GENERAL

The massive study on serum lipid lipoprotein profiles on healthy and diseased individuals is to reveal the mysteries of the most important pathogenic entity i.e. atherosclerosis.

For the process of atherosclerosis hypercholesterolemia is one of the important risk factors. A risk factor may be defined as "any habit or trait that can be used to predict an individual probability of developing that disease (Dhewpublication, 1981). Altered level of serum lipoproteins in particular elevated low density lipoproteins (LDL and diminished high density lipoproteins (HDL) appears to be strongest among other lipid levels. Moreover other factors viz. age, sex, smoking, obesity, hypertension, stress, impaired glucose tolerance (Diana B Petitti, 1979) and dietary habits and sedentary life style exert their influence on lipoprotein levels and thus the development of atherosclerosis. Many are reversible but others like age, sex, genetic factors are irreversible ones.

There are at least three independent prediction of risk for individuals. They are plasma cholesterol concentration (Ross, 1986; Inkeles and Eissenberg, 1981), cigarette smoking(Wissler, 1976) and elevated blood
pressure (Oberman Harlan et al, 1969).

To understand the pathogenesis the accumulation of fat in the arterial wall is typical sign of atherosclerosis. This uptake depends upon plasma lipids level as well as individual arterial wall factors and the uptake is largely of LDL cholesterol. Significant hyperlipoproteinemia is considered in those individuals who when below 20 years age has total serum cholesterol exceeding 200 mg% or plasma triglyceride levels exceeding 140 mg% while in those above 20 years of age the values should exceed 240 mg% for STC and plasma triglyceride more than 200 mg% usually individuals who are afflicted with atherosclerosis have more than one risk factor at a time.

Mayer (1981) and Harper gave the range of various fractions in human plasma. Total lipids range between 360-820 mg%. Total cholesterol b/w 107-320 mg% and triglyceride between 80-180 mg%.

HISTORICAL ASPECT

Lesions of atherosclerosis were identified in Egyptian mummies as early as fifteenth century B.C.. In mid nineteenth century Virchow made concept of injury to the arterial wall associated with inflammatory response resulting in lesion of atherosclerosis. Modern view started to stem from work of John French who noted that structural integrity of endothelial lining of artery was key to maintenance of normal functions and any breach to it might precede a sequential events to lesions of
atherosclerosis. Thereafter over many years, many theories concerning the etiology and pathogenesis of atherosclerosis has been put forth of which response to injury, monoclonal hypothesis and lipogenic hypothesis needs mention.

**LIPID LIPOPROTEIN METABOLISM AND ATHEROSCLEROSIS**

These are high molecule weight globular particles that transport nonpolar lipids primarily triglyceride and cholesteryl ester through plasma. Each lipoprotein particle contains a core of hydrophobic triglyceride and cholesteryl ester in various proportions with a polar surface monolayer of phospholipids along with unesterified cholesterol to stabilize the particle. It also contains specific apoprotein on surface which helps in binding to specific enzyme or transport protein on cell membrane.

Lipoproteins are divided according to their relative amount of protein and lipid and electrophoretic mobility into 4 major classes as chylomicrons, high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL). LDL is further divided into LDL₁ and LDL₂ and HDL into HDL₂ and HDL₃.

**EXOGENOUS PATHWAY**

The chylomicrons large triglycerides rich particles are produced in the intestine from dietary fat. Hence they are normally not present in plasma after fast of 12-14 hours. They are catabolized by lipoproteins
lipase and hepatic lipase to form chylomicrons
remnants triglycerides form free fatty acids (FFA).

**ENDOGENOUS PATHWAY**

VLDL synthesis occurs in liver and increased
in obese. VLDL, triglycerides are hydrolysed by lipo-
protein lipase and hepatic lipase.

LDL₃ are major cholesterol carrying lipoprotein
and most of it comes VLDL catabolism while some are
synthesized directly. LDL when degraded return to
cell as free cholesterol.

Direct HDL production occurs in liver and
intestine and also derived from chylomicrons and VLDL
catabolism. HDL serves as acceptor of lipid especially
free cholesterol from peripheral tissues including
vascular endothelium to the liver where excretion occurs
through bile involving plasma enzymes. HDL has also been
suggested to block peripheral LDL receptors thereby
reducing cholesterol uptake and storage in epithelial
cells of vessels thus an impairment of HDL levels acce-
lerates the excess deposition of fat in vessel wall.

Patients with IHD usually have raised trigly-
ceride and cholesterol concentration (Lewis et al, 1974)
and subnormal HDL levels (Castelli et al, 1977).

**RISK GROUP**

To relate risk to level of LDL than high risk
group includes individuals with LDL more than 170 mg/dl.
Low risk group for values less than 100 mg/dl and intermediate risk group for values 100-170 mg/dl. Recently ratio of LDL : HDL has been used as another indicator of risk. Individual with ratio greater than 5 as high risk group, values 3-5 at significant risk and at value 3 at average risk, values 2-3 at moderate risk.

WOMEN AND CARDIOVASCULAR DISEASE (CVD)

There is an almost universal clinical impression that CVD are more common in men than in women, a rate twice to that of women in age younger than 60. However, sex difference decreased with advancing age possibly due to menopause (Kannel et al, 1976).

Age specific death rates for CVD among women are substantially less than those of men the same age disparity is less pronounced after age 60 (Wolf, 1991).

Lower incidence of coronary heart disease in females has led to many to believe that endocrine factors are of importance for the homeostasis of lipid in the plasma but also for the deposition and metabolism of lipids in vessel wall.

LIPID LIPOPROTEIN LEVELS IN PRE AND POST MENOPAUSAL WOMEN AND CVD

In premenopausal women there is 15-20% cyclical suppression of total plasma cholesterol, HDL and LDL apo beta during luteal phase and HDL increases slightly during the second half of cycle (Kim and Kalkhoff et al,
1981). Young women of child bearing age has significantly low incidence of CVD than man of same age group, but this difference of incidence decreases with advancing age suggesting protective ovarian function and comes equal to that of man after age of 55-60 years. This fact is supported by study of James et al (1955), Weinrub et al (1957), Oliver et al (1959), Bengtson (1973) and Gordon et al (1978) that female undergoing early menopause were observed to have higher rate of CVD than with those of late menopause of same age group.

The possible reason for above fact has been suggested by lack of ovarian function and of oestrogens (Sjnaiderman et al, 1963). Oestrogen a safety factor causing increase HDL lowering of LDL and total cholesterol. It is not the free cholesterol that causes intimal damage of vessel but rather abnormal oxidation products of cholesterol. Oestrogens do protect against abnormal oxidation products (Imai et al, 1980).

Exogenous progesteron has just opposite effect on lipid lipoprotein levels (Bradley, 1982 and Wingerd et al, 1982).

Total cholesterol and LDL tended to rise during the early postmenopausal years while HDL do not change (Don Gambrell et al, 1991).
HYSTERECTOMIZED WOMEN AND PROTECTIVE OVARIAN FUNCTION

It has been suggested that functioning ovaries provide protection against CVD, thus hysterectomized women (non castrated) have ovarian function sufficient to exert protection against CVD, this fact was verified by several experiments.

Biological and Chemical Measurements

Normal level of urinary gonadotrophins and pregnanediol in hysterectomized women have suggested, maintained ovarian function (Knutsen, 1951; Disilveria et al, 1956; Whitelaw, 1958). Whereas Marx et al (1951) and Rust (1951) found increased gonadotrophins after hysterectomy only suggesting reduced ovarian function. It appeared to be related to the amount of interference with ovarian blood and nerve supply during operation.

Basal Temperature Curves

Hysterectomized women show a normal cyclical temperature curve for a period of about 4 years after operation (Fredrikson, 1952) and none of the oopherectomized woman shows this type of curve (Whitelaw, 1958).

Vaginal Smears

Bancroft-Livingston (1954) found that active vaginal smears were found in 95% of the hysterectomised women within 3 years of operation while in 60% after 5 years.
Gordon et al (1978), Colditz et al (1987) found in their studies that women had undergone bilateral oophorectomy had increased risk of coronary heart disease as compared to hysterectomy alone.

Whereby a contrary study by Ritterband (1963) found to significant difference in the prevalence of coronary heart disease in oophorectomised and hysterectomised women.

PREMATURE MENOPAUSE AND RISK OF CVD

Extensive post mortem studies by Aekerman et al (1950) and Wuest Dry and Edward (1953) demonstrated a direct relation of early castration with severity of CVD. Snazzerdän and Oliver (1963) and Higano (1963) found increased incidence of CVD in prematurely oophorectomised group.

Severity of disease has direct relation with the time interval from castration to premenopause, those castrated before age 40 and are expected to survive more than 14 years after castration are at high risk to developing coronary heart disease (Parrish et al, 1967 and Rosenberg et al, 1981).

Unilateral oophorectomy however increases less incidence of CVD in women in comparison to bilateral oophorectomy(Oliver and Boyd, 1959; Colditz et al, 1987).
OVARIAN AND ADRENAL STEROID PRODUCTION IN POSTMENOPAUSAL WOMEN

Relative contribution of ovaries and adrenals to the pool of steroids in post menopausal women is still the subject of controversy.

After menopause ovary releases androgens to the plasma. These get aromatised at extragonadal site into oestrogens (Mattingly et al, 1969). Androgens which are secreted mainly testosterone and moderate amount of androstendione. Ovary also secretes low levels of estrone (Judd et al, 1974). Robert et al (1976) assayed estradiol, androstendione and testosteron in peripheral blood, adrenal and ovarian vein of 11 postmenopausal women. Intravenous administration of HCG resulted in increased androgen production by the ovaries but not oestrogen while intravenous administration of ACTH hormone did not result in enhancement of ovarian and adrenal estrogens.

EFFECT OF HYSTERECTOMY WITH OR WITHOUT OOCHECTOMY ON LIPOPROTEIN METABOLISM

1. SERUM CHOLESTEROL

Increased serum cholesterol levels are regarded as an important risk factor for CVD. Oliver and Boyd (1959) showed significant rise in serum cholesterol in oophorectomised women. This rise occurs significantly in premature menopausal women in comparison to premenopausal

William and Kannel et al (1976) also showed increased serum cholesterol level in menopausal women than premenopausal women.

Bengston and Lindquist (1979) and carlton & Simons (1980) found significant rise in serum cholesterol levels after surgical menopause. This was supported also by Notelowitz et al (1983) and Fainsini et al (1984).

Jenson et al (1987) showed that both natural and surgical menopause are accompanied by high serum cholesterol.

Farish et al (1990) showed significant increase in total cholesterol at 6 weeks after oopherectomy and no significant change thereafter. Mitra and Asthana (1993) found no significant difference in levels of cholesterol after one month of operation.

2. **SERUM TRIGLYCERIDES**

Oliver and Boyd (1959), Sznajderman et al (1963) showed that serum triglycerides were significantly raised in study group of women with premature menopause as compared to healthy women of same age group.
This has also been supported by studies of Punnonen and Rauramo (1976), Carlton et al (1980) and Notelowitz et al (1983). They showed significant rise in serum triglyceride levels after one month of castration.

On the contrary study by Aitken et al (1971) showed significant rise in serum triglyceride with age, however, women without ovaries had slightly lower triglyceride value and a significantly slower rate of increase of serum triglyceride with age than women with intact ovaries. Pansini et al (1984), Parish et al (1990) also did not show any significant rise in triglyceride levels within three months of castration.

Mitra and Asthana (1993) did not find any statistically significant change in serum triglyceride after bilateral oophorectomy.

3. **HIGH DENSITY LIPOPROTEIN (HDL)**

HDL is heterogeneous group and has got two main subfractions \( \text{HDL}_2 \) and \( \text{HDL}_3 \). Low levels of \( \text{HDL}_2 \) are clearly related to high risk of atherogenesity while \( \text{HDL}_3 \) and total HDL not. Concentration of \( \text{HDL}_2 \) is higher in women than in men and the increased by oestrogen hyper-triglyceridemia. Exogenous androgen and progesteron lowers the HDL level.

In females there is a small linear increase in levels from childhood to about 60 years but there is no significant change in alpha fraction (William and Kannel,
1976). Punnonen and Rauramo (1980) showed that HDL levels before and one month after castration did not change significantly.

Notelowitz et al (1983) showed that HDL levels in oophorectomised women were 27% lower than in intact women. Pansini et al (1984) showed early decrease and subsequent increase levels of HDL within 3 months of oophorectomy which were apoprotein mediated.

Farish et al (1990) measured HDL subfractions to assess any change in relative amounts of cholesterol carried on HDL\(_2\) and HDL\(_3\). No significant change was found in either fraction.

Kushwaha et al (1991) found very little effect on HDL levels in oophorectomised baboons.

Mitra and Asthana (1993) did not find any difference in HDL levels in bilaterally oophorectomised women.

4. **LDL AND VLDL**

VLDL is endogenously produced lipoprotein (in liver) and contains apo beta 100. It is 20% of serum triglyceride. Its function is to transport cholesterol and endogenously produced triglyceride to body tissues. Metabolites are used for energy during the metabolic process and remnants left behind are taken by liver and converted to LDL. Accumulation of remnants favour atherogenesis and oestrogen reported to accelerate the clearance of remnants.
LDLs are major cholesterol carrying lipoproteins. Liver uses them for synthesis of bile acids and free cholesterol is secreted in bile.

Arnold B Ritterband (1963) showed that mean serum cholesterol and percent of beta lipoprotein in oopherectomised women under 50 were higher the hysterectomised women.

William and Kannel et al (1976) showed cholesterol in the prebeta fraction and beta fraction for women rises rapidly while remaining essentially unchanged for men older than that age group.

Noteiowitz et al (1983) showed that relative proportion of LDL and or VLDL did not differ significantly in oopherectomised women and intact women.

Pansini et al (1984) showed biphasic change in apoprotein beta levels in oopherectomised women within three months. Farish et al (1990) showed a significant rise in LDL cholesterol in the 6 weeks after bilateral rise in LDL cholesterol in the 6 weeks after bilateral oopherectomy from a mean of 3.57 m mol to 4.21 m mol/1.

Mitra and Asthana (1993) did not find any significant rise in LDL and VLDL levels after one month of castration.

**EFFECTS OF OESTROGENS IN FEMALES**

Aitken (1971) showed that administration of 20-40 kg of mestronol daily in oopherectomised. Women
was associated with significant fall in serum cholesterol and a significant rise in serum triglycerides.

Gustafson and Svanborg (1972) gave an estrogenic steroid in oopherectomised females and found significant rise in HDL and VLDL and decrease in LDL levels.

Patterson et al (1980) showed significantly reduced mean serum cholesterol and significant rise in serum triglyceride with sequential oestradiol valerate and norgestrel in post menopausal women.

A study from Howard Medical School, Stamfer et al (1985), examined subjects in which approximately 50% has used oestrogen at some time and 35% were current users (Primarin or conjugated oestrogen) in dosage of 1.2 or 0.6 mg/day. The risk of myocardial infarction either fatal or nonfatal, was approximately half of that who had never used them. Of the current users the risk was about one third of that who never used oestrogen.

Another study by Wilson et al (1985) gave conflicting results. The effect of oestrogen use on morbidity from CVD in post menopausal group gives a over 50% elevated risk for cardiovascular disease as compared with women group who had not taken oestrogen.

**ORAL CONTRACEPTIVES AND CAD**

Since oral contraceptives have both oestrogen and progestrone in varying quantities, and opposite effect of both on lipid lipoprotein profile, the study of Mammet
et al (1975) was first to demonstrate an increased risk of acute myocardial infarction with its use. The relative risk of users is as 4.5 as compared with non-users.


Engle et al (1983) showed role of oral contraceptives in developing myocardial infarction without atherosclerosis in more than 80% of their studied subjects. However, cigarette smoking was common in subjects.

**LIPOPROTEINS AS PREDICTOR OF CAD**

More than 90% of plasma cholesterol is carried by LDL and HDL. Concentration of LDL cholesterol are directly related to and predictive of CAD over a wide range (Gordon et al, 1981). This relation underlies the association between CAD and serum cholesterol for later reflects LDL concentration (Kannel et al, 1979). Moreover, morbidity and mortality rates from CAD in different communities are directly and linearly related with serum concentration of STC and LDL (Lewis et al, 1978). HDL concentration are even more strongly predictive of the risk of coronary heart disease in most (Gordon et al, 1981 & Goldbourot and Medatia, 1979) but not in all the persons (Wiklund et al, 1980).

Hyperlipidaemias as well as other risk factors probably run in families and may thus support the above concept for the development of CAD in individuals.
The ratio of LDL/HDL is about as efficient as any other lipid profile (Kannel et al., 1979). A ratio of 5 indicates average high risk, and beyond this are a definite cause of concern.