Hypertension can cause major changes in the arterial wall. Some of these are protective in nature and are associated with a remodeling of the artery to better withstand the increase in wall tension resulting from the elevated intravascular pressure. Other responses to vascular injury caused by hypertension, however, can predispose the artery to further adverse consequences. In this study, I will discuss the nature of these responses in the arterial media and intima and the mechanisms potentially responsible for these alterations.

Changes in the Arterial Media with Hypertension

Cellular Responses

The medial layer normally constitutes most of the thickness of an artery. During growth and development, paralleling the rise in blood pressure, there is a rapid increase in the number of medial smooth muscle cells (SMCs) and their organization into lamellar units. When comparing adults of different species, the number of lamellar units and the overall wall thickness reflect the size of the animal and the diameter of the vessel. The calculated tension per lamellar unit is relatively constant throughout a wide range of species and vessel sizes. Hypertension causes an increase in thickness in the arterial media (Figure 1) that serves to counteract the rise in wall tension.

The lamellar units of the arterial media are composed of SMCs and connective tissue components such as collagen, elastin, proteoglycans, and fibronectins. With hypertension, the number of lamellar units remains relatively constant, and increases in wall thickness are achieved by changes in both cellular mass and connective tissue content. Previous studies including those by Owens and Schwartz as well as ourselves have demonstrated that in most rat models of hypertension, SMC hypertrophy, which can be associated with nuclear polyplody, is the reason for the major increase in SMC mass. This might not be a uniform response, however, because in the rat with aortic coarctation, hyperplasia without hypertrophy or polyplody of arterial SMCs can occur.

Although the stimulus for arterial SMC growth as a result of hypertension is uncertain, studies involving cultured SMCs have been of considerable interest. Various vasoactive agents including catechol-
FIGURE 1. Photomicrographs showing cross-section of descending thoracic aorta in 20-week-old Wistar-Kyoto (WKY) (left panel) and spontaneously hypertensive (SHR) (right panel) rats. Note greater thickness of the aortic wall in SHR. Stained with hematoxylin-eosin (original magnification, x25).

amines\textsuperscript{7} and angiotensin II\textsuperscript{8} have reportedly stimulated growth of arterial SMCs. The angiotensin II effect can be seen with concentrations as low as $10^{-9}$ M and is associated with increases in cell size and protein content without an effect on cell number. The hypertrophy of the cultured SMCs caused by angiotensin II is associated with increased expression of the A chain of platelet-derived growth factor (PDGF) and of the proto-oncogene c-myc.\textsuperscript{9} Transforming growth factor-$\beta$ (TGF-$\beta$) also appears to stimulate the development of SMC hypertrophy and polyploidy in culture.\textsuperscript{10}

Our recent work in this area has been concerned primarily with the investigation of the effects of hypertension on the expression of growth factors in rat aorta. Although the in vivo experimental systems are more complex and the data are more difficult to interpret than with cell culture studies, there is an obvious need to study the problems in intact animals and to determine the relevance of the in vitro findings to the hypertensive state. We have demonstrated the expression in rat aorta of several growth factors including epidermal growth factor (EGF), insulin growth factors I and II, acidic and basic fibroblast growth factors, TGF-$\beta$ 1, and both chains of PDGF.\textsuperscript{11} We also have found that deoxycorticosterone (DOC)-salt hypertension caused an increase in aortic TGF-$\beta$ 1 expression of approximately threefold (Figure 2), although the expression of the other growth factors remained unchanged. Recently R. Cohen of our group has observed that TGF-$\beta$ 1 stimulates contractility of arterial rings (personal communication, 1989). The latter findings are interesting because TGF-$\beta$ is a polypeptide that appears to be involved in tissue inflammation and repair.\textsuperscript{12} It is carried in platelets and released in areas of injury. It is a potent chemoattractant for macrophages and can stimulate the production of collagen, fibronectins, and proteoglycans.\textsuperscript{13,14} It could therefore play a role in mediating some of the vascular responses to hypertension.

Although our data on arterial growth factors have as yet only involved measurement of steady-state levels of messenger RNA (mRNA) and not actual concentrations of growth-promoting proteins, it is reasonable to suggest that hypertension influences arterial SMC growth by affecting the balance between growth factors in a manner that would determine whether the cells divide, differentiate, or undergo hypertrophy. Several potential sources for the growth factors might be present. As already suggested, they could be produced in the vascular cells themselves and act through autocrine or paracrine effects. They could also, however, originate from blood-borne cells that penetrate the arterial wall (see further discussion) or from other blood constituents that could have increased entry into the artery as a result of the hypertension.

Several growth factors including PDGF\textsuperscript{15} and EGF\textsuperscript{16} have reportedly induced arterial vasoconstriction, and several vasoconstrictor agents including angiotensin II,\textsuperscript{8} $\alpha_1$ receptor agonists,\textsuperscript{7} endothelin,\textsuperscript{17} and serotonin\textsuperscript{18} stimulate growth of cells in culture. These common effects appear to be mediated through increases in intracellular Ca$^{2+}$, which is involved in both growth and contraction. The mechanisms for the rises in intracellular Ca$^{2+}$ appear complex, however, and can differ with different growth factors. For example, for PDGF, phospholi-
pressure (BP) from each group of rats is shown at the bottom of each lane. Total RNA was applied to each lane. Average systolic blood pressure (BP) from each group of rats is shown at the bottom of each lane. Top panel: TGF-β gene expression. (—) endothelium control, RNA extracted from endothelium-scraped aortas of untreated rats. Deoxycorticosterone-salt (DOC/salt) groups were all treated for 3 weeks (2-day exposure time). Bottom panel: β-Actin gene expression. Same blot previously hybridized with human TGF-β complementary DNA (cDNA) probe was rehybridized with a rat β-actin cDNA probe (3-hour exposure time). Reproduced with permission. 14

Effects of Hypertension on the Arterial Intima

The intimal changes induced by hypertension can initially be adaptive in nature but ultimately can predispose the vasculature to further damage.

Endothelial Alterations

Extensive endothelial abnormalities can be associated with hypertension. Soon after induction of DOC-salt hypertension, the endothelium will show changes in the shape of cells and an increase in their number.22,23 The latter can reflect a response to the increase in arterial diameter that leads to an augmentation in endothelial surface area. Functional abnormalities of the endothelium also can occur. Recently, several groups have reported that endothelium-dependent relaxation of the arterial wall is diminished in hypertensive as compared with normotensive animals (for review, see Reference 34). Additionally, intimal permeability to a number of substances including horseradish peroxidase, colloidal carbon, albumin, and lipoproteins can also be increased by hypertension.35-37

SMCs and blood-borne cells accumulate in the subendothelial space in response to hypertension. In the DOC-salt model, such accumulation is preceded by a pronounced increase in adherence to the endothelial

Another set of connective tissue proteins receiving considerable recent attention that have not been studied in hypertension are the fibronectins. These large glycoproteins with a molecular weight of approximately 500,000 are composed of two subunits with repeating sequences that bind fibrinogen, heparin, and collagen.26 In the artery, fibronectins are present in the subendothelial space, media, and adventitia.27 After balloon-catheter injury, the distribution of the different forms of fibronectin appears altered together with the phenotypic expression of SMCs.28 Fibronectins are also reportedly involved in many important cellular functions that are relevant to our current discussion including cell adhesion, differentiation, growth, and motility, as well as thrombosis and wound healing.29 The modulation of proliferation of cultured SMCs by TGF-β appears related to an increase in fibronectin synthesis and can be mimicked by addition of soluble fibronectin to the culture.30 TGF-β has also reportedly increased expression of fibronectin and of both units of the fibronectin receptor in lung fibroblasts.31

We recently have initiated studies on the influence of experimental hypertension on fibronectin expression in rat aorta. We have measured steady-state mRNA levels of fibronectin by Northern blot analysis and have shown a substantial rise in fibronectin gene expression after 2 weeks of DOC-salt administration.32 TGF-β has also reportedly increased fibronectin expression after 2 weeks of DOC-salt administration (I. Takasaki, unpublished observations). Similar results have been obtained after 6 days of angiotensin II infusion by Alzet minipump (Alza Corp., Palo Alto, California). Thus, elevation in blood pressure can cause changes in arterial fibronectins that could possibly alter cell growth and other arterial responses.

Extracellular Matrix Changes

The SMCs of the arterial media are encircled by a dense network of connective tissue. Recent data suggest that the organization of connective tissue might be influenced by a complex family of receptor proteins called integrins, which bind specifically to individual connective tissue components.23 Experimental hypertension causes an increase of arterial collagen, elastin, and proteoglycans, presumably as a result of stimulation of their production by SMCs. The rise in collagen and elastin is approximately proportional to the increase in arterial weight.25
surface of blood-borne monocytes, lymphocytes, and granulocytes (Figure 3). Platelet adherence to the intima is not typically present and neither is endothelial cell loss. We have observed increased motility of SMCs out of aortic explants obtained from hypertensive animals and increased growth potential of such cells. If similar changes also occur in vivo, then hypertension might stimulate medial SMCs to migrate into the intima where they could proliferate and contribute to the development of intimal thickening.

Many of the intimal changes caused by hypertension are broadly similar to those observed with aging or hypercholesterolemia. These include endothelial cell and SMC proliferation, increased permeability, and accumulation of proteoglycans and lipids.

### Table 1. Comparisons Between Arterial Intimal Changes Associated With Hypertension, Aging, and Atherosclerosis

<table>
<thead>
<tr>
<th>Intimal abnormalities</th>
<th>Hypertension</th>
<th>Aging</th>
<th>Hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC shape changes</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reduced EC-derived relaxation</td>
<td>+</td>
<td>...</td>
<td>+</td>
</tr>
<tr>
<td>Endothelial permeability</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Leukocyte adherence</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Macrophage accumulation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SMC migration</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SMC proliferation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Proteoglycans accumulation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intimal thickening</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lipid accumulation</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Atherosclerotic plaque</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

EC, endothelial cell; SMC, smooth muscle cell; +, present; 0, absent.
CONTROL WHHL

HYPERTENSIVE WHHL

FIGURE 4. Photomicrographs showing gross appearance of intimal surface in descending thoracic aortas. Unstained, perfusion-fixed, opened segments are pinned to black wax; uninvolved semitransparent areas appear white (original magnification, ×2). Top panel: Normotensive 6-month-old Watanabe heritable hyperlipidemic (WHHL) rabbit. Note periosteal distribution of lesions. Scale is metric. Bottom panel: Hypertensive WHHL rabbit 3 months after renovascular surgery showing diffuse involvement. Adapted from Reference 50.

ability, monocyte and SMC accumulation, deposition of connective tissue matrix, and intimal thickening (Table 1). These alterations also can be observed during the process of wound healing and can represent appropriate reparative responses of the arterial wall to injurious stimuli.

In various experimental models of hypertension and in hypertensive humans, atherosclerotic lesions are uncommon when plasma lipoprotein levels are low. The intimal changes previously described lead to thickening of the intima but do not generally progress to atherosclerotic plaque formation. That plasma lipoproteins play a key role in determining the intimal response to hypertension has been demonstrated in our recent studies involving the Watanabe heritable hyperlipidemic (WHHL) rabbit, which has a genetic defect in cellular receptors for low density lipoproteins (LDL). Induction of one-kidney, one clip hypertension in these rabbits for periods as brief in length as 3 months caused a pronounced increase in extent and severity of atherosclerosis in the aorta (Table 2 and Figure 4). We have also observed atherosclerotic lesions of the proximal coronary arteries, left ventricular hypertrophy, and patchy areas of myocardial cell loss in the hypertensive WHHL rabbit. The model therefore might be useful for studies of the effects of left ventricular hypertrophy on cardiac function and myocardial perfusion in the presence of coronary atherosclerosis.

Effects of Antihypertensive Drugs

Several antihypertensive drugs, particularly β-blockers and calcium antagonists, have inhibited atherogenesis in normotensive cholesterol-fed animals. The mechanism of effect of any of these agents remains unknown, although an obvious feature common to all of these drugs is their ability to lower blood pressure or alter hemodynamic stresses on the arterial wall. In

<table>
<thead>
<tr>
<th>Aortic region</th>
<th>Control</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total aorta</td>
<td>16±3</td>
<td>77±4*</td>
</tr>
<tr>
<td>Ascending and arch</td>
<td>47±15</td>
<td>99±1†</td>
</tr>
<tr>
<td>Descending thoracic</td>
<td>6±1</td>
<td>89±5*</td>
</tr>
<tr>
<td>Abdominal</td>
<td>15±2</td>
<td>37±11</td>
</tr>
</tbody>
</table>

Values are percentage of intimal surface (mean±SE).

*p<0.001, values represent mean±SE.

Table 2. Effects of One-Kidney, One Clip Goldblatt Hypertension on Aortic Surface Atherosclerosis in Watanabe Heritable Hyperlipidemic Rabbits

<table>
<thead>
<tr>
<th>Aortic region</th>
<th>Control</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total aorta</td>
<td>47.9±3.6</td>
<td>29.7±3.9*</td>
</tr>
<tr>
<td>Ascending and arch</td>
<td>76.3±4.3</td>
<td>76.3±3.7</td>
</tr>
<tr>
<td>Descending thoracic</td>
<td>48.9±5.2</td>
<td>15.3±3.9†</td>
</tr>
<tr>
<td>Abdominal</td>
<td>28.6±2.5</td>
<td>26.2±4.4</td>
</tr>
</tbody>
</table>

Values are percentages of intimal surface (mean±SE).

*p<0.01, values represent mean±SE.

†p<0.001, adapted from Reference 54.

Table 3. Effects of Captopril on Aortic Surface Atherosclerosis in Watanabe Heritable Hyperlipidemic Rabbits
FIGURE 5. Top panel: Cross-section through atherosclerotic plaque in descending thoracic aorta of 12-month-old control Watanabe heritable hyperlipidemic (WHHL) rabbit. This area was evaluated visually as an "advanced lesion." Note cellularity of the intimal lesion and thickness of the media. Bottom panel: Cross-section through an "advanced lesion" in a 12-month-old WHHL rabbit after 9 months of captopril treatment. Note sparse cellularity of the intima and the thinner media than shown in top panel. Both sections were stained with hematoxylin-eosin (original magnification, ×100).

contrast to their favorable effects in inhibiting atherosclerosis associated with cholesterol-feeding, however, propranolol,51 nifedipine,52 and verapamil53 have failed to influence atherogenesis in the WHHL rabbit. Because of the effects of angiotensin II on SMC growth as previously discussed and our interest in evaluating the action of antihypertensive therapy on the arterial wall, we recently performed a study to
examine the long-term effects of the angiotensin converting enzyme (ACE) inhibitor captopril on aortic atherosclerosis in the normotensive WHHL rabbit. Captopril was added to the diet in doses adequate to reduce serum ACE activity, and treatment was maintained for 3-12 months of life. A significant reduction in aortic atherosclerosis was observed in the captopril-treated rabbits as compared with control WHHL rabbits with the major inhibition occurring in the descending thoracic aorta (Table 3). Intimal cholesterol content was also reduced markedly in this region. The changes were independent of effects on plasma lipids but were associated with significant reductions in blood pressure. At any level of lesion severity as judged by gross examination, aortic intimal and medial thickness was considerably less in the rabbits treated with captopril than the control group of rabbits. Interestingly, the plaques of captopril-treated WHHL rabbits demonstrated a pronounced decrease in cellularity and an increase in intimal connective tissue (Figure 5). Several potential mechanisms could be responsible for the antiatherosclerotic effect of captopril. The effects on blood pressure would be expected to reduce wall tension and thereby influence medial thickness. A lower blood pressure might also reduce arterial permeability and lipoprotein entry into the artery. Perhaps relevant to these observations are our previously published data indicating that long-term reduction of blood pressure in normotensive rats might inhibit age-related changes in the aorta. Epidemiological data also support the concept that low levels of blood pressure may protect from vascular complications.

The captopril action might also be mediated by inhibiting angiotensin II formation and its effects on cellular proliferation, although studies in cultured SMC have shown that angiotensin II induces cell hypertrophy but not hyperplasia. A recent study has indicated that captopril and the ACE inhibitor cilazapril can reduce the degree of myointimal thickening occurring after balloon-catheter injury of rat carotid artery, consistent with an effect on cell proliferation.

Other Effects of Experimental Hypertension on the Arterial Wall

Hypertension can have a variety of other effects on the arterial wall. As examples, we have shown that several forms of experimental hypertension in the rat can induce pronounced reduction in both steady-state mRNA levels and immunoprecipitable protein concentrations of a fatty acid binding protein. Additionally, interesting modulation of steady-state mRNA levels of isoforms of sodium-potassium adenosine triphosphatase (Na⁺,K⁺-ATPase) have also been demonstrated in aortic tissue from hypertensive rats. The possible functional and pathological consequences of these various alterations in gene expression are uncertain.

Summary and Conclusions

Dynamic changes occur in the arterial wall in response to long-term blood pressure elevation. In the medial layer (Figure 6), there is a prominent increase in cellular mass, collagen, and elastin. The cellular changes typically involve SMC hypertrophy, which at times is also associated with nuclear polyploidy.

Cell culture studies have indicated that SMC growth can be stimulated by a variety of vasoactive agents including catecholamines and angiotensin II. Extending the cell culture studies to the in vivo situation, we have demonstrated that several growth factors are expressed by arterial cells and that hypertension can increase steady-state levels of mRNA for TGF-β and fibronectins in rat aorta. The fibronectin data are interesting considering their reported role in cell adhesion, growth, motility, and wound healing, and as mediators of TGF-β effects.

The intimal effects of experimental hypertension summarized in Figure 7 have many of the characteristics observed in response to aging or to hypercholesterolemia. Some of these alterations can result from any type of injury to the vessel wall and can sensitize the artery to atherosclerotic plaque formation in the setting of pronounced hyperlipidemia. Whether similar changes also can be affected in the
presence of relatively mild hypercholesterolemia of the degree observed in most hypertensive patients is unknown as yet.

Several antihypertensive drugs have been shown to inhibit the development of atherosclerosis in normotensive cholesterol-fed animals, which suggests that blood pressure lowering itself might somehow mediate a protective effect, even within the normal range of blood pressure. Our recent study demonstrating an inhibitory action of captopril on atherogenesis is particularly interesting because of the effectiveness of the drug in the WHHL rabbit model in which other antihypertensive drugs have as yet failed to inhibit the disease. Additionally, captopril therapy appears associated with a reduction in cellularity of atherosclerotic lesions, which suggests that the effect might at least in part involve an action on cellular growth.

The recent advances in cellular and molecular biology, the availability of tissue culture systems for studying vascular cells, and the development of new experimental animal models for studying how changes in blood pressure affect arterial disease in vivo provide excellent opportunities for future research in this field. An improved understanding of how hypertension influences vascular biology should lead to better methods for prevention of coronary atherosclerosis and myocardial infarction.

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Key Words • atherosclerosis • antihypertensive drugs • growth substances • essential hypertension • rabbit studies
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A V Chobanian

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