Perhaps no biologic function is as vital for survival as the appropriate distribution of fuels during "fight and flight" situations. Thus, the mammalian body is equipped with regulatory mechanisms designed to ensure an adequate supply of fuel to its various tissues in times of either feast or famine. The design is such that ingested substrates (carbohydrate, lipid and protein) are diverted to storage (liver, fat and muscle) during periods of feeding and are later utilized (glycogenolysis, gluconeogenesis and ketogenesis) during periods of food deprivation.

Glucose is the predominant metabolic fuel of the central nervous system (CNS) (Lund-Anderson, 1979). Accordingly, an acute alteration in circulating glucose normally triggers a complex physiological response that includes the release of several counterregulatory hormones (Gerich et al., 1976; Rizza et al., 1979; Cryer and Gerich, 1983). When deprived of glucose, cellular levels of ATP rapidly decline, leading to destructive changes in transmembrane ion gradient and electrical potential. Thus, the maintenance of plasma glucose within narrow limits is one of the most tightly regulated functions of the mammalian body. All mammals possess seemingly superfluous nervous, behavioral and endocrine mechanisms to ensure that glucose level is maintained in normal range. There are absolute backup regulatory mechanisms in the body to ensure that blood sugar level is maintained in situations that demand greater utilization by brain and effector organs.
The role of nervous system in the control of blood glucose and carbohydrate metabolism has been recognized for over 100 years, ever since Claude Bernard (1854) demonstrated the phenomenon of piqiture hyperglycaemia by stimulating the floor of the fourth ventricle of the dog and producing glucosuria. Thus, the hypothalamus is said to be the highest autonomic center that coordinates visceral activities in response to everchanging conditions of the internal and external environments, and it modulates hormonal secretion through production of hypothalamic releasing and inhibiting hormones and by sending neural signals to the endocrine organs. Hence, it has been inferred that the hypothalamus is an important integrative station for neural and hormonal regulation of peripheral metabolism (Shimazu, 1983).

The functional branches of the ventromedial hypothalamus (VMH)-splanchnic and lateral hypothalamus area (LHA)-vagal pathways, innervate various organs, to mediate neural and neural-hormonal influences on metabolic processes in the liver and other viscera (Shimazu, 1980). The specific metabolic events that are controlled by these functional neural circuits are reciprocal and appears parallel to that of the sympathetic and parasympathetic nerves, that is, they act generally in stimulating catabolic and anabolic processes. The role of sympathetic nervous system is that of producing an increase in blood glucose (Edwards and Silver, 1970), and the effects appear to be mediated principally by epinephrine. Interference with the integrity of the sympathetic nervous system by cordotomy or by adrenal denervation (Britton, 1925) results in an impaired recovery from insulin induced hypoglycaemia. The role of the parasympathetic nervous system has been anatomically carried out by the vagus nerve in the visceral regions. Vagal stimulation can accelerate glycogen synthesis in the liver and can decrease the blood glucose level (Wada et al., 1995).

Many interrelationships exist between the hormones and nervous systems. For instance, at least two glands secrete their hormones only in response to appropriate nerve stimuli, the adrenal medulla and the posterior pituitary gland, and few of the adenohypophyseal hormones are secreted to a significant extent in response to nervous activity in the hypothalamus (Guyton, 1981). Most of the endocrine glands are richly
innervated by both sympathetic and parasympathetic component of nervous system (Kesse et al., 1987) which regulate their secretion.

Interrelationships between the endocrine and nervous system permit the body to make adjustments that avert, rather than correct, imbalance; and they provide for interactions with environmental factors. The endocrine system is powerful, versatile and self-regulating. However, it is decidedly not neat; and it has little respect for time-honored traditions. Its boundaries merge imperceptibly with those of other regulatory systems, as its influences extent to all facets of biological function (Martin, 1985). The endocrine system establishes the kind of cell-to-cell communication that fosters cooperation, and it thereby accounts for many of the differences between cell aggregates and integrated individuals. It monitors and maintains the compositions of the body fluids and it favours specializations by commanding cells of one type to support the activities of another. Through influences on growth, differentiation, maturation, proliferation, and metabolism, it encourages each body component to realize its potential and to assume its appropriate role (Martin, 1985).

It is now known that both neural and endocrine systems coordinate and integrate the operation of the other systems in the body and bring about adjustments to meet environmental changes. However, under pathological conditions the neural and hormonal influence on glucoregulation in fed state gets distorted. A well known pathological condition is diabetes mellitus, which includes a group of disorders expressed by abnormal glucose metabolism. The two forms of primary diabetes, previously called "juvenile onset" and "adult onset" are now referred to as insulin dependent, Ketosis prone type I and non insulin dependent, Ketosis resistant type II, since either may occur at any age (Brown and Asbury, 1984). Diabetes causes wide spread damage to the peripheral nervous system, involving chiefly the somatic sensory and autonomic nervous system (Watkins, 1990). Type I or IDDM is caused by the lack of insulin and result from the autoimmune destruction of the insulin producing B-cells of the pancreas (Kolodka et al., 1995). In IDDM, a lack of insulin results in wasting hyperglycaemia and death from ketoacidosis (Vignati et al., 1985), with vigorous compliance
and intensive diabetes management in the severe microvascular complications of diabetes, their health and life expectancy can be improved (Trial Research group, 1983).

So far many complimentary studies have been undertaken regarding the etiology and pathogenesis of diabetes. Previous studies in our laboratory has emphasized the role of autonomic nervous system as a blood sugar regulator (Pilo et al., 1984c; Parikh, 1992). Its innervation in the endocrine gland and control on their secretion has also been highlighted (Pilo et al., 1984b). The role of autonomic nervous system in the regulation of liver metabolism and glycaemic state and whether the eventuality of dysfunction of autonomic nervous system (ANS) could precede the onset of diabetes or they are in some way causative, or whether these defects are secondary to the disease itself need to be clarified. In this light, the present study was undertaken to emphasize the control of sympathetic and parasympathetic nervous system in maintaining the metabolic homeostasis. The interplay between neural and hormonal system in the regulation of metabolic activities of liver has also been reviewed. An attempt has also been made to elucidate not only the cause of diabetes, but also its management.

The liver is the main target organ for insulin action and the principal effector organ in maintaining blood glucose homeostasis and ketogenesis. This organ can vary the amount of glucose it pumps into the general circulation or removes from it, in accordance with the requirements of the body. These requirements are transmitted by both neural and hormonal messengers which are sensed mainly through the actual concentration of glucose in the blood passing through the brain. Glucose sensing neurons are thus scattered within the brain, although those of the LH and VMH areas have been most extensively studied (Oomura, 1976; Oomura et al., 1982). These neurons in the hypothalamus are functionally and pragmatically referred to as "gluoreceptors" but they have not been identified physiologically as being true receptor structures. Neural messages are sent through sympathetic and parasympathetic nerve fibers innervating the liver. sympathetic fibers get activated by low blood sugar level and in turn favours the glucose mobilizing mechanisms. On the contrary, parasympathetic fibers functions in reverse pattern.
Hormones acting directly on the liver in minute to minute regulation of hepatic glucose output are glucagon, insulin and catecholamines (Gerich et al., 1981). There is a physiological link between the liver and the adrenal glands (Donovan et al., 1991; Yamaguchi, 1992; Hamilton-Wessler et al., 1994) which suggest the involvement of glucocorticoid in hepatic gluoregulatory activities. In addition, even the growth hormone and the thyroid hormones are involved in the regulation of glucose movements across the liver cell membrane (Gerich et al., 1981; Hers and Hue, 1983; Muller and Seitz, 1984).

Whole body glucose disposal results from both insulin and non-insulin mediated glucose uptake (Baron et al., 1988; Lang and Dobrescu, 1991). Insulin mediated glucose uptake (IMGU) occurs primarily in insulin sensitive tissues such as muscle, whereas non-insulin mediated glucose uptake (NIMGU) occurs in varying degrees in all tissues regardless of their sensitivity to insulin (Lang and Dobrescu, 1991). However, it is well established that insulin plays a major role in the regulation of gluconeogenesis by antagonizing the action of the gluconeogenic hormones, glucagon and adrenaline (Chisholm et al., 1983). Nevertheless, glucose is one of the most important regulators of insulin secretion from pancreatic β-cells with both short-term stimulatory and long term modulatory effects (Komatsu et al., 1995). Humoral factors, metabolic substrates as well as systemically and locally released hormones are the major regulators of insulin secretion.

Apart from this, the existence of a regulatory axis between the hypothalamus and the endocrine pancreas has been demonstrated in a variety of studies (Shimazu, 1983; Lautt, 1980a). Parasympathetic nerves also modulate insulin secretion. Stimulation of vagus nerves directly or indirectly by electrical stimulation of the lateral hypothalamic nucleus results in hepatic glucose uptake. Thus, the hypothalamo-insular axis seems to involve both neural and humoral pathways in order to have normal functioning (Knip et al., 1983).

The control of parasympathetic system on insulin secretion and its regulation of metabolic activities could be best explained from the results of studies carried out after subdiaphragmatic vagotomy, which caused insulin deficiency (chapter 6) and a significant
hyperglycaemia (chapter 2). High blood sugar level is rendered by increased activity of gluconeogenic enzymes such as G-6-Pase, LDH and SDH (chapter 2). Vagal abrogation decreased the AchE activity markedly (chapter 2) indicating the absence of cholinergic action due to vagotomy. Cholinergic blockade will decrease gastrointestinal motility and food absorption (Knip et al., 1983) accomplished by bloating of stomach (Oommen, 1992). Vagotomy is followed by enhanced glycogenolysis, lipolysis and proteolysis in the liver (chapter 2,3). Liver glycogen stores decreased concomitantly as indicated by enhanced glycogen phosphorylase activity and reduced glycogen synthase activity (chapter 2). The water content of the liver also decreased. All these taken together might be the cause of the decreased liver weight (chapter 1). However, adrenal gland showed hypertrophy (Chapter 1), favoured by enhanced ACTH level (Sule, 1997). Hormonal alterations caused by vagotomy also include change in thyroid activity. Serum T₃ level increased significantly whereas T₄ and TSH level decreased in response to vagal sectioning (chapter 7).

Along with insulin, the role of glucocorticoid in maintaining the gluconeogenic activities of the organisms is well documented (Kraus-Friedmann, 1984). Glucocorticoids influence carbohydrate metabolism by promoting the conversion of protein to glucose (gluconeogenesis), by inhibiting the peripheral utilization of glucose (possibly because they antagonize insulin) and by increasing glycogen deposition in the liver (Biggers et al., 1989; Donovan et al., 1991). Deficiency of glucocorticoids causes a lowered fasting blood sugar which is probably largely the result of reduced gluconeogenesis.

Bilateral adrenalectomy makes it impossible to maintain normal blood glucose concentration between meals because they cannot mobilize significant quantities of glucose by gluconeogenesis and/or glycogenolysis (chapter 6). Serum thyroid concentration also increased but it is not as significant as noticed in vagotomized rats (chapter 7). Furthermore, lack of cortisol reduces the mobilization of both protein and fats from the tissues (chapter 3), thereby checking many other metabolic functions of the body. The activity of membrane bound enzyme (phosphatases) was found to decline (chapter 3) indicating reduced transport
of metabolites through hepatocytes. Reduced ALT and AST activities suggest reduced gluconeogenic activities and hypoglycaemic state in these rats (chapter 2).

In addition to this, rats operated for both subdiaphragmatic vagotomy and bilateral adrenalectomy showed marginal hyperglycaemia (chapter 2). These animals showed muscular weakness and loss in body weight (Chapter 1). At the same time, liver weight also decreased in these rats which might be due to loss of water content from the liver (Chapter 1). The serum insulin level declined noticeably (chapter 6) but thyroid hormones showed slight increase (chapter 7). The glycaemic state in these rats is more or less like that of vagotomized rats. In these animals the glucose cycling has been described by several pathways of glucose metabolism which can "recycle" glucose. These include the Cori cycle (Reichard et al., 1963), concurrent glycogenesis and glycogenolysis (Newgard et al., 1984), and the substrate or "futile" cycles of the glycolytic pathways (Katz and Rognstad, 1976). The glucose -G-6-P-glucose (G/G-6-P) cycle is one substrate cycle. Thus, glucose is taken up from the circulation and again released back into the circulation as revealed by a concomitant increase in glycogen synthase and glycogen phosphorylase activity (chapter 2), thereby, suggesting parallel operation of glycogenesis and glycogenolysis (futile cycle). Even G-6-Pase activity increased slightly (chapter 2) rendering a marginal hyperglycaemia.

Influence of glucagon and catecholamine on carbohydrate metabolism has been highlighted in the present study using anti-sympathetic drug, Guanethidine sulphate. It destroys the sympathetic ganglion and decreases the hormonal secretion under its influence. Body weight of sympathecomized rats decreased compared to their controls receiving saline. In addition, liver weight also decreased, which could be due to the significant decrease in liver water content (chapter 1). Even hormonal profile was disturbed by sympathectomy. Functional status of thyroid decreased markedly, as indicated by decreased serum T3 level (chapter 7). Whereas serum insulin level in these rats increased (chapter 6) probably due to an enhanced parasympathetic response, in the absence of decreased sympathetic tone, and this could be the reason for the observed hypoglycaemic state. Decreased blood glucose level was accompanied with an enhanced glycogenesis and reduced glycogenolysis (chapter 4).
gluconeogenic activity declined in these rats, as indicated by reduced G-6-Pase and aminotransferase activities (chapter 4). Guanethidine induced sympathectomy enhanced proteogenesis and lipogenesis in the liver (chapter 5).

Among the more important endocrine responses to hypoglycaemia in the adult animals including rats and humans is activation of the hypothalamic-pituitary-adrenal (HPA). The steroids produced by the adrenal cortex promote gluconeogenesis by inducing key enzymes such as PEPCK (Sasaki et al., 1984; Magnuson et al., 1987; Nebes and Morris, 1987) and by facilitating breakdown of muscle for providing substrate for these enzymes (Munck et al., 1984). This process is especially important in the fasted animal. Adrenal medullary hormones, the catecholamines, are the key counterregulatory hormones to stress (Seidler and Slotkin, 1985; 1986). The hyperglycaemic effects of the catecholamines are complex. They involve both stimulation of hepatic glucose production and limitation of glucose utilization. They are mediated through both alpha and beta adrenergic mechanisms, and are the result of both direct and indirect actions in humans (Deibert and DeFronzo, 1980; Rizza et al., 1979; 1980a). Thus associated with changes in glucose metabolism are changes in glucoregulatory hormones. Following this, an attempt has been made to understand the role of these hormones in the regulation of metabolic sequel in the liver.

Although much is known about the hypoglycaemic response of counterregulatory hormones, less is known about the loci capable of sensing the fluctuations in glucose concentration and initiating the appropriate corrective measures during hypoglycaemia. Both the brain and the liver have been postulated to be the primary sites in the control of glucose homeostasis (Biggers et al., 1989; Donovan et al., 1991). The effect which is manifested more apparently by adrenal cortical and medullary hormones.

By far the best-known metabolic effect of cortical hormones is their ability to stimulate gluconeogenesis by the liver, often increasing the rate of gluconeogenesis as much as 6 to 10 fold (Guyton, 1981). The glucocorticoids not only have the inhibitory effect on protein synthesis but also seem to be essential for protein catabolism. However, lack of
adrenal hormones in adrenalectomized nullifies the gluconeogenic act of glucocorticoid. Thus the hypoglycaemic response of guanethidine got more pronounced by subjecting these rats to bilateral adrenalectomy simultaneously (chapter 4). The severe hypoglycaemic state in these rats is accomplished by significant increase in insulin level (chapter 6). Insulin increases the uptake of glucose from the circulation by hepatocytes as indicated by enhanced glycogenesis (chapter 4). On the contrary, concentration of thyroid hormones decreased significantly in these rats (chapter 7) suggesting reduced transport of metabolite across the hepatocytes. Even, lipid depots increased in these rats (Chapter 5). This increase in lipid and glycogen stores along with increased water content resulted in an increased liver weight (chapter 1). The activities of gluconeogenic enzymes (viz., aminotransferase, G-6-Pase) were not operative significantly (chapter 4), in turn favouring the hypoglycaemic state.

In vagotomized rats suppressed insulin level (chapter 6) and synergistic effect of glucagon, epinephrine and cortisol, markedly accelerate glycogenolysis. However, guanethidine induced sympathectomy obstructs adrenergic influence on hormonal secretion, thereby foiling the secretion of gluconeogenic hormones. Rats subjected to vagotomy and chemical sympathectomy together showed only a marginal hyperglycaemia (chapter 4). Probably, the hyperglycaemic state caused by vagotomy can be normalized to some extent by sympathectomy. In these rats, due to vagal sectioning insulin level in the serum declined noticeably (chapter 6). Even, thyroid activity reduced as indicated by decreased T3 and TSH levels (chapter 7). In addition, liver and adrenal weight increased with parallel increase in the water content (chapter 1). Increased adrenal weight was mainly due to the hypertrophy of cortical cells rendered by increased ACTH secretion. The hyperglycaemia observed in these animals could partly be a result of glycogenolysis seemingly induced by adrenal medullary hormones. Activity of membrane bound enzyme Na⁺-K⁺-ATPase declined (chapter 5), reducing the uptake of metabolite from the circulation.

Thus, a multitude of intrinsic physiological relationships carefully regulate and fine tune the glucose homeostasis which is ultimately important for the well being of the organism. Hyperglycaemic condition of vagotomized rats produces decreased glucose tolerance since
insulin level was low in these rats. However, in adrenalectomized and chemically sympathectomized rats glucose tolerance did not alter as was the case in controls. But when adrenalectomy and sympathectomy were performed along with vagotomy glucose tolerance curve and insulin response was marginally improved. Thus adrenergic deactivation, to a certain extent reduces the glycaemic level in VGX rats without enhancing insulin release.

Thereby, when various threads of evidence are assembled it seems that the pathogenesis of diabetic neuropathy is not explainable by any single mechanism, and development of neural lesions is linked to extraneural system complications. It appears likely that functional features interact with systemic abnormalities, to produce the complex of neurologic disturbances that results in diabetic neuropathy. Biochemical abnormalities in the milieu interior may further contribute to the early metabolic neuropathy.