

# Hypertension

## Editor's Comments

This issue of ASH Current Concepts in Hypertension includes two reviews of perhaps the most important new concept about the development of hypertension: the workings of the nitric oxide (NO) mechanism and how it interacts with dyslipidemia to accelerate atherosclerosis. Clinicians need to know the inner workings of this mechanism, in part because important therapies that work through the NO system are sure to come.

The recipient of this year's prestigious Tigerstedt Award at the ASH meeting, Dr. Myron Weinberger, describes the use of simplified diagnostic tests for primary aldosteronism. This condition may be a lot more common than most have thought.

Last, the newest concept in treating hypertension turns out to be an old concept that has been recast into a more modern, patient-friendly approach: combinations of drugs but in appropriate low doses.

Norman M. Kaplan, Co-editor

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## Upcoming Issue

## Abnormalities of Endothelium-dependent Vascular Relaxation in Patients with Essential Hypertension

After Furchgott and co-workers demonstrated that the contractile state of vascular smooth muscle was dependent on the presence and integrity of endothelial cells, abnormal endothelial function was recognized in several cardiovascular conditions, including essential hypertension.

*"Hypertensive patients have impaired vasodilation in response to agents that act through the endothelium . . ."*

Hypertensive patients have impaired vasodilation in response to agents that act through the endothelium (eg, acetylcholine). In contrast, the response to direct smooth muscle dilators (eg, sodium nitroprusside) is preserved.<sup>1</sup>

We hypothesized that a specific defect in the endothelium-derived nitric oxide (NO) system might contribute to the impaired response. NO is a soluble gas synthesized from the amino acid L-arginine in the endothelial cell by the enzyme NO synthase (Figure). NO diffuses from the endothelium into the underlying smooth muscle, where it activates guanylate cyclase; intracellular cyclic GMP levels thereby rise, leading to vascular relaxation via endothelium-derived relaxing factor (EDRF).

To assess the contribution of NO to abnormal endothelial function in essential hypertension, we examined the vascular effects of N<sup>G</sup>-monomethyl-L-arginine (L-NMMA) under baseline conditions and during endothelium-dependent vasodilation. L-NMMA is an arginine analog that competitively inhibits the synthesis of NO from L-arginine. Therefore, its use permits the study of NO significance in the vascular system. Our results showed that L-NMMA significantly increased vascular tone in normal subjects but produced much less vasoconstriction in hypertensive patients and did not significantly modify the response to acetylcholine.<sup>2</sup> Thus, the reduced vascular effects of L-NMMA in hypertensive patients indicate impaired production of NO by hypertensive arteries.

We next studied the effect of administering L-arginine, the natural precursor for the synthesis of NO on the responses to acetylcholine (ACh) and found that a reduced availability of substrate for NO production does not account for the impaired endothelial function of hypertensive arteries.<sup>3</sup>

Our research efforts were then aimed at identifying the cellular mechanisms that mediate the abnormal production of endothelium-derived NO and, consequently, vascular relaxation. Such abnormalities may reside in the endothelial cell surface receptor, in the signal transduction pathways, in the

function of NO synthase, in the pathways leading to release of NO, or in the mechanisms that participate in its subsequent degradation (Figure).

To determine whether abnormal responses were specific for acetylcholine, thereby implicating a selective defect in the muscarinic cell surface receptor or in its associated signal transduction pathway, we first studied substance P, which, although it recognizes a different receptor than does ACh, shares the same G protein-mediated signal transduction pathway. We found that hypertensive patients also have an abnormal response to substance P, that this response is related to a decreased release of NO, and that it significantly correlates with the response to ACh.<sup>4</sup> These findings indicate the abnormal endothelium-dependent vascular relaxation of hypertensive patients is not due to a specific defect of the muscarinic endothelial cell receptor.

We observed that hypertensive patients also have impaired NO-dependent vascular responses to bradykinin<sup>5</sup> which preferentially utilizes a different signal transduction pathway (Gq protein) (Figure). This suggests the endothelial dysfunction in this condition is not related to a specific defect of a single intracellular signal transduction pathway and implicates a more generalized abnormality of endothelial vasodilator function.

Since a potential mechanism for impaired endothelial regulation of vascular tone in hypertension is an increased breakdown of NO by superoxide anions, we examined the effect of superoxide dismutase (a scavenger of superoxide anions) on endothelium-dependent vasodilation and found that extracellular destruction of NO does not play a significant role in the impaired endothelial vasodilator function in hypertension.<sup>6</sup>

We still are not able to explain how NO-mediated relaxation is impaired but an important clinical issue is whether such an impairment in endothelial function can be reversed by appropriate antihypertensive treatment. We studied a group of hypertensive patients on two occasions: during conventional effective antihyper-

tensive treatment and after withdrawal of antihypertensive therapy for at least 2 weeks. No significant differences in the response to ACh or sodium nitroprusside were observed in the hypertensive patients between the two studies.<sup>7</sup> These results suggest that the endothelial abnormality in essential hypertension is either primary or, if secondary, becomes irreversible once the hypertensive process is established.

*“... the endothelial abnormality in essential hypertension is either primary or, if secondary, becomes irreversible . . .”*

In summary, our studies have identified an abnormality of endothelium-mediated vasodilation in hypertensive patients that is related to decreased activity of NO. The precise mechanism of this defect has not been determined but may involve decreased production or increased breakdown of this factor. Given the biological significance of NO in the regulation of vascular

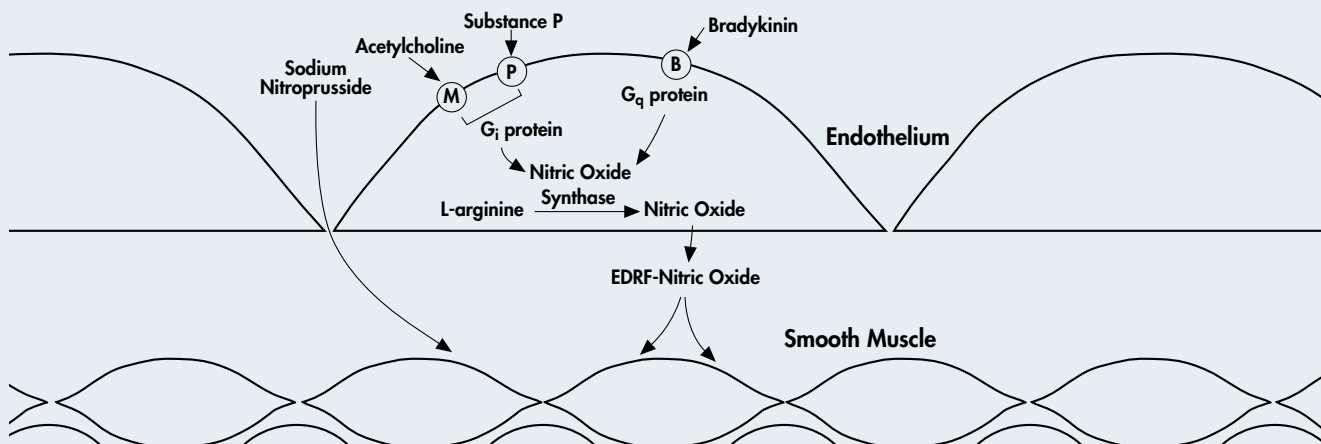
tone, its reduced activity must play an important role in the hypertensive process.

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## References

1. N Engl J Med. 1990; 323:22-27.
2. Circulation. 1933; 87:1468-1474.
3. Circulation. 1993; 87:1475-1481.
4. J Am Coll Cardiol. 1994; 23:1610-1616.
5. Circulation. 1995; 91:1732-1738.
6. Hypertension. 1995; 26:863-868.
7. J Am Coll Cardiol. 1993; 21:1145-1151.

## Abnormalities of Endothelium-dependent Vascular Relaxation in Patients with Essential Hypertension



Figure

## Dyslipidemia and Endothelial Dysfunction

In addition to the impressive evidence that endothelial function is impaired in hypertensive patients, there is equally strong evidence for similar endothelial impairment in hypercholesterolemic patients. Since hypertension and dyslipidemia so commonly coexist, there is greater potential for dysfunction.

Numerous investigators have shown in various models that hypercholesterolemic patients display a similar loss of endothelium-dependent relaxation as described by Dr. Panza in the preceding article. The decreased bioavailability of nitric oxide (NO) occurs at the level of the acetylcholine receptor or its signal transduction pathway.

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*“... hypercholesterolemic patients display a similar loss of endothelium-dependent relaxation . . . .”*

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Of particular interest is the recent demonstration that reduction of hypercholesterolemia will improve vascular function, specifically endothelium-dependent vasodilation in the forearm.<sup>1,2</sup> Along with the recent trials showing that reduction of elevated lipid levels reduces the incidence of coronary disease, the evidence that vascular function also improves when lipids are lowered adds further reason to identify and correct the dyslipidemias that are so common in hypertensive patients.

As of now, there is no convincing evidence that correction of hypercholesterolemia will lower blood pressure. At the least, there is no evidence that currently available lipid-lowering agents interfere with the action of antihypertensive agents at the vascular level.

At the same time these benefits of correcting dyslipidemia surfaced, prior concerns about the potential of worsening dyslipidemia by commonly used antihypertensive agents—diuretics and  $\beta$ -blockers—have been largely overcome. Serum cholesterol levels do rise with large doses of diuretics but, now that appropriately lower doses are being used, the effect is minimal or nonexistent. Similarly, serum triglycerides are raised and HDL cholesterol levels lowered by high doses of non-cardioselective  $\beta$ -blockers. Here again, smaller doses of selective agents induce less dyslipidemia. At the same time, small but definite improvements in lipid levels accompany the use of alpha-blockers.

All hypertensive patients should have their lipid levels measured. Care should be taken not to worsen their lipids by inappropriate therapy. If dyslipidemia is found aggressive therapy with diet and, if needed, drugs should be provided to protect maximally against premature cardiovascular disease.

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*“All hypertensive patients should have their lipid levels measured.”*

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### References

- Lancet. 1995; 346:467-471.  
Am J Cardiol. 1996; 77:37-40.

## Long-term Antihypertensive Therapy

New data from 20-year follow-ups of over 3000 participants in the Framingham Heart Study strongly suggest long-term antihypertensive therapy protects against cardiovascular (CV) disease mortality much better than seen in multiple short-term clinical trials.<sup>1</sup>

Three groups or cohorts, each 50 to 59 years of age, were followed for 20 years. More and more of the hypertensives in the later cohorts received antihypertensive therapy, the percentage of those treated going from 13% in the 1950 cohort to 78% of the men and 89% of the women in the 1970 cohort. No details on the types of antihypertensive therapy are given.

The average blood pressures decreased and the percentages of well-controlled hypertension progressively increased in each group. In addition, treated patients had lower cholesterol levels and less left ventricular hypertrophy but more glucose intolerance than those not treated. Those treated for up to 20 years had significantly less total and CV mortality during the second 10 years of followup than those not treated. The degree of protection progressively increased with each cohort (Table).

As the authors note, this is the first report of trends in the prevalence, treatment, and sequelae of long-term sustained hypertension. The study obviously differs from all of the short-term clinical trials which have shown protection but to lesser degrees. As the authors state, “This study evaluates the impact over time of the introduction of intensive antihypertension therapy for long-term sustained hypertension in a free-living general population. It is an observational study and not a clinical trial: comparison groups were not matched, treatment was not randomly assigned, and therapies were not administered according to strict protocols. In the general population, many factors contribute to the physician’s decision to administer therapy, and compliance is less certain than in clinical trials. For these reasons, results from population-based studies may provide more realistic evaluations of therapeutic interventions.”

Norman M. Kaplan, MD

### References

1. Circulation 1996; 93:697-703.

### Mortality Among Long-term Sustained Hypertensive Patients During Second 10 Years of Followup

Baseline	1950	1960	1970	Combined Cohorts
Follow-up period	1960-70	1970-80	1980-90	
On treatment Percent death/ CV death	41/26	29/10	31/9	31/11
Not on treatment Percent death/ CV death	42/26	38/24	44/15	41/24

Sytkowski et al. Circulation 1996; 93:697-703.

Table

## Simplified Screening for Primary Aldosteronism

While secondary forms of hypertension are uncommon, their discovery offers the potential of restoring normotension without a lifetime commitment to antihypertensive therapy with its attendant costs, financial and otherwise. Primary aldosteronism is second only to renal vascular hypertension as an identifiable cause. While identifying primary aldosteronism is not unduly difficult, the traditional techniques used have been arduous, time-consuming, and often fraught with false-negative and false-positive responses. As an example, serum potassium is frequently used to screen for primary aldosteronism despite the fact that 20% of such patients have potassium values within the normal range. The majority of hypertensive patients in whom hypokalemia is found have secondary aldosteronism resulting most commonly from diuretic administration.

Another feature of primary aldosteronism is suppressed plasma renin activity (PRA) but most patients with low PRA are “low-renin essential hypertensives.” Therefore additional maneuvers are needed to document hyperaldosteronism.

We systematically applied a protocol including appropriate stimulation and suppression to identify primary aldosteronism in 418 normotensive volunteers (for normative data) and 302 hypertensive

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*“Primary aldosteronism is second only to renal vascular hypertension as an identifiable cause.”*

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patients. We identified 62 subjects with primary aldosteronism based on failure to stimulate PRA normally in response to sodium and volume depletion, as well as the failure of plasma aldosterone levels to be suppressed normally by the intravenous administration of a 2-L saline load. Further evaluation of the patients with primary aldosteronism permitted us to separate them into 48 subjects with unilateral (adenomatous) adrenal disease and 14 with bilateral (hyperplastic) forms. This differentiation was made on the basis of localizing tests, including computed tomography and adrenal venous sampling and venography.

We further evaluated the use of a simple numerical ratio of plasma aldosterone (PA) to PRA in a random peripheral venous blood sample obtained before any maneuvers were undertaken: in the morning (8 am), after overnight fast, and following 2 hours of ambulation. We found the ratio permitted separation of primary aldosteronism from both essential hypertension and normal groups (Figure) and also provided some discrimination between the two forms of primary aldosteronism. Since a low PRA could result in a high PA:PRA ratio in the absence of aldosterone excess, the absolute level of PA should be increased.

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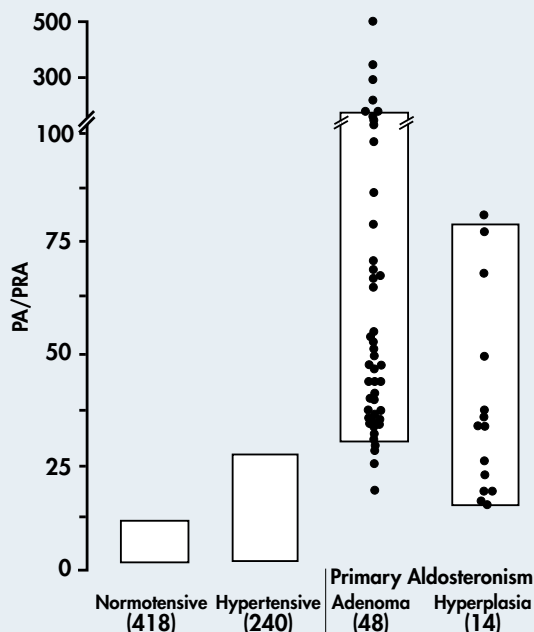
*“Since a low PRA could result in a high ratio in the absence of aldosterone excess, the absolute level of PA should be increased.”*

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None of the subjects we studied had taken antihypertensive medications for at least 2 weeks. We believe that this screening test can be used during some forms of drug therapy since the effects of most antihypertensive agents on renin and aldosterone levels are predictable. For example, diuretics and angiotensin converting enzyme inhibitors would be expected to raise renin, thereby lowering the ratio. An abnormal ratio is still seen in patients with primary aldosteronism since their PRA will likely remain suppressed. However,  $\beta$ -blockers and antisympathetic agents which reduce renin levels could produce an abnormal ratio and thus should not be used when this screening test is performed.

Patients demonstrating an abnormal ratio should be evaluated with localizing procedures to determine whether unilateral disease, amenable to surgical intervention, is present. The widespread availability of accurate, standardized measurements of PRA and PA by hospital and commercial laboratories makes this a practical and efficient screening test, eliminating the need for most other screening tests.

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Boxes indicate 90% confidence limits for the ratio of plasma aldosterone (PA) to plasma renin activity (PRA) in the four subject groups.

Note break in scale.

All four groups were significantly different ( $P < 0.001$ )

Figure

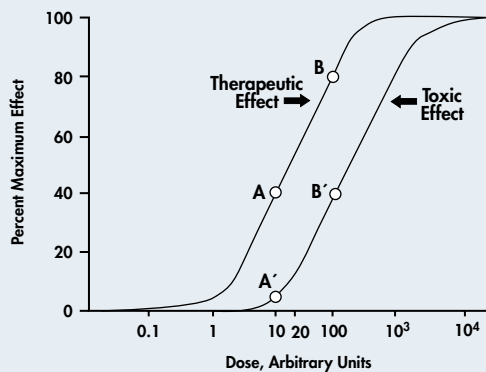
## Low-dose Combination Therapy for Hypertension

For initial therapy of most hypertension, full doses of multiple drugs in combination are not routinely prescribed because of inability to titrate each of the constituents and to separate individual side effects while unnecessarily exposing patients to superfluous therapy. However, if low doses of two antihypertensive agents with different modes of action are combined, this may benefit hypertensive patients by minimizing the dose-dependent adverse effects since smaller doses of drugs are used to achieve control.

*“... low doses of two antihypertensive agents with different modes of action are combined...”*

The concept has been nicely demonstrated by Fagan<sup>1</sup> (Figure). With a low dose of drug A, only a partial therapeutic effect is obtained and adverse effects (A') are minimal. If the dose is raised to B the greater effect will be accompanied by more adverse effects (B'). However, if a low dose of another drug is added, with its minimal side effects, the extra benefit will be obtained without more adverse effects which will stay at A'.

### Theoretical Therapeutic and Toxic Logarithmic-linear Dose-response Curves



The horizontal axis is a logarithmic scale with arbitrary dose units. The vertical axis is a linear scale showing percentage of maximal possible response. (Reproduced with permission from Fagan TC. Arch Intern Med. 1994; 154:1430-1431. Copyright 1994, Amer Med Assoc.)

Figure

Since multifactorial trials have documented that low doses of bisoprolol fumarate (an ultracardioselective  $\beta$ -blocker) and hydrochlorothiazide (HCTZ) in combination decreased systolic and diastolic blood pressures with few adverse effects.<sup>2</sup> We compared this combination to two popular monotherapies.<sup>3</sup> A randomized, multicenter, double-blind parallel group dose escalation trial was conducted with 2.5 to 10 mg bisoprolol combined with 6.25 mg HCTZ, 2.5 to 10 mg amlodipine, and 5 to 20 mg enalapril all given once daily. Following a 4- to 5-week placebo washout phase, 218 subjects with a diastolic blood pressure 95 to 114 mm Hg were randomized to one of three drug groups. Each drug was titrated to attain a sitting diastolic blood pressure  $\leq 90$  mm Hg 24 hours after dosing and the subjects were maintained on that dose for 8 weeks.

The low-dose combination was effective compared to the alternative therapies (Table). The percentage of patients escalated to the highest dose of the study was 31% for bisoprolol/HCTZ, 43% for amlodipine, and 49% for enalapril. The response rates (diastolic blood pressure  $\leq 90$  mm Hg or  $\geq 10$  mm Hg decrease from baseline) were 71% for the low-dose combination, 69% for amlodipine, and 45% for

enalapril ( $P < 0.01$  versus low-dose combination amlodipine). The percentage of patients with  $\geq 1$  spontaneously reported adverse clinical experiences was 29% for the low-dose combination, 42% for amlodipine, and 47% for enalapril ( $P = 0.04$  versus bisoprolol-6.25 HCTZ). There was no difference in drug-related adverse events among the groups. There were no clinically important deviations in laboratory values and no significant difference in quality-of-life scores as measured by the General Well-being Index.

This study demonstrated that low dose drug combination of a diuretic and  $\beta$ -blocker is as effective and safe as a calcium antagonist and a converting-enzyme inhibitor for the initial treatment of hypertension.

Prudent physicians will avoid initial fixed-dose combination therapy in patients who may be sensitive to the individual components (eg,  $\beta$ -blockers for those with asthma and diuretics for those with sulfur skin allergy). However, for appropriate patients, convenience, enhanced compliance, and cost savings would be predicted benefits

*“There are now three low-dose combinations on the US market.”*

that assume profound importance. There are now three low-dose combinations on the US market: bisoprolol-HCTZ; benazepril-HCTZ, and amlodipine-benazepril.

Currently, the only FDA-approved combination available on the market for initial therapy is bisoprolol/6.25 HCTZ. There

will certainly be more since the concept of improved efficacy without more adverse effects holds up in clinical practice.

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### References

1. Arch Intern Med. 1994; 154:1430-1431.
2. Arch Intern Med. 1944; 154:1462-1472.
3. Am Heart J. 1995; 130:359-366.

### Mean Change from Baseline to End of Treatment by Treatment Group for All Randomized Patients

	Bisoprolol -6.25 HCTZ	Amlodipine	Enalapril
Number	75	72	71
Systolic Pressure (mm Hg)	-13.4 <sup>†</sup>	-12.8 <sup>†</sup>	-7.3
Diastolic Pressure (mm Hg)	-10.7 <sup>†</sup>	-10.2 <sup>†</sup>	-6.6
Heart Rate (BPM)	-6.2	+2.1 <sup>†</sup>	+1.3 <sup>†</sup>

<sup>†</sup>  $p < 0.01$  vs enalapril

<sup>†</sup>  $p < 0.01$  vs bisoprolol-6.25 HCTZ

Table

# 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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