MEDICAL GRAND ROUNDS

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER

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ACROMEGALY

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On pituitary gigantism -- Reported in the local press about the Irish Giant.

June 5, 1783: "The whole tribe of surgeons put in claims for the poor departed Irish Giant and surrounded his house just as Greenland harpooners would an enormous whale. One of them has gone so far as to have a niche made for himself in the giant's coffin."

June 16, 1783: "So anxious are the surgeons to have possession of the Irish Giant that they have offered a ransom of 800 guineas to the undertakers. This sum being rejected they are determined to approach the churchyard and unearth him."

June 18, 1783: "The body was shipped on board a vessel last night in order to be conveyed to the Downs where it is to be sunk in 20 fathoms of water. The body hunters, however, are determined to pursue their valuable prey even to the profoundest depth and have therefore provided a pair of diving bells."

The remains eventually came into the possession of Sir John Hunter, the skeleton becoming a focal point of interest in his collection.

(Musa *et al:* *Am J Med* 52:399, 1972)

In 1886 Pierre Marie, a distinguished French physician, described two cases of a disorder with striking enlargement of the extremities which he called acromegaly (history reviewed by Lawrence, 1970). The name was derived from *akron* (extremity) and *mega* (large). Although other parts of the body were affected, Marie felt that hypertrophy of the extremities was the initial phenomenon and the most characteristic sign of the disease. His description of these two cases was so detailed that his paper became the basis for succeeding work on the disorder. Minkowsky, in 1887, was the first to state that the hypophysis was enlarged in all carefully examined cases. In 1891 Marie and Marinesco interpreted their postmortem findings of a hypophyseal tumor in acromegaly as a cause for glandular insufficiency, and for years investigators attempted unsuccessfully to produce acromegaly by glandular extirpation. Thus, although an earlier association of the pituitary with acromegaly was recognized, it was not until 1909 that Harvey Cushing, the pioneering neurosurgeon, clearly proposed the concept of hyperpituitarism as the cause for acromegaly and described the first case of acromegaly treated successfully by partial hypophysectomy. The first successful cure by radiation therapy was also described in 1909 by Beclere. Finally, in 1921, Herbert Evans demonstrated that gigantism could be produced in rats by parenteral injection of an extract of the anterior lobe of the pituitary and, thus, experimental proof was provided for the presence of hyperactivity of the pituitary gland in cases of gigantism and acromegaly. Newer techniques utilizing the heavy particle beam (1954) and the Bragg-peak proton-beam (1961) irradiation were developed. In 1957 Salmon and Daughaday described the role of a secondary "sulfation factor," later called somatomedins, in the action of growth hormone. A significant advance was provided by the development of a radioimmunoassay for human growth hormone (GH) by Hunter and Greenwood in 1962. Further technological advances in the late 1950's and 1960's led to revival of transsphenoidal hypophysectomy. In 1973 Niall established the correct amino acid sequence for human growth hormone. Further understanding of the regulation of growth hormone secretion has been provided by the isolation of somatostatin from the hypothalamus (Brazeau, 1973) and by the development of a number of pharmacological agents which alter GH secretion. More recently Liuzzi (1974) first noted that bromocriptine, a dopaminergic agonist, provided a genuine alternative of medical treatment of acromegaly. The very recent development of a radioimmunoassay for somatomedin C (Furlanetto, 1977) promises to facilitate the diagnostic evaluation and long-term management of the acromegalic patient. The recent synthesis of human growth hormone by recombinant DNA techniques and recognition that β-endorphin and possibly other opioids stimulate growth hormone release (Rivier, 1977), promise a continuation of the rapid and exciting advances in this area.

GROWTH HORMONE

Site of production: Acidophil cells make up 35-50% of the cells of the normal pituitary. Cushing early noted the association of an acidophilic tumor with acromegaly. However, the tinctorial characteristic of the tumor varies considerably so that typical acromegaly can result with a chromaphobe adenoma.

Structure: Growth hormone is a single-chain polypeptide with a molecular weight of 21,700. The amino acid sequence (191 residues) has been elucidated (Niall, 1973). Human growth hormone circulates as a monomer and as several larger molecular weight forms that spontaneously interconvert in plasma, suggesting that the larger MW forms are aggregates (Bieler, 1977). The larger MW

forms have less biological activity.

Metabolism: Growth hormone is transported in plasma unbound to protein and is cleared primarily by the liver. About 5 mg of GH is normally produced per day (Parker, 1963), and the half life is about 25 minutes (Glick, 1964).

Circadian rhythm: Like many hormones, growth hormone is secreted in a pulsatile fashion that is relatively reproducible in a given individual from day to day. A typical pattern is shown in Figure 1 (Takahashi, 1968). Normal individuals exhibit peaks in plasma growth hormone concentration of 15-75 ng/ml during sleep or during stressful stimuli throughout the day and, in contrast, almost always have circulating concentrations of less than 4 ng/ml 2-3 hours after meals.

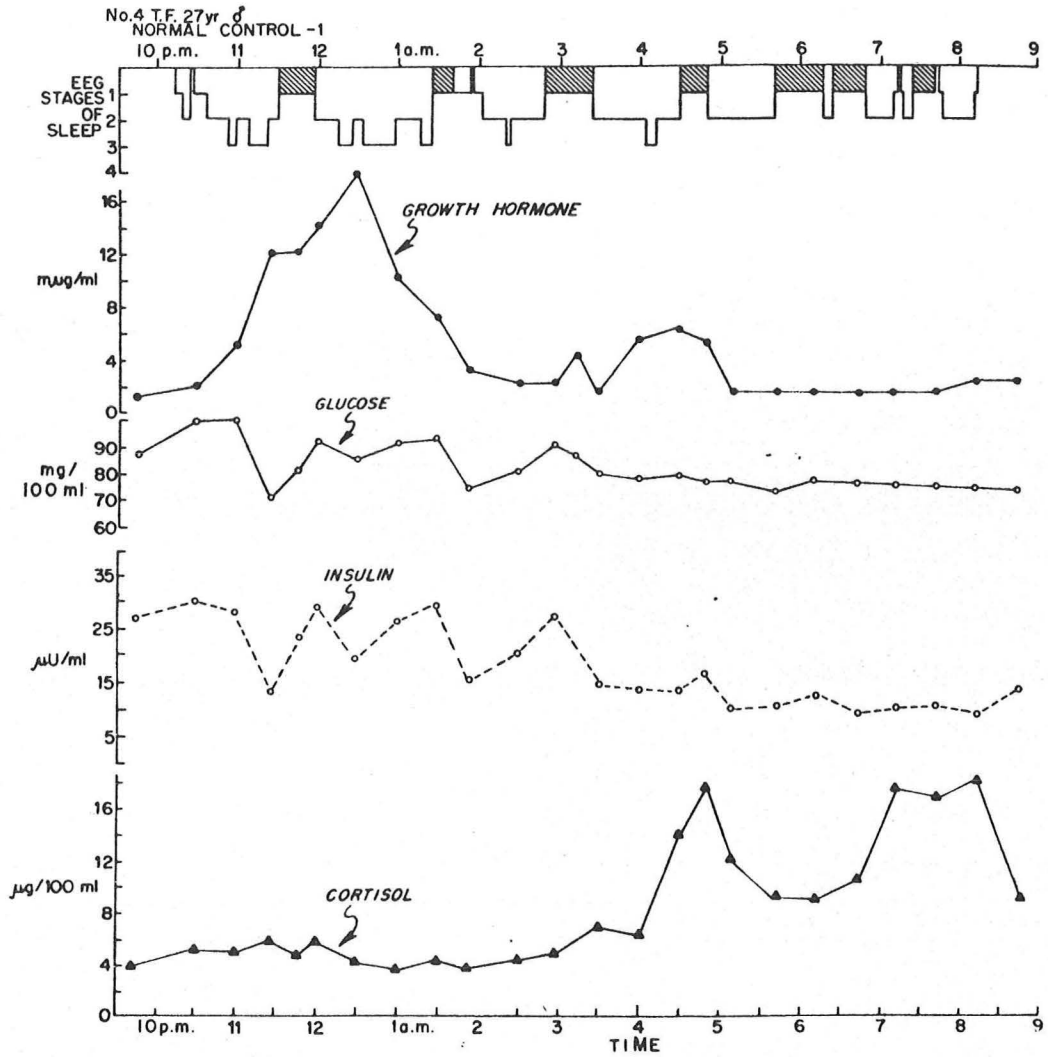


FIGURE 1 The plasma growth hormone, glucose, insulin, and cortisol levels and EEG-EOG monitored CNS activity during a normal night's sleep in a 27 yr old man (T. F.). In this and subsequent figures the levels of sleep are indicated at the top of the figure. Cross-hatched areas are periods of rapid eye movement.

Physiologic action: The many effects of growth hormone reflect the fact that its target organ is the whole body. The effects are mediated by DNA-RNA protein synthesis mechanisms and not by activation of adenyl cyclase-cyclic AMP pathways. The physiologic actions have been summarized by Daughaday and Parker (1965, Table 1).

TABLE I

PHYSIOLOGIC ACTIONS OF GROWTH HORMONE

Protein metabolism

1. Growth—increased protein synthesis
   - balance study
     - nitrogen storage
     - phosphorus storage[a]
     - potassium storage[a]
   - decreased urea excretion
2. Increased intracellular transport of amino acid
3. Increased ribosomal protein synthesis

Fat metabolism

1. Intracellular lypolysis
2. Increased plasma free fatty acids[a]
3. Increased oxidation of fat[a]
4. Ketogenesis stimulated in diabetes[a]

Carbohydrate metabolism

1. Diabetogenic in certain species (aggravation of human diabetes[a])
2. Diminution of insulin responsiveness[a]
3. Decreased conversion of glucose to fat in adipose tissue

Mineral metabolism

1. Calcium metabolism
   - intestinal absorption increased[a]
   - hypercalciuria, decreased renal tubular reabsorption of calcium[a]
2. Sodium retention[a]
3. Phosphorus retention with protein synthesis[a]
4. Hyperphosphatemia, increased renal tubular absorption of phosphorus[a]
5. Alkaline phosphatase increased[a]

Effects on certain organs and tissues

1. Visceromegaly (acromegaly)
2. Connective tissue
   - stimulation of chondroitin sulfate synthesis
   - stimulation of collagen synthesis
   - increased urinary hydroxyproline[a]
   - increased interstitial fluid volume

[a] Changes demonstrated in man during growth hormone administration.

SOMATOMEDINS

In 1957 Salmon and Daughaday demonstrated that growth hormone stimulates the incorporation of radiolabelled sulfate into proteoglycans of cartilage by inducing the formation of a secondary "sulfation factor" (reviewed by Van Wyck and Underwood, 1975). Further studies have indicated that normal plasma contains a number of these growth hormone-dependent substances that exhibit the following characteristics:

(1) Plasma concentration is regulated by GH,
(2) Sulfate incorporation into cartilage is stimulated,
(3) Many insulin-like metabolic actions *in vitro* are exhibited, though they are immunologically distinct from insulin.

Though these factors were originally referred to as the "sulfation factor," the more open-ended term somatomedin is now used. It is generally accepted that an important part of the action of GH, particularly its effect on the skeletal system, is mediated by somatomedins. Somatomedins are mainly produced by the liver following GH binding to hepatocyte receptors, and there is increasing evidence that muscle and kidney may be other sites of synthesis. The importance of somatomedins in the skeletal effects of GH is manifested by the Laron dwarfs, who have striking elevations in serum GH concentrations and exaggerated responses to GH stimuli, but a body habitus similar to children with severe hypopituitary dwarfism. These dwarfs have low circulating plasma somatomedin levels and do not respond to exogenous GH.

Four somatomedins have been characterized: (1) non-suppressible insulin-like activity, (2) multiplication stimulating activity, (3) somatomedin A, (4) somatomedin C. Somatomedin B, although under growth hormone control, is no longer classified as a somatomedin because it does not stimulate sulfate uptake into cartilage or have insulin-like activity.

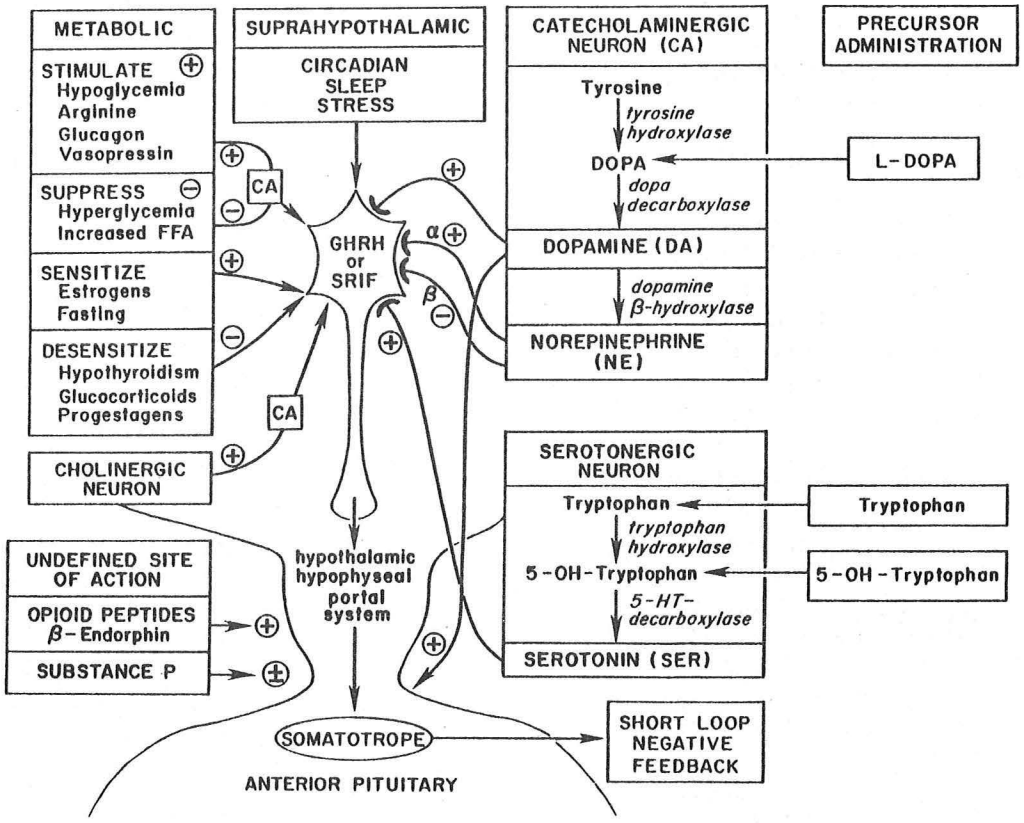
The question of whether somatomedin is synthesized *de novo* or is a cleavage product of hormone itself has not been completely resolved. In contrast to most peptide hormones, production and disposal of somatomedin appears to be relatively slow. Rises in plasma somatomedin levels do not occur until 3 hours after the intravenous injection of GH into hypopituitary children. After intramuscular injection of GH, somatomedin levels may not rise for several days.

Somatomedin levels in plasma: Accurate measurement of the plasma somatomedin content has previously been difficult due to the inherent imprecision of the cumbersome bioassay techniques, the presence of variable amounts of inhibitory substances, and problems with cross-reactivity of the different somatomedins in various competitive membrane binding assays (radioreceptor assays). A modest rise in plasma somatomedin levels has been reported with increasing age from birth to adulthood. Initial studies suggest that there are no known sex differences or circadian variations. It appears that somatomedin C is the somatomedin which is under the strictest growth hormone control and, thus, should potentially be the most valuable for the diagnosis of acromegaly and assessment of the chronic clinical status. In addition to the Laron dwarfs, other conditions have been associated with a discrepancy between circulating GH and somatomedin levels. These include kwashiorkor and renal insufficiency, in which circulating GH levels are high and somatomedins are low. In contrast, some children after surgical removal of a craniopharyngioma have been noted to have undetectable levels of growth hormone, normal somatomedin levels, and normal growth rates, severe hyperphagia, and massive obesity. The stimulus for somatomedin generation in these patients is unknown. Exogenous glucocorticoids and estrogens have been noted to decrease growth rates while causing a depression in somatomedin levels and little change in plasma GH levels. Thus, it is apparent that clarification of a number of questions about the relationship between GH and somatomedins should prove to be quite helpful for the understanding of acromegaly.

REGULATION OF GROWTH HORMONE SECRETION

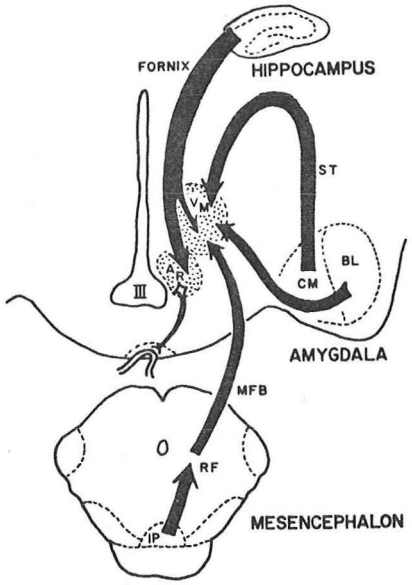
The sites of action of growth hormone are ubiquitous, and in this respect it is different from other pituitary hormones such as TSH, LH, and ACTH which have specific target organs that allow the operation of a classical negative feedback mechanism. The regulation of growth hormone secretion is complex, possibly to allow the many effects of GH to be regulated properly in spite of the lack of a negative feedback mechanism. An early approach to the regulation of growth hormone secretion involved the production of small lesions in the brain of experimental animals, particularly the rat. These studies must be interpreted with caution, for there are examples of striking discrepancies--for example, stress stimulates GH release in man but suppresses it in the rat. These studies indicate that neuroendocrine regulation of growth hormone secretion is mediated by the medial basal hypothalamus and, more specifically, implicate the ventromedial-arcuate region as the final common pathway for growth hormone control. This region of the hypothalamus, together with the adjacent lateral hypothalamus also functions as a final integrative center for homeostatic regulation of energy balance and food intake. Growth hormone secretion by the pituitary is thought to be regulated by two factors--a specific hypothalamic growth hormone releasing factor (GHRF) which has not yet been characterized and somatostatin, a somatotropin release inhibiting factor (SRIF). Since pituitary stalk section leads to a rapid fall in growth hormone secretion, it is thought that growth hormone, unlike prolactin, is primarily regulated through the activity of the growth hormone releasing factor; however, the interrelationships of these two releasing factors remain poorly defined at the present time (Figure 2).

REGULATION OF GROWTH HORMONE SECRETION



The following general mechanisms are operative in growth hormone secretion:

1. Suprahypothalamic regulation. Phasic changes in growth hormone secretion including episodic circadian secretion, stress-induced secretion, and sleep-associated GH release are probably mediated via brain centers. The major suprahypothalamic structures that mediate these mechanisms for growth hormone secretion have, in general, been identified by electrical stimulation studies in experimental animals. Stimulation of the hippocampus, basolateral amygdala, and the mesencephalic interpeduncular nucleus are effective in causing growth hormone release; whereas, stimulation of the corticomedial amygdala inhibits growth hormone secretion. These areas have major efferent connections with the ventromedial and arcuate nuclei. Thus, several regions of the limbic system appear to modulate GH release through both excitatory and inhibitory inputs to the hypothalamus (Figure 3). The



Major afferent pathways to the VMN-arcuate complex in the rat. ST, stria terminalis. VM, ventromedial hypothalamic nucleus. AR, arcuate nucleus. CM, corticomedial amygdala. BL, basolateral amygdala. MFB, medial forebrain bundle. RF, reticular formation. IP, interpeduncular nucleus.

Figure 3
(Martin, 1976)

suprahypothalamic mechanism is relatively independent of other stimuli to GH release such as hyperglycemia and the effects of catecholaminergic drugs. However, there is a variable influence of serotoninergic neurons on the sleep-induced mechanism so that sleep-induced growth hormone release can be blocked by serotonin antagonists. Sleep-associated growth hormone release often occurs coincident with stage III-IV sleep. A number of factors have now been described to decrease or abolish sleep-associated GH release (Table 2). However, there is increasing evidence that a common neural mechanism does not trigger slow wave sleep (SWS) and the release of growth hormone, because a number of examples of dissociation of these two events has been documented (Martin 1976). These dissociations include the following: (1) Cushing's disease in remission, (2) Nelson's syndrome, (3) hypothalamic

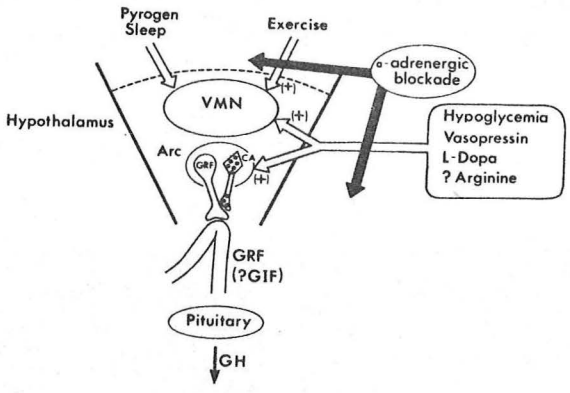
Table 2. Factors That Decrease SWS-Induced GH Release.

1. Metabolic or hormonal influences
   a. Excessive GH (acromegaly or exogenous administration)
   b. Cushing's disease
   c. Elevation in plasma free fatty acids
   d. Obesity
2. Central-nervous-system disorders
   a. Blindness
   b. Hydranencephaly
   c. Narcolepsy
3. Drugs
   a. Imipramine
   b. Medroxyprogesterone
4. Miscellaneous
   a. Age >50 yr

(Martin, 1973)

tumors, (4) steroid administration, (5) Addison's disease, (6) maternal deprivation syndrome, (7) administration of phenothiazines and tricyclic antidepressants. (8) Normal controls occasionally have SWS without GH release. Acute stress causes marked GH release, but the chronic stress of disorders such as the childhood maternal deprivation syndrome may result in chronic suppression of growth hormone release.

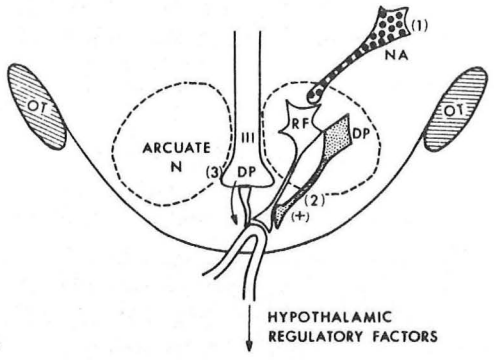
2. Monoamines in growth hormone regulation. The biogenic amines (dopamine, norepinephrine, and serotonin) are putative neurotransmitters in brain which are present in high concentrations in the medial basal hypothalamus. About 10-15% of neurons in the arcuate nucleus of the rat are catecholaminergic (containing norepinephrine or dopamine), of which the majority are dopaminergic. These monoamines have been implicated in the regulation of growth hormone secretion by studies involving the administration of precursors such as L-dopa, tryptophan, or 5-hydroxy-tryptophan to enhance the supply of these monoamines in the brain and by the use of a number of pharmacologic agents to define further the role of monoamines. For example, clonidine, a centrally-acting α-adrenergic agonist, stimulates GH release (Lal, 1975) and phentolamine, an α-adrenergic blocking agent, blocks GH release induced by L-Dopa, insulin hypoglycemia, vasopressin, and exercise (Martin, 1973; Figure 4). The exact mechanism of action of these biogenic amines in the regulation of growth hormone secretion is unknown. However, several mechanisms which have been postulated to explain the effects of catecholamines in mediating hypothalamic releasing factor secretion are depicted in Figure 5. Ascending noradrenergic inputs to the hypothalamus terminate directly on arcuate neurons and could, thereby, influence releasing factor/ transport into the hypothalamic-hypophyseal portal system. Secondly, dopaminergic neurons within the arcuate nucleus itself might facilitate releasing factor neurons directly by axonic synapses. A third and less likely possibility is that cerebrospinal transport of catecholamines regulates releasing factor neuron release. Stimulation of serotonin receptors by administration of tryptophan (Woolf, 1977) or 5-hydroxy-tryptophan (Imura, 1975) leads to an increase in GH release, though this mechanism has been somewhat inconsistent and weak. Sleep-induced GH release and the GH response to hypoglycemia are blocked by serotonin receptor antagonists (Bivens, 1973; Smythe, 1974).



Diagrammatic Representation of Adrenergic Control Mechanisms for GH Secretion.

Solid arrows indicate inhibition of GH stimulatory responses by α-adrenergic blockade. Pyrogen and sleep-associated GH release are not prevented by α-adrenergic blockade.

Figure 4
(Martin, 1973)



Possible Sites of Catecholamine Action in Potentiating Hypothalamic Hormone Release.

Numbers indicate three hypothetical mechanisms by which catecholamines may influence hypothalamic releasing-factor secretion (see text for explanation). NA represents noradrenergic neuron, RF releasing-factor neuron, DP dopaminergic neuron, III third ventricle, and OT optic tract.

Figure 5
(Martin, 1973)

3. Metabolic and endocrine.
   A. *Stimulate GH release:* These factors appear to pass through an intermediate catecholaminergic neuron which may block or augment their basic effect. For example, the administration of phentolamine, an α-blocker, usually blocks the effect; whereas, the administration of propranolol, a β-receptor blocker, augments the effect.
      (1) Hypoglycemia - presumably acts upon glucoreceptors in the region of the ventromedial nucleus or adjacent lateral hypothalamus.
      (2) Arginine - and other amino acids.
      (3) Glucagon - stimulates GH release even in spite of the attendant hyperglycemia which it produces.
      (4) Vasopressin - is usually active in stimulating GH release only during times of extreme stress such as surgery or when given in pharmacologic doses.
   B. *Suppress GH:* These factors also appear to be modified by the influence of an intermediate catecholaminergic neuron.
      (1) Hyperglycemia - acts through the same glucoreceptor mechanism in the ventromedial nucleus or adjacent lateral hypothalamus.
      (2) Increased plasma-free fatty acid concentration - this factor appears to be considerably more important in ruminants and animals other than man. Interestingly, the production of extremely elevated plasma levels of FFA with lipid infusions has been shown to modify sleep-induced GH release, an exception to the usual autonomy of sleep-associated GH release.
   C. *Sensitize GH release:*
      (1) Estrogens
      (2) Fasting
   D. *Desensitize GH release:*
      (1) Hypothyroidism
      (2) Glucocorticoid administration (pharmacologic doses)
      (3) Progestational agents

4. Cholinergic neurons. Administration of β-methylcholine, an acetylcholine analog, stimulates GH release in man. Other cholinergic agents such as pilocarpine and physostigmine stimulate GH release in experimental animals. Thus, cholinergic neurons appear to facilitate GH release, though in the rat this response is partially blocked by dopamine receptor blockers and α-adrenergic receptor blockers (Bruni, 1978). However, similar studies have not yet been reported in man.

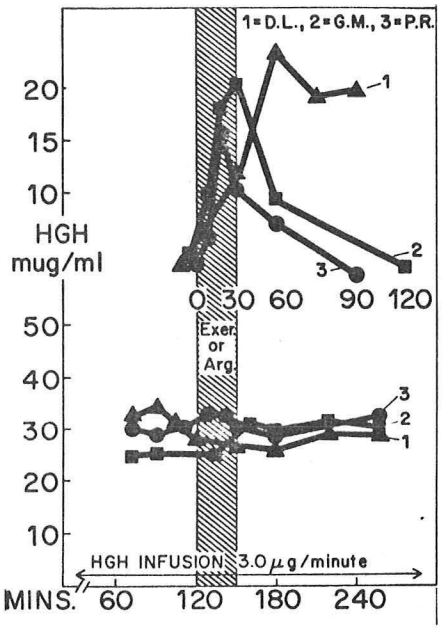
5. Undefined site of action.
   A. *Opioid peptides:* Morphine is known to have a number of diverse effects on brain metabolism including potent effects on dopamine, norepinephrine, and serotonin turnover in the brain. However, the stimulation of GH induced by acute administration of morphine cannot be fully blocked by α- and β-adrenergic receptor blockers or by serotonin receptor blockers. In addition, the response is attenuated, but not totally inhibited, by large hypothalamic lesions. However, the response is inhibited completely by somatostatin administration. Thus, it appears that morphine is capable of stimulating other receptor systems in the median eminence or in another hypothalamic area or possibly directly in the pituitary itself (Martin, 1975). The recent demonstration that β-endorphin is about 20-fold more potent than morphine in stimulating

GH release in the rat is of great interest (Rivier, 1977). This effect can also be blocked by somatostatin and is not totally inhibited by large hypothalamic lesions. It, thus, appears that opioid receptors are important in some way in modulating growth hormone release, though more specific studies in man have not been performed, and the site of these receptor mechanisms is unknown at present. Other opioids such as α-endorphin, δ-endorphin, and met^5-enkephalin do not have stimulatory effects on GH release in the rat (Chihara, 1978).

B. *Substance P:* Neurons containing this undecapeptide are highly concentrated in the hypothalamus. In the rat, substance P has a variable effect on GH release, causing stimulation at low dosages and suppression at higher dosages. There is some evidence that substance P may bind to opiate receptors at lower dosages and facilitate β-endorphin's action on GH release (Chihara, 1978). Like β-endorphin, the site of action of substance P is unknown, and neither cause GH release from pituitary cells grown in tissue culture. Since extensive hypothalamic lesions do not block its action, it is postulated that it has another site of action in the median eminence or pituitary area.

6. Autoregulation of growth hormone secretion. Circulating growth hormone appears to feed back either on the hypothalamus and/or pituitary to inhibit further growth hormone release and to cause pituitary depletion of growth hormone. For example, a constant infusion of GH results in the oblation of the stimulation of GH release by exercise or arginine infusion (Hagen, 1972; Figure 6).

Figure 6
(Hagen, 1972)

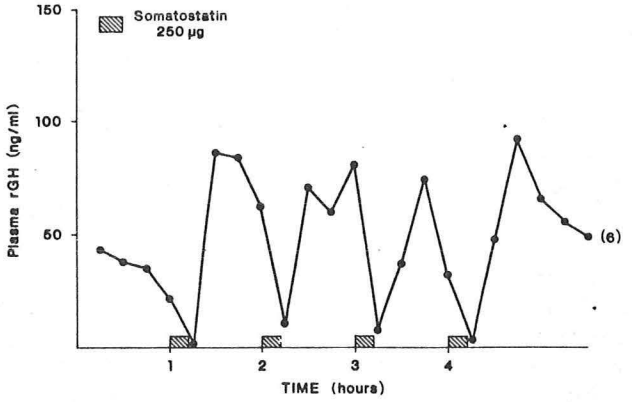


Pattern of growth hormone rise to exercise or arginine infusion in normal subjects (upper panel) and absence of growth hormone response to these stimuli during constant infusion of human growth hormone (lower panel).

7. Somatostatin. While attempting to characterize growth hormone releasing factor, Brazeau *et al* (1973) were repeatedly impressed by the demonstration of growth hormone release inhibitory activity in purified fractions of sheep hypothalamic extracts. They subsequently purified a tetradecapeptide which was named somatostatin or somatotropin release inhibiting factor (SRIF). During purification of somatostatin, these investigators chose only one of several areas

of SRIF activity, and so it is possible that other hypothalamic substances with SRIF activity will eventually be isolated.

Somatostatin has widespread inhibitory effects on hormone secretion, both across species and on different hormones. It is capable of preventing growth hormone secretion from the stimulatory effects of each of the previously considered categories (suprahypothalamic, monoamines, metabolic and endocrine, opiate receptors, substance P). The onset of action of SRIF is rapid, though transient, due to the short biological half life of less than 5 minutes in plasma. Following cessation of infusion, GH levels tend to rebound and may reach levels exceeding those prior to inhibition (Figure 7). This rebound phenomenon is prevented by hypothalamic VMN lesions in the rat, suggesting that a short loop feedback mechanism may contribute to the response. This observation of a short inhibitory action of SRIF associated with post-inhibitory rebound GH secretion has raised the question of whether physiological control of GH secretion requires a growth hormone releasing hormone. However, a number of compelling arguments remain for the existance of GHRH (Martin, 1976). Somatostatin is also widely distributed throughout the brain, particularly in the preoptic area and amygdala. It is, thus, possible that it affects growth hormone release by a number of different mechanisms.



Postinhibitory rebound secretion of GH after repeated infusions of somatostatin in the rat.

Figure 7
(Martin, 1976)

TABLE 3. *DRUGS AFFECTING GROWTH HORMONE RELEASE*

I. Complex effects
   - A. Synthesis inhibitors - ↓ GH
     1. Tyrosine hydroxylase
        α-methyl-*p*-tyrosine
     2. Dopamine-β-hydroxylase
        Disulfiram, fusaric acid
   - B. Amine depleters - ↓ GH
     Reserpine - ↓ DA, NE, SER
   - C. Amine uptake inhibitors - ↑ GH
     Tricyclic antidepressants, amphetamines
   - D. Amine releasers - ↑ GH
     Amphetamines

II. More specific effects
  A. Receptor antagonists
    1. Dopamine - ↓ GH
       Haloperidol, phenothiazines, pimozide, phentolamine (weak)
    2. α-adrenergic - facilitates ↓ GH
       Phentolamine, phenoxybenzamine
    3. β-adrenergic - facilitates ↑ GH
       Propranolol
    4. Serotonin ↓ GH
       Cyproheptadine, methysergide, phenothiazines (weak)
  B. Receptor agonists
    1. Dopamine - ↑ GH
       Bromocriptine, apomorphine, piribedil
    2. α-adrenergic - ↑ GH
       Phenylephrine, methoxamine, clonidine
    3. β-adrenergic - ↓ GH
       Isoproterenol
    4. Cholinergic - ↑ GH
       Pilocarpine, physostigmine, β-methylcholine
    5. Opiate - ↑ GH
       Morphine
  C. Serotonin synthesis inhibitors - ↓ GH
     p-chlorophenylalanine

Martin (1973), Frohman (1975), Sulser (1971), Lal (1973), Holland (1978), Müller (1977), Lal (1975), Martin, 1976.

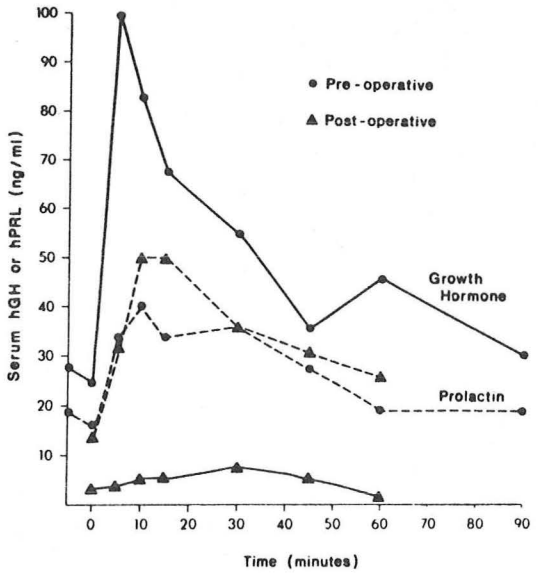
GROWTH HORMONE REGULATION IN ACROMEGALY

TABLE 4. *PARADOXICAL GROWTH HORMONE REGULATION IN ACROMEGALY*

A. Decrease secretion
  1. Dopamine receptor agonists
  2. Amphetamines
B. Increase secretion
  1. Dopamine receptor antagonists
  2. TRH, LRH
  3. Hyperglycemia

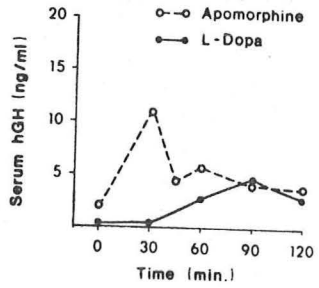
Abnormal growth hormone responses in the acromegalic patient (Table 4) have led to a lively debate about whether these responses reflect simply abnormal responses of the adenoma tissue or whether they suggest that acromegaly is a primary hypothalamic abnormality. Recovery from these paradoxical GH releases after transsphenoidal selective adenomectomy (Hoyte, 1975, Figures 8 & 9; Samaan, 1974) has provided strong evidence for the thesis of a primary pituitary abnormality. Matsukura (1977) noted that some of the *in vivo* GH responses before surgery correlated with *in vitro* studies utilizing whole homogenates of the removed pituitary tumors with assay for adenylate cyclase after stimulation with TRH, LRH, norepinephrine, dopamine, PGE_1,

glucagon, and rat median eminence extract. The TRH and/or LRH release of GH before surgery coincidentally related to the response of adenylate cyclase of each pituitary adenoma. However, there was no consistent correlation between the adenylate cyclase responses to biogenic amines and the GH release after L-Dopa or 5-hydroxytryptophan. These results then indicated the presence of multiple hormone receptors in the cellular membranes of GH producing pituitary adenomas as a cause for the initiation of the paradoxical responses. Similarly, dispersed cell cultures of human GH producing adenomas respond to TRH with GH release which can be inhibited by bromocriptine (Adams, 1979). Thus, these studies suggest that the process of dedifferentiation of pituitary adenoma tissue is an integral and probably primary event in the initiation of acromegaly in a subgroup of patients.



Serum GH and prolactin responses to TRH (500 μg iv) pre- and post-operatively: GH, solid lines; prolactin, broken lines; closed circles, pre-operatively; closed triangles, post-operatively.

Figure 8
(Hoyte, 1975)



Serum GH response to L-DOPA (500 mg orally) and apomorphine (0.75 mg subcutaneously), post-operatively. Note change of scale.

Figure 9
(Hoyte, 1975)

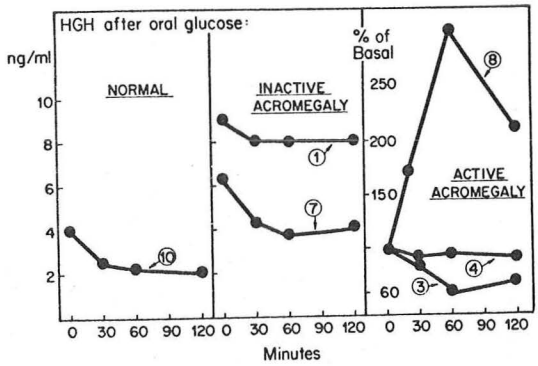
In contrast, other evidence suggests a primary hypothalamic disturbance as the cause for acromegaly. Other causes of paradoxical GH responses have been noted (Table 5). Some acromegalics have a striking increase in circulating growth hormone releasing factor in comparison to normal subjects (Figure 10). In addition, a minority of acromegalic patients exhibit a more normal regulation of GH compatible with regulation of secretion at a higher set point. Almost all acromegalic patients demonstrate a decrease in GH with the administration of serotonin antagonists. Furthermore, most patients demonstrate normal circadian variations in GH release, though the sleep-associated GH release is commonly lost. A smaller subgroup, however, demonstrate the classical responses to insulin hypoglycemia, arginine infusion, exercise, etc. (Figure 11). Cryer and Daughaday (1974) have reported that the usual modest effect of α-adrenergic blockade plus β-adrenergic stimulation in blocking GH release is potentiated in patients with acromegaly.

In acromegaly the GH response to L-tryptophan is absent, suggesting that the regulation of GH secretion by serotoninergic pathways may be qualitatively abnormal (Glass, 1979). However, the question of pituitary vs hypothalamic etiology was not resolved because one patient with acromegaly cured by transsphenoidal hypophysectomy had a restoration in the normal stimulation of GH by L-tryptophan.

Causes of "Paradoxical" GH Responses.

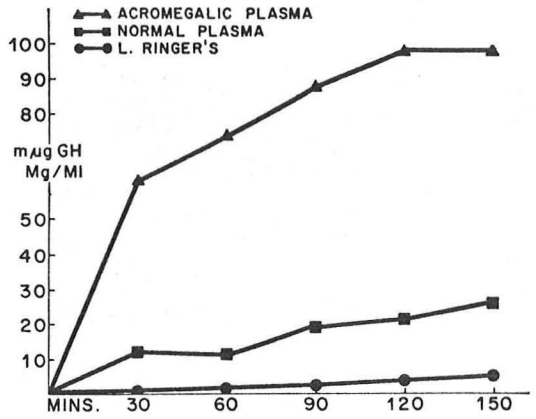
I. Normal response in neonate
II. Central-nervous-system disorders
  1. Hypothalamic tumors
  2. Huntington's chorea
  3. Wilson's disease
III. Endocrine-metabolic disorders
  1. Acromegaly
  2. Turner's syndrome
  3. Acute intermittent porphyria
  4. Renal failure
IV. Nutritional disorders
  1. Anorexia nervosa
  2. Kwashiorkor
  3. Breast carcinoma

TABLE 5 *(Martin, 1973)*



Patterns of serum growth hormone response to an oral glucose load where mean absolute growth hormone values for 10 normal subjects and 8 inactive acromegalic patients are shown as against per cent change from basal levels for 15 active acromegalic patients whose basal values ranged from 15 to 183 ng/ml serum.

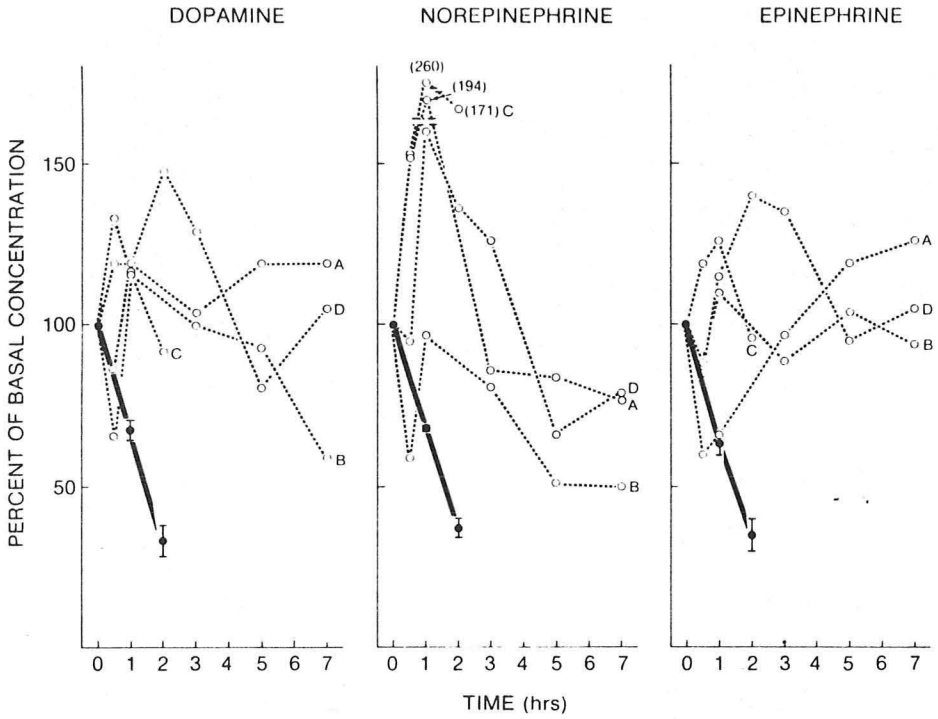
Figure 11
(Lawrence, 1970)



Comparison of growth hormone release from monkey pituitary halves incubated in the absence of plasma, or in the presence of normal or acromegalic plasma. Represented are a single acromegalic incubate, and the mean of 8 incubations with normal plasma.

Figure 10
(Hagen, 1971)

Further evidence for a primary hypothalamic disturbance in the regulation of GH secretion in acromegalics has been provided by Van Loon (1979). Plasma dopamine, norepinephrine, and epinephrine normally decrease in response to bromocriptine (Figure 12) or LRH (Figure 13) administration. However, acromegalic patients fail to show a decrease in any of these catecholamines. Van Loon has postulated that this failure to suppress plasma concentrations of these three catecholamines in response to these two stimuli is compatible with a defect in the regulation of GHRF in which a catecholaminergic neuron is responsible for modulating the release of GHRF. The nature of the defect remains unclear, though Van Loon postulates that it involves a defect in a presynaptic receptor mechanism in the catecholaminergic neuron since presynaptic mechanisms of action for bromocriptine and LRH have been demonstrated. These recent studies are of great interest and suggest that at least a subgroup of patients with acromegaly may have a fundamental hypothalamic defect. However, the clearly demonstrated normalization of GH regulation by removal of a pituitary microadenoma also presents a strong case for a primary pituitary etiology in other cases. These questions remain unresolved at the present time.



Plasma dopamine, norepinephrine, and epinephrine responses to bromocriptine (2.5 mg orally). ●—●, Normal men [data taken from Van Loon *et al.* (7)]; ○- -○, acromegalics A, B, C, and D.

Figure 12
(Van Loon, 1979)

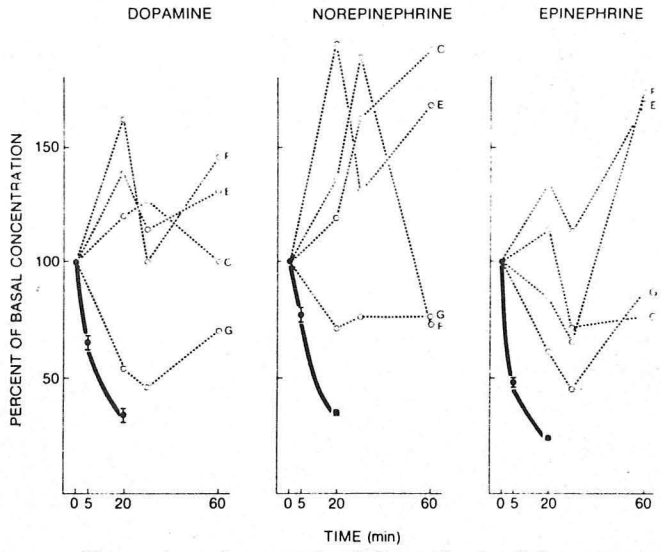


Figure 13
(Van Loon, 1979)

Plasma dopamine, norepinephrine, and epinephrine responses to LRH (100 μg iv). ●—●, Normal men [data taken from Van Loon (8)]; ○- -○, acromegalics C, E, F, and G.

CLINICAL MANIFESTATIONS

Incidence: 1:5,000 - 1:15,000 hospital admissions
Racial distribution: Widespread
Male/female ratio: Equal
Age of onset: 3rd decade most common; 4th & 5th decades common
Delay of 10-20 years from onset → diagnosis
Early death - rapidly growing tumors
Family history of acromegaly: 4% (? Multiple Endocrine Neoplasia, Type I)

Presentation
Early: (3-6 years)
Acral enlargement (hat, glove, ring, shoe size), weight gain
Coarsening of features - overgrowth of frontal, malar, nasal bones
Menstrual irregularities, amenorrhea
Increased sweating, heat intolerance
Slight hypertrichosis
Decreased libido and potency
Headache
Later:
Features of tumor enlargement
Complications - cardiovascular, diabetes mellitus, arthritis

Physical examination

A. General - hypertension, weight gain from ↑ protein synthesis and ECF
B. Skin - coarse and thickening, large pores, furrows, oiliness, ↑ odor, melanosis, fibroma molluscum, hypertrichosis
C. Head and Neck - enlarged paranasal sinuses, hearing loss or vestibular symptoms from bone overgrowth, optic atrophy, visual field loss, rhinorrhea, enlarged and furrowed tongue, increased interdental spaces, thyromegaly, vocal cord enlargement. The voice is characteristically deep, sonorous, and heavy from the changes in vocal cords and paranasal sinuses and difficulty in moving the tongue.
D. Chest:
Breasts - galactorrhea
Heart - cardiomegaly, evidence of CHF
Lungs - ↑ AP diameter, bronchiectasis rarely
E. Abdomen - hepatomegaly, splenomegaly
F. Joints and Extremities - acromegaly, arthritis
G. Neurologic - signs of tumor compression, mild proximal muscle weakness, peripheral neuropathy from bony overgrowth, carpal tunnel syndrome, and palpable peripheral nerves

Numerous other features on physical examination may reflect the complications of diabetes mellitus, HCVD, ASHD, and pituitary insufficiency.

The frequency of various clinical manifestations has been summarized (Table 6) by Daughaday (1974) and primarily derived from Davidoff (1926) and Gordon (1962).

TABLE 6

ACROMEGALY: FREQUENCY OF MANIFESTATIONS

	Per Cent
Parasellar Manifestations	
Enlarged sella	93 (80-93)
Headache	87 (75-87)
Visual impairment	62 (5-62)
Uncinate fits	7
Rhinorrhea	15
Pituitary apoplexy	(3)
Papilledema	3
Growth Hormone Excess	
Weight gain	39
Hypermetabolism	70
Hyperhidrosis	60
Impaired glucose tolerance	25 (37)
Clinical diabetes mellitus	12 (13)
Acral growth	100
Prognathism	Common
Arthritic complaints	(64)
Osteoporosis	Common
Soft tissue growth	100
Hypertrichosis	53
Pigmentation	40
Fibroma molluscum	27
Visceromegaly	Common
Goiter	25
Disturbances of Other Hormones	
Lactorrhea (?prolactin excess)	4
Hyperadrenocorticism	Rare
Hyperthyroidism	Rare
Increased libido	38
Decreased libido, male	23

Most of the data for the preparation of this chart were obtained from Davidoff. When other sources were used, the figures are placed in parentheses.

PATHOPHYSIOLOGICAL CHANGES IN ACROMEGALY

A. *Endocrine:*

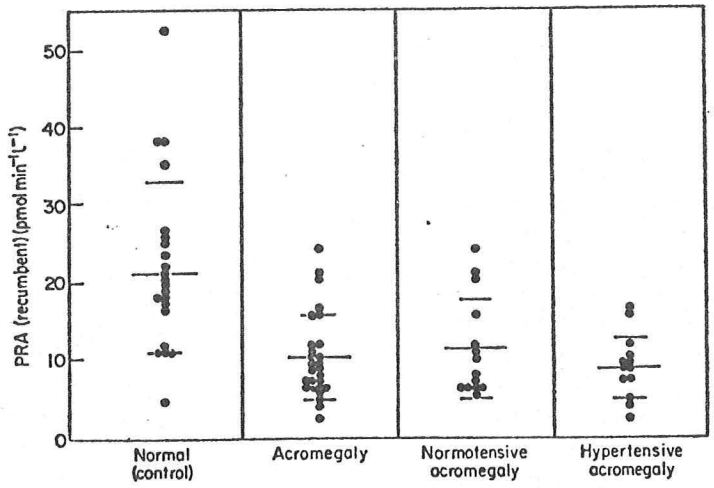
1. Thyroid - An elevated basal metabolic rate is noted in about 70% of patients with acromegaly. In addition, classical thyrotoxicosis has been noted in a low percentage of patients (Hamilton, 1972) and thyroid enlargement is noted in about 25%. However, recent extensive studies (Corrigan, 1978) have shown that thyroid function is normal except in those few patients who have thyrotoxicosis. These studies included determinations of total T_4, T_3, reverse T_3, TBG, free T_4, and free reverse T_3 concentrations.
2. Adrenocortical function - The majority of 61 patients with active acromegaly had an elevated secretion rate of cortisol and elevated urinary excretion rates of 17-hydroxy-corticosteroids (Charro, 1973). The 17-keto-steroids were significantly elevated only in men. Morning plasma cortisol, diurnal variation of cortisol, and urinary free cortisol were in the normal range. Those patients with an increased secretion rate of cortisol had an elevated metabolic clearance rate. There was a normal response to ACTH administration and to dexamethasone and metyrapone testing. Thus, it appears that the majority of patients with acromegaly have a hypersecretion of cortisol secondary to the hypermetabolic state induced by growth hormone. There is no evidence for a direct action of growth hormone on adrenal steroidogenesis (Roginsky, 1969). It appears likely that some of the early reports that growth hormone stimulated secretion of several adrenal corticosteroids were due to ACTH contamination of some of the growth hormone preparations which were used (Baumann, 1972; Cushman, 1966).

3. Diabetes - Growth hormone is diabetogenic (Luft, 1959). Impaired glucose tolerance is present in about half the cases of acromegaly, but clinical diabetes mellitus occurs in only about 10%. Compensation for the insulin resistance induced by GH is provided by hyperplasia of the islets of Langerhans, allowing an increased insulin response after glucose administration (Luft, 1967; Fineberg, 1970) and to intravenous tolbutamide administration (Beck, 1965). Since clinical diabetes appears with about the same incidence as the estimated gene frequency for diabetes in the general population, it is thought that most acromegalics with clinical diabetes have genetic diabetes.
4. Pituitary - About one-third of pituitary adenomas causing acromegaly also produce prolactin. In the past it was thought that growth hormone had sufficient intrinsic lactogenic activity so that it could induce galactorrhea. However, it would appear at present that most of these cases of galactorrhea are induced by simultaneous prolactin overproduction. About half of a group of 28 acromegalics had evidence of pituitary insufficiency (Goldfine and Lawrence, 1972). Hypogonadism was the most frequent followed next by loss of TSH and then ACTH. In general, hypopituitarism could not be related to tumor size, duration of disease, or therapy.

B. *Hypertension:*

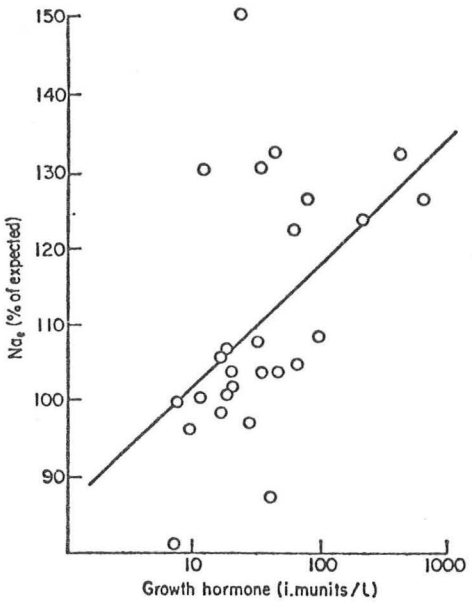
About one-third of acromegalic patients have hypertension. The cause of the elevated blood pressure is unknown, but it is clear that the majority of patients have low renin hypertension (Figure 14; Snow, 1977; Cain, 1972). Administration of human growth hormone to man has been accompanied by sodium retention and expansion of the extracellular fluid volume. It is presumed that the most likely explanation for the hypertension is that the sodium retention secondary to the excess production of growth hormone leads to hypertension. A positive correlation has been demonstrated between extracellular fluid volume and serum growth hormone concentration in acromegalic patients (Figure 15). Interestingly, primary aldosteronism has been described in several acromegalic patients (Strauch, 1972; Dluhy and Williams, 1969). The reason for this association is unknown. High levels of growth hormone have been associated with an increased incidence of both benign and malignant neoplasms in the rat, including adrenocortical adenomas. However, it is also possible that these cases with adrenal adenomas represent unuusal cases of multiple endocrine neoplasia type 1.

Figure 14
(Snow, 1977)



Fasting recumbent plasma renin activity (PRA) in control subjects and in patients with acromegaly PRA was not available in two acromegalic patients. Mean PRA (long bars) was significantly reduced in acromegalic patients ($P<0.001$); short bars show SD.

Figure 15
(Snow, 1977)



Relationship between fasting recumbent growth hormone concentration (09.00 hours) and Na_e in 26 acromegalic patients for whom both measurements were available. The regression line (O——O), $y = 14{\cdot}9x + 88{\cdot}3$ ($r = 0{\cdot}45$, $P < 0{\cdot}05$), is shown.

C. *Cardiac:*

The heart can reach enormous size--up to 1,295 gm in acromegaly (Hejtmancik, 1951). Though patients uncommonly present with evidence of severe congestive heart failure, a hypertrophic cardiomyopathy may accompany long-standing, poorly-treated acromegaly (Hirsch, 1969). Intraventricular conduction disturbances are common on the electrocardiogram, and recent studies (Martins, 1977) have shown that patients commonly have concentric left ventricular hypertrophy with decreased systolic time intervals. Though there has been some discussion about whether growth hormone *per se* could result in a hypertrophy cardiomyopathy without the presence of coexisting congestive heart failure or hypertensive cardiovascular disease, these investigators documented a few patients who clearly had no evidence of these other complications but who had a hypertrophic cardiomyopathy. However, these patients all had acromegaly of greater than 13 years duration and fasting growth hormone concentrations greater than 100 ng/ml. Most patients who were treated satisfactorily early in the course of acromegaly were left with normal cardiac function, suggesting that a considerable component of the cardiac changes are reversible.

D. *Renal:*

The kidneys exhibit a remarkable increase in size. The glomeruli may have twice the normal diameter and comparable increases in the size of the renal tubules. Remarkable changes in renal function have been described so that the glomerular infiltration rate may increase to over 300 ml/min, and there may be correspondingly dramatic increases in tubular reabsorption of glucose and tubular secretory maximum for PAH. However, when these changes are corrected for the increased extracellular fluid volume, the changes are normal (Ikkos, 1956). Growth hormone increases tubular reabsorption of phosphate and commonly leads to mild hyperphosphotemia.

E. *Skeletal:*

The articular and other limb changes in acromegaly have been summarized by Kellgren (1952). In Marie's original cases of acromegaly, attacks of rheumatism and pains in the limbs and back figured prominently, and there was an early emphasis by many clinicians upon joint changes. However, with later understanding of the pituitary etiology of the disease, attention shifted somewhat away from this area. However, joint changes are common in acromegaly. Kellgren (1952) noted articular symptoms in two-thirds of 25 patients. The most common and earliest manifestation was a hyperextensibility of the joints characterized by a striking overgrowth in the articular cartilage and soft tissues together with remodeling of the bones so that the trabeculae of the bone ends became thickened and much more widely spaced, giving a general appearance of porosis, while the shafts became narrow and dense (pipestem). These changes are particularly prominent in the metacarpals and metatarsals. Softening of the ligaments, muscles, and even skin cause the extremities to acquire a curious gelatinous or rubbery consistency. These patients presented a clinical picture characterized by limb pains, instability of the joints, recurrent synovial effusions, and palpable thickening of the synovial membranes of the knee and other joints. In contrast, a smaller percentage of patients presented late in the course of the disease with a clinical picture of markedly restricted joint motion from massive bony outgrowths. In these patients the massive bony outgrowths could be palpated around the joints.

F. *Neurological:*

1. Myopathy - Mastaglia (1970) evaluated neuromuscular function in eleven acromegalics. Mild proximal muscle weakness was present in 6 cases and serum creatinine phosphokinase levels were elevated in 5. Muscle biopsy revealed hypertrophy of both type I and type II fibers, enlargement of sarcolemmal nuclei and glycogen deposition. These patchy myopathic changes are probably responsible for the muscle weakness and easy fatigueability noted by some patients and the soft, bulky muscles noted in some patients (Kellgren, 1952).
2. Neuropathy - Carpal tunnel syndrome has been noted in about 35% of acromegalics (O'Duffy, 1973). It usually resolves after successful treatment of the acromegaly. Peripheral neuropathy can also be produced by bony overgrowth. Many patients note burning pains and paresthenias in the extremities from the peripheral neuropathy. A rare generalized hypertrophic peripheral neuropathy with perineural and endoneural fibrous proliferation and palpable peripheral nerves has been described (Stewart, 1966).

G. *Pulmonary:*

A few patients have ventilatory difficulties secondary to marked polypoid overgrowth of the nasal mucosa and kyphoscoliosis. Chronic bronchitis and bronchiectasis in a few patients has been attributed to these difficulties, and an increased death rate from respiratory complications has been noted (Wright, 1970).

H. *Associated diseases:*

1. Meningiomas (Bunick, 1978) - There appears to be an increased incidence of intracranial meningiomas associated with acromegaly. Though most of these cases are possibly explained by radiation-induced neoplasia, a few of the cases have preceeded irradiation.
2. Phakomatoses (Hoffman, 1978) - Acromegaly has been associated with several of the phakomatoses, occurring most commonly with neurofibromatosis and much less frequently with tuberous sclerosis.

3. Primary empty sella syndrome (Molitch, 1977) - GH producing tumors have rarely occurred in a primary empty sella. The common usage of computerized axial tomography for the diagnosis of pituitary tumors should allow the proper identification of those rare cases with coexisting primary empty sella syndrome.

ACROMEGALY - ROENTGENOLOGIC CHANGES

SKULL	%
Enlarged sella turcica	94*
Cranial vault - thickening or thinning	77
Enlarged paranasal sinuses	74
HANDS AND FEET	
↑ head, ↓ shaft of phalanges	87
Increased soft tissue	78
Joint cartilage hypertrophy	61
Large tufts of terminal phalanges	48
Osteoarthritis	48
Exostoses	39
SPINE	
Increased intervertebral disks	100
Osteoarthritis	75
Vertebral body changes (anterior apposition, posterior resorption)	50
THORACIC CAGE	
Anterior bulging of sternum	80
Increased AP diameter	60

*Lang and Bessler: *Am J Roentgenol* 86:321, 1961

ROUTINE LABORATORY STUDIES:

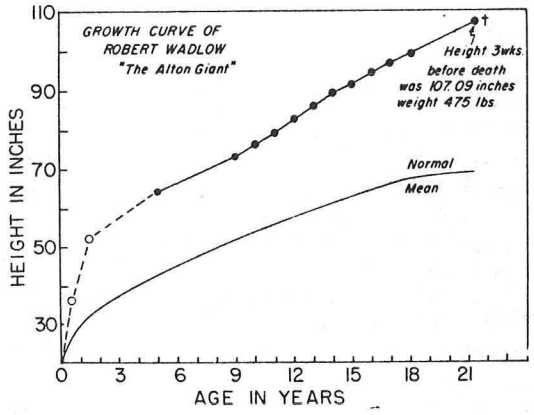
Routine laboratory studies are of very little use in the diagnosis of acromegaly. Before growth hormone measurements were available, an elevation in serum phosphorus was noted in a majority of patients. However, more recent series (Nadarajah) have noted increased serum phosphorus in only about 20% of untreated patients. Other routine lab studies usually reflect complications of the disease or the manifestations of accompanying diseases.

PITUITARY GIGANTISM

Pituitary gigantism is an extremely rare condition with bizarre and grotesque manifestations that often cause its victims to become local celebrities and side show curiosities. The remains of such unfortunate victims were highly prized by earlier physicians as medical museum pieces of great interest.

The pattern of growth induced by excessive secretion of growth hormone is determined by age and genetic factors. In contrast to adults with excessive growth hormone secretion, giants have the onset of excessive growth hormone secretion at the time of birth or about the time of puberty. Since many of these individuals are also hypogonadal, those giants who survive into adult life have the long extremities of enuchoidism combined with mildly acromegalic features. Almost all of them have died in early adult life of infections--particularly cellulitis of the lower extremities, progressive debility due to the myopathy and neuropathy of acromegaly, or the complications of the pituitary tumor or of hypopituitarism (Haigler, 1973; Ludwig, 1967). Occasional patients, though, have been recorded to live to up to 49 years of age (Musa, 1972). The growth curve of one of the larger typical giants, the Alton giant, is shown in Figure 16. The clinical and laboratory features share many resemblances to adult acromegaly. Occasional patients have been described who present with gigantism and hypopituitarism and a normal sella turcica (Ludwig, 1967). Several cases have been reported that were extremely resistant to treatment. Therefore, an aggressive early approach to normalize growth hormone production as much as possible should be made.

Figure 16



Growth curve of the Alton giant. The first two points (open circles) are estimates based on recorded weights and presumed normal body composition. (Reproduced from Daughaday, W. H., and Parker, M. L.: *Disease-a-Month*, August, 1962, by permission of Year Book Medical Publishers, Inc.)

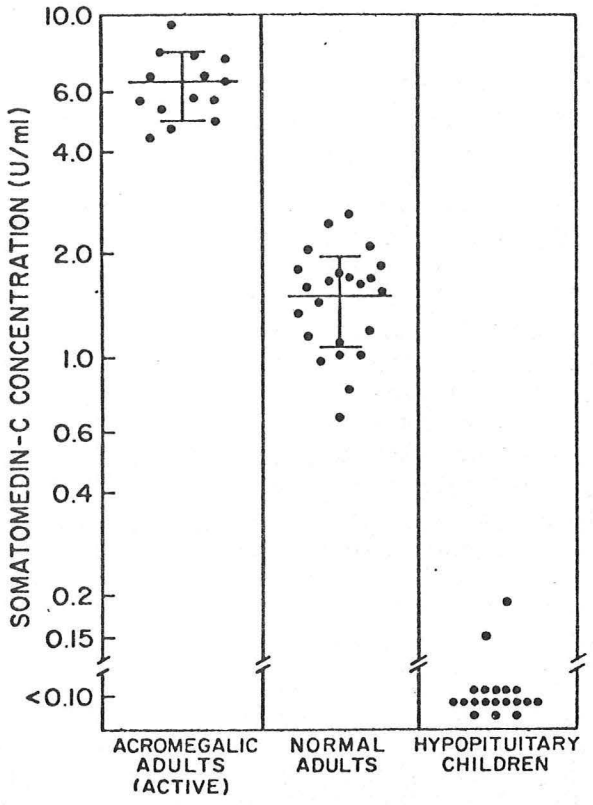
DIAGNOSIS OF ACROMEGALY

The diagnosis of acromegaly in a patient with the characteristic physical findings is usually made today by the measurement of serum growth concentration about 90 minutes after 75 gm glucose administration (normal response is to suppress to less than 5 ng/ml). Levels between 5-10 ng/ml can be considered indeterminant and higher values support the diagnosis of acromegaly. However,

several factors should be considered. First, the duration of the disease should be noted. Clinical manifestations of acromegaly are cumulative, so that marked elevations in the serum growth concentration in the presence of minimal acromegalic changes of recent onset are not unusual. Likewise, patients with long-standing active disease may have only slight GH elevations. Furthermore, many patients who have been treated appear to have a decrease in the clinical activity of the disease with persistence of minimal elevations in the serum growth hormone concentration. These findings have fostered the concept of "burned-out" acromegaly and have led to a number of therapeutic dilemmas about the need for further treatment.

As previously noted, most of the actions of growth hormone are mediated through somatomedins, and the transmission mechanism is poorly understood. It is hoped that the newer assay for somatomedin C may facilitate clinical assessment of the chronic activity of the disease. Furlanetto *et al* (1977) have reported a complete separation between serum somatomedin C concentrations in acromegalic adults, normal adults, and untreated hypopituitary children (Figure 17). This assay appears to provide a considerable improvement over some of the earlier bioassays and radioreceptor assays for somatomedins.

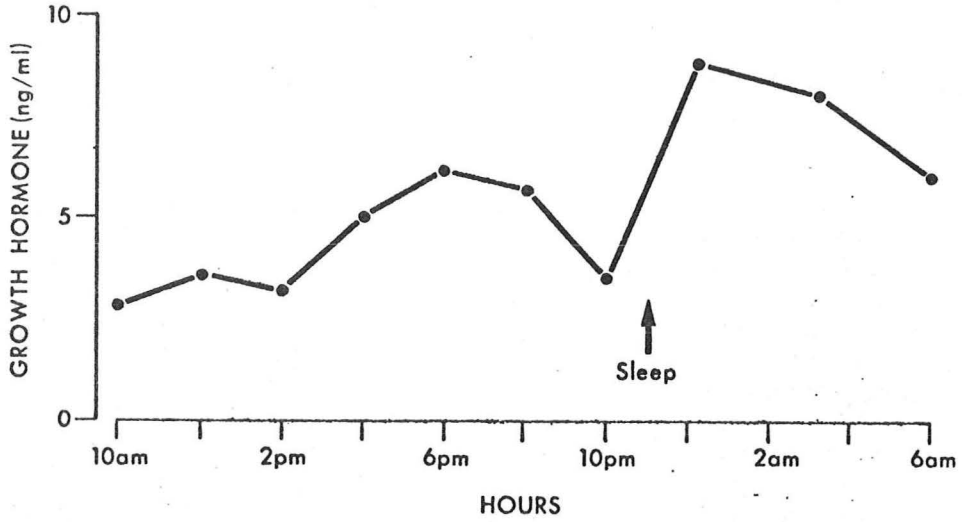
Figure 17
(Furlanetto, 1977)



Serum somatomedin-C concentrations in acromegalic adults, normal adults, and untreated hypopituitary children. Assays were performed by the nonequilibrium assay procedure. Bars indicate the mean±1 SD.

A case of acromegaly with relatively normal circadian variations in GH but elevated plasma somatomedin levels has recently been described (Feingold, 1979; Figure 18). Unfortunately, no validation of the somatomedin methodology

was provided in the report, but it appears that a relatively nonspecific assay was used. However, Clemmons (1979) has recently presented additional experience with the specific RIA for somatomedin C. They noted a much better correlation of serum SM-C levels with heel pad thickness than with glucose suppressed growth hormone and found 5 of 57 clinically active acromegalics to have "normal" GH suppression with glucose (all had 4-5 ng/ml) but elevated serum SM-C levels. Thus, the SM-C RIA does appear to provide a significant clinical advance. However, long-term studies are needed to validate this initial promising experience. Until the clinical utility of this and similar assays has been established and the assay becomes available for general clinical use, clinical criteria must continue to be utilized. The heel-pad thickness is not helpful for assessing chronic activity since it can remain abnormally thickened (Steinbach, 1964).



Graph showing the serum growth-hormone concentration over a 20-hour monitoring period.

Figure 18 (Feingold, 1979)

UNUSUAL CAUSES OF ACROMEGALY

1. Islet cell tumor of pancreas - producing immunoreactive GH. Removal of the tumor produced cure of the acromegaly (Caplan, 1978).
2. Carcinoma of lung - producing GH. One patient with worsening in glucose tolerance and symptoms compatible with hypertrophic pulmonary osteoarthropathy was found to have a lung carcinoma producing GH. No typical somatic manifestations were present (Greenberg, 1972).
3. Tumors producing a growth hormone releasing factor. Frohman (1979) has recently reported production of this factor by bronchial carcinoid and pancreatic islet cell tumors in patients with typical acromegaly.

NATURAL HISTORY AND PROGNOSIS

The natural history of acromegaly has been studied. Bishop and Briggs (1958) noted that 80% of 100 patients died before the age of 60--most from cardiovascular causes. The best study of this problem (Wright, 1970) involved the evaluation of post-mortem reports and hospital and clinic records of 194 patients, of which 55 died and 28% were not treated. The following conclusions were made:

1. The number of deaths was almost twice that expected from the general population of a similar structure.
2. An increased death rate from cardiovascular and respiratory disease in men and cerebrovascular and respiratory disease in women was noted.
3. Increased mortality was associated with hypertension and clinical diabetes, but not with chemical diabetes.
4. Increased mortality was not associated with the patient's sex, nor with optic chiasmal compression.
5. Treatment decreased the mortality rate.

Young (1965) has related the tumor histology to the clinical course. Typical adenomas were composed of well-granulated acidophils, were small (intra-sellar), and were not felt to contribute directly to the cause of death (usually a cerebrovascular cause). Atypical tumors were a heterogeneous group of larger tumors that were often morphologically indistinguishable from chromophobe adenomas and were associated with aggressive local growth and a tendency to recur. Physical findings of acromegaly were more striking in those patients with more typical acidophil tumors.

TREATMENT OF ACROMEGALY

1. Surgical - Surgical treatment of acromegaly appears to be the choice of treatment in most patients at the present time who do not have specific contraindications to surgery. Harvey Cushing early utilized the transsphenoidal approach to the pituitary. However, subsequent improvement in neurosurgical techniques for the frontal approach led to almost complete abandonment of transsphenoidal hypophysectomy (TSHS) until the early 1960's. Since then newer methodology including the use of televised radiofluoroscopic monitoring, the operating microscope, and improvements in general microsurgical techniques have allowed for considerable improvement in the technique of transsphenoidal hypophysectomy so that at present it is the most commonly used surgical technique. Several large series of transsphenoidal hypophysectomy for acromegaly have now been reported (Table 7, Figure 19). In general, the experience with transsphenoidal hypophysectomy is that 75-85% of newly-diagnosed previously untreated acromegalic patients can be cured with transsphenoidal hypophysectomy and approximately another 10-15% will have improvement. Those patients with small intrasellar tumors and with presurgical serum growth hormone levels of <50 ng/ml have a much better prognosis. The overall mortality from several series is now in the range of less than one percent, and the incidence of surgical complications is about 5%. One major advantage of transsphenoidal hypophysectomy is that circulating levels of growth hormone decrease immediately, and significant pituitary insufficiency occurs in only about 5-15% of cases. In fact, almost as many patients regain gonadotrophin function postoperatively as lose it (Williams, 1975). This latter factor obviously depends upon the surgical technique utilized and upon the size of the pituitary tumor.

Leavens *et al* (1977) and Faglia (1978) have reported their use of TRH stimulation before and after TSHS in patients with attempted total tumor removal. About 75% of patients with acromegaly will demonstrate a paradoxical increase with TRH. These investigators have compared the presurgical response to TRH with similar TRH testing done about 2-3 weeks postoperatively. Those patients who have a return to the normal TRH response (no stimulation with TRH) have an excellent prognosis with no recurrence of the pituitary tumor noted

over a 3-6 year period (Faglia *et al*, 1977). Patients with elevated serum GH (post-glucose) or with persistence in the abnormal TRH stimulation have not had complete tumor removal, and so they should then be reoperated with total hypophysectomy or submitted to pituitary irradiation. The choice of these latter two treatment modalities has not been satisfactorily compared. However, the choice of pituitary irradiation appears much better at present.

TABLE 7. *TREATMENT OF ACROMEGALY*

	Total # Pts.	Combined Rx # Pts.	Cured-% (normal GH)	% Improved	COMPLICATIONS - % *Hypopituitary* Partial	Total	*Non-endocrine* Morbidity	Mortality
								Surgical
A. Transsphenoidal Hypophysectomy								
Hardy (1979)	120	10	78	16	6	5		<1
Williams (1975)	59	14	78	19	8	15	7	0
U (1977)	38	8	79	18	7	0	13	0
B. Irradiation								Neurological Injury
1. Heavy particle			[37-2 yrs 94-9 yrs]					
Lawrence (1970)	120				25+		"low"	
Kjellberg(1978)	179		44	41	12+		34	0
2. Conventional								
Lawrence (1971)	28							
Roth (1970)	20		40	55				
Kramer (1973)	19		79	5	18	5	18	
Aloia (1978)	8		50	50	62			
C. Bromocriptine				(clinical)				Side Effects
Besser (1978)	73	48	20	77	Unchanged		50	1(?)
Cassar (1977)	12		33					

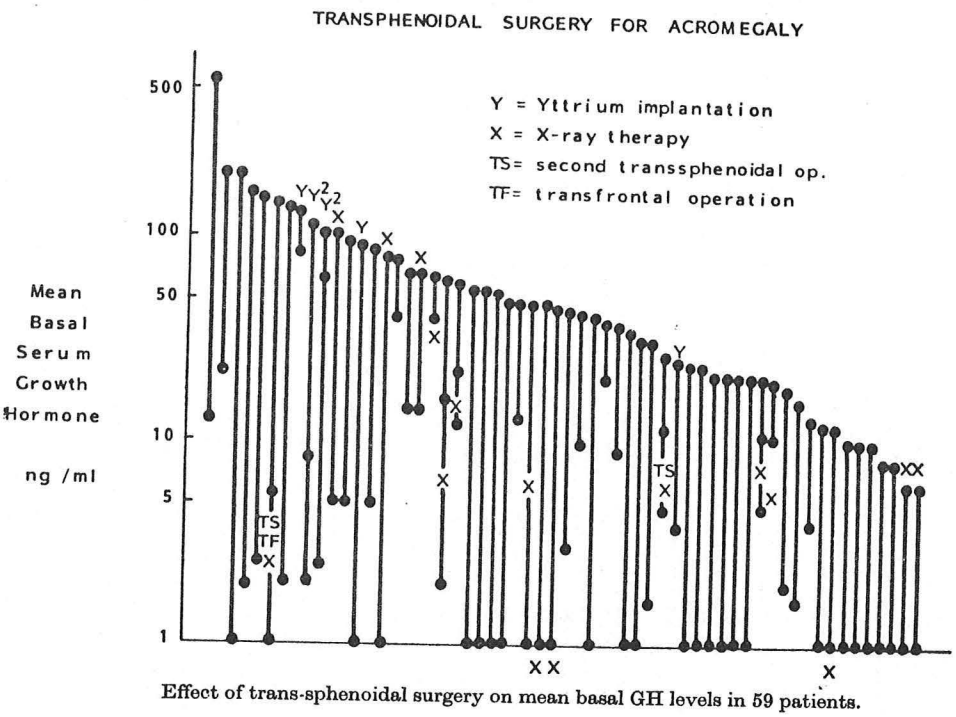


Figure 19 (Williams, 1975)

Effect of trans-sphenoidal surgery on mean basal GH levels in 59 patients.

Management of those patients with larger or more invasive tumors is more controversial. Hardy (1973) has classified pituitary tumors for treatment purposes, and this classification (Figure 20) is now widely used. Patients with Grade IV tumors also require radiotherapy (Table 8, Hardy, 1973). These results have remained about the same with a larger experience in 120 patients (Hardy, 1979) and have been duplicated in similarly classified patients (U, 1977, Table 9). However, comparison of surgical vs radiation therapy results in Grade II-IV patients with only slight suprasellar extension has not been made, and it is possible that these patients would best be treated with radiation therapy alone if there is any relative contraindication to surgery. Many cases with significant suprasellar extension are now being operated by TSHS instead of by the frontal approach if the extension is broad-based enough to allow for downward collapse of the soft gelatinous tumor tissue.

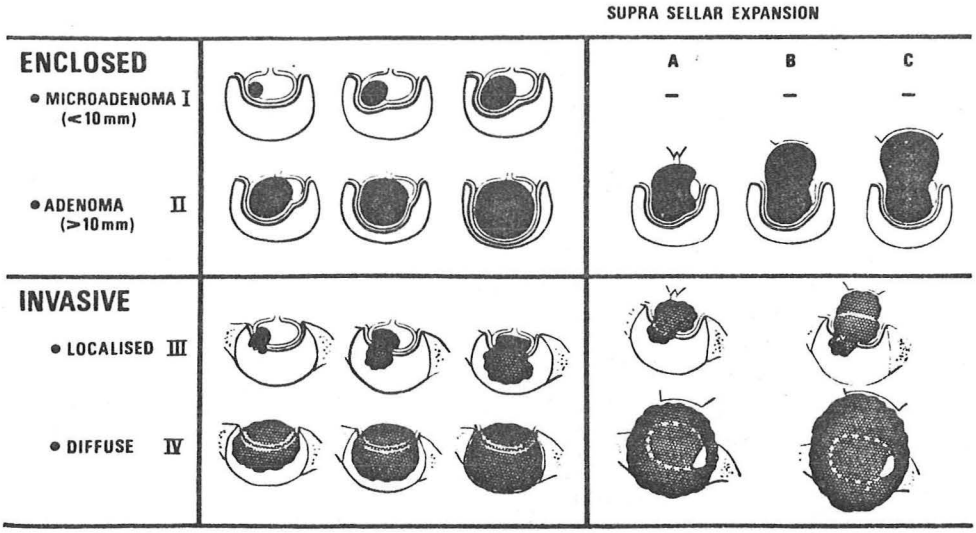


Figure 20 (Hardy, 1973)

Growth pattern of acidophilic adenomas.

Results in acromegaly (40 cases)

Type of lesion	No. of cases	Results		
		Cured	Improved	Unchanged
Enclosed adenoma				
Gr. I: microadenoma	10	8	2	0
Gr. II: adenoma				
no s.s.	14	12	2	0
with s.s.	5	1	3	1
Invasive adenoma				
Gr. III: local invasion				
no s.s.	3	2	1	0
with s.s.	2	2	—	0
Gr. IV: diffuse invasion				
no s.s.	3	—	1	2
with s.s.	3	—	1	2
Total	40	25	10	5

s.s. = suprasellar extension.

TABLE 8 *(Hardy, 1973)*

TABLE 9

Correlation between operative results and tumor grading in previously untreated patients (Group I)

Grade of Adenoma	Suprasellar Extension	No. of Cases	Results		
			Cured	Improved	Unchanged
Grade I		2	2	0	0
Grade II	none*	10	8	1	0
	slight	9	7	2	0
	moderate	5	3	2	0
	large	2	2	0	0
Grade III	none	6	6	0	0
	slight	2	2	0	0
	large	0	0	0	0
Grade IV	none	1	0	1	0
	slight	1	0	1	0
	large	0	0	0	0
total		38	30	7	0

*One nonsurgical death.

(U, 1977)

2. Radiation therapy - Radiation therapy continues to be one of the major treatment modalities for acromegaly. Radiation therapy can be provided by heavy particle irradiation and by conventional supravoltage irradiation. Even though there was considerable early enthusiasm for the use of heavy particle irradiation, it appears that the therapeutic benefit is only possibly slightly better than conventional radiation and is balanced by a higher incidence of side effects and a general inaccessibility to most patients (only two centers in the United States). Conventional radiation was extensively utilized before the days of growth hormone assays in the early 1960's, and there were a number of reports that gave a general clinical impression of therapeutic benefit in about 70% of patients (Lawrence, 1971). However, early reports after the advent of the radioimmunoassay for growth hormone suggested that there was very little change in growth hormone in most patients in the first 1-2 years after irradiation. This then led to a series of questions about the use of radiation treatment for acromegaly. However, a number of large studies (Table 7) have now satisfactorily documented the beneficial effect of both conventional and heavy particle treatment of acromegaly. It is apparent that the early confusion about the growth hormone results was based upon the fact that there is a progressive fall in serum growth hormone after pituitary irradiation so that there is an increasing percentage of response even after 9 years with both conventional (Figure 21) and heavy particle (Figure 22) radiation. In spite of the failure of growth hormone to fall satisfactorily in the first year after radiation, many patients still demonstrate a clinical response within a few months. The reason for this paradox remains unknown.

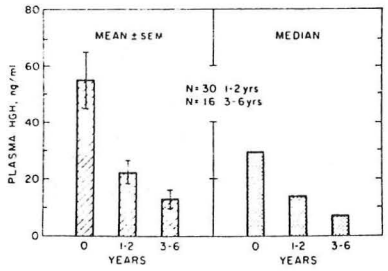
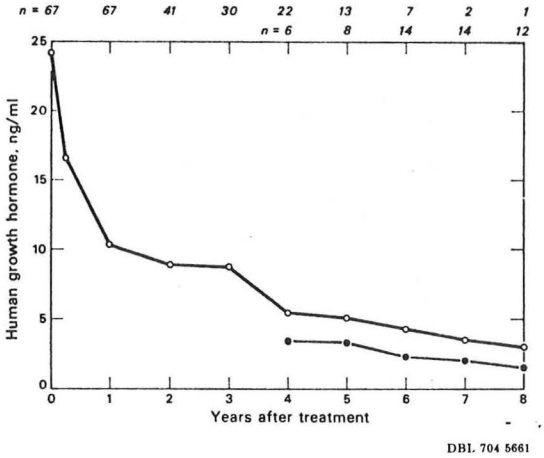


Figure 21
(Gordon & Roth, 1973)

Mean and median growth hormone concentrations for untreated acromegalic patients and for patients treated by supervoltage irradiation as a function of time.

Figure 22
(Lawrence, 1970)



Change in plasma growth hormone level, as measured by the radioimmunoassay method, in 82 patients with acromegaly who have been re-evaluated 1 or more yr after completion of heavy-particle pituitary irradiation. For 67 patients, growth hormone determinations were made both prior to and from 1 to 8 yr after therapy; these patients are represented by the solid line, the n's at the top of the graph indicating the number of individuals used in calculating the median for each time interval (refer to open dots). For 15 patients treated prior to October 1961, pre-irradiation growth hormone determinations were not made by this method, but determinations were made from 4 to 11 yr post irradiation; the superimposed dashed line represents this group, and the median values (refer to closed dots) are consistent with those of the other group.

In spite of its long-standing use, the incidence of side effects with conventional radiation is still somewhat difficult to assess. Earlier reports of conventional radiation simply remarked that side effects were few. More recent series (Kramer, 1973; Aloia, 1978; Jenkins, 1972) have evaluated the neurological and endocrine complications of conventional radiation therapy more carefully, but involve only a small number of patients. It appears that the incidence of gonadotropin abnormalities after radiation may be considerably higher than earlier appreciated. In addition, Kramer (1973) has described neurological morbidity consisting of severe visual impairment due to optic nerve vasculitis, central scotomata, marked memory loss, and severe recurrent headaches associated with an empty sella syndrome. There also has been an unusual incidence of malignant intracranial neoplasms following radiation therapy for acromegaly (Goldberg, 1963) so that the incidence of these neoplasms may be as high as 1%.

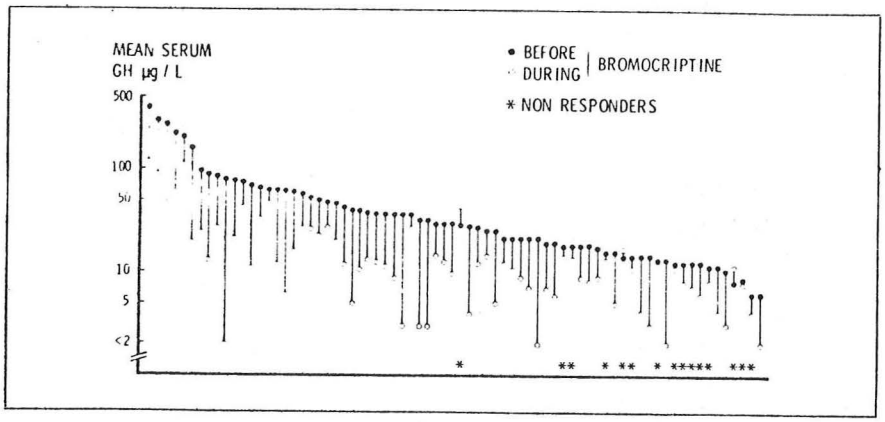
Other techniques of tumor ablation such as yttrium implantation (Hartog, 1965; Molinatti, 1962) and cryosurgery (Cross, 1972; Maddy, 1969) appear to offer few if any advantages over other methods of treatment and are not as generally available.

In summary, radiation therapy appears to be best suited for:

(1) Patients with surgical contraindications
(2) Patients who do not need rapid normalization of serum growth hormone

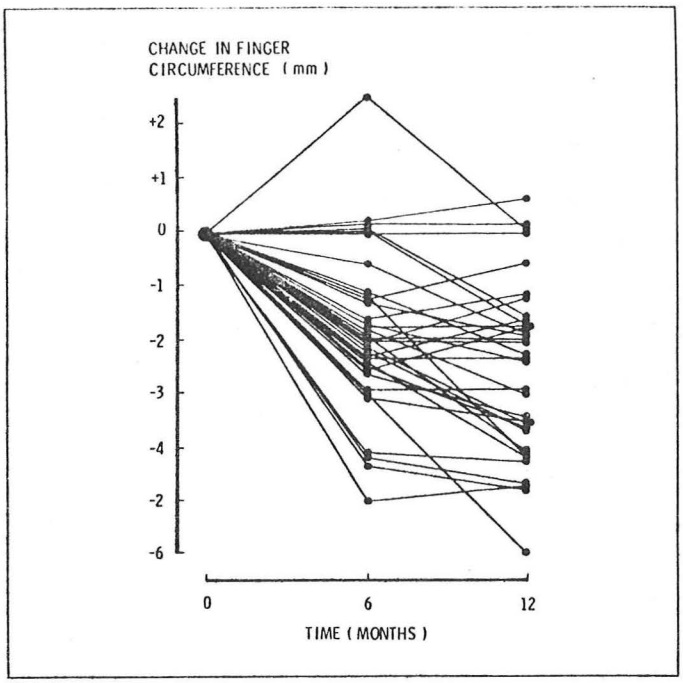
(3) Patients who are not cured by transsphenoidal hypophysectomy
(4) Patients who do not have access to skilled neurosurgeons

3. Medical treatment - Early attempts at medical treatment of acromegaly such as the use of estrogens, progestagens, and chlorpromazine are of historic interest. Larger experience with each of these agents proved to be unsatisfactory. At the present time the only medication which appears to provide valid medical therapy for acromegaly is bromocriptine, a dopaminergic agonist. Other dopaminergic agonists provide satisfactory lowering of growth hormone, but the duration of pharmacologic action is too short for practical long-term therapy. The use of bromocriptine has now been reported for a large group of patients (Besser, 1978; Figure 23). These investigators treated 73 patients with active acromegaly for between 3 and 25 months. They noted clear clinical improvement in 97% of patients and documented some of these clinical changes by decrease in symptoms, decrease in weight, resolution in visual field abnormalities, decrease in hand and ring sizes, and improvement in carbohydrate tolerance (Figure 24). However, interestingly, even though a significant reduction in growth hormone occurred in 80% of patients, only 20% of patients demonstrated a growth hormone level persistently below 5 ng/ml. These investigators have now obtained some preliminary evidence suggesting that bromocriptine decreases the circulating monomeric form of growth hormone, the most biologically active form, but does not decrease as much the circulating oligomers which are biologically less active. Somatomedin determinations are being planned for these patients and will be of great interest. Thus, further studies are required to place this treatment modality in perspective.



The change in mean serum GH before (●) and on (○) bromocriptine in 73 patients. The asterisks indicate patients classified as "non-responders". GH has been plotted on a logarithmic scale for convenience.

Figure 23
(Besser, 1978)



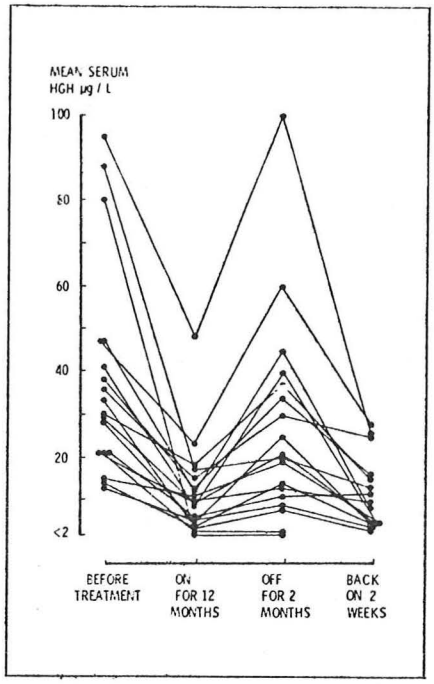
The change in finger circumference in 34 patients on bromocriptine for 12 months.

Figure 24
(Besser, 1978)

Even though bromocriptine offers promise of medical therapy for the first time, there still are a number of reservations to its use. First, many patients develop nausea and postural hypotension at the time that the treatment is initiated. These side effects can be minimized by starting the drug in the evening and gradually increasing the dose every 2-4 days by 2.5 mg. These side effects have not proved to be a persistent problem in the experience of Besser (1978), though other investigators have reported considerable problems. The major long-term side effect of constipation in about 50% of patients can be improved with the help of a bulk fiber laxative. Other side effects of note have included dryness of the mouth, alcohol intolerance, leg cramps, and hyperkinesis. Digital vasospasm induced by cold has occurred in about 40% of patients though the effect has only occasionally been disabling enough to require discontinuation of the treatment. Four of the 73 patients developed peptic ulcer and one died of septicemia following surgical treatment. Furthermore, since treatment must be given in 4 divided daily doses, problems with long-term patient compliance can be anticipated.

The eventual place of bromocriptine therapy in the treatment of acromegaly remains unknown at present. Additional studies are required to establish the incidence of long-term side effects. Even though Besser and others have enthusiastically proclaimed the use of this treatment modality, they still recommend conventional radiation therapy in a large majority of patients, because it is not established that any patients have a permanent cure. When both bromocriptine and radiation are given, bromocriptine is discontinued at 6-month intervals to determine if serum growth hormone levels have normalized (Figure 25).

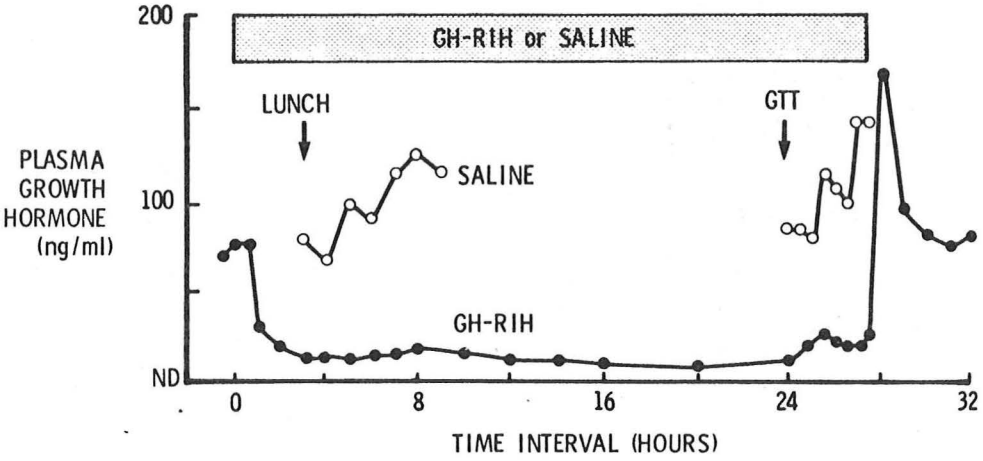
Figure 25
(Besser, 1978)



The withdrawal of bromocriptine in 18 responsive patients.

This treatment modality in conjunction with radiation therapy may prove to be quite valuable in those patients who are not good surgical candidates but in whom years of delay before the satisfactory effects of conventional radiation should be avoided. Those patients who have elevated plasma prolactin concentrations appear to be unusually sensitive to bromocriptine treatment of both the hyperprolactinemia and the acromegaly. Occasional patients demonstrate extremely rapid and outstanding therapeutic responses (Spark, 1979) and about 20% of patients have been noted to have evidence of shrinkage in size of the pituitary tumor with bromocriptine treatment alone (Wass, 1979). Bromocriptine has not been approved by the FDA for the treatment of acromegaly in the United States. However, its expected approval for this indication should provide another significant treatment modality.

Somatostatin infusion has been demonstrated to lower plasma growth hormone in acromegalic patients (Besser, 1976; Figure 26). It is hoped that future development of somatostatin analogues may provide another effective means of medical therapy.



Effect on circulating GH levels of 28-hr i.v. infusion of GH-RIH (1.3 µg/min) into a acromegalic patient compared with saline control in the same patient (GTT = 50 gm oral glucose tolerance test).

Figure 26
(Besser, 1976)

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