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INTRODUCTION

Tum penuria deinde cibi laguentia leto membra debat, contranunca rerum copia mersat.

In earlier times, starvation consigned languishing bodies to death; now, on the other hand, prosperity plunges them to the grave.

LECRETIUS, ca.50 B.C.
De Rerum Natura,
Chap.5, 1.1007.

1.1. Atherosclerosis, Definition and Incidence in Population

1.1.1. Atherosclerosis has been known for centuries, and until very recently, the disease was considered a necessary component of the ageing process. Epidemiological studies during the last 30 years, however, have revealed wide geographic differences in the incidence and prevalence rates of atherosclerosis. It has also been shown that significant atherosclerosis is not a necessary component of the ageing process. The recognition of genetic, environmental, and other factors that can accelerate the atherosclerotic process has made ageing an important, but not the only, determinant of the pathologic changes, which are influenced to varying degrees by several factors, some of which are yet to be identified. All the evidence at present indicates that coronary atherosclerosis is a multifactorial disease.

1.1.2. The renewed interest in this disease and in the search for its etiologic factors stems from the fact that the incidence has increased dramatically in the last 60 years, and this disease is now recognized as the leading
cause of death in the industrialized Western world (Schettler, 1977). It is not clear what has produced such an apparent steep rise in coronary atherosclerotic disease in this country. Although the atherosclerotic disease has been casually linked to the development of 'affluence' in some of the highly industrialized countries of the Western world, it is also likely that other factors, such as increased longevity, reduction of death due to other causes (perinatal mortality, infections and hitherto unidentified environmental factors), improved recognition and diagnosis, as well as a definite increase in the incidence and prevalence of atherosclerotic disease, have all contributed to the observed rise in morbidity and mortality in many countries throughout the world.

1.1.3 The magnitude of the problem can be realised from the following data:

In 1973, out of about 1,97,700 deaths in USA
1,03,700 (52%) were due to cardiovascular disease (CVD) most of which were caused by atherosclerosis. In contrast, in 1937, there were about 1,450,427 total deaths and only 209,570 (14%) were caused by cardiovascular disease [DiGirolamo and Schlant (1978)]. In Japan and countries of the Mediterranean basin, the incidence of coronary heart disease is low.

The world health organisation (WHO) has said that coronary heart disease threatens to become the greatest epidemic mankind has ever faced [Turner, 1980] and the increase in its incidence may be at least partly man-made.
1.2.1 Atherosclerosis is a disease of large and medium-sized arteries, in which the intima of the arterial wall is thickened by the development of fibrous tissue and accumulation of lipid. (Greek, athero-gruel or porridge and sclerosis-hardening).

1.2.2 The wall of a normal artery consists of three distinct layers, namely intima, media and adventitia [Taurisig, 1978].

1.2.2.1 The intima which lies immediately beneath the single layer of endothelium, consists of an extracellular connective tissue matrix in which are found a number of smooth muscle cells (SMCs). The intima is separated from the media by a sheet of elastic fibres, the internal elastic lamina.

1.2.2.2 The media is the muscular layer of the wall. In elastic arteries, such as the aorta, the media is composed of lamellar units, each containing a layer of elastic fibres and a layer of SMCs; in muscular arteries, the media consists wholly of SMCs. In the larger arteries, the small blood vessels known as vasavasorum penetrate a little way into the media, from the outside of the artery, but the inner part of media as well as intima are devoid of capillary and lymphatic supply. Naturally, the blood in the lumen of the artery itself supplies nutrients, by diffusion, to the inner part of the vessel wall. Nevertheless, the fact that this region is avascular may be significant in some of the pathological changes in atherosclerosis.
1.2.2.3 The **adventitia** is the outermost layer, made up of connective tissue and is the only layer known to contain fibroblasts.

1.2.3 Three principal types of lesion are recognised, namely, the fatty streak, fibrous plaque and complicated lesion and have been reviewed by Taursig, (1978).

1.2.3.1 **Fatty streaks** and dots are superficial fatty patches, yellow in colour, which are only slightly raised and do not cause narrowing of lumen. The deposited lipid (cholesterol and cholesteryl oleate) which is intracellular is contained in 'foam cells', which are lipid-laden SMCs. Streaks are common at all ages, and are the earliest and the most universal of the fatty changes in the intima.

1.2.3.2 **Fibrous plaques** are raised greyish-yellow areas of intimal thickening which protrude into the lumen of the artery. Histologically, the plaque consists of superficial accumulation of SMCs and fibrous connective tissue (collagen, elastin, mucopolysaccharide) lying under the intima [Smith, 1974]. The cells are loaded with lipid which now also lies extracellularly in the connective tissue. Beneath this fibrous layer, lies a larger deposit of free extracellular lipid and cell debris. The porridge-like appearance of this deposited fat gives atherosclerosis its name. An atheroma is a plaque in which there is an amorphous, necrotic mass containing much extracellular lipid lying beneath the fibrous plaque.
1.2.3.3 Complicated lesions are derived from the raised plaques as they become haemorrhagic, ulcerated and calcified. The complicated lesion is the cause of occlusion of the artery.

1.2.4 Understanding of the processes of atherosclerosis is founded largely on the classical theories of Virchow (1862) (arterial injury and infiltration of lipid) and Rokintansy (1852) (encrustation of mural thrombi) as refined by current experimental and clinical evidence.

1.2.5 Change in intimal permeability and endothelial cell injury is probably the initial event in atherosclerosis, and is triggered by hypertension [Esterly and Glagov, 1963] Constantinides, 1971] area of hemodynamic stress [Somer and Schwartz, 1972; Wissler, 1974], antibody-antigen complexes [Minick and Murphy, 1973], and release of vasoactive amines [Ross and Glomset, 1976 and Ross et al. 1977].

1.2.6 According to the lipid infiltration theory, the plasma lipoproteins are continuously entering the arterial wall through the endothelium [Smith and Slater, 1972]. Having entered the intima as a result of increased endothelial permeability, the cholesterol rich lipoproteins can be selectively trapped as a result of 'sieving' and by interaction with intimal connective tissues [Kramsch and Hollander, 1973]. Secondly, they are negatively charged and can therefore bind proteins by ionic interaction. Once bound in the intima, the lipoproteins are dissociated probably by enzymatic action, to release cholesterol and
its esters. Since cholesterol stimulates the growth of SMCs and production of connective tissue, a cycle of events can ensue in which cholesterol deposition promotes first the growth of SMCs, which in turn progressively traps more lipoproteins and the cycle continues.

1.2.7 Excessive synthesis of cholesterol and its ester causes cell death and their release into the extracellular lipid pool due to their inability to diffuse through the intima. Hence, a pool of insoluble cholesterol and its ester accumulates in the intima and frequently crystallises.

1.2.8 The fibrous plaque grows by thrombosis, in which mural thrombi form on the altered arterial surface, then become organised into fibrous tissue (similar to the lipid infiltration theory) and ultimately lead to vascular complications and the attendant symptoms [Lyford et al., 1967 and Mustard, 1974].

1.3 EXPERIMENTAL ATHEROSCLEROSIS

1.3.1 Animal studies (in primate and nonprimate species) have paralleled the epidemiologic studies in human beings and revealed immense information related to the pathophysiology of atherosclerosis and its inducibility by dietary and other manipulations. Animals can develop spontaneous atherosclerosis in most species, while appropriate techniques (such as use of high fat diet in association with hypothyroidism) can accelerate the development of lesions. [Constantinides, 1965; Lee et al., 1977; Stary et al., 1977; Wissler and Vesselinovitch, 1977; Mahley, 1979].
1.3.2 Experimental evidence has provided support for the following tentative conclusions:

1) High cholesterol feeding leads to elevation of plasma cholesterol levels and development of premature atherosclerotic lesions if sufficient time is allowed for the lesions to develop.

2) Initial stages of arterial lesions have shown the accumulation of lipid, frequently with chemical characteristics similar to those of circulating lipids.

3) A variety of experimentally induced cell injuries (by hypoxia, mechanical trauma, radiation, freezing, catecholamine injection) accelerate the development of the lesions at the site of injury, and focal accumulation of lipids is seen.

4) Hypertension combined with hyperlipidemia leads to acceleration and progression of atherosclerotic lesions.

1.3.3 Of interest, are the studies which suggest a degree of reversibility of atherosclerotic lesions in animals in which the experimentally induced cholesterol levels in plasma were corrected by a diet poor in cholesterol and/or by correcting the hypothyroid state [Kritchevsky et al, 1974; Vesselinovitch et al, 1976; Stary et al, 1977]. It must be emphasized that improvement in atherosclerotic lesions was greater when the etiological factors were removed early. An encrusted, fibrotic, and calcified lesion has very little potential for reversibility [DiGirolamo and Schlant, 1978].
1.3.4 Animal models are open to the objection that they are not necessarily identical to the situation in man. It is nevertheless comforting to find that experimental observations conform to the postulates derived from pathologic and epidemiologic studies in man, and that no major contradictory information has been produced.

1.4. ETIOLOGIC FACTORS IN THE DEVELOPMENT OF CORONARY ATHEROSCLEROSIS - THE EPIDEMIOLOGIC STUDIES

1.4.1 Coronary atherosclerosis and its etiology has been enriched not only by animal experimentation, but also by (a) Epidemiologic studies attempting correlation between the incidence and prevalence of coronary atherosclerosis at autopsy and in living populations, and in various parameters such as geographic differences, race, age, sex and diet (b) Pathophysiologic studies attempting to relate observed early vascular changes with a variety of possible etiologic factors.

1.4.2 A great deal of information has been derived from epidemiologic studies in different countries of the World and in different strata of the population within the same country. Geographic differences in the occurrence of coronary atherosclerosis have been reported both from autopsy material and from living population studies [McGill, 1968, Schettler and Wiezel, 1974]. Fig.1, illustrates the mortality rates due to coronary heart disease in males of 45-54 years of age, deaths per 100,000 in the different parts of the globe collected by W.H.O. 1974-75 [Turner, 1980]. The limitations and imprecision inherent in such studies are to be borne in mind; nevertheless, certain important trends
FIG. 1 Mortality due to coronary heart disease; male 45-54 years; deaths per 100,000; WHO 1974-1975.

(adapted from TURNER, 1980).
have been understood.

(a) Atherosclerosis is common in individuals from the affluent countries and in more affluent families in the underdeveloped countries.

(b) In the above area, it becomes more prevalent with age.

(c) Mortality due to coronary heart diseases is higher in older men than in women of child bearing age.

(d) Chemical correlation with certain biochemical and pathological changes (to be discussed subsequently).

1.4.3 Studies of McGill (1979) reveal that there was a decrease in the rate of mortality due to CHD during the years of world war II and the period is characterised by diet restriction.

1.4.4. In the seven countries study, Key (1970) showed a strong association between serum cholesterol concentrations and the incidence of coronary heart disease. In the same study there was no evidence to show a relationship between dietary cholesterol and CHD.

1.4.5 The food fats are divided into two categories, vegetable and animal fats, the latter may further be divided into three sub categories, dietary fat (milk and milk product], animal body fat and marine fat.

1.4.5.1 Vegetable fats such as soyabean oil, corn oil, sunflower oil, and to a lesser degree olive oil, are relatively unsaturated, as they contain substantial amounts of polyunsaturated fatty acids, mainly linoleic acid.
Animal fats are much more saturated and contain only small quantities of linoleic acid. Marine fats are highly unsaturated and contain fatty acids with even 5 to 6 double bonds in their molecule.

1.4.5.2 Consumption of these food fats varies significantly among countries (Fig.2). In countries with high coronary mortality, animal fats are usually the predominant food fat. The consumption of dairy fat is also high (particularly in Finland, New Zealand and Ireland). On the other hand, vegetable fats are consumed in modest quantities only (except in the USA) while the reverse is true in countries with low coronary mortality [Turpeinen, 1979].

1.4.5.3 Thus, the effect of diet from conclusions made by Turner (1980) was that population habitually consuming food of the type considered in the United Kingdom as wholesome, has a very high incidence of CHD, while the reverse is true for a population free of CHD.

1.4.5.4 The steps taken by US Agricultural Department to modify the pattern of diet among Americans are as follows (as illustrated by Stamler, 1979)

1. To avoid overweight, consume only as much energy (calories) as is expended; if overweight, decrease energy intake and increase energy expenditure.

2. Increase the consumption of complex carbohydrate and 'naturally occurring' sugar from about 28% of energy intake to about 48% of energy intake.
FIG. 2  Consumption of major types of food fats in certain countries with high and low coronary heart disease (CHD) mortalities

**Abb:**

V = Vegetable fats  M = Meat fats  D = Dairy fats  
FI = Finland  UK = United kingdom  GR = Greece  
US = United State  IR = Ireland  PO = Portugal  
NZ = Newzealand  IT = Italy  SP = Spain  
JA = Japan

(adapted from TURPEIN 1979)
3. Reduce the consumption of refined and processed sugar by about 45% to account for about 10% of total energy.

4. Reduce overall fat intake consumption from approximately 40% to about 30% of energy intake.

5. Reduce saturated fat consumption to account for about 10% of total energy intake and balance that with polyunsaturated and monounsaturated fats, which should account for 10% of energy intake.

6. Reduce cholesterol consumption to about 300 mg per day.

7. Limit intake of sodium, by reducing the intake of salt to about 5 g/day.

1.4.6 Information emerged from epidemiological studies available on the association of certain factors with coronary atherosclerosis has led to the formulation of a number of risk factors, some major, some minor, some reversible and some irreversible. However, at present 246 risk factors are speculated [Hopkins and Williams, 1981], although the presence of a risk factor in an individual patient gives no certainty of the presence or severity of coronary atherosclerosis. Neither should it be inferred from such studies that those individuals without an identified high risk factor will be free from the significant risk of developing coronary heart diseases.
1.5. NON-MODIFIABLE AND MODIFIABLE PRIMARY RISK FACTORS

1.5.1 Non-modifiable risk factors

1.5.1.1 Age

The development of atherosclerosis and the emergence of the coronary lesions above the surface of clinical recognition are dependent on time. Therefore, it is expected, and it has been confirmed, that age has a strong and consistent association with atherosclerotic lesions [McGill, 1968; Sternby, 1968]. Other factors, such as mode of life, undernutrition, or concomitant wasting disease, can significantly retard the atherogenic process or minimize its invasiveness. This argues in favour of the concept that a relation to age, although frequent, is not necessarily involved. Obviously, any risk factor or pathologic mechanism acting over a long period will result in a more extensive disease.

1.5.1.2 Sex

It is universally accepted that men are more prone to CHD than women of the child bearing age. After the menopause, however, there is a rapid narrowing of sex differences in the incidence of CHD. The observation of Sternby (1968) indicates that this is true for white population while sex difference is either less or not detectable in Negro population [Tejada et al., 1968]. The lower incidence of coronary heart disease (CHD) in women is because of the protective effect of estrogen,
differences in blood lipids, hematocrit and lesser cigarette smoking [Gordon, 1978].

1.5.1.3 Family History

It has been well established that certain family groups have a predisposition for or increased susceptibility to, premature CHD. In such cases, individuals with either parent or siblings affected by the disease prior to the age of 50 have a greater incidence of CHD. In certain cases the risk may be as high as 5:1 [Fredrickson and Levy, 1972].

Information is lacking with regard to the mechanism, transmission and whether a genetic tendency is modifiable and to what extent the genetic elements act in combination with environmental factors namely nutrition, socio-economic and other risk factors [Glueck et al., 1971, 1972; Tamir et al., 1972; Goldstein et al, 1973a,b; 1974a; Hewitt et al, 1979].

Risk factors may be amenable to correction, and should lead to a comprehensive approach in patients to detect the element that may mediate the genetic expression and enforce early correcting measures when feasible [Glueck and Tsang, 1972; Fredrickson and Breslow, 1973].

1.5.2 Modifiable risk factors

1.5.2.1 Elevated serum lipid levels

During the last 30 years, both retrospective and prospective studies have shown strong correlation between levels of circulating lipids and morbidity and mortality
rates from CHD. Among the serum lipids, cholesterol and low density lipoproteins (LDL) have been found to have higher associative and predictive value than triglycerides. But, there is an inverse relation to high density lipoprotein (HDL) cholesterol with triglyceride and very low density lipoprotein (VLDL) cholesterol in men and women [Carlson et al., 1975 a,b; Rhoads et al., 1976; Castelli et al., 1977a; Davis et al., 1980]. Stronger was the association with triglyceride for HDL$_2$ than HDL$_3$, [Nichols, 1967] two subfractions of HDL.

1.5.2.2 In the epidemiological findings of Japan and in countries of the Mediterranean basin, the incidence of CHD is low [Connor and Connor, 1972]. In Finland, USA, UK and New Zealand, it is very high. In USA, plasma cholesterol (PC) levels are about 240-250 mg/dL in men aged 55-59 years whereas in Japan these were very much lower at 160-180 mg/dL.

1.5.2.3 It has also become apparent that the older concepts of the range and upper limits of normal for blood cholesterol in a given population may be misleading, since the ranges of normal were obtained from measurements of healthy individuals at different ages. In view of the difficulty in recognizing early or latent CHD in otherwise healthy individuals, a limited significance should be attached to these relative 'normal' values. For all these reasons, it appears prudent to consider a normal or desirable level which is associated with lower morbidity and mortality
from international studies on a variety of population. From the standpoint of lessening the development of coronary atherosclerosis, a cholesterol concentration of 140-160 mg/dL would be desirable although it may be somewhat difficult to attain [DiGiolamo and Schlant, 1978].

1.5.3 Diet

1.5.3.1 A diet rich in total calories, total and saturated fats, cholesterol, refined sugars and salt is a major coronary risk factor. This is evident from a number of human population studies [Turner, 1980; Jossens, 1980; Hornstra, 1980] and in experimental studies. The case of Japan, where the incidence of CHD is lower, can be considered as an example. In Japan, there is a low intake of fat and a high intake of unrefined carbohydrates and vegetables [Ball, 1980].

1.5.3.2 Hence it may be inferred that in the long term an overall dietary improvement is likely to reduce the amount of coronary and other arterial disease since diet is the fundamental factor. This involves a reduction of total fats, especially saturated fats, a partial substitution with polyunsaturated fats and an increase of unrefined carbohydrate. Efforts on this line have already been initiated in USA [Krishnan, 1979] with the passing of the heart disease, cancer and stroke Amendment Act of 1965 based on the President's Commission (1968) on heart disease, cancer and stroke. The interest produced on chronic vascular disease (PL-89-239) focussed the
importance on the chronic disease, kindled new awareness and interest, and the accelerated productive potential has permitted significant health gain as can be seen by the reports of Walker (1977) on declining vascular mortality and changing US life style.

1.5.4 Hypertension

1.5.4.1 Elevated blood pressure is the second main risk factor with an established association to coronary atherosclerosis. Kannel (1977) has emphasized that the risk for CHD increases in proportion to the blood pressure (both systolic and diastolic) at any age and in either sex.

1.5.4.2 Epidemiological studies [Jablons et al., 1966] and experimental studies [Pick et al., 1974] suggest that hypertension accelerates atherosclerosis only if hyperlipidemia is present. The effect of hypertension is related to lipid abnormality.

1.5.4.3 In hypertension, there is an increase in hemodynamic stress on the arterial wall. The raised pressure causes endothelial damage and consequently increased permeability of lipid and platelet adhesion. Via its acceleration of atherosclerosis, hypertension leads to ischemic heart disease (IHD) and myocardial and cerebral infarction, these being the main long term effects of benign hypertension [Taurigs, 1978].
1.5.5 Cigarette smoking

1.5.5.1 Smoking is the third major risk factor in CHD. The risk of death from CHD is 2 to 6 times higher in smokers than in nonsmokers and the risk seems to be proportional to the number of cigarettes smoked per day. Pipe and Cigar smoking are associated with surprisingly less added risk possibly because of less smoke inhaled. Doyle (1972), Astrup (1973) and Wald et al., (1973) postulated that carbon monoxide and carboxy hemoglobin in blood are responsible for the increased risk of atherosclerotic complications namely (a) decreasing oxygen supply availability to peripheral tissues might be of practical importance in peripheral atherosclerosis (b) Carboxy hemoglobin levels may go as high as 20% in smokers.

1.5.5.2 Cigarette smoking has been associated with lower levels of HDL and their association seems to be independent of the effect of age, hormone used in women, obesity, alcohol use and physical activity [Enger et al., 1977 and Criqui et al., 1980]. Both nicotinic acid and carbon monoxide appear to affect serum lipid [Hulley et al., 1977; Augusti et al., 1979] and a biological action of some component of cigarette smoke on HDL cholesterol appears reasonable. There is good evidence that cessation of smoking reduces the risk of developing atherosclerotic heart disease [Gordon et al., 1974].
1.6. SECONDARY AND MISCELLANEOUS RISK FACTORS

1.6.1 Diabetes mellitus

Patients with diabetes mellitus (DM) have a greater prevalence of coronary atherosclerotic lesions and have evidence of early CHD than non-diabetics [Nora et al., 1980]. The decrease in HDL cholesterol in diabetes is found to be increased by insulin therapy [Lopes virella et al., 1977; Nikkila et al., 1978]. There is evidence that a high level of circulating insulin may have a role in the development of atherosclerosis [Stout, 1977]. Exposure of arterial tissues to insulin results in proliferation of smooth muscle cells and stimulates synthesis of cholesterol, phospholipids and triglycerides [Stout, 1979].

1.6.2 Obesity

Obesity has been frequently mentioned as a significant coronary risk factor. Obese subjects are significantly more prone to the development of hypertension, diabetes and hyperlipidemia than lean subjects. Glueck et al., (1980) has stated that both males and females older than the age of 12, weight/height, weight/height$^2$, weight/height$^3$ are negatively associated with HDL cholesterol and positively associated with the triglyceride level. These findings were consistent with those of adult population studies [Carlson et al., 1975 a and b; Rhoads et al., 1976].
1.6.3 Oral Contraceptives

There is substantial evidence that women receiving oral contraceptives have a consistently higher risk for CHD than non-users [Mann and Inman, 1975; and Beral, 1976]. The risk of death from CHD was increased 2-8 times in the age group of 30-39 years and 4.7 times in women 40-49 years of age. Numerous clinical studies have established that oral contraceptives produce hyperlipidemia.

Stokes and Whynn (1971) have observed that the effect of triglyceride concentration appears to be related to the dose of the estrogen component and not the progestational component of the oral contraceptive.

1.6.4 Temperament and behaviour

1.6.4.1 Rosenman and Freidman (1960) have concluded that people's behaviour significantly affects the incidence of coronary artery disease apart from other risk factors, by their observations made on an eight years follow up study in 1971 on western population. They classified type A behaviour in predisposing to CHD. Type B people are fairly easy going and relaxed while type A behaviour can be identified by an intense, sustained drive to self selected, but usually poorly defined goals, eagerness and inclination to compete and a persistent desire for recognition and advancement.
1.6.4.2 Type A people show a continuous involvement in multiple and diverse function constantly subject to time limits (deadlines), have a habitual tendency to speed up the rate of performance of many physical and mental tasks and an extraordinary physical and mental alertness [Rosenman, et al., 1975].

1.6.4.3 Hayes et al., (1980) observed that among women of type A, characterised by suppressed hostility, behaviour was associated with a very high incidence of coronary artery disease (CAD). Among men aged 45-64 years, type A behaviour was associated with a 2 fold risk of angina, myocardial infarction, when compared to type B behaviour among the white collar workers.

1.7 CLASSIFICATION AND DIAGNOSIS OF THE HYPERLIPIDEMIA

1.7.1 The classification of the lipoproteins into four major families is based on operational criteria like hydrated density and electrophoretic mobility. Based on their densities and behaviour in the ultracentrifuge, they have been described as chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). Each of the classes can be further fractionated into subclasses on the basis of density. On the basis of electrophoretic mobility, they are designated as α (HDL), β (LDL), pre-β (VLDL) and chylomicrons. The chylomicrons remain at the origin on electrophoresis. The hydrated density of the lipoproteins
are a primary consequence of their lipid content, whereas electrophoretic mobility is determined principally by their protein moieties.

1.7.2 Cholesterol and its esters, triglycerides and phospholipids are the lipid components of lipoproteins. The protein moiety of lipoprotein was shown to include several specific and well characterised apoproteins. A brief summary of the composition and properties of the plasma lipoproteins is shown in Table 1.

1.7.3 Hyperlipidemia is defined as an elevation of one or more of the families of plasma lipids, the most important of which are cholesterol, cholesteryl esters, triglycerides and phospholipids. Unesterified fatty acids are also considered as lipids. However, they are transported primarily with albumin, rather than with classes of macromolecules referred to as lipoproteins. Their orderly classification presents a great difficulty at the present time, for their etiology and pathogenesis are mostly unknown. Only in the rarest disorder, has the mechanism largely been unravelled as due to enzymatic defect.

1.7.4 Fredrickson/World Health Organisation Classification

1.7.4.1 The most widely employed classification system for primary hyperlipidemia is that of Fredrickson et al., (1967) which has been slightly extended and modified [Beautmont et al., 1970, Fredrickson and Levy, 1972]. The system has
<table>
<thead>
<tr>
<th>Source - Major</th>
<th>HDL</th>
<th>LDL</th>
<th>VLDL</th>
<th>Chylomicron</th>
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<tbody>
<tr>
<td>Intestine</td>
<td></td>
<td></td>
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<td>Intestine</td>
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<tr>
<td>Liver</td>
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Physical Properties -

Electrophoretic mobility

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β</th>
<th>pre-β</th>
<th>origin</th>
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</table>

Size (Å)

|       | 50-150 | 200  | 280-800 | 300-500 |

Molecular wt (daltons)

|       | 1.8-3.6x10⁵ | 2.7-4.8x10⁶ | 5-10x10⁶ | >0.4x10⁹ |

Density (g/ml)

|       | 1.063-1.21 | 1.006-1.063 | 0.95-1.006 | 0.95 or less |

Composition (%)

| Protein | 50   | 20   | 8-10  | 1    |
| Triglyceride | 2.5  | 10   | 50    | 85-90 |
| Phospholipid  | 30   | 23   | 18    | 4    |
| Cholesterol   | 18   | 45   | 19    | 6    |

Major apoprotein

| A-I and A-II | apoB  | apoB, C-III and E | apo B, C-I, C-II, C-III |

Minor apoprotein

| apoB, C-I, C-II, C-III, D, E | apo C-I, II, C-III, E | apo A-I, A-II, C-I, C-II, E |
taken an axiomatic view that since plasma lipids are transported as complex macromolecules (the lipoproteins), elevation of the lipoproteins rather than the raised lipid level is of consequence and forms a better system for classification.

1.7.4.2 Hyperlipidemia is best classified on the basis of the pattern of the abnormality of the plasma lipoprotein concentration. Electrophoresis of lipoproteins provides qualitative information on the lipoprotein pattern, and ultracentrifugation with the precipitation methods make it possible to quantitate the major lipoprotein classes, by measuring their lipid content.

The plasma lipoprotein pattern could be classified into six types. These correspond to distinguishable clinical syndromes, and individualised dietary and drug treatments have been proposed [Strisower et al., 1970, Levy, 1972; Gotto, 1978] (Table 2).

1.7.4.3 Another classification of hyperlipoproteinemia based on a more fundamental system [Lewis, 1973, Havel, 1975, Fredrickson, 1975] has also been suggested, although it has certain shortcomings. In this classification, serum lipoprotein patterns form the basis for diagnosis to arrive at the genetic defects, metabolic lesions or the clinical syndromes. The hyperlipidemic members of a particular family, who presumably share the same metabolic lesion, may have different lipoprotein patterns. This is evident
<table>
<thead>
<tr>
<th>Phenotype (definition)</th>
<th>Type I</th>
<th>Type IIa</th>
<th>Type IIb</th>
<th>Type III</th>
<th>Type IV</th>
<th>Type V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia with absolute deficiency of LPL or PHLA</td>
<td>Hypercholesterolemia Elevated LDL</td>
<td>Elevated LBL and elevated VLDL</td>
<td>Floating beta lipoproteins</td>
<td>Elevated VLDL</td>
<td>Elevated Hypercholesterolemia and elevated VLDL LPL or PHLA present but reduced</td>
<td></td>
</tr>
</tbody>
</table>

| Lipids | | | | Normal or ↑ | | Normal or ↑ Normal or ↑ |
|--------| | | | | | |
| Cholesterol | Normal or ↑ | ↑ | ↑ | ↑ | ↑ | Normal or ↑ Normal or ↑ |
| Triglycerides | Greatly ↑ | Normal | ↑ | ↑ | ↑ | Greatly ↑ |
| Plasma ratio (weight % of C/TG) | <0.2 | >1.5 | variable | approx. 1 | variable | >0.15 |
| Fasting chylomicrons | present | absent | absent | present | may be ↑ | absent |

| Lipoprotein pattern | | | | | | |
|---------------------| | | | | | |
| LDL | normal or ↑ | ↑ | ↑ | ↑ | ↑ or normal | ↑ or normal |
| VLDL | Mildly ↑ or normal | normal or ↑ | ↑ | ↑ | ↑ | ↑ |
| HDL | absent or ↓ | normal | normal | normal or ↓ | normal or ↓ | usually ↓ |

(contd...)
<table>
<thead>
<tr>
<th>Appearance of plasma</th>
<th>Cream layer over a clear infranatant</th>
<th>Clear or faintly turbid</th>
<th>Usually turbid may be also faint cream layer</th>
<th>Usually turbid</th>
<th>cream layer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic hyperlipidemia in which this phenotype may be present</td>
<td>Familial lipoprotein lipase deficiency</td>
<td>Familial hypercholesterolemia familial combined hyperlipidemia polygenic hypercholesterolemia</td>
<td>Familial broad β disease</td>
<td>Familial hypertriglyceridemia familial combined hyperlipidemia familial mixed or type V hyperlipidemia familial combined hyperlipidemia (rarely)</td>
<td>Familial hypertriglyceridemia</td>
</tr>
<tr>
<td>Secondary disease that may cause this lipoprotein deficiency</td>
<td>Diabetic acidosis hypothyroidism Dysglobulinemia</td>
<td>Hypothyroidism Dysglobulinemia Nephrosis Obstructive liver disease, autoimmune disease, Cushing's disease, Acute intermittent porphyria</td>
<td>Secondary causes are rare as: Diabetes mellitus Autoimmune hyperlipoproteinemia, obstructive liver disease, estrogens</td>
<td>Diabetes mellitus Hypothyroidism, Dysglobulinemia drugs, Hypothyroidism renal insufficiency</td>
<td>Glycogen storage disease, Alcoholism, Pancreatitis</td>
</tr>
</tbody>
</table>

Abbreviations: LPL = diacylglycerol lipase (lipoprotein lipase); PHLA = postheparin lipolytic activity; C = Cholesterol; TG = Triglyceride;

* Floating β lipoproteins indicate the presence of an abnormal plasma lipoprotein of density < 1.006 gm/ml with β electrophoretic mobility in addition to pre-β migrating lipoprotein.

* The VLDL arginine rich protein (apo E III) in type III is missing one of its three polymorphic appearance when using isoelectric focussing of this protein.
from case studies in which the co-existence of type IV and V occurs in a family, or type III and IV, or Type IIa and IIb, as reviewed by Lewis (1973).

1.7.5 Genetic classification

1.7.5.1 Study of lipid abnormalities within families permits a more accurate identification and classification of familial hyperlipidemias that differs somewhat from the usual classification. It may be borne in mind, however, that therapy is ordinarily selected on the basis of cholesterol and triglyceride levels and on the lipoprotein pattern. Schlant and DiGirolamo (1978) have pointed out that genetic classification is seldom of special importance in clinical practice.

1.7.5.2 Genetic data come from two large studies of families in which the index patients presented with myocardial infarction [Goldstein et al., 1973 b and c, Nikkila and Aro, 1973]. Goldstein described five distinct lipid disorders, which do not correspond exactly with the usual Fredrickson classes. Of these, three disorders (familial hypercholesterolemia, familial hypertriglyceridemia and familial combined hyperlipidemia), represent the dominant expression of three different and distinct autosomal gene mechanisms. The two other disorders are polygenic hypercholesterolemia and sporadic hypertriglyceridemia.

Goldstein et al., (1973 c) implicated the finding that a general population without a manifest CHD
frequently possesses heterozygosity for one of the three lipid-elevating genes. The most common types are probably polygenic or sporadic forms of hyperlipidemia which affect 4% of the population.

1.7.6 Therapeutic classification

A third approach to classification of hyperlipidemic states has been proposed by Tabaqchali et al., (1974). This is in essence a simplification of Fredrickson-Levy classification. Literature on the management of hyperlipidemia suggests that there is a considerable overlap in dietary and pharmacological treatments, prescribed for type I-V hyperlipoproteinemias [Tabaqchali et al., 1974; Gotto, 1978].

It is classified into two groups:

A) Primary hyperlipoproteinemias
   
   (1) Hyper-β lipoproteinemia in which cholesterol levels are increased, triglyceride levels are normal, and serum is clear on inspection (corresponds to type IIa in Fredrickson's classification).

   (2) Endogenous hypertriglyceridemia with or without associated hypercholesterolemia. Stored serum is diffusely lactescent except in the mildest (includes type IIb, III, IV and V) cases.

   (3) Exogenous hypertriglyceridemia: There is usually gross hypertriglyceridemia with relatively slight hypercholesterolemia. After storage, turbidity of the serum floats to the upper part of the sample, leaving the supernatant clear or virtually clear (corresponds to Type I).
B. Secondary hyperlipoproteinemia

The hyperlipidemia occurs as a result of the interaction between the underlying disease (alcoholic abuse, hypothyroidism, diabetes, chronic renal failure etc.) on one hand and other factors which may include nutritional patterns and obesity, additional, latent or overt disease and genetic determinants.

1.8 IDENTIFICATION OF PHENOTYPES AND MANAGEMENT OF HYPERLIPIDEMIA

1.8.1 The goal in defining and treating hyperlipidemia is to avert or delay the resultant complications. This is certainly attainable with respect to certain consequences of elevated lipid levels, since evidence that IHD can be reduced although incompletely is strongly suggestive [Stamler et al., 1972].

1.8.2 Type I Hyperlipoproteinemia

1.8.2.1 Type I is defined by an enormous elevation of chylomicrons and a complete absence of adipose tissue lipoprotein lipase. This enzyme is normally involved in the clearance of chylomicrons and probably of VLDL. A hepatic triglyceride lipase activity may be present, but the sine qua non for type I is the complete absence of adipose tissue activity. Being a primary or inherited disorder, type I is called familial lipoprotein lipase deficiency or familial hyperchylomicronemia. It is curious that VLDL levels are normal or at most significantly raised, possibly
that VLDL unlike chylomicra, can be metabolized by the lipoprotein lipase - independent pathway [Nicoll et al., 1975]. Another feature is low plasma LDL concentration, total serum cholesterol is usually high in untreated cases, but when chylomicronemia abates, strikingly low cholesterol levels are often observed.

1.8.2.2 Fat restricted diet is effective in controlling Type I. Caloric supplementation can be offered, and diet palatability enhanced by using 20-40 gm of medium chain triglyceride (MCT) per day. These fatty acids (C\textsubscript{12} or less) are not transported via chylomicron formation but are absorbed to albumin and pass directly through the portal system to the liver [Berkow and Talbott, 1977; and Sailer, 1979].

1.8.3 Type II Hyperlipoproteinemia

1.8.3.1 Type II phenotype is associated with hypercholesterolemia and hypertriglyceridemia. Hypercholesterolemia due to an increase in LDL is called Type IIa, if VLDL and triglyceride are elevated, the phenotype is IIb. These characters are inherited by two non-allelic genes. One is familial hypercholesterolemia and the other is combined hyperlipidemia. Data from Goldstein and Brown (1975a) suggest that this condition is due to a deficiency of LDL cell receptors resulting in a decrease in LDL catabolism.
1.3.3.2 Familial hypercholesterolemics who inherit a double dose of the gene succumb to severe coronary disease before reaching adulthood. The homozygotes have either a complete absence of LDL receptor or defective receptors. A biochemical marker for the heterozygous state is not currently available, although measurement of lymphocyte receptors represent a potential marker. This disease can be diagnosed in childhood. Other manifestations, usually do not occur until childhood. The first incidence of CHD occurs by the age of 40 to 45 years. The phenotype may be type IIa, IIb or even type IV. Unlike familial hypercholesterolemia, combined hyperlipidemia usually does not appear until childhood.

1.3.3.3 Total calories, should be adjusted to achieve and maintain an ideal body weight, especially in Type IIb. Cholesterol intake should be as low as 300 mg/day. Total calories from fat should be less than 40% of the total daily intake and polyunsaturated fats should be used in preference to saturated fats. Carbohydrate intake should not be controlled except to control the total calories. Refined sugar and sweets should be decreased in Type IIb.

In patients of heterozygous or homozygous type IIa [Levy et al., 1973; Gotto, 1973] and type IIb, the response to diet is seldom adequate. In these patients one usually institutes therapy with cholestyramine. In type IIa it causes a reduction in cholesterol and LDL by
15 to 20% over and above the effects of diet. Similarly, reduction is observed in type IIb. It acts primarily on the excretion of cholesterol and bile acids.

1.8.4 Type III hyperlipoproteinemia
1.8.4.1 Type III hyperlipoproteinemia (or broad β disease) is characterized by an elevation of both cholesterol and triglyceride and by 'floating β lipoprotein' on electrophoresis. Often there is an increase in plasma chylomicrons. The VLDL may have abnormally low triglyceride/cholesterol ratio of 1:1.

1.8.4.2 Type III can be inherited either as an autosomal recessive or autosomal dominant trait. The primary, familial type III usually appears in the second or third decade in man and about 10 to 15 years later in women. Many type III patients tend to be obese and have glucose intolerance. The biochemical defect is not clear, but may be either a failure of conversion of VLDL to LDL or an overproduction of VLDL.

1.8.4.3 Maintaining correct ideal body weight by correct amount of caloric intake. Recommended caloric distribution is as follows: protein, 20%; carbohydrate, 40% (mostly purified sugars and sweets eliminated); and fat, 40% (approximately 10% polyunsaturated, 20% monosaturated fats and 10% saturated fatty acids). Daily cholesterol intake should be less than 300 mg.
Combination of ideal weight, diet therapy and clofibrate is very effective. Nicotinic acid used in place of clofibrate is also effective but it usually has more side effects [Levy and Rifkind, 1973].

1.8.5 Type IV hyperlipoproteinemia

1.8.5.1 The third familial hyperlipidemia transmitted as a dominant trait is hypertriglyceridemia. This is almost certainly a dysfunction of triglyceride metabolism, most often the catabolism. Type V is similar to type IV except for the additional presence of elevated chylomicra which represent dietary or exogenous triglyceride. When hypertriglyceridemia becomes severe from over indulgence in alcohol or excess of weight gain, the phenotype may shift from IV to V. Weight control is a keystone of diet therapy for type IV.

1.8.6 Type V hyperlipoproteinemia

1.8.6.1 It is characterized by a combined increase in chylomicra and in VLDL. The basic defect in lipid metabolism is uncertain, but lipoprotein lipase activity is usually less abnormal than in type I. It is currently thought to be transmitted as a dominant trait with either type IV or type V in affected family members. The familial form more often appears in the second decade.

1.8.6.2 Total calories are restricted to achieve and maintain ideal body weight. Total fat is restricted to 30% of total calories, while carbohydrate are limited to
50% of total calories. Protein intake is limited only by total calories allowed and the content of saturated fat and cholesterol.

If plasma triglyceride levels cannot be reduced to normal by weight control and diet, the diet should be maintained and in addition, nicotinic acid therapy should be used, although it may exacerbate diabetes mellitus. Clofibrate is often of little benefit.

1.9 LIPOPROTEIN METABOLISM

1.9.1 Miller (1979) has defined the major function of the plasma lipoproteins as transport of endogenously synthesised and exogenous glyceride, to the sites of utilisation and storage, and transport of cholesterol, an essential structural component of cell-membrane, between sites of absorption, synthesis, catabolism and excretion.

1.9.2 The general structure of lipoproteins is that of a 'pseudomicelle' composed of an outer surface coat of specific apoproteins and polar lipids (unesterified cholesterol, phospholipid) and an inner core of nonpolar lipids (cholesteryl ester and triglyceride). The apoproteins are able to occupy the interfacial position by virtue of their amphipathic helices (in which polar and nonpolar groups) lie on opposite sides of the molecule [Bradley and Gotto, 1978]. They play critical roles in maintaining/structure of the particles and in regulating at least two enzymes.
involved in their metabolism, lecithin cholesterol acyl transferase (LCAT) and lipoprotein lipase (LPL).

1.9.3 Chylomicron

Chylomicrons are synthesized in the small intestine mucosa and are the major transport forms of dietary triglyceride. Ingestion of dietary lipid initiates intensive metabolic activity in the absorptive cells of the small intestine which culminate in the secretion of chylomicrons. It consists mainly of triglycerides and contains its full complement of esterified cholesterol [Imaizumi et al., 1978]. This lipoprotein was found to contain apolipoprotein B, A-I and A-II [Rachmilewitz et al., 1978; Rachmilewitz and Fainaru, 1979].

1.9.3.1 Following secretion into chyle (Fig. 3) and subsequent transfer into plasma, the 'nascent' chylomicron undergoes very rapid and extensive changes of surface components i.e., phospholipids, unesterified cholesterol (UC) and certain apoproteins [Minari and Zilversmit, 1963 and Imaizumi et al., 1978]. The major donors of UC or recipients of phospholipid are high density lipoproteins. Concomitantly with the transfer of lipid surface components there is also a change in apoprotein content of chylomicrons [Imaizumi et al., 1978 and Green et al., 1979]. The most prominent change is due to an increase in apolipoproteins C and E, which amounts to 56% to 75% and 11 to 15% of the total chylomicron protein in rat and human respectively.
**FIG. 3** Outline of phases of chylomicron metabolism.

(Adapted from STEIN & STEIN, 1979).
[Imaizumi et al., 1978 and Green et al., 1979]. At the same time there is loss of apolipoprotein A-I [Imaizumi, 1978 and Green et al., 1979].

1.9.3.2 The enzyme responsible for the hydrolysis of chylomicron triglyceride is lipoprotein lipase (LPL) which acts at the luminal surface of vascular endothelium. Prior to hydrolysis there is an attachment of chylomicron [Schoeffl and French, 1968] to the endothelial surface i.e. endothelial apolipoprotein receptor. In addition to the contact between LPL and the chylomicron surface there is anchoring of the particle through apolipoprotein E receptor (Fig. 4). In presence of apo C-II hydrolysis of triglyceride proceeds, and the liberated free fatty acids (FFA) are transported to various tissues. During the stage of hydrolysis there is a progressive loss of surface components, i.e. unesterified cholesterol, phospholipid and apoprotein C (Mjøs et al., 1975; Redgrave and Small, 1979).

1.9.3.3 The loss of lipid core results in a partial collapse of the particle, when more than 90% of the triglyceride is hydrolyzed and the loss of phospholipid is about 75% [Redgrave and Small, 1979]. This collapse promotes detachment of the remnant particles. Redgrave and Small (1979) provided evidence that in rat, the hepatocytes are the main sites of chylomicron remnant catabolism.
FIG. 4 Hydrolysis of chylomicron triglyceride (TG) which results in the liberation of free fatty acid (f.f.a.) is accompanied by the loss of apoprotein C, unesterified cholesterol (UC), phospholipid (PL) and formation of a core remnant particle which delivers its cholesterol ester to the liver.

(adapted from STEIN & STEIN, 1979).
1.9.4 Very low density lipoprotein

The site of synthesis of various components of plasma VLDL as well as their transport from endoplasmic reticulum through the golgi apparatus to the sinusoidal cell surface have been well characterised in rat liver [Stein and Stein, 1967 and Stein et al., 1974]. One might assume a similar step, in human liver. However, the nascent VLDL secreted in rat liver differs from human VLDL in lipid composition, i.e. while rat VLDL is secreted with its full complement of esterified cholesterol, human VLDL acquires most of its cholesteryl ester in circulation [Glomset, 1979]. Human hepatic VLDL differs from the intestinal chylomicron, which emerges also with most of its cholesteryl ester. The difference also lies in apolipoprotein E whose main source is liver. Thus apoE is a component of hepatic VLDL [Felker et al., 1977], but chylomicrons acquire apolipoprotein E only in the circulation. Another difference between hepatic VLDL and chylomicron is the much higher apolipoprotein B to triglyceride ratio in the former and high content of apo A-I in the latter.

1.9.4.1 The nascent hepatic VLDL undergoes a series of changes upon entry into the circulation. Hepatic VLDL become highly enriched in apoprotein C [Schafer et al., 1978]. Another modulation is a transfer of apolipoprotein E from the HDL range to VLDL [Glomset, 1979].
Concomitantly with the change in apolipoproteins, the nascent VLDL is transferred from particles poor in esterified cholesterol to a 'mature' plasma VLDL particle (Fig. 5). The process begins with the formulation of esterified cholesterol by the Lecithin cholesterol acyl transferase (LCAT) reaction, the preferred substrate is 'nascent' HDL [Glomset, 1979].

1.9.4.2 The main events occurring during delipidation are hydrolysis of triglyceride by lipoproteinlipase and delivery of FFA to peripheral tissues and a concomitant reduction of VLDL surface. The surface components consist of mainly phospholipids, UC and apolipoprotein C, which are transferred to a HDL density range and in negatively stained preparations appear in the form of stacked discs.

The remnant particle thus formed has retained all of its apolipoprotein B, has still about 20% of its original triglyceride load and has lost about half of its apolipoprotein E and more than 90% of apolipoprotein C [Eisenberg, 1978].

1.9.4.3 The remnant particle is further metabolized to LDL and two possible enzymes responsible for additional hydrolysis of triglyceride are hepatic triglyceride lipase (HTGL) or lipoprotein lipase (LPL) [Deckelbaum et al., 1979]. Thus delipidation of VLDL leads to the formation of LDL.
**FIG. 5** Transfer of esterified cholesterol into VLDL. "Nascent" HDL is a fraction of HDL - the preferred substrate of lecithin cholesterol acyl transferase (LCAT). The HDL₃ particle contains newly formed cholesterol ester (EC) which is transported to VLDL by a transport protein (TP).

(adapted from STEIN & STEIN, 1979).
1.9.5 Low density lipoprotein (LDL)

1.9.5.1 In normal subjects the cholesterol in LDL constitutes about 75% of total plasma cholesterol. The LDL particles are removed from the plasma with a fractional catabolic rate of about 45% of the plasma pool per day [Langer et al., 1972 and Soutar et al., 1977]. The 75% of cholesterol that circulates in plasma LDL is in the form of cholesteryl ester. The LDL delivers cholesterol to the extrahepatic cells and to the liver. The delivery is accomplished when LDL binds to the cell-surface receptor. These receptors appear to recognize apoB leading to the binding of LDL; an apo E containing sub class of HDL also interacts with this receptor probably due to the existence in both apoproteins of a homologous sequence containing arginine [Innerarity et al., 1978].

1.9.5.2 At 37°C binding of LDL to the receptor is followed by internalization of the lipoprotein by invagination of the Fuzzy Pit region of the plasma membrane to form an endocytic vesicle [Brown and Goldstein, 1979; and Goldstein et al., 1979]. (Fig. 6). The endocytic vesicle then migrates through the cytoplasm until it reaches the lysosomes, whereupon the membrane of endocytic vesicles, and the lysosomes fuse, exposing the bound lipoprotein to a variety of hydrolytic enzymes [Goldstein et al., 1974b]. The protein of LDL is hydrolyzed by lysosomal protease to amino acids [Goldstein et al., 1975]. The
Cholesteryl esters of LDL are hydrolyzed by a lysosomal acid lipase [Goldstein et al., 1975 and Brown et al., 1975].

1.9.5.3 In contrast to the cholesteryl ester, which is too nonpolar to cross the cellular membrane, the free cholesterol that is produced is able to passively cross the lysosomal membrane and gain access to the cellular compartment [Goldstein et al., 1974b,c], where it is used for membrane synthesis and exerts several important regulatory functions (Fig.6).

1.9.6 High density lipoprotein (HDL)

1.9.6.1 Investigations by Hamilton et al., (1976), Felker et al., (1977), Green et al., (1978) and several others have shown that the major apoproteins of HDL, apo A-I and apo A-II known as the A peptide may be acquired by chylomicron and/or VLDL, at least in part after their secretion. The nascent HDL, produced by perfused rat liver is a flattened discoid particle in which apo E is the main peptide, apo A-I being a relatively minor component while peripheral plasma HDL in rat and in man has preponderance of apo A-I [Hamilton et al., 1976 and Felker et al., 1977].

1.9.6.2 The source of A-peptide of HDL is of great importance, because of epidemiological evidence that plasma HDL cholesterol is inversely predictive of CHD [Miller and Miller, 1975]. Apo A-I and apo A-II are present in thoracic duct chylomicrons, both in rats [Havel, 1978].
Fig. 6 Adapted from Goldstein and Brown (1977)
and in humans [Kostner and Holasek, 1972]. Schafer et al., 1978) has documented the transfer of apo A-I and apo A-II thoracic duct chylomicron into HDL. Apo A-I has also been shown to be synthesised in the small intestine and not acquired from plasma [La Rosa et al., 1970; Imaizumi et al., 1978 and Glickman et al., 1978]. It is possible that chylomicron borne A-peptides are important sources of HDL-apo A. Furthermore, the flux of A-peptide enhanced by fat feeding [Imaizumi et al., 1978].

9.6.3 The nascent HDL obtained from perfused liver differs in structure and composition from HDL of the peripheral plasma [Havel and Hamilton, 1977 and Havel, 1978]. It is a discoidal bilamellar structure with apoprotein (4% of the protein) located at the edge, the surfaces comprising of free cholesterol and phospholipid. Apo A-I and apo C peptides are also present [Hamilton et al., 1976].

9.6.4 Under the influence of enzyme lecithin cholesteryl acyl transferase (LCAT) the free cholesterol of the nascent particles is esterified and forms a hydrophobic core of the particle, which is then remodelled to a mature spherical form. This remodelling appears to include the transfer of apo A-I and apo A-II of intestinal origin in chylomicrons [Havel, 1978] and VLDL surface material released during the action of lipoprotein lipase [Patsch et al., 1978]. Free cholesterol, phospholipid and apo C are also released from VLDL by lipoprotein lipase [Eisenberg, 1978 and Chajek and Gsenge, 1978].
HDL AND CENTRIPETAL CHOLESTEROL TRANSPORT

1.10.1 Glomset (1968) showed that LCAT and its preferred substrate HDL provide a mechanism for centripetal transport of free cholesterol from peripheral tissues. Tissues acquire cholesterol from plasma as LDL cholesterol. In the steady state, cholesterol must be transported away from the periphery at a rate concomitant to this uptake and synthesis. The major findings which support this concept are:

(a) Miller et al., (1976) have shown a negative correlation in man between plasma HDL cholesterol and mass cholesterol in both exchangeable pools in tissues.

(b) Recent observations favour the view that HDL cholesterol is taken up and metabolized by liver. Rat hepatocytes take up and hydrolyze cholesteryl ester, when incubated with HDL, the uptake showing saturation kinetics (Drevon et al., 1977). Studies in patients with bile fistula, in whom labelled lipoproteins, (in cholesterol moiety) were injected; it appeared in bile cholesterol and chenodeoxycholic acid earlier than the LDL borne label. However, much of this evidence is indirect, and examination of the role of HDL in a centripetal transport is very incomplete at present.

1.10.2 Homeostatic mechanism for cholesterol synthesis

Several mechanisms exist, which tend to stabilise the cholesterol content of the cell, important among these are:
(a) Cholesterol synthesis by the cell is regulated by the rate limiting enzyme, β-hydroxy β-methyl glutaryl coenzyme A reductase which is inhibited when the LDL concentration is increased. The synthesis of the enzyme protein is regulated by intracellular free cholesterol [Brown et al., 1974].

(b) Esterification of cholesterol so that excess can be temporarily stored.

(c) Variation in the number of cell surface receptors over a 10-fold range in response to the LDL levels in the environment [Brown and Goldstein 1975 and 1976], decreasing as availability of LDL increases.

1.11 THE GROWING AWARENESS OF THE IMPORTANCE IN HDL CHOLESTEROL

1.11.1 The renewed interest in the epidemiologic study of HDL cholesterol since 1970 [Glomset] is due to its negative association with the incidence of CHD [Miller and Miller, 1975]. The magnitude of association is found to be larger than that of any known risk factor. Major evidence of this negative association has been provided principally by the Honolulu study [Rhoads et al., 1976], the Cooperative lipoprotein phenotyping study [Castelli et al., 1977], and by three prospective studies, the TromsoHeart study in Norway [Miller et al., 1977], the Framingham study in USA [Gordon et al., 1977] and the Israeli Ischemic Heart studies [Gouldbourt and Medalie, 1979].
The Lipid Research Clinics program describes quantitatively the population distribution of HDL cholesterol [Heiss et al., 1980] and the association of HDL cholesterol with other lipids and lipoproteins [Davies et al., 1980] in several communities in USA, Canada, Israel and USSR. Evidence that these findings reflect an underlying relationship between HDL cholesterol and the severity of coronary atherosclerosis has been provided by angiographic studies [Jenkins et al., 1978; Pearson et al., 1979; Moore et al., 1979; Miller, 1981] and also in our laboratory by Suresh (1981). In all these studies the predictive power of HDL was at least as great as that of plasma total cholesterol concentration.

1.11.2 This epidemiological validation of the proposed physiological role of HDL has led to wide spread acceptance of the causative relationship between HDL and atherogenesis. This hypothesis is consistent with many clinical investigations (including earlier reports) such as:

(a) In certain populations such as the Masai and normadic tribes (Eskimos), total plasma cholesterol levels are comparable to those of men and women in Denmark [Bang et al., 1971] but have substantially higher HDL cholesterol levels and also greatly reduced incidence of CHD.

(b) HDL levels are higher in long distance runners which is consistent with the evidence that physical activity helps to prevent CHD [Wood et al., 1976; Huttunen et al., 1979; and Wood et al., 1979].
(c) High levels of HDL produced by alcohol ingestion are also consistent with the evidence that alcohol ingestion may be antiatherogenic [Barboriak et al., 1977; Belfrage, et al., 1977; Castelli et al., 1977b; Barboriak et al., 1979; Barboriak et al., 1980).

(d) After puberty, females have higher HDL levels and develop atherosclerotic lesions more slowly than men [Nichols et al., 1967 and Cheung and Albers, 1977].

(e) In families with high levels of HDL cholesterol premature CHD is rare and average life span is higher [Glueck et al., 1975, 1976].

(f) A small but significant increase of plasma HDL occurs during the treatment with clofibrate and related drugs and by administration of nicotinic acid [Blum et al., 1977, Cheung et al., 1978 and Enger et al., 1978]. It is worth mentioning, that an indigenous Indian Medicine Annapavala Sindhooram, formulated in our laboratory (Shanmugasundaram et al., in press), has been found to increase post heparin lipolytic activity and elevate HDL cholesterol [Marita and Shanmugasundaram, in press] in experimental atherosclerosis.

(g) Mahley et al., (1977) found that HDL cholesterol was increased substantially with the feeding of dietary cholesterol, which gave rise to a new HDL species especially rich in cholesterol and apo E, but poor in apo A that to HDLc appeared in circulation. Since apo E can
bind with cell surface receptors specific to apo B (of LDL) the binding of apo E in HDL with these receptors (for apo B) may be another mechanism by which HDL provides some protection against CHD [Mahley et al., 1977].

1.12 THE APOPROTEIN COMPONENT AND THE LIPOPROTEIN CLASSES

1.12.1 Applying several consecutive preparative methods of modern biochemistry, lipoprotein density fraction can further be subfractionated yielding lipoprotein entities which can be equated with adequate precision with lipoprotein families [Alaupovic et al., 1971; 1972 a,b; Kostner and Alaupovic, 1972; and Kostner, 1975].

1.12.2 Lipoprotein (LpA)

Lipoprotein A (Lp-A) consists of three major polypeptides apo A-I (R-Gn-I), apo A-II (R-Gn-II) and apo A-III (apo D) [Shore and Shore 1968; Kostner and Alaupovic, 1971 and Mc Conathy and Alaupovic, 1973]. LpA is the major component of the high density lipoprotein subclasses, comprising more than 85% of the total lipoprotein mass.

1.12.3 Lipoprotein B (Lp-B)

The major protein moiety apolipoprotein B contains probably only one kind of polypeptide with a molecular weight of approximately 250,000 daltons [Smith et al., 1972]; many different albttypic forms of Lp-B
have been demonstrated till now [Kostner, 1975]. The chemical nature of different allotypic forms of Lp-B remain to be elucidated. Krishnaiah and Wiegand (1974), suggested the possibility that heterogeneity may be due to protease activity of endogeneous or exogeneous origin found in the LDL preparation leading to artificial fragmentation of apolipoprotein B. Chen and Aladjem (1974) have shown the absence of such activity in LDL. In addition, Lp-B is found in chylomicron and VLDL increasing its relative content with increasing hydrated density [Kostner and Holasek, 1971, Eisenberg et al., 1972].

1.12.4 Lipoprotein 'a' (Lp(a))

Originally believed to represent an allotype of lipoprotein B [Berg 1963] Lp(a) turned out to be a normal component of the HDL₂ density class of almost any serum, with a molecular weight of more than $5 \times 10^6$ daltons [Harvie and Schultz, 1970 and Jurgens and Kostner, 1975]. Wiegandt et al., (1968), Schultz et al., (1968) were the first to describe the hydrated density of Lp(a) with a density range of HDL (d-$1.065-1.21$ g/ml) but precipitate only with antisera obtained for LDL, and not by HDL. Riedel et al., (1970) and Simons et al (1970) demonstrated that the Lp(a) lipoprotein develop pre-β mobility on agarose electrophoresis.
1.12.5 Lipoprotein C (LpC)

The protein part of LpC is a mixture of at least four different polypeptides [Brown et al., 1970]. According to electrophoretic mobility they are apo C-I [R-ser]
apo C-II (R-glu), apo C-III (R-ala₃) and apo C-III₂ (R-ala₂). The molecular weights of the apo C polypeptides range from 7 \times 10³ - 10 \times 10³ daltons. ApoC polypeptides form a metabolic entity to a certain degree (LpC) which is found in HDL. Chylomicron and VLDL can be regarded as a cluster of several lipoproteins with a predominance of LpC and LpB connected to triglyceride.

1.12.6 Lipoprotein D (LpD)

The finding of the fourth family LpD by Mc Conathy and Alampovcic (1973), which was originally designated as, thin line polypeptide Apo III (Apo D) can be found under experimental conditions, as the sole polypeptide of the lipoprotein fraction of HDL. The molecular weight of LpD is 21,000 daltons. Apo LpD in serum was detectable in all density classes but measurable only in HDL₂ (21%), HDL₃ (43%) and VHDL (36%) [Curry et al., 1977].

1.12.7 Lipoprotein E (LpE)

Lipoprotein E (LpE) is a recently recognised lipoprotein and is designated as arginine rich polypeptide (ARP). It has been found to be associated with VLDL and HDL. The apo E is a glycoprotein of mol wt 39,000 [Utermann, 1977] that splits into three main bands
E-I (pI ~ 5.3), E-II (pI ~ 5.4) and E-III (pI ~ 5.55) on isoelectric focussing.

LpE concentration may provide as a sample marker for the functional state of lipoprotein catabolism. Apo E variant is characterized by a deficiency of E-III in tri-glyceride rich lipoproteins [Utermann et al., 1977] and serve as a means for differentiation of type III and type IV hyperlipidemia.

1.12.8 Lipoprotein X (LpX)

A detailed study of LpX was made by Patsch et al., (1977) in plasma of patients with advanced obstructive liver disease. The different fractions Lp-X₁ (d = 1.038 g/ml) Lp-X₂ (d = 1.049 g/ml); Lp-X₃ (d = 1.058 g/ml) can be isolated by zonal ultracentrifugation. All three groups are rich in phospholipids (65%) and free cholesterol (25%) and are relatively poor in triglycerides (~ 5%). In all, the protein constituents contain a large fraction as an α helical structure (41 - 65%) and the fluidities of the lipid region of the particle are very low. All three contain serum albumin and apo C but only LpX₁,₂ contain apo A-I and apo E.

1.13 INCIDENCE OF ATHEROSCLEROTIC DISEASE IN INDIAN POPULATION

1.13.1 Epidemiological studies carried out in different countries, have evaluated the strength of the association between dietary fat, and the genesis of atherosclerosis.
The role of dietary cholesterol in human atherogenesis has led to the assumption, that, elevated serum cholesterol concentration is associated so closely with the progression of human atherosclerosis, that it is almost certainly an intervening variable in the process. This elevation needs only to be modest to be significant in atherogenesis. This assumption is part of the lipid hypothesis, supported by the data of WHO and FAO, which shows a highly significant correlation between atherosclerotic diseases, and cholesterol intake [Connor 1961; Masironi, 1970 and Connor and Connor, 1972].

1.13.2 India is a large country, (Fig. 7) inhabited by people belonging to different races, with multiple cultural patterns, such as food habits, socio-economic differences, and wide variations in the incidence of CHD, in the different regions. Table 3 shows the dietary pattern of people in different states obtained during a survey conducted by the Indian Council of Medical Research (ICMR 1962). It indicates that carbohydrates form the major sources of calories in Indian dietaries supplying from 69% to 85% of the total calorie intake. Calories from fat form 4% to 19% and those from protein form 9% to 14% of total calories [Mc Divitt and Mudambi, 1969]. This is strikingly different from the food habits in Europe and North America.
FIG 7. MAP OF INDIA
### TABLE 3

**CALORIES IN THE INDIAN DIET 1962 AS INDICATED BY DIET SURVEY IN EIGHT STATES**

<table>
<thead>
<tr>
<th>State</th>
<th>Total calories per ACU*</th>
<th>Percentage of calories from</th>
<th>Carbohydrates</th>
<th>Fats</th>
<th>Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORTHERN ZONE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punjab</td>
<td>2823</td>
<td>71</td>
<td>17</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Rajasthan</td>
<td>2378</td>
<td>75</td>
<td>11</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>2970</td>
<td>80</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><strong>NORTHEAST ZONE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bihar</td>
<td>2505</td>
<td>85</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>West Bengal</td>
<td>1946</td>
<td>73</td>
<td>17</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>CENTRAL ZONE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maharashtra</td>
<td>1986</td>
<td>69</td>
<td>19</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>SOUTHERN ZONE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>2324</td>
<td>80</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Madras (now Tamilnadu)</td>
<td>1937</td>
<td>81</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

---

* Adult Consumption Unit (ACU)

** Human Nutrition: Principle of applications in India by Mc Divitt and Mudambi (1969)
1.13.3 Table 4 shows the daily intake of calories and protein of different countries. The animal protein consumption in India is least while the highest intake is observed among the Americans and British, where the incidence of CHD is also very high.

Table 5 shows the net food supplies among different countries. In USA there is low consumption of cereals and very high consumption of animal fats and milk products which is very much parallel to the incidence of CHD, while the reverse is true for the countries with a low incidence of CHD.

1.13.4 Mathur (1959) found an incidence of 1.04% of CHD in the general population in Agra (North India). A breakup of this incidence in different socio-economic groups was high (4%), middle (0.6%) and low (0%). A similar observation was noticed by Padmavathi et al., (1959) in Delhi and by Bhalla and Tondon (1962) in Uttar Pradesh. Data on the incidence of CHD in South Indian population is sadly lacking.

1.13.5 The morbidity rate and incidence of coronary atherosclerotic disease in many states in India are not available. The only All India study available was made by the Indian Railway Medical Department on the incidence of mortality due to CHD in different railway zones during a 5-year period (1958-62) presented in Table 6. This
## TABLE 4

**DAILY INTAKE OF CALORIES AND PROTEIN IN DIFFERENT COUNTRIES**

<table>
<thead>
<tr>
<th>Name of Country</th>
<th>Calories/day</th>
<th>Proteins gm/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Animal</td>
</tr>
<tr>
<td>India (1964-65)</td>
<td>2110</td>
<td>6</td>
</tr>
<tr>
<td>Pakistan (1964-65)</td>
<td>2260</td>
<td>10</td>
</tr>
<tr>
<td>U.A.R. (1964-65)</td>
<td>2930</td>
<td>13</td>
</tr>
<tr>
<td>Japan (1965)</td>
<td>2350</td>
<td>25</td>
</tr>
<tr>
<td>U.S.A. (1965)</td>
<td>3140</td>
<td>65</td>
</tr>
<tr>
<td>U.K. (1965-66)</td>
<td>3250</td>
<td>53</td>
</tr>
</tbody>
</table>

Adapted from *Diet Atlas of India (1969)*
<table>
<thead>
<tr>
<th>Name of country</th>
<th>Cereals</th>
<th>Starchy foods</th>
<th>Sugar</th>
<th>Pulses and nuts</th>
<th>Vegetables</th>
<th>Fruits</th>
<th>Meat</th>
<th>Egg</th>
<th>Fish</th>
<th>Milk</th>
<th>Fats and oils</th>
</tr>
</thead>
<tbody>
<tr>
<td>India (1964-65)</td>
<td>404</td>
<td>37</td>
<td>50</td>
<td>61</td>
<td>8</td>
<td>45</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>125</td>
<td>11</td>
</tr>
<tr>
<td>Pakistan (1964-65)</td>
<td>457</td>
<td>27</td>
<td>48</td>
<td>17</td>
<td>37</td>
<td>75</td>
<td>10</td>
<td>1</td>
<td>4</td>
<td>200</td>
<td>16</td>
</tr>
<tr>
<td>U.A.R. (1963-64)</td>
<td>586</td>
<td>40</td>
<td>46</td>
<td>29</td>
<td>281</td>
<td>242</td>
<td>36</td>
<td>4</td>
<td>14</td>
<td>124</td>
<td>20</td>
</tr>
<tr>
<td>Japan (1965)</td>
<td>394</td>
<td>173</td>
<td>50</td>
<td>43</td>
<td>293</td>
<td>90</td>
<td>28</td>
<td>24</td>
<td>76</td>
<td>100</td>
<td>19</td>
</tr>
<tr>
<td>U.S.A. (1965)</td>
<td>182</td>
<td>123</td>
<td>133</td>
<td>22</td>
<td>268</td>
<td>225</td>
<td>273</td>
<td>49</td>
<td>14</td>
<td>657</td>
<td>60</td>
</tr>
<tr>
<td>U.K. (1965-66)</td>
<td>213</td>
<td>282</td>
<td>137</td>
<td>17</td>
<td>162</td>
<td>156</td>
<td>203</td>
<td>42</td>
<td>26</td>
<td>590</td>
<td>62</td>
</tr>
</tbody>
</table>

Adapted from Diet Atlas of India (1969).
<table>
<thead>
<tr>
<th>Railway Zone</th>
<th>No. of deaths</th>
<th>Total No. of employees (18-55 years)</th>
<th>Mortality rate per 100,000 employees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern</td>
<td>36</td>
<td>178,311</td>
<td>20</td>
</tr>
<tr>
<td>Western</td>
<td>41</td>
<td>162,264</td>
<td>25</td>
</tr>
<tr>
<td>North-Eastern</td>
<td>23</td>
<td>84,964</td>
<td>33</td>
</tr>
<tr>
<td>Eastern</td>
<td>88</td>
<td>176,633</td>
<td>50</td>
</tr>
<tr>
<td>North-East Frontier</td>
<td>36</td>
<td>63,120</td>
<td>57</td>
</tr>
<tr>
<td>Central</td>
<td>126</td>
<td>200,308</td>
<td>63</td>
</tr>
<tr>
<td>South Eastern</td>
<td>105</td>
<td>123,497</td>
<td>85</td>
</tr>
<tr>
<td>Southern</td>
<td>219</td>
<td>161,719</td>
<td>135</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>679</strong></td>
<td><strong>1,150,816</strong></td>
<td><strong>59</strong></td>
</tr>
</tbody>
</table>

*Data obtained from Epidemiology of Ischaemic heart disease in India with special reference to causation by Malhotra (1967 a,b).*
data was collected from 2 centres in each zone and among
the male workers in the age group 18-54 years. The incidence
of CHD was seven times higher for Southern Railway than
with centres of Northern Railway [Malhotra, 1967 a,b].

1.13.6 The greater incidence of CHD mortality among
South Indian Rail road workers may be taken in conjunction
with dietary habits studied by Malhotra (1967a,b) and from an
official diet survey (by ICMR) among the South Indians and
a group of North Indians (Punjabis) given in Fig.8. The
major differences are that the Southern have rice as a
staple food, while Northerners consume predominantly wheat
and millets and other cereals which have a higher fiber
content. Although consumption of milk and milk products,
oil and sugar is higher among the Punjabis, the relatively
this population may well be due to the fibre content
in the cereals. It is worth mentioning here that the
gradual increase in the CHD mortality among the railroad
workers of different regions supported by Malhotra (1967 a,b)
from the northern to the southern region is parallel to
the gradual increase in the consumption of rice.

1.13.7 The only major difference among the groups is
that coal is not used as a fuel (excepting for the railway
engines in 1958-62) in the southern region, while in the
north and in eastern India, it is used as a domestic
fuel also. The possibility of any protective effect by
FIG. 8  Food consumption pattern in South India and the Punjab.

one or more of the pollutants (such as Vanadium compounds) in smoke generated by coal gas cannot be ruled out.

1.13.3 The plasma lipid profiles in the normal population of India had not been studied in sufficiently large populations. The lipid profiles, should be studied in the low socio-economic and the middle class people, to arrive at the normal range for our populations. The literature available now on plasma lipid profiles studied by Padmavathi et al., 1959, Bandyopathy et al. 1964, Kumar et al., 1976, Ban, 1970, and Rao et al., 1980 are given in Table 7.

It may be seen that the levels vary within the accepted normal range.

1.13.9 Investigations on the plasma lipoprotein cholesterol distribution and the lipoprotein classes are sadly lacking in the Indian population. It is essential to identify hyperlipoproteinemia which is of diagnostic value.

1.13.10 The relatively low incidence of coronary artery disease in the Indian population may be due to genetic, dietary and other environmental factors and the study of plasma lipoproteins is therefore of prime importance.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Category</th>
<th>Age (years)</th>
<th>Cholesterol (mg/dl)</th>
<th>Method used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathur et al.,</td>
<td>1) Low income; unskilled</td>
<td>41-50</td>
<td>155±37.6</td>
<td>Zak</td>
</tr>
<tr>
<td>1959 Uttar</td>
<td>workers, male</td>
<td></td>
<td></td>
<td>et al (1964)</td>
</tr>
<tr>
<td>Pradesh)</td>
<td>2) Low income, skilled</td>
<td></td>
<td>178±24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>workers male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) Middle income group</td>
<td></td>
<td>194±15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4) High income group</td>
<td></td>
<td>216±10</td>
<td></td>
</tr>
<tr>
<td>Bandypatghya et</td>
<td>1) Laboratory attender</td>
<td>19-30</td>
<td>136±5.9</td>
<td>Zak</td>
</tr>
<tr>
<td>al (1964)</td>
<td>2) Student male</td>
<td></td>
<td>195±4.5</td>
<td>et al (1964)</td>
</tr>
<tr>
<td>Rajasthan)</td>
<td>3) Student female</td>
<td></td>
<td>190±0.00</td>
<td></td>
</tr>
<tr>
<td>Pinto and</td>
<td>1) Male</td>
<td>41-60</td>
<td>173±22.5</td>
<td>Sacket</td>
</tr>
<tr>
<td>Goffar (1964)</td>
<td>2) Female</td>
<td></td>
<td>184±31.4</td>
<td>et al (1925)</td>
</tr>
<tr>
<td>Bombay)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Srivastava et</td>
<td>1) Lower and middle income</td>
<td>41-50</td>
<td>137±7</td>
<td>Sacket</td>
</tr>
<tr>
<td>al (1966)</td>
<td>group (physically active)</td>
<td></td>
<td></td>
<td>et al (1925)</td>
</tr>
<tr>
<td></td>
<td>2) Lower and middle income</td>
<td></td>
<td>174±7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>group (sedentary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) Higher privileged class</td>
<td></td>
<td>199±7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(sedentary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ban et al 1970</td>
<td>Industrial workers</td>
<td>35-44</td>
<td>236±26</td>
<td>Zlatkis</td>
</tr>
<tr>
<td>(Madhya Pradesh)</td>
<td>Income Rs.300 and more</td>
<td>45 and</td>
<td></td>
<td>et al (1953)</td>
</tr>
<tr>
<td></td>
<td>above</td>
<td>240±30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumar et al (1975)</td>
<td>Chandigarh Males</td>
<td>30-60</td>
<td>210±81</td>
<td>Zak et al</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1964)</td>
</tr>
<tr>
<td>Rao and Sastry</td>
<td>Male</td>
<td>41-50</td>
<td>173±23</td>
<td>Abell</td>
</tr>
<tr>
<td>Pradesh)</td>
<td>Female</td>
<td>41-50</td>
<td>184±31</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 7

Plasma cholesterol levels of Indian population in different socio economic groups in different regions.
1.14 SCOPE OF THE PRESENT INVESTIGATION

1.14.1 This investigation is a part of a drive made in studying the lipoprotein cholesterol distribution in normal healthy people in the Madras region, with a view to assess the protective role of HDL cholesterol in the development of coronary artery disease.

1.14.2 The lipid distribution in the plasma lipoproteins were also investigated in patients with cardiovascular diseases, attending the cardiology unit of the Railway Hospital at Perambur, in the outskirts of Madras.

1.14.3 The study included not only railroad workers but also a large cross section of the population including the blue collar and white collar workers, students and professionals. The participants in the survey did not belong to the low socio-economic groups and were all well-fed and well educated.

1.14.4 The dietary pattern such as inclusion of meat, eggs, fish etc. (Indian dietary pattern is cereal based and meat, eggs or fish may substitute or complement vegetables and lentils), smoking habits, drinking habits, and a previous history of diabetes mellitus or heart disease including family history was recorded. Their association with cholesterol triglyceride and phospholipid distribution in plasma lipoproteins were investigated.

1.14.5 Investigations were made on the apoprotein-B levels in the serum of patients and they were compared with suitable age and sex matched controls.

1.14.6 The observations made are discussed in the light of the earlier literature.