Increasingly reliable estimates of the prevalence of coronary heart disease (CHD) emphasized the importance of this disease as contemporary health hazard. Cardiovascular disease is now the leading cause of death, with CHD accounting for two thirds of all deaths due to heart diseases. It has been estimated that well over half of all deaths annually, result from CHD, nearly three times the death rate from cancer, the second most prevalent disease. The basic lesion underlying coronary heart disease process is usually atherosclerosis which accounts for majority of such deaths (Tejada et al 1968).

Atherosclerosis is characterized by plaque-like thickening of intima and media of large and medium sized arteries; thickness being due to proliferating smooth muscle cells along with focal accumulation of lipids, blood products, complex carbohydrates and calcium deposits. (Yogamundi-Moem 1972). It is a complex process which may be regarded as a dynamic interaction amongst (a) the structural and metabolic properties of arterial wall (b) components of blood and (c) hemodynamic forces (Groen et al 1968). Multiple interrelated factors have been identified to influence the evolution of atherosclerosis. Factors such as hyperlipidemia, increased blood pressure and hormonal dysfunction may injure or disturb the structural or metabolic integrity of endothelium and can predispose to the formation of atherosclerosis (Ross and Glomset 1976). The characters of perturbing elements include (a) physical, such as area of high and low shear stress (b) biochemical, which includes
lipoproteins and insulin (c) endogenously derived vasoactive compounds; all influence the development of atherosclerosis (Sabbah et al 1986; Inkeles and Eisenberg 1981; Pyorala 1979; Davies 1986). Current evidence suggests that calcium may play a pathogenic role in atherosclerosis, since calcium ions may modulate a number of pathophysiological processes of initiation and development of atherosclerosis (Kramsch et al 1980; Henry 1985). Stress and sympathetic arousal also have been reported to potentiate the development of atherosclerosis (Manuck et al 1988). Furthermore, numerous circulating hormones and enzymes involved in the pathogenesis of hypertension such as vasopressin, catecholamine, angiotensin II and renin have been considered to be capable of altering arterial wall structure and metabolism (Constantinides and Robinson 1969; Robertson and Khairallah 1972). Hence, treatment of patients having hypertension plus CHD with antihypertensive agents is of importance. Different classes of antihypertensive agents have radically different effects upon these variables. Most of the prospective trials, conducted to evaluate the effect of pharmacologic reduction of mild to moderately elevated blood pressure on mortality and morbidity, have demonstrated a decline in hypertension related events such as stroke or congestive cardiac failure. In contrast, CHD has generally remained unaffected. In the Oslo study, the actively drug-treated group actually experienced a higher incidence of fatal and non-fatal coronary events than the control group (Leren and Helgeland 1986). It is proposed that metabolic disturbances in lipids, deterioration in glucose control or electrolyte imbalance due to drugs may somewhat offset the advantages from blood pressure
reduction. However, the control of hypertension and its attendant long-term complications remain a challenge to many clinicians and researchers. A number of antihypertensive drugs are now available but search continues for the ideal agent which can effectively control not only the blood pressure but also protect patients from development of coronary heart disease. Results from animal studies have been encouraging because, in addition to efficacious lowering of blood pressure, they appear to have potent antiatherogenic effects. In view of the above mentioned facts, the preliminary investigation was conducted in our laboratory, and different categories of antihypertensive agents were studied to evaluate their effects on plaque formation and other biochemical metabolites which may play an important role in the genesis of modern life threatening atherosclerosis.

In the present study, an attempt was made to measure serum lipids (total cholesterol, HDL cholesterol, phospholipid and triglyceride), serum calcium and blood glucose levels, as well as urinary level of ketogenic steroids and catecholamine metabolite (VMA), of diabetic and nondiabetic cholesterol-fed rabbits in order to determine any alterations in their levels (compared to control) following treatment with various antihypertensive agents and to correlate this effect with the development of atherosclerosis in normal and hyperglycemic conditions.
DIURETICS

These agents have been the cornerstone of antihypertensive drug-therapy. Following the use of diuretics as antihypertensive agents in patients with CHD, thiazide diuretics showed no reduction in ischemic heart disease inspite of lowering the blood pressure and also increased the incidence of coronary death in patients with hypertension and resting electrocardiographic abnormalities (MRFIT Research Group 1985). Data from clinical studies have shown that the diuretic treated hypertensive patients have 15% increase in coronary events as compared to the placebo group (Miall and Greenberg 1987) and a 24% increase in the incidence of fatal and non-fatal myocardial infarction as compared to the metoprolol-treated patients (Wikstrand et al 1991). In contrast to the above observations, the favourable effect of diuretic on coronary events has been reported by MacMahon et al (1986). They pointed out that pooled analysis of the studies performed with thiazide diuretic has not given any evidence that thiazide treatment increases the risk for coronary events; in fact, a modest 3-10%, beneficial effect on coronary events has been observed.

It has been debated whether negative effects on metabolic parameters and/or arrhythmias, due to electrolyte imbalance caused by diuretics could at least, in part, offset the possible benefit of blood pressure reduction on coronary artery disease. Perhaps the most significant metabolic effect of thiazide diuretics is their adverse influence on plasma lipid and lipoprotein levels. Several investigators have reported effects that include increase in the
levels of total blood cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides (Grimm et al 1981; Ames and Hill 1976). HDL cholesterol levels are minimally influenced by these agents. Weidmann et al (1983) have reported that diuretics have sustained adverse effect on serum cholesterol level, that continues as long as diuretics therapy continues. Potassium sparing diuretic such as spironolactone, however, does not influence the metabolic risk profile of the hypertensive patients (Jeunemaitre et al 1987). Carbohydrate metabolism was also adversely influenced by thiazides and to a lesser extent by loop diuretics, that includes deterioration in glucose control (O'Byrone and Feely 1990), while such effect was not observed with potassium sparing diuretics (Crane and Harris 1970). In the present study, diuretic agents such as hydrochlorothiazide, spironolactone and bumetanide administration to cholesterol-fed rabbits did not influence serum lipids (total cholesterol, HDL cholesterol, phospholipid and triglyceride) and serum glucose levels. The neutral effect of diuretics on serum lipid level, in the present study, may be explained on the basis that serum lipid levels are extremely high in treated animals and may mask any further elevation of serum lipid levels by these drugs.

Diuretics also induce electrolyte abnormalities and may increase the risk of sudden death in selected patients. According to Multiple Risk Factor Intervention Trial (1985) the failure to reduce cardiac mortality with adequate antihypertensive treatment is likely to be due to diuretic-induced electrolyte imbalance. Moreover, the calcium sparing properties of diuretics (Middler et al 1973), may also influence the cardiovascular disease, because many intracellular
and extracellular processes involved in the formation of atherosclerotic lesion requires calcium (Kramsch et al. 1980). However, there is evidence that in rabbits, calcium added to their saturated fat diet decreases the severity of atherosclerosis (Renand et al. 1983). The serum calcium level estimation in the present study indicates that diuretics (hydrochlorothiazide, spironolactone and bumetanide) administered to cholesterol-fed rabbits slightly although insignificantly increase the serum calcium level.

Although diuretics are known to adversely influence the CHD risk factors; in an experimental study Limas et al. (1984) found that short-term diuretic treatment of spontaneously hypertensive rats was effective in reversing aortic intimal changes, despite having little effect on blood pressure. In addition, a clinical study (Torrez et al. 1988) reported that diuretic therapy was devoid of any unfavourable effect on atherosclerotic vascular complication. In our study, of particular interest is the slight inhibitory effect of diuretics on the development of atherosclerotic lesion in cholesterol-fed rabbits. Aortic atherosclerotic plaque involvement was reduced in hydrochlorothiazide-treated rabbits by 12.8%, in spironolactone-treated rabbits by 9% and in bumetanide-treated rabbits by 3% following 10 weeks of study. Of course, the observed changes in the inhibition of atherosclerosis by diuretics do not reach the level of significance in this study. Diuretic drugs did not influence the tissue lipid deposition (e.g. in aorta, liver and adrenal gland) although a slight decrease in aortic cholesterol content was observed in hydrochlorothiazide treated rabbits. The urinary levels of
ketogenic steroids and catecholamine metabolite (VMA) were also not found to be modified following diuretic administration. According to our results, the apparently slight preventive effect of hydrochlorothiazide, spironolactone and to a lesser extent that of bumetanide on the development of atherosclerosis seems to be unrelated to their effect on serum lipids, glucose, catecholamines and ketogenic steroid levels as well as blood pressure, since these parameters were not modified following diuretic treatment. However, the slight increase in serum calcium level in hydrochlorothiazide and spironolactone-treated rabbits and its relation to inhibition of atherosclerosis remain to be defined.

CENTRALLY - ACTING ALPHA$_2$ - ADRENERGIC AGONISTS

Alpha$_2$-adrenergic agonists are known to decrease the blood pressure primarily through an action on the central nervous system leading to a decrease in sympathetic outflow. These drugs are devoid of significant adverse effects when administered to hypertensive patients. Although methyldopa was found to reduce HDL cholesterol levels and increase the ratio of total cholesterol to HDL cholesterol (Ames and Hill 1982), an overall significant reduction in LDL level and an increase in triglyceride levels was reported following methyldopa therapy (Dujovne et al 1984). Clonidine and guanabenz monotherapy have been reported to lower total cholesterol levels (Kirkendall et al 1978; Walker et al 1980). Furthermore, alpha$_2$ agonists cause no deterioration in diabetic controls during oral monotherapy (Ames and Hill 1982; Guthrie 1985). In the present
study, however, centrally-acting α₂ agonists such as clonidine and methyldopa administration to cholesterol-fed rabbits did not adversely influence the serum lipids (total cholesterol, HDL cholesterol, phospholipid and triglyceride) and glucose levels.

Alpha₂-adrenergic agonists have been reported to reduce the cardiovascular complications of hypertension. Doyle (1991) pointed out that methyldopa can generally reverse or prevent the cardiac hypertrophy, vascular proliferation and renal damage associated with experimental and clinical hypertension. Clonidine and methyldopa have also been reported to inhibit the development of hypertrophy of aorta in rat model of hypertension (Carlier and Rörive 1985). In present study, the effect of clonidine and methyldopa on the development of atherosclerotic lesion was investigated. Aortic atherosclerotic plaque involvement was slightly increased (15.1% as compared to control) in methyldopa-treated, whereas aortic atherosclerotic plaque involvement was unaffected in clonidine-treated cholesterol-fed rabbits following 10 weeks of study. However, the observed changes in the acceleration of atherosclerosis by methyldopa do not reach the level of significance in this study. Clonidine and methyldopa did not significantly influence the tissue lipid deposition (e.g. in aorta, liver and adrenal gland).

Clonidine therapy has been reported to lower serum cortisol level (Chiodera et al 1984), and, cortisol has been shown to potentiate diet-induced atherosclerosis in cynomolgus monkeys (Sprague et al 1980). In our study, the urinary levels of ketogenic steroids (indicators of serum cortisol level) were unaffected following clonidine and methyldopa treatment, indicating that this
parameter may not have a significant influence on development of atherosclerosis in clonidine and methyldopa treated cholesterol-fed rabbits. Clonidine and methyldopa are known to reduce serum catecholamines and renin concentration (Martin et al 1989; Gillespie et al 1962); higher serum catecholamine levels have been implicated in the development of arterial lesions both, directly and through influencing other pathogenic processes such as platelet aggregation and lipid metabolism (Halt 1974; Herd 1983). In the present study, urinary catecholamine metabolite levels (indicators of serum catecholamine levels) were found to be significantly lowered in both clonidine and methyldopa-treated rabbits, indicating that, reduction in catecholamine levels by these drugs may not have significant influence on the development of atherosclerosis in this model.

**ALPHA\textsubscript{1}–ADRENERGIC BLOCKERS**

By selectively blocking alpha\textsubscript{1}-adrenergic receptors in the vasculature, alpha\textsubscript{1}-adrenergic blockers lower the peripheral vascular resistance. They act as vasodilators to reduce blood pressure while maintaining normal cardiac output and renal blood flow (Lund-Johansen 1975 and 1986). In addition to blood pressure lowering effect, prazosin therapy has been reported to decrease total cholesterol, LDL cholesterol and triglyceride levels, as well as increase HDL cholesterol and HDL\textsubscript{2} subfraction levels (Leren 1987). Alpha\textsubscript{1} blockers also positively influence the carbohydrate metabolism. Swislocki et al (1989) has reported that, prazosin treatment to hypertensive patients, reduces the insulin resistance and
normalises the glucose tolerance. In our study, however, prazosin administration to cholesterol-fed rabbits did not influence the total cholesterol, HDL cholesterol, phospholipid and triglyceride levels. Blood glucose level also was not modified following prazosin administration.

In clinical study, Grimm and Hunninghake (1986) reported that prazosin and cholesterol lowering diet reduced the risk of coronary heart disease in hypertensive patients by 45% which is approximately two to three times greater than that have been reported with either a cholesterol lowering diet alone or diuretic therapy alone. In an experimental study, doxazosin an alpha-adrenergic inhibitor has been reported to decrease fatty streak formation in aortic arch of hyperlipidemic hamsters, similar to cholestyramine (Kowala et al 1981). The reduction in fatty streak was accompanied by 18% reduction in blood pressure and marked lowering of blood lipid level. Furthermore, in hypercholesterolemic rabbits treated with doxazosin, the area of fatty streak and aortic cholesterol ester content was reduced without any alteration in plasma lipid level (Swindel 1991). In the present study, we have found that prazosin is effective in preventing, although insignificantly the development of atherosclerotic lesions. Aortic atherosclerotic involvement was reduced by an average 18.1% in cholesterol-fed rabbits following 10 weeks of prazosin therapy. Aortic cholesterol content was also found to be slightly reduced. Following prazosin treatment to rabbits, the serum lipids (total cholesterol, HDL cholesterol, triglyceride and phospholipid), serum calcium, and blood glucose levels as well as blood pressure were
found to be unchanged in rabbits, indicating that the observed antiatherogenic effect of prazosin seems to be independent of its effect on these parameters. Since urinary ketogenic steroids and catecholamine metabolite (VMA) levels were found to be unchanged following prazosin treatment to rabbits, it also indicates that, the observed antiatherogenic effect of prazosin seems to be independent of its effect on these parameters.

The exact mechanism underlying the effect of prazosin on the development of atherosclerosis is yet not clear. It must be remembered that, the increased serum lipid levels is not the sole factor responsible for development of atherosclerosis. Atherosclerotic lesion is generally observed at sites facing abnormal blood flow, such as bifurcation (aortic branches) and aortic arches, which may be influenced by mechanical factors such as turbulence and pressure (Ku et al 1985; Dustan 1974). However, whether the possible direct effect of prazosin on vascular wall or its positive hemodynamic effect (Lund-Johansen 1986), or its favourable influence on carbohydrate metabolism (Hollenbeck et al 1984) and lipid profile (Swislocki 1989) play any positive role on slowing down the progress of atherosclerosis remains to be defined.

BETA-ADRENERGIC BLOCKERS

Beta-adrenergic blockers are competitive inhibitors of catecholamine binding at beta receptor sites. They considerably diminish or eliminate the influence of sympathetic nervous system on various tissues. These agents adversely influence the lipid profile.
They usually have little effect on serum total cholesterol level but their major effect is to reduce level of HDL cholesterol (particularly HDL₂ - cholesterol fraction) and to increase the plasma triglyceride levels. (Day et al 1984; Krone et al 1988). The adverse effect on lipids and lipoproteins are less with cardioselective beta₁ blockers (Day et al 1982) and beta blockers with both alpha and beta blocking properties (Pagnan et al 1979). However, a selective beta₁ blocker atenolol administration to cholesterol-fed diabetic and nondiabetic rabbits did not significantly influence the serum total cholesterol, HDL cholesterol, phospholipid and triglyceride levels in the present study. Beta-adrenergic blockers also aggravate diabetes by a direct action on the islets i.e. by decreasing the insulin secretion. Waal-Manning (1976) reported that, with a changeover from nonselective to a selective beta blocker therapy, an improvement in carbohydrate tolerance and insulin secretion has been reported in patients with impaired glucose tolerance. In our study, however, blood glucose level in diabetic and nondiabetic cholesterol-fed rabbits was not altered following atenolol treatment.

Beta blockers such as propranolol and metoprolol have been reported to lower the incidence of coronary and cerebrovascular complications in hypertensive patients as well as in patients surviving myocardial infarction (Hjalmarson et al 1981; Olsson et al 1985). It has been proposed that, the favourable influence on atherosclerosis might have contributed to the reduction in incidence of vascular complications. The antiatherogenic effect of beta blockers has been reported in several experimental studies. Kaplan et al (1987) reported that atherosclerosis induced by psychosocial stress
in moderately hypercholesterolemic monkey is inhibited following propranolol treatment. Also progression of atherosclerosis in hypercholesterolemic rabbits was found to be significantly inhibited following propranolol and metoprolol treatment (Chobanian et al 1985; Oslund-Lindqvist et al 1988). In the present study, we have found that atenolol inhibits, although insignificantly, the development of atherosclerosis. Aortic atherosclerotic plaque involvement was reduced by an average 25% in diabetic and 27.2% in non-diabetic cholesterol-fed rabbits following 10 weeks of atenolol treatment. Also aortic cholesterol and phospholipid content was markedly reduced, but lipids content of liver and adrenal gland remained unchanged in both the groups. Following atenolol treatment, the serum lipids (total cholesterol, HDL cholesterol, triglyceride and phospholipid), serum calcium and blood glucose levels as well as blood pressure were found to be unchanged in diabetic and non-diabetic rabbits, indicating that the antiatherogenic effect of atenolol seems to be independent of its effect on these parameters. Since urinary ketogenic steroids and catecholamine metabolite (VMA) levels were found to be unchanged following atenolol treatment, the antiatherogenic effect is also thought to be independent of effect of atenolol on concentration of ketogenic steroids and catecholamines in the serum.

The exact mechanism responsible for antiatherogenic effect of beta blockers is not yet clear. Yamori et al (1985) have suggested that the atherogenic process involves proliferation of smooth muscle cells which have migrated into the intima from the media. Beta adrenoceptors mediate a trophic effect on these cells
and inhibition of these beta receptors by beta-adrenergic blockers might result in reduced growth of intimal fibrous tissue. The antiatherogenic effect of beta blockers may be due to a combined effect on the biochemical and hemodynamic factors. Two biochemical effects of beta blockers may retard the development of atherosclerosis inspite of unchanged serum cholesterol level. One is a beta blocker-induced increase in prostacyclin biosynthesis (Beckman et al 1988) as prostacyclin has been postulated to prevent both growth of fibrous tissue and cholesterol accumulation in the arterial intima (Willis et al 1986). Another biochemical effect is a metabolic change in the LDL, therefore reducing its potential for deposition in the arterial wall (Linden et al 1988). The antiatherogenic effect of beta blockers may be reinforced by their favourable hemodynamic effect. The reduction in heart rate and pulse pressure by beta blockers has been reported to reduce cyclic stretching of the arterial wall; there is evidence, however, that the prevention of pressure related cyclic stretching of arterial segment markedly reduces the development of atherosclerosis within the segment (Thubrikar et al 1988; Lyon et al 1987). In addition, Chobanian et al (1985) suggested that antiatherogenic action of beta blocker (propranolol) in cholesterol-fed rabbits may be related to a direct action of the drug on the arterial wall.
CALCIUM CHANNEL BLOCKERS

The calcium channel blockers are a group of chemically and pharmacologically diverse compounds which interfere with the transmembrane-flux of calcium through specialized channels. The main mechanism underlying the antihypertensive effect of calcium channel blockers is vasodilatation which occurs as a result of interference with excitation-contraction coupling (Garthoff et al, 1983). Therapy with calcium channel blockers causes a slight rise in serum HDL cholesterol level while producing no effect on total serum cholesterol or triglyceride levels (Midtbo et al 1982; Rauramaa et al 1988); also, there is minimal or no influence on blood glucose or insulin responses (Charles et al 1981; Anderson and Rojdmark 1981). The present study shows that, nifedipine administration to diabetic and nondiabetic cholesterol-fed rabbits did not influence the serum lipids (total cholesterol, HDL cholesterol, phospholipid, and triglyceride) and blood glucose levels.

Treatment with nifedipine (Lichtlen et al 1989) and nicardipine (Waters et al 1987) in patients with coronary artery disease was shown to suppress the formation of new lesions. In experimental animals, high concentration of calcium channel blockers inhibited the proliferation of early aortic lesion. Nifedipine 40mg/day, significantly reduced the aortic atherosclerotic involvement and aortic cholesterol and calcium accumulation in cholesterol-fed rabbits (Watanable et al 1987). Similarly, diltiazem (Ginsberg et al 1983), nicardipine (Willis et al 1985) and verapamil (Blumlein et al 1984) reduced aortic atherosclerotic plaque and
cholesterol accumulation at high doses. Interestingly, isradipine at the dose twice the recommended human antihypertensive dose, significantly reduced aortic lesion and cholesterol accumulation (Habib et al 1986). The present study shows that, nifedipine at the highest recommended human antihypertensive dose level (1 mg/kg) significantly inhibits the development of the atherosclerotic lesion. Aortic atherosclerotic plaque involvement was reduced by 37.5% in diabetic and by 33.3% in nondiabetic cholesterol-fed rabbits. Also, aortic cholesterol content was found to be significantly reduced in both the groups, but lipids content of liver and adrenal gland remained unchanged.

Following nifedipine treatment, the serum lipids (total cholesterol, HDL cholesterol, triglyceride and phospholipid) serum calcium and blood glucose levels as well as blood pressure were found to be unchanged in diabetic and nondiabetic rabbits, indicating that antiatherogenic effect of nifedipine seems to be independent of its effect on these parameters. Since, urinary ketogenic steroids and catecholamine metabolite (VMA) levels were found to be unchanged following treatment with nifedipine, the antiatherogenic effect was also thought to be independent of the concentration of ketogenic steroids and catecholamines in the serum.

Several mechanisms have been suggested for antiatherogenic effect of calcium channel blockers, since they may influence a number of calcium regulated processes in the arterial wall and other tissues. The most likely mechanism for the protective effect of calcium channel blockers appears to be a decrease in the intracellular calcium concentration in the arterial wall smooth muscle
cells (Parmley 1990). Reduced smooth muscle cell calcium may decrease mitosis and collagen production (Berridge 1975) and smooth muscle cell migration and proliferation (Henry 1985; Nakao et al 1983). Their anticalcitonic action (Fleckenstein et al 1986) and related pronounced effect on lipoprotein uptake and metabolism (Stein et al 1985) and cell necrosis (Herry 1985) may also be identified as possible vasoprotective mechanisms. Calcium channel blockers may inhibit platelet activation (Man in't veld 1989) as well as inhibit certain platelet function such as calcium-dependent processes of adhesion, aggregation and release of platelet factors, which contribute to atherogenesis (Packman et al 1978; Greer 1987; Mehta and Megta 1981). In addition, a variety of cellular responses involved in the process of atherosclerotic lesion formation such as chemotaxis, adhesion, migration, proliferation, uptake and discharge of lipid, cell necrosis, thrombosis etc., are all examples of calcium-regulated events which may be influenced by calcium channel blockers (Henry 1990). Furthermore, calcium channel blockers decrease the contractility and after load, and thus could be expected to decrease blood turbulence and shear stress to endothelium of arterial wall (Antman et al 1980; Stone et al 1980), which may also contribute to the antiatherogenic property of these drugs.
Angiotensin converting enzyme (ACE) inhibitors are reversible, selective and competitive inhibitors of the ACE, which is responsible for conversion of inactive angiotensin I to active angiotensin II, a potent vasopressor. They reduce blood pressure primarily as a result of prevention of angiotensin II formation. ACE inhibitors produce no adverse effect on serum lipid levels and even cause beneficial effect on lipid profile when administered to hypertensive patients (Kohar et al 1984). Captopril also improves tissue insulin sensitivity and reduces the late glucose stimulated insulin response in patients with essential hypertension (Pollare et al 1989). In the present study, captopril and enalapril did not influence serum lipids and blood glucose levels following administration to diabetic and non-diabetic cholesterol-fed rabbits.

The beneficial effect of ACE inhibitors on cardiovascular complications have been reported in several studies. Regression of vascular hypertrophy has been described for several ACE inhibitors, including captopril (Loeb and Bean 1986), enalapril (Adams et al 1990), cilazapril (Clozel et al 1991) and perindopril (Christensen et al 1989). Also both captopril and cilazapril were able to reduce the extent of myocardial thickening occurring after balloon-catheter injury to the rat carotid artery (Powell et al 1989). In addition, captopril has been reported to inhibit aortic atherosclerotic plaque involvement in Watanabe heritable hyperlipidemic rabbits (Chobanian 1990).
In the present study, both captopril and enalapril significantly inhibited the development of atherosclerotic lesion in diabetic and nondiabetic rabbits. Treatment with captopril for 10 weeks reduced aortic atherosclerotic involvement by 68.7% in diabetic and by 72.7% in nondiabetic cholesterol-fed rabbits. Also, enalapril treatment reduced aortic atherosclerotic involvement by 75% in diabetic and by 75.7% in nondiabetic cholesterol-fed rabbits. Aortic cholesterol and phospholipid contents were also found to be significantly reduced, but the lipids content of liver and adrenal gland remained unchanged. Following captopril and enalapril treatment, the serum lipids (total cholesterol, HDL cholesterol, triglyceride and phospholipid), serum calcium and blood glucose levels as well as blood pressure were found to be unchanged in diabetic and nondiabetic rabbits, indicating that the antiatherogenic effect of captopril and enalapril seems to be independent of changes in these parameters. Since urinary ketogenic steroids and catecholamine metabolite (VMA) levels were found to be unchanged following captopril and enalapril treatment, the antiatherogenic effect of drugs may also be independent of their effect on these parameters.

Although the exact mechanism responsible for antiatherogenic effect of ACE inhibitors is yet unclear, several possible explanations can be proposed. ACE inhibitors, by inhibiting angiotensin II formation, could theoretically be beneficial to the vasculature. There is an evidence that high levels of angiotensin II, when associated with hypertension, may be vasculotoxic, particularly to the small arteries and arterioles (Giese 1973). Accordingly,
Gavras et al (1971) reported that angiotensin II causes extensive vascular lesion and myocardial infarction following intravenous administration to rabbits. Furthermore, the aberrant growth of vascular smooth muscle cells has long been recognized as a fundamental factor in the pathogenesis of hypertension and atherosclerosis (Owens and Schwartz 1983; Ross 1986). Angiotensin II may act as a trophic factor stimulating the growth of vascular smooth muscle and myocardial cells (Fouad-Tarazi 1987) and may alter the extracellular matrix in the arterial wall (Michel et al 1987). Recently it has been reported that angiotensin II acts directly by stimulating synthesis of new receptors for platelet-derived growth factor (PDGF), thereby potentiating the mitogenic action of PDGF (Bobik et al 1990). Furthermore, mas proto-oncogene product is an angiotensin receptor with mitogenic activity (Jackson et al 1988) and inhibition of angiotensin II could decrease mitogenic activity mediated by this receptor (Clozel et al 1991). In addition, the inhibitory effect of ACE inhibitors on sympathetic nervous system activity (Antonaccio and Kerwin 1981), or an increase in prostacyclin synthesis (Dzau 1988; Blumberg et al 1977) may also contribute to antiatherogenic effect of these drugs.

Considering the documented data (Nikkila et al 1965; Stamler et al 1961; Marquie 1978), which indicate that hyperinsulinemia plays an important role in the induction of atherosclerotic vascular disease and the observed aortic atherosclerotic plaque involvement in diabetic (insulin deficient) and nondiabetic rabbits in the present study, it seems that hyperglycemia per se may not be a sole factor in the induction of atherosclerotic vascular disease in the diabetic condition.