Chapter I

INTRODUCTION
Diabetes mellitus has plagued man for a very long time, since the writings from the earliest civilizations (Asia Minor, China, Egypt and India) refer to boils and infections, excessive thirst, loss of weight and passing of large quantities of a heavy sweet urine which often drew ants and flies. The earliest known record of diabetes (1552 B.C) is found in third Dynasty Egyptian Papyrus by physician Hesy-ra. He mentions polyuria (frequent urination) as a symptom of diabetes. In the first century A.D., Arateus described diabetes as the meeting down of flesh and limbs into urine. It is noteworthy that during 15th, 16th and 17th centuries doctors had to taste the urine of patients for sweetness in order to detect the disease. Soon there emerged two schools of thought concerning diets. One school, exemplified by the British physician Willis (1675), believed in dietary replacement of the sugar lost in the urine, comprising milk, barley water and bread, while the other believed in restriction of carbohydrate so as to reduce the effects which were attributed to an excess of sugar. In the early 18th century, first chemical tests were developed to indicate and measure the presence of sugar in the urine. French physician, Bouchardat, noticed the disappearance of glycosuria in his diabetes patients during the limited availability of food in Paris while under siege by Germany during the Franco-Prussian war of 1870 to 1871 and formulated the idea of individualized diets for his diabetes patients. In 1869, Paul Langerhan, a German Medical student, announced that the pancreas contains two systems of cells. One set
secreted the normal pancreatic juice; the function of other was unknown. However, several years later, these cells were identified as the “islets of Langerhan’s”. Later, Lane (1907) gave the idea of a single bihormonal metabolic regulator and reported that certain islet cells contained alcohol-precipitable granules, named them alpha cells and called the others beta cells. In 1922, Banting and Best prepared the first extract capable of reducing hyperglycemia and glycosuria, and mitigating the symptoms of diabetes. The name ‘insulin’ was given to the active principle of the extract from the islets of Langerhan’s (Iswariah and Guruswami, 1979). The crude pancreatic extracts were injected into depancreatized dogs and were successfully treated (Banting and Best, 1922). One year later, Kimball and Murlin (1923) reported that aqueous extracts of pancreas raised blood sugar levels of depancreatized dogs by 200mg/100ml or more and believed that this was due to a glucoregulatory hormone they named “glucagons” meaning “glucose-driving”. In 1955, oral drugs were introduced to lower blood glucose levels. In 1959, two major types of diabetes were recognized namely type I (Insulin-dependent diabetes) and type II (non-insulin-dependent diabetes).

Carbohydrates from various dietary sources are the primary exogenous source of glucose. Glucose is the main fuel for energy requirement of the body. Therefore, a continuous supply of glucose is necessary to ensure proper function and survival of all organs. Hence, mammals have evolved sophisticated systems to maintain glucose levels in the blood within tight limits, despite large fluctuations in food intake. Homeostatic mechanisms are in place to maintain blood glucose levels with a very narrow range (of around 5mm), protecting the body against hypoglycemia during periods of fasting and against excessively high levels (hyperglycemia) following the ingestion of a high carbohydrate diet. These goals are met chiefly through the hormonal modulation of the production of glucose by the liver and the peripheral uptake.
of glucose by skeletal muscle, heart muscle and fat. When mammals fast, glucose homeostasis is achieved by triggering expression of gluconeogenic genes in response to glucagon, and when they take a carbohydrate-rich diet, the function is taken over by insulin for its uptake and utilization peripherally. Defects in carbohydrate metabolizing machinery and consistent efforts of the physiological system to correct the imbalance in carbohydrate metabolism place an over-exertion on the endocrine system, which leads to the deterioration of endocrine control. Continuing deterioration of endocrine control exacerbates the metabolic disturbances leading primarily to hyperglycemia and subsequently, diabetes mellitus.

Diabetes mellitus is defined as a state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated (Tiwari and Rao, 2002). In this metabolic disorder there is a defective or deficient insulin secretory response (Lazarus and Volk, 1959) for normal function of many cells of the body resulting in persistent hyperglycemia (Mohan, 2000). In some cases elevated levels of glucagon secreted from the α cells of the islets of Langerhan's of pancreas contribute to the development of persistent hyperglycemia (Unger et al., 1976). Due to inadequate presence of insulin in the body, there are disorders of all kinds of metabolism, commonly with an increase in blood sugar accompanied by glycosuria, polyphagia, polyuria and polydipsia (Frank, 1962; Nelson, 1985). Insulin unavailability may be due to degenerative changes in β cells in the pancreatic islets, reduced effectiveness of the hormone owing to the formation of anti-insulin antibodies or inactive complexes, immune-mediated islet cytotoxicity or inappropriate secretion of hormones by neoplasm in other endocrine organs (Botazzo et al., 1976). In this disease glucose accumulates rapidly in the body fluids and as the blood glucose concentration increases beyond a certain point it is excreted by the kidneys. Glycosuria causes a continual waste of this essential nutrient and due to reduced
ability to use glucose produces a depression of the functions of brain, muscles and many other tissues and follows with other serious metabolic consequences (Rastogi et al., 1998).

Insulin is a major anabolic hormone. It promotes the uptake of glucose by cells and the formation of intracellular glycogen from glucose. It stimulates cells to utilize amino acids for protein synthesis rather than for gluconeogenesis and it promotes the uptake of free fatty acids by adipose tissue. Lack of insulin, therefore, results in a general catabolic state with loss of weight, hyperglycemia, diminished protein synthesis, increased gluconeogenesis, and hyperlipidaemia due to lipolysis in adipose tissue. Although the renal threshold is usually raised, there is heavy glycosuria that results in an osmotic diuresis, causing dehydration and thirst. In the liver, excess free fatty acids are converted via acetyl-Co A into ketone bodies which, in the absence of available glucose, are metabolized for cellular energy. The ketone bodies dissociate to produce hydrogen ions, with a resulting metabolic acidosis (Ketoacidosis). This complex of metabolic disturbances produces hyperosmolarity, hypovolaemia, acidosis and electrolyte imbalance, which have serious effects on the functions of neurons and result in one form of diabetic coma—keto-acidotic coma. The other major form, hyperosmolar non-ketotic coma, that results from massive dehydration and profound hyperglycemia in the absence of keto-acidosis. Relative or absolute over dosage with insulin causes hypoglycemia effects, including coma, which, unless treated, may prove fatal (Anderson, 1985).

Too much insulin may cause hypoglycemia, which is a serious symptom causing sweating, hunger, incoherence, convulsions, coma and death. On the other hand, glucagon, the hypoglycemic factor, exerts an effect upon blood sugar opposite to that of insulin and has positive inotropic effects on the heart, possibly as a consequence of stimulating cyclic AMP production (Rastogi et al., 1998). The unique biologic opposition of the two hormones endows the alpha-
beta cell unit with the ability to vary glucose flux in a manner physiologically appropriate to the prevailing circumstances while maintaining extra cellular glucose concentrations within remarkably narrow limits, irrespective of those circumstances. Levine (1972) demonstrated that insulin is the hormone of glucose efflux from the extra cellular space. If extra cellular fluid (ECF) glucose concentration is to remain unchanged during wide changes in glucose flux, glucose and influx must at all times remain approximately equal. This critical balance appears to be due to variation in the insulin-glucagon mixture.

For example, during violent exercise, efflux into muscle is markedly increased. Hypoglycemia is prevented by a proportionate increase in glucose influx, partly because of a marked increase in glucagons and adequate glucose delivery to the central nervous system thus, maintained. Conversely, during a meal, when exogenous glucose influx is increased glucose efflux is increased proportionately to prevent hyperglycemia through increased insulin secretion. glucose efflux rates often approaching the rate of influx. The insulin and glycogen thus serve the nutrient needs of the far-flung tissues of the body, directing the storage of nutrient. When these are in abundance and retrieving them as required in time of famine, flight, fight, or injury, always in perfect accord with the needs of the moment. At all times, hyperglycemia, hypoglycemia and unnecessary nitrogen losses are successfully avoided (Unger and Texas, 1976).

Diabetes mellitus is also referred to as “a disease of rich and prosperous”. Abnormal food intake causing obesity subjects the islets to constant strain, which results in degeneration of the islet cells (Boyd, 1970). The glycosuria often disappears when weight is reduced to a sufficient degree. When fully expressed, diabetes is characterized by fasting hyperglycemia, but the disease can also be recognized during less overt stages and before fasting hyperglycemia appears, most usually by the presence of glucose intolerance (Kahn and Weir, 1994).
The major symptoms of diabetes include excessive thirst, frequent urination, increased appetite, weakness and fatigue, and weight loss. Other symptoms may include muscle cramps, impaired vision and poor wound healing. These symptoms are correlated with the complications of diabetes. The diabetic complications include retinopathy, neuropathy, nephropathy, and atherosclerotic coronary artery disease, peripheral atherosclerotic vascular disease (Kaczmar, 1998), microangiopathy, ketoacidosis, hypersomolar non-ketotic coma and hypoglycemia (Mohan, 2000). The development of most complications of diabetes has been implicated by two biochemical mechanisms namely non-enzymatic glycosylation and polyol pathway mechanism (Mohan, 2000). In non-enzymatic glycosylation the free amino group of any body proteins binds reversibly to glucose and causes chemical alterations in the involved tissue proteins. Accumulation of glycosylation products on collagen and other tissues of the blood vessel wall form irreversible advanced glycosylation end products, which bind to receptors on different cells and produce variety of biologic and chemical changes. The polyol pathway mechanism is responsible for producing lesions in the aorta, lens of the eye, kidney and peripheral nerves. These tissues have an enzyme, aldose reductase that reacts with glucose to form sorbitol and fructose in the cells of the hyperglycemic patient. Intracellular accumulation of sorbitol and fructose so produced in the cells of the hyperglycemic patient results in entry of water inside the cell and consequent cellular swelling and cell damage. Also, intracellular accumulation of sorbitol causes intracellular deficiency of myoinositol, which promotes injury to schawn cells and retinal pericytes. These polyols results in disturbed processing of normal intermediary metabolites leading to complications of diabetes.
Classification of Diabetes Mellitus

Clinically, there are two major forms of diabetes namely type I and type II (Lacy and Kissane, 1977), and a number of specific diseases in which diabetes occurs as a secondary event (Anderson, 1985).

Type I diabetes, previously termed as juvenile-onset diabetes, or insulin-dependent diabetes mellitus (IDDM) (Mohan, 2000), is caused by absolute deficiency of insulin resulting from an immune-mediated, selective destruction of >90% of insulin-secreting beta cells (Kaczmar, 1998).

These patients, therefore, respond to exogenously administered insulin (Mohan, 2000). There are abnormalities of beta cell function and secretion. The patient is usually under 25 years at presentation, is wasted and may develop keto-acidosis. Currently, the pathogenesis of type I diabetes is explained on the basis of three mutually interlinked mechanisms i.e. genetic susceptibility, autoimmunity, and certain environmental factors (Mohan, 2000; Kumar et al., 2001). Type I diabetes has been found to occur most frequently in persons of Northern European descent indicating genetic susceptibility. The disease is much less common among other racial groups, including blacks, Native Americans and Asians. This disease can run in families and about 6% of children of first-order relatives with type I diabetes develop this disease. Among identical twins, the concordance rate (i.e. both twins affected) is 40%, indicating that both genetic and environmental factors must play an important role. Secondly, a higher frequency (80%) of type I diabetes has been observed in HLA-DR₃ and HLA-DR₄ individuals (Mohan, 2000).

Type I diabetes is believed to be an autoimmune disease (Palmer et al., 1983) that results in specific immunologic destruction of β cells of islets of Langerhan's. Presence of islet cell antibodies in type I diabetes, lymphocytic
infiltration in and around islets (insulitis) (Maclean and Ogilvie, 1959; Gepts, 1965; Bottazo et al., 1985), and association of type I diabetes with other autoimmune diseases supports the evidence of autoimmunity. About 10% of cases of type I diabetes have other organ specific autoimmune diseases such as Graves' disease, Addison's disease or autoimmune thyroiditis (Mohan, 2000). The another presentation of insulin-dependent diabetes mellitus has been recently demonstrated that with immunological testing approximately 10% of patients initially diagnosed of having non-insulin dependent diabetes mellitus (NIDDM) may have a slow onset form of IDDM that has been termed latent autoimmune diabetes in adults (Tuomi et al., 1993).

Epidemiological studies in type I diabetes have revealed involvement of certain environmental factors in its pathogenesis. The factors are certain viruses (coxsakie B virus, cytomegalovirus, mumps, measles and infectious mononucleases), chemicals (alloxan, streptozotocin, pentamidine etc.) and common environmental toxins. Thus, in type I diabetes some "environmental factor" initiates the "autoimmune destruction" of β cells in "genetically susceptible individuals".

**Type II diabetes.** or maturity onset diabetes, or non-insulin dependent diabetes mellitus (NIDDM), is more common and constitutes 80-90% cases of diabetes (Mohan, 2000). The basic metabolic defect in this type of diabetes is either a delayed insulin secretion relative to glucose load (deranged insulin secretion), or the peripheral tissues are unable to respond to insulin (insulin resistance) (Anderson, 1985). In this type, the patient is usually 40 years of age at presentation and 80% are obese. Ketoacidosis is not a feature but hyperosmolar non-ketotic coma may be a complication. The pancreas in NIDDM is usually of normal size (Rahicr et al., 1983; Kloppel et al., 1985) but with a tendency to fatty infiltration (Westermark and Wilander, 1978), most probably due to the obesity present in many of these patients.
Type II diabetes is further of two subtypes i.e., obese and non-obese. Obesity is a common finding in type II diabetes. There is impaired insulin sensitivity of peripheral tissues, such as muscle and fat cells to the action of insulin, in obese individuals (insulin resistance). Lack of exercise and obesity are considered major contributors to type II diabetes: roughly 90% of individuals with type II diabetes are obese. These conditions predispose to hyperinsulinemia. Increased insulin resistance results in increased fasting and postprandial beta cell synthesis, which leads to “beta cell burnout” and eventually, diabetes. The condition of insulin resistance may exist for many years before pancreatic beta cell function actually becomes impaired (Kaczmar. 1998). Weight reduction in such obese patients produces improvement in the diabetic state. It has been observed that insulin resistance is a factor not only in obese type II diabetes but also in non-obese type II diabetes. In such individuals, the increased insulin resistance of peripheral tissues is due to either decrease in the number of insulin receptors or there is post receptor defect.

There are some other types of diabetes such as Gestational diabetes, which refers to the hyperglycemia temporarily during pregnancy in individuals having inherited liability to develop this disorder. Although this form usually disappears following delivery, 40% of women with gestational diabetes will go on to develop type II diabetes later in life (American Diabetes Association. 1997). Other types of diabetes may be secondary to pancreatic disease or removal of pancreatic tissue; secondary to endocrine disease such as acromegaly, Cushing’s syndrome, pheochromocytoma, glucagonoma, somatostatinoma or primary aldosteronism; secondary to the administration of hormones causing hyperglycemia. Iatrogenic diabetes may develop during various forms of therapy by drugs (Antihypertensive drugs, thiazide diuretics, preparations containing estrogen, psychoactive drugs, sympathomimetic agents, etc.) (Harris
and Cahill, 1979). It is also occurring mainly in those patients who are genetically susceptible.

**Genetic and Spontaneous Animal Models**

In animals different types of diabetes have been identified. The classification of diabetic dogs and cats is modeled after the human classification (Suter, 1989) but especially in the diabetic dogs, many aspects are different while as diabetic cat resembles type II diabetic human patients more closely (Hoenig, 2002). In rabbits diabetes mellitus is essentially similar to the insulin independent diabetes mellitus in humans (Roth and Conaway, 1982). The non-obese diabetic (NOD) mouse and biobreeding (BB) rat are the two most commonly used animals that spontaneously develop diseases with similarities to human type I diabetes (Rees and Alcolado, 2005). Sand rat (Psamnomys Obesus) is model of nutritionally-induced type II diabetes mellitus and is prone to developing hyper-insulinemia, hyperglycemia and obesity when transferred to a high-energy diet. However, the potential to become diabetic decreases with age (Ziv et al., 1999). The fatty Zucker (Zucker diabetic fatty (ZDF)) rat has been valued as a model of obesity, as the characteristics of the model are described as hyperglycemia, early hyperinsulinemia, fasting hyperglycemia, abnormal glucose tolerance, hyperlipidemia and mild hypertension (Corsetti et al., 2000). The spontaneously diabetic KK mice are reported to have moderate obesity, polyphagia, polyuria, persistent glycosuria, glucose intolerance, moderate hyperglycemia, hyperlipidemia, insulin resistance of peripheral tissues and hyper insulinemia. The diabetic characteristics of KK mice and the variant KKAy are reverted to normal after 40 weeks of age (Suto et al., 1998). The OLETF (Otsuka-Long-Evans-Tokushima-Fatty) rat is a spontaneously diabetic rat with characteristic features of late onset hyperglycemia (after 18 weeks of age), a chronic disease state, increased urinary protein excretion, higher glomerular filtration rate, increased kidney weight etc. The clinical and
pathological features of the disease state in OLETF rats resemble those of human renal complications in human type 2 diabetes mellitus (Mori et al., 1996). The Cohen, diabetic rat is an exceptional, genetically derived, diet induced type 2 diabetes mellitus model that expresses genetic susceptibility to a carbohydrate rich diet, a central feature of type 2 diabetes mellitus in humans (Zangen et al., 2001).

Experimentally-induced Models

Diabetes mellitus in animals can be induced by chemical destruction or surgical removal of part of the β cell mass, lesioning the ventromedial hypothalamus, feeding with high fat and high sugar diets, malnutrition in utero, high doses of counter-regulating-hormones particularly glucocorticoids and prolonged cell exposure to hyper-insulinemia (Pickup and Williams, 2003; Keen et al., 1982).

The classification of drug-induced diabetes in the experimental animals varies with quality and quantity of drug. Alloxan diabetes has been commonly utilized as an animal model of insulin dependent diabetes mellitus (IDDM) (Szkudelski, 2001). Streptozotocin is used to induce both insulin dependent (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). The range of the streptozotocin dose is not as narrow as in the case of alloxan. The frequently used single intravenous dose in adult rat to induce IDDM is between 40 and 60 mg/kg between (Ganda et al., 1976). Multiple low doses of streptozotocin treatment is used predominantly in the mouse and the induction of IDDM is mediated by the activation of immune mechanisms (Szkudelski, 2001). NIDDM can easily be induced in rats by intravenous or intraperitoneal treatment with 100 mg/kg between streptozotocin on the day of birth (Portha et al., 1974). High doses of streptozotocin and alloxan induce insulin deficiency and type I diabetes mellitus with ketosis. However, doses calculated to cause a partial
destruction of beta cell mass can be used to produce a mild insulin deficient state of type II diabetes mellitus, without a tendency to cause ketosis (Portha et al., 1989). Streptozotocin is preferred because it has more specific beta cell cytotoxicity, but the sensitivity of this agent varies with species, strain, sex and nutritional state and there are batch differences in activity (Okamato, 1981).

**Incidence of Diabetes Mellitus**

Diabetes Mellitus is one of the most common metabolic disorders with a worldwide prevalence estimated to be between 1% and 5% (Meral et al., 2004). According to Roberts (2001), diabetes is a deadly diseases affecting an estimated 135 million people worldwide and the numbers are increasing in rural and poor populations throughout the world. According to the report of the International Diabetes Institute and the World Health Organization (WHO) that diabetes mellitus “appears to be epidemic in many regions of world“ and the figure will become double or even triple by the year 2010 (Yuan et al., 1993). In India, over 20 million people are affected by diabetes. These numbers are expected to increase to 57 million by 2025 (Arvind et al., 2002). The World Health Organization (WHO) has declared India as the country with the largest number of diabetic subjects in the world. By 2025, approximately 20 percent of the total diabetic patients worldwide would be from India (King et al., 1998). Diabetes mellitus is responsible directly for about 38,000 deaths annually and cardio-renal-vascular complications resulting from diabetes mellitus are responsible for additional deaths annually, making diabetes a leading cause of death in United States (Norris, 1985). As per the report of American Diabetes Association the prevalence of diagnosed diabetes in the US is about 3% of the population (Kumar et al., 2001). An estimated 16 million people in America have diabetes and is the seventh leading cause of death. Approximately 10% of the diabetic population is composed of type I or insulin-dependent diabetes, whereas the remainder of diabetes are type II or non-insulin dependent. It is
estimated that a third of the non-insulin dependent diabetics are unaware of their disease. Among diabetic complications about 85% of all diabetics develop retinopathy. 25-50% develop kidney disease and 60 to 70% have mild to severe forms of nerve damage. Diabetes patients are also 2-4 times more likely to develop cardiovascular disease and 2-4 times more likely to suffer a stroke (American Diabetes Association, 1997). The prevalence of diabetes mellitus varies widely around the world and among racial and ethnic groups, probably as a reflection of genetic and environmental factors that have yet to be totally elucidated (Kumar et al., 2001).

Diabetogenic Agents

Many pharmacologists and toxicologists have found different chemicals such as alloxan, streptozotocin, cyprohepatidine, vacor (N-3-pyridylmethyl-N'-P-nitrophenyl urea), pentamidine, hexamethylenamine or crude extracts of anterior pituitary etc. producing diabetes mellitus in animals (Copenhaver et al., 1975; Fischer, 1985). Insulin secreting cells appear to be more sensitive to chemical insult than other hormone secreting cells of the pancreas and the diverse nature of the chemical structures of the substances known to produce deleterious changes indicate that there may be a number of different mechanisms by which β cells are damaged. Until these mechanisms are elucidated there is a great risk of exposure to diabetogenic agents (Fischer, 1985).

Many chemicals have been found to cause diabetes mellitus (diabetogenic agents) in man and animals, which are listed below:
<table>
<thead>
<tr>
<th>Agent</th>
<th>Compound primarily used as</th>
<th>Species known to be Susceptible to diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alloxan</td>
<td>Experimental tool to produce diabetes in laboratory animals</td>
<td>Almost all</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>Anti-cancer drug and experimental tool to produce diabetes in animals</td>
<td>Almost all</td>
</tr>
<tr>
<td>Cyprohepatidine</td>
<td>Antihistamine – anti 5-HT drug</td>
<td>Rat, Mouse</td>
</tr>
<tr>
<td>Vacor (N-3-pyridylmethyl-N'-P-nitrophenyl urea)</td>
<td>Rodenticide</td>
<td>Human</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Antitrypanosomal drug</td>
<td>Human</td>
</tr>
<tr>
<td>Hexamethylmelamine</td>
<td>Anticancer drug</td>
<td>Rat</td>
</tr>
</tbody>
</table>

Alloxan, a simple nitrogenous organic compound, was discovered by Frederick Wohler and Justin J. Liebig while beginning with the synthesis of urea in 1828, then of uric acid and the naming of same 13 derivatives of uric acid, including alloxan. The name "alloxan", given by Wohler and Liebig, is recorded as being derived from a combination of allantoin (a product of uric acid among others excreted by the foetus into the allantoins) and "oxalsure" (oxaluric acid derived from oxalic acid and urea, found in the urine) (McLetchie, 2002). Alloxan was originally obtained by the action of dilute nitric acid on uric acid. Unlike its parent, uric acid, which presents as a suitable crystalline compound insoluble in water, alloxan presents as brownish-red crystals with great avidity for water and is very unstable with half life of a few minutes in room temperature, less at body temperature (McLetchie, 2002) and is longer at lower temperatures (Lenzen and Munday, 1991). Its chemical name is 2,4,5,6 (1H, 3H) pyrimidinetutrone:- 2,4,5,6 tetra oxo-hexahydropyridine
having the molecular formula $\text{C}_4\text{H}_2\text{N}_2\text{O}_4$ with molecular weight 142.07 (Rastogi et al., 1998). It is represented diagrammatically as follows:

**Chemical structure of alloxan**

The remarkable discovery that a single injection of alloxan can produce diabetes mellitus in laboratory animals was made in 1942 by John Shaw Dunn and Norman McLetchie. The action of alloxan in the pancreas is preceded by its rapid uptake by the beta cells (Weaver et al., 1978; Boquist et al., 1983). Rapid uptake by insulin secreting cells has been proposed to be one of the important features determining alloxan diabetogenicity.

The methylnitrosurea analog, Streptozotocin [STZ, 2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose)] is synthesized by Streptomyces achromogenes and is used to induce both insulin dependent and non-insulin dependent diabetes mellitus (Szkudelski, 2001). Its chemical structure is shown as:

**Chemical structure of Streptozotocin**
Streptozotocin has replaced alloxan as the primary compound as it selectively destroys beta cells of islets of Langerhan's (Fischer, 1985; Wang et al., 1994; Shenoy et al., 2002).

The antihistaminic drug, cyprohepatidine, and a number of related chemicals possessing a biphenyl methylpiperadine nucleus produce a reversible loss of pancreatic insulin when given in repeated doses (Fisher et al., 1975). Experiments employing isolated rat pancreatic islets indicate that cyprohepatidine is a selective inhibitor of proinsulin synthesis.

The changes in the rat endocrine pancreas produced by cyprohepatidine are obtained in beta cells but not the glucagon-secreting α-cells or somatostatin-secreting δ-cells. Morphologically, with continued treatment over an 8-day period, there is a progressive loss of insulin secretion granules and a vesiculation of the rough endoplasmic reticulum followed by the formation of large cytoplasmic vacuoles. All of these changes are reversible upon drug withdrawal.

Persons accidentally or intentionally ingesting vacor exhibit insulin-dependent diabetes mellitus if they survive the neurotoxicity of the agent (Johnson et al., 1980). The poison kills rodents by virtue of its toxicity to the peripheral nervous system but does not produce diabetes in laboratory animals including monkeys. Thus, there appears to be a strict species selectivity in the diabetes-producing effects of vacor.

Another agent found to produce diabetes in humans is the trypanocidal drug, pentamidine. An insulin-dependent hyperglycemic state is produced in patients, usually after several weeks of drug treatment. A number of pentamidine-induced diabetics have been reported, and the pattern of blood glucose changes resembles the transient hypoglycemic-permanent hyperglycemic phases characteristic of alloxan and streptozotocin administration to animals (Bouchard et al., 1982).
Another report indicates that the antineoplastic agent, hexamethylmelamine, produces a dose-dependent hyperglycemia in rats chronically treated with the drug (Molello et al., 1984). Its effects were limited to the insulin-secreting β-cells and appeared to be reversible upon withdrawal of the drug.

Management and Significance

The management of diabetes by replacement with antidiabetic drugs has revolutionized the concept of disease. Chakravarthy et al. (1980) have reported that a flavonoid fraction extracted from the bark of *Pterocarpus marsupium* Roxb. effectively reversed the alloxan-induced changes in the blood sugar level and the beta cell population in the pancreas. Further, the drug has been reported to possess protective effect when given prior to alloxan administration. Kedar and Chakrabarti (1983) have reported that oral administration of jambolan seed (1g/kg) in casein diet significantly lowered the elevated postmeal values of blood sugar, cholesterol, FFA and triglyceride to levels comparable to phenformin. Santhoshkumarai and Devi (1991) have reported that administration of Ayurveda drugs *Nisakathakathi kashayam, Rasnairandadi kashayam* and their mixture to experimental rabbits decreased fasting blood glucose and serum cholesterol and the effect was more significant in the case of the mixture. Maghrani et al. (2003) have suggested that the aqueous extract of *Retama raetam* posses significant hypoglycaemic effect in both normal and streptozotocin-induced diabetic rats. Halim (2003) has reported that combination of water extract of dried powder of root and leaves of *Abroma augusta* and *Azadiracta indica* respectively is helpful in lowering the blood sugar of alloxan-induced diabetic rats. Akhani and his associates (2005) have reported that the fresh as well as dried rhizome of ginger, *Zingiber officinale* possess a potential antidiabetic activity with regard to decrease in serum cholesterol, serum triglyceride, blood pressure, fasting blood sugar and increase in insulin levels in streptozotocin-induced non-insulin dependent diabetic rats.
Habib et al., (2005) have reported a significant decrease in blood glucose, eosinophils, monocytes and hemoglobin contents, and no significant change in total erythrocyte count, total leukocyte count and differential leukocyte count in normal rats treated with neem leaf extract, nayantara leaf extract and bitter melon fruit juice with the patent drug gliclazide. Bairy et al., (2005) have reported that the extract of Syzygium malaccense with their beneficial effects on blood sugar and hyperlipidemia associated with diabetes could serve as good adjuvant to other oral hypoglycemic agents. Baqui et al., (2005) have reported a significant improvement in biochemical and behavioural patterns of alloxan induced diabetic rabbits by the oral application of antidiabetic drugs. Iriadam et al., (2006) have reported that the extract of aerial parts of Artemisia herba-alba when administered orally produced a significant hypoglycemic effect in normal and streptozotocin-induced diabetic rabbits. Tedong et al., (2006) have demonstrated the efficiency of hexane extract of Anacardium occidentale in reducing the functional and histological alterations in the kidneys of streptozotocin-induced diabetic rats.

The perusal of literature indicates that most of the work on diabetes mellitus has been restricted to some biochemical indicators. Little work has been done to elucidate the other diabetes-related complications. Hence, the present study has been conducted to approach the understanding of the disease in elucidating the biochemical, behavioural and histological alterations. The objective of the study include:

1) In the study, rabbits were selected as experimental animals because of their timid and non-aggressive nature, easy handling and especially their close relation to primates. Being animal models, the results obtained can be extrapolated to other animals including man.
2) To study the biochemical alterations in the blood/serum in alloxan- and streptozotocin-induced diabetes mellitus in rabbits.

3) To study the effect of the induced diabetes on the behavioural patterns of the rabbits.

4) To study the subsequent effect of the disease on gross and histomorphological alterations in various organs of the diabetic animals.

5) To study the diabetogenic potential of alloxan and streptozotocin and their comparative effects on the biochemical and histomorphological patterns.

6) To study the efficacy of various herbal/allopathic drugs in combating diabetes and diabetes-related complications with regard to behavioural, biochemical and histomorphological alterations on the rabbits and to harvest their therapeutic efficacy.