All vertebrates in general and mammals in particular possess multiple neural, behavioral and endocrine mechanisms to ensure that glucose levels do not fall below a critical level or that glucose is restored in the event of hypoglycemia (Widmaier, 1990). In states of metabolic perturbations, these mechanisms are affected, and a defective response to glycemic conditions is ensued. Neural connections and actions are required to sense the glucose level, sensitize the tissues for hormonal actions and also prime the tissues for direct enzymic responses. The major modulator of metabolic homeostasis in the body is the autonomic nervous system (ANS). This is accomplished in two ways: Firstly by direct innervation of the tissues by the components that produce or consume glucose and secondly by innervation of the endocrine glands that execute the metabolic functions by their hormonal secretions.

The parasympathetic function is anatomically carried out by the vagus which originates in the medulla oblongata. It innervates the kidney after synapsing at the celiac ganglion. The neurotransmitter in the parasympathetic element of the ANS is acetyl choline (ACh), which is degraded by the enzyme acetyl cholinesterase (AChE), also found in the nerve endings. Histochemical techniques have revealed AChE positive fibers in mammalian kidneys (Barajas et al., 1976). The stimulation of vagus enhances glucose storage. This is done by augmenting glycogenesis and inhibiting glycogenolysis. It also modulates glucose metabolism through its innervation to the endocrine gland of utmost importance in blood sugar regulation- the pancreas. AChE positive nerves in goat, and muscarinic AChR in rat (Van Der Zee et al., 1992) have been localized in endocrine pancreas. Numerous
experimental investigators have demonstrated that electrical stimulation of vagus or application of ACh results in modification of hormone release from endocrine pancreas (Campfield et al., 1983) and stimulation of the cervical vagus in the dog elicited a prompt rise in insulin secretion (Frohman et al., 1967). The higher center of vagal control is the lateral hypothalamic area (LHA) in the CNS. It is this center which is the highest seat of parasympathetic control.

An alternate control of insulin and glucagon levels is via direct action of the autonomic nerves (Woods and Porte, 1974). Parasympathetic effects on the pancreas result in elevated glucose induced insulin secretion and decreased glucagon secretion (Girardier et al., 1976). Control of total body glucose utilization being multifactorial, is dependent on the amount of insulin secreted by the pancreatic B cells in response to glucose and on the effectiveness of secreted insulin in promoting glucose disposal (insulin sensitivity) (Bergman, 1989). In addition, glucose disposal is promoted by the mass action effect of glucose, independent of insulin (glucose mediated glucose disposal) (Gottesman et al., 1984).

The other set of hormones regulating the glucose homeostasis are the adrenal hormones- the catecholamines and the glucocorticoids. These hormones activate the enzymic pathways involved in glucose mobilization from glycogen stores by glycogenolysis and formation of new glucose from noncarbohydrate sources through gluconeogenesis. The control over the secretion of the adrenal also involves the ANS. Celler and Schramm (1981) provided the physiological evidence for post ganglionic fibers running in the splanchnic nerves to the rat adrenal medulla. In addition to this, the adrenal cortex of adult rats receives autonomic innervation from the medulla and from the nerves outside the adrenal gland (Vinson et al., 1994).

NE is a strong inhibitor of glucose stimulated insulin secretion (Varr and Tamarit-Rodriguez, 1991) and E is able to virtually obliterate the glucose uptake response to insulin (Capaldo, 1992). In response to insulin hypoglycemia, there is a rise in adrenal CA and pancreatic glucagon secretions, both of which are significantly implicated in glucoregulatory mechanisms (Yamaguchi, 1992) Zhang et al. (1995) have shown that both E and NE inhibit ACh release in a concentration dependent manner. The adrenal cortical hormones are also involved in glucose metabolism. They enhance glucose mobilization from both carbohydrate
and non-carbohydrate sources (Munck et al., 1984), and in turn favour hyperglycemia. In diabetic condition, apart from the impaired glucose disposal resulting from inulin insufficiency, there is an added problem of maintaining good glycemic control during stress situations, when the increased stress hormone levels adversely affect glucose utilization. Elevation in serum E is associated with increased fasting blood glucose and impaired glucose utilization in patients with established insulin dependent diabetes mellitus (IDDM) (Shamoon et al., 1980). The mechanisms involved include increased hepatic glucose production that is more marked than in normal subjects (Sacca et al., 1980) and decreased glucose uptake (Deibert and DeFronzo, 1980).

Though liver is considered to be the major source of blood glucose, there is a report of a significant contribution of kidney to glucose metabolism. Thus, in addition to its conventional excretory role, it is actively involved in glucose production. The kidney cortex is able to produce glucose because it contains the gluconeogenic enzyme Glucose-6-Phosphatase, a feature it shares with the liver, and thus plays an important role in glucose homeostasis (Mithieux et al., 1990). This has been demonstrated in dogs fasted overnight (Cersosimo et al., 1994; Ekberg et al., 1996). Minassian and Mithieux (1994) have shown that in the fed state, the renal gluconeogenesis provides only 5-10 % of total endogenous glucose production. After prolonged fasting, the kidney and the liver contribute almost equally to the endogenous glucose production, liver contributed approximately 55 % and the kidney 45 % of the total glucose output (Owen et al., 1969). Moreover, because of its capacity to produce glucose, the kidney is thought to contribute to the hyperglycemia of diabetes. G-6-Pase activity has been reported to increase slightly in STZ diabetic rats (about 50 %/g tissue) (Kang et al., 1982). Since long, nephropathy has been reported to be a serious complication of both Type I and Type II diabetes (Kussman et al., 1976). Well recognized renal functional and ultrastructural changes in man and experimental animals (Osterby, 1974; Mongensen, 1976) have been shown in animals made diabetic by alloxan and streptozotocin (STZ). It could be postulated that structural and functional changes would go hand in hand with alterations in the normal disposition of metabolic pathways.

The disturbances in metabolic pathways could be because of dysfunction of the neuroendocrine machinery. The endocrine secretions of the pancreas and the adrenal represent one of the most important integrated system for the control of metabolism in the
body. It is not the isolated effect of either of them, but rather the interplay and balance between the hormones of the pancreas and the adrenal. This chapter incorporates the results of an attempt that has been made to gain more knowledge on the effect of autonomic dysfunction on the enzymic pathways through which glucose level is maintained in a perfect homeostatic condition so essential for life. Various metabolic pathways in the kidney have been studied to find out the manner in which the kidney responds to the homeostatic need of the body. The parasympathetic constituent of the ANS was removed by performing subdiaphragmatic vagotommy. Adrenal, the gland responsible for most of the catecholamine secretion was eliminated surgically by performing adrenalectomy, and in yet another set, these two surgeries were executed in combination to observe the eventual effect that develops on the carbohydrate metabolism when both these governing factors are eliminated either alone or in combination.

MATERIAL AND METHODS
Male albino rats (*Rattus norvegicus albinus*) of Charles Foster strain weighing around 150-200 gm were used for the study. The animals were acclimatized at standard laboratory conditions with food and water *ad libitum*. They were divided into various groups and were subjected to different surgical operations:

I  VAGOTOMY (VGX)  
   SHAM VAGOTOMY (VGS)

II  ADRENALECTOMY (ADX)  
    SHAM ADRENALECTOMY (ADS)

III VAGOTOMY + ADRENALECTOMY (VGX + ADX)  
   SHAM VAGOTOMY + SHAM ADRENALECTOMY (VGS + ADS)

Overnight fasted animals of both experimental and control groups were sacrificed 48 hrs after the operations. Blood was collected from the jugular vein and the serum was used for estimating glucose. The kidney was excised, blotted free of blood and used for preparing various homogenates to carry out the various estimations:
Glucose level was estimated in serum by glucose oxidase method and expressed as mg/dl blood. Glycogen content of the kidney was estimated by the method of Seifter et al. (1950) and expressed as mg/100 mg tissue. Glycogen synthase activity was determined in the kidney by the method of Leloir and Goldemberg (1962) and expressed as μmol UDP formed/mg/protein/10 min. The activities of glycogen phosphorylase and glucose-6-phosphatase were estimated by the methods of Cahill et al. (1957) and Harper (1963) respectively and expressed as μmol phosphate released/mg protein/15 min. The activity of lactate dehydrogenase was measured in the kidney by the method of King (1971) as described by Varley (1980) and expressed as μmol lactate oxidized/mg protein/15 min. Succinate dehydrogenase activity was estimated by the method of Nachlas et al. (1959) and expressed as μg formazan formed/mg protein/60 min. Lipid was estimated by the method of Folch et al. (1957) and expressed as mg/100 mg non fat dry tissue. Acetyl cholinesterase activity was estimated using the method of Ellman et al. (1961) and expressed as μmol acetyl thiocholine iodide hydrolyzed/mg protein/min.

Statistical analysis:
Data were analyzed using Student's t-test to determine the significance. The level of significance was considered to be p < 0.05.

RESULTS (Tables 2.1, 2.2; Figures 2.1 through 2.6)
Serum glucose levels have been shown in Fig. 2.1A. In the vagotomized rats, a 62% increase was observed in the blood glucose level, whereas, the ADX rats were hypoglycemic, with a 26% reduction (p < 0.01). In the VGX + ADX rats, a hyperglycemia of considerable lesser magnitude (22%) was noticed.

Glycogen content of the kidney after vagotomy was depleted markedly, being 50% of the control animals, contrarily, ADX rats showed a 26% increase in renal glycogen content (p < 0.01). The VGX + ADX rats also showed a reduced (p < 0.01) glycogen content, but this decrease was of lesser degree (33%) than in the VGX rats.

Glycogen synthase, the enzyme involved in glycogen production showed a 50% decreased activity (p < 0.001) in the kidney of vagotomized rats. In contrast a rise of 33%
Table 2.1 Serum glucose, renal metabolites, and enzymes of carbohydrate metabolism and acetyl cholinesterase in rats subjected to vagotomy, adrenalectomy and vagotomy in combination with adrenalectomy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vagotomy</th>
<th>Adrenalectomy</th>
<th>Vagotomy + Adrenalectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham</td>
<td>Experimental</td>
<td>Sham</td>
</tr>
<tr>
<td>Glucose (mg/dl Serum)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>134.68±10.92</td>
<td>218.06±11.38</td>
<td>129.63±6.64</td>
</tr>
<tr>
<td>Glycogen (mg/100 mg Wet Tissue)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.04±0.002</td>
<td>0.02±0.002</td>
<td>0.054±0.002</td>
</tr>
<tr>
<td>Glycogen Synthase (µM UDP/mg Protein/10 Min.)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.02±0.001</td>
<td>0.01±0.002</td>
<td>0.030±0.002</td>
</tr>
<tr>
<td>Glycogen Phosphorylase (µM P released/mg Protein/10 Min.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90.29±3.13</td>
<td>116.29±5.74</td>
<td>97.87±4.22</td>
</tr>
<tr>
<td>Glucose-6-Phosphatase (µM PO₄ released/mg Protein/15 Min.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.39±0.023</td>
<td>0.55±0.024</td>
<td>0.37±0.020</td>
</tr>
<tr>
<td>Lactate Dehydrogenase (µM Lactate oxidized/mg Protein/15 Min.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>106.36±4.52</td>
<td>128.31±4.46</td>
<td>113.12±4.12</td>
</tr>
<tr>
<td>Succinate Dehydrogenase (µg Formazan formed/mg Protein/60 Min.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38.83±2.00</td>
<td>47.04±1.35</td>
<td>31.94±1.96</td>
</tr>
<tr>
<td>Lipid (mg/100 mg Non Fat Dry Tissue)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.23±0.22</td>
<td>3.41±0.17</td>
<td>4.149±0.20</td>
</tr>
<tr>
<td>Acetyl Cholinesterase (ACCh hydrolyzed/mg Protein/Min.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.04±0.002</td>
<td>0.014±0.001</td>
<td>0.039±0.002</td>
</tr>
</tbody>
</table>

* Values are expressed as mean ± SEM of 6 experiments; °p<0.05; ***p<0.02; ****p<0.01; *****p<0.001; NS Non Significant. " Values adopted from Yadav (1997).
Table 2.2  Percentage change (compared to controls) in serum glucose, renal metabolites, and enzymes of carbohydrate metabolism and acetyl cholinesterase in rats subjected to vagotomy, adrenalectomy and vagotomy in combination with adrenalectomy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vagotomy</th>
<th>Adrenalectomy</th>
<th>Vagotomy + Adrenalectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl Serum)</td>
<td>62*****</td>
<td>26***</td>
<td>22**</td>
</tr>
<tr>
<td>Glycogen (mg/100 mg Wet Tissue)</td>
<td>50****</td>
<td>26***</td>
<td>33***</td>
</tr>
<tr>
<td>Glycogen Synthase (μM UDP/mg Protein/10 Min.)</td>
<td>50****</td>
<td>33***</td>
<td>19*</td>
</tr>
<tr>
<td>Glycogen Phosphorylase (μM P released/mg Protein/10 Min.)</td>
<td>29***</td>
<td>15**</td>
<td>23**</td>
</tr>
<tr>
<td>Glucose-6-Phosphatase (μM P04 released/mg Protein/15 Min.)</td>
<td>41***</td>
<td>22**</td>
<td>27**</td>
</tr>
<tr>
<td>Lactate Dehydrogenase (μM Lactate oxidized/mg Protein/15 Min.)</td>
<td>21***</td>
<td>9*</td>
<td>4 NS</td>
</tr>
<tr>
<td>Succinate Dehydrogenase (μg Formazan formed/mg Protein/60 Min.)</td>
<td>21***</td>
<td>33***</td>
<td>19**</td>
</tr>
<tr>
<td>Lipid (mg/100 mg Non Fat Dry Tissue)</td>
<td>19**</td>
<td>20**</td>
<td>16*</td>
</tr>
<tr>
<td>Acetyl Cholinesterase (AChI hydrolyzed/mg Protein/Min.)</td>
<td>65*****</td>
<td>28**</td>
<td>56*****</td>
</tr>
</tbody>
</table>

*Values corrected to nearest whole number; * p< 0.05; ** p< 0.02; *** p< 0.01; **** p< 0.001; NS Non Significant.
® Values adopted from Yadav (1997)
Figure 2.1 Levels of serum glucose and renal glycogen in rats subjected to vagotomy (VGX), adrenalectomy (ADX) and their combination (VGX + ADX).

(A) Glucose levels

(B) Glycogen levels

** p < 0.02; *** p < 0.01; **** p < 0.001
Figure 2.2 Activities of Glycogen Synthase and Glycogen Phosphorylase in the kidney of rats subjected to vagotomy (VGX), adrenalectomy (ADX) and their combination (VGX + ADX).

(A) µM PO released/mg Protein/15 Min. µM UDP/mg Protein/10 Min.

(B) µM PO$_4$ released/mg Protein/15 Min.

* p < 0.05; ** p < 0.02; *** p < 0.01; **** p < 0.001
Figure 2.3 Activities of Glucose-6-Phosphatase and Lactate Dehydrogenase in the kidney of rats subjected to vagotomy (VGX), adrenalectomy (ADX) and their combination (VGX + ADX)

(A)

- Glucose-6-Phosphatase

(B)

- Lactate Dehydrogenase

* p < 0.05; ** p < 0.02; *** p < 0.01; NS Non Significant
Figure 2.4 Activity of Succinate Dehydrogenase and Total Lipid Content in the kidney of rats subjected to vagotomy (VGX), adrenalectomy (ADX) and their combination (VGX + ADX)
Figure 2.5 Activity of Acetyl Cholinesterase in the kidney of rats subjected to vagotomy (VGX), adrenalectomy (ADX) and their combination (VGX + ADX).

** p < 0.02; **** p < 0.001.
Figure 2.6 Percentage change in levels of serum glucose*, renal metabolites, and activities of key enzymes of carbohydrate metabolism and acetyl cholinesterase in the kidney of rats subjected to vagotomy (A), adrenalectomy (B) and their combination (C).

Values adopted from Yadav (1997).

* Values adopted from Yadav (1997).
was observed in the rats operated on for adrenalectomy. VGX + ADX rats showed a slight reduction (19%) in the activity of this enzyme.

Glycogen phosphorylase activity in the vagotomized rats was considerably elevated, being 29% more than the sham operated controls. ADX rats however manifested a 15% reduced activity (p < 0.02) of this enzyme. In the VGX + ADX rats a 23% increase (p < 0.02) was observed in the activity.

G-6-Pase, the culminating enzyme of both gluconeogenic and glycogenolytic pathway increased notably (p < 0.01) in the VGX rats, the rise being 41%, whereas ADX rats showed a 22% reduction in its activity (p < 0.02). VGX + ADX rats however showed a 27% rise in the activity of this enzyme (p < 0.02).

Lactate dehydrogenase activity increased both in the kidney of vagotomized rats (21%) and of adrenalectomized rats (9%). The VGX + ADX rats however manifested no change in the activity of this enzyme.

SDH activity after vagotomy increased by 21% in the kidney, unlike in the adrenalectomized rats, where it decreased (33%). In the VGX + ADX rats again a small decline (19%) was noted in the activity of this enzyme.

The lipid content of the kidney depleted by 19% after vagotomy. Adrenalectomized rats in contrast showed a 20% rise in the renal lipid content. VGX + ADX rats showed a 16% reduction in the lipid content of the kidney.

AChE, the marker enzyme for parasympathetic activity manifested a sharp reduction after both vagotomy (65%) and VGX + ADX (56%). In the adrenalectomized rats, a 28% increase in the activity of this enzyme was observed.

**DISCUSSION**

In the present study, when the neural connections were severed as in the case of VGX rats, an increase was observed in blood glucose level. Blood glucose concentration is maintained by the insulin, and the parasympathetic nervous system has an important influence on insulin
secretion. The parasympathetic influence is anatomically exerted by the vagus, and hence, its absence leads to delayed insulin secretion (Trimble et al., 1981). Vagotomy leads to the elimination of the cholinergic innervation to the B cells of the pancreatic islets, leading to loss of insulin secretion (Yadav, 1997), in turn causing an increase in the blood glucose level that is observed in the present situation. In a normal physiological condition, an increase in blood glucose is the main signal for insulin secretion by pancreatic B cells (Taylor and Agius, 1988; Unger, 1991). However, the glucose sensing apparatus, which modulates insulin secretion in response to changes in circulating glucose concentration is inoperative in IDDM. Moreover, during diabetes, the A cells of the pancreatic islets secrete glucagon as a response to falling insulin levels (Unger and Orci, 1983; McGarry et al., 1989). The rise in the glucagon/insulin ratio leads to metabolic alterations (Taylor and Agius, 1988). Vagotomy, a condition in which diabetes is simulated by removing the cholinergic innervation to the pancreatic B cells, shows a similar state of metabolic operation. Thus, the increase in glucose concentration could in part be due to a reduction in insulin secretion, as has been shown by Wasserman et al. (1989b) and partly be attributed to the enhanced sympathetic activity that could have ensued after the elimination of parasympathetic system, causing glycogenolysis and lipolysis.

The ADX rats manifested a significant hypoglycemia. The adrenal gland hormones, both medullary and cortical, help in counterregulating the hypoglycemia. The CA mediate hyperglycemia by means of their positive releasing effects on the pancreatic glucagon and adrenal glucocorticoids, which aid in mobilizing glucose from the glycogen stores. Adrenergic mechanisms are known to affect insulin secretion with E, which has long been categorized as a hyperglycemic response (Ansari and Gupta, 1994). NE is a strong inhibitor of glucose stimulated insulin secretion (Vara and Tamarit-Rodriguez, 1991).

In the animals with VGX + ADX, a hyperglycemia was observed. However, this hyperglycemia was not as significant as observed in VGX rats. This indicates that adrenalectomy in vagotomized rats does partially counteract the vagal dysfunction and thereby reduce the degree of hyperglycemia.

The varying glycemic states in these experiments are intricately related to the metabolic machinery of the tissues. This can be determined by examining glycogen
metabolism through the activities of the enzymes involved. Glycogen phosphorylase and glycogen synthase are the two key regulatory enzymes that catalyze the rate-limiting steps of glycogen degradation and synthesis respectively.

In the kidney of vagotomized rats, a decrease was observed in glycogen content and the activity of glycogen synthase, indicating decreased rate of production of glycogen. Shimazu (1983) has shown in liver that the activity of the rate limiting enzyme glycogen synthase involved in converting glucose-6-phosphate to glycogen was greatly increased by electrical stimulation of the peripheral end of the vagus. Acute vagotomy in rats diminishes the rate of hepatic glycogen deposition after glucose load (Mondon and Burton, 1971).

The balance between levels of insulin and glucagon is vital for metabolic homeostasis (Abrahamsen and Nishimura, 1995). Insulin is involved in both the acute and the chronic regulation of glycogen synthase and phosphorylase, the key regulatory enzymes of glycogen metabolism. High level of insulin, which provokes dephosphorylation and activation of glycogen synthase and/or G6P, the allosteric activator of glycogen synthase (Larner, 1990) may cause the activation of the enzyme activity. Lack of insulin would therefore lead to a decrease in the activity of this enzyme. Diabetes on the other hand has been shown to cause a decrease in the active form of the glycogen synthase (Valera et al., 1994) and an increase in both the active and total activities of phosphorylase (Venkatarao et al., 1995).

In ADX rats, an increase was observed in the activity of glycogen synthase. The adrenal hormones, both medullary and cortical, have actions opposing insulin. Catecholamines cause a significant reduction in plasma insulin levels (Porte and Wood, 1990). The elimination of these hormones by means of adrenalectomy might have led to the activation of glycogen synthesis by increasing the activity of glycogen synthase. This is established in the present study by the increase observed in the glycogen content of the tissue. Glycogen phosphorylase manifested a decline in the activity. Insulin causes a decrease in the total activity of phosphorylase (Lavoie and Van de Werve, 1991), while epinephrine activates the release of Ca++ and increased cAMP, which in turn leads to the phosphorylation and activation of glycogen phosphorylase by phosphorylase kinase (Newgaard et al., 1984). It has been recently shown that E inhibits insulin stimulated glycogenesis through inactivation of glycogen synthase and activation of phosphorylase (Raz et al., 1991). The diabetic condition that leads
to decreased circulating insulin levels would also result in significant increase in glucagon levels (Lavoie and Van de Werve, 1991). Thus, another explanation for the elevated blood glucose concentration would be that the elevated sympathetic tone after vagotomy would result in glucagon secretion causing a decreased glucose utilization rate.

The animals with VGX+ADX, the amount of glycogen deposition was reduced and a decrease was observed in the activity of glycogen synthase. This decrease was however, not as significant as in the ADX animals. The effect of vagotomy was not overshadowed by adrenalectomy in this group.

In the VGX animals, an enhanced activity of G-6-Pase was observed. An acceleration in the rate of gluconeogenesis can be inferred. Increased rates of gluconeogenesis usually occur when there are low circulating levels of insulin (Davis et al., 1995). In underinsulinized diabetic individuals, unrestrained gluconeogenesis contributes significantly to the elevated fasting hyperglycemia (Wahren et al., 1972). Massillon et al. (1996) have confirmed that prolonged insulin deficiency and hyperglycemia cause a marked increase in the hepatic G6Pase mRNA and increased activity, the increase correlating with the plasma glucose concentration in these animals. VGX lowers the insulin levels (Yadav, 1997). Therefore an increase in the activity of this enzyme is justified. Moreover, increased glucocorticoids (Chapter 6) and GH (Chapter 7) which are involved in enhancing gluconeogenesis (Munck et al., 1984), are seen to rise in this condition. Insulin infusion has been reported to reduce the activity of this enzyme (Kang et al., 1982).

In ADX animals, a decrease was seen in the activity of G-6-Pase, but it is not as significant as the decrease of glycogen phosphorylase. Ercan et al. (1995) have shown that gluconeogenesis is more important than glycogenolysis in supporting the plasma glucose concentration in the presence of an excessive insulin concentration. In the ADX + VGX animals also a small increase was observed. It appears that the effect of vagotomy over gluconeogenesis is more pronounced, because adrenalectomy is not able to check the activity of this enzyme. Nevertheless, the significance of the increment in the activity of this enzyme is considerably less than it is in vagotomy.
In the VGX rats, LDH activity is seen to increase. Sochor et al. (1986) have reported that STZ diabetic rats showed increased LDH activity in the kidney cortex. Glycogenolytic increase would be associated with a coincident rise in lactate production. This could enhance the operation of gluconeogenic cycle. Diabetic hepatocytes have been known to recycle a greater proportion of glycolytically derived pyruvate to glucose (Henley et al., 1996). One effect of vagotomy, therefore might be a channelizing of pyruvate into mitochondria. In the ADX condition also, LDH activity showed an increase, but no gluconeogenesis was observed, probably because lactate was not taken up, it did not contribute to gluconeogenic glucose production in either group (Abrahamsen and Nishimura, 1995). In the ADX + VGX rats the LDH activity showed a rise which was not very significant, indicating that lactate was not used as gluconeogenic precursor.

In the present study, SDH showed an increased activity in the kidney after vagotomy. Verma and Pilo (1987) have shown that SDH, a key enzyme of Krebs cycle showed an increased activity after 48 hrs of vagotomy. For gluconeogenesis to be in operation, adequate tissue oxygenation is essential (Krebs, 1963). In VGX rats, an increased sympathetic tone could be generated, which could activate glucagon secretion. An increased activity of SDH in tissues of diabetic rats has been reported (Nayeemunisha and Venkateshaprasad, 1978). Increased SDH activity in the absence of rapid glucose uptake denotes enhanced lipolysis in the initial stages, when the sympathetic tone remains high in the absence of parasympathetic influence. This is reflected in the decreased lipid content of the kidney after vagotomy. In the ADX rats, a decrease is observed in the activity of SDH. The lipid content of the tissue also increased significantly. Loss of catecholamines after adrenalectomy can be presumed to be the reason for this phenomenon, because, norepinephrine is known to stimulate SDH activity in kidney, heart and liver. (Shivaramakrishnan and Ramasarma, 1982). Moreover, catecholamines cause lipolysis (DeBodo and Altszuler, 1958). After adrenalectomy, catecholamine action would be reduced, therefore leading to the decreased lipolysis and hence there is an increase in the lipid content of the kidney. In the rats with VGX + ADX also a decrease was observed in the activity of this enzyme, but this change was not of an equal magnitude as in the ADX animals. The lipid content in the kidney decreased, but not as significantly as in the VGX rats. Loss of vagal fibers, along with adrenal gland could be the reason that the shift in the activity pattern of this enzyme and the lipid content is not compensated.
In VGX rats, AChE activity was observed to decrease significantly. Intact vagal innervation is necessary for maintenance of ACh sensitivity (Campfield et al., 1983). ACh secretion would decrease because of the interrupted discharge of the cholinergic fibers, and hence a decreased AChE activity was only expected. In the ADX rats, an increase was observed in the activity of AChE. As the vagal fibers remain functional and the loss of adrenergic tone would lead to an elevated cholinergic tone which is indicated by the increased activity of AChE. Zhang et al. (1995) have shown that both epinephrine and norepinephrine inhibit ACh release in a concentration dependent manner. Therefore, an elimination of the vagal cholinergic tone could be the reason for the elevated activity of this enzyme. In the rats with ADX + VGX, there was a decrease in the activity of this enzyme. Absence of catecholamines was accompanied by the inactivation of cholinergic fibers, the activity of AChE thus registering a decrease in this situation.

To summarize, the hyperglycemia occurring in the vagotomized rats can be attributed to the increased operation of glycogenolytic and gluconeogenic pathways, whereas the hypoglycemic condition after adrenalectomy was a consequence of suppression of these pathways, with an enhancement of the glycogenesis and lipogenesis in the renal tissue. When both these conditions were created in the animals together, the hyperglycemia caused due to vagotomy could be brought under control, with glycogenesis being reduced not as significantly as in the vagotomized rats. Moreover, the glycogenolytic and gluconeogenic cycles, and lipolysis were not as notably activated as in vagotomy. Thus adrenalectomy was to a certain degree effective in controlling the high blood glucose after cholinergic denervation brought about by vagotomy.