

# Hypertension

## Editor's Comments

### Vasoreactivity and Endothelial Dysfunction: Mechanisms and Clinical Implications

Since the breakthrough work of Furchgott defining the role of the endothelium as a protective antivasoconstrictive system and the subsequent work of Moncada and others demonstrating that the principal vasodilator substance produced by the endothelium was nitric oxide, there has been an explosion of biochemical and physiologic studies. Clinical studies have taken on a remarkable parallel. The purpose of this issue of *Current Concepts* is to integrate information from diverse sources to define how endothelial nitric oxide synthesis relates to the cluster of cardiovascular risk factors that includes hypertension, blood pressure hyperreactivity, insulin resistance, hypercholesterolemia, and atherosclerosis. By understanding the overlap in pathogenesis of these linked abnormalities, we will be better able to optimize treatment.

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## Vasoreactivity and High-risk Hypertension

The Framingham epidemiology studies clearly demonstrated a strong curvilinear relationship between *relative* cardiovascular risk and resting blood pressure in the population as a whole, with the highest office blood pressures accounting for a disproportionate increase in overall risk. Unfortunately, our precision in estimating risk in a given individual is diminished by the wide biologic variation in the expression of target organ damage across the hypertensive population and the inclusion in epidemiologic studies and clinical trials of large numbers of persons with stress-induced or “white-coat” hypertension. An improvement in the predictive power for a given individual was also part of the original Framingham analysis, where it was learned that glucose intolerance, hypercholesterolemia, cigarette smoking, and left ventricular hypertrophy each added their own independent curvilinear risk-predictive relationships to the one described for office blood pressure and overall cardiovascular risk. By adding these other variables to the clinical assessment profile, it became possible to identify patients at the highest overall risk—the ones most likely to derive benefit from therapy.

As additional analyses of cardiovascular risk were performed, it became clear that the coexistence of hypertension, obesity, hypercholesterolemia, glucose intolerance, and atherosclerosis occurred in proportions far beyond those predicted by chance alone. Various terms such as “insulin resistance syn-

### Orthogonal Relationship Between Vasoreactivity and Hypertension

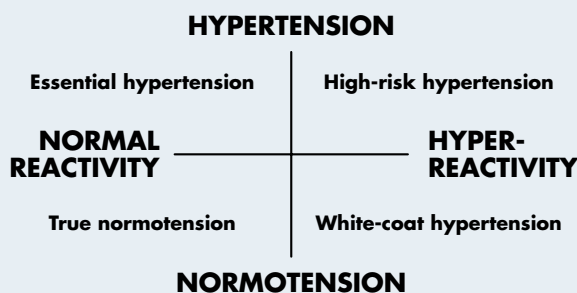


Figure 1

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drome or metabolic syndrome X” have been used to describe this clinical constellation but none of these names satisfactorily describes the complex interactive nature of this generalized cardiovascular and metabolic abnormality. Whether or not a single mechanism can be found that links together the Framingham risk factors has been the subject of much contemporary debate.

Two newer concepts may help further characterize the hypertension syndrome complex and define the high-risk subgroup: 1) the concept of exaggerated vasoreactivity as a predictor of increased risk and 2) the growing realization of the role played by the endothelium in protecting the health of the cardiovascular system. As it happens, both of these ideas may be linked by the common phenomenon of altered endothelial function and deficient nitric oxide production in high risk hypertension.

An integrated model that explains the orthogonal relationship between vasoreactivity and hypertension is presented in Figure 1. In this model, the presence of systemic hypertension is defined by an elevation in true resting blood pressure, a phenomenon that probably arises from neuroendocrine dysregulation of cardiac and vascular smooth muscle function. Exaggerated vasoreactivity, however, occurs via a different set of physiological alterations and is causally related to endothelial dysfunction. True normotension occurs when office and nonoffice blood pressures are normal, implying a normal vasoreactive response to stressors. White-coat hypertension occurs when nonoffice pressures are normal, office blood pressures are elevated, and there is an exaggerated vasoreactive stress response. Essential hypertension is present when there is sustained elevation of resting pressures in all settings. High-risk hypertension is defined by the coexistence of essential hypertension and exaggerated vasoreactivity. In this model, the influence of other cardiovascular risk factors on endothelial dysfunction and exaggerated vasoreactivity (e.g. hypercholesterolemia, cigarette smoking, gender, glucose intolerance) is accommodated.

Further research will be necessary to fully validate the model on a pathophysiologic basis. Pending such studies, however, the model remains useful in the clinical sphere because it reminds us of the important role of the endothelium in maintaining cardiovascular health. It also underscores the importance of defining and treating, in a comprehensive fashion, those individuals with high-risk hypertension. Finally, it predicts that treatment of hypertension alone, without a concomitant effort to reduce cholesterol, eliminate cigarette smoking, and control glucose intolerance, will result in only partial cardiovascular protection.

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## Coronary and Peripheral Vasoreactivity: Role of Endothelial Dysfunction

The endothelium synthesizes and releases several vasoactive factors, including nitric oxide. Under normal circumstances, when the endothelium is stimulated with a vasodilator such as acetylcholine, subsequent activation of nitric oxide synthase leads to local production of nitric oxide. As nitric oxide diffuses into the vascular smooth muscle underlying the endothelium, relaxation occurs. If endothelial function is abnormal, this vasodilatory influence is lost and a “paradoxical” vasoconstrictive response to acetylcholine occurs. Coronary arteries of patients with atherosclerosis demonstrate abnormal constriction in response to acetylcholine. The direct vasoconstrictive effect of acetylcholine is not modulated by nitric oxide’s vasodilation because nitric oxide is not available.

Ganz and coworkers discovered the importance of the endothelium to response patterns in human coronary arteries in a series of novel experiments. While local infusion of acetylcholine caused vasodilation in patients with normal coronary arteries, it caused vasoconstriction in patients with coronary artery disease. Nitroglycerin infusion proved these abnormal coronary arteries were capable of vasodilation. These experiments demonstrated the importance of the endothelium and nitric oxide in maintaining normal coronary arterial tone and responses to stressors.

Subsequent experiments have discovered the role of various risk factors in modifying coronary artery endothelial function and pathophysiology. Hypercholesterolemia, for example, has been identified as a cause of endothelial dysfunction. In patients with hypercholesterolemia, abnormal coronary vasoconstriction occurs in response to acetylcholine infusion. Treating hypercholesterolemia with lipid lowering agents (e.g., HMG Co-A reductase inhibitors) and antioxidants (e.g., probucol) improves abnormal endothelial function (Fig 2). Additional work has shown that other cardiovascular risk factors such as hypertension, diabetes, and cigarette smoking are associated with abnormal endothelium-dependent vasodilation.

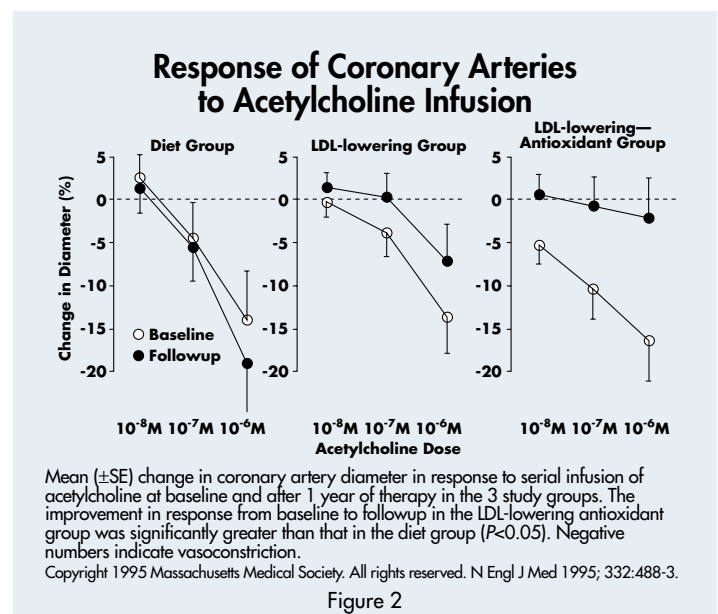


Figure 2

Endothelial dysfunction also occurs in peripheral arteries and resistance vessels of patients with cardiovascular risk factors. Cholinergic agonists induce less vasodilation in forearm resistance vessels of patients with hypertension, hypercholesterolemia, or diabetes than in healthy individuals (Fig 3). In the normal brachial artery, flow-mediated vasodilation has been shown to be another index of endothelial function. Hypercholesterolemia, cigarette smoking, and diabetes are associated with reduced flow-mediated, endothelium-dependent vasodilation, implicating endothelial dysfunction and deficient availability of nitric oxide. This abnormality occurs even in the absence of atherosclerosis, suggesting reduced bioavailability of nitric oxide may precede atherosclerosis.

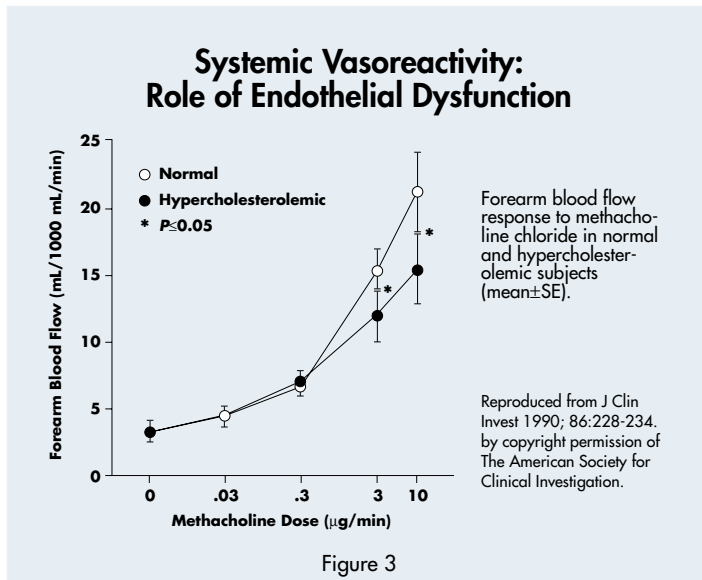


Figure 3

Ongoing studies continue to discover the role of the endothelium in modulating normal vascular responses to a variety of hormonal, metabolic, and physical stressors. When the endothelium is damaged, disrupted, or dysfunctional, abnormal vasoconstriction occurs.

The correlation of a systematic pattern of abnormal vascular reactivity with known factors that increase the risk for coronary and peripheral arterial disease strongly suggests long-term cardiovascular health depends on normal endothelial production of nitric oxide and that the endothelium can be considered the primary target of preventive cardiology. In the presence of disease, further studies will be required to identify optimal treatment patterns.

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### Suggested Reading

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## Risk Factors and Abnormal Venoreactivity

Various risk factors for cardiovascular disease have been identified for years and diverse mechanisms by which each risk factor contributes to the pathogenesis of cardiovascular disease have been proposed. During the last decade, it has become apparent that endothelial function plays a crucial role in cardiovascular disease. One of the primary functions of the endothelium is to maintain vascular tone and loss of endothelium-dependent vasodilation occurs early in the development of atherosclerosis. Assessment of endothelial function has been generally carried out by measuring flow-dependent dilation to acetylcholine in the human coronary or brachial arteries.

Recently we developed a technique that directly visualizes the vein using cross-sectional and M-mode ultrasonography. It has the advantage of examining direct local effects of vasoactive substances in an amount not causing systemic effects. Using this technique, we have demonstrated that insulin attenuates norepinephrine-induced venoconstriction by a cyclic-GMP dependent mechanism in healthy normal subjects.<sup>1</sup> After performing several studies to determine venoreactivity to norepinephrine and insulin in healthy normotensive populations with risk factors for cardiovascular disease, we observed insulin-mediated venodilation is attenuated in persons with high cholesterol, insulin resistance, menopause, and heavy drinking. Venodilatory response to sodium nitropruside, an endothelium-independent vasodilator, was not impaired in these groups suggesting presence of abnormal endothelium-dependent venodilation among these risk populations.

Previously we reported a series of parallel observations in which there was exaggerated blood pressure response to mental stress in patients with high cholesterol, insulin resistance, and after

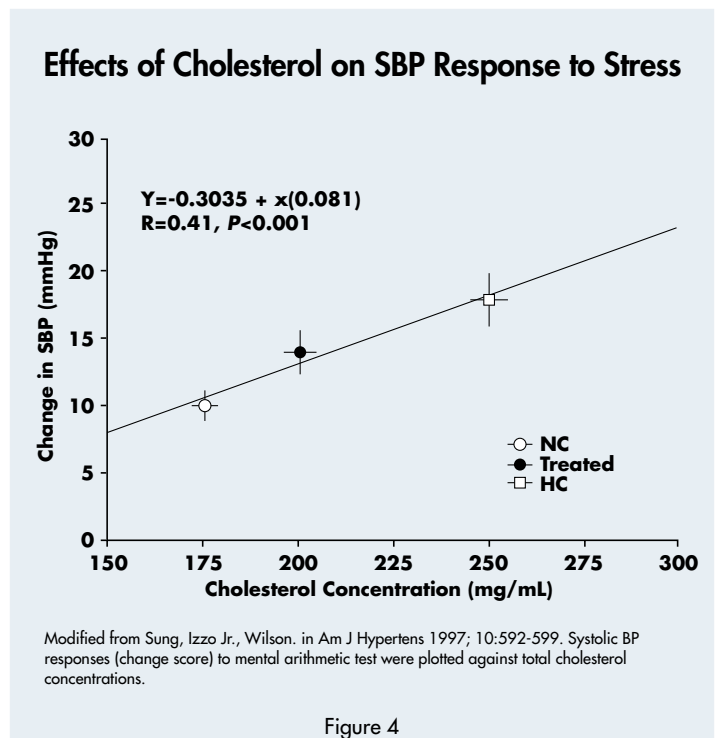


Figure 4

menopause.<sup>2,3,4</sup> The dorsal hand vein responses to norepinephrine and insulin in this population were closely related to systemic blood pressure responses to mental stress suggesting abnormal venous reactivity may reflect systemic blood pressure regulation. Further, treatment of hypercholesterolemia with HMG-CoA reductase inhibitors reduced blood pressure response to mental stress (Fig 4) and also normalized insulin-mediated venodilation in hypercholesterolemia. Patients with type II diabetes exhibited exaggerated cardiovascular reactivity and treatment with insulin sensitizer not only reduced insulin levels but also reduced blood pressure response to stress.

In summary, this venous model was able to identify abnormal insulin-mediated vasodilation in subpopulations at increased risk for cardiovascular disease. Impaired endothelial-dependent vasodilation may be a common mechanism by which various risk factors contribute to cardiovascular disease. Therefore, reversing or normalizing endothelial dysfunction at an early stage with nonpharmacologic and pharmacologic interventions may prevent atherosclerosis and hypertension.

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## The Relationship of Insulin Resistance to Vasomotor Control

The causes of premature cardiovascular disease are multifactorial. Hypertension, glucose intolerance, and hypercholesterolemia were among the earliest to be identified as independent risk factors. What has only been more recently appreciated is that these factors are interdependent. The coincidence of hypertension and insulin resistance (sometimes called syndrome X) has been the focus of intense research activity over the past decade.

How might insulin resistance and hypertension be correlated? To answer this question, one must determine the physiologic effects of insulin on the cardiovascular system in order to appreciate how altered insulin-mediated responses might lead to hypertension. Insulin has diverse cardiovascular effects including sodium retention (via its renal effects) and activation of the sympathetic nervous system (even in the absence of hypoglycemia). However, the predominant cardiovascular effect of insulin appears to be vasodila-

tion. Studies from our laboratory and others have demonstrated that in man insulin mediates vasodilation—both in the skeletal muscle arterial system and venous system.

Insulin vasodilates over a concentration range achieved physiologically—consistent with a role in regulation of vascular resistance, both tonically and in the postprandial surge in insulin. These effects are immediate and local (i.e., not dependent on downstream “metabolic” effects).<sup>1</sup> Insulin mediation of vasodilation is endothelial-dependent and has been blocked with the use of nitric oxide synthase antagonists.<sup>2</sup>

Beyond the role of insulin in regulating vasomotion, it has become clear that insulin-mediated vascular responses are themselves regulatable. Studies from our laboratory and those of Baron have demonstrated, both in normotensive subjects and those with established diabetes mellitus, that alterations in the gluco-regulatory effects of insulin parallel alterations in vascular sensitivity to insulin.<sup>3</sup> Further, using both assessment of limb blood flow (as a measure of arterial response) and dorsal hand vein distention (as a measure of venous response), insulin-mediated vasodilation has been shown to be impaired in hypertensive subjects.<sup>1</sup> Additionally, insulin-mediated vasodilation is regulated physiologically. In both normotensive and borderline/mild hypertensive subjects, severe salt restriction (to 20 mEq/day) reduced vascular sensitivity to insulin in normotensive subjects and aggravated impairment of insulin-mediated vasomotion in hypertensives.<sup>4</sup> However, whether a more moderate salt restriction (more similar to those used clinically to treat hypertension and heart failure) aggravates vascular insulin resistance is unknown at present.

Despite the significant advances in understanding of insulin-mediated vasomotion and its potential role in linking systemic insulin resistance to hypertension, significant questions remain. Whether insulin-mediated vascular responses turn out to be a better index of systemic insulin resistance or of endothelial dysfunction needs to be determined. Of greater clinical importance is the question of whether primary regulation of vascular insulin resistance improves blood pressure control. To date several classes of insulin-sensitizing drugs including the biguanides (i.e. metformin) and the thiazolidinediones (i.e. troglitazone) have been shown to improve both systemic insulin resistance and blood pressure control in hypertensive subjects. Whether this occurs via regulation at the level of vascular insulin resistance remains to be determined. Additionally, it is unknown whether conventional antihypertensive drugs have differing (or any) effects on vascular insulin resistance. Of greatest concern is whether or not any differences found in this regard have any long-term effect on hypertensive complication rates.

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## Fatty Acids and Neurovascular Regulation: A Possible Link Between Insulin Resistance and Hypertension

The prevalence of the cardiovascular risk factor cluster greatly exceeds that expected by chance, increasing the probability there is a common pathogenic denominator. While there is considerable interest in hyperinsulinemia and resistance to insulin-mediated glucose disposal as mediators of this syndrome, definitive proof that these are primary pathogenic factors remains elusive. We will focus on defects that reduce insulin's capacity to lower nonesterified fatty acids as a possible alternate explanation. As summarized previously,<sup>1</sup> the abdominal fat pattern is linked to increased nonesterified fatty acid (NEFA) concentrations and turnover that resist suppression by insulin. NEFAs may contribute to metabolic components of the risk factor cluster by reducing hepatic insulin uptake, increasing hepatic glucose output, synthesis of apoprotein B and very low density lipoprotein, and decreasing skeletal muscle glucose utilization. Research over the past decade also implicates a role for resistance to insulin's NEFA-lowering action in the enhanced neurovascular reactivity and tone observed in obese hypertensive patients.

An overweight group of hypertensive patients, when compared to normotensive controls of similar age and weight, had increased regional vascular  $\alpha$ -adrenergic reactivity and tone.<sup>2</sup> Obese hypertensives also had higher plasma NEFAs than lean normotensives<sup>3</sup> and plasma NEFAs were more resistant to suppression by insulin during a euglycemic clamp in abdominally obese hypertensives than in either abdominally obese normotensives or lean normotensives.<sup>4</sup> When the obese hypertensive and normotensive groups were combined, blood pressure correlated strongly with NEFA concentrations and turnover during the clamp independently of the relationship between glucose disposal and blood pressure.<sup>4</sup> Since studies by Bülow et al showed that raising NEFAs systemically in minipigs increased vascular resistance and blood pressure,<sup>5</sup> we speculated that the elevated NEFAs in obese hypertensives might contribute to the increased neurovascular tone and reactivity observed in our earlier studies.<sup>2</sup>

We explored this hypothesis by raising NEFAs in the hand veins of lean normotensives to levels seen in obese hypertensives with a local infusion of Intralipid (a source of triglycerides) and heparin to activate endothelial lipoprotein lipase and hydrolyze fatty acids from glycerol. This maneuver increased by 3- to 4-fold the vasoconstrictor sensitivity to phenylephrine, a selective  $\alpha_1$ -adrenoceptor agonist (Figure 5) but not to clonidine, a partial  $\alpha_2$ -adrenoceptor agonist.<sup>6</sup> Raising NEFAs locally in a dorsal hand vein also increased the magnitude and duration of neuroreflex venoconstriction.<sup>6</sup> Thus, NEFAs enhanced  $\alpha$ -adrenergic reactivity to exogenously administered and endogenously released catecholamines by local actions on  $\alpha_1$  adrenoceptors. In a pilot study of 6 healthy volunteers, raising NEFAs systemically by ~50% enhanced pressor sensitivity to phenylephrine.<sup>7</sup> These data suggest that elevated NEFAs in obese hypertensives may contribute to increased neurovascular tone and blood pressure through effects on  $\alpha_1$ -adrenoceptors.

These studies do not establish the mechanism of the acute effect by which NEFAs enhance vascular  $\alpha_1$ -adrenoceptor reactivity nor

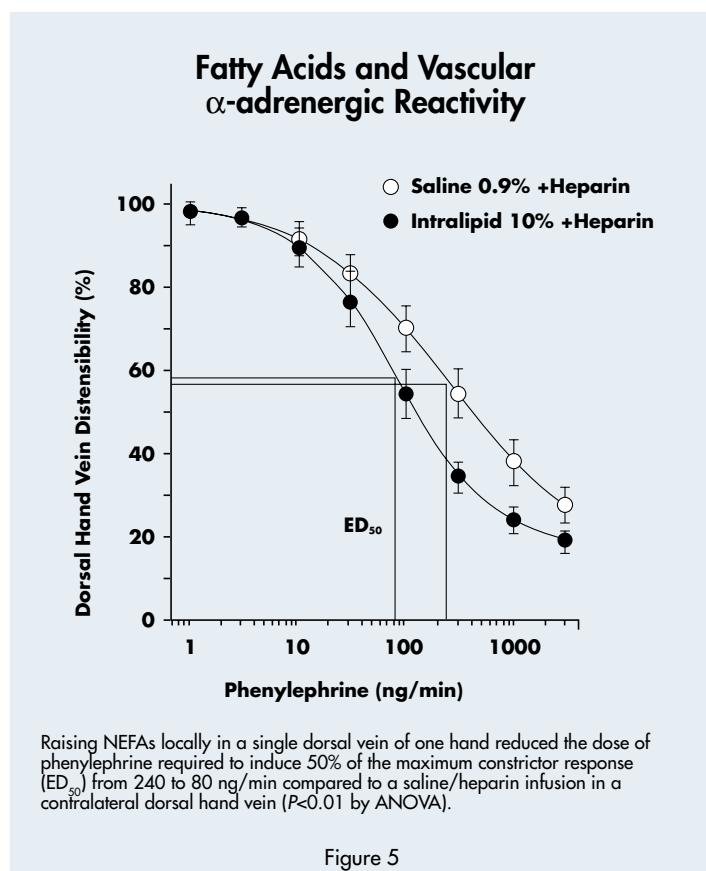
do they prove these effects persist in longterm. Moreover, abnormalities in regulating circulating NEFAs are also associated with changes in membrane composition that affect ion transport and signal transduction processes that, in turn, could influence vascular tone and reactivity. Despite the uncertainties, abnormalities of insulin's NEFA-lowering effects may comprise a key link to the increased neurovascular tone and blood pressures observed in subjects with the cardiovascular risk factor cluster and are an exciting research area.

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# American Society of Hypertension

The American Society of Hypertension (ASH) is the largest US organization dedicated exclusively to hypertension and related cardiovascular disease. ASH was founded in 1985 by Dr. John Laragh and 16 other world-famous clinicians and scientists in an effort to evaluate the vast accumulation of data on hypertension and to provide a separate forum for those involved in the study or management of high blood pressure. The mission of the Society became “to organize and conduct educational activities designed to promote and encourage the development, advancement, and exchange of scientific information in all aspects of research, diagnosis, and treatment of hypertension, and related cardiovascular diseases.”

Today, the Society boasts a membership of over 3,000 strong with 95% of its members holding an MD, PhD, or other advanced degree. The Society continues to fulfill its mission by annual meetings that provide registrants with the rare opportunity to exchange information and ideas with more than 2,500 fellow scientists from around the world. Highlights of the meeting include state-of-the-art lectures by renowned faculty, plenary sessions, original communications, poster presentations, technical and scientific exhibits, and provocative special symposia.

In addition, the Society publishes the prestigious *American Journal of Hypertension*, a monthly publication containing the latest information in both basic science and clinical research.

Membership in ASH is open to all those who have undertaken and accomplished meritorious original scientific investigation in the field of hypertension and/or related cardiovascular disease, those involved in the diagnosis and treatment of hypertension and related cardiovascular disease, and those with a demonstrated serious interest in the field. Among the benefits of ASH membership are association and interaction with clinicians and scientists who are world leaders in the field, a subscription to the *American Journal of Hypertension* and all its supplements, a listing in the ASH Member Directory used for patient referral, and a savings of 50% or more on registration fees for the annual scientific meeting.

The American Society of Hypertension sponsors three award programs annually. The first award program focuses on the area of ongoing research training in the field of hypertension for young clinicians planning a career in academic medicine. Another recognizes and rewards three scientists who have carried out a significant body of work in the field of hypertension or related cardiovascular diseases. The last award program recognizes and rewards five young physicians, currently residents or fellows, who have a demonstrated interest in the study of hypertension or who plan a career change into the field.

For further information on ASH membership, awards programs, future meeting dates or to add your name to the ASH mailing list, contact:

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