

## The Clinical Context of Vascular Compliance: Compromised Vascular Compliance as a Measure of Cardiovascular Risk

Based on a presentation by Jay N. Cohn, MD

### **Presentation Summary**

Hypertension is a disease of the blood vessel wall, not of the blood pressure, as is traditionally thought. As such, the concept of hypertension needs to be redirected to address atherosclerosis, the cause of most cardiovascular events.

The presence of an atherosclerotic plaque is a late manifestation of a disease process that probably begins in the endothelium that lines the blood vessel wall.

The blood vessel is a series of sequential vascular components that differ in structure and function and have different determinants of compliance. The large conduit arteries have a capacitor function and contain elastin and collagen; elasticity of these arteries is pressure dependent. Elasticity of the smaller reflecting sites into which these conduits branch and taper, is more dependent on nitric oxide from the endothelium and contributes to oscillations in the pulse wave; it is minimally pres-

sure dependent. Elasticity of the arterioles, which are the resistance vessels and contain very little collagen, is probably not pressure dependent.

There are striking differences, therefore, between compliance of the conduit arteries and reflecting sites and resistance in the arterioles.

A number of studies have looked at the effects of aging, hypertension, diabetes, smoking, and atherosclerosis on endothelial dysfunction, capacitive compliance, and oscillatory compliance. All of the studies reviewed in this presentation demonstrated decreased small artery elasticity or compliance and increased endothelial dysfunction with each of the disease processes.

Just as decreased arterial compliance may be the clinical marker for endothelial dysfunction, the marker for cardiovascular risk is endothelial dysfunction, not blood pressure itself.

**H**ypertension is a disease of the blood vessel wall, not of the blood pressure," said Jay N. Cohn, MD, Professor of

Medicine at University of Minnesota Medical School in Minneapolis. "Accordingly, we need to shift our concept of hypertension

“to address the true disease we are trying to prevent.”

That disease is the presence and eventual rupture of atherosclerotic plaque in the coronary, cerebral, or peripheral vascular circulation, and it is the source of most cardiovascular events, he said.

The presence of plaque is a late manifestation of a disease process that probably begins in the endothelium, or inner lining, of the blood vessel wall where numerous paracrine, autocrine, and hormonal substances—the most important of which is probably nitric oxide—are produced. It is the release of nitric oxide, Dr. Cohn said, that maintains the tone of the underlying vascular smooth muscle and inhibits platelet aggregation and structural alterations in the blood vessel wall. Thus, any reduction in release or bioactivity of nitric oxide plays a major role in impairing endothelial function and promoting platelet aggregation, both of which contribute to the formation of early atherosclerotic lesions. The lesions, which increase smooth muscle tone, decrease vascular compliance, and promote vascular smooth muscle hyperplasia. In addition, remodeling of the vasculature plays a role in reducing vascular compliance or elasticity.

### Vascular Structure and Compliance

The blood vessel is not a homogeneous entity but a series of 3 major sequential vascular components that differ in structure and function and have different determinants of compliance (Table 1), Dr. Cohn remarked.

The large conduit arteries, which are lined with elastin and collagen, are elastic and very pressure dependent. The higher the blood pressure, the greater the collagen engagement and the reduction in arterial compliance. The conduit vessels have a capacitor function because they distend during systole and contract during diastole, largely in response to

pressure changes in the vascular system. Therefore, the compliance of these large arteries is equal to the change in volume for any given change in pressure.

As these blood vessels branch and taper, there are so-called “reflecting” sites where oscillations or reflections in blood flow occur, with endothelium and underlying vascular smooth muscle playing major roles in inducing these oscillations. In contrast, elasticity of the reflecting sites, which contain some collagen, is minimally pressure dependent.

The third vascular segment is the arteriole or the resistance vessel, which is lined with endothelium and perhaps a single layer of vascular smooth muscle. Elasticity of the arterioles, which contain very little collagen, is probably not pressure dependent. Resistance is calculated from the ratio of blood pressure to cardiac output.

Mulvany has shown that arterioles change when hypertension is present. The walls thicken, either by growth (hyperplasia or hypertrophy) or by remodeling, a process in which the entire vessel becomes smaller, but the mass of the vasculature remains the same.<sup>1</sup> The remodeling process may

**Table 1.** Vascular Segment Structure and Its Relationship to Compliance

Conduit Arteries	Reflecting Sites	Arterioles
Elastin	Smooth muscle	Endothelium
Collagen	Endothelium	Smooth muscle
Elasticity is pressure dependent	Elasticity is minimally pressure dependent	Elasticity is not pressure dependent

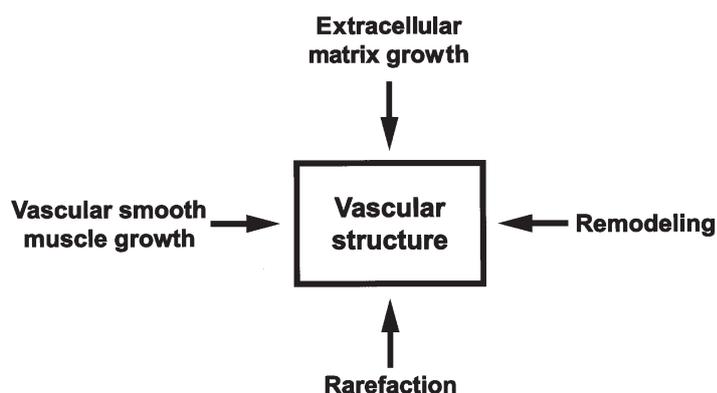
also be endothelium dependent. Other factors that influence the vascular structure and its total compliance and resistance are extracellular matrix growth and rarefaction, in which certain individuals, perhaps because of genetic determination, may have fewer blood vessels than normal (Figure 1).

There are striking differences between compliance of the conduit arteries and reflecting sites and resistance in the arterioles (Table 2), Dr.

Cohn said. Caliber, which is directly related to resistance, influences distensibility, which is the fractional increase in caliber or volume of the vessel based on its initial volume ( $\Delta v/\Delta p \times \text{initial volume}$ ). In contrast, caliber is independent of compliance, which is  $\Delta v/\Delta p$ .

“There is another vicious circle of hypertension that involves endothelial dysfunction,” Dr. Cohn noted (Figure 2). Endothelial dysfunction occurs as a result of reduced bioactivity of nitric oxide, causing the arterioles to constrict, which in turn increases systemic resistance and raises blood pressure. This rise in blood pressure further damages the endothelium and sets up a vicious circle leading to atherosclerotic events.

**Figure 1.** Factors Influencing the Vascular Structure



**Measuring Arterial Compliance and Interpreting the Results**

Dr. Cohn described several methods available or in development for measuring arterial compliance. Methods that measure large conduit artery capacitance or distensibility, he said, are considerably different from those that measure compliance in the smaller arteries and reflecting sites (Figure 3). He reviewed several studies in which compliance and related data were obtained by the measurement method based on a modified Windkessel model of the vasculature (Table 3).

One study measuring compliance noninvasively with the device based on the Windkessel model examined the effect of aging on the vasculature. The investigators found a marked decline in capacitive conduit compliance (C1) with increasing age, indicating that the vessels got stiffer over time. They found an even more precipitous drop in reflective or oscillatory compliance (C2) with increasing age, reflecting alterations in those distal sites as well.<sup>2</sup> As expected, systemic vascular resistance and the impedance index rose with age.

**Table 2.** Arterial Compliance vs Resistance

Compliance	Resistance
Function of all arteries	Confined predominantly to arterioles
Independent of caliber	Directly related to caliber
Pulsatile phenomenon	Mean phenomenon
Pressure dependent	Non pressure dependent
Influenced by wall thickness	Influenced by lumen size
Very sensitive to drugs	Moderately sensitive to drugs
Very sensitive to aging and disease	Moderately sensitive to aging and disease

“Age is a very important factor in the health of the vasculature,” Dr. Cohn said. There is also independent evidence that nitric oxide bioactivity falls with increasing age.<sup>3</sup> He recommended the use of a variety of agents and supplements to keep the endothelium healthy, such as aspirin, vitamin E, and perhaps angiotensin-converting enzyme (ACE) inhibitors like perindopril.

Another study showed that when hypertensive patients were compared with age-matched normal controls, C1 was lower and C2 was strikingly lower in the hypertensives.<sup>4</sup>

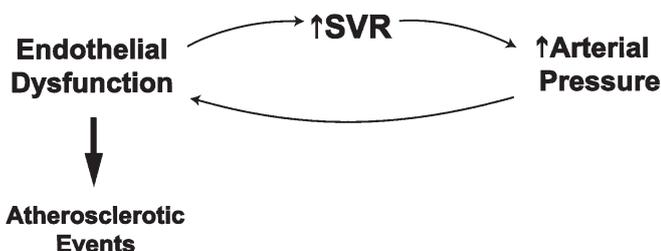
“We think the reduction in C1 is largely due to the rise in blood pressure but we know that the striking reduction in C2 is not dependent on pressure. Therefore, there appears to be a selective alteration in the distal vasculature that suggests it may be a more sensitive site at which to assess the influence of the endothelium,” he explained.

More importantly, McVeigh et al demonstrated that selective alteration in the distal vasculature occurs even in the absence of hypertension.<sup>5</sup> They studied a group of 28 normotensive patients with type 2 diabetes who were free of any vascular or target organ disease and compared them with a group of 22 normal controls matched for age, body size, blood pressure level, cardiac output, and stroke volume.

While the controls exhibited a notable rise in forearm blood flow in response to an infusion of acetylcholine into the brachial artery, the diabetic patients exhibited a significantly suppressed response, indicating reduced bioactivity of released nitric oxide. Systemic vascular resistance and C1 were identical in both groups, but C2 was markedly and consistently reduced in the diabetic patients compared with the controls.<sup>5</sup> When the diabetic patients were given fish oil, the endothelium and C2 normalized, demonstrating the poten-

tial for therapeutic intervention.<sup>6</sup> Dr. Cohn and his colleagues studied a group of postmenopausal women, 29 of whom had coronary artery disease and 23 of whom did not. Those with overt manifestations of coronary artery disease had significantly lower C2 than the controls.<sup>7</sup> They also compared C2 in a group of smokers and a group of nonsmokers. The smokers had significantly lower C2.<sup>8</sup>

**Figure 2.** Vicious Circle of Hypertension



**Figure 3.** Methods for Measuring Arterial Compliance

Large conduit artery capacitance/distensibility

- Impedance spectra (frequency domain)
- Stroke volume/pulse pressure
- Capacitive compliance (C1) (Windkessel)
- Pulse wave velocity
- Ultrasound caliber change/pulse pressure
- Magnetic resonance imaging

Smaller arteries/reflecting sites

- Late systolic pressure augmentation
- Oscillatory compliance (C2)
- Isolated small arteries (biopsy)

“What I am suggesting is that the decrease in arterial elasticity or compliance may be the clinical marker for endothelial dysfunction,” he emphasized.

**The Key Role of Endothelial Dysfunction**

Whether it is genetically induced or brought about by aging, smoking, insulin resistance, or diabetes, endothelial dysfunction is a major contributor to the atherosclerotic process, which itself leads to cardiovascular events.

There are, to be sure, a number of facilitators, including abnormal lipid levels and high blood pressure. Although the role of lipids is to accelerate the atherosclerotic process, it is not yet clear whether lipids themselves alter endothelial dysfunction. However, blood pressure may adversely influence endothelial dysfunction before endothelial dysfunction raises

the blood pressure, Dr. Cohn pointed out.

Evidence for that paradigm is as follows. First, the risk of endothelial dysfunction is directly related to blood pressure. Indeed, essentially all persons with blood pressure levels of 190/120 mm Hg have marked endothelial dysfunction, as demonstrated by C2. Reduced arterial compliance and endothelial dysfunction are far less common in persons with lower levels of hypertension, and virtually all persons with blood pressure levels of 100/60 mm Hg have normal endothelial function.

Just as decreased arterial compliance may be the clinical marker for endothelial dysfunction, he noted, endothelial dysfunction, not blood pressure, is the marker for cardiovascular risk.

Epidemiologic data relating blood pressure or lipid levels to cardiovascular risk produce a linear relationship—that is, the higher the blood pressure or lipid levels the greater the risk. However, this is a crude way to assess risk because it does not take into account that the true risk is at the vascular wall, Dr. Cohn said.

He noted that separating people into those with abnormal vessel walls and those with normal vessels would produce a steeper relationship curve between the risk factor and the risk of cardiovascular disease. This would allow clinicians to intervene, confident that they would be accomplishing something that is clinically beneficial in those at risk. Little or nothing is accomplished by intervening in those with normal vessel walls.

“If we can target our therapy toward those who are at risk, we can be far more efficient in evaluating the efficacy of drug interventions in the at-risk population,” he said. “This approach, however, would require that we redefine hypertension as a state of abnormal arterial function and structure associated with endothelial dysfunction, vascular

**Table 3.** Factors Affecting Endothelial Dysfunction, Capacitive Compliance (C1), and Oscillatory Compliance (C2)

Disease	Endothelial Dysfunction	C1	C2
Aging	+	↓	↓
Essential hypertension	+	pressure*	↓
Isolated systolic hypertension	?	↓	↓
Diabetes	+	↓	↓
Smoking	+	↓	↓
Atherosclerosis	+	↓	↓
Heart failure	+	↓	↓

\*Reduction in C1 is the result of an increase in pressure; + = yes; ↓ = decrease; ? = unknown.

smooth muscle constriction or remodeling, increased impedance to left ventricular ejection, and propensity for atherosclerosis often, but not always, manifested by an elevated blood pressure.”

... DISCUSSION HIGHLIGHTS ...

**Member of the Audience:** I take exception to your last conclusion. First, only 25% of people who have hypertension are being adequately controlled.<sup>9</sup> Second, hypertension itself is a cardiovascular risk factor independent of what develops later on. Obviously, hypertension accelerates aging, but animals and people who are normal except for high blood pressure tend to develop more arteriosclerosis and atherosclerosis later on. To propose that we treat only those who have already developed vascular disease is not a good idea.

**Dr. Cohn:** You are right from an epidemiologic standpoint. What you don't address is whether everybody gets disease.

It is certainly true that hypertensives have a higher risk for developing disease, but when you look at the Framingham data, the magnitude of the adverse effect of high blood pressure in the absence of any other coexisting risk factors is exceedingly small. The increment in risk is so small that many managed care organizations don't even believe high blood pressure is worth treating.

The reason is that we are not defining the group in which high blood pressure is playing a fundamental role. We have all seen people who are 90 years old who have been hypertensive since the age of 30, but they are not manifesting the vascular disease that we know is associated with hypertension. However, I do agree with you that none of this should lead us away from treating high blood pressure. Until we are ready to make

a major leap forward, we still have to control high blood pressure. Determining which patients need blood pressure control most because they are at highest risk should be an objective of our investigative efforts.

**Dr. Weber:** Your comments remind me of some work that Joel Neutel published a couple of years ago, making the point that family history of

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—Jay N. Cohn, MD

hypertension is already predictive of a change in compliance, suggesting that it really may be a more fundamental change than the blood pressure itself.<sup>10</sup>

**Dr. Cohn:** That is the genetic component, and it is probably the major feature of the abnormality of the vasculature.

**Member of the Audience:** Do you think the lack of a decrease in vascular resistance in the evenings or during the night in people who do not reduce their blood pressure, either naturally or with pharmacological treatment, is due to variability in the impedance index? Or, are people who continue to manifest this at other times of the day at a greater risk than is measured? I presumed that in your laboratory most of the measurements were taken during the morning.

**Dr. Cohn:** We have done some studies on diurnal variation and we will be publishing the results of some of these 24-hour and 7-day studies. We are now looking at ambulatory blood pressure compared with compliance in a group to determine whether the failure to lower blood pressure at night is a manifestation of reduced compliance or of endothelial dysfunction. The link between all these things needs to be emphasized, no question about that.

I also want to point out that we shouldn't discourage treatment of people without elevated blood pressure. If anything, we have to encourage treatment of people who don't have elevated blood pressure. In fact, less than half the people who have infarcts in this country have hypertension. What about the other 60%?<sup>11</sup> Even though they don't have elevated blood pressure, I am sure that if we treated them with a vascular protective agent, we could favorably affect their course. Obviously, hypertension is more than a matter of elevated blood pressure.

**Member of the Audience:** Your presentation was a beautiful summary of a lot of work. Are studies under way or do you anticipate sequential studies, particularly in families with a strong history of hypertension? If you are correct, then it seems to me that you ought to be able to identify the earliest predictive factor that will tell us when to start treating.

**Dr. Cohn:** We are certainly trying to do that. Dr. Weber pointed out, Joel Neutel has some data showing that arterial compliance is low before hypertension develops in families with a history of hypertension, and that's probably the time we should initiate therapy.

**Member of the Audience:** I believe that impedance is the best way to characterize the arterial system, and

compliance is just one of those components. Hypertension is a result of a hemodynamic lesion in the arterial system. We don't know how that lesion got there because there are many factors—neurogenic, physical, mechanical—that can cause a change in the vascular properties of the arterial system. We do know that blood pressure will rise when that arterial system lesion is big enough. Whenever the blood pressure goes up and stays up, it will cause additional arterial lesions. I am not so sure that compliance causes hypertension, although it is the mechanism that keeps blood pressure high. We don't know why the vascular lesion leads to a decrease in compliance, ultimately causing the blood pressure to keep spiraling up.

Also, many patients with severe atherosclerosis have no hypertension, so I think arteriosclerosis is more of a marker for hypertension than atherosclerosis.

**Dr. Cohn:** Everything you are saying is correct for the large conduit arteries. I am focusing on the smaller arteries as a marker for the individual who is at risk for developing the large artery abnormality that supports the rise in blood pressure and contributes to cardiovascular events. We are talking about different phases of the disease, and there is no question that blood pressure elevation contributes to alterations in the conduit artery, to the atherosclerotic process, to plaques, to widening pulse pressure, and to a high risk for events. But it starts at the small vessel level where the blood pressure may not be initially abnormal.

**Member of the Audience:** I was intrigued by your data on the noninsulin-dependent diabetics. Nephrologists are starting to think of microalbuminuria as a marker, perhaps, of vascular disease. Do you know whether those patients had microalbuminuria?

**Dr. Cohn:** No, they did not. None of them had microalbuminuria, but it was part of the workup. However, I agree with you that it is probably an early marker for this blood vessel disease at the renal level.

**Member of the Audience:** The NHANES [National Health and Nutrition Examination Survey] data indicate that less than 25% of patients are well controlled for 140/90 mm Hg.<sup>9</sup> If you look at 130/80 mm Hg as a target, the control rate is probably far less than that—maybe even in the single digits. You mentioned that patients who may have vascular abnormalities but don't manifest with high blood pressure are falling through the cracks right now. How do you propose to have this message trickle down to the primary care physician who treats patients on a daily basis? You are proposing that patients with vascular abnormalities definitely need to be controlled, even if their blood pressure levels are not high. How do you propose to get the word out? Even though the most recent JNC [Joint National Committee] recommendations reflect daily clinical practice more closely than ever before, the word doesn't seem to be filtering down to the people who should be using these data.

**Dr. Cohn:** You are identifying a major issue. There are so many things that have been inadequately done. For example, many people with heart failure are not getting an ACE inhibitor. How do you get the message out that people with heart failure should be getting proper treatment? We have a big job ahead of us, but we shouldn't let anything deter us from getting blood pressure well controlled in the community.

But that is not the end of the story. I think that we, as scientists, also want to move the field forward and we have to do both at the same time.

**Member of the Audience:** We are all aware of this tremendous clustering of risk factors around "hypertension" as an entity, be it dyslipidemia or insulin resistance or frank diabetes. Given that all of these risk factors are impacting on the process of atherosclerosis at the endothelial level, are there any data to support that reduced compliance in "hypertensives" with a variety of risk factors is related not so much to blood pressure but to the coexistence or the comorbidity of these other risk factors impacting at the endothelial level?

**Dr. Cohn:** We have not been able to tease out the influence of each of these risk factors on arterial compliance, even though we know that diabetics have low compliance, hypertensives have low compliance, and smoking reduces compliance. One might think that the coexistence of all 3 would have a greater impact, but we really don't know.

**Member of the Audience:** Dr. Cohn, you postulated that there might be a group of hypertensives who have normal compliance and that they may be at low cardiovascular risk. How many of those patients have you seen and how long have they been followed to determine whether or not they are, in fact, at low cardiovascular risk?

**Dr. Cohn:** We are collecting data on a large number of these people, but following them is obviously going to fall to the next generation. When I say there is a hypertensive population at low risk, I am referring to people with very modest blood pressure elevations; borderline stage 1, if you will. As I pointed out, everybody with a diastolic level above 110 mm Hg has low compliance. However, the vast majority of the 65 million hypertensives in this country have diastolic blood pressures between 90 mm Hg and 100 mm Hg and systolic levels of

135 mm Hg to 145 mm Hg or 150 mm Hg.<sup>12</sup> It is in that population where a casual blood pressure measured in the clinic may not tell you whether this person is at risk or not. All of us should be concerned about who should be treated and who shouldn't be because we don't know what to do with these people.

What I am saying is that there is a large group of borderline or mildly hypertensive individuals with and without vascular disease, and the presence of vascular disease is a marker for whether they should be treated. Do I know that? Absolutely not, but we need to follow these people and get more data.

**Member of the Audience:** We know that being male is a risk factor. Certainly the risk of atherosclerosis is markedly less among women, particularly premenopausal women. Can you comment on any observed gender differences in compliance?

**Dr. Cohn:** Women have a slightly lower compliance because they tend to be smaller and therefore have fewer blood vessels available for measuring total compliance. The normal range is a little different for women versus men. Once you begin with that normal range, their values go down after menopause, but our preliminary studies have shown that estrogen replacement restores C2 towards normal. So there appears to be a protective effect of estrogen on the small vessel endothelial level.

**Member of the Audience:** The diabetes data are interesting. It seems that there are diabetics who have no evidence of any complication. As you probably know, in early diabetic models, in rat models, there are data showing an increase in nitric oxide activity that is perhaps playing a role in the hyperfiltration of early diabetic nephropathy. There seems to be some discrepancy in what is happening sys-

temically and what is happening in the kidney.

**Dr. Cohn:** That is an interesting comment, and I don't think we have a good handle on it. I use the term nitric oxide bioactivity because it may not be the amount of nitric oxide that is reduced, but the oxidative stress that destroys it at the vascular wall. Perhaps that doesn't take place in the kidney; I am not sure. We have to come up with new ways of looking at that and we will probably gather a lot of data that will help over the next few years.

... REFERENCES ...

1. Mulvany MJ. Remodeling of resistance vessel structure in essential hypertension. *Curr Opin Nephrol Hypertens* 1993;2:77-81.
2. McVeigh GE, Bratelli CW, Morgan DJ, et al. Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis. *Hypertension* 1999;33:1392-1398.
3. Gerhard M, Roddy M-A, Creager SJ, Creager MA. Aging progressively impairs endothelium-dependent vasodilation in forearm resistance vessels of humans. *Hypertension* 1996;27:849-853.
4. McVeigh GE, Burns DE, Finkelstein SM, et al. Reduced vascular compliance as a marker for essential hypertension. *Am J Hypertens* 1991;4:245-251.
5. McVeigh G, Brennan G, Hayes R, Cohn J, Finkelstein S, Johnston D. Vascular abnormalities in non-insulin-dependent diabetes mellitus identified by arterial waveform analysis. *Am J Med* 1993;95:429-430.
6. McVeigh GE, Brennan GM, Finkelstein SM, Johnston GD, Hayes JR, Cohn JN. Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. *Arteriosclerosis & Thrombosis* 1994;14:1425-1429.
7. Cohn JN, Finkelstein S, McVeigh G, et al. Non-invasive pulse wave analysis for the detection of arterial vascular disease. *Hypertension* 1995;26:503-508.
8. McVeigh GE, Morgan DJ, Finkelstein SM, Lemay LA, Cohn JN. Vascular abnormalities associated with long-term cigarette smoking identified by arterial waveform analysis. *Am J Med* 1997;102:227-231.

**9.** Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension* 1995;25:305-313.

**10.** Neutel JM, Smith DHG. Hypertension: Where have we gone wrong and how can we fix it? *Am J Hypertens* 1998;11:150S-157S.

**11.** Cohn JN, Franciosa JA, Francis GS, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure. *N Engl J Med* 1982;306:1129-1135.

**12.** The Sixth Report of the Joint National Committee on Prevention, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413-2416.