The sympatho-adrenal system mediates the counterregulation of hypoglycemia. It acts through genesis of hyperglycemia by causing glucose mobilization from stored carbohydrate and by forming glucose from non carbohydrate sources by inducing gluconeogenesis. The sympathetic nervous system (SNS) has its innervation to the kidney through preganglionic nerve fibers travelling through lesser splanchnic nerve, which synapse at the celiac ganglion. Post ganglionic fibers arising from the celiac plexus form a secondary plexus, the renal plexus, which innervates the kidney. Adrenergic neurotransmitters epinephrine (E) and norepinephrine (NE) are released at these nerve endings.

Actions of epinephrine and norepinephrine are mediated via $\alpha$ and $\beta$ adrenergic receptors. Alpha adrenergic receptors have been identified in proximal convoluted tubules (PCT) by molecular, biochemical and physiological techniques (Sunderesan; 1987; Clark et al., 1990; Gesek and Schoolwerth, 1990; Feng et al., 1994). Ligand binding and immunohistochemical studies suggest the existence of beta-adrenergic receptors on renal tubule epithelium (Kudo et al., 1991; Taniguchi et al., 1993; Amenta et al., 1994).

The adrenal gland is practically a component of the sympathoadrenal system. It is innervated by the ANS. The adrenal medulla and the cortex are innervated by the pre and the post ganglionic autonomic fibers (Kesse et al., 1987). Celler and Schram (1981) provided the evidence for post ganglionic fibers running in the splanchnic nerves to the rat adrenal medulla. In addition to medullary inputs via the splanchnic nerve, the adrenal cortex of adult
rats receives autonomic innervation from the medulla and from the nerve fibers outside the adrenal gland (Vinson et al., 1994).

The importance of catecholamines in the counterregulation of insulin-induced hypoglycemia has been demonstrated in several animals models of sympathectomy, they are able to strongly antagonize insulin action on glucose disposal (Capaldo et al., 1995). Yamaguchi (1992) has shown that in response to insulin induced hypoglycemia, the sympathoadrenal system is activated, resulting in increase of adrenal catecholamines and pancreatic glucagon secretions, both of which are significantly implicated in glucoregulatory mechanisms. Many other workers (DeFeo et al., 1991; Fanelli et al., 1992) also have thoroughly appreciated the importance of adrenergic mechanisms to whole body glucose economy in a human model of prolonged hypoglycemia. The sympathoadrenal system is thus important in counteracting a hypoglycemic condition. It has been suggested that the increased activity of SNS and the resultant increase in the tissue CA levels contribute to the pathogenesis of diabetes (Dunbar et al., 1982). The effect of E to reduce insulin sensitivity is mediated by beta adrenergic receptors (Deibert and DeFronzo, 1980; Rizza et al., 1980).

Combined alpha and beta adrenergic blockade can accentuate the severity of insulin hypoglycemia (Sacca et al., 1979). Adrenergic blockade or sympathectomy thus provides a method of evaluating the contribution of the sympathoadrenal system to the maintenance of glucose homeostasis in the body. Many workers have carried out chemical sympathectomy by using various anti adrenergic drugs such as 6-hydroxy dopamine (6-OHDA) and guanethidine (Mehta, 1985; Oommen, 1992; Pillai, 1993; Anoopkumar, 1994). Since 6-OHDA leaves the adrenergic neuron cell bodies intact (Theonen and Tranzer, 1973), guanethidine has been used in the present study to achieve a total adrenergic destruction. Guanethidine is a guanidinium adrenergic neuron blocking agent which destroys peripheral sympathetic neurons without affecting other cell types (Burnstock et al., 1971; Eranko and Eranko, 1972). Adrenergic neurons are destroyed, but cholinergic systems are left completely intact (Jensen-Holm and Juul, 1971; Angeletti et al., 1972). This mechanism of destruction has been found to be immune mediated with lymphocyte infiltration in the sympathetic ganglia of drug treated animals (Jensen-Holm and Juul, 1971) and immunosuppressive drugs can protect the animals from adrenergic destruction (Manning et al., 1982; Zochodne et al., 1988). Lo et al (1991) have shown catecholamine depletion after guanethidine treatment.
Guanethidine is excluded from the CNS by the blood brain barrier (BBB) because it is highly ionized at physiological pH but uptake into sympathetic post ganglionic neurons occurs by the CA uptake pump (Furst, 1967; Johnson and Manning, 1984).

In the present study therefore, guanethidine was employed to produce chemical sympathectomy. To eliminate the sympathoadrenal system completely, adrenalectomy was carried out in chemically sympathectomized animals. Vagotomy was also performed in animals treated with guanethidine to observe how sympathetic and parasympathetic systems interact with each other by bringing about alterations or compensation in the metabolic pathways.

**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 subjected to various drug treatments in combination with different surgical operations.

**I** CHEMICAL SYMPATHECTOMY (CSX)
CONTROL CHEMICAL SYMPATHECTOMY (CSS)

**II** CHEMICAL SYMPATHECTOMY + VAGOTOMY (CSX + VGX)
CONTROL CHEMICAL SYMPATHECTOMY + SHAM VAGOTOMY (CSS + VGS)

**III** CHEMICAL SYMPATHECTOMY + ADRENALECTOMY (CSX + ADX)
CONTROL CHEMICAL SYMPATHECTOMY + SHAM ADRENALECTOMY (CSS + ADS)

At the termination of experiment, overnight fasted animals of both experimental and control groups were sacrificed. Blood was collected from the jugular vein, was allowed to settle and serum was obtained. The kidney was excised, blotted free of blood, and used for preparing homogenates for estimation of various biochemical parameters.

Glucose level was estimated in the blood by glucose oxidase method using the GOD/POD kit (Span Diag. Udhana), 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 μM 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 μM phosphate released/mg protein/15 min. Succinate dehydrogenase was estimated by the method of Nachlas et al. (1959) and expressed as μg formazan formed/mg protein/60 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 μM lactate oxidized/mg protein/15 min. Acetyl cholinesterase was estimated by the method of Ellman et al. (1961) and expressed as μmol acetyl thiocholine iodide hydrolyzed/mg protein/min. Lipid content of the kidney was estimated by the method of Folch et al. (1957).

Statistical analysis:
Statistical analysis was done by employing Student's t-test to determine the significance of the data. p < 0.05 was considered to be significant.

RESULTS (Tables 4.1, 4.2; Figures 4.1 to 4.6)

After chemical sympathectomy (CSX), a 28% reduction in the blood glucose level was found in the rats. In the animals treated for chemical sympathectomy and vagotomy in combination (CSX + VGX), a slight but significant rise was observed (24%). When both chemical sympathectomy and adrenalectomy (CSX + ADX) were carried out together, a marked decline of 44% (p < 0.001) was attained in the blood glucose level.

The glycogen content of the kidney was found to increase by 26% after chemical sympathectomy. In CSX + VGX animals, there was a 23% decrease in the glycogen content, however, after CSX + ADX, a very significant (p < 0.001) rise of 43% was obtained in the glycogen content of the kidney.

Glycogen synthase, the enzyme involved in synthesizing glycogen was found to have a 25% increase in activity (p < 0.02) in the kidney after CSX. Conversely, the CSX + VGX animals manifested a 23% reduction in the activity of this enzyme. However, a prominent increase of 48% (p < 0.001) was found in the activity of glycogen synthase after CSX + ADX.
Table 4.1 Serum glucose, renal metabolites, and enzymes of carbohydrate metabolism and acetyl cholinesterase in rats subjected to chemical sympathectomy singly and in combination with vagotomy and adrenalectomy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chemical Sympathectomy</th>
<th>Chemical Sympathectomy &amp; Vagotomy</th>
<th>Chemical Sympathectomy &amp; Adrenalectomy</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl Serum)</td>
<td>123.19</td>
<td>89.16***</td>
<td>80.13***</td>
<td>118.03</td>
</tr>
<tr>
<td>Glycogen (mg/100 mg Wet Tissue)</td>
<td>0.043 ± 0.003</td>
<td>0.034**</td>
<td>0.026 ± 0.01</td>
<td>0.026</td>
</tr>
<tr>
<td>Glycogen Synthase</td>
<td>96.18 ± 0.01</td>
<td>84.29**</td>
<td>83.92**</td>
<td>95.29</td>
</tr>
<tr>
<td>Glycogen Phosphorylase (μM UTP/mg Protein/10 Min.)</td>
<td>4.94 ± 0.016</td>
<td>3.29**</td>
<td>2.98**</td>
<td>3.68</td>
</tr>
<tr>
<td>Glucose-6-Phosphatase (μM Pi-releasing Protein/10 Min.)</td>
<td>0.35 ± 0.016</td>
<td>0.34**</td>
<td>0.023**</td>
<td>0.023</td>
</tr>
<tr>
<td>Lactate Dehydrogenase (μg Formazan formed/mg Protein/15 Min.)</td>
<td>32.46 ± 0.016</td>
<td>25.70***</td>
<td>25.13**</td>
<td>31.55</td>
</tr>
<tr>
<td>Succinate Dehydrogenase (μg Formazan formed/mg Protein/15 Min.)</td>
<td>4.14 ± 0.016</td>
<td>5.41***</td>
<td>5.24**</td>
<td>4.09</td>
</tr>
<tr>
<td>Lipid (mg/100 mg Non-Fat Dry Tissue)</td>
<td>4.18 ± 0.02</td>
<td>4.02**</td>
<td>0.22</td>
<td>0.22</td>
</tr>
<tr>
<td>Acetyl Cholinesterase (ACHe hydrolyzed/mg Protein/Mm.)</td>
<td>0.034 ± 0.002</td>
<td>0.039**</td>
<td>0.015**</td>
<td>0.015</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. Values adopted from Yadav (1997).
Table 4.2 Percentage change (compared to controls) in serum glucose, renal metabolites, and enzymes of carbohydrate metabolism and acetyl cholinesterase in rats subjected to chemical sympathectomy singly and in combination with vagotomy and adrenalectomy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sympathectomy</th>
<th>Sympathectomy + Vagotomy</th>
<th>Sympathectomy + Adrenalectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl Serum)</td>
<td>28*** ↓</td>
<td>24* ↑</td>
<td>44**** ↓</td>
</tr>
<tr>
<td>Glycogen (mg/100 mg Wet Tissue)</td>
<td>26** ↑</td>
<td>23** ↓</td>
<td>43**** ↑</td>
</tr>
<tr>
<td>Glycogen Synthase (μM UDP/mg Protein/10 Min.)</td>
<td>25** ↑</td>
<td>23** ↓</td>
<td>48**** ↑</td>
</tr>
<tr>
<td>Glycogen Phosphorylase (μM P released/mg Protein/10 Min.)</td>
<td>16** ↓</td>
<td>14* ↑</td>
<td>18*** ↓</td>
</tr>
<tr>
<td>Glucose-6-Phosphatase (μM PO₄ released/mg Protein/15 Min.)</td>
<td>23*** ↓</td>
<td>24* ↑</td>
<td>34**** ↓</td>
</tr>
<tr>
<td>Lactate Dehydrogenase (μM Lactate oxidized/mg Protein/15 Min.)</td>
<td>25** ↑</td>
<td>36*** ↑</td>
<td>20* ↑</td>
</tr>
<tr>
<td>Succinate Dehydrogenase (μg Formazan formed/mg Protein/60 Min.)</td>
<td>21** ↓</td>
<td>20** ↑</td>
<td>31**** ↓</td>
</tr>
<tr>
<td>Lipid (mg/100 mg Non Fat Dry Tissue)</td>
<td>31*** ↑</td>
<td>20** ↓</td>
<td>54**** ↑</td>
</tr>
<tr>
<td>Acetyl Cholinesterase (AChl hydrolyzed/mg Protein/Min.)</td>
<td>15* ↑</td>
<td>58**** ↓</td>
<td>33** ↑</td>
</tr>
</tbody>
</table>

*Values corrected to nearest whole number; * p<0.05; ** p< 0.02; *** p< 0.01; **** p< 0.001; ¤ Values adopted from Yadav (1997).
Figure 4.1 Levels of serum Glucose and renal Glycogen in rats subjected to chemical sympathectomy (CSX) singly and in combination with vagotomy (VGX) and adrenalectomy (ADX)

* p < 0.05; ** p < 0.02; *** p < 0.01; **** p < 0.001.
Figure 4.2 Activities of Glycogen Synthase and Glycogen Phosphorylase in the kidney of rats subjected to chemical sympathectomy (CSX) singly and in combination with vagotomy (VGX) and adrenalectomy (ADX)

(A) 

(B) 

* p < 0.05; ** p < 0.02; *** p < 0.01; **** p < 0.001.
Figure 4.3  Activities of Glucose-6-Phosphatase and Lactate Dehydrogenase in the kidney of rats subjected to chemical sympathectomy (CSX) singly and in combination with vagotomy (VGX) and adrenalectomy (ADX)

(A) Glucose-6-Phosphatase

(B) Lactate Dehydrogenase

* p < 0.05; ** p < 0.02; *** p < 0.01; **** p < 0.001.
Figure 4.4 Activity of Succinate Dehydrogenase and Total Lipid Content in the kidney of rats subjected to chemical sympathectomy (CSX) singly and in combination with vagotomy (VGX) and adrenalectomy (ADX).

(A) Succinate Dehydrogenase

(B) Total Lipid

Control  Experimental

** p < 0.02; *** p < 0.01; **** p < 0.001.
Figure 4.5 Activity of Acetyl Cholinesterase in the kidney of rats subjected to chemical sympathectomy (CSX) singly and in combination with vagotomy (VGX) and adrenalectomy (ADX)

* p < 0.05; ** p < 0.02; **** p < 0.001.
Figure 4.6 Percentage change in levels of serum glucose, renal metabolites, and activities of key enzymes of carbohydrate metabolism and acetylcholinesterase in the kidney of rats subjected to sympathectomy singly (A), and in combination with vagotomy (B) and adrenalectomy (C).

Values adopted from Yadav (1997).
The activity of glycogen phosphorylase declined by 16 % in the kidney in the CSX rats, while a small increment of 14 % was observed in the CSX + VGX rats. The activity was found to decrease by 18 % in CSX + ADX rats.

G-6-Pase the terminal enzyme of both glycogenolytic and glycolytic pathways was found to have a decreased activity of 23 % (p < 0.01) in the CSX rats. CSX + VGX rats, on the contrary manifested a 24 % increase (p < 0.05) in the activity of renal G-6-Pase. In the CSX + ADX rats, a drastic reduction of 34 % (p < 0.001) was found to have occurred in the activity of this enzyme.

LDH activity showed an increased activity in all the three conditions, the degree of this increase was however varied, viz. CSX (25 %), CSX + VGX (36 %) and CSX + ADX (20 %).

The other dehydrogenase, SDH showed a 21 % reduced activity (p < 0.01) in the kidney of CSX rats, whereas, an increased activity (20 %) was observed in the CSX + VGX rats. The CSX + ADX rats showed a significant reduction of 31 % (p < 0.001) in the activity of this enzyme.

In the kidney of the CSX rats, a rise of 31 % (P < 0.01) was found in the lipid content, while a depleted content (20 %) was manifested by the CSX + VGX rats. The kidney of the CSX + ADX rats however was found to have a marked rise of 54 % (p < 0.001) in the lipid content.

AChE, the marker enzyme for cholinergic activity increased slightly (15 %) in the kidney after CSX, but diminished very significantly by 58 % (p < 0.001) after CSX + VGX. The CSX + ADX rats showed a 33 % decrease in the activity of this enzyme in the kidney.

DISCUSSION
In the present study, a hypoglycemia was observed in the rats after the chemical sympathectomy achieved by means of chronic guanethidine treatment (50 mg/kg body weight, for four weeks). It has long since been considered that the sympathetic nervous system acts in the genesis of hyperglycemia by promoting mobilization of glycogen, protein and lipid
reserves of the body, and that its effects depend almost exclusively on neuroendocrine mechanisms, together with mediation of epinephrine released from the adrenal and of glucagon from the pancreas (Shimazu, 1983). The elimination of the sympathetic influence by means of sympathectomy, would result in the decrease in the release of the catecholamines and also glucagon, its secretion being under sympathetic control. The pancreatic islets are richly innervated with adrenergic nerves (Ahren et al., 1987), and it is known that glucagon secretion is stimulated by electrical activation of the sympathetic nerves in various species (Anderson et al., 1982; Bloom and Edwards, 1984). Also, electrical activation of sympathetic nerves is known to inhibit basal and stimulated insulin secretion (Anderson et al., 1982). Combined adrenergic blockade reverses the increase in glucagon (Bloom and Edwards, 1984). Ahren et al. (1987) showed that sympathetic nerve stimulation caused an increase in NE release at the pancreatic nerve endings and a concomitant inhibition of basal insulin secretion. Lo et al. (1991) have shown CA depletion after chronic guanethidine treatment, which markedly destroys peripheral sympathetic nerves, without affecting central adrenergic neurons in adult rats (Kvetmansky et al., 1979). Furthermore, this treatment has also been demonstrated to affect adrenocortical activity and reduce corticosterone secretion in adult rats (Kleitman and Holzwarth, 1985). Elimination of all these glucose mobilizing hormones from the system, would lead to the production of a hypoglycemic condition as observed in the present situation. In rats with CSX + VGX, a marginal hyperglycemia was observed. This could be because of the absence of the vagal cholinergic fibers, and in turn the block of insulin secretion, causing decreased glucose uptake. This shows that CSX is not able to overcome the hyperglycemic condition totally. A higher degree of hyperglycemia was, however, completely prevented by the combination of CSX + ADX. Loss of sympathetic innervation, as well as the adrenal hormones would lead to the manifestation of this glycemic state.

The glycogen content and the activity of the glycogen synthase showed an increase in the chemically sympathectomized rats. Craig et al. (1969), using intact rat diaphragms, showed that epinephrine decreased total glycogen synthase activity. Lack of the sympathetic tone to the kidney in the sympathectomized rats, would eventually lead to the elimination of the glycogenolytic effects, inducing the activation of glycogen synthase and in turn causing glycogen deposition in the tissue. Villar-Palasi et al (1969) have shown that addition of
insulin to the incubation medium of rat hemidiaphragms promoted an increase in the activity in glycogen synthase.

Another major effective control of carbohydrate metabolism is at the level of phosphorylase in glycogen metabolism (Hers and Hue, 1983). The activity of this glycogenolytic enzyme manifested a decrease, indicating a reduction in the rate of the breakdown of the storage polymer. This enzyme is activated by the catecholamines (Newgaard et al., 1984) and glucagon which increases glucose production by increasing glycogenolysis and stimulating gluconeogenesis (Brand et al., 1995; Ercan et al., 1995). This mechanism depends on increase in cAMP. cAMP initiated cascade reactions lead to activation of protein kinase, phosphorylase kinase and finally phosphorylase (Shimazu, 1983). Farah (1983) has shown that glucagon can stimulate the formation of cAMP in renal tissue. Popovtzer and Wald (1981) have demonstrated the increased cAMP production by glucagon in isolated renal cortical tubules and slices of the rat kidney.

In rats it has been demonstrated that the release of NE and E from the adrenal medulla is under both neuronal and non neuronal control (Khalil et al., 1986). The increase in glucose concentration could in part be attributed to the enhanced sympathetic activity, causing hepatic glycogenolysis and lipolysis, and partly to a reduction in insulin secretion (Wasserman et al., 1989b). CA can also act indirectly by stimulating an increased intracellular cAMP concentration and increase in glucagon release, via actions on alpha adrenergic receptors (Hooper et al., 1994). Glucagon in turn may also act on hepatocytes to increase intracellular cAMP concentration and an increase in glucose release (Foster and McGarry, 1992). Hooper et al. (1994) have shown that an increase obtained in plasma glucose concentration and glucagon by infusion of both E and NE supports the conclusion that these hormones act directly or indirectly to stimulate increased intracellular cAMP concentration in the hepatocytes. Prolonged infusions of a β, agonist (ritrodine) increase fetal glucose production (Tanenbaum and Cowett, 1985) and hepatic glycogen depletion by activation of glycogen phosphorylase (Warburton et al., 1988). CA cause a significant reduction in plasma insulin levels. This reduction was observed while the glucose levels were high, indicating that CA may have a direct suppressive effect on insulin secretion by B cells of fetal islets of Langerhans, similar to adults, in contrast, CA increase plasma glucagon levels by their direct actions on A cells of fetal islets (Porte and Wood, 1990).
G-6-Pase, the final enzyme in both glycogenolytic and gluconeogenic pathways showed a decreased activity in the kidney of the sympathectomized rats, reflecting a reduction in the operation of both these pathways. Gluconeogenesis is regulated in the rats and other mammals by several endocrine factors, among them catecholamines and glucagon being the key counterregulatory hormones (Havel and Taborsky, 1989). Glucagon increases the apparent rate of gluconeogenesis by 30-70% in fasted animals and as much as 24 fold in fed animals (Hers and Hue, 1983). Another key regulator of gluconeogenesis, and thus glucose homeostasis, is the adrenal cortex. The steroid products of this gland, the glucocorticoids, are critical for inducing several gluconeogenic enzymes in the adult liver and for providing substrate for these enzymes (Munck et al., 1984). Impaired secretion of glucagon, catecholamines resulting due to the obliteration of the sympathetic system could be the reason for the decrease in the activity of this enzyme. This is also seen in the rats with CSX + ADX, where the glucocorticoids are also eliminated due to adrenalectomy (Chapter 6). In the rats with CSX + VGX, no significant alteration is seen in the activity of this enzyme. Here, vagotomy seems to compensate for the metabolism disturbed due to the loss of these glucose mobilizing hormones.

The activity of LDH was observed to be increased in all the three treatments. In the current study, lactate mobilization showed a small increment during hypoglycemia. It must be stressed that the greater activation of lactate release during hypoglycemia occurred despite the fact that glucose disposal was not stimulated. Increased disposal of glucose would be predominantly be related to oxidative glycolytic pathways. Here, in CSX and CSX + ADX, however, SDH was found to be decreased, indicating no oxidative disposal. In CSX + VGX, SDH activity showed an increase, indicating oxidative metabolism. It has been reported that mitochondria isolated from rats treated with glucagon, epinephrine or glucocorticoids (Hers and Hue, 1983) have an increased rate of pyruvate metabolism. Also an increase was observed in respiratory chain activity (Hers and Hue, 1983) itself responsible for the proton promoted pyruvate transport. The loss in the activity of SDH would also be due to a decreased availability of FFA due to decreased lipid breakdown as can be inferred from the increased lipid content of the tissue in the former two conditions, and glycogen derived intermediates due to decreased glycogenolysis Thus, an influence of FFA on the glycolytic flow and / or entry into the citric acid cycle can readily be envisioned. In muscle, FFA
oxidation inhibits the entry of pyruvate into the citric acid cycle by inhibition of pyruvate dehydrogenase (Randle et al., 1963).

In the CSX animals, an increased lipid content is observed in the kidney. This could reflect either an increase in synthesis or a reduction in the lipolysis. Lipid synthesis *de novo* is decreased by NE, which also inhibits glucose utilization rate (Laychock and Bilgin, 1987). Carmine et al. (1992) have implied that adrenergic mechanisms contribute to the last phase of hypoglycemic glucose counterregulation in humans by stimulating lipolysis. Lack of this catecholamine after chemical sympathectomy could lead to elimination of its inhibitory regulation of lipogenesis, and thus augment the same. A similar condition is encountered in CSX + ADX rats, where in addition to the absence of the CA, glucocorticoids are also lacking. These hormones also increase lipolysis (DeBodo and Altszuler, 1958). In the animals with CSX + VGX, a slight decrease was observed in the content of lipid in the tissue. The individual effects of insulin as antilipolytic (Nurjhan et al., 1986) and E as lipolytic agent are well known. E effectively reverts the insulin suppressive effect on free fatty acid (FFA) release (Capaldo et al., 1992). This finding is well in agreement with previous *in vitro* studies (Abumrad et al., 1982) and provides evidence of a direct antagonism of insulin and E *in vivo* on FFA mobilization. Capaldo et al. (1992) have shown that E antagonizes insulin induced inhibition of FFA release in forearm tissues. Moderate hyperinsulinemia has been known to completely prevent E's effect on lipolysis and ketogenesis (Avogaro et al., 1990). Removal of insulin would eliminate its inhibitory effect over lipolysis, and therefore enhance the process. Furthermore, the increased levels of FFA would provide energy for gluconeogenesis and restrict peripheral glucose utilization due to substrate competition. The present findings thus open the possibility that an increased lipolysis can be a contributing factor behind B cell insensitivity to glucose.

AChE activity increased in the CSX and CSX + ADX rats, but decreased in the rats with CSX + VGX. In the first two conditions, the probable reason for the increase in the AChE activity is elevation of the parasympathetic tone after the elimination of the sympathetic system and the adrenal glands. In the animals with CSX + VGX, in spite of the sympathectomy, the loss of vagal fibers results in a decrease in the activity of this enzyme.
Contrary to the normal animal, in the diabetic animal, the plasma level of insulin is low or nil, that of glucagon elevated, consequently the insulin/glucagon ratio in the plasma is low. As a result, the rate of glucose production is well above normal. Since the metabolic clearance rate of glucose is also low, the animal develop hyperglycemia. Thus, if the increase in the rate of removal is relatively small, the increase in glucose production minimizes the fall in the concentration of plasma glucose, and no overt hypoglycemia develops. Performing VGX in CSX rats causes an increase in glucose production. There may be a primary increase in the rate of removal of glucose because of CSX. Nevertheless, no hypoglycemia develops, but a slight hyperglycemia occurs because of an increase in glucose production. In CSX + ADX, however, a significant hypoglycemic condition can be attained.

To conclude, the regulators of the metabolism function in a manner so intricate that blockade or ablation of one or a portion of one of the autonomic subdivisions is not sufficient to attenuate the hyperglycemic response. Accordingly, adrenalectomy (Chapter 1) or chemical sympathectomy alone may not be able to successfully reduce the hyperglycemia. But a combination of the two is effective in controlling the hyperglycemic state. Thus, simultaneous suppression of adrenergic activity and adrenal gland secretion may ameliorate the effects of insulin insufficiency.