2. INTRODUCTION
Despite the first significant findings on hypertension in the beginning of nineteenth century, little was known about the pathophysiological, pathological, clinical and epidemiological factors involved in the disease. Between 1900 and 1960, many antihypertensive treatments, including dietary changes or surgical procedures were investigated, but results were disappointing. During the same period the social importance of hypertension was recognised, the neurological, cardiovascular, nephrological and ocular complications associated with hypertension became obvious and the first effective antihypertensive drugs quartet, reserpine, hydralazine, methyldopa and thiazide diuretics, became available. However, as this "drug quartet" was not consistently effective and the tolerability profile of these drugs was sometimes troublesome, efforts during the next decade (1960 to 1970) centred mainly on increasing the pharmacological armamentarium. A number of $\beta$-adrenergic and alpha-adrenergic blockers and vasodilators were introduced into clinical practice in the 60s, with varying therapeutic success.

During the 1960s, the therapeutic aim was to lower diastolic blood pressure, which was regarded as the factor contributing most to the consequences of hypertension. However, it soon became apparent that convincing an asymptomatic patient to take regular treatment would be difficult, especially when treatment was not well tolerated. Thus, in the 1970s, the emphasis shifted to patient compliance. It was the era of "one tablet a day" to make compliance easy for the patient, and of stepped care therapy. The aim was to provide uniform therapy for all hypertensive patients at the expenses of individualised treatment.

It was then realised, however, that the real issue was not simply the treatment of hypertension per se, but the treatment of an individual with hypertension rather than hypertension alone. Selection of therapy needed to be based
on individualised target levels for diastolic pressure, varying approaches to treating systolic hypertension, and differences in age, race, gender, and life-styles; in addition, it was necessary to take into account the presence of concomitant diseases e.g. diabetes mellitus, renal disease, ischemic heart disease, chronic obstructive pulmonary disease, asthma, anxiety etc. Awareness of these factors contributed to a change in the approach to antihypertensive therapy in the 1980s. Indeed, the development and routine prescribing of ACE inhibitors and calcium antagonists played a significant role in the evolution of new therapeutic strategies for hypertension during this time.

In addition, the 1980s also saw an increased understanding of the many other factors involved in this disease, such as endocrine factors, endothelial, autocrine and paracrine functions; the myocytes and growth factors influencing the development of left ventricular hypertrophy and the remodeling of the heart and blood vessels, metabolic disorders involved in the pathophysiology of atherosclerosis target organ damage and the vascular resistance. Today a clinician has to consider many factors when selecting antihypertensive treatment for an individual and there is a need for a global approach to the therapy.

Hypertension and diabetes mellitus are common chronic conditions which frequently coexist and can significantly affect the individual health care needs (National Diabetes Data Group 1985). The prevalence of hypertension increases with age (National Diabetes Data Group 1985) and is common in both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). There are however, substantial differences in the etiology and natural history of hypertension in IDDM and NIDDM. The exact incidence of hypertension in the diabetic population is difficult to determine because of confounding factors such as type of diabetes, age, weight, metabolic control and
handedness (Tuck & Corry 1991). Hypertension appears to be critically important in diabetes mellitus, not only because of its increased prevalence, but also because it accelerates both the microvascular and macrovascular complications of diabetes mellitus. Macrovascular complication manifested as coronary heart disease (CHD), peripheral vascular disease, cerebrovascular disease, stroke and congestive heart failure are all accelerated in hypertensive diabetics as compared to normotensive diabetics and non-diabetic hypertensives (Fuller et al. 1993; Panzaram 1987). These macrovascular complications are major causes of morbidity in NIDDM and accounts for 49-75% of the mortality in these patients (Panzaram 1987). Evidence from different populations has identified hypertension to be the most significant risk factor for CHD in the diabetic subjects (Vasituta et al. 1985). Incidences of the peripheral vascular diseases are greatly increased in diabetics, with hypertension being an associated factor (Janka et al. 1980). Stroke occurs 2-6 times more frequently in the diabetics as compared to non-diabetic patients, with a doubling of frequency in the hypertensive as compared to normotensive diabetic population (Roemboldt et al. 1983). Hypertension is not only an important risk factor for macrovascular, but also for the microvascular complications of diabetes. Retinopathy rates in diabetics double when the systolic blood pressure exceeds 145 mm Hg (Knowler et al. 1980). Nephropathy 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). End stage renal failure occurs more frequently in elderly hypertensive patients, as well as in young and middle-aged subjects with diabetic nephropathy than in their normotensive counterparts (Campese & Bigazzi 1991). It has been further reported that hypertension may be causally related to diabetic cardiomyopathy (Factor et al. 1980). Rodrigues and McNeill (1986) reported that cardiac functions were significantly depressed after 12 weeks in
Wistar and spontaneously hypertensive rats made diabetic with streptozotocin. They concluded that the combination of hypertension and diabetes mellitus produces a greater myocardial dysfunction and is associated with significant mortality.

Diabetes is also associated with hyperlipidaemia and ketoacidosis. The elevated fatty acid levels have deleterious influence on cell membrane and myocardial function (Rodrigues & McNeill 1986). Derangement in lipid metabolism may occur concurrently with elevated blood pressure. Elevation in blood pressure and serum cholesterol levels increases the incidence of ischemic heart disease to a greater extent then would be expected from a summation of the individual risk factors (Wilhelmsen 1988). Theoretically, the association between these two factors implies that hypertension and lipid abnormalities may have a pathological link (i.e. at least in some subjects with the existence of one abnormality may lead to the development of other), or that genetic and/or environment factors contribute to the development of both conditions.

Glucose metabolism and hypertension may also be linked. It has been repeatedly shown that glucose intolerance and hypertension are additive or interactive risk factors for the incidences of atherosclerosis-related cardiovascular disease (Fuller 1988). Furthermore, in patients with elevated blood pressure, insulin sensitivity is reduced more often than in subjects with normal blood pressure (Ferrinnini et al. 1987; Pollare et al. 1990).

In the light of all the facts mentioned above, it is clear that controlling blood pressure in diabetics is positively more beneficial as far as progression of diabetic complications are concerned.

Thiazide diuretics produce dose related hypokalemia, which may cause a decrease in insulin secretion, increased insulin resistance and impaired control of NIDDM. In
diabetic patients with coronary heart disease, thiazides may produce ventricular arrhythmias because of decreased serum potassium levels (Joint National Committee 1984; Christlieb 1982). Thiazide diuretic can elevate the level of low-density lipoproteins and very low-density lipoproteins. Sometimes cholesterol levels are also increased. It can reduce glomerular filtration rate and renal blood flow (Rudd & Blaschke 1985). The antihypertensive efficacy is sharply diminished in individuals with renal insufficiency (Lowenthal & Dickerman 1983).

Cardioprotection and antianginal effects, the main advantages of β-blocker, are welcome in diabetic hypertensive patients. However, β-blocker produce a profound influence on catecholamine mediated metabolic effects. Different β-blockers may show different levels in diabetic hypertensive subjects. Non-selective β-blockers have been shown to affect serum lipid levels adversely (Johnson & Danylchak 1989; Sirtori et al. 1989; Lardinois & Neuman 1988; Dujovne et al. 1984). Selective β₁-blockers, such as atenolol and metoprolol are likely to adversely affect the serum lipid levels to a lesser extent than non-selective ones such as propranolol (Day et al. 1982). Atenolol treatment in streptozotocin induced diabetic rats could not prevent diabetes induced hyperlipidaemia, cardiomyopathy and cardiac dysfunction (Bangaru et al. 1991). It was rather found to worsen the condition.

Nifedipine reduces accumulation of atherosclerotic components and slow the progression of atherosclerotic lesions in cholesterol fed rabbits (Gotto 1990). Conflicting data is available as far as the influence of nifedipine on lipid levels is concerned (Vessby 1983; Ohman et al. 1985; Houston et al. 1990; Shah et al. 1995). Several studies suggest the diabetogenic effect of nifedipine (Abadie & Passa 1984) but the currently available data suggest that nifedipine does not have diabetogenic potential (Kellehar et al. 1988).
Angiotensin converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension and congestive heart failure. In hypertensive diabetics, ACE inhibitors seem to be metabolically neutral (Cleland et al. 1985). However, recently it has been shown that enalapril improve lipid profile in hypertensive subjects (Libretti & Catalan 1993) and in streptozotocin diabetic rats (Bangaru et al. 1992). ACE inhibitors have been shown to reduce proteinuria in diabetic and hypertensive diabetic patients with nephropathy (Taguma et al. 1985; Hommel et al. 1986). Recently, results of a US study clearly show that the antiproteinuric effect of enalapril does not predict an attenuation in the rate of progression of established clinical diabetic nephropathy (Bauer et al. 1992). Although, enalapril is highly effective in hypertension, its metabolic and renal effects needs further consideration.

Centrally acting agents like clonidine, methyldopa and guanabenz are also commonly used drugs in the management of hypertension. Methyldopa and guanabenz did not produce any unwanted metabolic side effects in diabetic patients (Benfield & Hunter 1982; Weber et al. 1984). Clonidine has been reported to decrease glucose tolerance in maturity onset diabetic without any significant effect on glycemic control (Guthrie et al. 1983). Despite this favourable effects and long term availability of clonidine for commercial use, there is a lamentable paucity of data on its lipid effects.

Thus, in a new therapeutic approach to the treatment of hypertension, the ideal agent should not only be efficacious and well-tolerated, but it should reverse hypertension induced cardiovascular changes, prevent progression of renal failure and should induce positive alterations in lipid and glucose metabolism. For these reasons, new and improved antihypertensive drugs with multiple action are of particular interest. The treatment of hypertension in
diabetics patients is somewhat different from therapy of isolated hypertension, since metabolic effects of antihypertensive drugs need special consideration.

SPECIFIC OBJECTIVES OF THE PRESENT INVESTIGATION:

1. To find out prevalence of hypertension among diabetic population.
2. To study the effects of long term treatment of antihypertensive drugs on hemodynamics, and lipid profile in patients with essential hypertension and diabetes mellitus.
3. To study the effects of long term treatment of antihypertensive drugs on glucose levels and kidney functions in patients with essential hypertension and diabetes mellitus.
4. To study the effects of six weeks treatment with clonidine and nifedipine in rats made diabetic as well as hypertensive with streptozotocin and/or deoxycorticosterone acetate (DOCA).
5. To evaluate the choice of antihypertensive drugs for the treatment of hypertension along with diabetes mellitus.