Studies of the mechanisms involved in the regulation of secretion and the functions of GH are difficult inasmuch as GH, unlike other pituitary trophic hormones, does not elicit specific activation in a single target peripheral gland or organ. However, recent development of sensitive and specific immunoassays for GH has allowed studies of the hormone in varying physiological states.

Pituitary GH secretion is under the control of the hypothalamus, where several neurogenic, hormonal and metabolic signals are integrated to modulate the secretion of two hypothalamic peptides, growth hormone releasing hormone (GHRH), a GH releasing hormone and somatostatin (SS), a GH release inhibiting hormone. GHRH stimulates the secretion of GH from the anterior pituitary. Topographical analysis of the neural regulation of GH release carried out by electrical stimulation of certain structures in the central nervous system (Bernardis and Frohman, 1971; Martin et al., 1975) revealed that the ventromedial nucleus of the hypothalamus (VMH), an area sensitive to hypoglycemia and causing hunger in hypoglycemia, and the arcuate nucleus (ARC) are important structures in enhancing GH release. Since somatotropin release inhibiting factor (SRIF) is a potent inhibitor of the GH release, the suppression of GH release apparently involved SRIF release. In the ventral LHA, scattered immunoreactive SRIF processes are known to be present (Makara et al., 1983). The stimulation of LHA would excite the SRIF fibers directly and this would result in the release of SRIF into the hypophysial portal blood which in turn suppresses GH release induced by GRF. The mechanism by which hypoglycemia induces a substantial release of
pituitary GH has not been elucidated. Abrams et al. (1964) have demonstrated in male squirrel monkeys that chronic lesions in the anterior ventral hypothalamus significantly reduce the GH response to hypoglycemia. It is tempting to speculate that hypoglycemia increases GH secretion by stimulating glucose receptors in the CNS, which in turn trigger the release of GHRH.

GH displays a wide variety of biological activities. In addition to promoting body growth, GH seems to possesses both insulin-like activities which have can result in transient hypoglycemia, increased glucose and amino acid transport and metabolism in a tissue (Knobil et al., 1961; Honeyman and Goodman, 1980) and the chronic and prolonged anti-insulin activities that can result in hyperglycemia, hyperinsulinemia, increased lipolysis and decreased glucose metabolism (Goodman and Schwartz, 1974; Davidson, 1987).

Hypoglycemia has been found by Roth et al. (1963a) to be a potent stimulus to the release of growth hormone. Prolonged fasting also raises the growth hormone level, and administration of glucose may result in a decrease of the hormone level in plasma. Roth et al. (1963b) have subsequently observed that the mechanism responsible for stimulating the secretion of GH is sensitive to low glucose concentration, fasting and muscular exercise. The increased GH secretion in these conditions makes FFA, an important oxidizable substrate available to the cells in increased amounts.

Kostyo and Nutting (1974) have reported that GH also exerts acute stimulatory effects on amino acid transport and the translation of preexisting mRNA molecules for various proteins in tissues such as skeletal muscle, heart, liver and fat. The results of the experiments carried out by Cameron et al. (1988) have shown the ability of the GH to stimulate amino acid transport and protein synthesis acutely in muscle. In a restricted intake situation, the dominant effect of GH is to mobilize lipid stores (Boyd and Bauman, 1989). GH secretion is sensitive to acute nutritional status and responds positively to fasting in humans (Hartman et al., 1992).

It is generally believed that among the above mentioned effects, the principal physiological action of GH is the antiinsulin activity, which results in hyperglycemia (Davidson, 1987). Therefore, as one of the glucose counterregulatory hormones, GH has
been proposed to be implicated in diabetes mellitus (Schaper, 1990). However, the exact role of GH in diabetes is not fully understood. In poorly controlled diabetes, nephropathy is a major complication, which ultimately results in kidney failure. Although controversial, an increasing body of data have implicated a role of GH in diabetic end organ damage. GH transgenic animals develop a glomerulosclerosis that resembles human diabetic nephropathy (Yang et al., 1993). Moreover, increased GH levels are involved with insulin resistance, which adversely affects diabetic control (Press et al., 1984). Therefore, it can be hypothesized that diabetic end organ damage is a result of two physiological abnormalities: 1. elevated levels of glucose and / or decreased levels of insulin, and 2. elevated levels of GH. Chen et al. (1995) have shown that diabetic GH transgenic animals possessed kidney lesions similar to those found in humans with diabetic end organ damage. This may be indicative of a synergistic effect between GH and hyperglycemia in generating a more advanced stage of nephropathy when compared to nondiabetic GH transgenic animals.

The exact role played by glucocorticoids in the regulation of GH secretion is a clinically and pathophysiologically relevant issue under active investigation. Investigations performed in the rat have suggested that the conflicting results obtained in vitro and in vivo regarding the effects of glucocorticoids on GH secretion are explicable by an enhancement of hypothalamic somatostatin (SS) release induced by glucocorticoids in vivo (Wehrenberg et al., 1990). Despite these clinical and experimental observations, many queries concerning the role played by glucocorticoids in the physiology of GH secretion in humans remain to be addressed. One of the most intriguing issues in this field is the extent and mechanism by which circulating levels of glucocorticoids influence the pituitary GH secretory response to an acute physiological or pharmacological challenge and whether short term glucocorticoid withdrawal alters in vivo somatotroph responsiveness to relevant secretagogues. Increased GH and CA levels are often seen in patients with IDDM during periods of poor metabolic control (Hayford et al., 1980).

With such a plethora of paradoxical reports about the action of GH, one can readily understand the perplexity the physiologists have been facing in interpreting the enigma of the regulation of GH secretion. Therefore, it was found necessary to investigate the profile of this hormone in various conditions of manipulation of the neuroendocrine and autonomic nervous systems. Each part of the autonomic nervous system has been obliterated in single and in
combinations, to evaluate the effect of GH secretion and, also to define the effects of these maneuvers on GH secretion.

MATERIAL AND METHODS
Male albino rats (*Rattus norvegicus albinus*) of Charles Foster strain, weighing between 150-200 gm were used for the study. The animals were acclimatized for one week under standard laboratory conditions (12:12 L:D) and were divided into various groups:

I VAGOTOMY (VGX)
SHAM VAGOTOMY (VGS)

II ADRENALECTOMY (ADX)
SHAM ADRENALECTOMY (ADS)

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

IV CHEMICAL SYMPATHECTOMY (CSX)
CONTROL CHEMICAL SYMPATHECTOMY (CSS)

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

VI CHEMICAL SYMPATHECTOMY + ADRENALECTOMY (CSX + ADX)
CONTROL CHEMICAL SYMPATHECTOMY + ADRENALECTOMY (CSS + ADS)

After the respective surgery or drug treatment, the overnight fasted animals were given mild anesthesia and sacrificed. Blood was collected by puncturing the jugular vein and allowed to clot for an hour. It was then centrifuged at 3-4°C to obtain clear serum which was used for estimating Growth Hormone.

GH was estimated by Radio Immuno Assay using a kit from Diagnostic Products Corporation (CA, USA). The assay procedure has been discussed in detail in Material and Methods. The concentration of GH in the serum is expressed as ng/ml.

Statistical Analysis:
Data were analyzed by Student's t-test, and the level of significance was considered to be p < 0.05.
Table 7.1 Serum Growth Hormone level in rats subjected to parasympathetic and sympathoadrenal manipulation.

| Treatment                        | Growth Hormone (ng/ml) |              |            |
|----------------------------------|------------------------|--------------|
|                                  | Sham                   | Experimental |
| Vagotomy                         | 108.20± 5.32           | 148.40 ± 6.01**** |
| Adrenalectomy                    | 107.40 ± 5.21          | 76.00 ± 3.41**** |
| Vagotomy + Adrenalectomy         | 107.60 ± 5.16          | 127.20 ± 6.53* |
| Chemical Sympathectomy           | 115.80 ± 5.76          | 91.20 ± 4.58*** |
| Chemical Sympathectomy + Vagotomy| 109.40 ± 5.11          | 132.80 ± 6.13** |
| Chemical Sympathectomy + Adrenalectomy | 111.80 ± 6.51   | 73.20 ± 4.03**** |

® Values are expressed as mean ± SEM of 6 experiments; * p< 0.05; ** p< 0.02; *** p< 0.01; **** p< 0.001
Table 7.2  Percentage change (compared to controls) in serum Growth Hormone level in rats subjected to vagotomy, adrenalectomy and chemical sympathectomy singly and in combinations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Growth Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagotomy</td>
<td>37° **** ↑</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>29 **** ↓</td>
</tr>
<tr>
<td>Vagotomy + Adrenalectomy</td>
<td>18 * ↑</td>
</tr>
<tr>
<td>Sympathectomy</td>
<td>21 *** ↓</td>
</tr>
<tr>
<td>Sympathectomy + Vagotomy</td>
<td>21 ** ↑</td>
</tr>
<tr>
<td>Sympathectomy + Adrenalectomy</td>
<td>35 **** ↓</td>
</tr>
</tbody>
</table>

° Values corrected to nearest whole number; * p< 0.05; ** p< 0.02; *** p< 0.01; **** p< 0.001.
Figure 7.1 Growth hormone level in the serum of rats subjected to parasympathetic and sympathoadrenal manipulation.

* p < 0.05; ** p < 0.02; *** p < 0.01; **** p < 0.001.
Figure 7.2 Percentage change in serum Growth Hormone level in rats subjected to vagotomy (VGX), adrenalectomy (ADX), sympathectomy (CSX) and their combinations.
RESULTS
GH profiles of the animals with various surgeries and drug treatments showed considerable variability. Vagotomized (VGX) rats manifested an increased concentration of GH, the hike being 37% (108.20 ± 5.32 to 148.40 ± 6.01, p < 0.001). Adrenalectomized (ADX) rats showed a 29% decline in GH level in the serum (111.80 ± 6.51 to 73.20 ± 4.03, p < 0.001). In the rats with vagotomy and adrenalectomy together (VGX + ADX), a small increase of 18% was observed (107.60 ± 5.16 to 127.20 ± 6.53, p < 0.05). Animals with chemical sympathectomy (CSX) showed a 21% reduction in the level of GH (115.80 ± 5.76 to 91.20 ± 4.58, p < 0.01). The animals with combined treatment for chemical sympathectomy and vagotomy (CSX + VGX) showed a 21% rise in the GH level (109.40 ± 5.11 to 132.80 ± 6.13, p < 0.02), whereas, the animals with combined treatment for chemical sympathectomy and adrenalectomy (CSX + ADX) registered a marked reduction of 35% in the concentration of GH in the serum (107.40 ± 5.71 to 76.00 ± 3.41, p < 0.001).

DISCUSSION
In the present study, the GH profiles of the animals with different manipulations in the parasympathetic and the sympathoadrenal systems have been studied.

The VGX animals showed increased GH level compared to the control level. GH secretion is affected by metabolic and nutritional perturbations (Frohman et al., 1992), one of the most important metabolic factors is blood glucose. The diabetogenic and insulin-antagonistic properties of GH are well documented. Chronically elevated GH levels in humans or animals can lead to glucose intolerance, insulin resistance and diabetes mellitus (Gerich, 1984; Press et al., 1984). Physiological concentrations of exogenous GH have also been shown to antagonize insulin action in humans (Bratusch-Marrain et al., 1982; Rizza et al., 1982a; Sherwin et al., 1983; Fowelin et al., 1993) whereas chronic GH deficiency is typically associated with hypersensitivity to insulin (Altszuler, 1974). In diabetic animals, hypophysectomy leads to decreased hyperglycemia and glycosuria (Scow, 1963; Altszuler, 1974) and increased glucose utilization in adipose tissue and liver (Goodman and MacDonald, 1969), consistent with a potential role of GH. Endogenous GH might contribute to hyperglycemia and insulin resistance in diabetes by suppressing tissue responses to the low
ambient levels of endogenous insulin and/or by insulin independent mechanisms. Serum glucose concentration showed a 10% decrease in diabetic rats treated with ArGH (Tatro and Schwartz, 1987). In the present situation where insulin level was lowered by performing vagotom on the rats (Yadav, 1997), GH was observed to increase, probably facilitating hyperglycemia. Isacss et al. (1987) have discussed that insulin can decrease rat GH synthesis and secretion and rat GH mRNA. The high concentration of GH that has been observed in VGX rats, can be attributed to this fact. Similarly, GH levels are elevated in poorly controlled diabetes and may contribute substantially to the metabolic derangement in this state (Press et al., 1984).

In vagotomy, the antiinsulin effect of GH seems to be in operation in renal metabolism. Increased breakdown of carbohydrate and lipid stores ensued in the kidney after vagotomy (Chapter 2) with increased glycogenolysis, and gluconeogenesis along with increased lipolysis. The profile of protein metabolism however was not amenable to the protein anabolic effect of GH (Kyotsko and Nutting, 1974), as protein catabolism and transamination did occur (Chapter 3).

In the animals with ADX, a slight decrease was observed in the GH level in the serum. Thus, after ADX withdrawal of adrenal hormones, one of which being corticosterone (Chapter 6), led to decreased GH secretion. Several studies have also investigated the effects of chronic hypocortisolemia on GH secretion in humans. Chronic hypoadrenalism has been shown to be associated with decreased GH responsiveness to pharmacologic stimuli in both rats (Wehrenberg et al., 1983) and man (Guistina et al., 1989a; b). Patients with idiopathic ACTH deficiency have impaired GH responses to arginine, L-dopa and insulin induced hypoglycemia, which are reversible during glucocorticoid replacement therapy (Guistina et al., 1989). The present study compatible to this observation, indicates that decrease in GH in ADX rats is because of the removal of the stimulatory effects of adrenal corticosteroids. In vivo, in the rat, seven days after adrenalectomy, the GH response to GHRH is decreased (Wehrenberg et al., 1983), probably through a reduction in pituitary GHRH receptors (Seifert, 1985). Bancroft (1981) has reported from studies on pituitary tumor cell line that glucocorticoids are known to stimulate the cellular production of GH. It has been shown that short term moderate glucocorticoid excess augments spontaneous pituitary GH secretion in normal humans (Casanueva et al., 1990). The present study exemplifies the stimulatory effect
that the glucocorticoids have on GH secretion. Lack of the glucocorticoid hormones due to the removal of the adrenal gland in the experimental group, would lead to the elimination of these stimulating factors. The decreased secretory response in adrenalectomy seemed to be justifying the hypoglycemic state of this treatment (Chapter 2). In the ADX rats, the metabolic picture in the renal tissue was of a decreased glycogenesis, lipolysis, proteolysis and in turn gluconeogenesis (Chapters 2, 3). Decreased glucose mobilization from carbohydrate and lipid agree to the decreased effect of GH due to lowered secretion. Protein metabolism however seemed to depart from the GH dependent anabolic effect, by manifested a decreased breakdown even after reduction in the secretion of GH.

In the animals with VGX + ADX, only a small increment was observed in the concentration of this hormone in the serum. Adrenalectomy could to a certain degree overcome the drastic increase in GH level that VGX alone could have caused. The slight increase in GH could have possibly added up to the hyperglycemic condition of this group and also the renal metabolic profile that showed a slightly catabolic trend (Chapters 2, 3).

CSX animals manifested a significant decrease in the GH levels. Here, sympathectomy results in the obliteration of the catecholamines, which have been known for some time to be important modulators of endocrine function at the hypothalamic level. The in vitro stimulation of GH release by β-adrenergic agents, including E and NE, is well established (Perkins et al., 1983; Krieg et al., 1986). in vitro studies have shown that β-adrenergic agents directly stimulate GH release from perifused pituitary cells (Perkins et al., 1983). The mechanism involves the classic β-adrenergic production of cAMP, one system which is also activated during GRF stimulated GH release (Cronin et al., 1982). The possibility of direct pituitary stimulation of GH release by a β-adrenergic agonist in vivo is also verified (Krieg et al., 1988). In CSX animals again a hypoglycemia was present agreeable to the decreased GH level. Renal metabolism also manifested an anabolic trend, showing a reduction in glycogenolysis, lipolysis and proteolysis, and in turn decreased gluconeogenesis (Chapters 4, 5).

In the CSX + VGX animals, an increase was observed in GH concentration in serum. The higher concentration could be due to the effect of vagotomy which did not appear to be surmounted by performing sympathectomy in the same animals. Increased GH could thus be
a contributory factor to the marginal hyperglycemia found in this group of rats. The renal metabolic profile also was of less catabolic in nature than in VGX in singly or in VGX + ADX.

In the animals with CSX + ADX, a significant decline was observed in the concentration of GH. This would indicate that the removal of both sympathetic system and the adrenal gland had a very significant inhibitory influence on the secretion of this hormone. The positive regulatory influence that the catecholamines and the adrenal cortical steroids appear to have on GH secretion was totally removed, thereby causing a reduced secretion of the pituitary GH. Thus, the drastic reduction in GH secretion could be one of the factors contributing to the severe hypoglycemia and the anabolic renal metabolic profile in this condition (Chapters 4, 5).

The slight increase in GH level in VGX + ADX rats and in CSX + VGX rats could be attributed to the dominant effect that vagotomy has on the status of this hormone; the significance level of this increment in the hormone concentration is however lower than in the VGX rats. It is more in CSX + VGX than in VGX + ADX animals. This shows that in CSX rats, the effect of vagotomy is more prominent; chemical sympathectomy not being able to alter the situation. However, in VGX + ADX rats, this increase is not very acute. This shows that adrenalectomy in vagotomized rats is able to check the rise in GH levels. This could be because in ADX rats, both the catecholamines and the glucocorticoids are removed, both of which have stimulatory effect on GH secretion. Therefore, it can be concluded that both CSX and ADX together are able to control the rise in GH much efficiently, than is either of the condition alone.