6. DISCUSSION
Although arterial hypertension is reported to be common in both IDDM and NIDDM, the exact incidence of hypertension in the diabetic population is difficult to determine because of the confounding factors such as type of diabetes, age, weight, metabolic control and heredity (Tuck & Corry 1991). In general, hypertension is commonly seen in association with NIDDM, occurring at a frequency of 30-58% within the diabetic population (Diabetes Drafting Group 1985; Turner 1985; Sparfka et al. 1988; Klein et al. 1985; Garcia et al. 1974; Jerrett et al. 1982; Vaishnava & Bhasin 1969). Pell and D’Alonzo (1967) reported the prevalence of hypertension in diabetic patients to be 54% more as compared to age, sex and weight matched control population. In our study, the prevalence of hypertension was found to be 47.85% within age and weight matched diabetic population. It was reported that the patients with NIDDM, in contrast to IDDM, were frequently hypertensive at the time of the diagnosis of their diabetes-mellitus (Vasiltupa et al. 1985; Gottlieb 1974; Pell & D’Alonzo 1967). The occurrence of hypertension among diabetics in our study was found to be variable. In majority of patients both the diseases were diagnosed at the same time.

Essential hypertension and diabetes-mellitus are independent risk factors for cardiovascular, renal and atherosclerotic vascular disease (Asplund et al. 1980; Chanal et al. 1985; Hope-Gill et al. 1979; Janka et al. 1980; Knowler et al. 1980). Co-existence of both these diseases not only accelerate the course of but also the risk for nephropathy, atherosclerosis, retinopathy, stroke and cardiovascular diseases (Asplund et al. 1980; Chanal et al. 1985; Hope-Gill et al. 1979; Janka et al. 1980; Knowler et al. 1980; Mogensen 1979). In diabetic hypertensive patients, the risk of cardiovascular death is doubled (Aromaa et al. 1984). Framingham study also demonstrated that the co-existence of diabetes and hypertension compounds the risk for cardiovascular events (Kannel 1972). In the present
study, the occurrence of cardiac dysfunction was found to be higher in patients with the coexistence of diabetes and hypertension than those with either essential hypertension or diabetes alone.

Despite the importance of hypertension in diabetes mellitus, pathophysiology and treatment of diabetic hypertension remains poorly understood. There have been quite limited studies in their focus, and no unifying concepts have emerged to allow a comprehensive understanding of the pathogenesis as well as treatment of hypertension particularly in type II diabetes. Currently, the selection of antihypertensive therapy appears to be based on at least 5 factors (Opie 1993). These include:

1. experience (communal or individual),
2. comparative outcome studies,
3. surrogate end-points,
4. quality of life parameters and adverse effects of the agent used, and
5. individualised choice-care for the patients.

In the late 1970s, the Joint National American Committee on the Detection, Evaluation and Treatment of High Blood Pressure (1977) recommended stepped care therapy. None of the recommendations were based on long term comparative outcome studies, and therefore, reflected opinion and clinical practice rather than scientific evidence per se.

In the following year, the WHO Expert Committee on Arterial Hypertension (1978) suggested that either a β-blocker or a diuretic could be used as the first-line therapy and the addition of a vasodilator can be used as a second line approach. Again, these recommendations must have been based on clinical experience and enlightened guess work. Zanchetti (1985) proposed that diuretics, β-blocker or angiotensin converting enzyme (ACE) inhibitors be used as first-line therapy for hypertension. Two years later, Zanchetti (1987) included calcium antagonists as alternative first-line agents. Recently, Fifth Joint National Committee (1993) added alpha-blockers and alpha-β-blockers as one of the 6 possible alternative therapies. The Medical Research
Council trials (Medical Research Council Working Party 1985; 1992) and other clinical trials focused the comparison of not more than 2 of the many possible first line therapy.

In the present study we have evaluated the comparative effects of 4 antihypertensive monotherapy in diabetic as well as non-diabetic essential hypertensive patients. It was observed that, while all the four agents used could produce an effective control of blood pressure in majority of the patients, there was marginal difference in their efficacy. The effective blood pressure control was achieved between 78-80% of the non-diabetic hypertensive patients with enalapril, clonidine and nifedipine. With atenolol it could be achieved in 75% of such patients. In diabetic hypertensive patients the control of blood pressure was relatively higher with enalapril (84.6%) and clonidine (83.0%) as compared to nifedipine and atenolol (72% and 75% respectively). These data in patients with non-diabetic hypertensive patients are in accordance with many other studies reported for enalapril (Gavras et al. 1981; Todd & Heel 1986), clonidine (Holmes et al. 1983; Weber et al. 1976), nifedipine (Buhler et al. 1983; Frishman & Charlap 1984; Robinson 1983) and atenolol (Kamlow et al. 1990; Webster et al. 1987). The studies indicating effectiveness of various antihypertensives in diabetic hypertensive patients are scanty. ACE inhibitors have been reported to be effective in the control of blood pressure in NIDDM hypertensive patients (Gambaro et al. 1985; Dominguez et al. 1987; Zanella et al. 1990; Lanza et al. 1985). Similarly, centrally acting agent, clonidine, have been shown to be effective form of monotherapy in diabetic hypertensive patients (Guthrie et al. 1983). Long term studies with calcium antagonists demonstrated a significantly reduced blood pressure without aggravating renal disease (MacGregor et al. 1990), cardiovascular, cerebrovascular or peripheral vascular disease (Bondi & Ciofalo 1988; Bursztyn et al. 1985), diabetes-mellitus (Chellingsworth et al. 1989) or asthma (Patel 1981).
Treatment with enalapril in diabetic and non-diabetic hypertensive patients significantly decreased the heart rate after 9 months of therapy (Table:5.8a & Table:5.8b). It has been reported that the heart rate is not significantly changed by captopril in hypertensive patients (Catalano et al. 1992) or by enalapril in diabetic hypertensive patients (Ferrier et al. 1992). However, a recent study with enalapril in hypertensive patients showed a significant reduction in heart rate (Libretti & Catalano 1993). Atenolol treatment significantly decreased the heart rate after 1 month in both the groups of patients which was further reduced to 16% at the end of 9 months of therapy. Administration of single oral doses of atenolol 50 or 100 mg is reported to produce a significant reduction in heart rate (Kamlow et al. 1990; Webster et al. 1987; Sandrone et al. 1994). Several clinical studies have already demonstrated a beneficial effect of β-blockers on morbidity and mortality in patients with myocardial infarction (Beta Blocker Heart Attack Trial Research Group 1982; Yusuf et al. 1985; Hjalmanson & Olsson 1991; Pitt 1992; Sandrone et al. 1994). It has been reported that the sympathetic activation observed after myocardial infarction could be related to a diminished baroreflex sensitivity (Schwartz et al. 1992). Beta blockers by increasing baroreceptor sensitivity (Pickering et al. 1972; Eckberg et al. 1976) might reduce efferent sympathetic activity directed to the heart, and thus restoring a physiologic sympathovagal balance.

Several experimental studies have shown that central alpha2-adrenoceptor stimulation with drugs like clonidine, guanfacine and guanabenz results in a reduction of peripheral sympathetic nerve activity (Pettinger 1975; Scriabine & Taylor 1984; Holmes et al. 1983). In humans, these agents reduce circulating plasma noradrenaline and adrenaline concentration (Hoeusler 1975; Reid & Hemilton 1980; Thananopavan et al. 1982), which again reflects a reduction in peripheral sympathetic nervous activity.
Accordingly, central alpha_2- adrenoceptor stimulation and the attendant fall in sympathetic nerve activity lead to a reduction in alpha_1- and alpha_2-mediated vasoconstriction, and thereby vascular resistance. At the same time, β-adrenoceptor mediated effects are reduced, resulting in a decrease in heart rate (Dziedzic et al. 1983; Weber et al. 1983). In the present investigation however, long-term treatment with clonidine failed to produce any significant decrease in heart rate in diabetic and non-diabetic hypertensive patients.

The acute administration of nifedipine has been shown to increase heart rate in cardiac patients, normal volunteers and hypertensive patients (Emanuelsson & Holmberg 1983; Fioretti et al. 1983; Banzet et al. 1983) by increasing baroreceptor-mediated β-adrenergic tone secondary to systemic vasodilatation (Lederballe Pedersen & Mikkelsen 1978). Nifedipine treatment significantly increased the heart rate in both diabetic as well as diabetic hypertensive patients. Single-dose studies indicate that the antihypertensive effects of nifedipine are primarily mediated through peripheral arteriolar dilatation with an accompanying increase in sympathetic tone which results in parallel increase in heart rate (Lederballe, Pedersen & Mikkelsen 1978). Various studies failed to show any significant increase in heart rate following acute or long term oral administration of nifedipine capsule (Bellocci et al. 1982; Corea et al. 1981; Littler et al. 1983). However, administration of nifedipine tablets in hypertensive individuals have been associated with increases in heart rate (Banzet et al. 1983). In our study sustained release nifedipine tablets also increase heart rate in diabetic as well as non-diabetic hypertensive patients and hence the results are in accordance with those reported by Banzet et al. (1983).

Several studies have demonstrated that reduction of blood pressure in patients with hypertension is associated
with a decrease in cerebrovascular events, but not the cardiovascular morbidity and mortality (Hypertension Detection and Follow-up Program Cooperative Group 1979; Multiple Risk Factors Intervention Trial Research Group 1982; Veterans Administration Cooperative Study Group 1970). Recent meta-analysis have also demonstrated that the benefits of antihypertensive therapy were particularly pronounced with respect to incidence of cerebrovascular disease (Black et al. 1984) rather than coronary heart disease (Alderman et al. 1982; Amery et al. 1985; Helgeland 1980; Miettinen et al. 1985; Wikström et al. 1988). A possible explanation for this difference is that several risk factors other than hypertension contribute to the pathogenesis of coronary heart disease, including hyperlipidaemia.

It has been reported that 40% of hypertensive persons have blood cholesterol levels > 6.23 mmol/liter (Working Group on Management of patients with Hypertension and High Blood Cholesterol 1991). Hypertension appears to be critically important when it co-exists with diabetes-mellitus because it accelerates both the microvascular and macrovascular complications of diabetes. Diabetes is also associated with hyperlipidaemia and ketoacidosis which produce deleterious effects on cell-membrane and myocardial function (Rodrigues & McNeill 1985). The association of total cholesterol levels with the incidence of coronary heart disease is well established (Keys et al. 1985; Shaper et al. 1985). The positive relation between plasma triglycerides concentration and coronary events has also been reported (Carlson & Botinger 1972). Data from the Framingham study suggested that high plasma triglyceride levels is one of the risk factors for coronary heart disease in women (Kannel 1987) and in men, particularly when hyperlipidaemia is associated with law levels of HDL-cholesterol concentration (Castelli 1986). LDL-cholesterol is also predictive of the risk of coronary heart disease.
Our study also shows that the total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride levels were adversely altered in NIDDM and uncontrolled hypertensive patients.

Hypercholesterolemia (i.e. high total cholesterol and low HDL-cholesterol) was found to be more prevalent in diabetic patients with or without hypertension. It was also found to be more common in hypertensive patients not receiving any antihypertensive therapy (uncontrolled hypertension). It was reported that oral hypoglycemic drugs did not affect lipid levels (Taylor et al. 1982; Rains et al. 1988). A meta-analysis of 14 major randomised trials has revealed that a reduction in diastolic blood pressure was associated with a 42% decrease in fatal or non-fatal stroke. In contrast, Colling et al. (1990) reported only a 14% reduction in fatal or non-fatal CHD. It was postulated that the compliance with antihypertensive treatment might reduce stroke risk by one-half and CHD by about one-fifth (Collins et al. 1990). In the present study incidence of hypercholesterolemia was found to be comparatively less in patients with hypertension receiving antihypertensive therapy. However, the incidence of hypercholesterolemia was still higher (Table: 5.4) in hypertensive patients with the co-existence of diabetes-mellitus, despite of the antihypertensive treatment. Hypertriglyceridemia was also found to be highly prevalent in patients with uncontrolled hypertension. The prevalence of hypertriglyceridemia was also higher in patients with diabetes-mellitus. However, it was comparatively less in patients receiving some antihypertensive drugs irrespective of whether they have had diabetes or not. Higher incidences of hyperlipidaemia in diabetic patients with or without hypertension might be one of the factors responsible for occurrence of cardiac dysfunction in such patients.

The Multiple Risk Factor Intervention Trial was one of
may affect negatively the plasma lipid levels (Smith 1978). Many other clinical studies later reported an increase in lipids during treatment with diuretics or β-blockers (Ferrari et al. 1991; Grimm 1986; Stamler et al. 1986; Williams et al. 1986). Therefore, the influence of antihypertensive drugs on plasma lipid levels has become important in the choice of appropriate antihypertensive treatment. In the present study treatment with enalapril in diabetic and non-diabetic hypertensive patients did not alter significantly the lipid profile after 3 months. However, 9 months treatment with enalapril caused a significant decrease in total cholesterol, LDL-cholesterol and triglyceride levels with an increase in HDL-cholesterol levels (Table:5.9a & Table:5.9b). These findings are in agreement with those reported with enalapril in essential hypertensive patients (Libretti & Catalano 1993). Ferrier et al. (1992) reported that, when enalapril was given to diabetic hypertensive patients it did not modify the serum total and lipoprotein lipid fractions, or apolipoprotein AI and B. However, it has been reported that captopril may reduce total cholesterol levels, with an increase in the ratio of HDL to LDL-cholesterol (Ghirlanda et al. 1986; Saltvedt et al. 1986; Catalano et al. 1992).

Among centrally acting agents, only guanabenz is reported to decrease total cholesterol levels in essential hypertensive (Kaplan 1984) as well as in diabetic hypertensive patients (Weber et al. 1984). No such reports are available for clonidine. In the present study clonidine was found to cause a significant decrease in total cholesterol, LDL-cholesterol and triglyceride levels with simultaneous increase in HDL-cholesterol levels in both diabetic and non-diabetic hypertensive patients. Unlike that of enalapril and clonidine, atenolol was found to adversely affect the lipid profile in both diabetic and non-diabetic hypertensive patients. Nifedipine, however, did not produce any significant alterations in lipid profile throughout the therapy.
Different beta blockers show different effects on serum lipoprotein levels in essential or diabetic hypertensive patients. Non-selective β-blockers have been shown to affect serum lipid levels adversely (Johnson & Danylichuk 1989; Sirtori et al. 1989; Lardinois & Neumen 1988; Dujovne et al. 1984). It was postulated that selective β-blockers such as atenolol are likely to affect adversely the serum lipid levels to a lesser extent than non-selective ones such as propranolol (Day et al. 1982). However, several other studies demonstrated that atenolol can affect serum lipid levels to an extent-quantitatively similar to non-selective β-blockers in either hypertensive patients (Fogari et al. 1989; 1991; Frick et al. 1987; Karlson et al. 1988) or in diabetic hypertensive patients (Feher et al. 1990). It has been reported that chronic treatment with atenolol in STZ included diabetic rats could not prevent diabetes induced hyperlipidaemia, cardiomyopathy and cardiac dysfunction. The cardiac dysfunction and cardiomyopathy were rather found to be aggravated (Bangaru et al. 1991). The present findings also atenolol was found to came an increase in triglyceride levels and decrease in HDL-cholesterol levels in diabetic as well as non-diabetic hypertensive patients. It has been proposed that unopposed alpha stimulation with β-blockers inhibits lipoprotein lipase with a subsequent rise in plasma triglyceride and fall in HDL-cholesterol concentrations (Day et al. 1982).

Several experiments in animal models, especially cholesterol-fed rabbits, have indicated that nifedipine may reduce accumulation of atherosclerotic lesions (Gotto 1990). However, conflicting data is available as far as the influence of calcium antagonists on lipid profile in patients with diabetic and non-diabetic hypertension is concerned. A number of studies have shown that nifedipine does not produce any significant effect on lipid parameters (Birkeback et al. 1989; Lehtonen et al. 1986; Pasanisi et al. 1986; Vessby et al. 1983; Ohman et al. 1985).
contrast, Houstan et al. (1990) reported a significant increase in HDL, HDL-2 and apolipoprotein AI and AII levels after the administration of nifedipine. Verapamil is also reported to improve lipid profile in essential hypertensive patients (Catalano et al. 1992; Libretti & Catalano 1993) but failed to improve lipid profile in diabetic hypertensive patients (Ferrier et al. 1992). In the present investigation, nifedipine did not produce any significant changes in lipid profile in diabetic as well as non-diabetic hypertensive patients throughout the 9 months of therapy.

It has been postulated that adverse changes in blood lipids by antihypertensive drugs are transient, however, extended trials have shown that derangement of blood lipid levels may persist indefinitely or at least for several years (Ferrari et al. 1991; MRFIT 1982; Grimm 1988). Because of the proven risk of potentiation between hypertension, diabetes and dyslipidaemia, it seems appropriate to choose antihypertensive drugs with beneficial or at least neutral effects on serum lipids. The results of the present study (animal as well as clinical) and that reported by others, suggest that enalapril and clonidine could be considered as the drugs of choice for the treatment of hypertension in a situation where the correction of dyslipidaemia is warranted. Further, it could be stated that atenolol should never be used and more studies are required to prove the efficacy of nifedipine in such situation.

Apart from vascular complications associated with diabetes and hypertension, poor glycemic control accelerate or precipitate diabetic nephropathy, retinopathy and macroangiopathy (Kroc Collaborative Study Group 1984; WHO Multinational Study of Vascular Diseases in Diabetes 1985). Therefore, it is deemed mandatory that the long-term care of diabetic patients is aimed at concomitant metabolic and blood pressure control. In the treatment of hypertension accompanying diabetes, thiazide or loop diuretics are reported to aggravated glucose intolerance in a dose
dependent fashion (Murphy et al. 1982), promote arrhythmogenic hypokalemia (Kaplan 1984b) and tend to elevate the atherogenic serum cholesterol levels (Ferrari et al. 1991). Even more disturbing is the recent observation of a 3.8 fold higher cardiovascular mortality in diabetic hypertensive patients treated with diuretic monotherapy than in diabetics with untreated hypertension (Warram et al. 1991). ACE inhibitors like captopril or enalapril have been shown to increase insulin sensitivity in NIDDM patients (Jauch et al. 1987; Catalano et al. 1992; Pollare et al. 1989; Santaro et al. 1992; Torlone et al. 1991) with a subsequent reduction in fasting blood sugar levels (Arauz-Pacheco et al. 1990; Ferrari et al. 1992; Prince et al. 1988). However, in contrast, several other studies have shown that ACE inhibitors did not cause any significant alteration in serum insulin or glucose tolerance in hypertensive patients or normotensive healthy subjects (Baba et al. 1993; Alleman et al. 1992; Seghieri et al. 1992; Chen et al. 1992; Santoro et al. 1992).

Atenolol treatment in non-diabetic hypertensive patients is reported to produce and a decrease in insulin sensitivity and reduced glucose tolerance (Pollare et al. 1986; 1989). There are contradictory reports on the effects of atenolol on the release of insulin. Hausmann & Goebel (1983) reported a decrease in C-peptide levels suggesting impaired pancreatic B-cell function. However, in contrast Koh et al. (1982) failed to detect a significant decrease in C-peptide levels and reported improved glucose tolerance. B-blockers are thus not considered to be ideal for diabetic hypertensive patients because they decrease the awareness of hypoglycemia and tend to promote glucose intolerance (Trost & Weidmann 1988; Chellingsworth et al. 1989).

There are contradictory reports for the effects of clonidine on glycemic control. In normotensive humans, acute administration of clonidine is reported to produce a rise in blood glucose levels, however, it has been shown that
chronic therapy does not produce any significant changes in blood glucose or insulin levels or insulin release in response to ingested glucose in either normotensive or hypertensive subjects (Boyar et al. 1980; Stornello et al. 1986). Metz et al. (1977) concluded that clonidine exerts a direct peripheral effect as an alpha-agonist to inhibit pancreatic insulin release. Several studies reported that clonidine impairs glucose tolerance in laboratory animals (Bock & Van Zweiten 1971; Itawa 1969) and in man (Lal et al. 1975; Metz et al. 1977; Mroczek et al. 1972). In diabetic hypertensive patients, clonidine has been reported to decrease glucose tolerance without any significant effect on glycemic control (Guthrie et al. 1983). However, Ishii et al. (1985) reported that the enhancement of serum insulin response to glucose following clonidine treatment is mainly attributable to the hyper-responsiveness developed in the pancreatic B-cells.

Like those of clonidine, reports on the effects of nifedipine on glycemic control are controversial. In vitro experiments have shown that insulin secretion is dependent upon calcium influx into pancreatic B-cells (Grodsky & Bennett 1966; Scheon et al. 1988). Calcium antagonists like nifedipine, diltiazem and verapamil have consistently been shown to inhibit insulin release in vitro and thereby may affect glucose tolerance in animal models and in humans (Chellingsworth et al. 1989; Gill et al. 1987; Parent et al. 1989; Davis et al. 1975). Impairment of insulin secretion by nifedipine has been reported in non-diabetic individuals (Guigliano et al. 1980) and in patients with impaired glucose tolerance (Charles et al. 1981). Plasma glucose levels are increased after nifedipine administration in non-diabetic hypertensive patients (Palumbo et al. 1988) and also in non-insulin dependent diabetic hypertensive patients (Chellingsworth et al. 1989).

Several clinical trials failed to show any clinically important therapeutic effect of short short term nifedipine
treatment. Glucose tolerance in healthy volunteers and in subjects with impaired glucose tolerance or diabetes mellitus (Abadie & Passa 1984; Anderson et al. 1982; Brauman et al. 1984; Deedwania et al. 1984; Tebtorio et al. 1989), as well as in long-term nifedipine treated diabetic and non-diabetic hypertensive patients (Baski et al. 1990; Fujii et al. 1990; Kazumi et al. 1989; Pasanisi et al. 1986). Despite the ambiguous findings, the balance of currently available data suggest that nifedipine does not have diabetogenic potential.

From the above discussion on the effects of various antihypertensive agents on the glycemic control (including insulin release and insulin sensitivity), it could be stated that:

1. Enalapril does not produce any effect on glycemic control except that it may cause an increase in insulin sensitivity.
2. Atenolol may cause an increase in blood glucose levels by virtue of decrease in insulin sensitivity.
3. There is a great deal of controversy with respect to the effects of clonidine and nifedipine on glucose tolerance and insulin sensitivity.

In the present study, during 9 months of treatment with enalapril, clonidine or atenolol the fasting glucose levels could be maintained below 110 mg/dl in non-diabetic hypertensive patients. However, in patients receiving nifedipine there was occasional rise in glucose levels but it was not significant. In diabetic patients, antihypertensive therapy seems to potentiate the effect of oral hypoglycemic agents. This was observed at least in the patients receiving either enalapril, clonidine or nifedipine. It was observed that (Table: 5.10a) there was significant decrease in fasting blood glucose levels in patients receiving antihypertensive therapy along with
glibenclamide, as compared to those who did not receive any antihypertensive therapy but only glibenclamide. Further, the dose of glibenclamide required in diabetic patients receiving any of the four antihypertensives was significantly less than those on glibenclamide alone.

The mechanism by which antihypertensive agents might have produced decrease in glucose levels and the dose of glibenclamide required could be attributed to the increase in insulin sensitivity. This has been reported by several workers for enalapril (Catalano et al. 1992), nifedipine (Shah et al. 1995) and clonidine (Our unpublished data). Atenolol has rather been reported to produce insulin resistance (Pollare et al. 1986; 1989). In our study, the dose of glibenclamide required was relatively higher in diabetic hypertensive patients receiving atenolol as compared to those receiving other antihypertensive agents.

As far as creatinine and urea levels are concerned, both levels were found to be high in non-insulin dependent diabetic and uncontrolled hypertensive patients. In NIDDM, the incidences of nephropathy may be as high as 50% (Febre et al. 1982).

Although, diabetes and hypertension are independent risk factors for the development of renal disease, nephropathy in diabetics progresses with increasing levels of arterial pressure (Parving et al. 1983). The risk of nephropathy increases three-fold in diabetics when there is a family history of hypertension (Krowlewski et al. 1988). Serum creatinine and urea levels were found to be significantly higher in 18% patients of diabetic hypertension and 15% patients of non-diabetic hypertension during 9 months of therapy. The results of the present study are in accordance with a report which shows increased serum creatinine levels following enalapril treatment as compared to a placebo in the patients with congestive heart failure (Kjekshus & Swedberg 1988). Therapy with ACE inhibitors generally results with improvement in renal hemodynamics.
(Kubo et al. 1984; Creager et al. 1981). However, in certain instances, ACE inhibitors may cause clinical (Cleland et al. 1985; Packer et al. 1987) and experimental deterioration (Ichikawa et al. 1984; Freeman et al. 1979). Moreover, acute dosing of enalapril decreases both creatinine clearance and glomerular filtration rate, possibly because of a sustained reduction in mean arterial pressure (Cleland et al. 1985). A slight and insignificant elevation of serum creatinine observed in the present study might be due to reduced renal perfusion which is quite similar functionally to that of renal artery stenosis in which glomerular filtration is maintained in the presence of reduced renal perfusion pressure through selective vasoconstriction of efferent arteriole by angiotensin II. The dependence of renal function on angiotensin II is characterised by the sodium depletion and dehydration that may occur with excessive diuresis. In such patients, a marked reduction in the angiotensin II level following ACE inhibition could be detrimental to renal function (Packer et al. 1986; Funck-Brentano et al. 1986). If renal deterioration (i.e. increased serum creatinine and blood urea) develops after treatment with an ACE inhibitor, the dosage of the drug may be decreased and/or the dosage interval may be increased. In light of these results, enalapril should be used with caution in patients at increased risk for renal failure. Clonidine, nifedipine and atenolol did not affect creatinine and urea levels in diabetic as well as non-diabetic hypertensive throughout the 9 months therapy.

Results of the clinical studies suggest that while enalapril, nifedipine and clonidine produce beneficial effects in diabetic patients as far as glycemic control and lipid profile are concerned, atenolol was not found to be suitable in similar settings. Using STZ-diabetic rat model, it was established from our laboratory that while atenolol produces deleterious effects in STZ-diabetic rats (Bangaru et. al. 1991), enalapril was found to produce a number of
beneficial effects in STZ-diabetic rats such as prevention of cardiac depression, hyperlipidaemia, hypertension, bradycardia etc. (Bangaru et al. 1992). Since clinical studies revealed a positive influence of the treatment with nifedipine and clonidine in diabetic patients, it was considered reasonable to undertake a similar study for these agents in STZ-diabetic rat model.

STZ is reported to produce dose dependent diabetogenic effect in rats, ranging from mild diabetes to severe ketotic stage at higher dose (Hofteizer & Carpenter 1973). Different laboratories have used different doses of STZ ranging from 30 mg/kg to 80 mg/kg. In the present study a dose of 40 mg/kg or less failed to induced diabetes-mellitus whereas, a dose above 50mg/kg was found to produce high mortality. The dose of STZ used in the present study (45 mg/kg) produced not only four fold increase in blood glucose levels but also a significant hypoinsulinaemia and glycosuria (>2%).

In DOCA hypertensive animals also STZ produced similar symptoms of diabetes mellitus, however, the mortality in these animals was higher as compared to normotensive diabetic rats. Higher mortality in hypertensive diabetic animals could be due to higher degree of disturbances in various systems as degenerative changes of diabetes are exaggerated when hypertension co-exists. There was no mortality in control or DOCA control groups. However, greater mortality was observed in control as well as in diabetic animals treated with clonidine. This mortality was found to be associated with fighting behaviour. Thus, central stimulation may be one of the reasons for the increased mortality after clonidine treatment. Inspite of greater mortality, clonidine exhibited a number of beneficial effects in diabetic rats.

There was a significant loss of body weight in diabetic as well as diabetic hypertensive groups over the period of six weeks. The maximum loss of body weight was observed within first 3 weeks. Clonidine treatment significantly
prevented loss of body weight in diabetic as well as in diabetic hypertensive animals. The loss of body weight in diabetic animals was accompanied by polyphagia and polydipsia. The loss of body weight could be due to dehydration (Hofteizer & Carpenter 1973) and the catabolism of fats and proteins during diabetes-mellitus (Oakley 1968). Clonidine treatment produced slight reduction in water and food intake in diabetic and diabetic hypertensive animals. Nifedipine treatment also significantly prevented the loss of body weight and reduced water intake in diabetic animals.

Hyperglycemic state is reported to cause a series of vascular changes. Short term elevation of blood glucose level affects the sorbitol metabolism causing generation of diacylglycerol with subsequent stimulation of protein kinase C which in turn, alters the cellular uptake of myoinositol. Elevation of blood glucose for a longer time causes non-enzymatic glycosylation of vital body proteins which leads to produce thickening of capillary basement membrane along with atherosclerosis (Haller et al. 1991). Thus, treatment of hypertension in diabetes must not worsen the glycemic control. In the present study the blood glucose levels in diabetic animals were found to be significantly higher as compared to control animals. Treatment of non-diabetic animals with DOCA did not produce any significant change in blood glucose or insulin levels. However, administration of DOCA in diabetic animals caused significant reduction in blood glucose levels without significant alteration in insulin levels. Thus, it may be possible that DOCA increases insulin sensitivity in diabetes. These results are in accordance with the results previously reported with that of DOCA treatment in STZ-diabetic rats (Hebden et al. 1990).

It was found in the present studies that treatment with clonidine in control and DOCA-hypertensive rats caused an increase in the blood sugar levels without affecting the insulin levels as compared to their respective control. However, treatment of diabetic or diabetic-hypertensive rats
with clonidine reduced significantly the blood glucose levels with a correspondence increase in insulin levels as compared to their respective controls. The presence of alpha\textsubscript{2}-adrenoceptors has been reported in \&-cells of islets of Langerhans and stimulation of these receptors causes inhibition of insulin secretion and hyperglycemia (Nakaki et al. 1980; 1981). It has been reported that acute or chronic treatment with clonidine in normal or spontaneously hypertensive rats, causes an increased in glucose levels via increase in hepatic glycogenolysis (Lewis et al. 1989; Rehbinder & Deckers 1968). A marked enhancement of glucose-induced insulin secretion has been reported in the pancreatic islets isolated from rats treated with clonidine for 10 days as compared to the islets obtained from control rats (Ishii et al. 1985).

It has been reported that clonidine increases the blood growth hormone levels in various animal species (Lovingier et al. 1976; Ruch et al. 1976; Lancranjan & Marbach 1977), and that prolonged exposure to this hormone causes an enhancement of the responsiveness of the pancreatic islets to glucose (Martin et al. 1968; Malaisse et al. 1968). Thus, it is possible that the enhancement of serum insulin levels in diabetic rats following clonidine treatment could be attributed to the hyper-responsiveness developed in the pancreatic cells.

In vitro studies with isolated perfused pancreas and islet cell plasma membranes have shown that the calcium ion movement plays an important role in insulin secretion (Grodsky & Bennett 1966; Scheon et al. 1988). Thus calcium antagonists may theoretically alter insulin release and consequently affect glucose tolerance. In fact, impairment of insulin secretion by nifedipine has been reported in non-diabetic individuals (Charles et al. 1981) and in patients with impaired glucose tolerance (Guigliano et al. 1980). However, several clinical trials failed to show any important therapeutic effect of nifedipine on glucose
tolerance in healthy volunteers and in subjects with impaired glucose tolerance or diabetes (Anderson et al. 1982; Brauman et al. 1984; Tebtorio et al. 1989). The results of the present investigation explain many of these controversial reports on the effect of nifedipine on insulin and glucose levels. In the present study treatment with nifedipine produced variable effect on insulin as well as glucose levels, not only in different groups of animals but also at different interval of time of the treatment. In control animals there was an increase in serum insulin observed at the end of 10 days of treatment with nifedipine. Later, nifedipine treatment caused a decrease in insulin levels. Serum glucose levels were found to be decreased after 10 days of nifedipine treatment but it was not significant. Similarly there was slight but insignificant increase in serum glucose levels at the end of 20 to 42 days of the treatment. In diabetic rats, nifedipine treatment caused a further decrease in insulin levels, without any further rise in serum glucose levels after 30 and 42 days of nifedipine treatment. This indicates increase in insulin sensitivity by nifedipine treatment. The development of insulin-resistance and increase in insulin sensitivity are time dependent mechanism (Ferrannini et al. 1990). Hence, it can be assumed that a short term treatment with nifedipine interferes with insulin release and a long term treatment with nifedipine causes an increase in insulin sensitivity that might be responsible for the normal glucose homeostasis.

Increase in blood pressure after treatment with alloxan or STZ has been reported previously by several workers (Bunag et al. 1982; Cavaliere et al. 1980; Funukawa 1983; Hayashi et al. 1983). In our study, blood pressure of diabetic animals was found to be significantly higher as compared to control animals. Number of factors seem to be involved in the pathogenesis of hypertension in diabetes-mellitus such as sodium retention, extra cellular fluid
volume expansion, altered activity of the somatic nervous system and renin-angiotensin system, increased cardiovascular reactivity towards noradrenaline and angiotensin II, renal impairment etc. Histological studies in the present investigation showed improvement in nephron in nifedipine treated diabetic rats suggesting that renal improvement may be one of the factors responsible for reduction of blood pressure in diabetic rats. Administration of DOCA produced rise in blood pressure which was significantly higher as compared to STZ induced hypertension. The mechanism by which DOCA causes rise in blood pressure is sodium retention, and hence the expansion of plasma volume. However, DOCA when given along with STZ did not develop severe hypertension. Thus, a sort of counteraction to diabetes induced hypertension was observed. The underlying mechanism of this could not known.

Clonidine treatment significantly prevented the development of hypertension in diabetic and hypertensive rats. Clonidine treatment is reported to reduce blood pressure by inhibiting increased sympathetic activity and hence the elevated levels of catecholamines at the point of origin, within the control nervous system (Haeusier & Finch 1972; Hukuhara et al. 1968; Schmmtt 1977).

Bradycardia is frequently observed in STZ diabetic rats (Savarese et al. 1979). The development of STZ induced bradycardia has been attributed to a down regulation of myocardial β-adrenoceptors and increase in circulating and heart catecholamines levels (Tomlinson et al. 1990). The hypothyroidism induced by diabetes may also be another factor responsible for changes in myocardial adrenoceptors (Vadlamudi & McNeill 1983; Fein et al. 1980; Ciaraldi & Marinetti 1977) as T₃ treatment of diabetic rats is reported to prevent bradycardia (Goyal & McNeill 1985). Rodrigues et al. (1985) also reported a characteristic decrease in heart rate and T₃ levels in Wistar Kyoto rats made diabetic with STZ.
DOCA treatment did not produce any significant change in heart rate in any groups. In the present study both clonidine and nifedipine treatment prevented not only the STZ-induced bradycardia, but also the hypothyroidism. There was a significant decrease in T₃ and T₄ levels with an increase in TSH levels in STZ diabetic rats. Clonidine treatment significantly increased the T₃ levels, similarly nifedipine treatment significantly also increased T₃ and T₄ levels with a decrease in TSH levels. Our data support the hypothesis that hypothyroidism may be one of the causes of diabetes induced bradycardia. Clonidine treatment also produced a significant decrease in heart rate in control as well as non-diabetic hypertensive animals. Nifedipine treatment did not produce any significant change in heart rate in control animals. The hypotensive and sympathoinhibitory effects of clonidine were reported to be associated with bradycardia which is primarily attributable to central inhibition of cardiac sympathetic tone; however, central activation of cardiac vagal activity also appears to contribute to bradycardia produced by clonidine (Scriabine et al. 1968).

Increase in left atrial filling pressure from 2.5 cm to 25 cm H₂O produced a gradual rise in left ventricular developed pressure (LVDP) in control animals. LVDP was found to be significantly lower in animals treated with STZ. It has been reported that STZ-induced diabetes causes a decrease cardiac myosin ATPase activity due to shift from the more active V₁ myosin isoenzyme to the less active V₃ form (Banerjee 1983). The contractile function is thought to be related to myosin ATPase activity and thus it is possible that this shift may contribute to the diminished cardiac contractility of STZ treated rats. STZ treatment has also been reported to reduce the levels of creatine kinase activity and mRNA levels, limiting the availability of substance for myosin ATPase (Popovich 1989). Depression of myosin ATPase could also in part be the result of
hypothyroidism because chronic administration of T₃ to rats following STZ treatment prevented the reduction in myosin ATPase activity and the shift in isoenzyme distribution (Dillman 1982). Hypothyroidism also depresses calcium transport by the sarcoplasmic reticulum (Suko 1971). Results from our investigation support the view that hypothyroidism is one of the factors responsible for cardiac depression since the combination of hypothyroidism and depressed cardiac contractility was seen in all STZ treated animals. In the present investigation clonidine prevented the development of LVDP, improved the index of hypertrophy and also prevented the histological changes of diabetic and diabetic hypertensive hearts. Clonidine is reported to favourably affect the myocardial oxygen supply-demand ratio by minimally altering coronary perfusion pressure, increasing diastolic perfusion time and reducing the inotropic state of ventricle in patients with congestive heart failure (Hermiller et al. 1983). Nifedipine treatment in diabetic rats also improved the index of hypertrophy. Nifedipine treatment is reported to prevent the diabetes induced cardiac dysfunction and cardiomyopathy (Shah et al. 1995).

In addition to hypothyroidism, alteration in lipid metabolism is another possible mechanism involved in cardiac depression by modifying the structure of cardiac plasma membrane and subcellular membrane. In the present investigation elevation of total cholesterol, triglycerides and LDL-cholesterol levels were observed in diabetic as well as diabetic hypertensive rats. These results support the previous reports which suggested an association of diabetes and alteration in lipid metabolism (New et al. 1963; Nikkila & Hormila 1978; Sosenko et al. 1980; Albrink et al. 1963). Élévation of serum lipids in diabetic state indicates either the defective removal and/or overproduction of one or more lipoproteins. Insulin plays a role in both production and removal of triglyceride rich proteins, which may be the major cause of lipid disorders of diabetes. Insulin has an
inhibitory action on HMGCOA reductase, which is the key rate limiting enzyme in the cholesterol rich LDL particles. Hypoinsulinaemia would therefore, be responsible for the elevation of cholesterol levels. Treatment of diabetic rats with nifedipine or clonidine reduced significantly the total cholesterol and triglyceride levels. Clonidine treatment also reduced the LDL-cholesterol levels, however, it did not affect the HDL-cholesterol levels in either of the groups. The possible mechanism involved in above changes by clonidine may be the improvement in hypoinsulinaemic state in diabetic as well as diabetic hypertensive animals. However, treatment with nifedipine reduced the lipid levels with a simultaneous decrease in insulin levels without affecting glucose levels in diabetic rats. The possible mechanism involved in these effects may be explained on the basis of insulin receptor supersensitivity.

Rats treated with STZ also develop changes in renal function including altered renal hemodynamics and structural changes which can be attributed to the development of diabetes. STZ itself has no significant nephrotoxic potential and that its direct effect on the kidney need not be considered when using the drug in order to study the effects of diabetes on renal function and structure (Evan et al. 1984). Rise in serum creatinine and blood urea nitrogen (BUN) levels have been reported in patients with diabetes. In the present investigation, we found significant elevation in serum creatinine levels only in diabetic as well as diabetic hypertensive rats. Clonidine treatment in diabetic group prevented this rise in serum creatinine levels. Nephropathy is frequently observed as a long term complication of diabetes-mellitus. It is believed that the increase in intraglomerular pressure associated with early diabetes-mellitus leads to the structural changes in the glomeruli. It was reported that morphometric analysis of the kidney tissue from diabetic animals showed that there were glomerular, interstitial as well as tubular changes.
Nifedipine prevented there structural changes in diabetic rats (Shah et al. 1995).

STZ also produced changes in various hepatic enzyme systems that may need to be considered carefully. Many fundamental alterations in hepatic function related to changes in metabolism also occur following the STZ treatment. Since, the liver is very important organ in carbohydrate metabolism, uncontrolled hyperglycemia could lead to adverse effects on the liver function. It has been reported that in patients with maturity onset diabetes show fatty infiltration of hepatocytes. This may be due to hyperlipidaemia. Elevated activity of alkaline phosphatase, SGOT and SGPT has been reported in patients with NIDDM (Falchuk & Trey 1985). In our investigation also elevated activity level of all the three enzymes in diabetic and diabetic hypertensive animals was observed. Treatment with clonidine in both the groups prevented the rise in SGPT activity. It also lowered the alkaline phosphatase activity in both the groups. Hepatic changes relating to altered hormonal systems are also seen following STZ treatment. Alteration of conversion from T₄ to T₃ due to reduction in activity of hepatic T 4-5′ deiodinase has been reported (Jennings 1984). Relative hypoxia is an important factor in the development of tissue change in diabetes (Ditzeł & Standl 1975). The exact mechanism by which clonidine produced beneficial effect on liver enzyme system remains unclear. The alpha-adrenergic agonist, effects of clonidine in the peripheral circulation might be responsible for the improved hepatic enzyme systems in diabetic and diabetic hypertensive animals. Histological study of the liver tissues from diabetic and diabetic hypertensive animals showed that there was some vacuolisation and disruption in the normal arrangement of hepatic cords and sinusoids as compared to the structure in liver tissue from control animals. Clonidine treatment prevented these degenerative changes in both the groups of animals.