MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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GROWTH HORMONE and GROWTH HORMONE SECRETING TUMORS of the PITUITARY ("ACROMEGALY"*)

*Marie, Pierre, Sur deux cas d'acromegalée, Rev. Méd. 6, 297, 1886.

GROWTH HORMONE (GH)

I. THE PITUITARY AND THE SITE OF GH PRODUCTION.

Human pituitary contains 4-10 mg of HGH, i.e., 4-10% of its dry weight.

A. Site of GH Production. Acidophile cells, which make up 35-50 percent of the cells of the normal pituitary are almost certainly the site of GH production. A.B. Russfield et al. (Amer. J. Path, 32, 1055, 1956) contends that acromegalics have amphophilic tumors and "atypical" chromophobe tumors are often seen in acromegaly (Young, et al, J. Clin. Endo. 25, 249, 1965). However, staining technics vary and much evidence points clearly to eosinphiles as the source of GH in normal pituitary and in "typical" acromegaly.

1. Immunofluorescent studies: Anti-HGH is localized to eosinophiles of both normal pituitary and of an adenoma from an acromegalic (Grumbach, 1962).

2. U. Schelin, Acta Path. Microbiol. Scand. (Suppl. 158, 1, 1962) finds EM-visible eosinophilic granules in so-called chromophobe cells and suggests they may be hyperactive acidophils.

II. PROPERTIES OF GH.

A. Amino Acid Sequence of HGH elucidated by Li, C.H., Liu, W.K., and Dixon, J.S., (Arch. Biochem. Biophys. Suppl. 1, 327, 1962).

TABLE I - MOLECULAR WEIGHTS OF 3 GH'S

	MW	Conformation
Human GH	29,000	single unbranched peptide
Simian GH	29,000	" " "
Bovine GH	46,000*	branched peptide

*Activity persists after 24% of amino acids have been removed ("inactive mantle shielding an active core" concept).

B. Species specificity - (Knobil, E. et al, Endo. 60, 166, 1957).

1. Biologic Species Specificity

TABLE II

Source of GH	Recipient Species: Human	Monkey	Rat (in vivo)	Rat (in vitro)
Human	+	+	+ (temporarily)	+
Monkey	+	+	+ "	+
Bovine	0*	0	+	+
Porcine	0	0	-	-
Whale	0	0	+	+

*"Active core" doesn't work in man.

2. Immunologic Species Specificity

a. Rabbit anti-HGH reacts with HGH, monkey GH, rat GH; it doesn't react with ovine, bovine, or canine GH.

b. Rabbit anti-BGH reacts with BGH, OGH, deer GH; but not with HGH, or MGH.

III. COMPARISON OF GH, PROLACTIN, AND PLACENTAL LACTOGEN

TABLE III - COMPARISON OF MOLECULAR WEIGHTS

(Andrews, Nature, 1966)

Species	GH	Prolactin	Placental Lactogen
Porcine	22,500	25,000	-
Ovine	24,000	20,500	-
Bovine	26,000	?	-
Human	20,500	?	-

A. Immunologic Comparison:

1. Anti-OGH reacts with ovine prolactin and anti-prolactin with GH. Human prolactin has never been separated from HGH and Hayashido thinks they are one and the same. (Hayashido, Ciba Colloquia on Immunoassay, Vol. 14, page 338, 1962).

2. Anti-HGH reacts with placental lactogen, but less avidly, (i.e. shallower dilution slope); fluoresceinated anti-HGH localizes in the synctitial layer of villous trophoblasts.

B. Biologic Comparison: (Josimovich, Endocrin. 71, 209, 1964).

TABLE IV - COMPARISON OF BIOLOGIC CROSS-ACTIVITY

	Activities				
	Luteotropic	Lactogenic	Crop sac	Growth	Lipolytic
Ovine GH	+	+	+	+	+
Human GH	+	+ (20% of OPL)	?	+	+
Human Prolactin	?	+	+	+	+
Ovine Prolactin	+	+	+	+	+
Human Placental Lactogen	+	+	0	Potentiates HGH	+

All these activities disappear simultaneously when incubated with reactive antiserum or when treated chemically.

Pertinent References on Placental Lactogen:

Josimovich, J. B., Endocrin. 71, 209, 1962.
Josimovich, J. B., Trans. N.Y. Acad. Sci. 27, 161, 1964.
Blizzard, R. M. et al, J. Clin . Endo. 26, 852, 1966.
Kaplan, S. L. and Greenbach, J. Clin. Endo. 24, 80, 1964.
Reggi, S. J. et al, Endocrin. 79, 709, 1966.
Sciara, J. J., Kaplan, S. L. and Grunback, M. M., Nature, p. 1005, 1963.
Bates, R. M. et al, Endocrin. 74, 714, 1964.
Samaan, N. et al, J. Clin. Endo. 26, 1303, 1966.
Josimovich, J. B., Endocrin. 78, 707, 1966.
Schultz, R. B. and Blizzard, R. M., J. Clin. Endo. 26, 921, 1966.

IV. METABOLISM OF GH IN VIVO:

1. Transport: Despite reported binding to beta and γ-2 globulin of HGH-I^{131}, C^{14}-acetylated HGH (Hadden, D. R. + Prout, T. E., Bull. of J. Hop. Hosp. 116, 122, 1965), Berson insists that results with HGH-I^{131} are artifactual and that native HGH circulates unbound to protein.

2. Disappearance Rate: The injection of unlabeled HGH and HGH-I^{131} gives a T/2 disappearance of about 27 minutes and 2.6% fractional turnover (Parker, et al, J.C.I. 41, 262, 1963). Boucher (Nature 210, 1288, 1966) found a 23-45 minute T/2 with a 3-6% fractional turnover rate. (Parker calculates from this a total daily secretion of 5 mg or 50-100% of the normal pituitary content. Endogenous HGH has a T/2 of 20-28 minutes (Glick, et al, J. Clin. Endo. 24, 501, 1964).

T/2 is higher in pregnancy 43 minutes (Gitlin, et al, J. Clin. Endo. 25, 1599, 1965), and in acromegalics 80 minutes (Boucher, 1966), and is low, 12 minutes in neonates (Cornblath, et al, J. Clin. Endo. 25, 209, 1965).

3. Distribution: After injection of HGH-I^{131}, TCA precipitable and anti-HGH-precipitable radioactivity is noted in the neurohypophysis, liver, kidney and muscle of rabbits 90 minutes after injection (Parker, et al, J.C.I. 1963).

V. EFFECTS OF GROWTH HORMONE (Its target organ is the whole body)

PROTEIN ANABOLIC ACTION:

GH in hypox rats or humans causes weight gain due to increase in body protein - body fat decreases. (This is reflected by measurable N retention, decrease in urea excretion and serum amino acids). This effect requires presence of insulin and is absent in diabetes. (Wright, et al, Am . J. Med. 8, 499, 1965).

In man, 0.1 mg - 10 mg/d of HGH in a panhypopit causes 2-4 g/d of N retention within 2 days; associated with P and K retention, this wanes within a few weeks.

Postulated Mechanism of the Protein Anabolic Effect of GH:

1. Transport Theory. Hypox——————>↓ in amino acid incorporation into amino acid pool of muscle (Kostyo, Am. J. Physiol. 299, 675, 1961). GH in vivo and in vitro causes increased protein biosynthesis by rat diaphragm. The in vitro effect is immediate, suggesting a transport effect (Noall, et al, Science 126, 1002, 1957; Kostyo, et al, Science 130, 1653, 1959; Reiss and Kipnis, J. Lab. Clin. Med. 54, 937, 1959), BUT, when transport is blocked by omitting sodium from the medium,

amino acid incorporation into protein is still stimulated by GH, indicating that its action is not solely through transport effect (Kostyo, J. L., Endo. 75, 113, 1964).

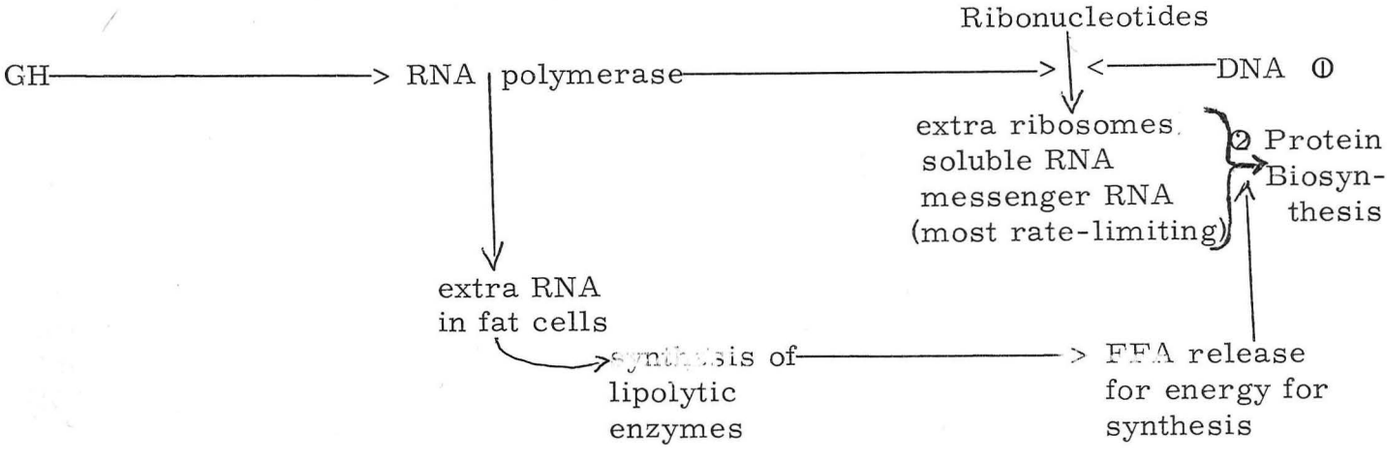
2. Messenger RNA Theory: (Korner, A., Rec. Prog. Horm. Res. 21, 205, 1965). Loss of body weight and protein in hypox rats is accompanied in the liver cell by:

1) ↓ RNA synthesis
2) ↓ Ribosomes
3) ↓ Soluble and messenger RNA
4) ↓ Incorporation of amino acids into protein;

all are restored by GH rx. Korner found that the level of circulating GH in the living rat influenced all components of the liver cell except DNA, i.e. protein, RNA (which is mostly ribosomes), and ability of ribosomes to assemble activated amino acids into peptide chains through RNA synthesis.

Since actinomycin (which inhibits DNA-directed RNA synthesis) does not block the effect, it must be a stimulation of RNA synthesis distal to DNA - perhaps at the enzyme RNA polymerase. He regards the increase in rate limiting messenger RNA (suggested by lack of polysomes in hypox rat liver and their appearance after GH) as the most crucial. The GH effect on RNA synthesis would increase size (hypertrophy), not the number of cells (hyperplasia), since no direct GH effect on DNA synthesis or mitosis has been found. In proliferating tissues, however, GH may increase the number of cells undergoing mitosis, perhaps secondary to stimulation of RNA and protein synthesis. In addition, GH may provide the fuel for protein synthesis by increasing FFA levels.

FIGURE I - KORNER'S HYPOTHESIS



① Locus of actinomycin block; ② Locus of puramycin block.

NOTE: What about linear growth? Is it explained by this concept? Probably not because: 1) Linear growth seems to be growth hormone-dependent, but not growth-hormone responsive, (W. H. Daughaday, et al, J. Clin. Endo. 19, 743, 1959; studies of sulfation factor (the rate at which $S^{35}O_4$ is incorporated in vitro into chondroitin sulfate of tibial cartilage from hypophysectomized rats) suggest otherwise.

TABLE V

SULFATION FACTOR (SF) AND IMMUNOREACTIVE HGH

Serum Specimen	SF	HGH mμg/ml
Normal serum	0.5 - 1.5	0.1 - 15.0
Hypopituitary serum	Very low	< 1.0
Acromegalic	High	High
Hypopit serum HGH added in vitro	Very low	Normal
Hypopit serum obtained <24 hrs. after start of HGH i.m.	Low	Normal
Hypopit serum obtained >24 hrs. after HGH i.m.	Normal	Normal

This could mean that sulfation factor is a different substance than HGH, although it exists only in the presence of GH. The >24-hour lag between the injection of GH and the appearance of SF in serum suggests one of the following schemes:

A. GH $\xrightarrow[\text{conversion}]{\text{in vivo}}$ SF ——————> linear growth

B. GH ——————> SF precursor ↓ SF ——————> linear growth

Immunoassayable HGH (vida infra) is a very labile hormone which may be concerned with moment-to-moment metabolic homeostasis while SF is a stable component of normal plasma not influenced by acute metabolic events. A similar scheme may apply to other forms of growth, e.g. renal compensatory hypotrophy (RCH) in rats (Fogleman and Goldman, 1966).

It is rumored that there is in Sweden a "pituitary" dwarf with normal immunoassayable HGH, but no sulfation factor, suggesting a block distal to GH secretion. It is probable that minimal levels of immunoassayable HGH are sufficient to maintain growth,** if one assumes normal end organ responsiveness.

** Zimmerman, T. S., et al (Am. J. Med. 42, 146, 1967) have reported normal and even increased growth in 2 patients with panhypopituitarism with "low or absent" levels of immunoassayable HGH and sulfation factor. Actually, their published data indicates that HGH was present and that failure of HGH to rise after insulin-induced hypoglycemia might have been due to inadequate hypoglycemic stimulus.

FAT METABOLISM:

1. In Vitro Studies:

a. "Insulin-like" Action (Goodman, H. M., Endo. 76, 216, 1965);

This could be an artificial effect seen only in special experimental setting, namely, when HGH is administered acutely, particularly to a hypoxed animal. Prolactin, oxytocin, and ACTH also have an insulinoid action, suggesting a non-specific peptide action, though MSH and TSH don't have the action. However, it occurs both in vivo and in vitro with isolated tissues from hypoxed animals at physiologic (10 mμg/ml) concentration. The insulinoid effects (Goodman, H. M., Endo. 76, 1134, 1965) are:

1) Increased glucose uptake in fat and muscle.
2) Increased oxidation of glucose to CO_2.
3) Increased conversion of glucose to fatty acids.

b. "Delayed" (2 Hours) Lipolytic Action:

This may be the true physiologic action of GH - it differs from the lipolysis of other lipolytic hormones, epinephrine, ACTH, glucagon, TSH, all of which have a prompt (10 minute) lipolytic effect through activation of the hormone-sensitive lipase.

TABLE VI.

INCUBATION OF ISOLATED FAT CELLS AND GH AND DEXAMETHASONE
(Fain, J. N., et al, J. Biol. Chem. 240, 3522, 1965)

GH (mμg/ml)	Dexamethasone (mμg/ml)	Release of FFA and Glycerol at 2 hours
10	0	2+
0	11	±
10	0	4+

Dexamethasone greatly potentiates lipolytic effect of GH. Insulin in physiologic concentration (10 uU/ml) readily inhibits it. Although glucose uptake by fat cells is reduced by GH, both lipolytic effect of GH and inhibitory effect of insulin are independent of glucose concentration.

NOTE: Puramycin and actinomycin D (to lesser degree) block GH lipolysis. This, plus the 2-hour time lag of the lipolytic effect suggests that GH stimulates lipolysis through synthesis of a lipolytic enzyme. Rapid lipolysis involving the hormone-sensitive lipase (e.g. ACTH) is not blocked by puromycin or actinomycin and obviously doesn't involve RNA synthesis.

2. In Vivo Studies of GH:

a. Acute Effects: 1) In intact animals, GH i.v. causes, within 30 minutes, an initial insulin-like decline in glucose, amino acids and FFA (greater in hypox), followed by a rise in FFA 2-5 hours after i.v. injection (Raben, M. S., Rec. Prog. Horm. Res. 15, 71, 1959; Pearson, O. H. et al, Tr. Assn. Amer. Phys. 73, 217, 1960; zahnd, G. et al Proc. Soc. Biol. Med. 105, 455, 1966).

2) In addition to effects on the fat cell itself, GH enhances muscle uptake of FFA so that at least 89% of O_2 uptake (in studies of forearm muscle) by muscle is attributable to FFA oxidation (Rabinowitz, D. et al, J. Clin. Invest. 44, 51, 1965).

b. Chronic Effects:
Lipolytic effect wanes after a few days, but lipogenesis is inhibited and fat disappears from the animal.

C. GLUCOSE METABOLISM:

Published reports of growth hormone's effect on CHO metabolism are most confusing (from insulin-like to diabetogenic). This is, in part, a consequence of 1) use of impure GH preparations; 2) failure to recognize GH species specificity; 3) use of pharmacologic doses; 4) and failure to dissociate direct action of growth hormone from systemic contraresponses which it generates.

1. In Vitro Studies:

a. Insulin-like Action: The GH-induced increase in glucose uptake by isolated rat diaphragm and fat pad is most apparent when animal tissues have been previously deprived of exposure to both insulin and GH (Goodman, 1965), and may, therefore, be unimportant in normal physiology. It may be a non-specific membrane effect on glucose transport since other peptides emulate it. According to Riddick, et al, (Diab. 11, 171, 1962), it occurs only with pharmacologic doses of GH.

b. Insulin Opposing Effect: Kipnis and his group (Kipnis and Cori, J. Biol. Chem. 235, 3070, 1959; Kipnis, et al, J. Biol. Chem. 234, 165, 1959; Kipnis, D. M., Ann. N.Y. Acad. Sci. 82, 354, 1959) have provided the best exposition of GH effect on glucose metabolism by muscle. Using the rat diaphragm and a non-metabolizable glucose analogue, 2-deoxyglucose, they find that either transport across the cell membrane or phosphorylation to the 6-PO_4 may be the rate-limiting factor in glucose utilization. Insulin lack can inhibit glucose transport into the cell and GH and cortisol can inhibit glucose phosphorylation if transport is not rate-limiting.

2. In Vivo Studies: We will ignore the early hypoglycemic effect in hypopituitary subjects (Zahnd, et al), which is probably pharmacologic or at least physiologically irrelevant, and the dog experiments with bovine GH, which are probably pharmacologic and irrelevant to man (deBodo, et al, Vitamins and Hormones 15, 205, 1957.

a. Local Effects in Man: Rabinowitz, et al (J.C.I. 44, 51, 1965) found that during HGH infusion at a concentration of 300-600 mμg/ml in the brachial artery, glucose uptake by deep and superficial tissues of the forearm was reduced by 50% within 30 minutes. Since this effect coincides well in time with increased FFA uptake by those tissues, it could represent either direct inhibition of glucose utilization by GH or indirect competition by FFA (Randle glucose-fatty acid cycle).

b. General Effects in Man: When HGH is given i.v. to normals (2.0 mg per hour x 5 hrs.) to produce levels seen in acromegaly, glucose level is not changed, nor does insulin rise. Therefore, it seems unlikely that any change

in net basal utilization has occurred. However, if a glucose load is given, it may or may not be associated with impaired tolerance, but it is always accompanied by 200-400% increase in insulin response to glucose (Stein, M., Kipnis, et al, J. Lab. Clin. Med. 1022, 1962), just as in acromegaly. This probably means 1) that there is no direct insulin-stimulating effect of GH on the beta cells (although in GH deficiency, insulin secretion is diminished either through diminished insulin need, i.e. greater insulin sensitivity, or as a part of generalized hyposomatotropic involution), and 2) that by increased insulin secretion, the interference with glucose utilization or at least the impaired tolerance imposed by excess GH, can, in general, be overcome in non-diabetics with intact islets. Whether chronic GH excess could exhaust human beta cells (as it exhausts canine beta cells) and thus cause diabetes in an otherwise normal human is not entirely clear, but seems unlikely in view of the relative rarity of diabetes in acromegaly.

D. MISCELLANEOUS EFFECTS OF GH:

1. Retention of PO_4^{--}, K^+, and Ca^{++}

2. Na^+ and Cl^- retention, increase in ECF volume and sometimes edema.

3. Increased glomerular filtration, renal blood flow, and PO_4^{--} absorption. (Corvilain, J., J. Clin. Invest. 41, 1230, 1962).

VI. GROWTH HORMONE PHYSIOLOGY

A. Evidence for Control by Hypothalmic Growth Hormone Releasing Factor (GHRF):

(Reichlin, S., Endo. 69, 225, 1961; McCann, S. M., Am. J. Phys. 202, 393, 1962; Schally, et al, Endo. 71, 164, 1962; Deuben, R. R., Endo. 75, 408, 1964).

a. The physiologic response of GH secretion to hypoglycemia is abolished in man 1) by stalk section (Roth, et al), or 2) by hypothalmic disease (Landon, J., et al, J. Clin. Invest. 45, 437, 1966, or 3) in monkeys by experimental lesions in the median eminence (Reichlin, N. E. J. M. 275, 600, 1966), although basal values of GH are unaffected. This suggests that reflex secretion of GH in response to some stimuli are mediated via the median eminence, but that basal secretion is autonomous.

b. Furthermore, 1) glucose injection into the eminence during insulin-hypoglycemia inhibits GH secretion while glucose injection into the pituitary does not. (Reichlin, N. E., J. M. 275, 600, 1966), and 2) GH secretion can be stimulated by electric excitation of the ventral median eminence.

c. Isolation of GHRF: 1) Is it vasopressin? Probably not. Garcia and Geschwind (Nature 211, 372, 1966) report that hypothalmic extracts caused a striking rise in GH, whereas only a minimal response to enormous quantities of vasopressin was noted. 2) GHRF has been isolated by Dhariwal, et al, (Endo. 77, 432, 1965). (For a complete review, see Glick, et al, Rec. Proc. Horm. Res. 21, 241, 1966).

B. Normal Range of Fasting Plasma HGH: (Unger, R. H. et al, Nature 205, 804, 1965)

Fasting men - 0-1 mμg/ml
Fasting women are higher - 1-10 mμg/ml

This sex difference occurs only in the non-basal state (Frantz, A. G., J. Clin. Endo. 25, 1470, 1965); if subjects are tested in basal state, no sex difference is found. Estrogens seem to increase the GH response to the most minimal exercise, and men given estrogens will have HGH values in the range of non-basal females.

C. Stimuli of High Secretion:

1. Situations in which Conservation of Glucose is Important: (This is the work of Berson's group and is reviewed by Glick, 1965).

a. Hypoglycemia. HGH secretion rises after hypoglycemia of all types:

1) Insulin Hypoglycemia: GH rises 15-30 minutes after nadir of blood glucose and may stay high for hours unless glucose is given. Failure of GH to rise to >25 mμg/ml after a fall in glucose of 50% or more may indicate a loss of integrity of the hypothalmic-pituitary axis and is an excellent clinical test of pituitary function. NOTE: Sluggish response occurs in obesity.

2) Alcohol Hypoglycemia

3) Tolbutamide Hypoglycemia

4) Chronic Hypoglycemic States (retroperitoneal fibrosarcoma, insulinoma, fructose-induced hypoglycemia): Sustained HGH elevation.

b. "Intracellular Hypoglycemia":

1) 2-deoxy-glucose: This non-metabolizable glucose analogue causes hyperglycemia, but accompanied by symptoms of hypoglycemia. It also causes a rise in HGH, suggesting that intracellular deficit of glucose metabolites in hypothalmic center is the mechanism of hypoglycemic stimulation of HGH.

2) Rapid fall in blood glucose after hyperglycemia to levels above normal causes a rise in HGH.

3) Starvation causes a sustained rise, which is glucose-suppressible, but later is non-suppressible.

c. Exercise: Minimal to moderate exercise stimulates GH release, but this can be aborted by glucose administration. Strenuous exercise causes a non-suppressible HGH rise. (Hunter, et al, Quart. J. Exper. Physiol. 50, 407, 1965)

d. Stress: Surgical stress causes a striking rise in GH, which can't be suppressed with glucose, analagous to ACTH secretion, which is not suppressed by cortisol, (Ketterer, et al, Clin. Res. 1965). Mental stress may stimulate it to a lesser degree (Glick).

TELEOLOGIC OBSERVATIONS: In each of the foregoing situations, GH may satisfy the obvious need for conservation of glucose for the brain, by providing a shift to FFA as the principal fuel of those tissues for which glucose is

not an obligatory substrate. For example, in exercise, when penetration into cells is no longer rate limiting, a GH-cortisol block to glucose phosphorylation would prevent hypoglycemia; in surgical stress, danger of diminished cerebral blood flow may cause a firing of GH and ACTH-cortisol to block non-essential glucose utilization; the temporary hyperglycemia of surgery may assure adequate cerebral glucose delivery despite reduced cerebral blood flow.

2. Situations in which Protein Anabolism is Useful:

a. Protein Feeding (Merimee, et al, N.E.J.Med. 276, 434, 1967), Arginine (Merimee) and amino acid mixtures (Fajans) cause a dramatic rise in HGH which is not suppressed by hyperglycemia, suggesting a difference in both mechanism and purpose from hypoglycemia-induced HGH secretion. Arginine infusion, too, is a good clinical test for hypopituitarism. The HGH rise follows the insulin rise, providing two anabolic allies to encourage protein synthesis.

b. Total Starvation. If more than 25% of body protein is consumed, death occurs. The HGH response to starvation may serve, not only to save glucose, but to limit protein loss.

c. Protein Starvation: (Kwashiorkor-Pimstone, et al, Lancet 79, 1966.

D. Suppressors of Growth Hormone:

1. Hyperglycemia: Hyperglycemia will suppress the following physiologic stimuli to increased HGH secretion, presumably via the hypothalmic center.

a. Acute Hypoglycemia

b. Mild or moderate exercise

c. Mental stress

d. Brief starvation (<4 days)

NOTE: This is the basis of a test to differentiate autonomous from physiologic hypersomatotropinism. However, hyperglycemia will not suppress HGH secretion elevated by the following stimuli:

a. Strenuous exercise (Hunter, et al)

b. Chronic hypoglycemia

c. Arginine infusion (Merimee)

d. Surgical stress (Ketterer, H., et al)

e. 2-deoxyglucose administration (Glick)

f. Severe prolonged starvation (Pimstone, 1966; Unger, 1965)

It will suppress HGH secretion elevated in the following diseases:

a. Autonomous HGH producing adenoma (vide infra) (Glick, et al)

b. Acute intermittent porphyria (it may cause a paradoxical rise (Perlroth, et al, Metab. 16, 945, 1965)

c. Severe diabetic ketoacidosis (Unger, R. H., J.A.M.A. 191, 945, 1965)

NOTE: In diabetic ketoacidosis, ↑HGH may result from exclusion of glucose by insulin lack from an insulin-requiring glucose-suppressible hypothalmic center, thus creating the clinical counterpart of the intracellular deficit of glucose metabolites induced by 2-deoxyglucose administration.

d. Anorexia nervosa

2. Glucocorticoids: Chronic steroid therapy blunts the HGH response to hypoglycemia (Frantz). Cushing's disease should be characterized by low HGH and Addison's disease by high. Steroids also suppress linear growth in children.

CLINICAL MANIFESTATION OF GROWTH HORMONE-SECRETING TUMORS

("Acromegaly" is a poor term for the disease since it is a physical sign, not a diagnosis, it may not be present at all and, when it is, "megaly" of non-acral parts is usually present also.)

TABLE VII

TYPES OF PITUITARY TUMORS IN ACROMEGALY

(Young, D.G., et al, J. Clin. Endo. 25, 249, 1965)

	Typical	Atypical
Size	< 2 cm	> 2 cm.
Behavior	Benign, localized	Locally aggressive
Appearance		
Granules	Uniform acidophilic granules	Varying degrees of granulation - many agranular "chromophobes"
Mitosis	Absent	50% have mitotic figures
GH Content	High GH content by tibia test	Low GH content of tumor
Clinical		
Average age	64 years	37 years
Average duration	40 years	6 years
Rx	Non-surgical	Surgical
Signs of Compression	Absent	Present
Relative Frequency	Less common	More common

PERSONAL VIEW: Don't write off a unitarian hypothesis on the basis of Table VII because: 1) acidophilic granules may be present on EM in cells which are agranular under light; 2) the larger, more invasive tumors may merely represent a less well differentiated acidophilic tumor; 3) Young's series really is comparing necropsy material ("typical cases") versus surgical specimens ("atypical cases").

I. CLINICAL CONSEQUENCES OF HYPERSOMATOTROPINEMIA

A. Somatotropic Effects: (presumed to be a consequence of increased RNA and protein synthesis in every tissue of the body, leading to hypertrophy and hyperplasia, and often neoplasia).

1. General: Weight gain due to ↑ protein synthesis and ↑ ECF, not to fat.

2. Integument:

a. Skin. Coarsness and thickening of skin, big pores and furrows, may alert a young woman to the disease at its earliest, most subtle stage (See Case #1, M.H.). Difficulty in doing a venipuncture may alert an M.D. Later, thick, doughy enlargement of nose, brows and acral parts are more characteristic, and make it diagnosable at a casual glance. Heel thickness test is positive; melanosis and fibroma molluscum may be seen. Connective tissue is increased and so is subcutaneous ECF.

b. Sweat and Sebaceous Glands. Sweating and sebaceous activity are increased. Oiliness and unpleasant odor to the skin may be an early complaint.

c. Hair: Slight hypertrichosis of body and face may be noted by females. Hirsutism occurs uncommonly.

3. Generalized visceromegaly: All organs are proportionately enlarged and kidneys have supernormal function.

4. Upper respiratory:

a. Glossomegaly. Furrows and papillary hypertrophy of tongue; heavy speech.

b. Larynx: Hypertrophied, with enlarged cavity, cavernous voice.

c. Sinuses. Markedly enlarged - may cause cavernous voice and headaches.

5. Muscle: Hypertrophy has been reported, but is very rare; more often there is unexplained weakness (NOTE: Could this be 2^{o} to glycogen depletion due to block of glucose phosphorylation block? Saltin states that after strenuous exercise, work performance is poor until glycogen stores are repleted.) Late in the disease, weakness, creatinuria may be 2^{o} to hypopituitarism.

CNS: Although 8th nerve deafness, vestibular symptoms, carpal tunnel syndrome, sciatica, and paresthesias (30%) are common in acromegaly, they are usually ascribed to nerve entrapment by hypertrophy of connective tissue, or bone. Rare cases of progressive peripheral neuropathy with papable neuromegaly associated with perineural and endoneural hypertrophy and axial degeneration have been reported (Stewart, Arch. Neurol. 14, 197, 1966). Neurofibromatosis (Von Reklinghausen's) also has been reported.

6. Erythropoietic System: In the rabbit GH causes marked reticulocytosis, but no ↑ in Hct., or Hg because of associated hemodilution (Halvorsen, Acta Physiol. Scand. 66, 203, 1966). There are no known clinical manifestations attributable to this in acromegaly, however.

7. Endocrine System:

a. Islets of Langerhans. Histologically the islets seem to share proportionately in the general somatotropism. Insulin levels are high after a glucose meal in active acromegaly with or a normal GTT, and low in hypoxed patients. (Is this a reflection of change in peripheral tissue sensitivity to insulin, or is it a consequence of the beta cell mass, or both? Probably both, since the insulin response to glucose increases when GH is added in vitro to pancreatic slices of hypox rats, suggesting increased sensitivity to glucose of beta cells in presence of GH. (Bowman, R.P. and Bosboom, R.S., Acta Endocrinologia 50, 202, 1965).

1) Insulinomas: These coexist with eosinophilic adenomas and are regarded as a form of the multiple endocrine adenoma syndrome. Berson has suggested that the latter is a consequence of prolonged hypoglycemic stimulation from the former (seems very unlikely). Probably either hereditary syndrome or an expression of GH-induced increase in neoplastigenicity.

2) Diabetes: Not common - statistics range from 30% to 10% depending on criteria. No evidence that HGH causes in man the beta cell lesion and metahypophyseal diabetes which F. G. Young produced in dogs. Normal beta cells should be able to compensate for excess HGH and thus prevent true diabetes. (Although 25% of acromegalics have abnormal GTT's we don't feel that they all have true diabetes.) In Table VIII it is of interest that all acromegalics with overt diabetes had thickened MCBM's; but the one with an abnormal GTT (patient C.D.), did not. We suspect that most of the 12% of overt diabetics acromegalics have genetic trait.

TABLE VIII

MUSCLE CAPILLARY BASEMENT MEMBRANE THICKNESS (MCBMT)

IN ACROMEGALICS (Siperstein, et al)

Patient	Diabetic Status	MCBMT (Å)
W. G.	↑ FBS on insulin	1832
D. H.	↑ FBS on orinase	3384
R. G.	↑ FBS on insulin	1806
C. H.	Normal GTT	1204
A. J.	Non-diabetic	1149
C. D.	Abnormal GTT (> 220 mg %)	1288

b. Thyroid: Thyroidomegaly in 25-50% and ↑ BMR in 50%, but true hyperthyroidism is rare.

c. Parathyroid: Enlarged in acromegaly. Summers, et al (Lancet ii, 601, 1966) report chief cell hyperplasia and adenomas in hypercalcemic acromegalics. One case of hypercalcemia was corrected when the pituitary adenoma was removed, suggesting secondary parathyroid hypersecretion rather than primary autonomous lesion. Multiple endocrine adenoma syndrome may also involve these two glands. Always be suspicious of hyperparathyroidism if the PO_4 is < 4 mg % in an active acromegalic!

d. Adrenal Cortex: Adrenals are enlarged in acromegaly, especially zona fasciculata and zona reticularis. Roginsky, Shaver and N. P. Christy (J. Clin. Endo. 26, 1101, 1966): 1) plasma cortisol levels are normal; 2) cortisol secretion rate is usually high; 3) diurnal varietion is normal; 4) 17-ketosteroid and 17-ketogenic steroid excretion is usually high but suppresses adequately during cortisol rx. Since GH has no immediate effect on steroidogenesis, direct stimulation by GH of adrenal protein synthesis or of ACTH secretion seem unlikely. May represent compensatory attempt to suppress HGH secretion with cortisol, or to make up for increased urinary loss, or both.

e. Gonads: Gonadatropins may be high; in males libido may be increased early, decreased subsequently, and impotence may appear late, probably due to compression hypopituitarism. In females, amenorrhea and decreased libido are very common.

7. Bone and Soft Tissues: Increased bone mass through subperiosteal new bone formation with tufting of acral bones, osteophytic proliferation of vertebrae, and overgrowth of mandible, frontal, malar, and nasal bones and thickening of calvarium. In addition to new bone formation, reabsorption is also accelerated and may overshadow it and lead to demineralization. This effect is not understood.

Bone pain is very common due to osteoarthritis and osteoporosis.

8. Lactogenesis:

Since human prolactin can't be distinguished immunlogically, biologically, or physically from HGH, the occasional gynecomastia and lactorrhea of acromegaly must at present be classified as a direct target effect of ↑ HGH. Sometimes this dominates the picture and acromegalic change is minimal (Forbes-Albright Syndrome). (It has been suggested that estrogen-induced gynecomastia is 2^{o} to its stimulation of HGH.

9. Neoplasia:

Increased incidence of benign and probably of malignant tumors.

B. Lipolytic and Anti-lipogenic Effects:

No obesity in this disease despite weight gain (due to increased body protein and ECF). Body fat is low despite puffy appearance (cf. anti-lipogenic effect). Plasma FFA are generally normal or slightly elevated in the few cases studied.

C. Glucose Conserving Effect:

Inhibition to glucose utilization by direct inhibition of phosphorylation or by competitive hyperlipacidemia may be compensated for by increased insulin secretion, so that GTT is usually normal but at the price of hyperinsulinemia. Impaired tolerance and overt diabetes were discussed above.

II. CLINICAL CONSEQUENCES OF THE TUMOR (MECHANICAL SYNDROME)

The rigid enclosure of the sella creates mechanical problems for expanding tumors. "Typical" eosinophilic tumors tend to grow more slowly, to be benign, and more frequently located in the upper lateral region where most eosinophilic cells are situated. "Atypicals" are more aggressive and may invade surrounding tissues.

A. Radiologic Signs:

Sellar enlargement (> 12 cm. by 15 cm) in 93% (Ray, Bronson, Clin. Neurosurgery Proc. Congress and Neurol. Surgeons, p. 31, 1962 - excellent review) and in Cushing's series, but these are surgical referrals, (many "atypicals"). Tumor may be very small (typical), may be extrasellar, or there may be no tumor - just hyperplasia. May encroach or enter sphenoid sinus. Erosion of clinoids and ballooning of sella (more common with "atypical" tumors.

B. Headache:

Attributed to pressure on sellar diaphragm, but may persist after hypox. Location of pain may be frontal, temporal, vertical, or generalized. Pituitary hemorrhage and apoplexy are rare complications.

C. Spontaneous Cerebrospinal Rhinorrhea:

Rarely tumor erodes into sinus.

D. Visual Field Defects:

Upward pressure may, fairly early, compress the optic chiasm and nerves against the anterior communicating arteries and cause superior temporal visual loss, at first demonstrable only with red objects. Bitemporal hemianopsia may appear late. Rarely extrasellar growth ruptures optic nerve, involves cavernous sinus nerves, and hypothalamus.

E. Hypopituitarism:

Increased intrasellar pressure will lead to destruction of the normal pituitary gland and to deficiency of some or all pituitary hormones, including, in the late, "burned-out" stage, HGH. Hormone deficiencies must be diagnosed, and, if present, treated before surgery.

III. DIAGNOSIS OF SOMATOTROPIN-PRODUCING ADENOMA

A. History: Increase in hat, glove, ring, shoe size, Change in appearance. Amenorrhea, hypertrichosis, change in libido, hyperhidrosis, skin thickening, skin oiliness, skin odor, difficulty with venipuncture, headache.

B. Physical signs:

1. Acromegaly: Pathognomonic

2. Subtle skin changes or borderline changes in acral parts are hard to evaluate, esp. in Negroes.

3. Visual Field Defect:

C. Radiographic signs:

1. Heel thickness ↑
2. Bone changes
3. Sellar enlargement

D. Laboratory Findings:

1. Hyperphosphatemia (> 4.5 mg %): Not very helpful.

2. Urinary Hydroyproline Excretion (Jasin, Fink, Wise and Ziff, J. Clin. Invest. 41, 1928, 1962). Shown to be correlated with growth, reflecting collagen turnover of bone. Is apparently elevated in active acromegaly and should be an excellent index of activity. Also elevated in other states with increased turnover (hyperparathyroidism, Paget's, osteomalacia, etc.)

3. Evidence of Insulin Resistance:

a. Standard insulin tolerance test: Failure to fall 50% or more after 0.1 U/kg iv suggests resistance;

b. Immunoreactive insulin levels above 150 uU/ml during oral GTT suggest insulin resistance, (also seen in obesity, hyperlipemia, mild diabetes, starvation, etc.)

4. Elevated Sulfation Factor: Not available clinically.

5. Elevated immunoassayable HGH levels (Radioimmunoassy of Roth, Glick Berson and Yalow is easy to do, specific, sensitive, precise.)

a. Basal HGH (at complete bed rest): Normally < 3 mμg/ml. Values below 2 mμg/ml virtually exclude active acromegaly. Values above this are not specific; even mental stress may cause elevations. Active acromegalics may have a fasting HGH level below 10 mμg/ml.

b. Glucose Suppression Test: (25-50 g. i.v. (or 200 g p.o.): Essential to the diagnosis. In normals HGH falls to zero during hyperglycemia; in acromegalics any of the following types of HGH response may be seen during hyperglycemia.

1) No decline in HGH (Case # 1)
2) Paradoxical further rise in ↑ HGH (Case # 4)
3) Partial suppression of HGH (Case # 2, 3)
4) Normal suppression to zero (very rare).

IV. NATURAL HISTORY OF THE DISEASE

A. "Fugitive" course: Very brief duration with minimal acromegaly.

B. Intermittent course: Unpredictable waxing and waning of activity over an indefinite number of years.

C. Progressive course: Slow, inexorable progression through the years; patient proceeds to the grim end-stage of the disease, and becomes an ugly, disfigured, arthritic cripple with back pain, headache, cardiopulmonary disorders, visual disorders, and hypopituitarism. Progression may halt spontaneously at any point short of this, however.

NOTE: Course of the adenoma and the hypersomatotropinism may be entirely independent, i.e., florid hypersomatotropinism may continue while tumor size remains fixed (e.g. after x-irradiation), or tumor may expand and the endocrine disease extinguishes itself. Also the HGH level and the tissue disease may not be well correlated; high levels may occur in mild acromegaly and low levels in severe cases.

V. TREATMENT OF THE DISEASE

(NOTE: Is this disease a benign disorder, or a slowly malignant one despite its long and slow course? This point is not clear, though the large series of Gordon et al, (Canad. Med. J., 87, 1106 1962) suggests benignity. However, the tragic consequences of the disease may not be predicted, and even disfigurement which may be trivial to some may be catastrophic to an attractive young girl.

A. Treatment of the Mechanical Disease. (Manifested by severe and intractable headache, or impending loss of vision due to chiasmal compression.)

1. Surgical ablation is Rx of choice.

a. Subfrontal approach via left coronal suture is procedure of choice, according to Bronson Ray and Kemp Clark. Risk is no greater (1%) than anesthesia alone if done by a neurosurgeon experienced in the procedure (few are, however). Advantage is direct vision of vital structures and of sella itself which must be cleaned out completely to avoid recurrence of tumor.

b. Trans-sphenoidal approach (blind approach) 1) Risk of damage to carotid artery and nerves of cavernous sinus and to 2) Meningitis 3) CSF rhinorrhea.

2. Cryosurgery: Not recommended for large tumors if excision is possible.

3. Radiation: Used only if surgery is absolutely contraindicated.

B. Treatment of the Endocrine Syndrome

1. Late Stage: In the absence of a mechanical syndrome, rx is probably not indicated since HGH may be normal. If progression or ↑ HGH is still present, the most benign rx, i.e., radiation, is the rx of choice, since the damage has already been done and the patient is probably quite old. Uncontrollable diabetes or headache might warrant cryosurgery. Hormone replacement rx as indicated.

2. Active Stage: Aggressive therapy is indicated if florid acromegaly is present, i.e., the activity must be stopped unless you think the disease will remit.

a. X-irradiation (5,000 rads to fossa). Totally ineffective in reducing HGH; may stop tumor expansion but this is hard to document (Glick et al, 1965).

b. Alpha particle therapy (4000-9000 rads) (Lawrence and Linfoot, JAMA 186, 236, 1963). May be effective - HGH falls slowly over 12 months, often without loss of pituitary function (Linfoot and Greenwood, J. Clin. Endo. 25, 151, 1964). Previous x-irradiation disqualifies the patient, as does a large sella. Long-term follow-up data not yet available and recurrence rate unknown.

c. Yttrium^{90} or Au^{198} intrasellar implantation have all the hazards of transphenoidal surgery and few of its advantages.

d. Cryosurgery: (Dashe et al, JAMA 198, 591, 1966). Generally very effective (Lazarus et al, Lancet II, 90, 1966) even when, as happens rarely, GH is not totally eliminated. Dramatic "diuresis" of soft tissue disease in 24 hours. Complications same as transphenoidal surgery. Recurrence rate unknown but HGH stays down for at least 12 months, the longest follow-up date. Favored by most workers today as treatment of choice. May not induce apituitarism.

e. Total hypox: Sure cure which presupposes (probably correctly), that apituitarism is better than acromegaly. But make sure 1) that they have had their children, and 2) that a real expert in this type of surgery does it.

(Personal View: None of the available data are adequate for final judgement. Therefore, ideally, if there is no rush, I would try alpha particle therapy first, and wait a year; if no response has occurred I would then employ cryosurgery.)

3. "Pre-acromegalic" Stage (Case #1). Careful follow-up; treatment with alpha particles if progression of sellar size or tissue changes are perceived.

TABLE IX - THERAPIES FOR ACTIVE HGH-SECRETING ADENOMA

Procedure	Mortality	Morbidity	Effect on Tumor Growth	Effect on HGH Production	Contraindications	Present View
X-ray	0	0	May halt growth?	No significant effect	Previous full dose of x-ray	Of little value, a mere gesture (except perhaps to stop tumor growth)
Yttrium ^{96} or Au ^{198} Implantation	< 1 %	Sellar abscess; Meningitis; CSF rhinorrhea; Blind approach with risk of injury	Should halt growth if dose is adequate	Should reduce HGH if dose is adequate	Previous irradiation; large tumor size	Seems like a ridiculous choice of Rx now that cryosurgery is here
Alpha particle Rx	0	0	Seems to halt growth	Reduces HGH in many cases after a year	Previous X-ray; large tumor size	Most benign procedure with chance to avoid apituitarism. Further study required. Available only in Berkeley.
Cryosurgery	< 2 %	Same as above plus danger of inadvertent hypothalamic or optic nerve freezing.	Should halt growth if properly done	Usually reduces HGH to or near zero	Mechanical manifestations of tumor compression	Faster than particles. Easier than hypox and with a chance to avoid apituitarism. Further follow-up needed.
Hypophysectomy Subfrontal	< 2 %	Craniotomy. (But very well tolerated and without complications if done by skilled surgeon)	Completely removed	Completely eliminated	Few	Complete cure at price of apituitarism. Use only for mechanical syndrome and only if an expert is available.
Transphenoid	< 2 %	Same complications and dangers listed for yttrium implantation.	Cured if removal is complete	Cured if removal is complete	Very large tumor size	Probably obsolete now that cryosurgery is is here.

CASE # 1

FIRST KNOWN DIAGNOSIS OF "PREACROMEGALIC" HYPERSOMATOTROPINISM

Mrs. M. H. is a 25 year-old, white, housewife, who was in apparent good health until three years ago when she noted the abrupt onset of amenorrhea. There were no other complaints at this time. Her private physician noted a cyst on the right ovary. Although the use of "birth control pills" did result in bleeding, she never again had a spontaneous menstrual period. Ten months ago, she noted swelling of hands and feet and her ring which previously could be removed with ease became very difficult to remove. Seven months ago she noticed the onset of retro-orbital headaches which were constant although they fluctuated in intensity. At approximately the same time, she noted an increase in hair over the thighs, linea-alba of the abdomen and the appearance of chin hair. Her skin became coarse, blotchy and a mild acne appeared. There was a sharp decrease in libido and she has not had intercourse for at least 8 months. These symptoms were accompanied by increase in nervousness and irritability, fatigue and a sense of lethargy, although she denies any clear cut muscle weakness. Although she has always had a chronic backache, in recent months she had joint pains, primarily in the shoulders. She denies increase sweating, thickness of the skin or skin odor. She does, however, note tinnitus and although she has had a period of deafness, this is attributed to "stuffed ears". Her shoe size has increased from 7 1/2 to 9. She has had a history of sinusitis for many years. In recent months, her husband notes periobital edema. The patient claims to have gained 15 pounds in two years but attributes this to her "birth control pills". She has two children, age 3 1/2 years and 8 years.

The patient was diagnosed as having acromegaly by Dr. Marrow. Skull plates revealed some enlargement of the sella turcica which had a diameter of 17 mm. in March 1966 and increased to 18 mm. in August 1966. In August 1966 her visual fields were normal. Growth hormone assay performed in our lab revealed all specimens during an oral glucose tolerance test to be greater than 40 mμg/ml. In May 1966 she began x-ray therapy and received a total of 3800 R. The course was terminated on 6-24-66. She has been receiving one grain of proloid each day for several months. The rest of the history is non-contributory. There is no diabetes in her family and her system review is entirely negative.

PHYSICAL EXAMINATION: Reveals a slightly nervous, worried, young lady who is in no acute distress and does not appear chronically ill. She has no clear-cut acromagalic features at this time. The skin shows no thickening and she knows of no difficulties in venipunctures during recent tests. There is no acne or fibroma molluscum. There is fine hair over the chin, increased hair over the linea alba and the patient states that the hair over her thighs and legs, which does not seem to be excessive, does represent an increase for her. There is no prognathism or glossomegaly. Her thyroid is not enlarged. Hands and feet are normal. A complete physical was negative, except as already indicated. However, a complete pelvic examination by a gynecologist was recommended, to evaluate the apparent ovarian cyst.

X-RAY: X-rays of the skull were interpreted as revealing modest enlargement of the sella turcica. There was neither ballooning nor erosion of the anterior clinoids. There was little or no frontal sinus enlargement ordinarily seen in acromegaly. No prognathism or frontal bossing was noted.

GROWTH HORMONE ASSAY: The plasma growth hormone levels during a glucose tolerance test indicate non-suppressible hypersomatropinemia and support the diagnosis of a functioning eosinophilic tumor. Insulin response was not excessive.

Date	Test	Specimen	Glucose (mg %)	HGH (mμg/ml)	Insulin (μU/ml)
8-9-66	Oral GTT (100 g)	Fasting	104	> 40.0	-
		30 min.	203	> 40.0	-
		1 hour	184	> 40.0	-
		2 hour	108	> 40.0	-
		3 hour	78	> 40.0	-
12-13-66	Oral GTT (100 g)	Fasting	90	28.0	35
		30 min.	187	30.0	114
		1 hour	190	28.0	119
		1 1/2 hr.	166	28.0	129
		2 hour	126	24.4	99
		2 1/2 hr.	87	22.0	47
		3 hour	103	34.0	55

COMMENT: The insidious onset and slow rate of progression of acromegaly support the view that the adenoma and the hypersomatotropinemia which it produces undoubtedly antedate the appearance of enlargement of acral parts by a considerable period of time.

Radioimmunoassay technics for the measurement of growth hormone in the plasma (1, 2) provide specific methods for the diagnosis of hypersomatotropinemia long before the appearance of acral enlargement. In the present patient treatment was begun in the absence of overt acromegaly.

She will be followed by Dr. Linfoot for possible alpha particle rx, although previous x-ray may contraindicate this.

CASE #2 - ASYMPTOMATIC ACROMEGALY IN A POORLY CONTROLLED DIABETIC

W. G. - A 47-year-old C. M. civil servant who five years earlier was found to have glycosuria and was treated with Orinase. Five months ago he developed nocturia 4-5 times, nocturnal polydipsia, weight loss and increased appetite, and was admitted to the Dallas Veterans Administration Hospital for control of diabetes. He admits to increased sweating and decreased libido of uncertain duration and believes that his hat, glove and shoe sizes have increased. He has a history of duodenal ulcer and nephrolithiasis but is, otherwise, negative (no headache, back pain, etc.). No family history of diabetes.

PHYSICAL EXAMINATION revealed evidence of facial involvement with facial coarsening, moderate glossomegaly and prognathism and large hands and feet. Visual fields normal. No microaneurysms.

X-RAY: Thickened soft tissues of heel, feet and hands. Enlarged frontal sinus. Sella not enlarged.

LABORATORY FINDINGS: Oral GTT (180 g)

Specimen	Glucose (mg%)	HGH (mμg/ml)
Fasting	176	30.0
1/2 hour	244	20.0
1 hour	348	20.0
1-1/2 hours	420	21.5
2 hours	420	24.0

Muscle capillary basement membrane thickening was present (>1800 Å)

RX: Because of poor control, insulin dose crept up to 150 U daily, but subtle nocturnal symptoms suggested overinsulinization. The dose was gradually reduced to 80 U and control of diabetes improved markedly.

Patient was referred to Dr. Linfoot in Berkeley for alpha particle therapy.

COMMENT: Case illustrates asymptomatic early acromegaly developing in a diabetic. It was detected only through the diagnostic acuity of a resident. HGH was high and was only partially suppressed by marked hyperglycemia.

CASE #3.

R. R. - This patient is a 41-year-old, colored male, first seen at Parkland where symptoms and signs of acromegaly were recognized. He was referred to the Dallas Veterans Administration Hospital. He had had increase in the size of his hands and fingers along with change in his facial features dating back several years. He had gained 25 pounds in the past year. He had had a CVA in 1949, with a residual right hemiparesis. He was treated with radiation therapy to the pituitary area, receiving cobalt 60, a total 4,025 r. in 30 days. The patient's physical examination had changed clinically. Re-examined 9 months later, he appeared not to have changed clinically.

Laboratory work done on this admission revealed a BMR + 5%, PBI 4.3 mcgms.%, 17 hydroxys of 4.7 mgs. per 24 hours and 17 keto steroids of 10.4 mgs per 24 hours.

ORAL GTT (150 g)			i.v. GTT (45 g)		
	Glucose (mg%)	HGH (mμg/ml)		Glucose (mg%)	GH(mμg/ml)
Fasting	101	192	Fasting	90	128
1/2 hour	160	112	5 minutes	380	122
1 hour	184	78	10 "	269	112
1-1/2 hrs.	151	120	20 "	233	100
2 hours	124	144	30 "	206	104
3 hours	154	124	45 "	241	110
			60 "	167	144
			90 "	123	220

He was considered to have panhypopituitarism and received cortisol, synthroid, and testosterone. (His chart was lost, and no other pertinent information was available).

COMMENT: It is clear that the patient remains a florid acromegalic 9 months after radiotherapy. He exhibits marked hypersomatotropinism which is poorly suppressed, if at all, and no amelioration of soft tissue disease has been documented. He was thought to have evidence of compression damage to function of normal pituitary cells which required replacement rx. It would seem that more effective rx is indicated to arrest acromegaly and to prevent further pituitary destruction. Alpha particle therapy may now be contraindicated because of the previous irradiation, so that cryosurgery may be the safest alternative.

CASE #4.

J. B. - A 51-year-old white male who was first suspected of acromegaly in 1951 when he was seen at McKinney Veterans Administration Hospital. Skull plates taken because of sinusitis showed questionable atrophy of the dorsum of the sella. In 1955 he reported to his Lubbock local medical doctor that his hat size had changed from 6-7/8 to 7-3/4"; shoe size from 8 to 12, and glove size from 8 to "unfittable". His 1951 dentures no longer fit. His libido had waned, he noted weakness, severe headache and scotomata. He developed classical signs of acromegaly without sellar enlargement or eye signs and, in 1958, was finally treated with 3,000 of X-irradiation. In 1961 he was thought to be inactive. He developed a laryngeal polyp, leukoplakia, giant rugal folds of stomach, keratosis, but no evidence of increasing tumor size or advancing acral enlargement. In 1967 skull and its soft tissues were thought to have become thicker, but nothing else had changed. Glucose suppression test in 1967:

ORAL GTT (143 g)

	Glucose (mg%)	HGH (mμg/ml)	Insulin (uU/ml)
Fasting	79	6.0	9
30 minutes	161	8.0	89
1 hour	212	10.5	125
1-1/2 hour	205	9.0	215
2 hours	166	8.0	218
2-1/2 hours	121	13.5	160
3 hours	121	9.5	123

COMMENT: He illustrates a very slow course of the disease, which seems to be virtually non-progressive, and of waning activity. However, he is probably active and has evidence of hyperplastic and neoplastic tendency. He has a paradoxical rise with glucose suppression. He has cardiopulmonary disease and alpha particle therapy might be considered, had he not had previous X-ray. As it is, he will probably just be followed in the hope of spontaneous "burning out" of endocrine activity.