General Consideration

Regulation of glucose homeostasis is the well orchestrated, yet delicate physiological process, which is ultimately important to the well-being of a complex living organism such as a mammal. Since glucose is such an important fuel for the brain and other tissues, it is crucial that the body handle it judiciously. Glucose homeostasis implies the maintenance of the circulating glucose concentration in a narrow concentration range under a wide variety of conditions.

A constant glucose level can only be maintained when the production of glucose and the removal from the circulation are balanced. When either, the rate of production or utilization exceeds the other, a state of disequilibrium will prevail, resulting in hyperglycemia or hypoglycemia, either of which can be harmful. A dynamic interaction must, therefore exist between the systems regulating the glycemia which would culminate in the fine regulation of metabolic processes.

The endocrine and nervous system are two major integrators of mammalian physiology. The functions of endocrine glands can be recognized in many areas, mainly the maintenance of the milieu interieur, a narrowly regulated mixture of substrates, cofactors, enzymes and conditions that provide an optimum environment for the biochemical machinery of the body. There are also challenges imposed by more marked environmental changes, that is the response to emergency demands, such as starvation, infection, trauma and psychological stress. The function of glucoregulation is elicited by many hormones such as insulin,
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glucagon, catecholamines, glucocorticoids and growth hormone. The endocrine glands having no anatomic continuity, are dependent on the vascular system for the distribution of their products and considerably on the autonomic innervation for regulation.

The role of the nervous system in the control of blood glucose and carbohydrate metabolism has been recognized, ever since Claude Bernard (1849) demonstrated a pique hyperglycemia by stimulating the floor of the fourth ventricle of the dog and producing glycosuria. Neural signals can contribute to the regulation of the blood glucose level, both by having direct effects on tissues that produce or consume glucose and through the control of hormonal secretion (Wada et al., 1995). In the study of the precise pathways by which the CNS mediates its influence, the importance of the ANS has been long recognized (Britton, 1925). Frohman et al. (1967) have demonstrated the importance of parasympathetic system demonstrating increased insulin secretion by vagal stimulation, and an inhibition of the same after vagotomy. The role of the sympathetic nervous system is that of producing an increase in blood glucose, the effects principally mediated by epinephrine. Interference with the integrity of the sympathetic nervous system by cordotomy (Cantu et al., 1963) or by adrenal denervation (Britton, 1925) results in an impaired recovery from insulin induced hypoglycemia. In a parallel fashion, sympathetic blocking agents impair the metabolic effects attributable to infused E (Porte, 1966).

Thus, the nervous and endocrine systems become the principal mediators of physiologic adaptation to the changing ambient conditions. In general terms, neural reactions are faster and are therefore more important immediate responses, whereas hormonal effects serve to complete a homeostatic adaptation. It is not surprising therefore that neural influences play a major role in unifying the responses of endocrine glands.

Here it is essential to mention that it is hypothalamus, the supreme autonomic center that coordinates visceral activities in response to the everchanging conditions of the milieu interieur and exterieur. It modulates hormonal secretion through production of 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, 1981). Out of the hypothalamic nuclei, the ventromedial hypothalamic area (VMH) and the lateral hypothalamic nucleus (LHA) are
considered to act reciprocally in several regulatory functions. Ban (1966) has concluded on physiological and anatomical bases that LH belongs to the parasympathetic system and VMH belongs to the sympathetic system. This has also been confirmed by Bray and York (1979). The VMH is the satiety center, mediates glucagon release and in turn glycogenolysis, gluconeogenesis, lipolysis and a subsequent hyperglycemia. On the other hand LH is the center for feeding. It stimulates insulin release, glycogenesis, lipogenesis and inhibits gluconeogenesis. Thus VMH and LH act generally in stimulating catabolic and anabolic processes.

A variety of neurological disturbances are known to occur in diabetes mellitus, producing multiple signs and symptoms related to different segments of the nervous system. Findings regarding the peripheral nervous system are the most common, and in fact, peripheral neuropathy may be the most common complication of diabetes (Ellenberg, 1976). Dysfunction of the autonomic nervous system is reported to occur at an incidence of 20% to 40% in diabetes (Clarke et al., 1979). This finding is seldom appreciated because the symptoms of autonomic neuropathy are often vague and constitute a panorama of complaints attributed to other etiologies. The widely held belief that the problems associated with autonomic neuropathy are not life-threatening has been refuted by Ewing et al. (1976), sudden death, silent myocardial infarction and renal failure being common among patients with diabetic autonomic neuropathy. Nephropathy is a serious complication of both type I and type II diabetes mellitus with well recognized renal functional and ultrastructural changes (Osterby, 1974). In addition, insulin requirements seem to be higher in patients with diabetic nephropathy (Ortved-Andersen, 1976).

Diabetic nephropathy has been in picture since Erasmus Darwin in 1801, first noticed this phenomenon, by observing that the urine of certain diabetics coagulated on being heated. He attributed this to albuminuria. Electron microscopic studies showed glomerulosclerosis and thickening of the glomerular basement membrane and Bowman's capsule (Lannigar, 1964). These changes were also observed in pancreactomy (Doyle, 1964). Vargas et al. (1970) have shown both tubular and interstitial changes in the kidney of alloxan diabetic rats. Increase in kidney size due to hyper trophy (Ku et al., 1987), and hyperfiltration (increased GFR) (Mongensen, 1971) are the changes which induce hemodynamic perturbations that proceed inexorably towards renal failure and death.
Apart from its conventional role in the phenomenon of excretion, kidney is also involved in glucoregulation by means of glucose production. Krebs (1963), Scrutton and Uttar (1968), Exton (1972) and Guder and Ross (1984), have all shown glucose formation and gluconeogenic activity in kidney cortex. Adrogue (1992) has shown that renal contribution to systemic glucose production is 10-20% under normal physiological conditions and 30-35% during starvation a part of which could be from gluconeogenesis, because kidney contains G-6-Pase (Mithieux et al., 1990), the terminal enzyme of the gluconeogenic pathway. Minassian and Mithieux (1994) reported similar results, showing that in fed state, the renal gluconeogenesis caters 5-10% of total endogenous glucose production, while in the fasting state, the kidney and the liver contribute almost equally to the endogenous glucose production; the liver furnishing 55% and the kidney 45% of the total glucose output. A significant input of the kidney to glucose production in fasted dogs has also been reported by Cersosimo et al. (1994) and Ekberg et al. (1996). Oommen (1992) and Pillai (1993) have shown an important share of the kidney in glucose metabolism and have measured the activities of various enzymes of glucose metabolism in the kidney. These authors have ascertained the role of ANS in the regulation of renal metabolic function which has been indicated earlier by Patel and Pilo (1977), Pilo and Patel (1978), and Verma et al. (1987).

The kidney is well innervated by the autonomic nervous system, getting its parasympathetic supply through the vagus and the sympathetic supply through the splanchnic nerve. Parasympathetic innervation to the mammalian kidney has been evidenced by the presence of AChE positive fibers (Barajas et al., 1976). AChE activity has also been confirmed by Oommen (1992) in rat kidney and has been shown to respond to autonomic manipulations. α-adrenergic receptors have been identified in proximal convoluted tubules (PCT) and in the medullary thick ascending limb (MTAL) (Clark et al., 1990; Gesek and Schoolwerth, 1990; Feng et al., 1994). β1-adrenergic receptors have also been demonstrated on renal tubules (Kudo et al., 1991; Taniguchi et al., 1993; Amenta et al., 1994).

With this foreground, it was thought important to gain more knowledge regarding the regulation of renal metabolism. Looking at the important role the autonomic nervous system plays in the regulation of metabolic homeostasis, and that any disturbance in the integrity of the ANS would cause a departure from normal metabolic state of the body, it becomes
essential to investigate the functioning of each of the component of the ANS, and its allied endocrine glands. Because kidney plays an important role in glucose metabolism, it becomes mandatory to search for the errors in the metabolic pathways that would develop due to disturbances in the ANS. Dysfunction of the autonomic nervous system complicates the clinical course of patients with diabetes mellitus. Therefore, to investigate this pathogenesis, the present study was therefore aimed at elucidating the errors in renal metabolism by creating autonomic nervous system disturbances by removing one by one and in combination the components of the ANS.

Two of the most important determinants of the flux of fuels into and out of storage forms are the pancreatic hormones insulin and glucagon. In most situations these hormones are antagonistic and thereby play a role in fine regulation of many metabolic processes.

An increased concentration of glucagon relative to insulin is believed to change metabolic processes toward catabolism and away from anabolism. By that, it is meant that breakdown of macromolecules such as glycogen, triglycerides and protein is accelerated to provide a source of fuels, and the biosynthesis of macromolecules from energy-yielding precursor components is reduced. Thus, glycogenolysis is accelerated and glycogenesis decreases, amino acids are preferentially diverted to gluconeogenesis at the expense of protein synthesis, lipolysis increases and lipogenesis decreases. These are the results of a low insulin : glucagon ratio. Nitrogen balance becomes negative, being followed by body-weight loss.

In normal physiological conditions, an increase in blood glucose is the main signal for insulin secretion (Taylor and Agius, 1988; Unger, 1991). The glucose sensing apparatus, which modulates insulin secretion in response to changes in circulating glucose concentration is inoperative in IDDM (McGarry et al., 1989). The increase in glucagon : insulin ratio leads to metabolic alteration (Taylor and Agius, 1988). IDDM is thus characterized by elevated blood glucose levels, the result of perturbations of glucose uptake and metabolism in both liver and extrahepatic tissues (Henly et al., 1996), both insulin and glucose mediated glucose uptake being impaired (Ward et al., 1991). In patients with NIDDM, defects in insulin secretion and insulin action both contribute to the metabolic disturbances (DeFronzo et al., 1983), reduced insulin-mediated glucose uptake by peripheral tissues or insulin resistance being characteristic of virtually all patients with NIDDM (DeFronzo et al., 1981, 1985).
Insulin and GH have important and complex interrelationships. The actions of GH antagonize those of insulin and modulate the tissue responsiveness to insulin (Bratusch-Marrain et al., 1982; Press et al., 1984). GH levels are elevated in poorly controlled diabetes and may contribute substantially to the metabolic derangement in this state (Press et al., 1984).

Glucagon plays an important role in glucose homeostasis by promoting glucose production, so that blood glucose is replenished in both normal and emergency situations. Thus, the primary function of glucagon is to prevent hypoglycemia. In addition to metabolic and endocrine factors, glucagon secretion is influenced by neural factors. Electrical stimulation of ventromedial hypothalamic nucleus results in increased glucagon secretion (Frohman and Bernardis, 1971). This is relevant since VMH is a center responsible for neural regulation of carbohydrate metabolism (Shimazu, 1983). The effects of glucagon are counterregulated by insulin, and apparently it is the glucagon to insulin ratio rather than the absolute level of each hormone that determines the metabolic responses of the target organs (Parilla et al., 1974).

Pancreatic islets are richly innervated with adrenergic nerves (Ahren et al., 1981) and electrical activation of sympathetic nerves is known to inhibit basal and stimulated insulin secretion (Holst et al., 1981; Miller, 1981). It has been assumed that this inhibition of insulin secretion is mediated by NE via the α-adrenoceptors, since the effect is abolished by the α-adrenoceptor antagonist phentolamine (Bloom and Edwards, 1984). Ahren et al. (1987) have shown that activity of local sympathetic nerves of the pancreas inhibits basal insulin and stimulates basal glucagon secretion, and that pancreatic infusions of NE produce stimulation of glucagon secretion.

Simulating the activation of the adrenal medulla by E infusion induces glucagon secretion (Ahren et al., 1988). Activation of the local sympathetic innervation of the pancreas by electrical stimulation also increases pancreatic glucagon secretion (Ahren et al., 1987). The activation of each of these autonomic inputs to the pancreas has been demonstrated in response to hypoglycemia. Activation of sympathetic nerves innervating the adrenal medulla results in an increase of circulating E (Gale et al., 1983).
The involvement of the adrenal cortex in carbohydrate homeostasis has been recognized long back and was definitively confirmed by Long et al. (1940) who demonstrated that adrenocortical extracts promote gluconeogenesis. Glucocorticoids play a crucial role in facilitating the mobilization of amino acids from the skeletal muscle. They influence the release of amino acids from skeletal muscle in several ways. Of major importance is their ability to inhibit the synthesis of proteins (Bolander et al., 1981). In addition to the inhibitory effect on protein synthesis glucocorticoids seem to be essential for protein catabolism (Goldstein et al., 1995). Corticosteroids are well known to inhibit glucose uptake in a variety of tissues (Nosadini et al., 1983; Baron et al., 1987; McMahon et al., 1988). The regulation of glucocorticoid secretion is done by ACTH, the adenohypophysial hormone, required for maintenance and functioning of the adrenal cortex. An elevated concentration of ACTH causes an enlargement of the gland and increases the synthetic activities in the cortex (Masui and Garren, 1970).

An alternate control of insulin and glucagon levels is via direct action of the autonomic nerves (Woods & Porte, 1974). Parasympathetic effects on the pancreas result in elevated insulin levels and in elevated glucose induced secretion of insulin (Girardier et al., 1976). Inhibition of vagal nerve stimulation would lead to reduced insulin secretion. To examine the effects of this hormonal alteration on renal metabolism, vagotomy was performed subdiaphragmatically in rats.

At sacrifice it was noted that the rats showed the stasis of food, reducing the food intake. A bloating of the stomach was observed, indicating the completeness of vagotomy (Campfield et al., 1983). These symptoms are also observed in the patients of diabetes having gastrointestinal tract disorders (Niakan et al., 1986). The body weight of these rats did not show much alteration. AChE activity, an indicator of the cholinergic supply, showed a decline confirming the success of vagotomy. The glycemic state was highly elevated. The increase in glucose concentration could be mainly due to a reduction in insulin secretion after vagotomy, as shown by Wasserman (1989) and Yadav (1997), and also be partly attributed to the enhanced sympathetic activity that might have succeeded the elimination of the parasympathetic system. The major physiological function of insulin is to prevent hyperglycemia. This is accomplished by inhibiting glucose release and stimulating the peripheral utilization of glucose, the most potent stimulus for insulin secretion being a rise in
blood glucose (Grodsky, 1970). Parasympathetic input stimulates and sympathetic influence inhibits insulin secretion (Porte and Robertson, 1973). When the renal profile was observed, the metabolic trend seemed to have an inclination towards a catabolic state, as reflected by the decrease in the storage metabolites of the kidney, viz. glycogen, lipids and also protein. The enzymes involved in the breakdown showed an enhanced activity, indicating the operation of glycogenolysis and gluconeogenesis, viz. Phosphorylase, G-6-Pase, LDH and SDH. Gluconeogenesis has the major function of preventing the level of blood glucose from falling below normal. The availability of blood glucose is essential for the efficient functioning of tissues such as brain that depend exclusively on it for energy supply. Because ingested carbohydrate is not continuously available and because carbohydrate is an inefficient form of fuel and thus stored only in small amounts (Cahill, 1970), gluconeogenesis is an often used metabolic pathway. However when gluconeogenesis is accelerated to produce more glucose than necessary, it contributes to the pathological state in some diseases, most notably diabetes. Physiological changes in plasma glucagon have been shown to alter hepatic glucose production via changes in both glycogenolysis and gluconeogenesis (Cucchiaro et al., 1990). Glucagon administration rapidly increases the blood glucose concentration (Ercan et al., 1995). An elevation in glucagon level after the removal of the parasympathetic tone could be the reason for the present state of the enzyme activities. The transaminases also showed a high activity. It is well known that insulin deficiency is accompanied by negative nitrogen balance and protein wasting. It has been demonstrated that insulin promotes protein synthesis (Pain et al., 1974). Studies in the postabsorptive state in normal man demonstrated that insulin inhibits amino acid release from forearm tissue (Pozefsky et al., 1969), together these data suggested that insulin exerts its anabolic action by reducing proteolysis and increasing protein synthesis (Nair et al., 1987). Glycogenesis, lipogenesis decreased, as could be seen from reduced activity of glycogen synthase. The enzymes involved in uptake of glucose such as alkaline phosphatase, decreased, whereas the lysosomal acid phosphatase decreased. Na⁺-K⁺-ATPase activity increased. These parameters reflected a catabolic profile, however, the renal weight was seen to rise. The reason for this could be the beginning of hypertrophy of the renal tissue which is also observed in diabetes leading to impaired functioning (Sochor et al., 1986; Ku et al., 1987). Hormonal measurements showed increased glucocorticoid corticosterone (Chapter 6) and GH (Chapter 7) levels. These two hormones have catabolic functions and have been implicated in the errant metabolism in the pathology of diabetes. Goldstein et al. (1995) have demonstrated that cortisol affects gluconeogenesis by increasing
the supply of gluconeogenic precursors. GH has antiinsulin activities, which result in hyperglycemia, increased lipolysis and decreased glucose metabolism (Goodman and Schwartz, 1974; Davidson, 1987). Vagotomy caused a decrease in the concentration of ACTH. This could be through the negative feedback signal due to increased corticosterone level after vagotomy.

When adrenalectomy was carried out in rats, a reversal of the state observed in vagotomy was manifested. A hypoglycemic condition was present in these rats. Body weight of these rats was reduced. Renal weight was also reduced, with a decline in water content of the tissue, which can be attributed to the loss of aldosterone due to adrenalectomy (El Mernissi and Doucet, 1987). The metabolites however showed an anabolic trend. With increased deposits of glycogen, lipid and protein. Glycogenesis and lipogenesis were enhanced whereas, glycogenolysis, gluconeogenesis, proteolysis were curbed, as manifested by the reduced state of enzymic activities in the kidney. Here in this condition an increased insulin (Yadav, 1997) and decreased corticosterone (Chapter 6), GH (Chapter 7), and decreased adrenal medullary catecholamines due to adrenalectomy, could be the causative factors for this. E-stimulated glucose production under physiological conditions is associated with inhibition of insulin secretion (Porte et al., 1966) and decreased peripheral glucose utilization (Sacca et al., 1977). Moreover, epinephrine stimulates the secretion of glucagon (Gerich et al., 1973). The hyperglycemic effect of E is thereby amplified. Catecholamines have a catabolic effect on protein metabolism (Connolly et al., 1991). The renal metabolism of this state can be attributed to the loss of the adrenal hormones, both medullary and cortical, and also enhanced secretion of insulin and lowered GH. The lowered GH level could be due to the absence of the potentiating action that the glucocorticoids have on GH release (Casaneuera et al., 1990). ACTH concentration showed an increase in the adrenalectomized animals. Removal of the adrenal cortex, and the resulting fall of the plasma cortisol level would alleviate the suppressive effect of cortisol on the ACTH secretion, which becomes enhanced, and is detected in the peripheral blood in excess.

To find out if adrenalectomy would check the glycemic elevation found in the case of vagotomized (VGX) rats, adrenalectomy (ADX) was performed in VGX rats. It was observed that the hyperglycemia was arrested to a certain degree by performing this operation. The gluconeogenic pathway had a low rate of operation, G-6-Pase and LDH did
not rise very significantly, the transamination from alanine was checked, and lipolysis was also not as high as in VGX. Thus, it was seen that these pathways could be manipulated by adrenalectomy, mainly influenced by the changing hormonal profile. Corticosterone level was also reduced in this condition (Chapter 6), with the expected increase occurring in ACTH level. CA loss due to adrenal ablation affects the metabolism. GH showed a minor increase in this condition (Chapter 7). Whereas insulin stimulates glucose utilization and fat synthesis in adipose tissue, catecholamines promote lipolysis both in vivo and in vitro (Vernon & Clegg, 1985). Though a decrease in insulin level would curtail the process of glucose utilization, loss of the adrenal catecholamines, glucocorticoids and a reduced level of GH, would check lipolysis and, on the whole, this would result in lessening the degree of the hyperglycemia produced by performing vagotomy. Roth et al. (1963a,b) have reported that catecholamines exert a positive control on GH, that is, they stimulate its release. The low level of GH could be because of the decreased CA level, in turn helping to lower the glycemia.

The physiological significance of the neurally mediated glucose output is that it provides a rapid supply of glucose to the circulation under emergency situations. If this phenomenon exceeds the demand of the body, it would lead to hyperglycemia. This could be checked by inhibiting the production by performing sympathectomy. To find out the effect of sympathetic denervation, chemical sympathectomy was performed in rats by injecting guanethidine, an antiadrenergic drug. Guanethidine is a guanidinium adrenergic neuron blocking agent which destroys peripheral sympathetic neurons without affecting the cholinergic system (Burnstock et al., 1971; Eranko and Eranko., 1972; Angeletti et al., 1972). It has a definite advantage of complete sympathectomy, over 6-hydroxy dopamine, another adrenergic blocker that leaves the neuron cell bodies intact. Guanethidine administration causes catecholamine depletion (Zochodne et al., 1988; Lo et al., 1991) and also inhibits glucocorticoid secretion (Kleitman and Holzwarth, 1985b). The kidney thus loses its sympathetic control. An increased weight of the kidney was observed. The anabolic pathways seemed to be activated, the catabolic ones being curbed, favoring the hypoglycemic condition found in these rats. The result was that glycogen, lipid and protein content of the renal tissue increased. The enzymes involved in uptake and deposition such as alkaline phosphatase and glycogen synthase showed an increased activity, whereas breakdown enzymes such as phosphorylase showed reduced activity, as did gluconeogenic enzymes such
as G-6-Pase and transaminases. SDH activity was also reduced, indicating a decrease in the oxidative metabolism of the renal tissue. Also insulin increased in this treatment (Yadav, 1997), corticosterone level decreased (Chapter 6), GH concentration decreased (Chapter 7), CA decreased (Zochodne et al., 1988; Lo et al., 1991). CA have a stimulatory effect on GH secretion (Krieg et al., 1986), which would be abolished because of chemical sympathectomy, leading to reduced level of this hormone. Also direct sympathetic innervation of the kidney is eliminated, causing reduced breakdown. The stimulatory effect of catecholamines on the activity of hepatic glycogen phosphorylase and the consecutive glycogenolysis is a well known phenomenon in mammals (Sutherland and Cori, 1951). Bloom and Edwards (1975) reported that electrical stimulation of the splanchnic nerve enhanced secretion of glucagon and inhibited the secretion of insulin, independent of the adrenal gland. Secondly the stimulation to the organ directly by means of innervation would result in enhancing phosphorylase activity or gluconeogenesis in the tissue. A significant rise was observed in the ACTH secretion. Removal of the sympathetic system would leave only the ACTH to regulate glucocorticoid release. The decrease in the corticosterone might have induced the rise in the level of the trophic hormone.

To explore the possibility of these changes helping to reduce the hyperglycemia caused by vagotomy, chemical sympathectomy and vagotomy were performed in combination. The hyperglycemia caused by vagotomy was lowered due to sympathetic system inhibition. Renal metabolism however did not show a profile indicating a total anabolic state. Glycogen and lipid deposition both decreased, protein breakdown and transamination was however checked. There was only a small increase in glycogenolysis and gluconeogenesis. It seems that gluconeogenesis from protein precursors was restrained. Thus the effect of VGX was only partially counteracted when sympathectomy and vagotomy were both performed together. Here, the hormonal profile showed increased corticosterone and also increased ACTH (Chapter 6), GH (Chapter 7) and a decrease in insulin (Yadav, 1997). Thus the effects of these alterations seem to have been manifested by the metabolic pathways involved in glycogen deposition and breakdown, lipolysis, proteolysis and in turn gluconeogenesis.

When both CX and ADX were performed together, a very significant hypoglycemia was obtained. Glycogenesis increased in the kidney, whereas glycogenolysis was checked.
Both lipid and protein increased, gluconeogenesis decreased. Glucose uptake was increased. Insulin showed an increased level (Yadav, 1997) and corticosterone decreased leading to the expected rise in ACTH (Chapter 6). GH (Chapter 7) and CA (Zochodne et al., 1988; Lo et al., 1991), both decreased. The very significantly low level of GH could be due to the removal of both catecholamines and corticosteroids, both of which have a stimulatory effect on GH release (Krieg et al., 1986; Casaneuva et al., 1990) causing a shift in the metabolic trend from catabolism to anabolism. Thus, removal of both, the sympathetic innervation to the kidney and also humoral CA and adrenal steroids aided by decrease in GH can all be important factors in eliciting control on the glycemic state.

From the present study, it can be inferred that the exquisite control of biological events by the nervous system and the hormones depends on the quantitative relationship among the individual elements of the system, namely the parasympathetic and sympathetic nervous systems, and the adrenal glands, the pancreas and the anterior pituitary. The neuroendocrine responses to a variety of noxious influences are generally characterized by the stimulation of sympathetic neurons and the release of hormones which tend to elevate plasma glucose. In pathophysiological condition, increased counterregulatory hormone release usually occurs without stress or exercise, and it is this state that is associated with hyperglycemia and carbohydrate intolerance. The enhanced sympathetic nerve activity along with inhibition of parasympathetic activity with a consequent insulin deficiency, and the elevated levels of the hormones such as catecholamines, glucocorticoids and growth hormone, which have been implicated in creating and aggravating the clinical state of diabetes mellitus can be brought under control by manipulating their activities and secretion. It is substantiated by the changes observed in the metabolic pathways of the tissue that the kidney is involved in glucoregulation, and that it responds to the need of the body for glucose. Because of its contribution to glucose production, it might be implicated in the excessive glucose production, and in turn hyperglycemia of the pathogenesis of diabetes.