Diabetes mellitus (DM) is a state of chronic hyperglycemia (the state of having an excessive concentration of glucose in the blood) which may result from many environmental and genetic factors often acting jointly (WHO, 1980). Diabetes mellitus is associated with a fair number of complications, vascular, eyes, kidneys, neurological and other such as intercurrent infection.

MORTALITY AND MORBIDITY:

Diabetes mellitus is one of the leading causes of death in the developing countries. In the U.S.A. it is the fourth leading cause of death and in at least 30 other developed countries it is also a leading cause of death (WHO, 1980).

Diabetes mellitus is a global problem. It affects at least 30 million people throughout the world and the cases were reported to be increasing rapidly with the aging of the populations, changes in the life style and improvements in diagnosis. It is only during the past two decades or so world wide population surveys have been done (Kean, M.I. College of General Practitioners). In the united states about 6 percent of all adults have diabetes including both diagnosed and undiagnosed cases (WHO).

Rates are thought to be lower in the developing countries especially in rural areas. It is probable there is one unknown case for each known case (Drury, M.I., 1979).
Although the prognosis is continually improving the life expectancy of diabetics as a group is still only three fourths that of their non diabetic peers (Drury, "I., 1979).

PROBLEM IN INDIA:

Diabetes mellitus is as common in India as in other parts of the world. Surveys have shown that there is a large reservoir of undiagnosed diabetes in India. Urine examination of nearly 50,000 people visiting an exhibition in Bombay revealed a 3.15 percent incidence of reducing substance in urine (Patel, J.C., 1968).

The incidence of glycosuria was detected in 2.91 percent of 3846 persons examined in Chandigarh (Berry, J.N., 1966).

Pilot surveys carried out by the diabetic association of India showed prevalence rates varying from 1 percent in the general population to 7 percent in office going adults (Patel, J.C.; 1968).

Surveys have also shown that the disease exists in all strata of the population and in all parts of the country.

CLASSIFICATION:

The basic categories are those recommended by the National Diabetes Data group except from division into Primary and Secondary type (Table I).
Primary applies that no associated disease is present while in the secondary type some other identifiable condition cause or allows a diabetic syndrome to develop.

Insulin dependence in their classification is not equivalent to insulin therapy. Rather than the term means that the patients is at risk for ketoacidosis in the absence of insulin. Quite often most of the patients of NIDDM requires insulin for control of hyperglycemia but they do not develop ketoacidosis if insulin is withdrawn.

Table I


A. Insulin - deficient Diabetes Mellitus (IDDM)
   (Insulin dependent ketosis prone).
   1. Onset in childhood (classic Juvenile onset diabetes).
   2. Onset in adulthood (usually non obese Diabetes may be mild but is insulin dependent).

B. Insulin - Non deficient Diabetes Mellitus (INDDM)
   Insulin non dependent, Non ketosis prone managed with weight loss and/or diet. Progression to true insulin deficiency is rare.
   1. Onset in adulthood (Usually obese insulin therapy used most commonly after dietary compliance failure).
   2. Onset in childhood (Usually non obese may be autosomal dominant in some families).
SECONDARY DIABETES:

A minority of cases of diabetes occurs as a result of a recognisable pathological process or secondary to the treatment of some other conditions.

1. Pancreatic Diabetes i.e. Pancreatitis, Haemochromatosis and carcinoma cause destruction of pancreas and lead to impaired secretion and release of insulin. Diabetes will also follow pancreatectomy.

2. Insulin Antagonists:
   a. Growth Hormone: It can produce permanent diabetes in experimental animals and in about 30 percent of patients with acromegaly are diabetic.
   b. Adrenocrotical Hormones: Such as cortical patients with cushing syndrome. ACTH or corticosteroid therapy.
   c. Adrenaline - raises blood sugar, patients with phaeochromocytoma frequently show a diabetic blood glucose tolerance testing.
   d. Thyroid Hormone: In excess will aggravate the diabetic state and some patients with hyper-thyroidism show impaired glucose tolerance.
   e. Gestational Diabetes.

3. Iatrogenic Diabetes: In susceptible individuals treatment with corticosteroids and thiazides may precipitate diabetes.

4. Liver Disease: Particularly cirrhosis and hepatitis may be associated with impaired glucose tolerance.
DIAGNOSIS:

The WHO expert Committee on Diabetes (1980) recommended that a 75 gm glucose load should be used and that the following concentrations of glucose in venous whole blood (estimated by a specific enzymatic assay) should be accepted as diabetes as impaired glucose tolerance as shown in table II.

Values for plasma glucose are about 15 percent higher than those of whole blood.

Table II

Adult - Load 75 gm glucose in 250-350 ml of water and children - 1.75 mg/kg body weight (to a maximum of 75 mg)

<table>
<thead>
<tr>
<th>Glucose concentration/Lit.</th>
<th>Venous whole blood</th>
<th>Capillary whole blood</th>
<th>Venous plasma</th>
</tr>
</thead>
</table>

A. Diabetes Mellitus

1. Fasting 7.12 gm 7.12 gm 7.14 gm (7.70 m mol) (7.70 m mol) (7.8 m mol) and/or

2. 2 hour after 7.18 gm 7.20 gm 7.20 gm (7.10 m mol) (7.11 m mol) (7.11 m mol)

B. Impaired Glucose tolerance

1. Fasting 7.12 gm 7.12 gm 7.14 gm (7.70 m mol) (7.70 m mol) (7.8 m mol)

2. 2 hour after 7.12-1.8 gm 7.14-2 gm 7.14-2 gm (7.10 m mol) (7.11 m mol) (7.11 m mol)

At times there is confusion regarding the chemical and clinical stages of diabetes mellitus. This disorder may be classified into 4 stages:
1. Pre-diabetes:

The persons in this stage have normal carbohydrate metabolism but will eventually develop diabetes. This group includes the persons with a diabetic identical twin. Persons with diabetic parents close relatives and women with a poor obstetric history such as large newborns abortions or toxaemia.

2. Sub-clinical:

In persons with subclinical diabetes the results of the glucose tolerance test are normal but the results of cortisone glucose tolerance test are abnormal. These persons demonstrate impaired carbohydrate tolerance during periods of stress, which include pregnancy, obesity, trauma, severe emotional states, steroid or thiazide treatment, impaired nutrition infections and endocrinopathies such as cushing syndrome and thyrotoxicosis. These individuals require long term evaluation.

Diabetes is precipitated by these stressful conditions because of an increased release of growth hormone and an epinephrine induced supression of insulin secretion.

This is the first stage of islet cell decompensation.

3. Latent Diabetes:

Individuals in this stage are asymptomatic. They may or may not have glucosuria. The fasting blood glucose level is usually normal but may be elevated. The glucose tolerance test is abnormal.
4. **Overt Diabetes** :

The last stage of the disease may be further divided into an acute and chronic phase. Patients with acute overt diabetes have the classical symptomatology — glucosuria and hyperglycemia. Patients with chronic overt diabetes have long term vascular complications glucosuria and hyperglycemia. The fasting blood glucose level is elevated in this stage of disease.

**GLUCOSE TOLERANCE TEST** :

Most of the patients do not need a glucose tolerance test in order for the physician to make the diagnosis of diabetes mellitus. It is because of the fact that most of the times the symptomatology is so clear that we hardly need G.T.T. just blood sugar and urine examination is sufficient to diagnose. It must be remembered that a negative urine test for glucose does not rule out diabetes mellitus.

If the glucose tolerance test is necessary for diagnosis, the patient should be prepared for 3 days before the test with a high carbohydrate diet as advocated by Conn and Fajans (1961). The diet should contain 50 percent of calories as carbohydrate, 35 percent as fat and 15 percent as protein.

The fasting period before testing should be 9 hours for premature, 12 hours from full term infants and an overnight fast of 14 to 16 hours for older children. The patient should be at rest during the test.
The doses of glucose for oral test are as under:

<table>
<thead>
<tr>
<th>Age</th>
<th>Amount of glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 8 months</td>
<td>2.5gm/kg body weight</td>
</tr>
<tr>
<td>1/2 - 3 years</td>
<td>2 gm/kg body weight</td>
</tr>
<tr>
<td>3 - 12 years</td>
<td>1.75 gm/kg body weight</td>
</tr>
<tr>
<td>12 years -</td>
<td>1.25 gm/kg body weight</td>
</tr>
<tr>
<td>Adults</td>
<td>(Maximum = 75 gm)</td>
</tr>
</tbody>
</table>

Five blood samples are usually drawn fasting, 1/2 hour, 1 hour, 1 1/2 hour and 2 hours. The 1 1/2 hours value determines whether the 2 hours blood glucose level... is a rebound effect after a normal 1 1/2 hours sampling or whether it is a true elevation of blood glucose during the period from 1 hour to 1 1/2 hours after sampling is begun.

Diagnosis of diabetes mellitus is made by Fajans and Conn's criteria (1959) is the results for a whole blood determination equal or exceed all three of the following values 1 hour = 160 mg/dl, 1 1/2 hour = 140 mg/dl and 2 hours = 120 mg/dl.

For plasma or serum the values are 185 mg/dl, 160 mg/dl and 140 mg/dl respectively.

If one employs the U.S. Public Health Service's criteria or the Wilkerson Point system (O'Sullivan, 1967) a total of 2 points is diagnostic of diabetes mellitus.

The points used to diagnose diabetes mellitus are determined by the presence of whole blood values equal to or exceeding the following:
Occasionally the glucose may nauseate the person causing pylorospasm gastric retention and delayed absorption of glucose. The resulting blood glucose curve will be flat which is a normal variant. It has been reported as occurring in 20 percent of consecutive patients having a glucose tolerance test and is seen more frequently in the test result of slender young persons (White House, 1975).

The test can be repeated in 3 days if one wishes.

**Intravenous Glucose Tolerance Test:**

If there is difficulty in oral feeding or a question of absorption of the glucose solution, the intravenous tolerance test is indicated.

To perform I.V. tolerance test 0.5 gm of glucose per kg of body weight is administered I.V. as a 20 percent solution or administered over a period of 4 min. as a 50 percent glucose solution. 20 percent solution is recommended as the 50 percent may be injurious to the blood vessels and subcutaneous tissues if there is infiltration of these areas. The blood samples are drawn and analysed in the same way as oral glucose tolerance test.
ETIOLOGY OF DIABETES MELLITUS:

The various disorders of fluid, electrolyte and foodstuff metabolism that characterise uncontrolled diabetes are secondary to insulin deficiency either relative or absolute.

The juvenile onset diabetic generally exhibits an absolute deficiency of hormone. The plasma insulin concentrations both basal and stimulated are consistently reduced and the patient bears close metabolic resemblance to the pancreatectomized.

The maturity onset diabetic is more complicated. Basal insulin secretion is normal or even increased but insulin secretion following glucose stimulation is reduced. Initial reports of hyperinsulinemia in maturity onset diabetic are probably explained by the concomitant obesity that affects about 80 percent of all maturity onset diabetic. When insulin levels in obese maturity onset diabetic are compared with those of nondiabetic obese subjects the insulin levels in the diabetic group are significantly lower than those of non diabetic.

TYPE I DIABETES MELLITUS:

In the patients of insulin dependent diabetes mellitus (Type-1) by the time diabetes appears most of the beta cells in the pancreas have been destroyed. The destructive process is almost certainly autoimmune in nature. The overview of the pathogenetic sequence is as follows:

I. Genetic susceptibility to the disease must be present.
II. An environmental event initiates the process in genetically susceptible individuals, rival infection is believed to be a common triggering mechanism. The best evidence that an environmental insult is required comes from studies in monozygotic twins, in whom the concordance rate for diabetes is no more than 50 percent. If diabetes were a purely genetic illness concordance rates would have been approximately 100 percent.

III. Inflammatory response in the pancreas called insulinitis. The cells that infiltrate the islets are activated T lymphocytes.

IV. Alteration or transformation of the surface of the beta cells such that it is no longer recognised as 'self' but is seen by the immune system as a foreign cell or 'Non self'.

V. Development of an immune response because the islets are now considered as 'Non self'. Cytotoxic antibodies develop and act in concert with all mediated immune mechanisms. The end result is the destruction of beta cells and the appearance of diabetes.
Hyperglycemia associated with cystic fibrosis is probably transmitted by an autosomal recessive mode of inheritance whereas the hyperglycemia associated with myotonic dystrophy is transmitted by an autosomal dominant mode.

Since Mac Donald found an equal incidence of adult onset diabetes among ancestors of juvenile diabetes and non diabetics. This suggests different modes of inheritance for type-1 and type-2 diabetes (Mac Donald, 1979).

In long term studied of monozygotic twins, Tattersall and Pyke (1977) found a 93 percent concordance rate for adult onset disease and 50 percent concordance rate for juvenile onset diabetes.

Therefore genetic factors appear to be predominant in non-insulin dependent diabetes but presumably environmental factors are needed to trigger the onset of insulin dependent diabetes mellitus.

Another approach to the study of inheritance of IDDM is human leucocyte antigen (HLA) typing. These cell surface antigens are associated with the rejection of tissue transplants. The genes coding for HLA antigens A D C D and D R (D. related) occupy 4 loci along the short arm of chromosome number 6.

It was observed that certain HLA antigens were found with unusually high frequency in patients with specific disease. The strength of this association was termed "relative risk".
Table III
Pathogenesis of Type-1 Diabetes Mellitus.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Step Event</th>
<th>Agent in response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Genetic susceptibility</td>
<td>HLA-DR 3, DR 4 (T cell receptor)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Environmental event</td>
<td>Virus ?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Insulinitis</td>
<td>Infiltration of activated T lymphocytes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Immune attack on Beta cells.</td>
<td>Islet cell antibodies cells mediated immunity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 6.     | Diabetes Mellitus            | 90 percent Beta cells destroyed.  
                        | (alpha cells unopposed)                                      |

Inheritance of Type-1 Diabetes

Although it has been observed that "diabetes runs in families the precise risk of developing diabetes has been difficult to establish because of such variables as diet obesity, ethnic background, age of onset and the variety of diagnostic criteria. Family studies have not been consistent with any single mode of inheritance. This has lead to the concept of genetic heterogeneity that is diabetes mellitus is a symptom complex which is the result of many different genetic mechanisms (Anderson, 1980).
Initial population studies it was found a higher proportion of HLA antigens $B_15$ and $CW_3$ in insulin dependent diabetics than in controls (Cudworth, 1979; Nerup, 1974). As the work proceeded on HLA typing even stronger associations with a 3 to 6 fold relative risk of IDDM were found with $DR_3$ and $DR_4$ (Nerup J., Platz D., 1976).

In 3 population studies on 199 caucasian patients with IDDM the relative risk associated with $DRW_3$ was 5.69 and in 76 caucasian patients the relative risk associated with $DRW_4$ was 2.84 (Christy, 1979). In contrast other antigens such as $HLA_A_{11}^*, A_{W32}^*, B_5^*, B_7^*$, $DR_2$ and $DRW_2$ were found less commonly in populations with IDDM than in control populations and it has been postulated that these alleles may exert a protective effect for the development of type-1 diabetics (Christy, 1979; Cudworth, H., 1978 and Ludwig, H., 1976).

In Europe HLA $B_{15}$ is found more frequent in northern European whites while HLA $B_{18}$ is found more frequently in the southern European population.

In Japan where HLA $B_8$ occurs rarely and HLA $B_{15}$ is common in general population, $B_{22}^*, DRW_3$ and $DRW_4$ antigens are found in statistically significant proportion of patients with IDDM (Sakuranii, 1982 and Wakisaka, 1976).

In black American population where the frequency of HLA $B_8$ is low IDDM is strongly associated with $DRW_3$ and $DRW_4$ antigens (Rodey, 1979). Similarly
Mexican American patients with IDDM have significant increase in HLA DR\textsubscript{4} compared with a control population (Zeidler, 1982). The Eskimo population has a very low frequency of HLA B\textsubscript{8} and the prevalence of IDDM is extremely low (Christy, 1979 and Segild, 1966).

Today, 63 population studies have thus far demonstrated an increased relative risk for the development of IDDM associated with HLA B\textsubscript{8}, B\textsubscript{15}, B\textsubscript{18}, Cw\textsubscript{3}, Dw\textsubscript{4}, DR\textsubscript{3} and DR\textsubscript{4} types in caucasian population. The presence of Dw\textsubscript{3} and DRw\textsubscript{4} in the Japanese black American and Mexican American population appears to have the highest correlation with IDDM. Further studies on non white populations are needed to better define the genetic profile of the group at risk to develop IDDM.

The studies on identical twins suggest that the risk in siblings would not be greater than 50 percent (Goffieb, 1972 and Tattersal, 1977). Recent studies on 64 unrelated families demonstrated and confirmed that the probable risk for developing IDDM is approximately 30 percent for HLA identical siblings (Ginsberg, 1982).

**THE ROLE OF VIRAL INFECTION OR TOXIC CHEMICAL IN TYPE-1 DIABETES**

There are several lines of evidence to support the role of viral infections in the etiology of IDDM. Indirect evidence for the association of viral infections with the acute onset of IDDM includes data on seasonal variation and the temporal association of childhood viral infection with onset of disease. The
increased prevalence of new cases of IDDM in the winter. Late summer and early autumn does correspond with the increased prevalence of common viral infections in the community and suggests a possible and effect relationship. The estimated time of onset of IDDM in 2511 children living in 4 different American states followed a similar seasonal pattern (Fleegler, 1979 and Mac Millan, 1977). The same analysis of the onset of diabetes in 351 Australian children showed peaks of onset in fall and winter month albeit in different calendar months. Similar studies in Great Britain show the same seasonal pattern (Gamble, 1969).

Specific infections reported to be associated with the onset of IDDM include. Rubella, mumps, coxsackie virus. Infectious hepatitis, infectious mononuclecosus and cytomegalovirus (Craighead, 1981). The development of diabetes days or months after mumps virus infection has been reported in case studies since 1899 (Harris, 1899; Hinden, 1962; Kremar, 1947; Masseritakis, 1970).

Although pancreatitis is common in mumps viral infection but there are no reported pathologic studies that demonstrate specific insular lesion associated with mump viral infection. Chronic persistent rubella viral infection of the pancreatic tissue of infants with congenitally acquired disease has been demonstrated but islet cell lesions have not been described in pathological studies (De Prins, 1976; Monif, 1965; Singer, 1967).
The most direct evidence for the role of viral infections in the pathogenesis of IDDM was reported by Yoon et al (1979). They recovered coxsackie (virus group B type IV) from the pancreatic tissue of a child who died with meningoencephalitis and new onset diabetes. Pathologic studies of the pancreas demonstrated insulinitis. The isolated virus was then injected into susceptible mice and resulted in beta cell destruction and diabetes.

It is also possible that viruses may be only one of many causes of type-I diabetes and other environmental insults such as toxic chemicals may damage beta cells and cause hyperglycemia. In experimental animals drugs such as alloxan and streptozotocin selectively destroy the beta cells of islets and induce insulin deficiency. Like and Rossini showed that whereas a single large dose of streptozotocin is directly toxic to the beta cells, multiple small doses of the drug appear to get in directly by altering the beta cells so that they become more vulnerable to attack by the immune system of the animal. Since only certain strains of mice are susceptible to this type of experimental destruction of islets, it appears that genetic factors are important for medication of the chemical insult and/or the immunologic response (Rossini, 1977). Recently a rodent poison, Yacor, which has a molecular structure similar to the nitrosamine streptozotocin was introduced in the United States. After accidental injections of this
rhodenticide an insulin deficient, ketosis, prove form of diabetes mellitus associated with severe toxic neuropathy has been reported (Miller, 1978 and Prosser, 1978).

**DISORDERED IMMUNE MECHANISMS IN THE ETIOLOGY OF TYPE-1 DIABETES**

The role of immunologic factors in initiating or perpetuating destruction of islet cells is supported by the pathologic studies of pancreata of children with diabetic ketoacidosis. Mononuclear cell infiltrates in and around the islets of Langerhans have been demonstrated in these pancreata (Gepts, 1965). In 1940 Von Meyenburg coined the term 'Insulinitis' to describe lymphocytic infiltration of the islets (Von Meyenburg, 1940). There is now unanimous agreement that there is a specific lesion found in patient with type-1 diabetes who die early in the course of the disease (Gepts, 1981).

In patients with type-2 diabetes insulinitis has never been observed.

Although the cause of the destruction of beta cells in IDDM has not been elucidated the morphologic evidence of insulinitis suggests that an autoimmune reaction to beta cells either primary or triggered by viral infection in a genetically susceptible host may be operative.

Another line of evidence to support the role of autoimmunity has been the clinical association between diabetes and autoimmune endocrine disorders such as
Hashimoto's thyroiditis, Grave's disease, Addison's disease, autoimmune oophoritis and orchitis. Idiopathic hypoparathyroidism and hypophysitis. Other associations between diabetes and non endocrine autoimmune disease include pernicious anaemia, vitiligo, rheumatoid arthritis, idiopathic thrombocytopenic purpura, myaesthesia gravis, Sjogren's syndrome and chronic active hepatitis (Volpe, 1977).

Ogle first reported on coexistence of diabetes and adrenal insufficiency in 1866. Similarly multiple reports have suggested an association between diabetes and autoimmune thyroid disorders (Mac Guish, 1975).

In 1974, two independent studies confirmed the existence of islet cell antibodies in the sera of type-1 diabetic patients with other autoimmune granular disease (Mac Guish, 1974; Bottazza, 1974).

Studies on large series of patients demonstrated that this islet cell antibody was not detected in healthy control subjects and rarely found in the patients with NIDDM (Delprete, 1977; Irvine, 1977).

These studies provide support for the possible pathogenetic role of autoimmune mechanism in diabetes mellitus but the key question remains: are the islet cell antibodies merely an epiphenomenon as the result of islet cell damage by viruses or toxines, or do they participate in producing progressive islet cell damage?

Therefore, further studies are needed to define the character of the islet cell antigens to determine
quantitatively the titer of antibody and to standardize the assay procedures. Then the value of islet cell antibodies as a marker for continuing destruction of beta cells can be assessed.

So further work may better define this process and the applicability to human type-1 diabetes.

**PHYSIOLOGIC HETEROGENEITY IN TYPE-2 DIABETES**

In contrast to type-1 diabetes NIDDM on type-2 diabetes is characterised by the absence of inflammatory cells in the islet, no circulating islet cell antibodies, no particular HLA association and no seasonal trend or suggestion of association with viral illnesses.

Clinically the age of onset of type-2 diabetes is usually above 40 years. The appearance of symptom is insidious, metabolic ketoacidosis is rare. In type-1 diabetes the circulating insulin levels are characteristically diminished whereas in type-2 diabetes the insulin levels may be decreased, normal or increased. These variable patterns of insulin secretion strongly suggest heterogeneous causes. The site of abnormality may be either the beta cells secretory response to glucose or the target tissue response to insulin or both.

In type-2 subjects with normal or increased secretion of basal insulin glucose stimulated release of insulin is diminished. However in these subjects the beta cell responsiveness to other insulin secretagogues such as Arginine, glucagon and Tolbutamide is normal. (Halter, 1981, Palmer, 1976). These studies suggest a
specific abnormality involving glucose recognition or metabolism by the beta cell or both. Studies of pancreatic pathology in type-2 diabetes demonstrate extremely variable and non-specific findings (Gepts, 1981).

In contrast to pathologic findings early in the course of type-1 diabetes, there is no evidence of islet hyperplasia and this suggests a decreased responsiveness to hyperglycaemia.

Possible functional abnormalities of beta cell could include limitations of islet cell re-application, abnormalities of insulin biosynthesis and storage, deficient glucoreceptors in the beta cell membrane, defective adenylyl cyclase system, impairment of calcium flux into the beta cell and derangement of microtubular microfilamentous system necessary for secretion.

In fact, patients have recently been described in whom the biosynthesis of a structurally modified with insulin with greatly impaired biologic activity accounted for hyperglycaemia (Given, 1980; Haveda, 1982). The patient had increased levels of immuno reactive insulin without hypoglycaemia and responded appropriately to exogenous administration of insulin.

The high incidence of obesity in type-2 diabetes suggests the pathogenetic importance of insulin resistance. Obesity is associated with resistance of muscle, liver and adipose tissue to the action of insulin. Numerous studies have documented a reduction
of insulin receptors on these cells as well as on circulating monocytes. The reduction may contribute to the insulin resistance of obesity (Bar, 1976 and Ollfsky, 1976). The reduced insulin binding to circulating monocytes and in vivo resistance to the action of exogenously infused insulin has been observed in non obese as well as obese patients with type-2 diabetes (De Francesco, 1979).

GENETIC HETEROGENEITY OF TYPE-2 DIABETES:

The most impressive evidence for a genetic component in the pathogenesis of type-2 diabetes is the observations of the high concordance rate of NIDDM in monozygotic twins, even when they are geographically separated (Tattersall, 1972). These findings suggest that environmental modifications may not appreciably modify the incidence of NIDDM but may affect the clinical course and onset of disease. The pattern of genetic inheritance for majority of people with type-2 diabetes remains unknown. However there is again evidence for genetic heterogeneity from the observations of Fajans and Tattersall on a group of patients with maturity onset diabetes of the young (referred to as MODY) (Tattersall-1976; Fajans, 1976). MODY was defined as a patient in whom diabetes was discovered before the age of 25 years and in whom fasting hyperglycemia could be normalized without insulin for more than 2 years. The patients are usually resistant to ketosis.
Four lines of evidence suggest transmission as an autosomal dominant trait.

1. Three generation direct transmission has been demonstrated in over 20 families.
2. A 1:1 ratio of diabetic to non-diabetic children is found when one parent has the disease.
3. About 90 percent of obligate carriers have diabetes.
4. Direct male to male transmission excludes X-linked inheritance.

No HLA relationship has been identified in type-2 NIDDM and autoimmune mechanisms are not believed to be operative.

Further efforts to define distinguishing features of autosomally dominant inherited form of type-2 diabetes resulted in the theory of Leslie and Pyke that chlorpropamide induced alcohol flushing may be a marker of thin disorder (Leslie-1978). Facial flushing induced by chlorpropamide and alcohol was reported to be common in patients with type-2 diabetes and rare in patients with type-1 diabetes.

In twin and family studies facial flushing induced by chlorpropamide and alcohol appeared to be dominantly inherited trait. Other investigators did not confirm these striking finding (Kobberling, 1980).

HYPERLIPIDEMIA

Diabetes mellitus is a pan metabolic disorder and hyperlipidemia is a common problem in patients with
poorly controlled diabetes mellitus. Depending upon the
degree of diabetes control and the type of diabetes (type-1
and type-2) it has been observed that the frequency of
elevated plasma lipid level ranges between 20% to 90%.

In general diabetics as a group tends to
have higher lipid level than non diabetics.

With the advancement in methods of determi-
nation of various components of blood lipids our knowledge
regarding the lipid metabolism is expanding rapidly. An
analysis of blood plasma showing the major lipid classes
is given in Table IV.

\[ \text{Table IV} \]
\[ \text{(Mayed, 1981 and Harper)} \]

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Mean</th>
<th>Range (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lipid</td>
<td>570</td>
<td>360-820</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>142</td>
<td>80-180</td>
</tr>
<tr>
<td>Total phospholipid</td>
<td>215</td>
<td>123-180</td>
</tr>
<tr>
<td>Lecithins</td>
<td></td>
<td>50-200</td>
</tr>
<tr>
<td>Cephalin</td>
<td></td>
<td>50-130</td>
</tr>
<tr>
<td>Sphenomylin</td>
<td></td>
<td>15-35</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>200</td>
<td>107-320</td>
</tr>
<tr>
<td>Free cholesterol</td>
<td>55</td>
<td>26-106</td>
</tr>
<tr>
<td>Free fatty acid</td>
<td>12</td>
<td>6 - 16</td>
</tr>
</tbody>
</table>

No simple answer is available as to what
concentrations of serum lipids justify treatment i.e. what
level constitutes the upper limits of normality. 'Norms' for several apparently healthy populations have been published, based on 10th and 90th percentiles (Lewis et al, 1974a; Fredrickson and Levy, 1972; Goldstein et al, 1973). These define statistical cut off points for particular populations. However, there are wide geographical differences in the distributions of serum lipid levels. There can therefore, be no universally applicable normal ranges (Keys, 1970; Keys and Fidauza, 1960).

In most populations the sex difference in cholesterol levels is too small to justify separate normal ranges for men and women, but in London (Lewis et al, 1974a) Stockholm (Carlson and Ericsson, 1975) quite sex differences have been reported in serum triglyceride concentration. Although serum lipid concentrations are low in cord blood and in early childhood (Goldfrey, Cullen, 1972). Levels do not show a consistent trend in adults. There is no consensus as to whether age adjusted normal ranges should be employed in adults.

Apart from age, sex and geographical differences, serum lipid values show seasonal variation, maximum in the winter (Carlson and Lindstedt, 1969). They are also affected by stresses, recent major illnesses such as myocardial infarction. Energy balance affects serum lipid concentration triglycerides and to a lesser extent cholesterol levels show a weak positive correlation with increasing degree of obesity and usually decrease during
weight reduction. To some extent this relationship may be explained by the greater turnover of plasma free fatty acids, in obese subjects and by enhanced cholesterol synthesis in adipose tissues.

The serum cholesterol elevating effect of dietary saturated fat is well known and dietary cholesterol also tends to increase serum cholesterol levels. Though with wide individual variation polyunsaturated fats decrease serum levels of cholesterol and triglyceride. Very high intakes of all carbohydrates elevate serum triglyceride concentrations. Their response is usually evanescent. In susceptible individuals alcohol too has a pronounced effect in elevating triglyceride levels.

In addition there is considerable interlaboratory variation (Whitehead, Browning and Gregory, 1973) particularly when manual methods are employed. Prolonged venous occlusion prior to the blood sampling increases cholesterol concentration because of haemoconcentration (Koerselman, Lewis and Pilkington, 1961).

All the lipids in plasma circulate in combination with protein (Fredrickson et al, 1967; Tria and Scanu, 1969). The free fatty acids are bound to albumin. These complexes of lipid and proteins are called as "lipoprotein". Lipoproteins are necessary for the transport of non polar lipids primarily cholesterol and triglyceride through plasma.

The usefulness of cholesterol and triglyceride in clinical classification of hyperlipidemia and hyper-
lipoproteinemia at present far outweigh that of other lipids (Fredrickson, 1970).

The relationship of diet to the hypercholesterolaemia and atherosclerosis remains an area of intense interest and persistent controversial in the sixth decade of this very century. There was a period of 'cholesterophobia'. Cholesterol is the pivotal element of atherosclerosis. Still it is not possible to give a unitary view of atherosclerosis, but among the numerous etiological factors, lipids are considered to be the agents of high atherogenesis (Alderberg et al, 1956; Albrink et al, 1961; Higano et al, 1961 and Paterson et al, 1968).

PLASMA LIPID METABOLISM:

Lipid transport through plasma depends on the packaging of these water insoluble molecules with specific apoproteins into lipoproteins which exist in colloidal solution in plasma. Lipoproteins are also present in intestinal lymph (Cockner-Hughes and Isselbacher, 1969) and the smaller lipoproteins are also detectable in peripheral lymph too (Reichi et al, 1973).

Plasma lipoproteins are usually defined by ranges of physical properties, the four major classes are:

1. High density lipoprotein (HDL, Alpha lipoprotein).
2. Low density lipoprotein (LDL, Beta lipoprotein).
3. Very low density lipoprotein (VLDL, pre-beta lipoprotein).
4. Chylomicron.
Each of these classes is polydisperse comprising particles with a range of molecular diameters hydrated densities, lipid and protein compositions. It is useful to distinguish two subclasses of LDL. These are:


b. Minor one, intermediate density lipoprotein (IDL or LDL₁) which is chemically and metabolically intermediate between VLDL & LDL₂.

**HIGH DENSITY LIPOPROTEIN (HDL)** (Scannu, 1969).

This is isolated in the ultracentrifuge in the density range 1.063-1.21 mg/dl and is a relatively small particle containing on average 50 percent lipid. It is secreted in nascent form by the liver (Hamilton, 1972) and small intestine and contains free cholesterol and phospholipid, chiefly lecithin as its major lipid components.

Nascent HDL is a flattened disc shaped molecule HDL proteins include two major components both with terminal glutamine, collectively known as apo A; minor components include the group of apoproteins called as apo C and also apo B, the arginine rich polypeptide (Alaupovic, 1972; Havel and Kane, 1973) and apo D. The apoproteins serve a partly structural role and some are of ufunctional importance in activating or inhibiting certain enzymes which play a major role in lipid transport.

The major functions of HDL appear to be a direct role in the centripetal transport of cholesterol from peripheral tissues to the liver (Glomset, 1968) and an indirect role in facilitating triglyceride transport.
High Density Lipoprotein (Alpha lipoprotein)

Very Low Density Lipoprotein (VLDL, Pre-beta lipoprotein)

- Triglyceride
- Free cholesterol
- Phospholipids
- Cholesteryl ester
- Protein Apo AI
  - Apo AII
  - Apo C

Transport of endogenous and dietary triglyceride and cholesterol

Activation of Lipoprotein Lipase

Centripetal transport of cholesterol
Activation of lecithin
Cholesterol acyl transferase

Source of Apo C for VLDL, chylomicron.
Cholesterol is synthesised in most tissues with the exception of the adult central nervous system. However, the major organ for disposal of cholesterol from the body is liver.

Plasma HDL readily takes up free cholesterol in vitro (Bondjers and Bjorkerud, 1974). In HDL, this cholesterol is esterified by the circulating enzyme lecithin:Cholesterol acetyl transferase (LCAT) by transfer of an unsaturated fatty acid molecule from alpha-position of lecithin (also present in HDL). The cholesteryl ester so produced is transported to the liver in HDL, or may be transferred to other lipoprotein in exchange for triglyceride (Gjone and Norum, 1974).

In familial HDL deficiency (Tangier disease) cholesterol accumulates in peripheral tissues. Particularly the reticuloendothelial system (Fredrickson, Gotto and Levy, 1972). Familial LCAT deficiency is characterised by virtual absence of cholesteryl esters in plasma and characteristic lesion due to lipid deposition affect particularly the kidney and eye (Gjone and Norum, 1974).

**CENTRIFUGAL LIPID TRANSPORT**

This is mediated by very low density lipoproteins. Intermediate density lipoproteins and low density lipoprotein (VLDL, IDL and LDL₂). VLDL is a heterogeneous class of large molecules rich in triglyceride containing also cholesterol. Cholesteryl ester and phospholipid with about 10% of protein. VLDL is secreted by the liver and to a lesser extent by the small intestine mucosa in nascent
form (Hamilton, 1972; Bennett et al., 1975). It rapidly converts to its mature form after its secretion acquiring apo lipoprotein C by transfer from HDL. Its cholesteryl ester content is probably similarly obtained from HDL (Ojone and Norum, 1974). VLDL secreted by the liver contains triglyceride of endogenous origin normally this triglyceride is derived entirely from esterification of free fatty acid (FFA) taken up from plasma by this organ (Havel, 1961 and Böberg et al., 1972).

Bartes, Nestel and Carroll (1972) have shown that under abnormal circumstances, FFA is partly replaced by other substrates, perhaps including dietary carbohydrates and hepatic triglyceride stores. This occurs in alcoholism obesity and during the short term consumption of a very high carbohydrate diet.

Lipoprotein Lipase;

The enzyme lipoprotein lipase plays a major role in triglyceride uptake and massive hypertriglyceridemia develops in subjects in whom it is deficient, a rare genetic disorder (Havel and Gordon, 1960). The enzyme functions at the luminal surface of the capillary endothelium hydrolysing triglyceride contained in VLDL and chylomicrone. The enzyme is synthesised in the parenchymal cells e.g. adipocytes and it is transported to its capillary endothelial site of action and is simultaneously chemically modified in response to the nutritional state (Cryer, Davis and Robinson, 1973; Garfinkel and Schotz, 1973).
Dietary fat is incorporated into triglyceride rich lipoproteins by mucosal cells of small intestine and these reach plasma via thoracic duct. The largest of these particles are chylomicra defined as having a flotation rate(Sf) value exceeding 400.

Chylomicra are largest lipoprotein particles containing chiefly triglyceride and only 1-2 percent of apoprotein. The metabolism of endogenous and exogenous triglyceride appears to involve a common removal mechanism (Havel, 1965; Brunzell et al, 1973).

Another lipase of hepatic origin has been described (Krauss, Levy and Fredrickson, 1974). It too can hydrolyse triglyceride present in lipoprotein. Chemically it is identical with extrahepatic lipoprotein lipase apart from its carbohydrate moiety (Augustein, Freeze and Brown, 1975).

VLDL and chylomicra entering plasma rapidly acquire a normal complement of apoprotein C by transfer from HDL. One of the C apoprotein C_{11} is the specific activator of extrahepatic lipoprotein lipase (Havel et al, 1970b; La Rosa et al, 1970) and renders the triglyceride contained in these particles subject to attack by this enzyme.

Chylomicra and VLDL are depleted of triglyceride in step wise fashion (Higgins and Fielding, 1975). Partially de-lipidated products returning to the circulation before further metabolism occurs.
Low Density Lipoprotein (Beta Lipoprotein, LDL₂)

- **Triglyceride**
- **Phospholipids**
- **Free cholesterol**
- **Cholesteryl ester**
- **Protein: Apo B**
  - Apo C

Centrifugal transport of cholesterol

Chylomicrons

- **Triglyceride**
- **Phospholipid**
- **Cholesterol and ester**
- **Protein**

Transport of dietary triglyceride and, dietary cholesterol

Activation of lipoprotein Lipase
Therefore a series of delipidation products are present in the circulation, progressively decreasing in size and triglyceride content and relatively enriched in cholesterol.

Finally chylomicron remnants (containing absorbed cholesterol) are produced and are avidly trapped by the liver (Redgrave, 1970). VLDL is converted to LDL which after further remodelling by unknown mechanisms is converted to LDL₂. This LDL₂ is derived from VLDL and is not evidently secreted by liver as such.

Sigurdsson, Nicoll and Lewis (1975) have examined quantitatively this lipoprotein conversion using labelling of apoprotein moiety.

**LDL CATABOLISM**

The studies by Guiderman et al (1974) on heptectomy-pigm has yielded the surprising conclusion that much LDL uptake from plasma must be extrahepatic. In 1973 Goldstein and Brown presented the first of a series of papers describing an LDL receptor on the surface of human cultured skin fibroblast. Smooth muscle cells and adipocytes appear to have similar LDL receptors. Thus LDL receptors regulates LDL catabolism and also cholesterol synthesis in the fibroblast. Current work is suggesting that the receptors appear, heterogenous and possibly including several classes with differing binding affinities (Carew, Koschinsky and Steinberg, 1975) and are less specific than has been supposed reaching under some circumstances with VLDL and normal and abnormal HDL.
(Mahley et al, 1975).

The response to high cholesterol intake in man includes regression of cholesterol synthesis and enhanced biliary excretion of cholesterol. Some individuals react to a high cholesterol intake with a negligible rise in plasma cholesterol levels and only modest increase in exchangeable pools of cholesterol, while others show a marked increase in tissue levels and less often in plasma cholesterol concentration. Highly efficient regulatory mechanisms have been found in one ethnic group. The Tasini who maintain low plasma lipid despite a high milk intake (Ho et al, 1971).

**Classification of Hyperlipoproteinemia and Hyperlipidemia**


<table>
<thead>
<tr>
<th>Type of lipoproteinemia</th>
<th>Major elevation in plasma</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Lipoprotein</td>
</tr>
<tr>
<td>Type I</td>
<td>Chylomicron</td>
</tr>
<tr>
<td>IIA</td>
<td>LDL</td>
</tr>
<tr>
<td>IIB</td>
<td>LDL and VLDL</td>
</tr>
<tr>
<td>III</td>
<td>Remnants</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
</tr>
<tr>
<td>V</td>
<td>VLDL &amp; Remnants</td>
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</tbody>
</table>
Table VI

<table>
<thead>
<tr>
<th>Plasma lipids and lipoproteins</th>
<th>Relative atherogenecity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>4+</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1+</td>
</tr>
<tr>
<td>Chylomicron</td>
<td>0</td>
</tr>
<tr>
<td>VLDL</td>
<td>2+</td>
</tr>
<tr>
<td>LDL</td>
<td>4+</td>
</tr>
<tr>
<td>IDL</td>
<td>4+</td>
</tr>
<tr>
<td>HDL</td>
<td>0 or negative</td>
</tr>
</tbody>
</table>

Hyperlipidemia in Diabetes Mellitus

Hypertriglyceridemia in diabetes is usually caused by accumulation of very low density lipoprotein (VLDL) and rarely chylomicrons in the plasma (Nikkila, 1973 and Nikkila, 1974). Hypercholesterolemia may also develop secondary to increased very low density lipoprotein levels through changes in plasma LDL and HDL levels also occur with variable degree of diabetic control (Dunn et al, 1981).

A. In Type-1 Diabetes (Insulin Dependent)

All agree that lipids may be elevated when blood glucose levels are extremely high and the disease is uncontrolled. With some what better blood glucose control, lower levels of plasma lipids have been reported (Keding et al, 1952). Wolff and Salt reported higher
levels of cholesterol, esterified fatty acids and beta lipoproteins in 35 juvenile diabetics whose blood sugar levels were above 200 mg per 100 ml. New et al (1963) reported significantly higher levels of cholesterol in diabetics than in non diabetic either under or over the age of 30 years. However, Transman et al (1960) using a higher range of normal for cholesterol (150-392 mg per 100 ml) did not conform these findings. Although Stone and Conner (1963) and Kinsell (1952) have recommended reducing cholesterol and saturated fat in the diabetic diet.

Lloyd (1970) has placed the predominant emphasis on diabetic control stating that "the findings of hyperlipidemia in a child with treated diabetes mellitus almost always indicates inadequate insulin control.

In type-1 diabetes there is acute insulin deficiency which results in a rapid increase in both free fatty acid mobilization from adipose tissue and secretion of VLDL and ketone bodies, from liver (Balasse, 1972). This enhanced VLDL-triglyceride synthesis from liver appears to be short lived however since after one or more days of insulin deficiency the ability to secrete VLDL-Tg by liver diminishes (Basso L.Y., 1970).

Clearance of triglyceride from the plasma is also impaired. The later effect is thought to be the result of decreased activity of the enzyme lipoprotein lipase (Fielding, 1972) which requires the presence of insulin for maintenance of adequate tissue level (Pykalisto, 1975). Further there are some acquired
abnormalities of VLDL structure which renders this lipoprotein less able to interact with lipoprotein lipase.

D. In Type-2 Diabetes (Non Insulin Dependent Diabetes Mellitus (NIDDM))

NIDDM is associated with alterations in plasma lipoprotein (Barach, 1952; Albrink, 1963 and Goldberg, 1981). Most patients with type-2 diabetes are not insulin deficient but rather have normal or elevated plasma insulin which are low only in terms of relatively plasma glucose level (National Diabetes Data Group). In type-2 diabetes often there is mild to moderate degree of hypertriglyceridemia but do not appear to have significant reduction in plasma lipoprotein lipase activity (Nikkila, 1977).

There are subtle abnormalities in post heparin lipolytic activity have been reported in untreated patients with type-2 diabetes and these were found to correct with improved diabetic control (Brungell, 1975).

One of the most consistent findings in non insulin dependent diabetes is a high concentration of VLDL (Albrink, 1963; New, M.I., 1963; Harvard et al, 1984). Elevations in the production of VLDL, triglyceride have been observed in the majority of studies of NIDDM (Nikkila, 1973; Taskivan, 1986). VLDL apolipoprotein (Apo B) production has also been reported to be elevated (Kissebah, 1982) although this elevation may not be observed in obese diabetics (Taskinen, 1986).
In contrast to consistent observations of increased VLDL, triglyceride, higher LDL cholesterol levels in non insulin dependent diabetics have been observed in some studies (Billimoria, 1976; Howard, 1978; Taskinen, 1982) but not in others. Kisselbah et al (1983) reported that LDL production rate was elevated and clearance impaired in a group of mild non insulin dependent diabetics.

Kisselbah et al (1982) also observed in hyperlipemic NIDDM that there was less conversion of VLDL to LDL.

In type-2 diabetes plasma HDL cholesterol levels tends to be decreased (Calvert, 1978) but increase towards normal range with treatment (Calvert, 1978; Paise, 1978).

In type-1 diabetes HDL cholesterol levels have been reported to be normal or increased (Nikkila, 1973) when compared with age, weight and sex matched normals.

So hypercholesterolemia in diabetes can occur because of two reasons:

a. Increase in plasma VLDL level results in secondary increase in the plasma cholesterol level since VLDL carries about 20% of its total lipid content as cholesterol.

b. Diabetes appears to have significant effects on plasma LDL metabolism.

The exact mechanism is yet not clear but it has been suggested that:

i. VLDL is the major precursor for LDL in the plasma (Eisenberg, 1973) and increased synthesis of VLDL in diabetes leads to increased formation of LDL.
ii. There is decreased catabolism of LDL in poorly controlled diabetes because of a decreased ability of LDL to interact with its cell surface receptors has been proposed (Klitzman, 1982).

The decreased catabolism of LDL appears to be due to glycosylation of plasma LDL (Klitzman, 1982) which alters the configuration of LDL so that it is less able to interact with specific LDL receptor responsible for majority of LDL catabolism in normal individuals (Brown, 1981).

**Effect of Oral Hypoglycemia and Insulin on Lipid Level**

It is clear that the severe hyperlipidemia found with poor control in insulin dependent diabetes is reversed by treatment with insulin (Bagdade et al, 1967; Chance et al, 1969 and Salt et al, 1960). The study of Hayes (1972) found that the treatment of moderate hyperglycemia in untreated maturity onset patients (Type-2) result in a lowering of triglyceride level and frequency of lipoprotein abnormalities.

Interesting differences emerge when the responses of diabetics to different treatments are considered. While both treatment groups showed a fall in plasma lipid concentration over the first month. Only those diabetics who only subsequently received sulphonyl ureas showed continued improvement at one year.

Previous studies (Morris et al, 1964; Holeman, et al, 1978) have also shown a simultaneous fall in blood
glucose and triglyceride following the administration of sulphonyl ureas. It is because of the fact that either sulphonyl ureas have an additional triglyceride lowering effect or that there is another factor apart from blood glucose levels affecting triglyceride values.

Lewis et al (1972) have shown that treatment of diabetic patients with insulin reduces their free fatty acid concentration but the levels are still higher than controls. The triglyceride levels were also reduced by insulin. Shapiro et al.(1973) in a study of cholesterol and triglycerides in white and Bantse showed that treatment with insulin did not have significant effect in lowering lipids in the white population.

**Effect of diet on Lipid Level in Diabetes**

High fat and low carbohydrate:

In the Rockefeller Monography (Allev, 1919) the authors stated that lipemia is largely associated with the fat intake and with other diabetic symptoms.

Ervin (1919) stated that "the lipemia of a diabetic will disappear with the elimination of fat from the diet. Bang (1919 believed that the lipemia was in part alimentary. Joslin (1921) suggested that a relation between the high protein fat diets of former days and the high degrees of lipemia reported and stated that with restricted diet, particularly of fat, the blood fat rapidly falls. Bloor (1921) has supported a suggestion of Allens (1917) that there was lacking a pancreatic hormone which is necessary for the proper removal of the fat from
the blood. Bloom continued by conceiving that the factor of overwork must be taken into consideration in examining into the cause of diabetic lipemia and that the patients has fat tolerance which can be raised or lowered according as the ingested fat is restricted or increased when large amount of fat are ingested, the mechanism for the utilization of fat might be expected to breakdown and he reported a case in which he alleged that a high lipemia resulted from a dietetic indiscretion which consisted in the ingestion of milk and cream.

Low fat and High Carbohydrate in Diet:

Low fat and high carbohydrate in diets while recently avoided in the treatment of diabetic patients, have been shown to lower serum cholesterol levels and reduce the severity of vascular complications while improving glucose tolerance and lowering insulin requirements (Ellis, 1934; Rabinowitch, 1935; Singh, 1955; Kemper, 1958 and Van Eck, 1959).

However, increase in the concentration of plasma triglyceride (Hyperlipemia) have been noted in non diabetic subjects during the administration of low fat high carbohydrate diets. Many of the patients with essential hypertension who had been maintained on rice diet (85-95 percent carbohydrate) for several months developed a neutral fat lipemia (Watkin, 1950 and Hatch; 1959). A major proportion of patients with essential
hyperlipemia became more markedly lipemic when carbohydrate was isocalorically substituted for fat in the diet (Ahrens, 1961).

The lipemic effect of these low fat high carbohydrate diets may however be only temporary. In a recent study of the long term effects of reduction of dietary fat calories in South African white and Bantana prisoners, it was observed that serum triglyceride levels returned to normal after several months (Automis, 1961). Elevated levels in patients with essential hyperlipemia maintained on rice diets also returned towards control values after 3 months (Kao, 1959). Previous observations in diabetic subjects appeared to indicate that hyperlipemia—was not the result of increased dietary fat levels (Blix, 1926) induced amelioration of lipemia during treatment with high fat diets had been reported (Cowie, 1921; Marsh, 1923).

Various lipid parameters like STG, STC, LDL, HDL and VLDL after ingestion of high fat cholesterol breakfast in diabetic patients is a grey area and needs a lot of work to be done.

**BODY WEIGHT AND FAT TOLERANCE**

Barritt (1956) observed no significant correlation between body weight and the duration of lipaemia in response to standard fat meal. Similarly Broute Stewart and Blackburn (1958) were unable to find any association between skinfold thickness and fat
tolerance. On the contrary, Beinfield and Chessin (1954) tested the fat tolerance of extremely obese male individuals (20-40 years) and their lipemia was considerably prolonged but not elevated, compared with that of normal males of corresponding age. The fat tolerance rose appreciably after weight reduction was enforced.

**AGE AND FAT TOLERANCE**

Age is the most important factor influencing the plasma lipids. Various controversial results are available regarding the relationship between fat tolerance and age. Becker, Mayer and Necholes (1949, 1950) found that the chylomicron count after a fat meal rose more in subjects over 50 years of age than the subjects under 50 years of age. Warder et al (1952) and Swartz, Rordow and Dussmanox (1952) reported similar results of turbidity measurements, however, contrary results had been observed by the Gruner and Hilden (1953).

Results of Harzatein, Wang and Adleisberg (1953) are more illustrative. They found that the total fat persisted longer in serum after loading in old subjects (mean age 62 years) than in younger subjects (mean age of 24.9 years). After fat loading with 1 gm/kg body weight 200% cream the total fats after 2 hours, were similar in young and old subjects. After 6 hours the total fats had returned to their basal level in the young group but remained elevated in old age group. Barrit
(1956) could not show any significant correlation between age and the degree of lipemia induced by fat meal in terms of turbidity measurements and total fat estimations.

SMOKING AND FAT TOLERANCE:

When habitual smokers were tested with a fat meal the postprandial rise in serum lipid was lower in the smoking than in the non-smoking group (Konthinen and Rajasalmi, 1963). Marden et al (1952) found that one cigarette per hour caused the chylomicron count to rise in a group of young subjects but not in elderly subjects.

Reduction in high density lipoprotein have been observed after smoking (Bierman, 1983).