Brief Review

Epinephrine and the Genesis of Hypertension

John S. Floras

Several lines of evidence suggest a psychophysiologic link between stress, adrenomedullary activation, and the genesis of hypertension. Experimental data support four important concepts: 1) epinephrine stimulates prejunctional β1-adrenergic receptors that facilitate norepinephrine release from sympathetic nerve endings; 2) epinephrine can be converted into a cotransmitter by neuronal uptake and on subsequent release augment the simultaneous discharge of norepinephrine; 3) exogenous epinephrine can induce sustained hypertension in rats; and 4) there is a period of critical sensitivity to endogenous epinephrine in a genetic model of rat hypertension. Plasma epinephrine concentrations are elevated in many young subjects with borderline or mild hypertension. The hypothesis that intermittent surges in epinephrine could initiate or promote the development of primary hypertension by amplifying peripheral neurotransmission, both directly (facilitative effect) and indirectly (cotransmitter action), is supported by reports that hemodynamic and noradrenergic responses to sympathetic activation can be augmented by increases in endogenous epinephrine or by its local or systemic (up to 30 ng/kg/min) infusion. Such responses have been documented in both normotensive and hypertensive subjects and can be blocked by propranolol. Although the weight of evidence (mostly indirect) indicates that epinephrine can augment norepinephrine release in humans, the epinephrine hypothesis, itself, remains unproven. Expression of hypertension by this mechanism may be restricted to a specific epinephrine-sensitive subset of individuals with a genetic predisposition to high blood pressure. (Hypertension 1992;19:1-18)

A decade ago, it was proposed that the primary abnormality in essential hypertension may be increased release of epinephrine from the adrenal medulla. According to this hypothesis, small repetitive increases in circulating epinephrine cause hypertension indirectly, rather than directly, by stimulating prejunctional β1-adrenergic receptors that facilitate exocytotic norepinephrine discharge from sympathetic nerve endings (Figure 1). An episodic or sustained increase in norepinephrine release could then initiate, permit, or promote the development of high blood pressure.

Folkow has identified “excitatory psychoemotional influences” as one of two environmental stimuli that may reinforce or sometimes precipitate primary hypertension in those with a genetic predisposition for high blood pressure. The concept that episodic increases in plasma epinephrine, if of sufficient magnitude, could act as the physiological link between such “stressful” environmental influences and the development of hypertension in predisposed individuals is intuitively attractive. Thresholds for epinephrine’s cardiovascular and metabolic actions are at plasma concentrations that can be replicated by mental stress. Early hypertension in many subjects is associated with a pattern of enhanced autonomic cardiovascular drive at rest and increased sympathoadrenal reactivity, analogous to the hypothalamic defense reaction, in response to mental stress but not in response to physical tasks. In the mind of the lay public, “stress” has long been associated with “adrenaline” and the genesis of hypertension. This concept has been reinforced by reports of hypertension after the stress of battle or exposure to noise, descriptions of relations between stress, personality, and blood pressure and plasma epinephrine concentrations, and documentation in prospective studies of environmental changes that promote or protect against primary hypertension.

A facilitative effect on peripheral noradrenergic transmission has been observed both during and after exposure to epinephrine. Aftereffects of epinephrine are presumed to be through conversion of epinephrine from a hormone to a cotransmitter since this catecholamine can be incorporated into postgangli-
FIGURE 1. Schematic representation (much simplified) of prejunctional and postjunctional adrenergic receptors at the sympathetic neuroeffector junction in the peripheral nervous system. Left panel: Low level nerve stimulation releases norepinephrine (NE), which has a higher affinity for inhibitory $\alpha_2$ than facilitative $\beta_2$-adrenergic receptors. Center panel: Direct activation of prejunctional $\beta_2$-adrenergic receptor by circulating epinephrine (EPI) facilitates neurotransmitter release. Right panel: Sustained aftereffects of EPI incorporated into sympathetic varicosity (neuronal uptake) and converted from hormone to neurotransmitter. Positive feedback loop by which activation of prejunctional $\beta_2$-receptor by neurally released EPI facilitates NE release and augments effector cell response. Effector cell responses to facilitation of norepinephrine release are increased vascular contraction ($\alpha_i$) and increased heart rate ($\beta_i$).

The functional sympathetic nerves and released, with norepinephrine, up to 24 hours after its uptake. Through this local positive feedback mechanism, endogenous epinephrine, within the synaptic cleft, could augment norepinephrine release both during episodes of sympathoadrenal activation and afterwards when plasma concentrations have returned to basal levels (Figure 1). The sustained, indirect aftereffects on norepinephrine release of brief, repetitive increases in plasma epinephrine concentrations may be of greater functional importance in the genesis of hypertension than its immediate direct, and often brief, cardiovascular actions as a circulating hormone.

In addition to these actions at the neuroeffector junction, stimulation of $\beta_2$-adrenergic receptors by epinephrine also facilitates hypothalamic and adrenal catecholamine release. As both norepinephrine and epinephrine are released from these tissues, these observations suggest a potential positive feedback loop that would allow epinephrine to augment its own release via "autoreceptor" stimulation. In this way, a relatively small increase in epinephrine could amplify neurotransmission through several closely linked central as well as peripheral $\beta_2$-adrenergic mechanisms.

Although these two components (facilitative and cotransmitter) of the epinephrine hypothesis are supported by a number of studies in isolated tissues, intact normotensive animals, experimental models of hypertension, and in humans, not all experimental data are consistent with the epinephrine hypothesis. A review of these experimental data will be presented briefly with principal emphasis on evidence for facilitated release of norepinephrine and induction of experimental hypertension by epinephrine. Review of investigations in humans will focus on 1) evidence for increased circulating epinephrine in primary hypertension, 2) evidence for enhanced prejunctional $\beta_2$-responsiveness in early hypertension, 3) evidence for facilitated release of norepinephrine by epinephrine in normal and hypertensive humans, and 4) the functional significance of augmented sympathetic neurotransmission by epinephrine as it relates to circulatory regulation.

Experimental Evidence for Facilitated Release of Norepinephrine by Epinephrine

Direct Effects of Epinephrine on Norepinephrine Release

Evidence that epinephrine and other $\beta_2$-adrenergic receptor agonists can facilitate exocytotic norepinephrine release from sympathetic varicosities by stimulating prejunctional $\beta_2$-receptors (Figure 1) has been extensively reported and reviewed. Facilitative prejunctional $\beta_2$-receptors have also been described. Functionally, one could consider three potential roles for such receptors: as autoreceptors activated by neuronally released norepinephrine, as "heteroreceptors" activated by epinephrine transformed from a hormone to a neurotransmitter by its uptake and storage in sympathetic varicosities (Figure 1). There is little evidence that the neurotransmitter norepinephrine potentiates...
its own release. Rather, epinephrine, whose affinity for β2-adrenergic receptors is more than 200-fold greater than that of norepinephrine, appears to be the "natural agonist" for these receptors in humans. Prejunctional β2-adrenergic receptors may respond preferentially to circulating as opposed to neurally released catecholamines.

Facilitated release of [3H]norepinephrine from tissues preloaded with the labeled neurotransmitter has been documented in vitro at epinephrine concentrations in the range of 10^-10 to 10^-6 M. This is within the physiological range of plasma epinephrine concentrations. At higher concentrations (more than 10^-8 M), epinephrine, like norepinephrine, acts on prejunctional α2-adrenergic receptors to inhibit sympathetic neurotransmission (Figure 1). That this facilitative action is a nonspecific effect of epinephrine is unlikely since it is abolished or attenuated by β2-adrenergic receptor blockade. Although prejunctional β2-adrenergic receptor-mediated facilitation of norepinephrine release appears due to increased Ca^2+ entry into nerve terminals, resulting in increased intraneuronal cyclic AMP, the exact mechanism by which α2-receptor stimulation inhibits neurotransmitter release has not been established.

The maximal enhancement of norepinephrine release by epinephrine is relatively small (from 13 to 133%, depending on tissue and preparation) when compared with the effect of α2-adrenergic receptor antagonists on stimulated norepinephrine release, and the functional consequence of β2-adrenergic receptor stimulation varies from species to species. The facilitative effect of isoproterenol on electrically stimulated norepinephrine release from adrenergic nerves of saphenous veins is greater in humans than in the dog and is associated with an augmented (human) as opposed to a diminished (canine) contractile response when these two interventions are combined (Figure 2). Such quantitative differences make it difficult to predict responses to epinephrine in humans from experimental observations in other species.

Inhibitory prejunctional α2-receptors and facilitative β2-adrenergic receptors have been documented in a number of human vascular tissues, including omental arteries and veins, digital arteries, and saphenous veins, and functionally important β2-receptors have been demonstrated in the human heart. Whether prejunctional inhibitory α2-adrenergic receptors (autoreceptors) must first be blocked to detect the facilitative effects of β-adrenergic receptor (heteroreceptor) stimulation on norepinephrine release in humans will depend on a number of factors (such as the ratio and sensitivity to agonists of prejunctional α2/β2-adrenergic receptors and the width of the junctional cleft) that vary from tissue to tissue. The strength of negative feedback regulation by α2-adrenergic receptors, for example, is inversely proportional to the width of the junctional cleft. It should not be surprising, therefore, to find variations in the effects of epinephrine on neu-
rotransmitter release or neurogenic vasoconstriction in different vascular beds in humans.41,42,53,64

**Sustained Aftereffects of Epinephrine on Norepinephrine Release**

In 1932, Burn68 observed augmented neurogenic vasoconstriction in vivo both during and after exposure to epinephrine, but the latter response fatigued after successive nerve stimulation. Burn suggested this effect of epinephrine was due to its storage and subsequent release.

The affinity of neuronal uptake-1 for epinephrine is about half that for norepinephrine.23 In the mouse, about 35% of injected epinephrine and about 55% of injected norepinephrine appear to be taken up and released by this neuronal mechanism.69

Myocardial extraction and stimulated release of epinephrine have been documented in dogs and in human subjects.22,70 Approximately 75% of this extraction can be blocked by desipramine.70 In dogs, the ratio of epinephrine to norepinephrine released on stellate stimulation is comparable to the ventricular content of these catecholamines.22,70 Esler and his colleagues70 have documented cardiac epinephrine spillover, averaging 2 ng/min or 2% of the corresponding norepinephrine spillover, in six patients with untreated congestive heart failure (but not in resting healthy volunteers), and higher levels of neuronal epinephrine release from their gut, liver, lungs, and kidneys. Approximately 25% of the total plasma epinephrine appearance rate in these patients with heart failure could be attributed to regional overflows from these organs.

In marked contrast to its plasma half-life, measured in minutes,71 the half-life of neuronal epinephrine is approximately 4 hours.20 Since the release of epinephrine may be detected up to 24 hours after its neuronal uptake,18-21,47 the potential for neurally released epinephrine to increase the simultaneous discharge of norepinephrine by stimulating prejunctional β1-adrenergic receptors, and thereby augment neurogenic vasoconstriction at the neuroeffector junction, should persist long after a surge in endogenous epinephrine subsides and its local concentration returns to basal levels.20,26 To illustrate this concept, Majewski et al72 demonstrated in anesthetized rabbits a 50% increase in norepinephrine spillover into plasma after an epinephrine infusion. This was at a time when tissue epinephrine concentrations were elevated, but plasma epinephrine concentrations were not. These effects on norepinephrine release could be attenuated by propranolol and abolished by prior uptake-1 blockade (desipramine).72

Whether neurally released epinephrine exerts such positive feedback in humans remains controversial.41,42 Molderegs and colleagues41 could not detect any facilitative aftereffect of newly taken up (tritiated) epinephrine (10 nmol/l) on norepinephrine release from human saphenous veins.

**Rat Models of Hypertension**

Several groups29,48,73,74 have shown that infusion or depot implantation of epinephrine in doses that do not increase its plasma concentration can cause sustained elevation of blood pressure in normotensive rats. This conclusion has been challenged by others.75 The increase in blood pressure in two of these protocols could be blocked if metoprolol was coadministered.29,48 These particular experiments suggested that a threshold uptake into atria of 46 pmol epinephrine/g tissue was sufficient (but 14 pmol/g insufficient) to generate an autofacilitative feedback loop.29 Stress-induced hypertension (immobilization) in normal rats appears also critically dependent on the presence of epinephrine.76

Spontaneously hypertensive rats (SHR) are similar to humans with primary hypertension in that neurohumoral alterations and excitatory psychosocial stimuli reinforce their genetic predisposition to high blood pressure.2 SHR display several characteristics of augmented sympathoadrenal activity. Plasma and ganglionic epinephrine concentrations,77,78 epinephrine synthesis,79 sympathetic ganglionic β2-receptor concentrations,78 and adrenergic responses to stress80 are all increased when compared with Wistar-Kyoto (WKY) rats, and central epinephrine concentrations and PNMT activity rise in parallel with blood pressure.81

Surgical resection of the adrenal medullae of 4-6-week-old SHR attenuates the development of hypertension without affecting these animals' growth or heart rates.52 This is the period of most rapid growth and development in this strain; increased vascular resistance is already established by 4 weeks of age.82 The pressor response to neurally released norepinephrine in these experiments was reduced in the isolated perfused mesenteric bed of demedullated rats and could be augmented by adding epinephrine to the perfusate. In contrast, there was no apparent difference between sham and demedullated SHR in postjunctional responsiveness to norepinephrine or epinephrine in this vascular bed.52

The antihypertensive effect of demedullation could be abolished by selective β2-agonists or epinephrine depot implants and restored by concurrent selective β2-adrenergic receptor blockade.83 Because these observations52,83,84 contradict an earlier report that adrenal demedullation does not affect established hypertension in adult SHR85 and are inconsistent with a large body of evidence for reduced sensitivity and responsiveness of postjunctional β-adrenergic receptors in SHR (particularly older SHR86), Borkowski82 has proposed that β2-adrenergic receptor-mediated facilitation of norepinephrine release by epinephrine contributes to the development (rather than the maintenance) of hypertension in this model during a period of "critical sensitivity."

A number of other approaches have been used to detect prejunctional facilitation of norepinephrine release in SHR. These include quantitation of neu-
rotransmitter release or neurogenic vasoconstriction in pithed rats or in isolated vascular beds. In one such study, acute bilateral adrenal demedullation reduced pressor responses in pithed SHR, whereas the subsequent infusion of epinephrine (50 ng/min) enhanced pressor responses to nerve stimulation without affecting those induced by norepinephrine. This potentiation by epinephrine could be abolished by pretreatment with ICI 118,551 (a β2-selective antagonist) but not by atenolol.87

Several groups have described facilitated norepinephrine release and augmented neurogenic vasoconstriction by β-adrenergic receptor agonists in the mesenteric,61,88 renal,36 and portal vasculature of SHR and WKY rats; responses in the mesenteric vascular bed were potentiated in SHR.61,88 Interpretation of responses in isolated vascular beds is complicated by tissue and species variation in prejunctional β- and α-adrenergic receptor distribution, density, or responsiveness to agonists. At low concentrations (5.5 nM/l), epinephrine potentiates electrically induced norepinephrine overflow from mesenteric sympathetic nerves of SHR and augments the pressor response to this stimulus in this vascular bed but has the opposite effect in normotensive WKY rats.90 Both effects of epinephrine are antagonized by propranolol. At higher doses (14 nM/l), epinephrine decreases norepinephrine spillover in both strains, but this attenuation is muted in SHR and can be reversed by administration of the prejunctional α-receptor antagonist yohimbine.90

Feldman96 has reviewed evidence for reduced postjunctional β2-adrenergic receptor sensitivity and responsiveness in adult SHR. Whether a parallel reduction in prejunctional β2-adrenergic receptor responsiveness occurs with age and stage of hypertension is unclear. Prejunctional responsiveness to the infused β2-receptor agonists salbutamol and propranolol can be demonstrated at concentrations below those at which their postjunctionally mediated vasoconstrictor effects become apparent.91 That prejunctional β2-responsiveness decreases with age is supported by two observations. Facilitation by isoproterenol of electrically stimulated norepinephrine release is greater in superfused spleen strips of SHR than WKY rats at 5 weeks of age but is similar in preparations obtained from 15-week-old animals.92 Second, isoproterenol-induced vasodepressor responses are intact in 6–8-week-old SHR (i.e., in the developmental stages of hypertension) but are attenuated in 16-week-old SHR.93

Epinephrine would therefore appear to play an important role at a critical stage of enhanced β2-adrenergic receptor responsiveness in the initiation and development (but not in the maintenance) of spontaneous hypertension in rats.

### Plasma Catecholamine Concentrations in Primary Hypertension

Investigation of the contribution of the sympathetic nervous system to the initiation and maintenance of primary hypertension has focused principally on indirect measures of sympathetic traffic such as venous plasma norepinephrine concentrations. This is despite recognized limitations of this approach.94–96 Although few clear-cut differences between normotensive subjects and patients with high blood pressure have emerged from these studies,97 virtually all group comparisons in subjects 40 years or younger have demonstrated increased venous plasma norepinephrine concentrations in those with primary hypertension.98–100 Organ-specific evaluation of sympathetic activity by the radiotracer kinetic technique has also documented increased total and regional (cardiac, renal) norepinephrine spillover into plasma in young hypertensive subjects.101 More recently, microneurographic studies have demonstrated increased sympathetic traffic to muscle in young subjects with borderline hypertension.102–104 These observations suggest an important sympathoneural contribution to the initiation of hypertension in many of these young subjects.

What is the evidence that epinephrine release, either intermittent or sustained, is increased in younger subjects during the developmental stages of hypertension or that increased plasma norepinephrine concentrations and the augmented norepinephrine spillover in these subjects are a consequence of facilitated neurotransmitter release by epinephrine? In normotensive subjects, plasma epinephrine concentrations remain stable or decrease with age, whereas norepinephrine concentrations tend to rise.98–105 The positive correlation between age and norepinephrine is absent in hypertensive subjects.106 If epinephrine release were relatively enhanced in young individuals genetically predisposed to hypertension, its facilitative effects at the adrenergic terminals could augment norepinephrine spillover, and its action on adrenal β2-receptors could autofacilitate its own release.28,35

Elevated venous plasma epinephrine concentrations have been documented in borderline hypertension,35,100,108 in hypertensive subjects with rapid resting heart rates,98 and in many subjects with well-established essential hypertension, at rest, in response to mental stress, and during activities such as submaximal exercise and the cold pressor test.7,98,108–112 Although these increases in resting venous plasma epinephrine concentrations are modest, with average values of 13 pg/ml or about 30% above those recorded in normotensive subjects, they are reported in most studies.98

Kjeldsen and his colleagues112 have detected elevated arterial as well as venous plasma epinephrine and norepinephrine concentrations in middle-aged men with long-standing untreated essential hypertension. Arterial plasma epinephrine concentrations were increased by 73 pg/ml or 80% above those in age-matched normotensive subjects and were signif-
significantly greater than venous concentrations in both groups, indicating uptake of epinephrine by forearm tissue. The arteriovenous difference for epinephrine was greater, in absolute terms, in the hypertensive subjects. Of particular interest, in the context of the epinephrine hypothesis, was the observation that venous norepinephrine concentrations were slightly below arterial levels in the normotensive subjects, whereas they were 10% above arterial concentrations in the hypertensive group. Since forearm extraction of epinephrine and norepinephrine is similar, these findings are consistent with both increased adrenal epinephrine release and augmented norepinephrine release from this specific vascular bed in these hypertensive subjects, but they do not demonstrate a causal relation between the two observations.

One problem with the epinephrine hypothesis is that not all studies (only three of 15 reviewed by Goldstein and Lake to 1982) show distinct increases in both catecholamines in hypertension. Subjects were not always subgrouped according to age in these reports. A second difficulty is that plasma epinephrine concentrations in borderline hypertensive subjects have not been shown to predict the subsequent development of sustained hypertension. Unfortunately, most investigators have studied venous not arterial epinephrine concentrations, and because venous measurements often differ substantially from arterial epinephrine concentrations, particularly during stimuli such as mental stress or orthostasis, they will underestimate adrenomedullary epinephrine release. The arteriovenous difference for epinephrine is therefore difficult to mount a strong challenge to the epinephrine hypothesis based on apparently negative observations derived from venous sampling.

To obtain an integrated measure of catecholamine output over time, Brown and his colleagues obtained sequential 24-hour urine collections for epinephrine and norepinephrine from 268 placebo-treated patients (mean age 51 years) enrolled in the Medical Research Council Trial for Hypertension and compared these values with those of similar collections from age- and sex-matched normotensive controls. Urine catecholamines were not increased, but since few of the hypertensive subjects were aged less than 40 years, these data provide little insight into epinephrine's potential contribution to the initiation or development of high blood pressure.

**β<sub>1</sub>-Adrenergic Receptors in Primary Hypertension**

Whether the facilitative effect on norepinephrine release of normal or increased circulating epinephrine is potentiated early in the development of primary hypertension should depend on the responsiveness of prejunctional β<sub>1</sub>-adrenergic receptors to this agonist at this time. Many young patients with borderline or mild established hypertension have characteristics consistent with increased postjunctional β<sub>1</sub>-adrenergic receptor responsiveness, such as increased heart rate, cardiac output, or forearm blood flow. Often these patterns can be "normalized" by β-blockade. Although increased forearm vascular, natriuretic, and platelet responses to low-dose epinephrine infusion have been documented in one group of 40-year-old hypertensive men, the majority of studies of older subjects and those with established hypertension have demonstrated decreased postjunctional β-adrenergic responsiveness to infused agonists.

Since most investigators have documented increased lymphocyte β<sub>1</sub>-receptor density in hypertension, reported reductions in postjunctional β<sub>1</sub>-receptor responsiveness in these subjects could represent a progressive defect in β<sub>1</sub>-adrenergic signal transduction as hypertension becomes established. Indeed, Feldman et al described similar β-receptor densities in a relatively small number of normotensive and borderline hypertensive subjects, but lymphocyte β<sub>1</sub>-receptor–stimulated adenylate cyclase activity was reduced, indicating a functional uncoupling of the lymphocyte β<sub>1</sub>-adrenergic receptor from the adenylate cyclase complex in borderline hypertensive subjects. More recently, Feldman et al documented a reduction in isoproterenol-mediated venodilation in young subjects (less than age 35 years) with borderline-to-mild hypertension. Both defects could be reversed by sodium restriction.

A difficulty in interpreting such comparisons of normotensive and hypertensive subjects is that lymphocyte β<sub>1</sub>-receptor numbers and β-adrenergic–stimulated adenylate cyclase activity are, themselves, subject to modification by exogenous or endogenous epinephrine. A transient doubling of β-receptor binding sites in mononuclear cells and a greater heart rate response to a pulse of isoproterenol can be induced by a prior 30–60-minute infusion of epinephrine or isoproterenol. A single session of exhaustive exercise has similar effects. Thus, as well as facilitating noradrenergic transmission, a transient rise in epinephrine might also amplify acutely β-adrenergic receptor–mediated chronotropic responses through such a postjunctional mechanism.

Although some of these observations could be considered consistent with the concept of a period of increased sensitivity to epinephrine during the developmental stages of hypertension, the assumption that prejunctional and postjunctional β<sub>1</sub>-adrenergic receptor number and responsiveness are altered in parallel in primary hypertension is, as yet, unproven.

**Prejunctional Modulation of Norepinephrine Release by Epinephrine in Humans**

*Direct Effects of Epinephrine on Norepinephrine Release*

Musgrave et al detected increases in both arterial and venous norepinephrine concentrations in response to 10 ng/kg/min epinephrine. A venous-arterial norepinephrine gradient was present at rest in their hypertensive but not their normotensive subjects, and this gradient increased during the infusion. Nezu et al documented higher venous
norepinephrine concentrations during an epinephrine infusion of 1.25–1.50 μg/min (about 20 ng/kg/min) and prevented this epinephrine-stimulated increase in plasma norepinephrine concentration by β-adrenergic receptor blockade. Despite these promising observations, on the whole systemic infusions of β-receptor agonists such as epinephrine, isoproterenol, and salbutamol have not had consistent effects on plasma norepinephrine concentrations, and whenever increases in norepinephrine concentrations have been observed, these have been similar in magnitude in normal and hypertensive subjects.

This lack of consensus reflects two major difficulties with this experimental approach. First, when epinephrine is infused systemically in doses as low as 0.05 nmol/kg/min (8.5 ng/kg/min) (i.e., to replicate plasma concentrations documented during mental stress or physical exercise), plasma cyclic AMP concentrations (a marker for stimulation of β-adrenergic receptor) rise by 50%, but heart rate, stroke volume, and pulse pressure also increase. These hemodynamic perturbations will alter sympathetic outflow reflexively and also modify the release and/or clearance of norepinephrine independently of any prejunctional influence on noradrenergic transmission. Second, high plasma or local concentrations of epinephrine could inhibit norepinephrine release by stimulating prejunctional α-adrenergic receptors. Those studies that have demonstrated increased norepinephrine concentrations have infused epinephrine at doses of 30 ng/kg/min or less, whereas Brown et al. did not detect any increase in plasma norepinephrine concentrations in normal subjects during epinephrine infusions of 50 ng/kg/min unless idazoxan, an α-blocker, was administered concurrently.

An alternative experimental strategy has been to determine whether endogenous or exogenous epinephrine alters the noradrenergic response to stimuli that increase central sympathetic outflow. De Champlain documented augmented noradrenergic responses to standing in hypertensive subjects with high plasma epinephrine concentrations. In another study by Vincent and his colleagues, hypertensive subjects increased norepinephrine spillover (radiotracer technique) by 20%–50% (not shown) were also augmented by epinephrine. *p<0.05; **p<0.01. Reproduced with permission.

**FIGURE 3.** Line plots show plasma norepinephrine concentrations before and after cold pressor and isometric exercise test, during systemic infusion of saline (○) or epinephrine (30 ng/kg/min) (●). Blood pressure responses to these two stimuli were also augmented by epinephrine. *p<0.05; **p<0.01. Reproduced with permission.

To quantitate its effects on central sympathetic outflow, plasma norepinephrine concentrations, and norepinephrine spillover, Persson et al. recorded arterial and central venous pressure, arterial and femoral venous catecholamines, peroneal muscle sympathetic nerve activity (microneurography), and norepinephrine spillover (radiotracer technique) during the stepwise infusion of epinephrine in doses selected to replicate its physiological plasma concentration in healthy volunteers (0.05–0.6 nmol/kg/min; i.e., about 10–100 ng/kg/min). Although limited by its small sample size and lack of a control study day, this technically demanding investigation is noteworthy in several respects: even at its lowest infusion rate epinephrine decreased diastolic blood pressure, and increased sympathetic traffic to muscle, norepinephrine spillover, and venous norepinephrine concentration from pre-epinephrine values was larger than the fractional increase in total muscle sympathetic nerve activity (Figure 4). The authors' interpretation of these observations was that epinephrine, at physiological concentrations, could augment norepinephrine spillover by two distinct mechanisms: increased central sympathetic nerve outflow and facilitated norepinephrine release.
Sustained Aftereffects of Epinephrine on Norepinephrine Release

That endogenous epinephrine, transported into sympathetic varicosities, could subsequently increase the simultaneous neural discharge of norepinephrine in humans was demonstrated by Nezu et al., who increased endogenous epinephrine concentrations by injecting 1.0 mg glucagon. After an initial brisk peak, epinephrine concentrations subsided to basal levels within 20 minutes, whereas norepinephrine concentrations remained elevated. This pattern differs from the parallel time course of glucagon-stimulated norepinephrine and epinephrine release from the isolated adrenal gland. Propranolol did not influence the immediate surge in both catecholamines but abolished the subsequent sustained elevation of norepinephrine. Noradrenergic responses to glucagon and epinephrine were similar in normotensive and hypertensive subjects.

Persson et al. documented greater increases in muscle sympathetic nerve activity and norepinephrine spillover after, not during, the epinephrine infusion described earlier, but the fractional increase in venous norepinephrine at this particular time was less than the fractional increase in muscle sympathetic nerve activity (Figure 4). Thus, there was no evidence for any additional prejunctional influence of neuronally released epinephrine on norepinephrine spillover. Rather, changes in norepinephrine spillover, at this time, appeared to be a reflex response to an abrupt drop in central venous pressure when epinephrine was stopped. Both Brown et al. and Musgrave et al. have commented on a dissociation between plasma norepinephrine (increased) and epinephrine concentration (basal) after systemic infusion of epinephrine. Because central hemodynamics were not measured in these studies, these observations may also be explained simply by a fall in central venous pressure and do not prove sustained facilitated norepinephrine release by epinephrine.

Functional Consequences of Facilitated Norepinephrine Release by Epinephrine in Humans

Because of difficulties in interpreting noradrenergic responses to epinephrine infusions, more recent efforts have focused on the functional cardiovascular consequences of increases in plasma epinephrine concentrations. The general purpose of these experiments was to determine whether hemodynamic responses (e.g., changes in blood pressure, heart rate, and forearm vascular resistance) to stimuli that increase central sympathetic outflow could be augmented during or after an infusion of epinephrine.

Direct Effects of Epinephrine

For example, systemic infusion of epinephrine (30 ng/kg/min) has been reported to amplify increases in both blood pressure and plasma norepinephrine during a cold pressor test and isometric exercise, suggesting that the augmented pressor responses to these stimuli are due to facilitated norepinephrine release (Figure 3). These effects of epinephrine could be blocked by propranolol. On the other hand, epinephrine did not affect heart rate, possibly reflecting the contribution of parasympathetic withdrawal, as opposed to sympathetic activation, to the chronotropic responses to these particular activities.

Our strategy has been to evaluate in humans the functional significance of the reported facilitated release of norepinephrine by epinephrine as it relates to neurogenic vasoconstriction. In our first study, in normotensive men, we examined the effect of intra-arterial epinephrine and isoproterenol on ipsilateral forearm vascular responses to vasoconstriction evoked by applying lower body negative pressure (LBNP), a reflex stimulus to norepinephrine release. Forearm blood flow was measured by strain gauge plethysmography, and blood pressure was recorded directly from the brachial artery. Forearm vasoconstrictor responses to LBPN at —40 mm Hg were compared with responses to intra-arterial infusion of the neurotransmitter norepinephrine before, during, and 30 minutes after infusion of epinephrine (50 ng/min) or isoproterenol (10 or 25 ng/min) into the brachial artery. We reasoned that if stimulation of prejunctional β-adrenergic receptors by epinephrine or isoproterenol was functionally important, these agonists should potentiate the vasoconstrictor response, mediated via the neural release of norepinephrine, to LBPN but should not augment the forearm vascular response to norepinephrine infusion, which would be mediated via stimulation of postjunctional α-adrenergic receptors. The ratio of vasoconstrictor responses to LBPN/norepinephrine could therefore be used as an index of the neural release of the neurotransmitter norepinephrine.

The forearm vasoconstrictor response to LBPN was preserved during intra-arterial infusions of epinephrine and isoproterenol, whereas the response to infused norepinephrine was significantly attenuated (Figure 5). Consequently, the ratio of vasoconstrictor responses to LBPN/norepinephrine
increased threefold during the infusion of epinephrine and more than 20-fold during isoproterenol. These observations provide indirect evidence that \( \beta \)-adrenergic receptor agonists can facilitate the release of norepinephrine from the adrenergic terminal in humans.

Two distinctive features of this study, relative to previous investigations in humans, deserve emphasis. These apply to the interpretation of vasoconstrictor responses during as well as 30 minutes after these infusions (see below). First, to localize their influence to peripheral neuroeffector sites and avoid potential effects on central and ganglionic sites or sensory afferents, we infused these catecholamines into the brachial artery at doses that restricted their effects to the experimental arm. Measurement of central venous pressure, systemic blood pressure, heart rate, and forearm blood flow in the contralateral arm confirmed these agonists had no detectable systemic effects.

Second, we measured forearm blood flow simultaneously in the experimental and the contralateral arm to confirm that LBNP caused a stable reproducible neurogenic vasoconstriction over the course of these experiments in the absence of local interventions (Figure 5). Differences between responses observed before, during, and after epinephrine or isoproterenol in the experimental arm could thus be ascribed to the local effects of these intra-arterial agonists rather than to systemic or "time" effects.

In subsequent experiments, we set out first to determine if these local effects of epinephrine could be replicated by systemic infusion to achieve plasma levels achieved during physiological stress and second to determine whether heart rate responses to LBNP at -40 mm Hg are also augmented during epinephrine. Infusion of 1.5 \( \mu \)g/min epinephrine (about 20 ng/kg/min) led to forearm vasodilation and a subtle but significant increase in heart rate. Since the forearm vasoconstrictor response to intra-arterial norepinephrine is proportional to the initial forearm vascular resistance, we anticipated that by causing forearm vasodilation, epinephrine would also attenuate the vasoconstrictor response to LBNP unless countered by increased norepinephrine release during this stimulus. The vasoconstrictor response to LBNP was not attenuated but rather augmented by about 50% during the epinephrine infusion. The heart rate response to LBNP was not altered by epinephrine. We attributed this observation to the strong influence of vagal withdrawal on heart rate responses to this stimulus in healthy young men, but these contrasting effects of epinephrine on heart rate and vascular responses to LBNP might also be explained by differences in the ratio of responsiveness to epinephrine of facilitative \( \beta_2 \)-inhibitory/\( \alpha_2 \)-prejunctional adrenergic receptors in vascular as opposed to cardiac sympathetic nerves.

**Direct Effects of Epinephrine in Primary Hypertension**

There is no clear consensus on this point. Kjeldsen et al., who compared responses to epinephrine...
infusion (from 10 to 40 ng/kg/min) in age-matched (40 years old) normotensive and hypertensive subjects, documented a fall in blood pressure, forearm vasodilation, and increased natriuresis and kaliuresis in the latter group; they therefore postulated a hyperresponsiveness to low-dose epinephrine infusion in mild essential hypertension. On the other hand, the effects, in our protocol, of intra-arterial epinephrine on neurogenic vasoconstriction and by inference neurotransmitter release appeared to be similar in age-matched normotensive and young borderline hypertensive subjects\(^{145}\) (Figure 6).

**Sustained Aftereffects of Epinephrine**

Several groups have observed sustained increases, often lasting several hours, in blood pressure after epinephrine infusion into normotensive subjects.\(^{100,146-148}\) The dose and duration of epinephrine given in these studies ranged from 20 to 40 ng/kg/min for 30–60 minutes\(^{100,146,148}\) to 15 ng/kg/min sustained for 6 hours.\(^{147}\) In the latter study, 24-hour intra-arterial ambulatory blood pressure was used to document, in normal subjects, the effect of 6-hour infusions of epinephrine, norepinephrine (30 ng/kg/min), and dextrose administered in a random cross-over design. During its infusion, epinephrine caused a 10-fold increase in its plasma concentration and lowered mean arterial pressure. Epinephrine concentrations returned to baseline levels less than 5 minutes after the infusion stopped. The subsequent 18-hour recording documented persistent elevation of mean arterial pressure by as much as 12% above those levels recorded on the day dextrose was infused (Figure 7). The pressor effects of prior epinephrine infusion were particularly evident during episodes of documented sympathetic activation.

Between 40% and 70% of arterial epinephrine is removed in one circulation through the forearm (more than half via uptake-\(^{149}\))\(^{112,113,149-151}\) and approximately 45% of arterial epinephrine is extracted in a single passage through the heart and kidney.\(^{70,105}\) Therefore, it seems reasonable to assume that both cardiac and vascular mechanisms could contribute to any sustained pressor response subsequent to epinephrine.\(^{147}\) Brown et al\(^{31,134}\) documented persistent tachycardia after a 2-hour infusion of epinephrine of 100 ng/kg/min was stopped, even though its plasma concentration returned to basal levels within minutes.\(^{20,71}\) Sustained tachycardia was not observed in a small number of subjects pretreated with desmethylinepramine to reduce neuronal uptake of epinephrine\(^{31}\) or when isoproterenol, which is not taken up by sympathetic nerves,\(^{23,134}\) was substituted for epinephrine. Brown et al\(^{31,134}\) proposed that the dissociation between the short plasma half-life of epinephrine and the slow decay of the tachycardia after its infusion was due to a cyclical process of reuptake and release of epinephrine from cardiac nerves. However, there are problems with this interpretation. Resting tachycardia is not seen after epinephrine infusions of 50 ng/kg/min or less.\(^{100,147,148,152}\) Other potential causes of this sustained tachycardia, such as metabolic,\(^{153}\) hemodynamic, reflex, or central effects of infused epinephrine were not excluded, and the potential effect of prior epinephrine infusion on postjunctional responses to the neurotransmitter norepinephrine was not examined in these studies.

Earlier, we presented our experimental approach to the evaluation in humans of the functional significance of the reported facilitated release of norepinephrine by epinephrine.\(^{33}\) In these experiments, we also explored the possibility that neuronally extracted epinephrine might have a sustained aftereffect on the forearm vasoconstrictor response to neurogenic stimulation. Our hypothesis was that if epinephrine were incorporated into the sympathetic nerve endings of the forearm during its arterial infusion and later released as a cotransmitter with norepinephrine, we might find a selective augmentation of reflex vasoconstriction after an epinephrine infusion. Further, we hypothesized that such augmentation would not be detected after an isoproterenol infusion.

Thirty minutes after these infusions, resting forearm vascular resistance was at its initial, preinfusion level. From similar baselines, the forearm vasoconstrictor response to LBNP increased by about 65% 30 minutes after epinephrine, but this response was not affected by prior infusion of isoproterenol (Figure 5). The ratio of forearm vasoconstrictor responses to LBNP/norepinephrine was not altered by prior infusion of isoproterenol but was more than threefold higher 30 minutes after epinephrine\(^{33}\) (Figure 6). These observations provide further support for the concept that epinephrine augments neurogenic vasoconstriction by a peripheral Neuroeffector action. Since epinephrine has a half-life in plasma of only a
few minutes, we attributed the augmented ratio of responses to LBNP/norepinephrine 30 minutes after epinephrine (but not isoproterenol) to facilitated release of norepinephrine by epinephrine that had been taken up into the adrenergic terminal, converted into a cotransmitter, and coreleased with norepinephrine during subsequent reflex stimulation.

To test this hypothesis, eight normal men were studied on 2 separate days at least 1 week apart, 2.5 hours after taking at random either placebo or a dose of desipramine (125 mg p.o.), shown to block completely neuronal uptake of norepinephrine in the forearm. On the placebo day, the forearm vasoconstrictor response to LBNP -40 mm Hg was significantly augmented by about 40% 30 minutes after an hour of systemic infusion of epinephrine at 1.5 μg/min (about 20 ng/kg/min) but tended to be less after epinephrine and desipramine. Resting mean arterial pressure and the heart rate response to LBNP after epinephrine administration were also greater on the placebo day. Thus, systemic as well as local infusion of epinephrine in a dose known to achieve plasma concentrations documented during physiological stresses and to increase plasma norepinephrine concentrations by α-adrenergic mechanism can have sustained aftereffects on blood pressure and on specific chronotropic and vascular responses to reflex sympathetic activation. Fellows et al reported similar heart rate and forearm vascular responses to LBNP (−50 mm Hg) applied 15 minutes after a 30-minute infusion of epinephrine (50 ng/kg/min). Since resting heart rates were not increased after epinephrine, doses administered in these two studies may not have been sufficient to maintain synaptic concentrations of epinephrine at levels necessary to facilitate norepinephrine release at rest; yet the doses caused sufficient loading of the adrenergic terminal to achieve such concentrations locally during the reflex stimulus to norepinephrine release.

**Sustained Aftereffects of Epinephrine in Primary Hypertension**

Whether the aftereffects of epinephrine infusion differ in normal and hypertensive subjects has not been firmly established. Although Nezu et al documented similar increases in systolic and diastolic blood pressure in normotensive and hypertensive subjects up to 90 minutes after an epinephrine infusion (20 ng/kg/min) (Figure 8), persistent elevation of blood pressure and heart rate 20 minutes after epinephrine (39 ng/kg/min) was seen in another study only in a hypertensive group even though arterial epinephrine concentrations had returned to basal levels by this time. Epinephrine clearance was identical in the two groups of subjects.

Because elevated plasma epinephrine concentrations and characteristics consistent with increased β-adrenergic receptor responsiveness are often seen in borderline hypertension, we hypothesized that the local direct and sustained aftereffects of epinephrine on neurogenic vasoconstriction would be exaggerated in such subjects. However, when tested, this was not the case: the effect of prior intra-arterial epinephrine infusion on the ratio of forearm vasoconstrictor responses to the LBNP/nor-
Responses to epinephrine might have been with the concept of a period of critical sensitivity to gic receptor from the adenylate cyclase complex concentrations and/or "hyperadrenergic" characteristics. The latter were not prominent in our subjects. Responses to epinephrine might have been similar because of substantial overlap in prejunctional /3-adrenergic receptor density, affinity for agonist, or /3-adrenergic-mediated adenylyl cyclase activity in our two groups122,124-126 or because of the functional uncoupling of the lymphocyte /3-adrenergic receptor from the adenylyl cyclase complex reported to occur in young subjects with borderline hypertension.128,129 Such functional uncoupling may have minimized any quantitative differences in /3-adrenergic receptor number or affinity for agonist in our young normotensive and hypertensive subjects.129 Indeed, a specific comparison of the effects of infused isoproterenol on plasma norepinephrine concentrations did not detect any difference in this response between normotensive and borderline hypertensive male subjects.135 Last, exaggerated responses in patients with borderline hypertension may reflect increased central neural (presynaptic)134 or peripheral ganglionic78,107 rather than peripheral neurotransmitter (prejunctional) sensitivity to epinephrine. Evidence in support of this latter possibility was provided by the comparison, in young normotensive and borderline hypertensive men, of the effects of prior administration of epinephrine (1.5 /g/min for 30 minutes) on muscle sympathetic nerve responses to LBNP at -10 mm Hg and to a cold pressor test.107 Interventions were applied before and 30 minutes after epinephrine. The immediate direct effects of epinephrine on systolic and pulse pressure, heart rate, and postganglionic muscle sympathetic nerve activity were similar in the two groups, but the aftereffects of the infusion were only seen in the borderline hypertensive subjects: pressor and chronotropic responses to the cold pressor test were augmented, and the sympathoneural responses to both interventions more than doubled (Figure 9).

Potential Contribution of Epinephrine to the Genesis of Hypertension: Summary, Implications, and Future Directions

Several lines of evidence now suggest a psychophysiological link between stress, adrenomedullary activation, and the genesis of hypertension in some humans genetically predisposed to the development of high blood pressure. These include results of experiments in a number of animal preparations that support the facilitative and cotransmitter components of the epinephrine hypothesis, are consistent with the concept of a period of critical sensitivity to epinephrine in a genetic model of hypertension (the SHR), or demonstrate that exogenous epinephrine can induce sustained hypertension.

Evidence in support of the hypothesis that epinephrine participates in the initiation of primary hypertension by amplifying peripheral neurotransmission may be summarized as:
1) Resting and stimulated arterial and venous plasma epinephrine concentrations are elevated in many young subjects with borderline or mild essential hypertension.98,100,108-112,157 Mental stress is one such provocative stimulus. Increased plasma norepinephrine concentrations and regional norepinephrine spillover have also been documented in many young borderline or mildly hypertensive patients.98-101 Because the results of some investigations differ from these general conclusions,98-114,158 it should be emphasized that this hypothesis is not contingent on documentation of increased plasma epinephrine concentrations alone. The magnitude of neuronal epinephrine uptake as a reflection of the frequency and intensity of adrenomedullary epinephrine release may be more important than basal epinephrine concentrations.

2) Increases in endogenous epinephrine cause sustained increases in plasma norepinephrine and blood pressure in normotensive and hypertensive subjects. These effects can be abolished by propranolol.100

3) Endogenous epinephrine is taken up into human peripheral sympathetic nerves.70,112,113,149-151 Increased forearm uptake of epinephrine in hypertension may be associated with greater forearm norepinephrine release.112

4) Exogenous epinephrine, infused at a rate of 30 ng/kg/min or less, has functionally significant immediate (direct) effects and subsequent (indirect) aftereffects on norepinephrine concentrations6,66,100,133,136,139,140 that are similar in magnitude to its effects on norepinephrine release as documented in experimental preparations.62 Direct effects have been observed at rest and during provocative maneuvers that increase efferent sympathetic traffic such as isometric exercise or the cold pressor test. These effects are also blocked by propranolol.140 Increases in norepinephrine concentrations persist after plasma epinephrine concentrations return to baseline levels.66,100,133 These effects are not
seen at higher doses of epinephrine unless \( \alpha_2 \)-receptors are blocked.\(^6^6\)

5) Exogenous epinephrine has functionally significant immediate (direct) effects and subsequent (indirect) aftereffects on neurogenic circulatory regulation that are similar in magnitude to its effect on neurotransmitter release as documented in experimental preparations.\(^4^2\) Direct effects include greater blood pressure responses to handgrip and the cold pressor test\(^1^4^0\) and a relative augmentation of neurogenic forearm vasoconstriction.\(^3^3,14^3\) Local infusion of epinephrine has sustained aftereffects on neurogenic vasoconstriction in the forearm.\(^3^3,14^5\) Sustained aftereffects of its systemic infusion appear to be dose-dependent: at low doses (15–40 ng/kg/min) the aftereffects include a persistent increase in blood pressure, augmentation of neurogenic vasoconstriction, and neurogenic tachycardia\(^1^0^0,14^3,14^6–14^8,15^6\); at higher doses (100 ng/kg/min), prior epinephrine infusion causes persistent tachycardia.\(^3^1,13^4\)

6) Aftereffects of epinephrine on sympathetic outflow are enhanced in borderline hypertensive subjects.\(^1^0^7\)

These studies have defined two temporally and functionally distinct roles for epinephrine in the regulation of vascular resistance. As a circulating hormone, it causes an immediate and transient vasodilation via its direct action on postjunctional vascular \( \beta_2 \)-receptors. Its humoral actions are brief, include additional circulatory response analogous to the defense reaction, and dissipate rapidly. As an autocrine agent, it causes indirectly a delayed and sustained vasoconstriction. These aftereffects have been interpreted as caused by the peripheral conversion of epinephrine from a circulating hormone to a cotransmitter, which when released neuromodulator, acts on prejunctional neuronal \( \beta_2 \)-receptors. By augmenting the simultaneous discharge of norepinephrine neurotransmitter release, epinephrine could raise blood pressure transiently through both cardiac and vascular mechanisms during periods of increased sympathetic outflow or at rest after its plasma concentrations subside to basal levels. Through this mechanism, repetitive surges in endogenous epinephrine could initiate, promote, or permit the development of primary hypertension. In addition, the trophic effects of intermittently increased neurotransmitter release,\(^1^5^9\) when continued over months or years, could initiate early structural changes in resistance and capacitance vessels that would intensify responses to constrictor signals\(^4^1,16^0\) and allow for sustained elevations in blood pressure independent of this neurogenic trigger to hypertension.

This neurogenic mechanism is attractive but as yet unproven. Evidence challenging the hypothesis that epinephrine participates in the initiation of primary hypertension by amplifying peripheral neurotransmission may be summarized as:

1) The conclusion that augmented neurogenic vasoconstriction during and after local epinephrine infusion is due to increased norepinephrine release\(^3^3,14^5\) is based on indirect evidence. There have been no published reports of forearm catecholamine uptake and release in this model, the effect of local \( \beta \)-adrenergic receptor blockade on these responses has not been assessed, and it is not known whether their kinetics are altered in young hypertensive subjects. Furthermore, indirect actions of epinephrine that could augment neurogenic vasoconstriction, such as local induction of endothelin,\(^1^6^1\) or that could facilitate norepinephrine release, such as generation of angiotensin II\(^1^1^2^6–1^6^3^2\) or alteration of ionic fluxes across the adrenergic terminal,\(^1^3^4,16^6–1^6^8\) have not been specifically excluded in this preparation.

2) Pressor and noradrenergic response to mental stress, tilt, and the cold pressor test are not blunted in adrenalectomized women when compared with responses in women with intact adrenal function.\(^1^4^1\) Given the unique opportunity presented by such patients, it would be of interest to compare the direct effects and aftereffects of both brief and sustained epinephrine infusion on responses to these interventions in these two groups.

3) Selective \( \beta_3 \)-adrenergic receptor blockade has not proved to be particularly effective in the management of hypertension.\(^1^0^9,1^7^0\) Majewski and Murphy\(^4^4\) have proposed that this is because the potential antihypertensive effect of such drugs on neurotransmitter release is offset by concurrent abolition of \( \beta_3 \)-adrenergic receptor-mediated peripheral vasodilation.

4) Immediate or delayed noradrenergic, pressor, and neurogenic chronotropic or vascular responses to epinephrine (and other \( \beta \)-agonists) are not always augmented in subjects with borderline or mild essential hypertension.\(^1^0^0,1^3^5,1^4^5\)

5) There are no prospective evaluations of the predictive value of increased epinephrine concentrations in childhood or adolescence as a marker for later hypertension development.

These points highlight a number of present difficulties with the epinephrine hypothesis and suggest a number of future experiments. Additional questions would have to be addressed in humans before epinephrine could be considered a causative mechanism of primary hypertension.

A general series of questions pertains to those phenomena attributed to the facilitative and cotransmitter effects of exogenous epinephrine themselves. Can they be replicated by increases in endogenous epinephrine? How long after surges in epinephrine does this exaggerated response to neural stimulation persist? How quickly does it decay?

A second series of questions pertains to other potential functional consequences of facilitated neurotransmitter release by epinephrine (e.g., effects on venous tone, renal hemodynamics, and renal tubular sodium absorption and renin release). Given the primacy of the kidney in long-term blood pressure regulation, future assessment of the potential contribution of epinephrine to the genesis of primary hypertension should include a characterization of any
effects and in particular any sustained aftereffects it may have on renal hemodynamics and function.

Finally, as suggested by Folkow, expression of hypertension by this mechanism may be restricted to a specific subset of individuals with a genetic predisposition to high blood pressure, who have more frequent or exaggerated surges of epinephrine in response to psychological or physiological stimuli or greater central or peripheral sensitivity to this catecholamine. Such individuals may manifest sustained increases in heart rate and cardiac output after episodic increases in epinephrine and greater neurogenic vasoconstrictor responses to reflex stimuli than those without this predisposition. A third or more of primary hypertensive individuals may fall into this category. However, if a period of “critical prejunctional β2-adrenergic receptor sensitivity” to the facilitative effects of epinephrine on norepinephrine release, similar to that described in SHR, precedes the clinical detection of borderline or mild essential hypertension or if the prejunctional β2-receptor is functionally uncoupled from its adenylate cyclase complex once structural vascular changes have developed, the most compelling tests of the epinephrine hypothesis, whether longitudinal or interventional (e.g., inhibition of adrenal epinephrine syntheses or peripheral β2-antagonism), will require identification of such individuals at the earliest and mildest stage of their disease, well before the development of clinically established hypertension.

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