REVIEW OF LITERATURE
Fig. 1: Diagrammatic representation of structure of lipoprotein particle.
INTRODUCTION : LIPOPROTEIN OVER-VIEW

The lipids are a heterogeneous group of compounds, having common property of being (a) relatively insoluble in water and (b) soluble in non-polar solvents such as ether, chloroform and benzene, (Mayer, 1977).

Lipids are important dietary constituents not only because of their high energy value but also because of the fat-soluble vitamins and the essential fatty acids which are found with the fat of natural foods. Fat serves as an efficient source of energy and serves as an insulating material in the subcutaneous tissue and around certain organs. Combinations of fat and protein (lipoproteins) are important cellular constituents.

The problem of transporting a large quantity of hydrophobic material, i.e. lipid, in an aqueous environment, is solved by associating the more insoluble lipids with more polar phospholipids and then combining them with cholesterol and protein to form a hydrophilic lipoprotein complex. It is in this way that triglyceride (TG) derived from intestinal absorption of fat or from the liver are transported in the blood (Gurr & James, 1975). Lipids in plasma are transported by lipoprotein particles containing several lipids including triglyceride, cholesterol, cholesteryl esters, and phospholipids, and proteins designated as apolipoproteins. In short lipoprotein molecules are spherical structures with the least soluble lipids inside the core. This is surrounded by lipids capable of interacting with water as well as proteins called as apoproteins as depicted in Fig. 1 (Natio, 1987).
Many classes of lipids are circulated in the blood as lipoproteins. Pure fat is less dense than water. As the proportion of lipid to protein in lipoproteins increases the density decreases. Use of this property is made in separating the various lipoproteins in plasma by ultracentrifugation as depicted in Table 1 & 2.

Table 1: Concentrations of various lipids in human plasma.

<table>
<thead>
<tr>
<th>Lipids in Plasma</th>
<th>Concentration in mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Total Lipid</td>
<td>570</td>
</tr>
<tr>
<td>Triglyceride (TG)</td>
<td>142</td>
</tr>
<tr>
<td>Total Phospholipid</td>
<td>215</td>
</tr>
<tr>
<td>Total Cholesterol (TC)</td>
<td>200</td>
</tr>
<tr>
<td>Free Fatty Acids (non-esterified) (FFA)</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 2: Properties of various lipoproteins of human plasma.

<table>
<thead>
<tr>
<th>FRACTION</th>
<th>DENSITY</th>
<th>COMPOSITIONS</th>
<th>Percentage of Total Lipid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Protein (%)</td>
<td>Total lipid (%)</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>&lt;0.96</td>
<td>0.99</td>
<td>0.88</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.960-1.006</td>
<td>0.93</td>
<td>0.56</td>
</tr>
<tr>
<td>LDL-1 OR IDL</td>
<td>1.006-1.019</td>
<td>0.89</td>
<td>0.29</td>
</tr>
<tr>
<td>LDL-2</td>
<td>1.019-1.063</td>
<td>0.79</td>
<td>0.13</td>
</tr>
<tr>
<td>HDL2</td>
<td>1.063-1.125</td>
<td>0.67</td>
<td>0.16</td>
</tr>
<tr>
<td>HDL3</td>
<td>1.125-1.210</td>
<td>0.43</td>
<td>0.13</td>
</tr>
<tr>
<td>Albumin-FFA</td>
<td>&gt;1.281</td>
<td>1.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Lipoprotein in plasma are typically classified on the basis of their electrophoretic mobility and hydrated density. They are separated by electrophoresis into the beta (beta-lipoprotein), alpha\textsubscript{2} (pre beta lipoproteins) and alpha\textsubscript{1} (alpha-lipoproteins) in globulin zones. Five major classes of lipoproteins in plasma are separated, according to their hydrated density, into chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low-density lipoproteins (LDL) and high density lipoproteins (HDL). The lipoproteins that remain at the origin in electrophoresis are equivalent to chylomicrons, the pre-beta lipoproteins to VLDL, the beta lipoproteins to LDL and the alpha lipoproteins to HDL. The major cholesterol transporting lipoproteins in plasma are LDL, whereas dietary triglycerides are carried primarily by chylomicrons and endogenous by VLDL. Chylomicrons, the largest of the lipoproteins, are formed in the intestine and carry triglycerides of dietary origin, whereas VLDL are secreted by liver and are the principle carriers of triglycerides synthesised in the liver (Lee and Hatch, 1963; Gofman et al., 1954).

Heterogeneity among VLDL has also been observed in studies involving ultracentrifugal, chromatographic, and electrophoretic techniques (Kuchinskiens & Carlson, 1982; Pagnan et al., 1977; Patsch et al., 1978; Quarfordt et al., 1972; Sata et al., 1972). Nondenaturing gradient gel-electrophoresis, however, usually shows two distinguishable VLDL bands, which have been referred to as "large" and "small" VLDL. Similarly IDL has been broadly subdivided into two subspecies IDL-1 and IDL-2 which are overlapping in size and density, but can be readily distinguished as two bands by nondenaturing gradient gel-electrophoresis (Musliner et al., 1986). The properties of various subspecies of VLDL and IDL are depicted in Table 3.
Various analytical techniques have been used to study LDL heterogeneity in human subjects. (Hammod & Fisher, 1971; Krauss & Burke, 1982; Lee and Downs, 1982; Lindgren et al., 1972). Equilibrium density gradient ultracentrifugation and nondenaturing gradient gel-electrophoresis have proved most useful (Lindgren et al., 1972; Shen et al., 1981). Most subjects display distinct isopyonic banding on density gradients, distributed among four major density groups, designated as LDL-I, LDL-II, LDL-III and LDL-IV (Krauss, 1987). The properties of various subspecies of LDL are depicted in Table 4.
Early studies of HDL by analytical ultracentrifugation recognize three subfractions i.e. HDL₁, HDL₂ and HDL₃ based on differential flotation rates. Gradient-gel electrophoresis further distinguish at least two subspecies within HDL₂ i.e., HDL₂a and HDL₂b and three within HDL₃a, HDL₃b and HDL₃c (Lindgren et al., 1972). The properties of various subspecies are depicted in Table 5.

<table>
<thead>
<tr>
<th>Subspecies</th>
<th>Density range (Kg/L)</th>
<th>Particle Size (nm)</th>
<th>Flotation rate (F°₁₂₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL₂b</td>
<td>1.063-1.100</td>
<td>9.7-12.9</td>
<td>3.5-9.0</td>
</tr>
<tr>
<td>HDL₂a</td>
<td>1.100-1.125</td>
<td>8.8-9.7</td>
<td>2.5-5.5</td>
</tr>
<tr>
<td>HDL₃a</td>
<td>1.125-1.147</td>
<td>8.2-8.8</td>
<td>1.5-3.5</td>
</tr>
<tr>
<td>HDL₃b</td>
<td>1.147-1.167</td>
<td>7.8-8.2</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>HDL₃c</td>
<td>1.167-1.200</td>
<td>7.2-7.8</td>
<td>0.0-1.5</td>
</tr>
</tbody>
</table>

Traditionally, emphasis has been placed on the lipid content of these lipoproteins but during the last 15 years, the functional and structural significance of the specific lipid binding proteins of the lipoproteins, the apoproteins, has been increasingly appreciated. The ABC nomenclature for the apoproteins, first suggested by Alaupovic (1971) is generally followed as depicted in Table 6 along with the various characteristics of the major human plasma apolipoproteins (Osborne Jr and Brewer Jr, 1977, Scanu and Landsberger 1980).
Table 6: Major apolipoproteins in human plasma.

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Major Density Class</th>
<th>Major site of synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-I</td>
<td>HDL</td>
<td>Liver, Intestine</td>
</tr>
<tr>
<td>A-II</td>
<td>HDL</td>
<td>Liver</td>
</tr>
<tr>
<td>A-IV</td>
<td>Chylomicrons</td>
<td>Intestine</td>
</tr>
<tr>
<td>B-100</td>
<td>Chylomicrons-VLDL-IDL-LDL</td>
<td>Liver, Intestine</td>
</tr>
<tr>
<td>B-48</td>
<td>Chylomicrons-VLDL-IDL</td>
<td>Intestine</td>
</tr>
<tr>
<td>C-I</td>
<td>Chylomicrons-VLDL-HDL</td>
<td>Liver</td>
</tr>
<tr>
<td>C-II</td>
<td>Chylomicrons-VLDL-HDL</td>
<td>Liver</td>
</tr>
<tr>
<td>C-III_{0.2}</td>
<td>Chylomicrons-VLDL-HDL</td>
<td>Liver</td>
</tr>
<tr>
<td>D</td>
<td>HDL</td>
<td>?</td>
</tr>
<tr>
<td>E_{2.4}</td>
<td>Chylomicrons-VLDL-HDL</td>
<td>Liver</td>
</tr>
<tr>
<td>F</td>
<td>HDL</td>
<td>?</td>
</tr>
<tr>
<td>G</td>
<td>VLDL</td>
<td>?</td>
</tr>
<tr>
<td>H</td>
<td>Chylomicrons</td>
<td>?</td>
</tr>
<tr>
<td>Apo(a)</td>
<td>LDL-HDL</td>
<td>Liver</td>
</tr>
</tbody>
</table>

In human plasma Apo A exists as two isoproteins designated as Apo A-I and Apo A-II. The two major apolipoproteins of HDL are Apo A-I and A-II. Apo-B exists as two isoproteins designated as Apo B-48 and Apo B-100 which can be separated by sodium dodecyl sulfate-gel electrophoresis (Kane, 1980; 1983). Apo B-48 and Apo B-100 are the principal structural apolipoproteins of chylomicrons (Higuchi et al., 1988) where as Apo B-100 is virtually the only apolipoprotein on LDL (Osborne Jr and Breawer Jr, 1977; Scanu and Landsberger, 1980). There are three common Apo E isoproteins identified as Apo E₂, Apo E₃ & Apo E₄, which are encoded by the E-2, E-3 and E-4 alleles (Davignon
et al., 1988; Uterman et al., 1975; Uterman and Vogelberg, 1979; Zannis and Breslow, 1981). Apo E\textsubscript{2} is associated with type III hyperlipoproteinemia (Gregg et al., 1981; Havel et al., 1981), Apo E\textsubscript{3} is the most common isoprotein and is considered the "normal" apoprotein and Apo E\textsubscript{4} with increased concentration of LDL in plasma (Zannis and Breslow, 1981).

During the last decade, several physiological functions have been identified for the apoproteins in plasma as depicted in Table 7 (Kane et al., 1980).

<table>
<thead>
<tr>
<th>FUNCTION</th>
<th>APOLIPOPROTEIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cofactor for Enzyme:</td>
<td></td>
</tr>
<tr>
<td>Lipoprotein lipase</td>
<td>C-II</td>
</tr>
<tr>
<td>Lecithin cholesterolacyl transferase</td>
<td>A-I</td>
</tr>
<tr>
<td>Ligand on Lipoprotein Particle for Interaction With Receptor Site on Cells</td>
<td></td>
</tr>
<tr>
<td>Remnant receptor</td>
<td>E</td>
</tr>
<tr>
<td>LDL receptor</td>
<td>B-100, E</td>
</tr>
<tr>
<td>HDL receptor</td>
<td>A-I</td>
</tr>
<tr>
<td>Structural Protein on Lipoprotein Particle</td>
<td></td>
</tr>
<tr>
<td>Intestinal chylomicron</td>
<td>B-48, B-100</td>
</tr>
<tr>
<td>Hepatogenous VLDL</td>
<td>B-100</td>
</tr>
<tr>
<td>HDL</td>
<td>A-I</td>
</tr>
</tbody>
</table>
Apoproteins can function as:

A. **Co-factor or activator of enzymes involved in lipid-lipoprotein metabolism:**

1. Apo C-II is required for the enzyme activity of lipoprotein lipase (EC no. 3.1.1.34), the enzyme responsible for hydrolysis of lipoprotein triglycerides to free fatty acids and monoglycerides (Havel et al., 1970; LaRosa et al., 1970).

2. Apo A-I activates LCAT (EC no. 2.3.1.43), which catalyzes the esterification of cholesterol to cholesteryl ester (Fielding et al., 1972).

B. **Ligand on the lipoprotein particle that interacts with cellular receptors for specific lipoproteins:**

1. Apo B-100 and Apo E interact with the LDL receptor to initiate absorptive endocytosis followed by the catabolism of LDL (Zannis and Breslow, 1981; Goldstein and Brown, 1977).

2. Apo E has also been proposed to interact with the putative remnant receptor, which may play an important role in removal of hepatic chylomicron remnants by the liver (Zannis and Breslow, 1981).

3. Apo A-I has been proposed to interact with a putative HDL receptor and facilitate the removal of cholesterol from peripheral cells for transport back to the liver (Glomset, 1968; Oram et al., 1983; Schmitz et al., 1985; Suzuki et al., 1983).

C. **Structural protein on lipoprotein particle:**

1. Apo B-100 and Apo B-48 are required as structural constituents of lipoprotein particles for the secretion of triglyceride-rich lipoproteins from the intestine and liver.
2. Apo A-I has also been proposed as an important structural protein for the biosynthesis of HDL.

**Lipoprotein Metabolism:**

The concentration of a lipid present in blood plasma at any moment depends on both the transporting lipoproteins, rate of entry into the circulation and its rate of removal or clearance from the circulation. The metabolic relationship of the major classes of lipoproteins containing Apo B-100 and Apo B-48 consist of two major "cascades". A conceptual overview of the pathways of lipoprotein metabolism is depicted schematically in Fig. 2 (Schmitz et al., 1985).

The first Apo B cascade involves the stepwise delipidation of triglyceride rich chylomicrons secreted by the intestine. The major function of chylomicrons is to transport dietary lipids from the intestine to peripheral tissues and the liver. Recently, chylomicrons secreted from the human intestine have been shown to contain either the B-100 or B-48 apolipoprotein (Higuchi et al., 1988). Shortly after secretion, the triglyceride-rich chylomicrons acquire two apolipoproteins, Apo C-II and Apo E, from HDL. Apo C-II activates lipoprotein lipase, an enzyme attached to the capillary endothelium which catalyzes the hydrolysis of triglycerides to free fatty acids and monoglycerides. After entering the plasma, the triglycerides on the chylomicrons undergo hydrolysis, and the lipoproteins are remodeled, forming "remnants" that have the hydrated density of VLDL, and then of IDL. Chylomicron remnants have been proposed to be removed from the plasma predominantly by two receptors, the remnant receptor and the LDL receptor, which have an affinity for Apo E. The chylomicron remnants are ultimately taken up by the hepatocyte where their constituents are catabolized.
Fig. 2 Schematic overview of the metabolism of the principal human lipoprotein classes
The second Apo B cascade involves the hydrolysis of triglyceride-rich VLDL secreted by the liver. Virtually all of the triglyceride-rich Apo B containing lipoproteins secreted by the human liver contain Apo B-100 (Edge et al., 1985). Shortly after secretion, the triglyceride rich Apo B-100 containing VLDL acquire Apo E and Apo C-II from HDL. The triglycerides on VLDL also undergo hydrolysis by lipoprotein lipase, and the VLDL are serially converted to lipoproteins having the density of IDL and finally of LDL. During the conversion to LDL the majority of the apolipoproteins C-II and E dissociate from VLDL remnants and IDL, reassociating with HDL. The end product of the cascade, LDL contains almost exclusively Apo B-100. It has also been proposed that a second lipolytic enzyme, hepatic lipase is also involved in the conversion of IDL to LDL, which functions both as a phospholipase and triglycerol hydrolase.

The Apo B-100 containing LDL formed from IDL interact with LDL receptors on the plasma membranes of cells in the liver, adrenal, and peripheral cells, including smooth-muscle cells and fibroblasts. The LDL receptor has a high affinity for both Apo E and Apo B which after interaction with LDL, the lipoprotein and receptor undergoes endocytosis and the components of LDL are catabolized (Davignon et al., 1988; Goldstein and Brown, 1977).

HDL are synthesized by several pathways, including direct synthesis and secretion of nascent HDL by the liver and intestine. HDL particles in plasma also acquire apolipoproteins and lipids from the remodeling of triglyceride-rich Apo B-containing lipoproteins. HDL functions as a “reservoir” for apolipoproteins for example Apo C-II and Apo E. During lipoprotein metabolism HDL has been proposed to interact also with a putative HDL receptor, which facilitates the transport of excess cholesterol from cells back to the liver. (Glomset, 1968). This hypothetical pathway has been termed as “reverse cholesterol transport” which is initiated by the interaction of HDL with the putative HDL receptor to remove from cells primarily unesterified cholesterol, which is then esterified in plasma by the enzyme Lecithin cholesterol acyltransferase (LCAT). The cholesterol esters are transferred to the core of
HDL and are exchanged between HDL, VLDL and LDL, a process mediated by 
cholesterol-exchange protein. Cholesteryl esters, therefore may be transported 
back to the liver directly by HDL or after exchange by VLDL and LDL as shown 
in Fig. 3.
Fig. 3 Schematic overview of reverse cholesterol transport
This is a group of disorders characterized by quantitative and/or qualitative abnormalities of plasma lipoproteins. Accumulation of excessive amounts of lipoproteins in plasma is usually the result of either an abnormality of the catabolic system or an abnormal structure of the lipoprotein particle, which decreases its ability to interact with the catabolic mechanism. Fredrickson (1967) first attempted to classify the dyslipoproteinemias according to genetically determined lipoprotein molecular abnormalities. A few individuals in the population exhibit inherited defects in their lipoproteins leading to the primary hypo or hyperlipoproteinemias. Others having defects such as diabetes mellitus, hypothyroidism, and atherosclerosis shows abnormal lipoprotein patterns which are very similar to primary conditions and are called secondary hypo or hyperlipoproteinemias.

A. Hyperlipoproteinemia:

1. Type-I Hyperlipoproteinemia:

In patients on a regular diet after an over-night fast, chylomicrons are present in huge amounts and cause the cloudy-milky appearance of the plasma. Serum TG are extremely elevated, whereas cholesterol concentrations may be normal or only slightly high. It is a rare disorder characterized by very slow clearing of chylomicrons from the circulation, leading to abnormally raised levels of chylomicrons. The condition is due to a deficiency of lipoprotein lipase with raised pre-beta lipoproteins but with a decrease in alpha and beta lipoproteins. The condition is fat induced. It may be corrected by reducing the quantity of fat in the diet, but high-carbohydrate diets lead to raised levels of pre-beta lipoproteins due to synthesis in the liver.
2. Type-II Hyperlipoproteinemia:

It is also called Familial hyper-cholesterolemia. It is a common disorder of lipoprotein metabolism and characterized by hyper-beta-lipoproteinemia, which is associated with increased plasma total cholesterol. The pre-beta-lipoproteins also may be elevated and the patient may have somewhat elevated TG levels but the plasma remains clear.

Lipid deposition in the tissue (eg., Xanthomas, atheromas) is common. A type II pattern may also arise as a secondary result of hypothyroidism. The disease appears to be associated with reduced rates of clearance of beta-lipoprotein (LDL) from the circulation. Reduction of dietary cholesterol and saturated fats may be of use in treatment.

3. Type-III Hyperlipoproteinemia:

It is also called Familial Dysbetalipoproteinemia. It is a disorder of lipid metabolism manifested clinically by accelerated atherosclerosis of the coronary and peripheral arteries. Affected subjects are commonly over weight and often show abnormal glucose tolerance, including frank diabetes mellitus. Plasma triglyceride levels are elevated and usually the presence of an abnormal form of VLDL, beta-VLDL, floating beta-lipoprotein) which shows beta mobility on electrophoresis. The beta-VLDL particle is smaller and heavier than normal VLDL, and contains a high proportion of cholesterol relative to its triglyceride content. The biochemical abnormality of dysbetalipoproteinemia has recently been characterized as a quantitative and qualitative abnormality of Apo E (Havel, 1973; Utermann, 1975; Zannis, 1980; Ghiselli, 1981).

The total amount of Apo E in VLDL of patients with dysbetalipoproteinemia is increased; however, these patients usually have a typical Apo E isoforms E-2. Homozygosity for the E-2 allele gives rise to the
E-2/2 phenotype, which predisposes the subject to dysbeta lipoproteinemia. The disease dysbetalipoproteinemia is more sensitive to both dietary changes and to lipid-lowering medications such as nicotinic acid and clofibrate.

4. Type-IV Hyperlipoproteinemia:

It is also called Familial Hypertriglyceridemia. It is characterized by hyperprebeta-lipoproteinemia associated with high levels of endogenously produced TG and VLDL. Cholesterol levels rise in proportion to the hypertriglyceridemia, and glucose intolerance is frequently present. Both alpha and beta lipoproteins are subnormal in quantity. This lipoprotein pattern is also commonly associated with maturity onset diabetes, obesity and many other conditions including alcoholism and the taking of progestational hormones. Treatment of primary type-IV hyperlipoproteinemia is by weight reduction, replacement of much of the carbohydrate in the diet with unsaturated fat, low cholesterol diets and with hypolipidemic agents.

5. Type-V Hyperlipoproteinemia:

Fredrickson (1968) used the term familial Type-V hyperlipoproteinemia to identify a group of patients with familial hypertriglyceridemia having elevated levels of both VLDL and chylomicrons. The lipoprotein pattern is complex since both chylomicrons and pre beta-lipoproteins are elevated, causing both triglyceridemia and cholesterolemia. Glucose tolerance is abnormal and frequently associated with obesity and diabetes. The reason for the condition, which is familial, is not clear and treatment is weight reduction followed by a diet not too high in either carbohydrate or fat.
B. Hypolipoproteinemia:

1. Abetalipoproteinemia:

   This is a rare inherited disease characterized by fat malabsorption, fat soluble vitamin deficiencies, absence of beta-lipoprotein (LDL) in plasma. Biochemically, the disorder is manifested by hypocholesterolemia and total absence of plasma Apo B and hence the lipoproteins (chylomicrons, VLDL, and LDL) that usually contain it. Both the intestine and the liver accumulate acylglycerols.

2. Hypobetalipoproteinemia:

   The disease is inherited as an autosomal dominant trait. Plasma lipid concentrations, definitely overlapping the normal range, and with low but detectable Apo-B levels.

3. Familial alphalipoprotein deficiency:

   It is also called the Tangier disease. This is a rare disorder inherited as an autosomal recessive trait and characterized by severe deficiency of plasma HDL. Patients with Tangier disease frequently develop premature atherosclerotic disease. The unique plasma lipid pattern of patients with Tangier disease includes a markedly low cholesterol and a moderately raised triglyceride level. HDL levels are extremely low or undetectable, and LDL levels are also reduced. HDL from Tangier disease patients differs from normal HDL by having a very low Apo A-I : Apo A-II ratio (Assmann, 1977), and an abnormal Apo A-I isoprotein composition due to a structural defect (Zannis, 1982; Kay, 1982). These abnormal apolipoproteins are probably responsible for the increased and altered catabolism of HDL in Tangier disease patients (Schaefer, 1978).
CORONARY ARTERY DISEASE (CAD) : LIPOPROTEIN OVERVIEW :

Coronary artery disease is the result of progressive atherosclerosis of one or more of the major epicardial or surface coronary vessels. As a result of this process, the lumen of the involved coronary artery is narrowed and the blood supply to area of the myocardium is limited. At rest, this marginal blood flow may be sufficient to meet the oxygen demands of the heart; however, during physical or emotional stress, an imbalance between oxygen supply and demand occurs. This imbalance leads to myocardial ischemia and angina pectoris.

Coronary artery disease (CAD) remains the major cause of morbidity and mortality in all developed countries in the world. In India it has already climbed the “charts” from 14th to 4th place only behind tuberculosis, communicable diseases and malnutrition. People with high concentration of plasma cholesterol have more severe atherosclerosis and more frequent heart attacks than people with normal or low plasma lipid levels. The first evidence linking cholesterol concentrations in plasma to human atherosclerosis came from case control studies that showed that coronary heart disease patients had higher concentrations of cholesterol in plasma than did the controls. Subsequently, longitudinal epidemiologic studies, such as the Framingham Study, found that the concentration of cholesterol in plasma predicted the risk of coronary heart disease (Dawber et al., 1957). In humans, LDL cholesterol concentrations were directly associated and HDL cholesterol concentrations were inversely associated with clinical atherosclerotic disease (Havel, 1979). A similar positive association of LDL cholesterol and a negative association of HDL cholesterol with atherosclerotic lesions were found in human (Solberg and Strong, 1983). The first firm proof that a lowering of the cholesterol level reduces the rate of myocardial infarction and infarction mortality in man was given by the Lipid Research Clinics Programmes (1984).
Age- and gender-adjusted reference ranges for concentrations of cholesterol, triglyceride, and lipoprotein in plasma have been developed (The Lipid Research Clinics Population Studies Data Book, 1980). The National Cholesterol Education Program (1988) has defined plasma triglyceride 250 mg/dL, LDL cholesterol value 160 mg/dL as increased and HDL cholesterol concentration 35 mg/dL as decreased. Increased concentration of LDL cholesterol and decreased concentration of HDL cholesterol have been associated with an increased risk of premature CAD (Gotto Jr, and Farmer, 1988). Other risk factors for premature CAD include sex, family history of myocardial infarction, cigarette smoking (more than 10 cigarettes per day), hypertension, diabetes and obesity (Report of National Cholesterol Education Programme, 1988).

The existence of multiple size subpopulations within the major lipoprotein classes has potentially important implications for the pathogenesis of atherosclerosis. Gofman et al., (1950) using analytical ultracentrifugation, demonstrated a strong association between IDL mass and atherosclerosis in human subjects. High concentrations of IDL cholesterol have been reported in populations of myocardial survivors in Japan and Italy (Avogaro et al., 1980; Kameda et al., 1984), as well as in subjects with angiographically documented coronary disease (Tatami et al., 1981). Analyses with the Type-II Coronary Intervention Study of the National Heart, Lung, and Blood Institute provide further evidence that IDL is particularly important in coronary atherosclerosis (Krauss et al., 1987) Cholestyramine-induced reductions in IDL were reciprocally correlated with small but significant increases in HDL cholesterol. It is possible, therefore, that the inverse association between HDL cholesterol and coronary risk may be in part due to relationships with IDL metabolism, and that low HDL concentrations may be a marker for the presence of increased concentrations of atherogenic lipoproteins (Musliner and Krauss, 1988).
One of the results that emerged from this pioneering American prospective study is the general rule that **A 1% FALL IN CHOLESTEROL PREDICTS A 2% REDUCTION IN CARDIAC HEART DISEASE RISK.**

Further studies examined the association between total cholesterol and coronary disease in women, and it emerged from these studies that total cholesterol was significantly predictive of subsequent coronary disease in women (Gordon et al., 1977; Kannel, 1987). Cardiovascular diseases also are the leading cause of serious morbidity and disability in women. Among older women, coronary heart disease and arthritis are the disorders associated with the greatest amount of disability, as measured by limitation in major kinds of activity, bed days and restricted activity days per condition (Fried et al., 1987).

Although numerous investigations have explored and identified risk factors for heart disease in males, only a few studies have examined and quantified risk factors (including serum lipids and lipoproteins) for coronary disease in women. An increased concentration of total cholesterol in plasma is strongly associated with increased risk for CAD (Kannel et al., 1979). The Adult Treatment Panel of the National Institutes of Health has recently recommended designating a total cholesterol concentration of 200 mg/dL in plasma as “desirable,” between 200 and 240 mg/dL as “borderline high”, and 240 mg/dL as “high” (Report of the National Cholesterol Education Programme, 1988). However, Castelli and Anderson (1986) have stated that the Americans who develop CAD have plasma cholesterol 200 mg/dL, and about half of the myocardial infarctions occur in those with cholesterol 250 mg/dL. Undoubtedly, other risk factors for CAD, such as hypertension, cigarette smoking, diabetes, and obesity contribute to its development in such patients, but about 50% of CAD is not explained by the conventional risk factors including hypercholesterolemia (Wilson et al., 1987).

Numerous studies have shown that concentrations of HDL subspecies (HDL2 and HDL3) are decreased in men with coronary disease with the
proportionate reduction in HDL\textsubscript{2} being usually greater than that in HDL\textsubscript{3}, although the absolute difference in some cases was larger for HDL\textsubscript{3}. Where multivariate analysis was used to compare discriminating power, HDL\textsubscript{2} was a better predictor of risk than HDL\textsubscript{3} (Laakso et al., 1985; Hamsten et al., 1986; Wallentine and Sundin, 1985). However it is not yet clear whether measurement of HDL\textsubscript{2} is superior to total HDL cholesterol as a predictor of risk, because the content of Apo A-I and Apo A-II is thought to contribute to HDL particle heterogeneity and concentrations of these apolipoproteins in plasma which might be relevant to the relationship of HDL subspecies with risk for atherosclerosis (Musliner and Krauss, 1988).

It has been suggested that concentration of Apo A-I & Apo B serve as better markers for CAD than lipoprotein cholesterol value (Maciejko et al., 1983; Sinderman et al., 1980; Dahlen et al., 1986; Naito, 1985). The advantage of apolipoproteins in addition to the precision with which they can be determined, is the fact that their concentrations in plasma change very little between fasting and non-fasting states (Cohn et al., 1988). The quantification of Apo A-I, Apo-B, may be used to determine the risk of premature cardiovascular disease (McLean et al., 1987; Fless et al., 1986; Brunzell et al., 1984; Naito, 1987). Increased concentrations of LDL Apo-B with relatively normal concentrations of LDL cholesterol in plasma have an increased risk for developing premature atherosclerosis. Generally, the concentration of Apo B in plasma is positively associated and the concentrations of Apo A-I is negatively associated with atherosclerotic disease (Brunzell et al., 1984). In these association, the apolipoprotein may simply be another marker for the lipoprotein as Apo B can be identified readily in human atherosclerotic lesions (Hoff and Morton, 1985). The measurement of the plasma concentrations of the major apolipoprotein of LDL (Apo B) and of the major apolipoprotein of HDL (Apo A-I) may provide additional information in assessing risk of CAD (Brunzell et al., 1984). Studies exclusively on quantification of apolipoproteins A-I, A-II and B, have shown that the concentrations of Apo B are higher and those of Apo A-I are lower in patients with angiographically documented coronary disease than in symptomatic
patients without coronary disease. Moreover, discriminant analysis indicates that the concentrations of apolipoproteins A-I and B in plasma are better discriminators than lipids of lipoprotein cholesterol for identifying patients with coronary artery disease (Brunzell et al., 1984; Kladetzky et al., 1980; Noma et al., 1983; Kukita et al., 1984).

Increased concentrations of Apo B and decreased concentrations of Apo A-I were also correlated with the severity of coronary artery disease. Kottke et al., (1986) in a study of 304 patients undergoing coronary angiography, has confirmed that the concentrations of apolipoproteins A-I, A-II, and B are better discriminators than cholesterol, triglyceride, and HDL-cholesterol in plasma. When the ages of the patients and the Apo A-I, Apo A-II, and Apo B concentrations were included in a discriminant functions analysis, more than 75% of the cases could be correctly classified as having angiographically significant coronary artery disease. In women, only the concentrations of triglyceride and Apo B in plasma correlated significantly with the severity of coronary artery disease. (Fruchart et al., 1982). Among lipoprotein constituents, the concentrations of Apo B and LDL cholesterol showed strongest correlation with the extent and severity of coronary atherosclerosis.

In patients with familial combined hyperlipidemia, as well as analyses of patterns of LDL subspecies in myocardial infarction survivors, suggest a link between LDL-III and an atherogenic lipoprotein profile because of higher concentrations of IDL and LDL-III concentration with lower concentrations of HDL₂. Variations in the concentrations of any or all of these subspecies which may contribute to the relationship of HDL to coronary disease risk (Musliner and Krauss, 1988). Now it is a well established fact that plasma LDL is directly and HDL is inversely related to the CAD. LDL are the major carriers of plasma cholesterol and increased concentrations of LDL is causative factor in development of atherosclerosis (Lipid Research Clinics Program : II, 1984) and conversely the risk for CAD decreases with increasing plasma concentrations of HDL (Kannel et al., 1979; Wilson et al., 1987). LDL and HDL in plasma
comprise multiple particle subpopulations differing in size, density, and chemical composition. Heterogeneity within VLDL and LDL has been established but further work on the metabolic processes by which subspecies arise and whether increase or decrease in the concentrations of specific subspecies are associated with altered atherosclerotic risk are a subject of debate till date (Musliner and Krauss, 1988).
HYPERTENSION:

Hypertension emerged from the early epidemiologic studies of coronary heart disease as a strong predictor of coronary heart disease, and it repeatedly has been shown to be associated with accelerated progression of atherosclerosis in both humans and experimental animals (Solberg et al., 1983; Robertson et al., 1968). The incidence of cardiovascular disease and the factors that predispose to it— including blood lipids, uric acid, glucose intolerance, and obesity are more common in hypertensive persons than in the general population. The Framingham study on the role of blood lipids in the evaluation of cardiovascular disease in hypertensive persons, as based on 30 years of follow-up suggests that blood lipids are fundamental in the atherosclerotic process and their effect are accelerated by hypertension. Thus hypertensive risk of coronary disease varies widely, depending on co-existing risk factors, especially blood lipids (Kannel, 1988).

Coronary disease is now the commonest sequela of hypertension. The excess risk being concentrated in those with an increased LDL/HDL ratio, impaired glucose tolerance, electrocardiogram abnormality, and cigarette smoking. Hypertension is a component of a multifactorial coronary risk profile, which includes the blood lipids and thus for the judgement of urgency for treatment requires the knowledge of the concentrations of the blood lipids.

DIABETES:

Concentrations of insulin in blood are also related to the extent of atherosclerosis, at least in the animal experimental model (Russell et al., 1987). Gillum (1987) has shown that the waist/hip ratio also increase with age - a ratio that is also correlated directly with concentrations of insulin and triglycerides.
and inversely with HDL cholesterol, and is a risk factor for heart attacks (Stern & Huffner 1986). In well controlled patients with insulin dependent diabetes mellitus, the concentrations of Apo A-I and Apo-B are within the normal range. In poorly controlled diabetes mellitus, the concentrations of Apo-A-I and Apo-A-II are slightly decreased or remain within the normal range, but Apo-B increases considerably (Richard et al., 1983; Schernthaner et al., 1983).

Triglyceride is increased because of uncontrolled diabetes, pancreatitis, hypothyroidism, and nephrotic syndrome (La Rosa, 1977). Diabetes, is representative of a secondary disease, and is associated with abnormalities in serum lipids and lipoproteins (Laakso et al., 1986). In studies of diabetic patients with and without coronary artery disease, the patients with CAD have higher serum concentrations of Total cholesterol, LDL cholesterol, and Triglyceride and lower concentrations of HDL cholesterol. Lipid and lipoprotein concentrations in diabetic patients without CAD are not significantly different from those in nondiabetic controls. Hughes et al., (1987) suggest that insulin therapy in non insulin-dependent diabetes mellitus causes dramatic desirable improvements in the concentrations of TG, LDL cholesterol, and HDL cholesterol in serum. In a alloxan diabetic rabbits the ratio of LDL cholesterol : HDL Cholesterol is significantly increased on administration of tolbutamide however insulin administration showed a decrease and no change was seen with glibenclamide administration suggesting that the atherogenic index for the three antidiabetic drugs can be categorised as insulin glibenclamide tolbutamide (Anmamala & Augusti, 1991).
Although exogenous estrogens and progesterones are strong modifiers of lipids and lipoproteins, the association of endogenous estrogens and progesterones with the concentrations of lipids and lipoproteins is less clear. In premenopausal women, serum estrogen and progesterone varies throughout the menstrual cycle, with high concentrations of estrogen and low progesterone during the follicular phase, leading to an estrogen dominant condition. During the luteal phase, the high concentrations of circulating estrogens are opposed by high concentrations of circulating progestins, such that neither hormone is dominant. A few studies have reported small changes in total cholesterol (Basdevant et al., 1981; Oliver and Boyd, 1953; Gustafson et al., 1974), whereas others have found no consistent variations in lipid concentrations during the menstrual cycle (Woods et al., 1987; Tikkanen et al., 1986; Ahumada et al., 1985; Demacker et al., 1982). Lipoproteins were usually not evaluated in these reports, although one study did observe that HDL remained “remarkably stable” during the cycle (Basdevant et al., 1981) and Kim and Kalkhoff (1979) in their study found a suppression of LDL during the luteal phase. Woods et al., (1987) observed that menstrual cycle can also effect lipids, with triglyceride value being significantly higher during the ovulatory phase than at other time.

Exogenous hormone use as oral contraceptive therapy has long been known to influence the concentrations of lipids and lipoproteins, because oral contraceptives contain both synthetic estrogens and progesterones at doses considered necessary to suppress ovulation. The estrogens used in formulations are almost exclusively ethinylestriadiol and mestranol; the progesterones commonly used are the testosterone - derived 19-nor agents such as norethisterone or norgestrel. In the 1960s and 1970s, oral contraceptive formulations had relatively high doses (100 + 0.150 mg) of estrogen, i.e., the
“high-dose” agents associated with an increased risk of thromboembolic
disease which resulted in a reduction of the estrogen content of oral
contraceptives to 35 to 50 mg, i.e., the “low-dose” pills. Bush and co-workers
(1985, 1987) showed that estrogens clearly are potent lipid-altering agents,
causing an increase in HDL cholesterol and a decrease in LDL cholesterol. The
impact of progesterones on lipids and lipoproteins is less clear, although it has
been suggested that the 19-nor progesterones adversely affect lipid and
lipoprotein concentrations and decrease HDL cholesterol and increase LDL
cholesterol. However, information on the effect of other progesterones
progestins on lipid and lipoprotein concentrations is scanty. Low-dose oral
contraceptives adversely affect lipid and lipoproteins, although the extent to
which this occurs appears to depend on the dose and type of progesterone
used, (Bradley et al., 1978; Wynn, 1986).

Different doses of norgestrel with same dose of estrogen showed that
women using the higher dose (250 mg) had HDL concentrations 16% lower
than that of controls, whereas women taking the lower dose (150 mg) had HDL
concentrations 7% lower than the controls (Basdevant et al., 1981). Further
clinical trial on women given oral contraceptives with a constant dose of
estrogen and either norethisterone or norgestrel found that HDL concentrations
were significantly decreased in both groups (-4% and -7% respectively) and
total cholesterol was increased by 9% and 2% respectively (WHO special
programme of Research., 1985). Whereas Lipson et al., (1986) suggested that
when the dose of estrogen was held constant and the type of progesterone
varied women taking the more androgenic drug norgestrel had significantly
lower HDL concentrations (-14%) after one year than did women given the less
androgenic progesterones etynodiol diacetate (-2%) or norethindrone acetate
(+2%) and the total cholesterol was increased by 5% to 11% and LDL
concentrations by 6% to 18% in all three groups. The largest increase in LDL
had been demonstrated with combinations of the lowest estrogen dose and the
strongest anti-estrogenic progesterone (Bradley et al., 1978; Wahl et al., 1983)
and higher potencies of progesterones proportionately decrease HDL concentrations in contraceptive users (Brooks, 1984; Wynn, 1986).

Harting et al., (1984) suggested that menopause has long been assumed specifically, the loss of ovarian function and endogenous estrogens puts women at an increased risk of coronary disease. Two basic regimens commonly used to treat women for menopausal symptoms include unopposed estrogen therapy and cyclic estrogen - progesterone therapy. Unopposed estrogen therapy differs from oral contraceptive therapy in two significant ways (a). The estrogens most commonly used in menopausal therapy are low dose natural formulations instead of the relatively high dose synthetic agents used in oral contraceptives; (b) No progesterone progestin is added at any time to the regimen. Use of cyclic estrogen progesterone progestin therapy during the perimenopausal period differs from oral contraceptive therapy in that the estrogens are usually low-dose natural formulations and the prescribed progesterone usually are 17 alpha formulations (i.e., progesterone, medroxyprogesterone acetate) rather than the more androgenic 19-nor agents (i.e., norethisterone, norgestrel). Unopposed oral estrogen therapy has been shown to increase HDL cholesterol and to decrease LDL cholesterol. Total cholesterol is only moderately affected, because the decrease in LDL cholesterol for the most part is reinforced by the increments in HDL cholesterol. The magnitude of the estrogen induced changes in the lipoproteins are great enough to influence risk of coronary diseases. On a usual dosage schedule, HDL concentrations are increased by about 9% to 13% and LDL concentration are lowered by about 4% to 10%. The effect of estrogens on lipids and lipoproteins appears to be dose dependent and is also a function of the type of estrogen used; i.e., synthetic estrogen have a more potent effect on lipids and lipoproteins than do the natural agents (Bush et al., 1988).

Harting et al., (1984) reported that, among inactive women, those who were postmenopausal, had HDL cholesterol concentrations 8% lower, and total cholesterol and LDL cholesterol concentrations 6% and 15% higher,
respectively than those of premenopausal women; however, postmenopausal subjects were, on average, 16 years older than the premenopausal subjects. Hallberg and co-workers (1967a; 1967b) suggested that 48 years old women, who were postmenopausal had total cholesterol concentrations 9% higher than those who were premenopausal, whereas 50 years women has the concentrations of total cholesterol varied by length of time since menopause. Women who had been menopausal for less than three years have total cholesterol concentrations 10% higher, and women who have been menopausal for more than three years have total cholesterol concentrations 27% higher than premenopausal women.

Aromatization of androstenedione in fat and other tissues is the primary source of postmenopausal estrogen and estradiol and the concentrations of the hormones being directly related to the degrees of obesity. Thus, fat postmenopausal women have higher concentrations of estrogen, but not of HDL cholesterol, than thinner women (Solbert and Strong; 1983). HDL cholesterol concentration is higher in women with high concentrations of estrogen and estradiol in serum, especially during the early postmenopausal period. The substantial increase in cholesterol concentration among women with increasing age may be primarily due to weight gain or increasing fatness as they get older, or due to changes in the sex-steroid hormone metabolism. Exogenous estrogens lower the concentrations of total and LDL cholesterol (Bush and Barrett-Connor, 1985).

Stokes et al., (1985) reported that the risk of heart attack among obese postmenopausal women may not be greater than that among thinner postmenopausal women. Cauley et al., (1987) found no relationship between the concentrations of estrogens and testosterone in serum and the risk of heart attack among men and exogenous estrogens has been not shown to be effective in reducing the risk of heart attack among men. Women have a better insulin response to glucose load, at least before menopause, and especially during adolescence and young adult life (Donahue et al., 1987). Perhaps the
changes in insulin metabolism during adolescence and the premenopausal and postmenopausal periods play a predominant role in the progression of atherosclerosis. Obesity or increased fatness is also related to the concentrations of insulin in blood, because fatty individuals are relatively insulin resistant. Postmenopausal obese women have higher concentrations of insulin, which are inversely correlated with HDL cholesterol which suggests relationship between insulin concentrations and subsequent risk of heart attack (Pyorala, 1979; Ducimetiere et al., 1980; Welborn and Wearne, 1979).

Artificial menopause, oophorectomy, has been shown both in experimental animals and women to increase the extent of atherosclerosis. Conversely, estrogen - replacement therapy has been also shown to reduce the risk of subsequent CHD deaths, if not atherosclerosis, among oophorectomized women (Bush and Barrett - Connor., 1985). Higher concentrations of HDL cholesterol and Apo A-I in women than in men may be the most important biological markers of susceptibility to atherosclerosis (Wallace and Anderson., 1987; Brunner et al., 1987).

The menopausal period represents a gradual change in hormonal concentrations, but it is extremely unlikely that the gradual cessation of ovarian hormone function and its replacement by hormones from the adrenal and their aromatization in fat tissue to estrone would result in an immediate increase in heart attacks. Secondly the most puzzling aspect of the menopause and the sex related difference in atherosclerosis is the failure of the concentrations of HDL cholesterol to decline among women after the menopause (Colditz et al., 1987). In every crossectional population study, these concentrations do not change among postmenopausal women. The concentrations of HDL cholesterol and Apo A-I are highly correlated with the extent of coronary artery disease, as well as the risk of heart attack in both men and women (Wallace and Anderson, 1987; Brunner et al., 1987). Estrogen therapy, especially among postmenopausal women, reportedly reduces the risk of heart attack by increasing the concentration of HDL cholesterol, and HDL cholesterol does not
decline in the postmenopausal period, thus suggesting that estrogen deficiency results in increased atherosclerosis and clinical CHD becomes somewhat tenuous and makes questionable the efficacy of estrogen replacement therapy, except among women who had a premature oophorectomy or a postmenopausal decrease in adrenal steroid secretion or aromatization to estrogen concentrations to result in a decrease in HDL cholesterol, accompanied by an increase in both coronary atherosclerosis and heart attacks (Kuller and Orchard, 1988).

In women ages 45 to 54 years who participated in the LRC prevalence study, lipids and lipoproteins varied with ovarian function (Bush et al., 1984). Women who were naturally menopausal or who had a bilateral oophorectomy had significantly higher concentrations of total cholesterol and LDL cholesterol than did menstruating women. Bengtsson et al., (1986) found that becoming menopausal was associated with a modest but significant increase in total cholesterol (6%), and a significant increase in body weight and that “exercise by postmenopausal females may help prevent adverse lipid and lipoprotein changes”. Harting et al., (1984) & Svanborg et al., (1977) suggested that menopause may be associated with a more adverse lipoprotein profile.
Life Style is essentially the way we choose to live. The fact is that certain fundamental life style choices, ultimately dictate health and longevity for each of us. Some of these choices for example are diet - what and how much to eat; exercise - whether we exercise regularly or not; smoking - whether we break the habit or not and alcohol - whether we drink as medicine or addict.

**DIET:**

Now-a-days Indians stray away from their native diet, and make a significant dietary change to a reliance on processed foods and fast foods which are rich in fat, salt and calories and low in fibre, which increases the incidence of CHD. The evidence linking atherosclerosis with increased concentrations of cholesterol in plasma come first from experimental animals. In 1908, Ignatovski, studying the possible toxic effects of dietary protein, found that feeding milk, butter, meat and eggs to rabbits produced human like atherosclerotic lesions. A few years later, Antischkow (1967) determined that the dietary component responsible for the lesions was cholesterol, and that the lesions were associated with an increased concentration of cholesterol in serum. After this the cholesterolemic effects of saturated fats were discovered in humans. Similar effects were demonstrated in animals (Kritchevsky et al., 1956) and the additional increases in plasma cholesterol further augmented experimental atherosclerosis. LDL cholesterol concentrations usually are increased in plasma as a result of a diet containing relatively large amounts of cholesterol and saturated fat. The nutrients of specific interest have been the type of fat, monounsaturated, polyunsaturated or omega-3 fatty acids, primarily from fish oils, the types of carbohydrate and dietary fiber and coffee and alcohol consumption. Keys (1979) stated the mathematical formulation that the serum cholesterol would increase by 2-7 mg/dL for each 1% of total calories supplied by saturated fat, and decrease 1.3 mg/dL for each 1% of the calories supplied.
by poly-unsaturated fat. All of these studies were done by iso-caloric dietary replacement of various fats and carbohydrates.

Grundy (1986; 1987) suggested that decrease of dietary fat by replacement with carbohydrate also decrease HDL cholesterol and sometimes increase triglyceride concentrations. In addition, mono-unsaturates are as effective as poly-unsaturates in reducing cholesterol concentrations in blood. Normal concentrations of VLDL cholesterol can promote cholesterol esterification in human monocytes. Cholesterol loaded macrophages derived from blood monocytes are prominent in atherosclerotic plaques (Sacks and Breslow, 1987). The inter-relationship among HDL cholesterol, insulin, triglycerides, obesity and atherosclerosis appear to be operative only in association with the common source, the high cholesterol and saturated - fat diet (Knuiman et al., 1987).

Various dietary components, including cholesterol saturated and unsaturated fatty acids, carbohydrates, fiber and total caloric intake have been hypothesized to influence cholesterol and lipoprotein concentrations in serum: One small cross-sectional study examined the association between the poly-unsaturated/saturated (P/S) ratio of dietary fats and serum concentrations of LDL and VLDL cholesterol in healthy young (Ages 18-35 years) men and women (Boberg et al., 1986). The correlation between the P/S ratio and the concentration of LDL and VLDL cholesterol was stronger for men than for women. Data collected in the First National Health and Nutrition Examination Survey (NHANES I) also show no association between dietary cholesterol and total serum cholesterol in either women or men. It is also stated that there is no relationship between a surrogate measure of the P/S ratio and total serum cholesterol. (National Centre For Health Statistics; 1983).
Energy intake in excess of utilization results in obesity. Weight gain and obesity are directly related to total cholesterol and LDL cholesterol in serum. Obesity during childhood and adolescence is also directly correlated with the cholesterol concentrations in serum. (Freedman et al., 1985). Weight loss in adults is clearly associated with a decrease in cholesterol. Fat distribution and obesity, even in younger individuals, appear to be much more closely related to the concentrations of TG, VLDL, HDL cholesterol and insulin (i.e., affecting carbohydrate metabolism) than to the concentrations of total cholesterol or LDL cholesterol (Stern & Haffner, 1986; Wing et al., 1987; Baumgartner and Roche., 1987; Haffner et al., 1988; Zimmet et al., 1986). An increase in insulin concentration hyperinsulinemia usually reflects peripheral insulin resistance and is associated with increased VLDL secretion by the liver (Patsch et al., 1983). Decreased activity of lipoprotein lipase a major enzyme associated with the metabolism of VLDL particles and the onset of hypertriglyceridemia and a decrease in HDL cholesterol. Thus there appears to be some association between the degree of obesity and the cholesterol concentrations. However, the disparity between the degree of obesity hyperinsulinemia, diabetes, and the cholesterol content of blood as suggested by Haffner et al., (1985) may be due to either genetic or environmental factors, especially the characteristics of the diet.

Glueck et al., (1980) suggested that obesity was significantly and negatively correlated with HDL cholesterol concentrations in both women and men, and this correlation was independent of age, smoking, alcohol use and estrogen use. Evidences suggest that a centripetal fat pattern (greater proportion of fat in the trunk, as opposed to extremity adiposity) in women is associated with decrease in HDL cholesterol, regardless of total body fat (Baumgartner et al., 1987). Howard et al., (1987) in his study on Pima Indians demonstrated that, compared with lean women, obese women have higher concentrations of total and LDL cholesterol and lower concentrations of HDL.
cholesterol. Follick et al., (1984) hypothesised that obesity decreases HDL whereas weight loss is associated with subsequent increases in HDL cholesterol and both short and long-term weight loss results in higher concentrations of HDL cholesterol in both obese men and women. Framingham Offspring study data suggests that in non-obese men and women, weight gain was significantly associated with subsequently lower HDL, whereas weight loss was a significant predictor of increase in HDL cholesterol (Hubert et al., 1987).

Obesity is clearly associated with an adverse lipid and lipoprotein profile in both women and men, inducing increase in total cholesterol and LDL cholesterol and decrease in HDL cholesterol. Obesity appears to influence lipids and lipoproteins to the same degree in women as in men and also appears to be independent of exogenous estrogen use, smoking and alcohol consumption. It has been suggested that exercise can substantially increase HDL cholesterol and beneficially influencing total cholesterol and LDL cholesterol (Huttunen et al., 1979; Wood & Haskell, 1979). Wood et al., (1977) demonstrated among women runners that total cholesterol and LDL cholesterol concentrations were 8% and 9% lower and HDL concentrations were 34% higher than in non-runners.

Weight gain also increases total cholesterol and LDL cholesterol in serum and reduces HDL cholesterol, causing a deterioration in the TC/HDL cholesterol ratio apart from change in concentrations of both cholesterol and its atherogenic LDL component which are increased by excess calories, weight gain and dietary cholesterol and saturated fat. The NHANES I survey shows that women in the highest quintile of body mass have total cholesterol concentrations approximately 19% higher than women in the lowest body-mass quintile. Obesity is inversely associated with HDL cholesterol in both sexes (National Centre for Health Statistics, 1983; Glueck et al., 1980). LRC Prevalence study suggest that persons in the highest decile of body mass have HDL concentrations approximately 10% to 15% lower than those in the lowest decile.
TOBACCO CONSUMPTION OR SMOKING:

In India tobacco is consumed orally or in combination with betel-nut. Similarly, Snuff is used on the gums by local application or massage. Tobacco smoking is practised in the form of "bidi", "Chillum" or "hukka". In all these varieties raw unprocessed tobacco is used and is much more dangerous than the "processed, low tar, low nicotine" tobacco, used in some cigarettes. Tobacco smoke is a heterogeneous mixture of more than 4000 substances having diverse biological effects. However, nicotine, tar, carbon monoxide are most important. Adverse effects are generated by direct vasoconstriction, reflex, tachycardia, stimulation of catecholamine production, impaired oxygen delivery, decreased coronary blood flow, increased myocardial irritability and oxygen consumption, increased platelet aggregation, coronary, artery spasm, increased total cholesterol and decreased HDL-cholesterol.

Cigarette smoking increases the risk of coronary heart diseases (U.S. Office on smoking and Health, 1983). Several studies of autopsied humans have shown slightly more extensive fibrous plaques in the coronary arteries and aorta of smokers than in those of non-smokers. Cigarette smoke is a very complex mixture of chemicals, which on inhalation, affect the cardiovascular and hemostatic system (Mc Gill Jr., 1979; 1988).

Cigarette smoking appears to have the greatest and most consistent impact on serum HDL cholesterol, because smoking lowers HDL cholesterol, and that this effect may be somewhat more pronounced in women than in men (Garrison et al., 1978; Haffner et al., 1985; Halfon et al., 1984; Freedman et al., 1986; Criqui et al., 1980). Taylor et al. (1981) reported that HDL cholesterol concentrations in smokers compared with non-smokers are 13% lower in women and 6% lower in men. Criqui et al. (1980) found that, among moderate smokers, HDL concentrations were 5% lower in men & 8% lower in women (compared with non-smokers) and among heavy smokers, they were 12% lower in men & 14% lower in women. On the other hand, Freedman et al. (1986) found
that HDL cholesterol decreased less in young women who began smoking than in young men who began smoking (-17% vs -40% respectively), although smoking enhanced the age-related reduction of HDL in both sexes. Smoking increases LDL cholesterol, TG and decreases HDL cholesterol and is positively related to CHD mortality in both sexes (Brischetto et al., 1983; Criqui et al., 1987). Smoking is inversely associated with HDL concentrations. Smoking 20 cigarettes per day had shown increased relative risk for CHD to 1.94 for men and 3.17 for women (Haffner et al., 1985). The dose-response relationship between smoking and HDL cholesterol in women and in men exists and this effect is independent of sex-hormone use, body mass, and alcohol consumption (Garrison et al., 1978; Criqui et al., 1980). Further there is an increase in the level of total cholesterol with decrease in HDL cholesterol in smoker subjects as compared with that of control non-smokers, and also there is a significant increase in total cholesterol with a significant decrease in HDL-cholesterol in heavy smokers as compared to moderate smokers (Shamraj and Gopal Krishnan, 1989; Kulkarni et al., 1991).

ALCOHOL CONSUMPTION:

The LRC Prevalence study showed that alcohol consumption is strongly associated with increased HDL cholesterol in both men and women (Ernst et al., 1980). Suggesting that greater alcohol intake being associated with higher concentrations of HDL cholesterol. The strength of the association between alcohol intake and HDL cholesterol are similar in women and men, and the effect of alcohol consumption on HDL cholesterol concentration in women is independent of sex hormone use. In women drinkers HDL cholesterol concentrations is 6% to 18% greater than nondrinkers (Taylor et al., 1981; Haffner et al., 1986; Castelli, et al., 1977).

Thus alcohol consumption is strongly and positively related to the concentration of HDL cholesterol in women and in men. Criaui et al. (1987) has suggested that moderate alcohol consumption is protective against coronary
disease in both men and women, and that this protective effect is due to the higher concentrations of HDL in alcohol users.

A sustained alcohol intake increases HDL cholesterol, decreases LDL cholesterol, and increases TG concentrations in serum (Castelli et al., 1977). Alcohol intake apparently affects HDL\textsubscript{3} more than HDL\textsubscript{2} (Haskell et al., 1984). A decrease in HDL\textsubscript{2} particles containing only apo-A-I has been observed with increased alcohol intake (Puchois et al., 1986). Alcohol may act via the clotting mechanism and other unknown mechanisms (Marmot et al., 1981; Landolfi & Steiner, 1984) but the major effect of alcohol is on the concentrations of TG in serum (Castelli et al., 1977).