Hypertension and Atherosclerosis

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IT APPEARS increasingly likely that no single agent will be identified as the sole cause of atherosclerosis. However, of the various known contributing factors which may influence the course of the disease, hypertension appears to be the most important. Despite the present emphasis on disorders of lipid metabolism the fact remains that neither hypercholesterolemia nor hypertriglyceridemia is essential for the development of atherosclerosis. In the presence of hypertension and "normal" concentrations of lipids in the blood, however, such lesions will develop over an appropriate length of time.

The failure to place sufficient emphasis on hypertension in research on atherosclerosis is especially surprising in view of our present ability to control the level of blood pressure with antihypertensive agents. The intriguing possibility that the acceleration of atherosclerosis associated with hypertension can be reduced by antihypertensive treatment at the appropriate time has been little explored either experimentally or clinically.

The purpose of this review is to re-emphasize the relationship between hypertension and atherosclerosis and to indicate the possibilities of therapeutic modification. For purposes of clarity it will first be necessary to define the relationship between the two disorders.

Although hypertension and atherosclerosis usually are interrelated it should be clearly understood that they are distinct diseases [*1*]. Atherosclerosis affects large- and medium-sized arteries. Its pathologic hallmark is the subintimal lipid-containing plaque developing over a medial lesion of unknown cause. The anatomic consequences of hypertension involve the arterioles primarily. The known mechanisms for production of experimental hypertension in animals (renal arterial constriction, section of the baroreceptor nerves) are quite different from the dietary methods used for producing experimental "atherosclerosis." Typically these methods are specific for each kind of lesion. In man hypertension can exist independently of atherosclerosis and vice versa. This deviation is most often seen in the economically underdeveloped countries in which atherosclerosis, especially of the coronary arteries, is minimal despite a high prevalence and mortality from hypertensive disease [*2,3*]. Hypertensive persons in these countries are more likely to have hypertensive complications such as cerebrovascular hemorrhage, malignant hypertension, uremia and dissecting aneurysm as opposed to coronary artery disease which is the most common cause of death in the hypertensive population in this country. Population studies do show however that atherosclerosis is universal in man, groups differing mainly in the extent of lipid infiltration of these lesions.

Despite their pathogenetic distinctness there is a close relationship between the two diseases [*4*]. Whatever the ultimate cause of atherosclerosis may be, there is no question that hypertension makes it worse. This conclusion is supported by an impressive collection of clinical and experimental data.

In the rabbit Heptinstall, Barkley and Porter [*5*] showed that high blood pressure increased the amount of cholesterol-induced atheroma. The correlation between the level of blood pressure and the degree of atheroma formation was much greater than that between the level of serum cholesterol and extent of atherogenesis. In rabbits with bilateral lumbar sympathectomy fed cholesterol more severe atherosclerosis of the lumbar aorta and iliac arteries developed. When Snyder and Campbell [*6*] produced an experimental constriction

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of the abdominal aorta sufficient to cause a sharp pressure drop distal to the narrow segment in sympathectomized rabbits, severe atherosclerosis developed in the aorta above but not below the constriction. In thyroidectomized dogs fed cholesterol Sako [7] found that experimental coarctation of the aorta resulted in a limitation of atherosclerotic lesions to the proximal vascular tree, including the coronary arteries. This occurred only when the degree of constriction was such as to produce a pulse pressure above the coarctation that was 30 mm. Hg or higher than that below. These are crucial experiments because they demonstrate in the same animal a predisposition for atheroma to develop selectively in the areas of elevated blood pressure. Similar effects of coarctation on atherogenesis have been observed repeatedly in man. For example, I have seen the aorta of a thirty-two year old man with severe hypertension in the brachial but not the femoral arteries in whom autopsy disclosed extensive early plaque formation above the coarctation whereas the abdominal aorta was completely free of such lesions.

A similar effect has been noted after correction of occlusive lesions at the aortic bifurcation [8]. Following surgical intervention atherosclerosis progresses in the arteries of the lower extremities which were previously much less involved. This progression occurs in older patients at a much faster pace than in younger patients with similar blood pressures and concentrations of lipids. These findings suggest the presence of an additional "tissue factor" associated with aging in the pathogenesis of the lesions.

The importance of the level of blood pressure in localization of the atherosclerosis is indicated by still other observations. In man in the erect position the arterial pressure is higher in the dependent parts of the body. Atherosclerosis tends to be more severe in these areas of higher pressure, in the abdominal aorta as opposed to the thoracic aorta, and in the lower extremities as opposed to the upper extremities. The veins are usually free of sclerotic lesions even though after fatty meals the mesenteric veins contain the highest levels of lipids including cholesterol. However, when venous pressure is chronically elevated, as in varicosities, arteriovenous fistulas of long duration, in the portal vein of patients with portal hypertension and in the hepatic veins of patients with prolonged periods of high venous pressure, phlebosclerosis is common [9]. Whether these lesions are pathogenetically similar to atherosclerosis is debatable but the analogy is obvious.

Burch and Phillips [9] have stressed that atherosclerosis is not a generalized process but tends to be localized. Blood which has the same concentration of lipids flows through all the vessels of the body and yet atherosclerosis is regionally different in extent, tending to be most severe in regions of highest pressure, such as in the lower aorta, at sites of bifurcation, at the outer circumference of the aortic arch and in areas proximal to the points of sudden narrowing such as coarctation. This does not imply that for any given level of blood pressure alterations in lipid metabolism are not important, but rather that the localizing factors appear to have the greatest influence, and of the latter hypertension is the best defined.

The pulmonary arterial system normally is perfused with a pressure much lower than that in the systemic arterial system. This low pressure system area is remarkably free of atherosclerosis as compared to the higher pressure systemic circulation unless chronic pulmonary hypertension develops. Rosenthal and O'Neal [10] induced chronic pulmonary hypertension sufficient to produce right ventricular hypertrophy in the rabbit by the intravenous injection of plastic beads. Feeding these rabbits cholesterol resulted in a considerably greater increase in pulmonary artery atherosclerosis than in the control group fed cholesterol. A similar excess of atheroma in the pulmonary arteries has been found in patients with long-standing and severe pulmonary hypertension associated with congenital heart disease [11].

Deming and his associates [12] produced hypercholesterolemia and atheromatosis in the rat by feeding cholesterol, cholic acid and thiouracil. If the animals were first made hypertensive the atherosclerosis developed more rapidly, was more severe and sometimes led to sufficient atherosclerosis to produce myocardial infarction. When the blood pressure was controlled by antihypertensive agents much less atherosclerosis developed in such treated rats than in untreated rats [13]. This observation has great significance for the prevention of accelerated atherosclerosis in patients with hypertension, a question which will be discussed in more detail. In a later experiment Daly, Deming and their associates [14] produced hypertension in one member of a parabiotic

pair of rats. Some of the parabiotic pairs were fed a normal diet whereas others received the atherogenic diet. After 14 weeks the atherogenic diet alone failed to increase the concentration of cholesterol in the aorta of the normotensive member of the pair despite serum cholesterol values above 1,000 mg. per cent. However, in the hypertensive partner the cholesterol content of the aorta was increased in both the group fed the atherogenic diet and in those given the normal diet even though the serum cholesterol levels were not elevated in the latter.

The time factor may be important in these experiments. Sako [*7*] found in dogs with experimental coarctation of the aorta that proximal localization of atherosclerosis in hypercholesterolemic animals was most evident at six months, but that lesions were widespread both above and below the coarctation after eighteen to twenty-four months. Sako's observations suggest that the most important effect of hypertension is to increase the rate of development of atherosclerosis in animals fed an atherogenic diet. A similar influence of blood pressure on the rate of atherogenesis is also found in man [*15*].

The mechanism by which hypertension accelerates the development of atherosclerosis is unknown. Several possibilities have been suggested. One theory proposes that serum lipids, including cholesterol, are carried into the vessel wall by ultrafiltration through the arterial intima [*16*]. Because filtration pressure is increased in hypertension the equilibrium across the intimal surface will be changed to favor greater deposition of lipid. This simple concept finds some support in the *in vitro* experiments of Wilens [*16*] who showed that the amount of lipids collected in the wall of excised iliac artery during perfusion with serum was proportional to the perfusion pressure.

There is more experimental support for another possible explanation, namely, that hypertension changes the arterial wall in some way so as to make it a more favorable substrate for the development of atherosclerosis. Thus, Hollander et al. [*17*] found that experimental coarctation of the aorta led to an increase in mucopolysaccharides in the wall of the aorta proximal to the lesion prior to the accumulation of lipids. Fisher and Geller [*18*] found that aortic strips from the hypertensive rabbit exhibited an elevated metabolic rate as evidenced by an increase in oxygen consumption *in vitro*. In their hypertensive rats Daly, Deming et al. [*14*] found no alteration in absorption or excretion of cholesterol but rather that there was an increase in the rate of synthesis of cholesterol from radioactive labelled acetate. This was evident even in pieces of hypertensive aorta incubated *in vitro,* the average increase being about twentyfold as compared to the normal aorta. Experiments with labelled cholesterol in the intact animal suggested that the increased cholesterol in the aorta of the hypertensive animal could not be accounted for on the basis of filtration from the plasma but rather indicated increased synthesis in the aortic wall. If these results are applicable to hypertensive man they have considerable therapeutic import since they indicate that hypertension changes the conditions locally in the aortic wall so that the local synthesis of cholesterol is increased. If this is true it may be that reduction of blood pressure must be obtained early in the course of hypertension before local damage has occurred.

In man, an association between hypertension and atherosclerosis was noted by pathologic observation over thirty years ago [*4*]. In the coronary arteries Lober [*19*] found that the degree of coronary sclerosis increased progressively with age from early childhood through the seventh decade and was consistently more severe in male than in female subjects. The degree of coronary atherosclerosis was much greater in hearts with evidence of hypertension than in nonhypertensive hearts from persons of the same age and sex. Burch and De Pasquale [*20*] emphasized an important "experiment" of Nature which occurs in patients with anomalous origin of the left coronary artery. In this condition the left coronary artery originates from the pulmonary artery whereas the right originates from the aorta. Thus, the blood pressure in the right coronary artery is considerably higher than in the left. Postmortem examination of patients surviving to adult life disclosed minimal atherosclerosis of the anomalous left coronary artery and marked atherosclerosis of the right coronary artery, the degree of changes depending on the age of the patient at the time of death.

In investigating the effects of body weight on prevalence rates of coronary atherosclerotic heart disease, Spain, Nathan and Gellis [*21*] observed that when hypertension and diabetes mellitus were excluded overweight was not associated with a higher incidence of coronary

disease. However, patients with hypertension or diabetes had more coronary atherosclerosis regardless of body weight.

The vast collection of data gathered in 1959 for the Society of Actuaries by Lew [*22*] on four million lives and 102,000 deaths of incurable persons led to the conclusion that life expectancy of both sexes at all ages varies inversely with blood pressure, either systolic or diastolic. A number of prospective studies have confirmed the relationship between hypertension and coronary artery disease. Yater and his associates [*23*] in a follow-up study of World War II veterans observed a close correlation between hypertension and the subsequent development of coronary heart disease. Dawber and Kannel [*24*] at Framingham demonstrated a correlation between blood pressure and subsequent development of coronary artery disease which was evident at all levels of blood pressure down to the subaverage. Kannel et al. [*25*] concluded that blood pressure and serum cholesterol were independently related to the development of coronary artery disease. The combined experience from various population studies in this country [*26*] indicates that the risk of developing coronary artery disease is approximately doubled when either the serum cholesterol or blood pressure levels are elevated.

This raises the question whether a reduction in elevated blood pressure levels to normal will reduce the risk of subsequent coronary artery disease. The therapeutic trials that have been carried out in hypertension have been devoted almost entirely to the evaluation of long-term drug therapy on morbidity and mortality in severe hypertension. The value of antihypertensive drug therapy in malignant hypertension has been demonstrated in numerous studies [*27–32*]. More recently, well controlled prospective studies have shown that treatment of moderately severe to severe essential hypertension results in a marked decrease in morbidity. In a prospective, randomized control study Wolff and Lindeman [*33*] found that the incidence of morbid events in treated patients was one third of that observed in the control group. In a prospective study by Hamilton [*34*] of hypertensive patients with diastolic pressures of 110 mm. Hg or higher the incidence of complications in the untreated patients was over three times higher than in the treated group.

The largest prospective, randomized double-blind study was carried out by the Veterans Administration Cooperative Study on Antihypertensive Agents [*35*]. Approximately half of these patients received antihypertensive therapy which effectively controlled blood pressure whereas the other half received only symptomatic therapy. Within the first three years of follow-up it became apparent that in the placebo-treated control patients whose prerandomization diastolic blood pressures averaged 115 to 130 mm. Hg (the cut-off point) serious complications were developing at an accelerated rate. The ratio of pathologic events was fourteen times higher in the control group than in the treated group. This carefully controlled trial provides convincing evidence of the value of treatment in patients with greater than mild elevations of diastolic blood pressure.

In reviewing the details of these studies it becomes apparent that the complications prevented were primarily accelerated hypertension, cerebrovascular accidents, dissecting aneurysm and congestive heart failure. It seemed that untreated patients, particularly male patients, whose diastolic blood pressures are in excess of 114 mm. Hg are a particularly high-risk group for the rapid development of "hypertensive" as opposed to atherosclerotic complications. Thus, in the Veterans Administration study only three of the twenty-nine complicating events were due to myocardial infarction. In the series of Wolf and Lindeman there were only two cases of "sudden death," both in the treated group, and two of angina in the placebo-treated control group. The majority of the complications in Hamilton's series were strokes, a type of complication which may not definitely be ascribed to atherosclerosis. Of twenty-one complicating events only three were due to coronary thrombosis and one of these occurred in an actively-treated patient. From these therapeutic trials in more severe grades of essential hypertension, it is not possible to determine whether a reduction in blood pressure has a beneficial effect on the development of coronary artery disease, the most important complication of atherosclerosis. Perhaps data on this subject will be forthcoming from the ongoing trial of the Veterans Administration involving hypertensive patients whose initial diastolic pressures are between 90 and 115 mm. Hg. It is of interest that atherosclero-

tic complications are relatively more prevalent in this group than in patients with higher levels of blood pressure. As yet (approximately four years of follow-up) no highly significant difference in morbidity has developed between the treated and placebo-treated control groups. However, since atherosclerosis is a slowly developing process it may take more time for a difference to appear.

It is possible that hypertension, if present for a specified length of time, produces irreversible damage in the arterial walls, thereby making them susceptible to the continued accelerated development of atherosclerosis even after the blood pressure has been reduced. A changing pattern of hypertensive complications has been noted in recent years. Prior to effective antihypertensive therapy the most common causes of death were congestive heart failure, cerebral hemorrhage and uremia. In the modern treatment era Hodge and Smirk [*36*] have found that coronary artery disease including "sudden death" accounted for approximately half of the mortality. Congestive heart failure has become an uncommon cause of death in hypertensive patients treated with antihypertensive agents. Smirk's experience is consistent with mine. It appears likely that hypertensive patients saved from an earlier death due to hypertensive complications may subsequently fall victim to coronary artery disease. It is not possible to make any definitive conclusions as to whether antihypertensive therapy will delay the accelerated development of atherosclerosis in patients with well established hypertension. The results of sufficiently long-term controlled trials are not available at this time to provide a basis for a sound decision.

Pathologic studies have demonstrated that hypertension produces extensive changes in the walls of the aorta and large arteries. These vessels become dilated, their elastic laminas become fragmented and collagenous tissue increases. As a result of these changes the compliance of the arterial walls is reduced. These structural changes are similar to those associated with aging in normotensive subjects who are also susceptible to the development of atherosclerosis. The primary difference in the hypertensive subject is that the lesions occur in exaggerated form and at an earlier age. In hypertension there are also pathologic changes in the arterioles of the adventitia which may further aggravate structural abnormalities in the arterial wall. None of these structural changes are reversed by treatment with antihypertensive agents. Once they have occurred the arteries may remain more susceptible to atheroma formation even after the blood pressure has been reduced.

These considerations are admittedly speculative. However, they seem to explain the facts as they are known at present. If true, and if accelerated atherosclerosis is to be prevented, the therapeutic implication would favor very early treatment of hypertension. Such a therapeutic program represents a mammoth undertaking which may not be feasible at this time or on the basis of current knowledge but trial studies are surely indicated.

If there is a strong family history of coronary disease, or if diabetes mellitus or hypercholesterolemia is present, treatment of mild hypertension appears more justified than if they are not.

In the meantime, further studies of the effects of antihypertensive treatment on atherogenesis are urgently needed. The only investigation in animals has been that of Deming [*13*] who began the administration of antihypertensive agents in rats one month after the induction of experimental hypertension. Further studies in a variety of species are required to confirm this observation. In addition, it should be determined whether reduction of blood pressure after longer periods of sustained hypertension will also have a protective effect on the subsequent development of experimental atherosclerosis.

A relationship between elevated blood pressure levels and an increased rate of atherogenesis has been definitely established. Hypertension is an important, if not the most important, of the known risk factors in coronary artery disease. Reduction of elevated blood pressure with presently available antihypertensive agents seems to be a reasonable approach to retarding the accelerated rate of atheroma formation. However, definitive proof of this hypothesis in man still is lacking. The available evidence suggests that in order to prevent atherosclerosis, control of the blood pressure must be accomplished early in the course of the hypertensive process.

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