REVIEW OF LITERATURE
Hyper lipoproteinemia are disturbances of lipid transport that result from accelerated synthesis or retarded degradation of lipoproteins that transport cholesterol and triglycerides through plasma. Elevated plasma lipoprotein levels are important clinically because they can cause atherosclerosis and coronary heart disease. A reduction in plasma lipoprotein cholesterol levels achieved by diet and/or drugs, reduces the risk of myocardial infarction in subjects of hyper lipoproteinemia (Peto et al, 1985).

Cholesterol is a neutral derived lipid and is designated as 3-hydroxy-5, 6 cholestane. It is widely distributed in all cells of the body, but particularly in nervous tissue. It is the parent compound of all steroids synthesized in the body. It occurs in animal fats but not in plant fats. The major portion of body cholesterol arises by synthesis (about 1gm/day), whereas only about 0-3 gm/day is provided by the average diet.

Cholesterol enters the body with chylomicrons. Triglycerides of chylomicrons are hydrolyzed and residual particles, called chylomicron remnants are removed by the liver. The liver likewise secretes triglyceride rich lipoproteins called VLDL, which are degraded into smaller VLDL remnants. This can be removed by the liver or converted to LDL. the LDL are the major cholesterol carrying lipoproteins in the plasma. The major pathway for removal of LDL is via LDL-receptors. It has been found that patients with familial hyper cholesterolemia have defective LDL-
receptors on cells which means that they are unable to clear cholesterol, thus leading to high plasma cholesterol levels. These are receptors on cell membranes which control the uptake of LDL and hence cholesterol from plasma into cells. The activity of these LDL receptors is under feedback control. LDL is the carrier of cholesterol and is responsible for the delivery of cholesterol to peripheral cells, where the cholesterol can be utilized for cell membrane or for steroid hormone synthesis depending upon the tissue (Thomas, 1990).

When the circulating levels of LDL-cholesterol are so high that they saturate above route, the large quantities of cholesterol enter the cells by a second uncontrolled route. This Cholesterol does not stop cells own synthesis of cholesterol nor does it influence the LDL receptors on the cells. The result of this is that the concentration of Cholesterol in cells can rise to abnormally high values leading to development of atheroma and eventually coronary heart disease (Thomas, 1990).

Several large surveys reveal a positive correlation between the concentration of plasma Cholesterol and risk of CHD. There is no level of Cholesterol below which coronary events are absent. But it has been shown by Framingham study and Multiple risk factor intervention trial (MRFIT) that risk of CAD rises beyond serum Cholesterol level of 180mg/dl. A long term prospective study in our population to assess the relation of serum lipids and CAD is lacking. We will have to go therefore, by the recommendations of NCEP which desires the level of total Cholesterol to be below 200 mg/dl and that of LDL-c below 130 mg/dl.
TYPES OF HYPER LIPOPROTEINEMIA:

Hyperlipoproteinemia has been classified by following two approaches. One approach is based on the pattern of lipoprotein abnormalities (Frederickson et al/WHO, 1988) (Table 1) while the other is related to clinical, genetic and metabolic entities (Lewis, 1988; Brown et al, 1990; Edwin, 1990) (Table 2, 3).

As evident in table 2 and 3 hyperlipoproteinemia can be designated as either primary or secondary. Primary hyperlipoproteinemia can be divided into two major groups; those caused by an inherited single gene defect (Monogenic) and those that appear to be caused by a combination of multiple subtle genetic factors that act together with environmental insults (Multifactorial or polygenic).

Secondary hyperlipoproteinemias are the complications of more generalized metabolic disturbances such as diabetes mellitus, hypothyroidism, and excess alcohol intake etc.

COMPLICATIONS OF HYPERLIPOPROTEINEMIA:

Hyperlipoproteinemia is associated with a wide variety of clinical conditions ranging from silent abnormalities of plasma lipid concentration to grave and life threatening cardiovascular, abdominal and neurologic conditions.

Of particular importance is the evidence that certain plasma lipoprotein abnormalities are causally related to ischemic heart disease and other are predictive of high risk of this disorder (Lewis, 1988; Kannel et al, 1979). Raised plasma lipoproteins are
### Table 1: Types of Hyperlipoproteinemia

<table>
<thead>
<tr>
<th>Type</th>
<th>Chylomicrons</th>
<th>VLDL</th>
<th>Remnants</th>
<th>LDL</th>
<th>Plasma Cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>++</td>
<td>N</td>
<td>N</td>
<td>Low</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IIa</td>
<td>-</td>
<td>N</td>
<td>N</td>
<td>++</td>
<td>+</td>
<td>+ +</td>
</tr>
<tr>
<td>IIb</td>
<td>-</td>
<td>++</td>
<td>N +</td>
<td>++</td>
<td>+</td>
<td>+ +</td>
</tr>
<tr>
<td>III</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>Low</td>
<td>+</td>
<td>+ +</td>
</tr>
<tr>
<td>IV</td>
<td>-</td>
<td>+ +</td>
<td>N</td>
<td>N</td>
<td>+</td>
<td>+ +</td>
</tr>
<tr>
<td>V</td>
<td>++</td>
<td>++</td>
<td>N</td>
<td>Low</td>
<td>+</td>
<td>+ +</td>
</tr>
</tbody>
</table>

Classification of Fredrickson, Levy and Lees (1968) Extended by WHO Committee.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Primary Disorder</th>
<th>Kinetic Disorder</th>
<th>Plasma Cholesterol</th>
<th>Plasma Triglyceride</th>
<th>Lipoprotein in excess</th>
<th>WHO Type</th>
<th>Atherosclerosis Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hypercholesterolemia - xemia</td>
<td>LDL receptor defect impaired LDL Catabolism and LDL overproduction</td>
<td>+ +</td>
<td>Normal</td>
<td>IDL</td>
<td>Ila</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Familial combined - hyperlipidemia</td>
<td>over production of LDL and VLDL</td>
<td>+</td>
<td>+</td>
<td>LDL, VLDL</td>
<td>Ila, IIb</td>
<td>++</td>
<td>IV</td>
</tr>
<tr>
<td>Familial Hyper-Triglyceridemia</td>
<td>impaired catabolism of VLDL and ApoB, with over production of VLDL triglyceride.</td>
<td>+</td>
<td>+ +</td>
<td>VLDL</td>
<td>CM</td>
<td>V, IV</td>
<td>?</td>
</tr>
<tr>
<td>Drylonicromasia</td>
<td>Lipoprotein lipase deficiency or ApoIII clearance</td>
<td>+</td>
<td>+ +</td>
<td>CM, VLDL</td>
<td>I, VII</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Remnant hyperlipoproteinemia</td>
<td>Abnormal ApoE and other genetic or acquired disorders impaired remnant particle catabolism, reduced conversion to LDL, with or without IDL over production.</td>
<td>++</td>
<td>++</td>
<td>IDL, CM remnants</td>
<td>III</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Common hypercholesterolemia</td>
<td>LDL overproduction</td>
<td>+</td>
<td>Normal</td>
<td>LDL</td>
<td>Ila</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Hyper Cholesterol</td>
<td>Hyper Triglyceridemia</td>
<td>Plasma lipoprotein elevation</td>
<td>WHO TYPE</td>
<td>Mechanism of hyperlipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------</td>
<td>----------------------</td>
<td>----------------------------</td>
<td>----------</td>
<td>------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+++</td>
<td>- IV **VLDL secretion, *VLDL Catabolism due to lipoprotein lipase activity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++ Ila *VLDL and IDL Catabolism.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic Synd.</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>++ +++ Ila, IIb **VLDL secretion, Direct secretion of LDL from liver,*VLDL &amp; LDL Catabolism.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++ - IV *hepatic secretion of lecithin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+++ IIV *VLDL Catabolism due to reduced lipoprotein lipase activity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+++ - IV **VLDL secretion *VLDL &amp; Chylomicron Metabolism due to reduced lipoprotein lipase activity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++ + Iib **secretion of VLDL with conversion to LDL.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia Nervosa</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++ Ila *biliary excretion of cholesterol and bile acids.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Porphyria</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++ Ila Unknown.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+++ - IV **VLDL secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+++ - IV **VLDL secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ ++ Ila, Iib **VLDL secretion with conversion to LDL.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* DECREASED
** INCREASED
important clinically because they can cause two life threatening diseases, atherosclerosis and pancreatitis (Brown et al 1987).

**HYPERLIPOPROTEINEMIA AND ATHEROSCLEROSIS:**

Atherosclerosis, a sequel of hyperlipoproteinemia is a patchy nodular type of arteriosclerosis. The lesions commonly classified as fatty streaks, fibrous plaques and complicated lesions. They are characterized by an accumulation of lipid filled smooth muscle cells and macrophages (foam cells) and fibrous tissue in focal areas, of the intima. There is a relation between fatty streaks and fibrous atherosclerotic plaques. In the coronary arteries, the extent of fatty streaks may be a better indicator of clinically significant raised lesions later in life. The most characteristic lesion of advancing atherosclerosis is probably represented by fibrous plaques, also called pearly plaques or raised lesions. The plaque is much thicker than intima. Although the lipid, like that of fatty streaks, is mainly cholesterol ester, the principal esterified fatty acid is linoleic rather than oleic acid. Thus plaque cholesterol composition differs from fatty streaks, but resembles closely to plasma lipoproteins. The complicated lesion is a calcified plaque containing various degrees of necrosis, thrombosis and ulceration with increasing degree of necrosis and accumulation of gruel the arterial wall weakens progressively, and rupture of the intima may occur causing aneurysm and haemorrhage. Arterial embolism form when fragments of plaque dislodge into lumen. Stenosis and impaired organ function result from gradual occlusion of vessels as plaque thicken and thrombi form (Edwin, 1987). Although the
term generalized atherosclerosis is commonly used, lesions are irregularly distributed; different vessels are involved at different ages and to varying degrees (Edwin, 1987).

Atherosclerotic plaques vary in composition. Their major components include smooth muscle cells, cholesteryl esters and other lipids, collagen and glycosaminoglycans. In patients dying of myocardial infarction the great majority have severe extensive coronary atherosclerosis, superadded coronary thrombosis is usually present in the vessel supplying the area of full thickness myocardial infarction, and increasing evidence indicates a role of localized coronary spasm in precipitating at least some acute occlusions (Lewis, 1988).

The earlier attempts to investigate the biochemical nature of the atherosclerotic lesion incriminated cholesterol (vogel, 1847, Windaus, 1910), modern investigations continue to show cholesterol, particularly cholesteryl esters, as the principal lipid ingredient of the atherosclerotic lesion (Smith, 1965; insull et al 1966, Bottcher et al, 1960).

Epidemiologic studies of the evolution of cardiovascular disease due to atherosclerosis have for many years emphasized the importance of serum total cholesterol as a precursor of coronary heart disease (MC Gee et al, 1976; intersociety commission for heart diseaese resources, 1970; kannel et al, 1971; carlson et al, 1972; gordon et al, 1974; keys, 1970; westlund et al, 1972 and Rosemann et al 1967). As a result of great amount of researches conducted into the transport and intermediary
metabolism of blood lipids during the past three decades. Attention has been focused on the partition of the serum total cholesterol in the various lipoprotein fractions (Gofman et al., 1966; Fredrickson et al., 1967) and the atherogenic potential of each of the lipoprotein fractions.

**HYPERLIPOPROTEINEMIA AND ISCHEMIC HEART DISEASE:**

A strong association between hyperlipoproteinemia and ischemic heart disease is proved beyond doubt. The cause and effect relationship between these two is suggested by various researchers (Kannel et al., 1971; 1977; Westlund et al., 1972; Martin et al., 1984; Hiroyasu et al., 1989; Edwin, 1990 and Lewis, 1988). Atherosclerotic lesions resembling to those in human being can be produced in animal models if they were fed with high fat and cholesterol diet. These lesions show regression when cholesterol levels are reduced by dietary change or medication (Kannel et al., 1979). Several trials and their comparison by Peto (1981) suggests that the extent of reduction in risk of ischemic heart disease is directly related to the degree of reduction in plasma cholesterol.

Serum cholesterol levels are positively correlated with diastolic blood pressure, which again is a risk factor for ischemic heart disease (Hiroyasu et al., 1989). Hypercholesterolemia with high levels of LDL has been identified as a major independent risk factor for ischemic heart disease. Hypertriglyceridemia with high level of VLDL is also associated with a higher incidence of CHD, but itself is a less definite
predictor of atherosclerotic heart disease (Tripathi et al, 1990). Risk of development of ischemic heart disease has been shown to be a graded function of levels of total plasma cholesterol and more particularly so of LDL - cholesterol (Tripathi et al, 1990).

On the other hand recent studies showed a strong inverse relationship between levels of HDL cholesterol with incidence of coronary heart disease. Higher the proportion of HDL - cholesterol to total cholesterol lesser is the risk of cardiovascular disease (Kannel et al, 1979).

The association of cholesterol with IHD appear mainly to be due to LDL - cholesterol with which it is highly correlated. Low level of total or LDL - cholesterol appear to be associated with increased risk of non-cardiovascular deaths. But studies in two populations - London and Paris - indicate that this inverse portion is confined to deaths in the very early years of the follow up (Mann et al, 1987).

Prospective studies showed that increase in total triglycerides and VLDL levels are usually associated with an increased IHD rate. This increased risk is apparent when the triglyceride level exceeds 150 mg/dl, but only two studies have suggested that the association is independent of other factors of lipid metabolism (Mann et al, 1987).
Recent workers have focussed their attention to the possibility that HDL may be a protective factor. Where HDL has been measured in prospective studies, low levels has been seen to be productive of subsequent IHD, and in communities where IHD is uncommon HDL level are high. In people over 50 years of age the predictive value of HDL appears to be stronger than that of LDL, while below the age of 50 it seems that the LDL might be more important prediction of IHD (Mann et al, 1987).

**CHANGES IN LIPID LIPOPROTEIN LEVELS AFTER HIGH CHOLESTEROL DIET:**

Effect of long term and short term feeding of high cholesterol fat diet evokes variable responses and is subject to individual variation. Dietary fat and cholesterol causes changes in specific lipoprotein in a variety of species (Mahley et al, Arora RC et al). Quantitatively a change in specific lipoprotein may be dramatic in one species than in other. These changes have been associated with the development of atherosclerosis in experimental models (mahley et al).

**TOTAL SERUM CHOLESTEROL (STC):**

In 1956 Ancelkey’s JT Anderson et al concluded that serum cholesterol level is essentially independent of the cholesterol intake over the whole range of natural human diets. But later on it was proved beyond doubt that feeding cholesterol rich diet for 2-8 weeks raised STC in blood (Arora R.C. et al Messsinger et al, Conner et al, Deborah Applebaum et al).
In an earlier report, Bruhn (1940) observed a 20% rise in mean cholesterol level after a fat load. Effect of high cholesterol fat load on post prandial cholesterol levels has also been studied in the past by several workers, but insignificant difference has been found between post prandial and 10-14 hours fasting values (Albrink and Mann, 1956, Pomerange et al, 1954; Schilling et al, 1964). On the other hand Nikkila and Konttinen (1962) demonstrated a significant decrease in cholesterol level six hours after a fat rich diet in soldiers. Hanno Krauss, Picter Groot (1987) reported insignificant changes in STC after feeding 0.5 gm/m2 of cholesterol and taking reading at 2 hrs interval for 14 hours.

In adolescents with initial cholesterol levels greater than 200 mg/dl, a 50 percent decrease in cholesterol intake led to an appreciable drop (15.6%) in cholesterol level, but the effect was much more modest (8.3%) in those with lower initial levels (Gandy et al 1972).

In a survey of school age children examining the influence of nutrients on LDL-cholesterol, it was concluded that the higher intake of cholesterol and lower ratio of P/S was associated with higher values of LDL cholesterol. Strict vegetarians have been reported having lower serum cholesterol than non vegetarians (Gacks et al, 1975; Knuiman et al, 1982). However in 7 different studies summarised recently, significantly weak correlation were noted between serum lipids and dietary P/S ratio (Mellies and glueck, 1983).
The replacement of animal protein with vegetable protein in the diet has been suggested to reduce the diet linked atherogenic risk (Carrol, 1982). However, sacks et al (1983) found no appreciable correlation between intake of protein, when consumed above minimum requirement, and serum cholesterol level.

Studies with animal models showing that sucrose and fructose are atherogenic, prompted human studies, which have not shown consistent changes. In one study, isocaloric replacement of starch with sucrose in mixed diet did not lead to changes in serum cholesterol (Mann and Truswell, 1972), as were documented in another study (Reiser et al, 1978).

Serum cholesterol was higher during the first 9-12 months of life in breast fed babies, but there was little difference subsequently (Friedman and Goldberg, 1976; Huttunen et al, 1983). In addition to its high cholesterol content (20 mg/dl), breast milk has decreased P/S ratio of fatty acids when compared to formulas. In a report dealing with feeding habits and serum lipids in infants and children, there was a direct correlation between serum lipids and the amount of saturated fat as well its P/S ratio in infants aged 6-10 months, but no such correlation was found in 3-4 years old children. The type and duration of early feeding practices had little influence on subsequent serum lipid levels (Anderson et al, 1979). Results of human studies, therefore do not agree with animal work, which suggest that a low post natal dietary cholesterol homeostatis. In fact it was shown that children aged 7-12 years who were fed low cholesterol formulas has a lower mean serum cholesterol than those fed cow's milk or breast milk (Hodgson et al, 1976). Another study could
not document any effect of a low versus a moderate cholesterol intake during first six month of life in response to large cholesterol intake during second 6 month of life (Blueck, 1972).

**HIGH DENSITY LIPOPROTEINS (HDL):**

Conflicting reports have appeared on effect of dietary cholesterol on HDL levels.

Borden et al (1964) reported enhanced levels of HDL in cholesterol fed rats while Haft et al (1962) and Kritchevsky (1965) reported no change in HDL levels in cholesterol fed rats. Reiser et al (1966) and Howard et al (1968) reported decreased level of HDL cholesterol in rats fed with high cholesterol diet.

Narayan (1971) reported that HDL2 decreased drastically about 50% in rats fed with high cholesterol diet. These results confirmed the earlier observation of Reiser et al (1966) that rat serum HDL level was decreased irrespective of whether a saturated or unsaturated fat was used in the diet supplemented with cholesterol.

In short term feeding studies, marked reduction in dietary fat and isocaloric increase in carbohydrate resulted in decrease in HDL- cholesterol in conjunction with elevation of serum triglycerides and VLDL. Studies of HDL composition have shown a decrease in ratio of apolipoprotein A-I to A-II and a decrease in HDL cholesterol to protein ratio (Schonfledd et al, 1976) consistent with a selective decrease in HDL2 species (Blum et al, 1977).
There are evidence that substitution of large quantities of polyunsaturated fat for saturated fat in diet can result in lower levels of HDL lipids and proteins (Nichaman et al, 1967). An increase in the PiS fat ratio from 0.25:1 to 4:1 in diet fed to four normal subjects for five weeks resulted in reduction of HDL cholesterol and apolipoproteins A-I concentration of 33 and 21 percent respectively with an associated reduction in HDL2: HDL3 ratio (Shepherd et al, 1978) other studies have however reported either no change (Lewis, 1978; Shore et al, 1981) or increase (Jackson and Blueck, 1980) in levels of HDL cholesterol with feeding of diets enriched in polyun-saturated fats.

High dietary intake of cholesterol, in the form of 3-6 egg yolk per day has been reported to produce increase in apolipoprotein E-containing HDL-subspecies in human (Mahley et al, 1978). This effect was seen whether or not there was an increase in total plasma cholesterol. Despite the fact that HDL containing apolipoprotein E represented only a minor fraction to the total HDL, its presence was shown to account for an increase of 2.6 to 4 times the binding of HDL to LDL receptors of fibroblasts as compared to pretreatment HDL (Mahley et al, 1981). But this was not observed in another study (Applebaum et al, 1979). Recently it has been reported that level of HDL-cholesterol and serum apolipoprotein A-I but not apolipoprotein E increased with the feeding of diets high in both cholesterol and saturated fat (Tan et al, 1974).
Finally, in evaluating the effects of dietary variables on HDL is that, while levels of HDL cholesterol and plasma apolipoprotein A-I are similar after overnight fast and the non fasting state (Henderson et al, 1980) changes in levels and composition of HDL have been shown to occur actually after meals containing fat cholesterol, phospholipid and C- apolipoprotein level in HDL2 increases and cholesterol in HDL decreases (Havel, 1973; Baggio et al, 1980) in conjunction with transfer of chylomicron lipids to HDL during the course of their catabolism. Recently it has been shown that HDL apolipoprotein A-I level increased when fat was consumed in divided doses over a 10 hours period but not when the same amount of fat was ingested as a single load (Key et al, 1980).

LOW DENSITY LIPOPROTEIN (LDL):

High fat and cholesterol diet causes an elevation in LDL level in most animals (Mahley, 1979). The response in man varies, but in those subjects who have an elevation in plasma cholesterol, there is an elevation in plasma LDL levels. Deborah applebaum et al (1979) demonstrated a significant rise of LDL level in human volunteers after feeding 500 mg of egg yolk cholesterol per day for 30 days.

Age related difference in rise of LDL was demonstrated by Arora and Gupta et al (1987). They found that rise of total serum cholesterol after feeding high fat high cholesterol breakfast for one week was much more pronounced in young volunteers with major portion of rise being contributed by increased HDL contrary to
this in older age groups the rise of HDL was less marked with LDL contributing mainly in the increased levels.

Baudet et al demonstrated that there was significant fall in level of LDL in five volunteers, 3 hours and 5 hours after taking butter diet they attributed this fall due to defect in VLDL hydrolysis by serum lipases and due to metabolic blocking in liver or in adipose tissues.

In addition to this the diet included LDL are larger then LDL from the same species on low fat, low cholesterol diet. In a study performed by Rudel and co-workers in 1979 on rhesus monkey showed that, high cholesterol diet induced LDL have molecular weight which are 1.5 fold larger than those of control LDL. Further more St. clair and Leight (1978) have reported that the diet induced large LDL are capable of stimulating cholesteryl esterification and accumulation in smooth muscle cells to a greater extent than are normal LDL.

An additional alteration in the LDL induced by the high cholesterol diets involve the apoprotein constituents. In normal LDL, the B apoprotein is the major detectable apoprotein moiety, however, in several species the LDL contain a variable amount of the E apoprotein following cholesterol feeding (Mahley et al, 1977; Rudel et al, 1979).

PLASMA ChOLESTEROL AND LDL RECEPTORS :

A decade of intense investigations has established a central role for lipoprotein receptors in regulating plasma cholesterol
traffic. Operationally the IDL/LDL receptor system can be considered the primary transport mechanism for endogenous cholesterol. LDL are generated in the plasma by the degradation of intermediate density lipoprotein IDL. Generated LDL is removed relatively slowly from plasma by binding to LDL receptors in the liver and extranepatic tissues (Kita et al., 1982). In rabbits, rats and hamsters, more than half of the total LDL receptors are located in the liver. However the precise distribution of these receptors in man is unknown.

Hepatic LDL receptors are suppressed whenever the liver content of cholesterol increases or its demand for cholesterol is reduced. This receptor suppression occurs when a high cholesterol diet is consumed (Hui et al., 1981) or when bile acids are infused (Angelin et al., 1983). Conversely, LDL receptors increases when hepatic cholesterol synthesis is blocked by drugs compactin or mevinolin (Goldstein et al., 1982; Bilheimer et al., 1983), when bile acid binding resins are given (Shepherd et al., 1980) or when an ileal by pass is created (Spengel et al., 1982). Fasting has also been shown to suppress LDL receptor in rabbits (Goldstein, 1982). LDL receptors can be stimulated by thyroxine (Thompson, 1981) and by pharmacologic doses of oestrogen (Winder, 1980). Hepatic LDL receptors decline when rabbits are fed a diet composed only of sucrose and casein (Chao et al., 1982). In dogs, hepatic LDL receptors fall with ageing (Mahley et al., 1981).

All of the changes in receptor activity alter the rate of uptake of LDL by the liver and cause reciprocal changes in plasma LDL levels. Whenever hepatic LDL receptors are suppressed, the
plasma LDL level rises, conversely whenever these receptors are induced, the plasma LDL level falls.

**SERUM TRIGLYCERIDES AND VERY LOW DENSITY LIPOPROTEIN (STG AND VLDL):**

The level of STG rises considerably after fat ingestion. Rise in the triglycerides level after fat ingestion has been reported after giving different amounts of the fat load and measuring the blood levels at different time intervals (Nikkita and Konttinen, 1962; Denborough, 1963). Angeretial (1963) has reported a significant correlation between fasting, 3 1/2 hours value and 7 1/2 hours value of serum triglyceride post prandially.

Clafsky et al (1976) noted a biphasic plasma triglyceride curve with an initial peak occurring 1-3 hours after feeding and a second peak after 4-7 hours.

The first peak was accounted by increase in chylomicron levels in more than 98% cases, whereas second peak represented rise in VLDL level in 82%.

In 1957, Havel concluded that increment in the concentration of triglycerides in the serum following ingesting of fat is entirely the result of an increase in their concentration in VLDL.

Excess production of VLDL and triglyceride is more often due to secondary abnormalities than to primary factors, perhaps the most common cause is high caloric intake associated with obesity.
excess alcohol and excess carbohydrate. Increased levels are also found in diabetes mellitus, nephrotic syndrome and hypothyroidism with obesity. Delayed clearance of triglyceride from the serum is noted in cases of ischemic heart disease after high fat diet (Arora et al, 1987; Brown et al, 1961).

**BETA VLDL AND CHOLESTEROL FED MAN**

In addition to a report by Mistry et al (1976) beta VLDL can be induced by cholesterol feeding in man, preliminary studies from the Gladstone foundation laboratories for cardiovascular disease indicates that certain individual respond to high fat, high cholesterol diet by producing lipoproteins which are capable of delivering cholesterol to macrophages. The beta VLDL may occur transiently as minor components of the human plasma fractions after diets high in fat and cholesterol are consumed, and may cause repeated cholesterol deposition in cells in the arterial wall over the years. The beta VLDL either chylomicron remnants or hepatic lipoprotein may represent the atherogenic particle postulated several years ago by Zilversmit. This alteration in the lipoprotein fraction may represent the most significant diet induced changes in lipoprotein predisposing to accelerated atherosclerosis.

**ATHEROSCLEROSIS: A POST-PRANDIAL PHENOMENON**

The possibility of atherosclerosis being a post prandial phenomenon was first proposed by Zilversmit (1973). He hypothesized that chylomicron remnant or beta VLDL may occur
transiently as minor components of the human plasma fractions after diet high in fat and cholesterol is consumed. And this may cause repeated cholesterol deposition in the cells of the arterial wall over the years, while the fasting cholesterol level may remain normal during the lifetime.

If atherosclerosis is a post prandial phenomenon then premature CAD must be common in hyperchylomicronemic states. However in familial lipoprotein lipase deficiency enormous quantities of chylomicrons accumulate in plasma but accelerated atherosclerosis has not been reported (Fredrickson et al, 1979).

TREATMENT OF HYPERLIPIDEMIA:

Abundant evidence has accumulated to show that treatment of hyperlipidemia will diminish or prevent atherosclerosis and its complications including ischemic heart disease (Kannel et al, 1979; Lewis, 1988; Edwin, 1990; Lipid research clinic programme 1984 a, 1984b). Numerous population studies have shown that an elevated total cholesterol or LDL cholesterol in plasma constitutes a major risk factor for the occurrence of atherosclerotic events (Goldstein et al, 1973; Keys, 1975; Hiroyasu et al, 1989 and Martin et al, 1986).

In 1984, the result of the lipid research clinics coronary primary prevention trial, a multicentre, randomized, double blind study, provided strong evidence that a reduction in plasma concentrations of LDL cholesterol can reduce the risk of coronary artery disease (Lipid research clinics programe 1984a, 1984b). These conclusions were confirmed in 1987, by Helsinki Heart study which showed that treatment of men with more moderate
hypercholesterolemia (mean total cholesterol 239 mg/dl) could.reduce the incidence of coronary artery disease.

The drug used was Gemfibrozil, and the clinical benefits were.correlated with a fall in LDL cholesterol, an increase in HDL-cholesterol, and a decrease in plasma triglycerides.

Analysis of the relationship between cholesterol and coronary artery disease suggests that a 25% reduction of the total plasma cholesterol would reduce the incidence of coronary events by nearly 50% (Lipid Research Clinics, Programme, 1984b).

Epidemiological studies have revealed a negative correlation between the plasma concentration of HDL, which normally accounts for the 20-30% of the total plasma cholesterol, and the risk of coronary artery disease (Miller, 1980). In hypertriglycerideremic individuals frequently having low concentration of HDL, when treated with drugs that lower VLDL concentration, the HDL will often return to normal levels. The fibric acids and HMG COA reductase inhibitors raise HDL and lower LDL.

Gemfibrozil a fibric acid derivative reduces the serum total cholesterol, triglycerides, LDL and apo-B lipoprotein (Saba et al, 1988; Frick et al, 1987) and a significant increase in HDL (Frick et al and Grundy, 1984).

**AIMS OF TREATMENT:**

Ultimate aim is to reduce the risk of CAD as low as possible. On the basis of present knowledge, NCEP recommends a TC level of 200 mg/dl and LDL level 130 mg/dl as desirable. A
simplified approach on the basis of NCEP recommendation is as follows:

PRESENT MANAGEMENT STRATEGIES:

1. Lifestyle measures:
   i. Reduction of obesity.
   ii. General lipid lowering diet.
      a. * Saturated fatty acids
      b. * Cholesterol
      c. ** Polyunsaturated fatty acids
      d. ** Complex carbohydrates
      e. ** Soluble dietary fibre
   iii. Chylomicronaemic diet
      a. * All long chain fatty acids
      b. ** Medium Chain Triglycerid
   iv. Regular and appropriate aerobic exercise.

* - Decreased
** - Increased

2. DRUGS:
   i. Cholesterol lowering
      a. Cholestyramine.
      b. Cholestipol.
      c. Probucol
      d. Mevinolin.
   ii. Triglyceride and cholesterol lowering.
      a. Nicotinic acid and derivatives
      b. Benzafrbate.
      c. Gemfibrozil.

3. Invasive procedures
   i. Partial ileal by pass
   ii. Plasma exchange.
ALL ADULTS ≥ 20 YRS OF AGE
NON-FASTING TOTAL CHOLESTEROL

Non-fasting total cholesterol

High* Desirable
(>240mg/dl) (<200mg/dl)

Borderline*
(200-239mg/dl)

Risk estimation**

Obtain total lipid profile
(HDL, LDL, VLDL, Tg)

>225 >160 130-159 <130

Risk factor Repeat 5 yrs
(HTC, LDL)

Present Absent

Set Treatment Goals Annually repeat Yearly TC
(LDL <130, if risk factor present, TC
LDL(160 if no risk factors) dietary modification

Dietary modification
(2-6 months)

Drug, with Goal not achieved Goal achieved.
diet modification

Therapy 6 monthly follow up.

* Repeated measurements
** Risk factors - Definite CAD (by history or investigation)
- other
  * Male Sex
  * Family history of CAD (MI or sudden death of parents or siblings 55 yrs of age)
  * Cigarette smoking.
  * Hypertension.
  * Low HDL-Cholesterol (<35 mg/dl)
  * Diabetes mellitus.
  * H/o atherothrombotic stroke or peripheral vascular occlusive disease.
  * Obesity >30% overweight

Risk factors present indicates either definite CAD or 2 other risk factors.
It is a fibric acid derivative, advocated for the treatment of hyperlipoproteinemia, it is a structural congener of clofibrate.

**PHARMACOLOGICAL ACTIONS:**

It reduces progressively cholesterol, serum triglycerides, VLDL, LDL and apolipoprotein B values during treatment (Saba et al, 1988).

It produces a pronounced decrease in the triglycerides level (43%) and a decrease in LDL cholesterol level (10%) (Frick et al, 1987).

It causes a significant increase in HDL cholesterol. Its ability to increase significantly HDL levels have been proved unequivocally by a number of studies (Frick et al, 1987; Lewis and Multicentric collaborative study group, 1983; Kesaneimi and Grundy, 1984).

In the Helsinki Heart study (Frick et al, 1987) Gemfibrozil caused a 10% increase in HDL cholesterol level over 5 years. In another study carried out by Lewis and multicentric study group, almost 23% increase in serum HDL cholesterol has been reported.

**MECHANISM OF ACTION:**

Gemfibrozil reduces the turnover of VLDL, triglycerides, plasma free fatty acids and VLDL, apo-B, suggesting a decrease in hepatic VLDL secretion. It also increases the activity of
lipoprotein lipase. Thus it produces its effect both by decreasing the synthesis and increasing the clearance of VLDL (Illingworth, 1987).

Gemfibrozil increases the rate of synthesis of the major apoproteins of HDL to lipoprotein A1 and AII by approx. 25%. Additionally, a suppression of hepatic triglyceride lipase may also contribute towards increasing the levels of HDL (Natio, 1987).

**PHARMACOKINETICS:**

Gemfibrozil is well absorbed from Gastrointestinal tract. Peak blood level occur in 1-2 hours and after administration of a single dose of 600 mg the plasma concentrations achieved are about 15 mcg/ml in 2 hours and 5 mcg/ml after 9 hours.

Plasma half life is 1.5 hours after a single dose, 1.3 hours after multiple doses. Approximately 70% of administered dose is excreted in urine and 6% encountered in faeces. It undergoes enterohepatic circulation.

**ADVERSE REACTIONS:**

It is well tolerated in most persons. The most frequent side effect noted are changes in bowel function, abdominal pain, diarrhoea and occasional nausea in 3-5% patients, less common side effects are muscle tenderness and skin rashes. Uncommon side effects are eosinophilia, decreased plasma alkaline phosphatase and increased transaminases. It may increase biliary
lithogenicity. However several studies have shown that likelihood of gemfibrozil causing new or enlargement of already present gall stone is only about 1-1.5%.

Safety of gemfibrozil in pregnancy and during lactation has not been yet established. It is not advocated in severe renal or hepatic dysfunction, pre-existing gall bladder disease and in hypersensitive individuals.

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