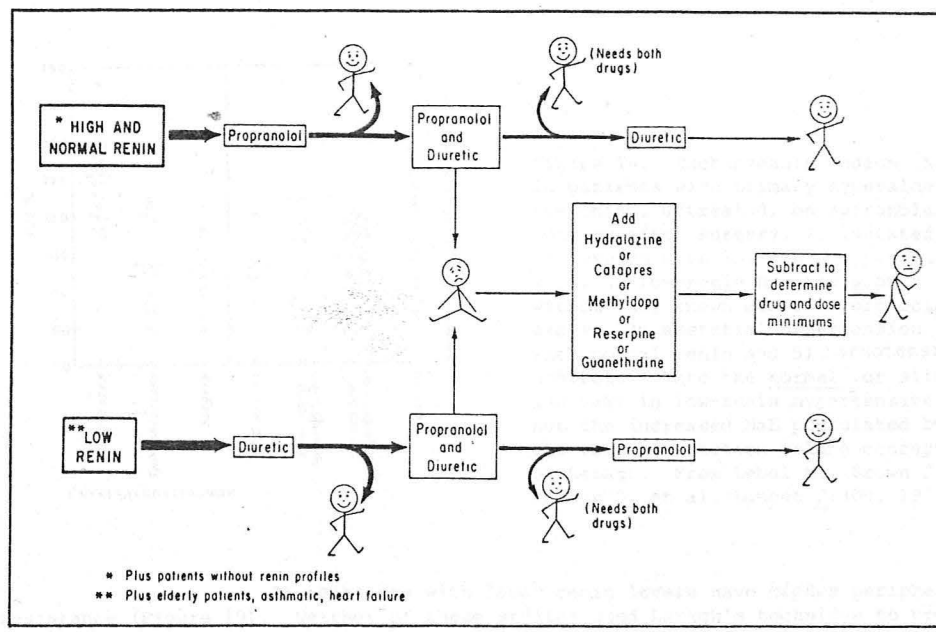


Figure 17. A flow diagram depicting John Laragh's proposal for initial monotherapy of hypertension based upon renin profiles. From Laragh J.H., Am. J. Med. 61:797, 1976.

B. Evidence Against the Relevance of Renin Suppression in the Anti-hypertensive Action of Beta-blockers:

1. Hemodynamic Measurements:

a. Laragh's concept is based on the premise that when renin is high, vasoconstriction is the predominant mechanism for the hypertension and when renin is low, volume is the predominant mechanism. But when vasoconstriction (i.e. peripheral resistance) and volume have been measured along with renin levels, the reverse has been found:

1) Patients with low renin levels have the same (or lower) plasma volume and total body exchangeable sodium than do patients with normal renin levels (Figure 18).

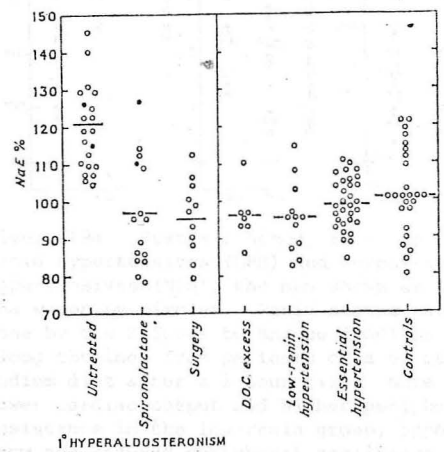


Figure 18. Exchangeable sodium (NaE) in patients with primary hyperaldosteronism, untreated, on spironolactone or after surgery, 2) isolated DOC excess with low-renin hypertension, 3) low-renin hypertension without any known mineralocorticoid excess, 4) essential hypertension with normal renin and 5) normotensive controls. Note the normal (or slightly low NaE) in low-renin hypertensives, not the increased NaE postulated by the vasoconstriction-volume concept of Laragh. From Lebel M., Brown J.J., Kremer D. et al, Lancet 2:308, 1974.

2) Patients with *lower* renin levels have *higher* peripheral resistance (Figure 19). Neither of these studies used Laragh's technique to profile the patients' renin status and might therefore not refute his premise. However, in another study by London et al (1977), the renin status was done in a manner similar to Laragh's and here again, the reverse was found: the higher the renin, the lower the peripheral resistance.

b. If renin suppression is critical to the action of Beta-blockers, the hemodynamic consequence would be a *fall* in peripheral resistance. But as shown by everyone who's looked, peripheral resistance initially rises with Beta-blocker therapy (Figure 13).

2. Time and Dose Relations:

The effect of propranolol upon renin is fast and dramatic, with maximal suppression seen within an hour by use of small doses. But the antihypertensive action of propranolol requires much larger doses and a longer time (Figure 20).

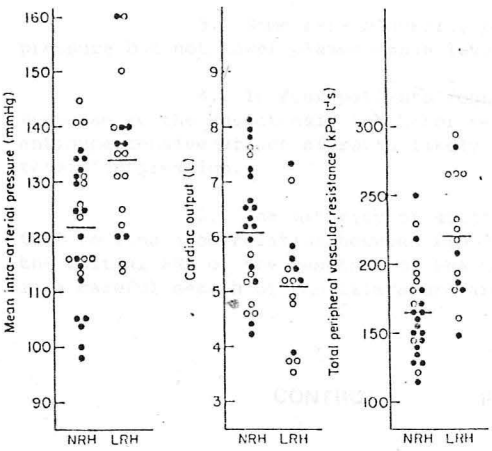


Figure 19a. Systemic hemodynamics in low-renin hypertensives (LRH) and normal-renin hypertensives (NRH), the men shown as dots, the women by circles. Renin status was done by the Skinner technique (PRC) on blood obtained from patients on a 50 mEq sodium diet after a 1 hour tilt. Note the lower cardiac output and higher peripheral resistance in the low-renin group, opposite from the reduced peripheral resistance postulated by the vasoconstriction-volume concept of Laragh. From Schalekamp M.A.D.H., Birkenhäger W.H., Zaal G.A. et al, Clin. Sci. 52:405, 1977.

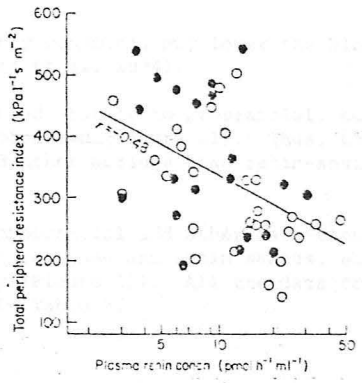


Figure 19b. The relation between total peripheral resistance and the log of plasma renin concentration for men (circles) and women (dots) with essential hypertension. The PRC was done by the Skinner technique on blood obtained from patients on a 130 mEq sodium diet while supine. From Fagard R., Amery A., Reybrouck T. et al. Clin. Sci. 52:591, 1977.

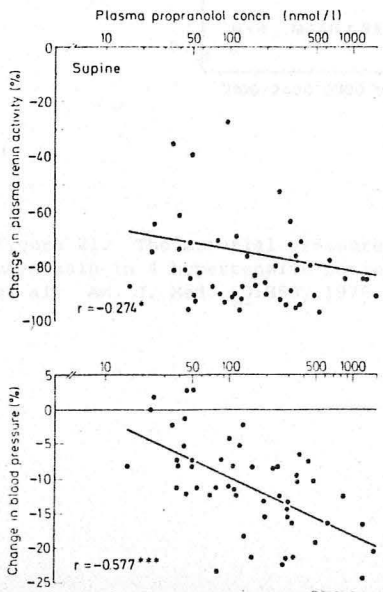


Figure 20. The changes in supine and standing blood pressure (BP) and plasma renin activity (PRA) as related to the log of plasma propranolol concentration in 16 hypertensives with initially normal PRA. From Leonetti G., Mayer G., Morgonti A. et al. Clin. Sci. 48:77s, 1975.

3. Some beta-blockers, particularly pindolol, may lower the blood pressure but not lower plasma renin levels (Stokes et al, 1974).

4. In four patients found to respond acutely to propranolol, no response to the angiotensin inhibitor saralasin occurred (Figure 21). Thus, the antihypertensive effect of renin likely reflected other actions than renin-angiotensin suppression.

5. The majority of studies with propranolol and other beta-blockers fail to find a correlation between blood pressure response and renin status, either the initial PRA or the response of PRA to therapy (Figure 22). All the data found in a careful search of the literature are shown in Table 7.

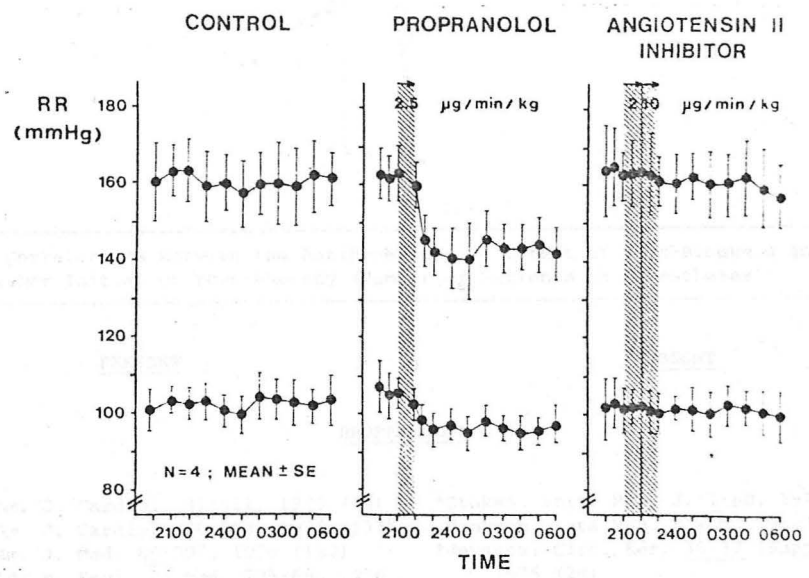


Figure 21. The arterial pressure responses (RR) to intravenous propranolol or saralasin in 4 hypertensive patients. From Stumpe K.O., Kolloch R., Vetter H. et al. Am. J. Med. 60:853, 1976.

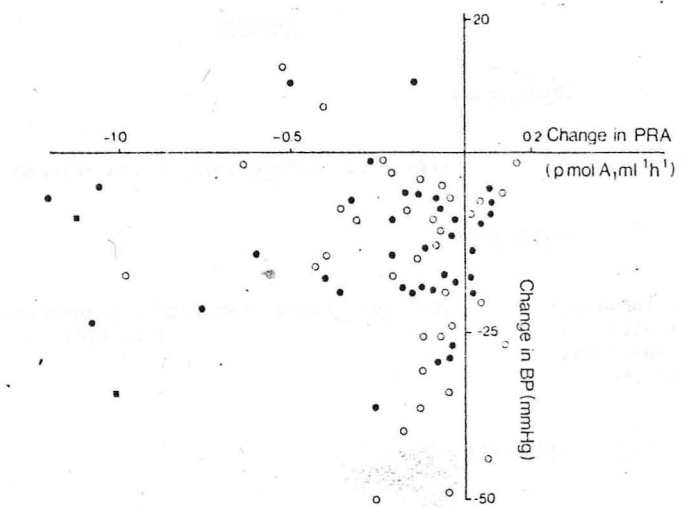


Figure 22. The changes in blood pressure (BP) as related to changes in plasma renin activity (PRA) in patients treated with propranolol (circles) or pindolol (dots). The correlation is not significant. From Morgan T.O., Roberts R., Carney S.L. et al. Br. J. Clin. Pharmacol. 2: 159, 1975.

Table 7: Correlations Between the Antihypertensive Effect of Beta-Blockers and Renin Status, Either Initial or Post-therapy (Number of Patients in Parentheses).

PRESENT	ABSENT
PROPRANOLOL	
*Buhler: Am. J. Cardiol. 32:511, 1973 (74)	*Stokes: Brit. Med. J. 1:60, 1974 (27)
*Buhler: Am. J. Cardiol. 36:653, 1975 (137)	Hansson: Acta Med. Scand. 195:397, 1974 (14)
*Drayer: Am. J. Med. 60:897, 1976 (187)	†Geyskes: Circ. Res. 36-37 (Supple. 1):248, 1975 (28)
*Hollifield: N. Engl. J. Med. 295:68, 1976 (40)	Leonetti: Clin. Sci. 48:491, 1975 (20)
Karlberg: Brit. Med. J. 1:251, 1976 (32)	†Bravo: N. Engl. J. Med. 292:66, 1975 (20)
Stumpe: Am. J. Med. 60:853, 1976 (46)	*Morgan: Br. J. Clin. Pharmacol. 2:159, 1975 (39)
Weidmann: Klin. Wschr. 54:765, 1976 (33)	Gordon: Drugs 11 (Suppl. 1):156, 1976 (15)
	*Woods: N. Engl. J. Med. 294:1137, 1976 (48)
	Lijnen: Beta-adrenoreceptor Blocking Agents, ed. Saxena, Amsterdam, 1976 (17)
	Witzgall: Klin. Wschr. 55:351, 1977 (17)
	Mookherjee: Arch. Int. Med. 137:290, 1977 (2
	Matsunaga: Jap. Heart J. 18:24, 1977 (23)
	*Zweifler: Am. J. Cardiol. 40:105, 1977 (24)
	Nielsen: Acta Med. Scand. Supple. 602:97, 1977 (19)
	*Espiner: New Zealand Med. J. 86:216, 1977 (1
	Birkenhager: Adv. Int. Med. 39, Springer, Berlin, 1977 (37)

Table 7. -continued-

PRESENT	ABSENT
ACEBUTOLOL	
Menard: Am. J. Med. 60:886, 1976 (44)	Fournier: Clin. Sci. 51:477s, 1976 (18)
ALPRENOLOL	
Castenfors: Acta Med. Scand. 193:189, 1973 (17)	*Collste: Europ. J. Clin. Pharm. 10:89, 1976 (16) Pedersen: Europ. J. Clin. Pharm. 12: 93, 1977 (27)
ATENOLOL	
Zech: Postgard. Med. J. 53 (Suppl. 3): 134, 1977 (32) Philipp: Dtsch. Med. Wschr. 102:569, 1977 (16)	Amery: Am. Heart J. 91:634, 1976 (33) Byers: Clin. Pharm. Ther. 19:502, 1976 (16) Wilcox: Brit. Med. J. 2:547, 1977 (26)
BUNOLOL	
	*Gavras: J. Clin. Pharm. 17:350, 1977 (11)
METOPROLOL	
von Bahr: Clin. Pharm. Ther. 20:130, 1976 (16)	Hansson: Europ. J. Clin. Pharm. 11:239, 1977 (9)
OXPRENOLOL	
	Kaplan: Systemic Effects of Antihypertensive Agents, ed. Sambhi, Stratton, New York, 1976 (15) *Salvetti: Europ. J. Clin. Invest. 7:331, 1977 (84) Thomas: Aust. N. Z. J. Med. 6 (Suppl. 3): 44, 1976 (51)

Table 7. -continued-

PRESENT	ABSENT
PINDOLOL	
	Anavekar: Clin. Exp. Pharm. 2:203, 1975 (15)
	*Morgan: Br. J. Clin. Pharm. 2:159, 1975 (37)
	Tenyi: Europ. J. Clin. Invest. 7:325, 1977 (22)
	Fyhrquist: Acta Med. Scand. 202:55, 1977 (31)
PRACTOLOL	
	Esler: Clin. Pharm. Ther. 15:484, 1974 (11)
SOTOLOL	
	Verniory: Clin. Sci. 51:9, 1976 (23)
TIMOLOL	
	Aronow: Circulation 54:47, 1976 (11)
TOLAMOLOL	
	*Vlachakis: Clin. Pharm. Ther. 21:9, 1977 (10)

* Use Method of Buhler et al to assess renin status
† Concomitant diuretic therapy

C. A Dual Mechanism:

A study by Hollifield et al (1976) may help explain the conflicting data (Table 8). In patients with initially high renin, small (160 mg a day) doses of propranolol lowered blood pressure significantly. In patients with low renin, much higher doses (640-960 mg) were needed. Thus, the small number of hypertensives with high renin levels (including those with renovascular hypertension) may respond briskly to relatively small doses of propranolol, presumably acting at least in part by suppression of renin. In the majority of hypertensives, propranolol works by other mechanisms, though an element of renin suppression may be involved in many.

Table 8: Differing Responses to Varying Doses of Propranolol

	High-renin	Low-renin
	Mean Blood Pressure	
Placebo	128	131
160 mg	117	131
320 mg	114	123
640 mg	107	117
960 mg	104	114

data from Hollifield et al, N. Eng. J. Med. 295:68, 1976.

In those with low renin, the blood pressure may paradoxically rise with propranolol monotherapy (Drayer et al, 1976). This likely reflects their retention of fluid, reflected in an average 2.7 kg weight gain. In patients with initially normal renin levels, the suppression of renin by propranolol, even if not important in lowering the blood pressure, likely prevents the tendency toward fluid retention that accompanies a lowering of blood pressure by all other adrenergic blocking drugs and vasodilators. If the renin starts low and can't be suppressed further, aldosterone levels likely do not fall as much (Weber et al, 1977) and sodium is retained.

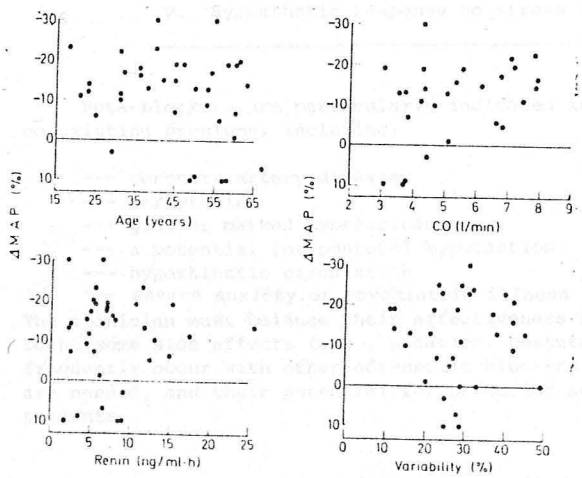


Figure 23. The lack of relationship between propranolol-induced change in supine mean arterial blood pressure (MAP) and age, cardiac output (CO), plasma renin concentration and the degree of variability of the blood pressure during a 24 hour period. None are significantly correlated. From Birkenhäger W.H., DeLeeuw P.W., Wester A. et al, in Advances in Internal Medicine and Pediatrics, Vol. 39, ed. P. Frisk, G.A. von Harnack, G.A. Martini et al. Springer-Verlag, Berlin, 1977.

Though this paradoxical rise in pressure could be used to argue for renin profiling before use of propranolol, the more logical conclusion is not to use propranolol without concomitant diuretic therapy. With a diuretic, propranolol will work better and no concern need be held about paradoxical rises in pressure. There remains no valid argument to obtain a renin profile before institution of antihypertensive therapy. The situation concerning the use of renin or other possible predictors of antihypertensive response to propranolol has perhaps best been shown by Birkenhäger et al (1977), wherein no relation was noted between the response of the blood pressure after propranolol with any of the possible "predictive" features (Figure 23).

After 14 years of use, propranolol has been found to be effective, generally safe and capable of long time control of mild to moderate hypertension. Monotherapy beginning with propranolol has great charm but I believe that it remains prudent to initiate therapy with a diuretic and modest salt reduction. Over 50% of hypertensives will be controlled by these alone. If the blood pressure remains too high, a beta-blocker is a logical second drug, along with other available adrenergic blockers. Table 9 is a set of guidelines for the use of propranolol in the treatment of hypertensives.

Table 9. Propranolol in Mild to Moderate Hypertension

1. Starting dose 40 to 80 mg twice a day.
2. Antihypertensive effect in hours, maximal in weeks.
3. Control achievable in > 80% and well maintained.
4. Total daily dose required = 10 to 4000 mg.
5. Concomitant diuretic enhances effect.
6. Side effects in 25% even with prior selection.
7. Side effects not increased with higher doses.
8. No alteration in pressure by posture, heat or exercise.
9. Sympathetic response to stress suppressed.

Beta-blockers are particularly indicated in hypertensives who have certain co-existing problems, including:

--- coronary artery disease
--- arrhythmias
--- gout or marked hyperuricemia
--- a potential for postural hypotention
--- hyperkinetic circulation
--- severe anxiety or psychiatric illness

The clinician must balance their effectiveness and relative freedom from minor but bothersome side effects (e.g., sedation, postural hypotention and impotence) which frequently occur with other adrenergic blockers against their cost, if large amounts are needed, and their potential for producing serious side effects in susceptible patients.

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