INTRODUCTION
Atherosclerosis is a leading cause of death not only in developed countries but also in developing countries, where rapid industrialization is changing the life style. In spite of it, there are no known drugs that are able to prevent or even limit this dreadful disease.

The term "Atherosclerosis" is derived from two Greek words 'athere' meaning "porridge" or 'mush' and 'scleros' meaning "hard". This apparently contradictory combination describes the fact that the lesion begins as a soft deposit and hardens as it ages. However, "Atherosclerosis" has a variety of meanings depending upon the approach to the problem. According to clinicians, atherosclerosis encompasses a wide variety of clinical entities which may include myocardial infarction, angina pectoris, cerebrovascular disease and occasionally changes which can be detected only on an electrocardiogram. It is defined by the WHO, as a variable combination of changes of the intima of the arteries consisting of the focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits, associated with medial changes. Atherosclerosis is, therefore, a complex and multifaceted condition which may be a collection of pathological states with overlapping similarities of arterial abnormalities. Generally, atherosclerosis, either of aorta or of coronary arteries, involves the formation of lipid deposits inside the walls of blood vessels. These fatty substances appear mainly in
the smooth muscle cells and foam cells within the arterial linings. In space between these cells small amounts of the cholesterol can be detected. Very fine fibers of a material behaving like fibrin also show up within the lining as well as on its surface. At this early stage the forerunner of atherosclerotic lesion can be recognized in the form of fatty streaks. It is believed that 90\% of all genuine forms of angina pectoris and myocardial infarction are associated with the sclerotic changes in the coronary artery (Schettler, 1961). The arteries affected with atherosclerosis exhibit thickening of arterial wall intima, usually hypertrophy of the media, with clearly demonstrable lipid deposits. Since all these factors lead to decrease in the size of arterial lumen, it results in restriction of the flow of blood at reasonable pressure. Thus the restricted supply of oxygen and nutrients to coronary muscle leads to diminished performance and finally heart failure.

A. ETIOLOGY

Many risk factors like diet, lack of exercise (Kannel, et al., 1970), stress (Friedman, et al., 1970), cigarette smoking (Paffenberger, 1970), hypertension and elevated serum lipid levels have been correlated with atherosclerosis. Among all these risk factors, it is now well established that hyperlipidemia plays very important role in
development of atherosclerotic lesions. At first, it seems simple and straightforward but in fact it is not. The situation is complicated because:

1. There are several different plasma lipids.
2. The plasma lipids do not occur in free form but are combined with proteins to form lipoprotein complexes. Therefore, hyperlipoproteinemia is considered a prelude to atherosclerosis.

The etiology of hyperlipoproteinemia may be primary or secondary. The primary one is due to genetically determined defects in lipid or lipoprotein metabolism which are exaggerated by environmental factors through unknown mechanisms. The secondary hyperlipoproteinemia is caused by some well defined diseases (hypothyroidism, diabetes mellitus, nephrotic syndrome, biliary obstruction, pancreatitis and dysglobulinemia) which must be excluded in considering the etiology of the disease. Most of the risk factors, which have been correlated with atherosclerosis and coronary heart disease, do not correlate with stroke or cerebral vascular changes. Hypertension, however, is associated with stroke (Chapman, 1970; Paffenberger et al., 1970; Kannel et al., 1970). No single factor can be exclusively said to have a role in the etiology of atherosclerosis. High blood pressure along with hypercholesterolemia are crucial for development of atherosclerosis (Robertson 1962). Certain metabolic disorders like serum uric acid (Montoye et al., 1967; Benedek, 1967.), lowered serum albumin (Rashev et al., 1967), lowered
lipoprotein lipase (Petrova, 1967) and lowered endogenous heparin (Velican, 1967) have also been implicated in the etiology of atherosclerosis.

B. Atherosclerosis and Lipoproteins

Lipids are transported in blood plasma in association with proteins. Some polar lipids are transported with albumin (FFA, bile acids) or by specific binding proteins—retinal binding proteins. Nonpolar lipids are transported in large complexes containing polar lipids and specific proteins. These macromolecular complexes are known as lipoproteins. A striking feature of the plasma lipoprotein is the lability of its concentration in a given species in different pathological and physiological states and also in different animal species. Among mammals these differences can not be explained solely on the basis of the differences of the rate at which the nonpolar lipids are transported in the blood. Even within the species, evidence for the differences in the metabolic pathways of a given lipoprotein class is emerging (Havel, 1975). However, there is exchange and/or transfer of molecules between different lipoprotein particles as well as between lipoproteins and plasma membranes of various cells (Nilsson-Ehle et al., 1980) during various events of lipoprotein metabolism. Lipoproteins have been classified mainly into four types: chylomicrons, very low densi-
ty lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). Detailed molecular models, suggesting a highly organized structure for HDL (Smith et al., 1978; Edelstein et al., 1979) and LDL (Day and Levy, 1976; Atkinson et al., 1977; Smith et al., 1978), have been proposed. The larger particles, VLDL and Chylomicrons, seem to consist of a central triglyceride droplet surrounded by a monolayer of phospholipid, cholesterol and apolipoproteins (Shen et al., 1977). Of these lipoproteins, chylomicrons are of exogenous origin, derived from the dietary fat, synthesized in the gut and enter into the bloodstream via the thoracic duct. Upon reaching the capillary bed of several extrahepatic tissues the chylomicrons are absorbed to the endothelial surface forming an enzyme substrate complex with enzyme lipoprotein lipase. As a result of the activity of this enzyme, triglycerides are hydrolyzed and the liberated fatty acids are taken up into the tissue, esterified, stored and oxidized for future energy needs. The transport of exogenous triglycerides in this manner via chylomicrons is highly efficient so that chylomicronemia ensues within few hours after fatty meal. This process can account for the transport of as much as several hundred grams of triglycerides daily. In either genetic or acquired deficiency of lipoprotein lipase the capacity to transport triglyceride is quite limited and chylomicronemia may persist from meal to meal. This condition is also termed as exogenous hyperlipidemia.
The remaining three lipoprotein classes are of endogenous origin, normally present in fasting blood. In the fasting state majority of plasma triglycerides (synthesized endogenously in the liver) are contained in the TG rich very low density lipoprotein and hypertriglyceridemia, often but not always, means an increase of VLDL, which is sometimes associated with an increase of both HDL- and LDL- TG. The function of plasma lipoproteins in TG transport is well documented (Havel, 1972). The main function of VLDL is to transport TG from liver to peripheral tissues. In a manner analogous to the synthesis of chylomicrons from exogenous lipids in the intestinal mucosa, the TG rich VLDL are synthesized in the endoplasmic reticulum of parenchymal cells of liver and intestinal mucosa. The VLDL synthesized in the liver is termed as nascent VLDL, the composition of the core of the nascent VLDL closely resembles whereas the surface monolayer differs from the plasma VLDL (Hamilton, 1973). Several evidences indicate that the surface of the lipoprotein is modified once they enter the extracellular environment. This modification depends upon the exposure to a large amount of HDL, thus hepatogenous VLDL acquires C-apoproteins from HDL. The cholesterol content in the surface also increases while that of phospholipid falls (Hamilton, 1973). The LPL-activating apolipoprotein apo C increases the affinity of the particle with lipoprotein lipase and enhances the catalytic rate of the enzyme on component triglycerides (Fielding, 1973; Nilsson-Ehle,
et al., 1980). The hydrolysis of the triglyceride core of VLDL normally occurs rapidly at the surface of blood capillaries in several tissues (most notably adipose tissue and heart), where most of the triglyceride fatty acid is taken up into the tissues for storage or oxidation. The partially degraded particles (remnants) are rapidly metabolized by the liver. These remnant particles, whether derived from chylomicrons or VLDL, contain only a fraction of triglycerides, phospholipids and apo-C originally present but they retain all of the cholesterol esters and apo-B and the bulk of the cholesterol. The liver accounts for removal of almost all the remnant cholesterol ester and cholesterol (Bergman et al., 1971). It has been suggested that VLDL remnants may follow two pathways: (i) incorporation as unit into the liver and (ii) conversion, also presumably involving the liver, to LDL (Faergeman et al., 1974). In humans LDL are thought to be the major catabolic product of VLDL (Bilheimer et al., 1972). The level of VLDL and its triglycerides can be affected by hormones which increase (norepinephrine, growth hormone) or decrease (insulin) the supply of fatty acid used for hepatic triglyceride synthesis.

Since cholesterol esters and cholesterol are major components of atherosclerotic lesions, the interaction of the cholesterol carrying lipoproteins in plasma with the cells of the arterial wall seems to be important. An increased level of cholesterol carrying lipoprotein-
LDL is associated with an increased risk of developing atherosclerotic cardiovascular disease. As LDL levels increase more LDL presumably filters into subintimal regions and the cholesterol carried in LDL accumulates within the arterial wall (Vega et al., 1985). The contribution of LDL to atherosclerosis, however, may not be determined solely by plasma LDL concentrations. The disturbances in metabolism of LDL may also affect the atherogenicity of this lipoprotein. For example, it has been proposed that normal LDL must be modified before it can induce the development of foam cells (Brown and Goldstein, 1983). Other metabolic abnormalities may also render LDL more atherogenic. There are several reports of such abnormalities (Sniderman, et al., 1980; Brunzell et al., 1983; Teng et al., 1983; Vega and Grundy, 1984). There is also considerable evidence that elevated level of plasma triglyceride is also a risk factor for IHD. Since LDL and VLDL both are considered to be atherogenic, it seems desirable to develop therapeutic agents which specifically lower these atherogenic lipoproteins. Since total serum cholesterol concentration represents a composite of that of all serum lipoproteins, measuring serum cholesterol alone does not allow a distinction between reduction in atherogenic or nonatherogenic lipoproteins or both, to be made. The removal of HDL from the blood seems to be accomplished primarily by the liver (Rachmilewitz et al., 1972). Therefore, cholesteryl esters carried by HDL or in remnants of TG rich
lipoproteins are transported to the organ in which cholesterol is excreted from the body. The cholesterol esters that enter LDL, either from catabolism of TG rich lipoproteins or by transfer from HDL, may have a different fate. Studies of Sniderman et al. (1974) suggested that removal of LDL from blood is not impaired by hepatectomy and a high affinity receptor for LDL is present on the surface of fibroblasts (Brown and Goldstein, 1974). Binding to this receptor is rapidly followed by hydrolysis of the esters and the apo-B (Goldstein & Brown, 1977). This receptor mediated endocytosis results into the elimination of LDL particles from the blood circulation. Different lipoproteins have quite different functions in transport of cholesterol. LDL serve to supply cholesterol (mainly as ester) needed for membrane and hormone synthesis, from liver to peripheral tissues, whereas HDL efficiently transports cholesterol from various tissues to the liver for final elimination (Glomset, 1979). This reverse cholesterol transport renders HDL to be antiatherogenic agent. However, LDL cholesterol is ultimately derived from dietary cholesterol transported in chylomicrons, or from cholesterol secreted from the liver in VLDL (plus a small amount secreted in HDL). The key roles for LCAT and for HDL in the transport of cholesterol to the liver are also suggested by the genetic disorders of LCAT deficiency and Tangier disease, whereas that of LDL may find negative expression in abetalipoproteinemia (Havel, 1975). Because of the inverse
association of HDL with the incidence of coronary heart disease, as demonstrated by a number of clinical and epidemiological studies (Miller and Miller, 1975; Bahler et al., 1980; Tyroler, 1980), major interest has been focused on this lipoprotein (Miller 1980a).

High density lipoproteins form a heterogeneous group of particles which can be divided, on the basis of density, into two subfractions HDL₂ and HDL₃. The concentrations of these subfractions vary independently of each other and they have separate metabolic pathways (Nikkila, 1981). HDL₂ is larger and less dense and contains more phospholipid and free cholesterol than HDL₃ (Shen et al., 1977). Their concentration is influenced by many physiologic variables such as hormones, diet, sex and physical activity. The variation in total HDL concentration reflects mainly those of HDL₂ subfraction (Gidez et al., 1982). HDL₂ is supposed to be the component that is most closely related with atherosclerotic vascular disease (Hammett et al., 1979; Miller, 1980b). In contrast to other lipoproteins, HDL is not turned over as a single compound. Its constituents may enter and leave the mother particle at different rates and undergo exchange or bidirectional shuttling between HDL and other lipoproteins or cell membranes. The primary HDL particle is elaborated by liver and intestine and secreted into blood as disc shaped nascent HDL. When comes into circulation, this particle combines with apo A-I and donates apo C and apo E to chylomicrons and VLDL. After esterification of cholesterol by LCAT
enzyme, it takes a spherical form and becomes HDL (Glomset, 1980). During subsequent steps of intravascular metabolism, HDL acts as an acceptor of cholesterol, phospholipids and apoproteins that are released during degradation of TG-rich lipoproteins (chylomicrons and VLDL) by lipoprotein lipase at extrahepatic capillary beds. Upon this process, HDL is transformed into HDL (Patsch al., 1978). The rate of this reaction is the key determinant of plasma HDL and total HDL concentrations, as indicated by close positive correlation between lipoprotein lipase activity and HDL (or total HDL) levels (Nikkila et al., 1978). The HDL concentration, on the other hand, is not related to the lipoprotein lipase activity or shows a weak negative correlation (Taskinen and Nikkila, 1981).

There is preliminary evidence for the role of hepatic lipase in the hepatic uptake of HDL cholesterol and phospholipids (Nikkila et al., 1980). Some authors have suggested that only HDL is selectively degraded by the hepatic lipase, which possesses a high phospholipase activity (Van Tol et al., 1980). It has been speculated that HDL could lose only part of its surface lipid in the liver and be converted back to HDL which is returned to plasma and starts the cycle again. A shuttle of HDL and HDL between peripheral tissue and liver would nicely fit the proposed role of HDL in "reverse" cholesterol transport (Glomset, 1970). The process of conversion of plasma HDL to HDL, involving neutral lipid exchange and role of triglyceride
lipases, has recently been documented by Deckelbaum et al. (1986). Thus total plasma HDL concentration is regulated by the following factors—(1) the rate of input of nascent HDL into plasma (2) the activity of lipoprotein lipase at peripheral capillaries (3) the activity of hepatic lipase in the liver.

Further regulatory sites may exist particularly for the synthesis and catabolism of apo A-I and apo A-II. Diet, exercise and many hormones probably influence HDL through the two lipolytic enzymes.

C. HYPOLIPIDEMIC COMPOUNDS

The implication of blood lipids as a contributing factor in the pathogenesis has led to widespread search for compounds which safely and effectively control the concentration of cholesterol and triglycerides in the blood and hopefully in the tissues. Modern medicine is faced with the challenge of helping hundreds of millions of individuals with undetected coronary atherosclerosis, many of whom will eventually develop ischaemic heart disease and probably die as a consequence. To reduce the incidence of clinically unrecognized coronary atherosclerosis, a risk free, noninvasive, and so far nonexistent method of detecting the progress of coronary atherosclerosis in man is long overdue. Until such a method becomes available the most feasible alternative is to substitute an animal model in which
coronary atherosclerosis can be induced to study its progression, regression or arrest.

The involvement of cholesterol in the atherogenic process has led to various forms of treatment intended to reduce serum cholesterol concentrations and, consequently, the high incidence of early mortality, found in cases of familial hypercholesterolemia. The use of low fat and low cholesterol diet is the oldest therapeutic approach to reduce the risk of coronary heart disease. Since diet therapy alone does not seem to be very effective, the use of hypocholesterolemic agents along with dietary regimes is often required. Serum cholesterol can be effectively lowered by using inhibitors of HMG Co-A reductase, the rate limiting enzyme of cholesterol biosynthesis. In addition, stimulation of cholesterol excretion and degradation to bile acids and inhibition of absorption of dietary cholesterol and biliary cholesterol may also reduce blood cholesterol level up to some extent but these manipulations appear to be less feasible. Using animal systems a large spectrum of hypolipidemic drugs has been investigated differing in their degrees of efficacy and modes of action. They may decrease serum lipid levels by impairing lipid absorption, lipoprotein synthesis or release, or by stimulating lipid or lipoprotein catabolism (Sirtori et al., 1973).

Clofibrate, Nicotinic acid, esterogenic substances, Triparanol, Hydroxylamines, Mevinolin and Probucol are the examples of the inhibi-
tors of cholesterol biosynthesis. Clofibrate, ethyl-p-chlorophenoxy isobutyrate (CPIB) is an effective hypolipidemic drug, most widely used in clinical practice. Thorp and Waring (1962) first reported the inhibition of hepatic cholesterol synthesis in CPIB-fed rats. The ability of CPIB to lower postprandial plasma optical density as well as triglycerides and lipoprotein suggested an action on lipoprotein lipase (Strisower and Strisower, 1964). CPIB has been shown to inhibit cholesterol biosynthesis at the step involving conversion of acetate to mevalonate (Gould et al., 1966) thereby inhibiting overall synthesis of steroids. CPIB also affects several other metabolic pathways. Maragoudakis (1969) reported inhibition of fatty acid synthesis by CPIB treatment. Tolman et al. (1970) reported stimulation of lipoprotein lipase activity in adipose tissue. Stimulation of adenyl cyclase activity following CPIB treatment has also been reported (Greene et al., 1970). CPIB inhibits liver lipid biosynthesis and induces liver cholesterol depletion. Increase in lipoprotein lipase activity results into increased catabolism of VLDL and elevated HDL cholesterol level, thus it helps in mobilization of tissue cholesterol. Borreback et al. (1979) reported increased levels of hepatic acyl-Co A hydrolase activities in clofibrate fed rats. Hazzard et al. (1984) demonstrated significant decrease in plasma cholesterol and triglycerides, VLDL-cholesterol and triglycerides and an increase in HDL-cholesterol upon clofibrate feeding. However, it was associated with increase in reports of nausea.
Clofibrate (CPIB)
[Ethyl p-chlorophenoxy isobutyrate]

Methyl clofenapate

Probucol (DK-581)
[4,4'-(isopropylidene dithio)bis(2,6-di-t-butyl phenol)]

DH 990
[2-[(3,5-di-t-butyl-4-hydroxy phenyl)thio]hexanoic acid]
HCG-004
[2-(4-(4-chlorophenoxy)-phenoxyl) propionic acid]

AT-308
[3-(4-(4-ethoxycarboxyl-1-methyl ethoxy) phenyl)-5(3 pyridyl)-1,2,4-oxadiazole]

Halofenate (MK-185)
[2-aceto amidoethyl (p-chlorophenyl) (m-trifluor-methyl phenoxy) acetate]
Tibric acid
[2-chloro-5{(cis-3,5-dimethyl-piperidono sulphonyl) benzoic acid}]

Eritadenine
(Lentysine)

5-methyl tetrazole derivatives
Various clofibrate analogues have also been described as hypolipidemic and hypocholesterolemic agents. Halofenate, structurally related to clofibrate is a hypolipidemic and hypouricemic drug (Sirtori et al., 1972). It has been found to be effective in lowering serum triglycerides in rat (Kritchevsky and Tepper, 1972). Another analogue 3[4-(1-ethoxycarboxyl-1-methylethoxy)phenyl]-5(3 pyridyl)-1,2,4-oxidazole (AT-308) is effective in lowering serum cholesterol of normal rats significantly. Methyl clofenapate (Craig and Waltom, 1972) and 2-[4(4'-chlorophenoxy)-phenoxy] propionic acid or HCG-004 (Granzer and Nahm, 1973) have also been reported to be hypocholesterolemic and hypolipidemic compounds.

Bezafibrate (a fibric acid derivative) is a new hypolipidemic drug. Recently it has been reported to lower plasma triglycerides in hypertriglyceridemic patients (Eisenberg et al., 1984). It was also found effective in reversing most, if not all, of the plasma lipoprotein abnormalities found in these patients. Reports are also available to show its stimulating effect on enzymes, lipoprotein lipase and hepatic lipase (Vessby et al., 1982) during treatment of hypertriglyceridemic patients. This drug is also known to accelerate LDL degradation via the receptor pathway (Stewart et al., 1982). Gavish et al. (1986) reported a decrease of plasma cholesterol and triglycerides, VLDL-cholesterol, LDL-cholesterol and an increase of HDL-cholesterol along with the increase in postheparin plasma lipase in patients with
type II A and type II B hyperlipoproteinaemia in response to bezafibrate therapy.

Mevinolin and compactin (ML-236B) belong to a new class of cholesterol lowering drugs that appear highly effective in relatively low doses. The primary action of these drugs is to competitively inhibit HMG Co-A reductase. These drugs have been used to reduce plasma cholesterol levels in many animal species (Alberts et al., 1980; Kovanen et al., 1981; Tobert et al., 1982). Clinical studies have shown that mevinolin and compactin effectively reduce plasma levels of LDL in normal subjects (Tobert et al., 1982) and in patients with heterozygous familial hypercholesterolemia (Yamamoto et al., 1980; Bilheimer et al., 1983). The inhibition of cholesterol synthesis by mevinolin appears to trigger a compensatory increase in the receptor mediated catabolism of LDL resulting into the increased utilization of lipoprotein cholesterol by the cells (Grundy and Bilheimer, 1984).

Probucol (4,4'-(isopropylidenedithio) bis(2-6-di-t-butylphenol)) or DK-581 has been reported to be effective for the treatment of hypercholesterolemia. It effectively reduces plasma cholesterol by inhibiting cholesterol biosynthesis in human and a number of animal species (Miettinen and Toivonen, 1975; Martz, 1979; Simson et al., 1981). Probucol also decreases the activity of plasma lipoprotein lipase and HDL- and LDL-cholesterol concentrations in rat (Strandberg et al., 1981). A possible mechanism of action of probucol has been proposed
by Balasubramanium et al. (1981) involving its effect on LDL and HDL metabolism and on the key enzymes of cholesterol metabolism. The drug triparanol is also an inhibitor of cholesterol biosynthesis and it is also found to interfere with the luminal absorption of cholesterol (Bhattacharya and Eggen 1984.)

A derivative of thiophenol, DH-990 has also been reported to lower normal serum cholesterol levels in mice, rats and monkeys (Renzi et al., 1974). Tibric Acid (2-chloro-5-(cis-3,5-dimethyl-piperidono-sulfonyl) benzoic acid) also reduces plasma lipids in normal rats in doses as low as 5 mg/kg/day (Pereira and Holland, 1974). Tiadenol, (bis(hydroxyethylthiol) 1-10 decane), is an absorbable hypolipidemic agent (Baggio, et al., 1979). Tiadenol treatment was remarkably effective in inhibiting fructose induced hypertriglyceridemia. Its mode of action differs from that of clofibrate and related compounds (Franceschini, et al., 1981).

Buchanan and Sprancmanis (1973) have synthesized a series of hypocholesterolemic 5-methyltetrazole derivatives: two of them are especially active in lowering cholesterol levels in normal rats by 47 and 30%.

Among Bile acid sequestrants, one type of hypocholesterolemic drugs whose mechanism of action is understood, is the kind that binds bile salts and thereby decreases cholesterol absorption. Anion exchange resins are the good examples. They bind bile acids in the intestinal lumen and prevent their reabsorption resulting into their
excretion in the faeces. These sequestering agents, thus, interfere with the enterohepatic circulation of bile acids. Since bile acids are synthesized in the liver from cholesterol, cholesterol catabolism is accelerated. As a result of which plasma cholesterol concentration decreases. When administered to human subjects, these resins are known to alter lipoprotein composition such that LDL are smaller, more dense, and have a decreased cholesterol:protein ratio (Witztum et al., 1979). Bile acid sequestrant resins are widely used in the therapy of hypercholesterolemia as they specifically lower plasma LDL concentration by enhancing the fractional catabolic rate (FCR) of LDL via receptor mediated pathway (Slater et al., 1980; Kovanen et al., 1981; Hui et al., 1981; Chao et al., 1982). Examples of such lipid lowering agents are cholestyramine, colestipol and secholex.

Cholestyramine was found to reduce plasma cholesterol levels in man and animals (Glueck et al., 1971; Fellin et al., 1975). Cholestyramine induced changes in LDL composition and metabolism have also been reported using guinea pigs as animal models (Witztum et al., 1985).

Colestipol is an insoluble copolymer of tetraethylene pentamine and epichlorohydrin. It was found effective in decreasing reabsorption of bile acids and enhancing their faecal excretion (Parsons, 1972). Colestipol treatment resulted in a reduction of total cholesterol in plasma as well as in tissues (Good et al., 1973; Miller et al., 1973).
Hazzard et al. (1984) reported significant decrease in plasma and LDL cholesterol while an increase in VLDL-TG was observed after colestipol treatment in hyperlipidemic volunteers. However, this treatment was associated with reports of constipation and nausea. Secholex has been tested alone and in combination with clofibrate (Evans et al., 1973; Howard and Evans, 1974). The combined therapy was found more effective as compared to secholex alone.

D. GENESIS OF THE PRESENT WORK

Hyperlipidemia has been well recognized in the etiology of atherosclerotic lesions. Therefore, a logical therapeutic approach could be the search of compounds which could safely and effectively lower the lipids in blood and hopefully in tissues. Since more than 70% of the total input body cholesterol is derived from de novo synthesis in human (Dietschy and Wilson, 1970), it is expected that compounds inhibiting cholesterol biosynthesis may prove more useful in combating hypercholesterolemia. The most suitable target for this inhibition would be HMG Co-A reductase, the rate limiting enzyme in cholesterol biosynthesis (Rodwell et al., 1976). HMG is known to inhibit cholesterogenesis between HMG Co-A and mevalonate (Rabinowitz and Gurin, 1954) and competitively inhibits the enzyme HMG Co-A reductase (Fimognari and Rodwell, 1965).
During the last two decades, this laboratory is actively engaged in gaining an insight into the mechanism of hypolipidemic action of HMG.

1. The oral administration of HMG in normal as well as hypercholesterolemic rats resulted in significant reduction of serum cholesterol. The combined feeding of cholesterol and HMG also significantly reduced the serum and hepatic cholesterol levels (Beg and Siddiqi, 1967; Beg et al., 1968) and it had no hepatotoxic effect at the microscopic level. The animals receiving fat-rich cholesterol diet showed a maximum significant reduction in ester cholesterol and triglycerides after HMG treatment (Beg and Siddiqi, 1968).

2. HMG was found to inhibit hepatic cholesterogenesis (Beg and Lupien 1972). Saleemuddin and Siddiqi (1972) showed that i.p. administration of HMG caused an increase in hepatic HMG Co-A hydrolase activity and suggested a physiological control mechanism for cholesterol biosynthesis.

3. HMG had been shown to exert a protective effect in experimental atherosclerosis in rabbits. It had no significant effect on serum enzymes like GOT, GPT, LDH, CPK and alkaline phosphatase (Lupien et al., 1973). In an independent study Yusufi and Siddiqi (1974) established hypolipidemic property of HMG in rabbits. As all serum lipids were reduced, it was suspected that hypolipidemic action of HMG could be mediated through its action on lipoproteins.

4. In alcohol induced lipemia in man, HMG markedly reduced elevation of serum triglycerides, LDL and phospholipids (Yousufzai et al., 1976).
5. In an effort to demonstrate the hypolipidemic action of HMG under varied dietary and experimental conditions, it was demonstrated that HMG effectively counteracts the lipemic and atherosclerotic response of massive doses of vitamin D₂ and there is a lowering of serum LDL (Yousufzai and Siddiqi, 1976a). HMG is more effective against hypertriglyceridemia in rats (Yousufzai & Siddiqi, 1976b).

6. HMG administration alongwith atherogenic diet in rats significantly decreased cholesterol and phospholipids of serum, aorta and heart. The triglyceride levels in serum, liver and epididymal fat were significantly decreased (Yousufzai and Siddiqi, 1977a). The effect of HMG with different carbohydrate diets appeared to be independent of the type of the carbohydrate (Yousufzai and Siddiqi, 1977b).

7. HMG induced lowering of lipid parameters in serum β-lipoproteins and liver would be due to either inhibition of VLDL synthesis or VLDL triglyceride release in liver. Since HMG failed to prevent orotic acid induced fatty liver (Yousufzai and Siddiqi, 1977c), it ruled out the possibility of HMG inhibiting the release of VLDL and LDL.

8. HMG has a high LD₅₀ without toxic or teratogenic effects (Savoic and Lupien 1975a) and is promptly absorbed from the gut (Savoic and Lupien 1975b). In a double blind trial in hypercholesterolemic patients, effect of different doses of HMG on plasma and LDL were studied (Lupien et al., 1979). The patients responded well to
HMG treatment without any evidence of adverse clinical or biological effect. All patients maintained excellent compliance to medication suggesting that HMG, because of its lack of toxicity, may be useful as an adjuvant to diet in treatment of familial hypercholesterolemia.