SPECIAL ARTICLE

Hypertension, Antihypertensive Drugs and Atherosclerosis

By WILLIAM HOLLANDER, M.D.

HYPERTENSION is one of the major precursors of atherosclerotic vascular disease which is the leading cause of death in the United States and other Western nations. Atherosclerosis involving the coronary, cerebral and peripheral circulations is responsible for approximately half of all deaths in this country each year, with coronary heart disease accounting for two-thirds of the mortality. The National Health Survey indicates that about 15 to 20% of American adults have hypertension while 5% of this population have definite or suspect coronary heart disease. It is also estimated that about 50% of men and 75% of women with coronary disease have hypertension. Between the years 1955 and 1965 the crude death rate from hypertensive heart disease is reported to have declined by 46%. However, during this same period, the mortality rate from coronary arteriosclerotic heart disease is reported to have increased by about 11%. It is difficult to evaluate these findings since hypertension as a cause of death is often not recorded on death certificates.

The results of a number of epidemiological studies indicate that the risk of every manifestation of coronary heart disease, including angina, coronary insufficiency, myocardial infarction and sudden death is significantly related to the antecedent level of both systolic and diastolic blood pressure. These observations, together with the experimental evidence that hypertension accelerates and aggravates atherosclerosis, suggest that early detection and treatment of hypertension could result in a substantial reduction in morbidity and mortality from coronary heart disease. A number of recent surveys indicate that the great majority of the hypertensive population are either unaware of their disease or are receiving inadequate treatment.

The purpose of this communication is to consider some of the mechanisms by which hypertension may influence the course of atherosclerosis as well as to review the current status of antihypertensive drugs in the prevention and management of coronary heart disease.

I. Pathogenesis of Atherosclerosis

According to the recent report by the Task Force on Arteriosclerosis the basic lesion in atherosclerosis is the atheromatous fibrous plaque, which is an elevated pearly grey intimal lesion. The typical atheromatous plaque consists of a core of lipid, mainly free and ester cholesterol, covered by a cap of fibrous tissue. This lesion appears to be responsible for the clinical manifestations of atherosclerosis since it progressively narrows the arterial lumen as it increases in size and ultimately impedes the blood flow to the tissues. The atheromatous plaque also appears to set the stage for complicating thrombosis and occlusion. The fatty streak, in contrast to the fibrous plaque, is a flat intimal lesion which by itself does not obstruct the affected artery and cause ischemic symptoms. The lesion is characterized by cellular hyperplasia primarily of smooth muscle cells and the deposition of lipid, especially cholesterol, in these cells. Some extracellular lipid also has been described in these lesions. The importance of the fatty streak lies in the possibility that it may develop into a plaque.

A unifying view of some of the important mechanisms that have been implicated in the pathogenesis of the atheromatous fibrous plaque is presented in figure 1. This concept, which represents the work of many investigators, assigns a key role to the arterial smooth muscle cell and the endothelial cell in the development of atherosclerosis, with the smooth muscle cell being responsible for the formation of the basic lesion, the fatty streak.
HYPERTENSION, DRUGS AND ATHEROSCLEROSIS

Figure 1

Unified concept of atherosclerosis.

for the metabolic changes in the artery and the endothelial cell for the permeability changes. The endothelial cells lining the arterial intima have been shown to contain contractile proteins which may participate in the regulation of vascular permeability by altering the openings between the interendothelial junctions. The arterial smooth muscle cell is the predominant cell in the artery and is viewed as a multifunctional cell which in the presence of an atherogenic stimulus or mediator multiplies and synthesizes increased and altered amounts of lipids, mucopolysaccharides and connective tissue proteins including collagen and elastin. The proliferation and interaction of connective tissue with lipids and low density and very low density lipoproteins appear to be important mechanisms in fibrous plaque formation.

As illustrated in figure 1, an atherogenic or injury stimulus such as hypertension or hyperlipidemia may have direct effects on the smooth muscle cell and endothelial cell or indirect effects on these cells that are mediated via plasma and tissue factors such as platelets, lipoproteins and certain vasoactive amines including histamine, serotonin and angiotensin. The work of Mustard and others indicates that many factors which lead to vascular injury and atherosclerosis also may injure the platelets and cause them to aggregate and release substances many of which are potentially inflammatory and atherogenic. The substances which may be released by platelets (platelet “release reaction”) include ADP, histamine, serotonin, epinephrine, prostaglandins, permeability factors, elastase and other proteolytic enzymes.

Recent studies in our laboratory lend strong support to the view that the smooth muscle cell in the artery plays a major role in the formation of the atheromatous plaque. In these experimental studies it was found that the antimitotic and anti-inflammatory agent, colchicine, inhibited cell proliferation and the formation of the “fatty streak” and the fibrous plaque in the aorta of rabbits fed an atherogenic diet. These same studies also indicate that some of the other pathways of fibrous plaque formation postulated in figure 1 can be interrupted by certain other antiproliferative drugs and anti-inflammatory drugs.

The biochemical effects of some of these agents in experimental atherosclerosis are summarized in table 1. Atherosclerosis was induced in rabbits by feeding for eight weeks a diet containing 2% cholesterol and 8% peanut oil according to the
method of Krutchvesky et al. The treated animals were fed colchicine (0.03 mg/kg) or penicillamine (200 mg/kg) in addition to the atherogenic diet. Penicillamine was tested because of its known inhibitory action on collagen and elastin biosynthesis. As shown in table 1, the atherogenic diet produced comparable rises in plasma cholesterol in the treated and untreated animals. However the aortas of rabbits fed the atherogenic diet plus colchicine had fewer lesions and contained significantly less free and ester cholesterol as well as collagen and elastin than the aortas of rabbits fed the atherogenic diet alone. In contrast to colchicine, penicillamine did not alter the extent of atherosclerosis or the deposition of cholesterol in the lesions, but it did inhibit the connective tissue proliferation in the lesions, as indicated by their microscopic appearance and content of collagen and elastin. Thus penicillamine appears to selectively suppress the fibrosis in the atheromatous plaque while colchicine appears to inhibit both the fibrosis and lipid deposition in the plaque. These agents and others are currently being tested in experimental hypertensive vascular disease.

II. Interrelationships between Hypertension and Atherosclerosis

There is substantial evidence in man and experimental animals that a sustained elevation of arterial blood pressure regardless of its cause aggravates and accelerates atherosclerosis. A number of investigators have studied coronary atherosclerosis in autopsy material from normotensive and hypertensive man and have concluded that coronary atherosclerosis is more severe in hypertensive than in normotensive man. McGill, and Robertson and Strong have evaluated the extent and type of atherosclerotic lesions in coronary arteries and aortas collected from various areas of the world. They have found that the hypertensives as compared to the normotensives had more extensive fibrous plaques or “raised lesions” as well as a slight but significant increase in the extent of fatty streaks in the coronary arteries and abdominal aorta. Studies of hypertension and atherosclerosis in experimental animal models including rabbit, dog, rat and monkey are consistent with the findings in man and also indicate that hypertension increases the extent and severity of atherosclerosis. Hypertension also may play a role in the thrombotic complications of atherosclerosis. There is experimental evidence that elevation of arterial pressure can precipitate coronary thrombosis by causing rupture of the surface of the atherosclerotic plaque. The mechanism for the initiation of the thrombosis has been postulated to be an interaction of the exposed intimal collagen with the blood platelets, causing platelet aggregation. Recent studies suggest that the coronary thrombus in acute myocardial infarction might be a secondary event, occurring after the infarction, rather than a primary event.

Although hypertension can aggravate atherosclerosis, it is not clear that hypertension per se, in the absence of other atherogenic factors, can cause atherosclerosis. The arterial changes characteristic of hypertension include (1) increased thickness and rigidity of the arteries, (2) hyperplasia and hypertrophy of arterial smooth muscle cells, (3) increased deposition of acid mucopolysaccharides, collagen and elastin in the arteries, and (4) increase in the arterial content of sodium, chloride, potassium, calcium and water. Proliferation of smooth muscle cells and connective tissue also occurs in atherosclerosis but these changes are focal, involve mainly the intima and are accompanied by deposition of lipid mainly free and ester cholesterol. The actual mechanism by which hypertension aggravates atherosclerosis has not been established. However the available evidence

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Aortic cholesterol</th>
<th>Collagen</th>
<th>Elastin</th>
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<tbody>
<tr>
<td></td>
<td>Serum cholesterol</td>
<td>Free</td>
<td>Ester</td>
</tr>
<tr>
<td></td>
<td>(mg/100 ml)</td>
<td>(mg/g dry wt)</td>
<td>(mg/g dry wt)</td>
</tr>
<tr>
<td>Normal control</td>
<td>28 ± 3</td>
<td>2.7 ± 0.5</td>
<td>0</td>
</tr>
<tr>
<td>Atherogenic diet without drugs</td>
<td>4,052 ± 965</td>
<td>10.2 ± 2.4</td>
<td>13.1 ± 4.8</td>
</tr>
<tr>
<td>Atherogenic diet + Colchicine</td>
<td>3,971 ± 901</td>
<td>4.5 ± 0.8*</td>
<td>4.4 ± 0.3*</td>
</tr>
<tr>
<td>Atherogenic diet + Penicillamine</td>
<td>4,012 ± 805</td>
<td>10.0 ± 1.5</td>
<td>17.7 ± 5.2</td>
</tr>
</tbody>
</table>

Each value represents the mean and standard deviation of eight experiments.

*Significantly lower than the values of the atherogenic diet without drugs (P < 0.01).
appears to indicate that the changes in connective tissue metabolism and endothelial permeability associated with atherosclerosis are augmented by hypertension. In both hypertension and atherosclerosis an increase in vascular permeability as well as in the arterial synthesis of DNA, collagen, elastin and acid mucopolysaccharides has been reported.11, 16, 18, 36-41

There is considerable evidence that the adverse effect of hypertension on atherosclerosis is due at least in part to the direct mechanical effects of a high level of arterial pressure on the arterial wall. The mechanical stress on the arteries is influenced by a number of factors including (1) the lateral pressure exerted on the arterial wall, (2) changes in arterial wall tension associated with changes in intraluminal pressure and vessel radius, (3) changes in shearing stress caused by blood velocity gradient changes and turbulence of flow, and (4) differences in the relative deformability of the layers of the arterial wall.42-43

Studies in experimental hypertension of coarctation of the aorta provide strong support for a mechanical effect of hypertension on the structure and metabolism of the arterial wall. Table 2 shows some of the biochemical changes that occur in the hypertensive and relatively normotensive portions of the coarcted aorta of dog. The detailed methods of study have been described previously.37 The coarctation was surgically produced in the mid-thoracic aorta and was 10-12 months in duration. As compared to the corresponding aortic segment of normal dog, the hypertensive segment of the aorta above the coarctation contained significantly increased amounts of acid mucopolysaccharides, collagen and elastin while the relatively normotensive segments below the coarctation contained normal amounts of collagen and elastin and significantly reduced amounts of acid mucopolysaccharides. In contrast to these findings, the cholesterol content of the aorta above and below the coarcted site showed no significant changes suggesting that hypertension may have a direct effect on the connective tissue metabolism of the arteries without necessarily altering the metabolism of lipids in these vessels.37 This view is supported by previous studies of coarctation of the aorta44 in which it was found that the rate of influx of plasma cholesterol into the aorta did not change as the content of acid mucopolysaccharide and salt and water increased in the hypertensive aortic segment above the coarctation. Studies in experimental renovascular hypertension indicate that the connective tissue changes in hypertensive arteries may not be reversible following the “cure” of the hypertension.45

In addition to mechanical factors, there is a growing interest in the role of vasoactive agents and chemical mediators of injury or inflammation in accelerating atherosclerosis and hypertensive vascular disease. Certain of these agents also have been implicated in the pathogenesis of hypertension and include catecholamines, renin and the prostaglandins. A number of experimental studies indicate that high plasma levels of catecholamines, renin and angiotensin can alter the metabolism of the arterial wall and produce vascular damage which may be potentiated by mineralocorticoids and diets high in sodium content.46-49 In rabbits intravenous infusions of norepinephrine have been reported to produce atherosclerosis.50 Constantinides and Robinson, as well as Robertson and Khairallah,51, 52 have shown that angiotensin may increase the permeability of the arterial intima by causing contraction of the endothelial cells and opening the interendothelial junctions. Similar effects of serotonin, histamine and bradykinin on small vessels have been described.53 Prostaglandins also have been reported to play a role in vascular permeability and inflammation.54-55 However there is conflicting

Table 2

<table>
<thead>
<tr>
<th>Composition of Aorta in Normal and Coarcted Dogs</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Upper thoracic aorta</td>
</tr>
<tr>
<td>Normal dog</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
</tr>
<tr>
<td>Total acid mucopolysaccharides (mg/g dry wt)</td>
</tr>
<tr>
<td>Collagen (mg/100 mg dry wt)</td>
</tr>
<tr>
<td>Elastin (mg/100 mg dry wt)</td>
</tr>
<tr>
<td>Cholesterol (mg/g dry wt)</td>
</tr>
</tbody>
</table>

Each value represents the mean and standard deviation of ten experiments.

*Significantly different from normal control values.
evidence about the precise nature of their involvement.66

There is increasing evidence that the mechanical effects of hypertension on the heart as well as on the arteries can have an unfavorable effect on the course of coronary artery disease.67–60 These effects of hypertension which include the precipitation of coronary insufficiency and congestive heart failure are diagramed in figure 2. The arterial pressure is an important hemodynamic determinant of coronary blood flow and myocardial oxygen consumption.61–62 Consequently changes in blood pressure can alter the balance between myocardial oxygen supply and demand—an imbalance which can result in myocardial ischemia. It is generally agreed that the major hemodynamic variables directly related to myocardial oxygen requirements include (1) the intramyocardial tension (product of ventricular systolic pressure and radius of the ventricle divided by its wall thickness), (2) the heart rate, and (3) the contractile state of the ventricle.61–62

In hypertension the left ventricular systolic pressure increases resulting in an increase in the left ventricular intramyocardial tension. These changes operate to increase myocardial oxygen requirements and thereby enhance the likelihood of angina pectoris and coronary insufficiency in hypertensive patients who have coronary disease with a relatively fixed coronary blood flow.59, 60 Lowering of the blood pressure in these patients may reduce attacks of angina pectoris and improve the adequacy of the coronary circulation by reducing myocardial oxygen need as a result of diminishing myocardial wall tension.59, 60, 63–65 However, marked lowering of the blood pressure may precipitate angina and coronary insufficiency as a result of reducing coronary perfusion relative to demand.59, 60, 63

Congestive heart failure is another major complication of hypertension which may occur in the presence or absence of coronary artery disease.66 It is usually preceded by left ventricular hypertrophy and appears to result mainly from the excessive work load placed upon the heart by the elevated arterial pressure; however, complicating arteriosclerotic heart disease may also contribute to congestive heart failure. Transitory left ventricular failure preceded by a rise in blood pressure has been described during an attack of angina pectoris.67–68

Heart failure is not only reversible but also is preventable by controlling the blood pressure.69–74

III. Current Status of Antihypertensive Treatment of Hypertensive Cardiovascular Disease

The Veterans Administration study has presented convincing evidence that antihypertensive drug treatment is capable of preventing serious complications of hypertension in individuals with moderate and severe hypertension.71 Life table analysis of the results in patients with initial diastolic blood pressure of 90 through 114 mm Hg indicated that the risk of a fatal or non-fatal complication over a five-year period was reduced from 55 to 18% by combination drug treatment with hydrochlorothiazide, reserpine and hydralazine. Congestive heart failure, stroke and progressive renal damage were sharply reduced or eliminated in the treated patients. However the incidence of myocardial infarction and sudden death was essentially the same in the control and treated groups. These and other studies indicate that coronary heart disease remains a major problem in the hypertensive patient.72–74

The inability to demonstrate a significant effect of antihypertensive treatment on complicating ischemic heart disease is not necessarily inconsistent with the clinical and experimental evidence that elevated blood pressure accelerates and aggravates atherosclerosis. It is possible that a larger sample size or a longer period of follow-up might have revealed differences not apparent in the Veterans Administration Study. It also is possible that if treatment were started at an earlier age before the develop-
ment of advanced coronary atherosclerosis, the results might have indicated a protective effect of antihypertensive treatment against ischemic heart disease. A large percentage of the patients in the Veterans Administration study were over 40 years of age; more than half of the patients presented with cardiovascular or renal abnormalities and almost 30% of the patients were known to have had hypertension for 10 years or longer. The problem of reversibility of advanced atherosclerosis is an important one and requires further study. The control of other risk factors such as plasma lipids, smoking and weight also might enhance the effectiveness of treatment since these factors also appear to increase susceptibility to coronary heart disease.

Although it has not yet been demonstrated that antihypertensive treatment is effective in preventing complicating coronary heart disease, a recent study in Rochester, Minnesota, indicates that antihypertensive treatment may be beneficial in hypertensive individuals with clinical manifestations of ischemic heart disease. In this study of about 1500 residents with coronary heart disease, the data showed that patients with ischemic heart disease with borderline or established hypertension had a higher mortality rate than normotensive patients with coronary heart disease. Antihypertensive treatment was reported to improve survivorship which was related to a decrease in the incidence of congestive heart failure, myocardial infarction and cardiac death including sudden death.

Since there is no evidence that antihypertensive treatment alone can cause regression of atherosclerosis, it appears likely that the reported beneficial effects of treatment were due at least in part to an improvement in cardiac performance as well as in the adequacy of the coronary circulation as a result of reducing the mechanical effects of the hypertension on the heart (fig. 2). As discussed above a lowering of blood pressure may improve cardiac function by decreasing myocardial wall tension and the oxygen requirements of the heart muscle. It also is possible that antihypertensive treatment may improve prognosis by decreasing the frequency of complicating coronary thrombosis.

IV. Renin and Coronary Risk Factors in Hypertension Complicated by Atherosclerosis

The antihypertensive drugs, besides lowering blood pressure, have other actions which may potentially influence the course of hypertension. At present there is no evidence that the atherosclerotic complications of hypertension can be influenced by different drug regimens. In experimental animals the antihypertensive drugs currently in use have been shown to have a protective effect against hypertensive vascular disease and atherosclerosis. Nevertheless, a number of laboratories have been interested in this problem in man and are currently focusing attention on the effects of individual antihypertensive drugs on coronary risk factors and certain hormonal factors which have been implicated in the pathogenesis of ischemic heart disease. Recently the concept has been advanced that the level of plasma renin activity may influence the development of coronary heart disease and stroke and that those antihypertensive drugs which reduce plasma renin activity may protect against these complications.

It appears that those drugs like propranolol and alpha methyl dopa which inhibit renin secretion also diminish sympathetic neural activity, while those drugs like the diuretics and hydralazine which stimulate renin, augment sympathetic activity. These changes in renin secretion may be due in part to an effect of these drugs on the sympathetic nerves and receptors since there is considerable evidence that the sympathetic nervous system plays a role in controlling renin secretion, an effect which is mediated via the beta-adrenergic receptors in the kidney.

Our laboratory has examined plasma renin activity as well as some of the major coronary risk factors in 75 patients with essential hypertension, 35 of whom had a history of myocardial infarction. The patients were studied on a 120 mEq sodium and 40 mEq potassium diet. At least three weeks before the study the patients had been taken off all medications. A complete workup was done to exclude any known cause of hypertension. On the third day of the study plasma renin activity was measured after the patients had been upright for four hours. Plasma renin was measured by the method of radioimmunoassay of generated angiotensin I and double-checked by the bioassay method of Boucher et al. Plasma cholesterol, triglycerides, lipoprotein electrophoresis, sugar and uric acid were determined after an overnight fast of 14 hours. The results of the study are summarized in tables 3 and 4.

As shown in table 3 the age, sex and race of the patients in the normal and hypertensive groups were comparable. The duration of the hypertension also was not significantly different in
the groups. The mean plasma renin activity in the hypertensive groups with and without complicating myocardial infarction was 2.1 ± 1.7 and 2.1 ± 1.6 respectively, as compared to 2.4 ± 1.4 ng per milliliter per hour in the normal control group. The differences of renin between the groups were not statistically significant. As compared to normal subjects, 25% of the patients with uncomplicated hypertension and 20% of the patients with complicating hypertension had low renin levels of less than 0.75 ng per milliliter per hour (table 4). The distribution of high renin levels in the hypertensive groups also was about the same with about 15% of the patients in each group having elevated levels.

In 18 patients in whom plasma renin activity also was measured during antihypertensive drug treatment, there were no significant changes in plasma renin following withdrawal of the drugs. Drug treatment in these patients was given continuously for more than one year and included a diuretic in combination with one or more of the other antihypertensive drugs. These observations suggest that prolonged treatment with combinations of drugs does not necessarily change plasma renin activity, although certain drugs when given alone may alter plasma renin activity.

The results of the present study do not support the concept of Brunner et al.80 that the level of plasma renin activity by itself exerts a powerful influence over the development of coronary heart disease in hypertensive patients. Conclusions similar to ours have been drawn by other workers in studies of plasma renin levels and vascular complications.94-96 In order to answer conclusively the question of whether plasma renin is a major coronary risk factor, a large prospective study is required. The studies reported to date have been relatively small and mainly retrospective in selected groups of patients, many of whom have received prior antihypertensive treatment for prolonged periods.

With regard to coronary risk factors, the levels of blood pressure in the hypertensive groups with and without coronary heart disease were comparable whereas hyperlipidemia, hyperglycemia and hyperuricemia and gout were more prevalent in the hypertensive group with coronary disease (table 4). Hyperlipidemia (as defined as cholesterol level greater than 250 mg/100 ml, triglyceride level greater than 150 mg/100 ml or both) was found in about 65% of hypertensive patients with atherosclerosis as compared to 33% of hypertensive patients without atherosclerosis. The hyperlipidemia as revealed by lipoprotein electrophoresis of the sera was either due to type II or IV hyperlipoproteinemia according to the classification of Frederickson, Levy and Lees.94 The mean cholesterol and triglyceride levels were significantly higher in the

<table>
<thead>
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<th>Table 3</th>
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<tr>
<td>Summary of Mean Data in Hypertensives with and without a History of Myocardial Infarction</td>
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</table>

<table>
<thead>
<tr>
<th>Data</th>
<th>Patients</th>
<th>Age</th>
<th>Duration of hypertension</th>
<th>Syst. B.P.</th>
<th>Diast. B.P.</th>
<th>Chol.</th>
<th>Triglyc.</th>
<th>Fasting sugar</th>
<th>Uric acid</th>
<th>Renin</th>
<th>Female</th>
<th>Black race</th>
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<tr>
<td>Normotensive</td>
<td>25</td>
<td>53</td>
<td>--</td>
<td>132</td>
<td>78</td>
<td>251</td>
<td>114</td>
<td>79</td>
<td>6.1</td>
<td>2.4</td>
<td>56</td>
<td>20</td>
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<tr>
<td>Hypertensive</td>
<td>40</td>
<td>55</td>
<td>8.8</td>
<td>186</td>
<td>113</td>
<td>255</td>
<td>127</td>
<td>89</td>
<td>6.7</td>
<td>2.1</td>
<td>62</td>
<td>25</td>
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<tr>
<td>without M.I.</td>
<td>35</td>
<td>54</td>
<td>8.6</td>
<td>184</td>
<td>112</td>
<td>295</td>
<td>106</td>
<td>112</td>
<td>5.0</td>
<td>2.1</td>
<td>54</td>
<td>20</td>
</tr>
<tr>
<td>with M.I.</td>
<td>6</td>
<td>6.2</td>
<td>14</td>
<td>10</td>
<td>50</td>
<td>121</td>
<td>40</td>
<td>5.0</td>
<td>2.6</td>
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M.I. = Myocardial Infarction.

*Significantly higher than values of hypertensives without M.I. (P < 0.05).

<table>
<thead>
<tr>
<th>Table 4</th>
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<td>Percent of Hypertensives with Abnormal Blood Tests</td>
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<table>
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<tr>
<th>Data</th>
<th>Low renin &lt;0.75 ng/ ml/hr</th>
<th>High renin ng/ml/hr</th>
<th>Cholesterol &gt;100 mg/100 ml</th>
<th>Triglyceride &gt;150 mg/100 ml</th>
<th>Hyperlipoproteinemia &gt;100 mg/100 ml</th>
<th>Fasting sugar &gt;200 mg/100 ml</th>
<th>Uric acid &gt;8 mg/100 ml</th>
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</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td>25%</td>
<td>15%</td>
<td>33%</td>
<td>13%</td>
<td>18%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>without M.I.</td>
<td>20%</td>
<td>14%</td>
<td>65%</td>
<td>51%</td>
<td>23%</td>
<td>31%</td>
<td>11%</td>
</tr>
<tr>
<td>with M.I.</td>
<td>20%</td>
<td>14%</td>
<td>65%</td>
<td>51%</td>
<td>23%</td>
<td>31%</td>
<td>11%</td>
</tr>
</tbody>
</table>

M.I. = Myocardial Infarction.
hypertensives with atherosclerosis than without atherosclerosis. About 31% of the patients with atherosclerosis had hyperglycemia (fasting blood sugar greater than 110 mg/100 ml) as compared to 15% of the patients without atherosclerosis. The differences in mean blood sugar in the groups were statistically significant.

The serum uric acid was elevated to above 8 mg/100 ml in 31% of the patients with atherosclerosis as opposed to 10% of the patients without atherosclerosis. Complicating gouty arthritis occurred in five of 11 patients with hyperuricemia and atherosclerosis and in one of four patients with hyperuricemia without atherosclerosis.

The importance of coronary risk factors in coronary heart disease is supported by the current study. To what extent prior antihypertensive drug treatment influenced the results of the study is not known. The answer to this question would require a study with different drug regimens in an untreated hypertensive group as well as in a treated group.

V. Evaluation of Individual Antihypertensive Drugs in Atherosclerosis

At present there are no well-controlled studies on the effects of individual antihypertensive drugs on the course of hypertension and its complications. However, as mentioned above, the antihypertensive drugs have certain actions and side effects which potentially may influence the development of complicating atherosclerosis and coronary heart disease. These drug actions, which are discussed below, include aggravation of coronary risk factors, alterations in the metabolism of renin, catecholamines and sex hormones, and the induction of immunological disturbances.

Diuretics

A comprehensive review of the clinical pharmacology of the diuretics and other antihypertensive drugs has recently been presented by Page and Sidd. The diuretics, which include the thiazides and the mineralocorticoid antagonist, spironolactone, are among the most widely used drugs in the treatment of hypertension. They are usually used alone or in combination with other drugs since they have additive effects on the blood pressure and counteract the salt and water retention caused by other antihypertensive drugs. The manner in which the diuretics lower the blood pressure has not been established but it appears to be closely related to the effects of the compounds on sodium metabolism. The antihypertensive effects of the diuretics are associated with a reduction in body sodium and plasma volume which appear to cause secondary increases in plasma renin activity. Laragh et al. have suggested that the diuretic induced hyperreninemia is undesirable because of the potential vasculotoxic effect of renin. It is conceivable that renin and angiotensin could play a role in the pathogenesis of atherosclerosis since these agents, as discussed above, are capable of influencing the permeability and metabolism of the arterial wall.

Some of the mechanisms involved in the hyperreninemia caused by the diuretics have been investigated by our laboratory. In Table 5, the effects of chlorothiazide and spironolactone on plasma renin activity and catecholamine excretion are compared.

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Table 5

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Blood pressure (mm Hg)</th>
<th>Plasma renin (ng/ml/hr)</th>
<th>Urinary Epinephrine (µg/100 mg creatinine)</th>
<th>Plasma volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8</td>
<td>187/114 ± 10/16</td>
<td>2.1 ± 1.4</td>
<td>4.5 ± 1.3</td>
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<tr>
<td>Clorothiazide (1 gm/day)</td>
<td>8</td>
<td>182/102 ± 8/5</td>
<td>7.4 ± 1.9</td>
<td>7.7 ± 2.2</td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
<td>186/113 ± 10/5</td>
<td>2.0 ± 1.3</td>
<td>4.2 ± 1.1</td>
</tr>
<tr>
<td>Spironolactone (100 mg/day)</td>
<td>8</td>
<td>164/100 ± 8/6</td>
<td>7.7 ± 2.0</td>
<td>7.5 ± 2.0</td>
</tr>
<tr>
<td>Control</td>
<td>5</td>
<td>181/111 ± 7/4</td>
<td>2.2 ± 0.9</td>
<td>4.4 ± 1.2</td>
</tr>
<tr>
<td>Low sodium diet (10 mEq/day)</td>
<td>5</td>
<td>165/102 ± 6/4</td>
<td>8.2 ± 2.1</td>
<td>7.9 ± 1.8</td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td>174/104 ± 5/4</td>
<td>2.6 ± 1.2</td>
<td>4.7 ± 1.1</td>
</tr>
<tr>
<td>High sodium diet (250 mEq/day)</td>
<td>4</td>
<td>179/109 ± 5/4</td>
<td>0.7 ± 0.2</td>
<td>3.3 ± 0.8</td>
</tr>
</tbody>
</table>

Values represent the mean and standard deviation.
with those of a low and high dietary sodium intake in patients with essential hypertension. Plasma renin activity and urinary catecholamine excretion were determined in the supine and upright positions before and after treatment with chlorothiazide (1 gm/day) or spironolactone (100 mg/day) for 21 days. Measurements were made during a 120 mEq sodium and 40 mEq potassium diet. After resting in the supine position for three hours, the patient assumed the upright position for an additional three hours. During these periods urine was collected and analyzed for norepinephrine, metabolites and creatinine by methods previously described.49 At the end of each period plasma renin activity and plasma volume also were measured. The effects of a 10 mEq and a 250 mEq sodium diet given each day for a period of seven days were studied similarly.

During chlorothiazide or spironolactone treatment plasma renin activity and catecholamine excretion increased significantly both in the recumbent and upright positions in association with a decrease in plasma volume and blood pressure (table 5). A low sodium diet produced similar changes in these measurements. On the other hand a diet high in sodium suppressed both catecholamine excretion and plasma renin activity and slightly increased plasma volume and blood pressure. These results support the view that the changes in catecholamine excretion and renin caused by diuretics as well as a low sodium diet are physiological and represent a homeostatic response to a decrease in plasma volume and body sodium. Although a high dietary sodium intake reduced renin activity and catecholamine excretion, the results do not permit the conclusion that a high sodium diet is preferable to a low sodium diet in the treatment of hypertension. It is well established that diets high in sodium may aggravate hypertensive cardiovascular disease while diets low in sodium may be beneficial.

The stimulation of catecholamine release by diuretics can have an undesirable effect in patients with pheochromocytoma. As shown in figure 3, furosemide given intravenously to a patient with proven pheochromocytoma caused a precipitous rise in blood pressure which was preceded by a marked diuresis, a fall in blood pressure and an increase in plasma norepinephrine from 10.9 to 23.3 ng/L. The increase in blood pressure responded promptly to the alpha adrenergic blocker, phentolamine. Thereafter the blood pressure became stabilized following rehydration of the patient. Similar results were obtained in a repeated study.

![Figure 3](image-url)

**Figure 3**

Effect of diuretic treatment (furosemide) on the blood pressure and plasma norepinephrine levels in a patient with pheochromocytoma.
Certain coronary risk factors can be influenced by the diuretics. Hyperglycemia, hyperuricemia and gouty arthritis are well known side effects of the thiazide diuretics. In an occasional patient, the hyperglycemia precipitated by thiazide treatment has been observed to be accompanied by hyperlipidemia and hyper-prebetalipoproteinemia. These observations are not unexpected in view of the frequent association of hypertriglyceridemia and type IV hyperlipoproteinemia with uncontrolled hyperglycemia and diabetes. Hypokalemia is a frequent side effect of thiazide treatment. It is usually asymptomatic but can precipitate serious cardiac arrhythmia in patients receiving digitals.

Gynecomastia is an occasional side effect of spironolactone treatment. Its cause has not been established but it potentially might influence the course of the hypertension. A recent study in man suggests that gynecomastia may be related to an increase in estrogenic activity and a decrease in testosterone activity caused by the drug. Experimental studies have shown that sex hormones can exert profound effects on vessel wall morphology and metabolism. Treatment with estrogen has been found to suppress the marked morphological changes and accelerated accumulation of connective tissue proteins in the aorta of male hypertensive rats. In contrast, androgen treatment appears to accelerate the accumulation of connective tissue in the aortic wall. In addition to direct vascular effects, sex hormones also may have indirect effects on vessel wall structure and function, since they have been reported to be capable of influencing blood coagulation and the risk of thrombosis.

**Propranolol**

Propranolol, a beta adrenergic blocking agent, has important antihypertensive properties in addition to antianginal and antiarrhythmic actions. Its hypotensive effect is associated with a decrease in cardiac output caused by blocking of the cardiac beta adrenergic receptors. Recently propranolol has been reported to be uniformly effective in reducing blood pressure in hypertensive patients with high renin activity and ineffective in patients with low renin activity. When used with a diuretic or a diuretic plus hydralazine, propranolol has added effects on the blood pressure and appears to inhibit the reflex stimulations of sympathetic nerves caused by these other drugs. Propranolol also appears to counteract the stimulatory effects of diuretics and hydralazine on renin secretion as indicated by the data presented in table 6. In this study propranolol given alone produced about a 70% reduction in plasma renin activity whereas chlorothiazide or hydralazine alone increased plasma renin activity about 220% and 110% above control values respectively. When propranolol was given in combination with either one of these drugs, it partially inhibited the rise in plasma renin activity caused by these drugs. In addition, the combined drug treatment produced a greater fall in blood pressure than was observed with the individual drugs. These observations support the view that the renin release caused by the diuretics and hydralazine is mediated

### Table 6

*The Effect of Propranolol on Renin Stimulation by Chlorothiazide and Hydralazine*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Chlorothiazide</th>
<th>Placebo</th>
<th>Propranolol</th>
<th>Propranolol + Chlorothiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure (mm Hg)</strong></td>
<td>185/115 ± 14/11</td>
<td>167/102 ± 12/9</td>
<td>182/113 ± 13/10</td>
<td>173/105 ± 11/19</td>
<td>160/95 ± 10/9</td>
</tr>
<tr>
<td><strong>Pulse rate (beats/min)</strong></td>
<td>72 ± 4</td>
<td>80 ± 5</td>
<td>74 ± 4</td>
<td>62 ± 3</td>
<td>65 ± 3</td>
</tr>
<tr>
<td><strong>Plasma renin (ng/ml/hr)</strong></td>
<td>2.4 ± 1.2</td>
<td>8.7 ± 1.9</td>
<td>2.4 ± 1.1</td>
<td>0.7 ± 0.2</td>
<td>3.7 ± 1.1</td>
</tr>
<tr>
<td><strong>Blood pressure (mm Hg)</strong></td>
<td>187/116 ± 15/12</td>
<td>168/102 ± 10/5</td>
<td>184/112 ± 15/11</td>
<td>175/105 ± 12/9</td>
<td>155/92 ± 9/7</td>
</tr>
<tr>
<td><strong>Pulse rate (beats/min)</strong></td>
<td>74 ± 4</td>
<td>96 ± 7</td>
<td>73 ± 4</td>
<td>62 ± 3</td>
<td>70 ± 4</td>
</tr>
<tr>
<td><strong>Plasma renin (ng/ml/hr)</strong></td>
<td>2.3 ± 1.0</td>
<td>4.8 ± 1.3</td>
<td>2.3 ± 1.0</td>
<td>0.7 ± 0.2</td>
<td>2.9 ± 1.2</td>
</tr>
</tbody>
</table>

Values represent the mean and standard deviation of ten studies.

Each treatment period with placebo, chlorothiazide (1 gm/day) and/or propranolol (240 mg/day) lasted one week, at the end of which time plasma renin activity was measured under controlled conditions as described in the text. Hydralazine (20 mg) was injected intravenously and twenty minutes later a peripheral blood sample was drawn for a renin assay.
in part via beta adrenergic receptors and that the inhibition of renin secretion as well as beta adrenergic blockade by propranolol might account for its additive effects on the blood pressure. It is noteworthy that propranolol administration also has been reported to suppress the plasma renin response to sodium depletion and the upright position.59

Because propranolol also has antianginal and antiarrhythmic properties it is one of the drugs of choice in the management of hypertensive patients with complicating angina pectoris. However the drug is generally used in combination with a diuretic because propranolol, especially when given alone, may precipitate congestive heart failure by diminishing myocardial contractility. The antianginal effects of propranolol appear to be due to blockade of the cardiac beta adrenergic receptors and resulting decrease in myocardial oxygen requirements. The actions of the drug which reduce myocardial oxygen demand include reductions of heart rate, myocardial contractility and intramyocardial systolic tension resulting from a lower arterial pressure.111 In patients with a history of asthma or chronic lung disease, propranolol may precipitate or aggravate bronchial spasm.

Hydralazine

Hydralazine is a moderately potent antihypertensive drug which lowers the blood pressure by having a direct relaxing action on arteriolar smooth muscle. The vasodilatation caused by the drug appears to reflexively stimulate the sympathetic nervous system to increase heart rate and cardiac output. The latter actions of hydralazine increase myocardial oxygen requirements and thereby may precipitate or aggravate angina pectoris and coronary insufficiency in patients with coronary artery disease.59 Combined use of hydralazine with drugs which diminish sympathetic neural activity like reserpine, propranolol and guanethidine may prevent or reduce myocardial stimulation of the drug and enhance its antihypertensive effectiveness. Hydralazine is a strong stimulator of renin secretion especially in patients with renal hypertension.112, 113 As discussed above, this effect appears to be mediated in part through beta adrenergic receptors since it is suppressed by propranolol. Long-term administration of hydralazine, especially in doses of more than 200 mg/day, can produce immunological disturbances which include circulatory antinuclear antibodies, positive L.E.-cell tests and a syndrome resembling lupus erythematosus. These side effects are reversible but undesirable in view of the experimental evidence that immunological factors may play a role in the pathogenesis of atherosclerosis.114, 115 It is noteworthy that Perry has reported that those patients who develop hydralazine toxicity may live longer and have a lower blood pressure than a similar treated hypertensive group without hydralazine toxicity.116

Reserpine

Reserpine is a mild antihypertensive agent, which causes a gradual reduction of blood pressure and peripheral vascular resistance as a result of depleting the sympathetic nerve endings of catecholamines. Reserpine also has a serotonin depleting action which conceivably might influence the course of hypertensive vascular disease since serotonin as well as the catecholamines has been implicated in platelet aggregation and vascular injury.21, 51 The compound is frequently used in combination with a diuretic and/or hydralazine in the treatment of moderate to severe hypertension because it has additive effects on the blood pressure and counteracts the reflex sympathetic stimulation caused by these other drugs. Reserpine has a sedative and bradycrotic effect in addition to a hypotensive action. These actions likely operate to reduce the oxygen requirements of the heart muscle and thereby may account for the usefulness of reserpine in the management of hypertensive patients with coronary heart disease and angina pectoris.117, 118 The variety of side effects produced by reserpine appear to result from its pharmacological properties with the major side effect being mental depression.

Alpha Methyl Dopa

Alpha methyl dopa is a potent antihypertensive drug that causes a fall in blood pressure by decreasing peripheral vascular resistance. It appears that the drug acts by displacing norepinephrine in the sympathetic nerve endings with alpha-methyl norepinephrine, a so-called “false neurotransmitter” that fails to increase peripheral vasoconstriction. Methyldopa also decreases plasma renin activity.80 The compound is usually used in combination with a diuretic and is effective in the treatment of moderate and severe hypertension. Methyldopa may augment the antihypertensive effect of diuretics by counteracting the secondary stimulatory effects of the diuretics on the release of catecholamine and renin. The action of methyldopa is relatively rapid and smooth. A postural fall in blood pressure commonly occurs but this is usually
asymptomatic. The drug causes a number of reactions that may have an immunological basis. These include a positive direct Coomb's test, hemolytic anemia and positive tests for lupus and rheumatoid factor. The possible role of immunological factors in atherosclerosis has been mentioned above.

**Guanethidine**

Guanethidine is a powerful antihypertensive agent which like reserpine and methyldopa blocks chemical neurotransmission at the sympathetic nerve endings. Decrease in blood pressure results from a decrease in cardiac output as well as some reduction in peripheral resistance. The compound is usually reserved for the treatment of severe hypertension in combination with a diuretic. The effect of guanethidine on the blood pressure is mainly postural, although blood pressure shows some reduction in the supine position. Overdosage of the drug may result in severe orthostatic hypotension which can precipitate coronary insufficiency probably by reducing perfusion pressure and coronary blood flow.

**Conclusions**

There is substantial clinical and experimental evidence that atherosclerosis is accelerated and aggravated by hypertension. This effect of hypertension appears to be due largely to the physical stress placed on the arterial wall by a high level of arterial pressure. It also appears to be preventable by controlling the blood pressures. However, the vascular effects of hypertension, especially the connective tissue changes in the arteries, may not be reversible by lowering of the blood pressure alone.

Hypertension also has a mechanical effect on the heart which results in an increase in the work load and oxygen requirements of the myocardium. These effects may precipitate or aggravate coronary insufficiency as well as lead to cardiac hypertrophy and congestive heart failure. Reduction of blood pressure may prevent these complications by improving cardiac performance and the adequacy of the coronary circulation relative to demand.

The role of the renin-angiotensin system, catecholamines, prostaglandins and other humoral factors in the pathogenesis of hypertensive cardiovascular disease and complicating atherosclerosis may be important but, as yet, has not been established.

It has been clearly shown that antihypertensive treatment will prevent many of the cardiovascular complications of hypertension. These include stroke, congestive heart failure, acceleration of hypertension, progressive renal damage and dissecting aneurism. The major complication of hypertension remains coronary artery disease, the prevention of which likely requires early diagnosis and treatment including the control of other risk factors such as plasma lipids, weight and smoking.

Antihypertensive treatment is also indicated in hypertensive patients with overt coronary heart disease especially since control of the blood pressure has been found to improve the prognosis in these patients.

The antihypertensive drugs have different mechanisms of actions and side effects which potentially could influence the course of hypertension and complicating atherosclerosis. These different drug effects include aggravation of coronary risk factors, alterations in the metabolism of renin, catecholamines and sex hormones, induction of immunological disturbances and changes of behavioral patterns. However, there is no evidence at the present time that the atherosclerotic complications of hypertension can be influenced by different drug regimens.

Certain antiproliferative and anti-inflammatory agents that have a specific inhibitory effect on the atherosclerotic process and its complications are currently being investigated in experimental atherosclerosis and hypertensive vascular disease. It is conceivable that some of these agents might prove to be useful in the management of these diseases.

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