Acromegaly

Ariel L. Barkan

In the majority of cases, acromegaly is due to GH hypersecretion by a somatotroph pituitary tumor. The etiology of acromegaly is not known, and may be related to GHRH hypersecretion, intrinsic pituitary defect, or a combination thereof. Recent physiologic data and molecular biology techniques provide insights into the pathophysiology of this condition. Treatment options include surgery, radiation, and judicious administration of pharmacologic compounds inhibiting GH secretion and tumor growth. (Trends Endocrinol Metab 1992;3:205–210)

• **Case Report**

A 51-year-old woman was referred because of suspected acromegaly. She was known to have hypertension with left ventricular hypertrophy for more than 10 years and had been treated with diuretics and β blockers. She also had repeated bouts of supraventricular arrhythmia that were resistant to medical therapy, and 4 years ago she underwent radiofrequency ablation of the atrioventricular node. She had uterine fibromata and 6 years ago underwent abdominal hysterectomy. At the time of surgery, the anesthesiologist noted that her large tongue and excessive palatal soft tissue caused difficulty with intubation. Five years ago, she began to complain about diffuse joint pain and was evaluated by several rheumatologists. The diagnoses of degenerative joint disease, mixed connective tissue disease, nonspecific myopathy, and arthropathy of unknown origin had been proposed, and some relief was obtained with nonsteroidal antiinflammatory drugs. She had a long history of euthyroid goiter, but she received no thyroxine suppression. She also suffered from severe headaches that resisted pain medications. A diagnosis of depression was entertained and the pa-

tient had received counseling over the past year. A new rheumatologist noticed rough facial features and referred the patient to us. Questioning revealed an increase in shoe and ring size since age 30–35, malodorous perspiration, heavy snoring, and sleep apnea. The patient had obvious acromegaly, with rough facial features, multiple skin tags, and fleshy and moist hands and feet. There was no visual field defect or sign of extraocular muscle impairment. She had bilateral carpal tunnel syndrome. Magnetic resonance imaging (MRI) revealed a $12 \times 16 \times 20$-mm pituitary tumor almost reaching the optic chiasm and displacing both cavernous sinuses. Her plasma GH ranged between 30 and 70 µg/L (nl<5) and plasma IGF-I was 1400 µg/L (nl<270). After oral glucose load, plasma GH did not decline below 30 µg/L and, after an intravenous bolus of TRH, plasma GH rose from 47 to 672 µg/L. Her baseline GH profile (Q10-min sampling for 24 h) is shown in Figure 1.

The patient had mild hyperprolactinemia (27 µg/L; nl<20) but normal thyroid and adrenal function, and plasma LH and FSH were elevated appropriately for her age. She was begun on injections of the long-acting somatostatin analogue octreotide, 100 µg t.i.d. subcutaneously. Her headaches vanished almost immediately and arthritic pain improved within 1 month. There was also a significant decrease in soft tissue hypertrophy and abolition of excess perspiration, snoring,

and sleep apnea. After 4 months of therapy, her plasma GH was <1.5 µg/L in multiple samples, and plasma IGF-I fell to 410 µg/L. Repeat MRI disclosed shrinkage (Figure 2) of her pituitary tumor ($8 \times 12 \times 16$ mm). At transsphenoidal surgery, the tumor was very soft and was easily removed. The postoperative course was uneventful. One year after surgery, she is in a good general health, with normal plasma IGF-I levels, random GH levels <1.5 µg/L, and disappearance of the GH response to TRH. Adrenal and thyroid function remain normal. She still has vague joint pain, but there was a complete resolution of headache, carpal tunnel syndrome, and depression. She remains hypertensive and continues on diuretics and β blockers.

• **Discussion**

Acromegaly is a chronic debilitating disease characterized by persistent GH and IGF-I hypersecretion. Clinical presentation of patients with acromegaly is unmistakable: coarse facial features with pronounced skin folds, large hands and feet with obvious excess of soft tissue, and excessive perspiration are seen virtually in every patient. Careful history reveals presence of these signs for 5–15 years prior to diagnosis, during which time a multitude of other diagnoses are often entertained and various treatments applied. Acromegaly is probably the best example of the maxim that one finds only what one is looking for. The patient presented here had multiple symptoms and signs related to acromegaly, including arthropathy, heart disease, goiter, headache, and soft tissue hypertrophy for many years before an astute physician made the correct diagnosis. Once suspected, however, acromegaly is easily confirmed by appropriate laboratory tests.

Pathophysiology

The most obvious clinical manifestation of acromegaly, that is, excessive growth, is limited to acral enlargement if the disease process starts after closure of the epiphyses, or may include accelerated statural growth (gigantism) if the disease process begins well before puberty. In light of this clear clinical distinction, it is of interest that even though the disease is usually diagnosed during the third or fourth decade of life, the average height of the patients is 5–6 cm above the ethnic

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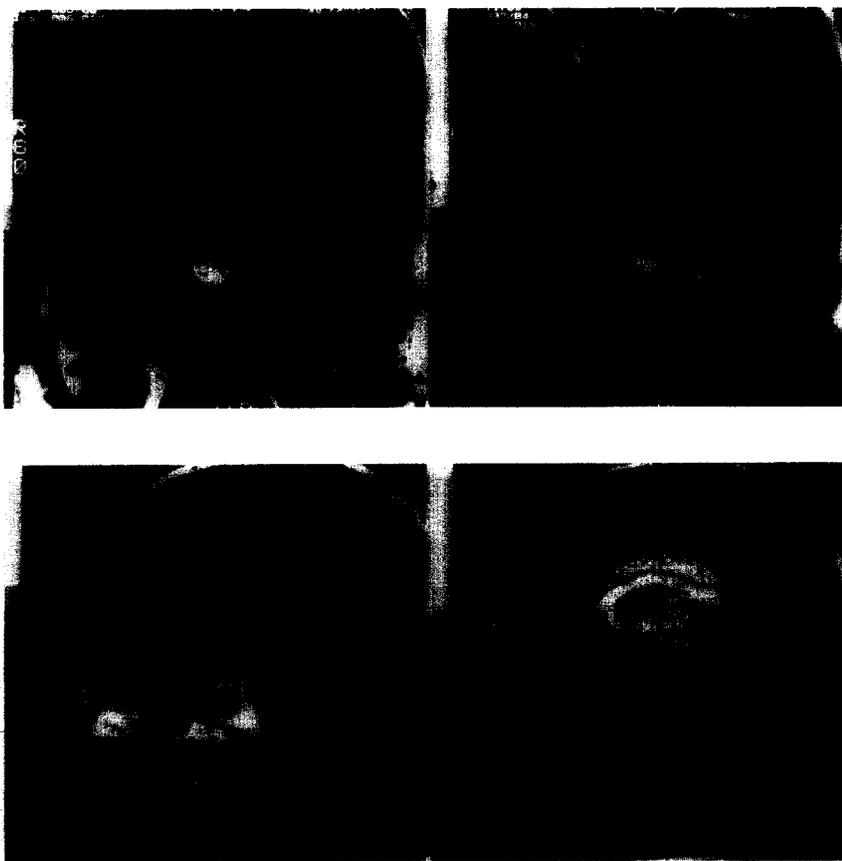
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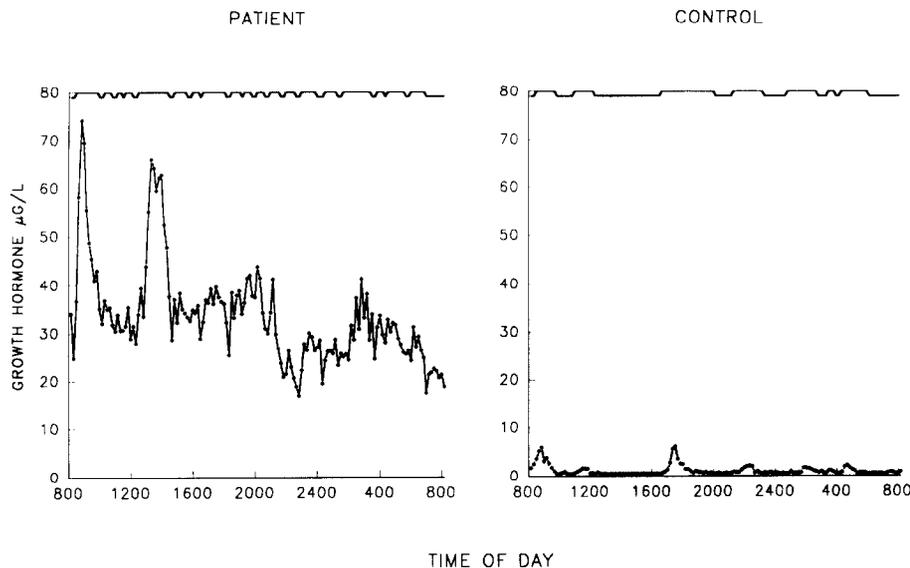
Figure 1. Pulsatile GH profiles in a patient with acromegaly **(left)** and in age-, sex-, and body mass index-matched control **(right).** Plasma GH was measured every 10 min for 24 h, and the data were subjected to cluster analysis. GH pulses are marked above each profile.

mean, and their siblings and parents are also unusually tall (Perheentupa et al. 1986). This height excess appears to be arrived at during or immediately after the expected pubertal growth spurt. It is, therefore, tempting to speculate that there may be some genetic tendency for increased GH secretion that may culmi- nate as a clinical disease in some individuals and that acromegaly is a disease of peripubertal onset. Indeed, during puberty there is a significant augmentation of GH secretion (Mauras et al. 1987) and the plasma levels of IGF-I increase dramatically, often reaching levels that are seen in active acromegaly. The accelerated somatic growth, disproportionate growth of hands and feet, roughening of facial features, and increased perspiration and oiliness of skin that occur during normal puberty all resemble acromegaly. Of course, this stage is transient and a gradual decrease in GH secretion toward the functional GH deficiency of old age begins shortly after puberty. However, unusually tall children exhibit biochemical abnormalities of GH secretion usually associated with acromegaly, such as incomplete GH suppression by glucose, GH responses to TRH, and augmented GH responses to GHRH, and most have radiologic evidence of enlarged pituitary gland often resembling an adenoma (Batrinos et al. 1987; Hindmarsh et al. 1986). The physiologic processes underlying augmentation of GH secretion at puberty and its subsequent decline during adulthood are unknown. Similarly, it is not known whether failure of the postpubertal restraint mechanism may result in persistently high GH secretion with subsequent development of acromegaly.

Figure 2. Pituitary MRI scans before **(left)** and after **(right)** 4 months of therapy with octreotide acetate, 100 µg every 8 h subcutaneously.

The question of whether acromegaly is a pituitary or a hypothalamic disease has been debated for decades. Until recently, however, there were no tools to answer this question. Previous studies have concentrated on the description of GH responses to various suppressive and stimulatory pharmacologic compounds purportedly acting on the pituitary or the hypothalamus. Recent insights into physiology and cell biology of different components of the GH-secreting system promise to provide a more direct understanding of the physiopathology of acromegaly.

GH is produced and secreted exclusively by the pituitary somatotrophs. Hypothalamic regulation of GH secretion is accomplished by an interplay of two factors: GHRH and somatostatin (SRIF). Animal studies have demonstrated convincingly that both neurohormones are secreted periodically and, likely, 180° out of phase. Periodic pulses of GHRH are primarily responsible for the generation of GH pulses while tonic SRIF secretion

maintains low interpulse GH levels (Plotsky and Vale 1985; Frohman et al. 1990). Additionally, periodic declines in SRIF secretion may promote acute discharges of GHRH and augment pituitary responses to GHRH pulses. Our understanding of the neuroendocrine mechanisms governing GH pulsatility in humans is likely to become more comprehensive in the near future as a result of the recent development of ultrasensitive (~ 5 pg/mL) chemiluminescent GH assays. GHRH is a potent mitogenic agent for pituitary somatotrophs and it also induces GH gene transcription and GH release (Billestrup et al. 1986). A simplified scheme of neuroendocrine and cellular events leading to somatotroph proliferation and GH synthesis and secretion is shown in Figure 3. Since acromegaly is associated with both GH hypersecretion and increased somatotroph proliferation, it is likely that the underlying mechanism(s) of this disease involve an abnormality somewhere along this pathway. Thus, both GHRH excess (hypothalamic cause) as well as an abnormality in the intracellular components of the pathway (pituitary cause) may be responsible for the initiation and progression of the disease. Additionally, a combination of both the GHRH excess and pituitary mutation (a "two stage" hypothesis) should be considered (Melmed 1990). According to this theory, primary pituitary mutation is an initiating event, and GHRH excess leads to clonal expansion of the mutant somatotroph. Conversely, accelerated somatotroph proliferation as a result of GHRH-induced mitogenesis may render somatotrophs prone to developing mutations (Butterworth and Goldsworthy 1991), likely along the GHRH-activated pathway. Several recent experimental paradigms and some clinical correlates provide support to each of these possibilities.

Accelerated GH pulse frequency (3–4 times normal) in patients with acromegaly is invariably found in studies employing frequent (Q5–20 min) blood sampling (Barkan et al. 1989; Hartman et al. 1990; Roelfsema et al. 1990). Whether these GH pulses represent accelerated GHRH pulse frequency is still a matter of debate. The nocturnal augmentation of GH secretion is still present in patients with acromegaly, indicating persistent control of GH secretion by the CNS. Importantly, even after the GH-producing tumor is completely removed and the patient enters
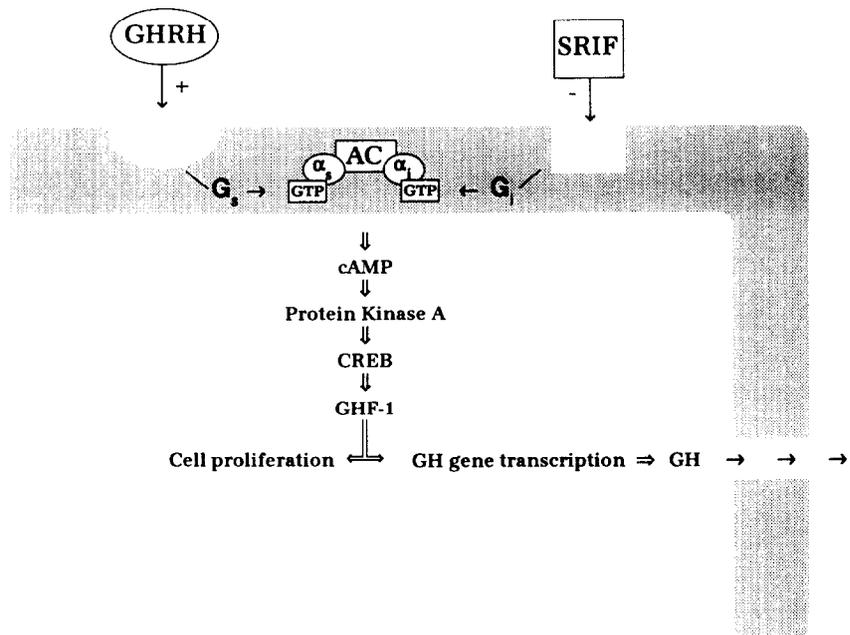
Figure 3. Simplified scheme of neuroendocrine and intracellular events leading to somatotroph proliferation and GH secretion. Upon binding of GHRH to its pituitary membrane receptor, the GHRH–receptor complex activates a G_s protein by promoting replacement of GDP by GTP in the guanine nucleotide binding site of the α subunit (α_s). The activated αs then stimulates adenylate cyclase (AC), thus increasing production of cAMP. All effects of GHRH upon the somatotroph can be reproduced by cAMP (Billestrup et al. 1986). Somatostatin (SRIF) interferes with this process by activating the inhibitory G_i protein that suppresses AC activity. An increased intracellular level of cAMP activates protein kinase A, which in turn phosphorylates the cAMP response element binding protein (CREB). Phosphorylated CREB binds to the promoter of the GHF-1-Pit-1 gene, thereby initiating its transcription. The resultant GHF-1-Pit-1 protein fulfills two functions: activation of GH gene transcription and induction of somatotroph proliferation (Castrillo et al. 1991).

an apparently stable remission, GH pulse frequency remains abnormally rapid (Ho et al. 1991). These studies suggest that acromegaly may be a hypothalamic disease caused by GHRH excess (presumably, high frequency of GHRH pulses). GHRH-transgenic mice develop GH hypersecretion, gigantism, and pituitary mammosomatotroph hyperplasia with subsequent adenoma formation (Asa et al. 1990). Interestingly, an identical morphologic picture was recently described in a child with acromegaly that was likely due to central GHRH excess (Zimmerman et al. 1991).

On the other hand, absence of somatotroph hyperplasia in the periadenomatous pituitary tissue and monoclonality of GH-producing tumors support the "pituitary" origin of acromegaly (Herman et al. 1990). Although unquestionably compelling, this evidence can hardly be regarded as final. Several models indicate that hormonal induction of pituitary tumors may begin with hyperplasia that subsequently progresses into

adenoma (Scheithauer et al. 1985). Moreover, some pituitary tumors appear to be polyclonal (Schulte et al. 1991), and a transition from a polyclonal pattern to monoclonality has been demonstrated in other neoplasms (Woodruff et al. 1982). One can imagine, for example, that during the GHRH-induced process of somatotroph hyperplasia, elevated plasma IGF-I may cause physiologic involution of hyperplastic GH-producing cells, while one cell develops a resistance to the negative feedback of IGF-I and continues to proliferate, giving rise to a monoclonal adenoma. In support of this is the persistence of rapid GH pulsatility in acromegalic women with pregnancy-induced further elevation of IGF-I (Beckers et al. 1990) and the absence of acceleration of GH pulse frequency in acromegalics after fasting-induced fall in plasma IGF-I (Ho et al. 1990).

Animals made transgenic for cholera toxin (Burton et al. 1991), thus having permanently activated adenylate cyclase (AC), develop pituitary hyperplasia and

gigantism. Other models of altered cAMP-dependent cascade, namely, insertion of a mutant CREB gene (Struthers et al. 1991) or inhibition of GHF-1–Pit-1 synthesis (Castrillo et al. 1991), result in somatotroph hypoplasia and dwarfism. It is easy to imagine that different mutations may constitutively activate CREB or GHF-1, thereby producing somatotroph hyperplasia and gigantism. Interestingly, in the GHRH-transgenic mice, no GHF-1 protein is detected within the hyperplastic pituitary somatotrophs, while it is abundant in the areas of adenomatous transformation in the same pituitaries (Osamura et al. 1992). Recently, two mutations in the α subunit of G_s protein have been described in 40% of human somatotropinomas (Spada et al. 1990). These mutations lead to constitutive activation of AC, conceivably mimicking the effect of GHRH. The mutations have been proposed to be the mechanism of GHRH-independent formation of somatotropinomas. It is of interest, however, that the same mutations significantly increased mitogenic responsiveness of 3T3 cells to exogenous activation of AC (Zachary et al. 1990), bringing us back to the "two stage" hypothesis of pituitary oncogenesis. Animals transgenic for an oncogene working outside of the "GHRH pathway" develop pituitary tumors incapable of secreting GH (Stefaneanu et al. 1992).

In the majority of patients (>99%), acromegaly is due to a GH-producing pituitary tumor. Several histolic varieties of pituitary somatotropinomas have been described (Melmed 1990), and they may reflect different physiopathologic processes or different cellular precursors. Rarely, tumors may develop in the pharyngeal pituitary tissue (Warner et al. 1982). Since a pharyngeal pituitary remnant is present in everyone, the extreme rarity of tumor development in this structure is puzzling. Again, it is tempting to speculate that this is due to the absent hypothalamic input to the ectopic pituitary and that the primary cell mutation may not arise in the absence of hypothalamic stimulation or may by itself be insufficient to result in tumor formation. Interestingly, functional and morphologic survival of human somatotropinomas transplanted into nude mice is improved by GHRH administration (Puchner et al. 1991).

The "ectopic GHRH" syndrome is a rare but important form of acromegaly. Among some 30 patients described thus far (Sano et al. 1988), most had carcinoid or islet-cell tumor as a source of ectopic GHRH. Usually, these patients have diffuse somatotroph hyperplasia as a manifestation of high circulating levels of GHRH (usually >1 ng/ml), but occasionally a true pituitary adenoma may develop. In contrast, acromegaly due to a GHRH-producing hypothalamic or pituitary gangliocytoma is always associated with a true GH-secreting adenoma instead of hyperplasia (Asa et al. 1984). The reason for the morphologic difference between the two forms of GHRH-induced disease is uncertain, but may be related to a difference in the duration of the disease process, since the "ectopic GHRH syndrome" may be diagnosed earlier, in the course of workup for metastatic carcinoid or islet-cell tumor. Indeed, as mentioned above, a transition from hyperplasia to adenoma has been demonstrated in GHRH-transgenic mice and in one patient with an apparently central source of GHRH hypersecretion. Recent description of GHRH mRNA in somatotropinomas, but not in other pituitary tumors or in normal pituitary tissue, further blurs the distinction between different types of acromegaly (Wakabayashi et al. 1992).

In summary, the question of hypothalamic versus pituitary cause of acromegaly has not been resolved yet. The current in vivo studies are necessarily limited to an indirect assessment of GHRH secretion by measuring plasma GH profiles, whereas the in vitro investigations study the final morphologic product of the disease, that is, the tumor, and cannot draw any conclusions about the preexisting neurohormonal milieu to which this tissue had been exposed. The final answer is likely to come from in vivo studies in patients with acromegaly that will utilize recently developed methods: direct sampling of the pituitary portal blood (Paradisi et al. 1989) and the use of GHRH-receptor antagonists (Lumpkin et al. 1989) analogously to the use of GnRH antagonist in patients with FSH-producing tumors (Daneshdoost et al. 1990).

Diagnosis

Clinical presentation of a patient with acromegaly is usually straightforward and the clinical impression is easily confirmed by appropriate laboratory tests.

Plasma GH is almost always elevated to >5 µg/L, but may fluctuate widely during the day. Traditionally, oral glucose loading has been used to substantiate the diagnosis, since plasma GH declines to <2 µg/L in practically all normal subjects, but remains above this limit in all patients with acromegaly. Recent availability of IGF-I assay further simplifies the diagnostic process. A single elevated IGF-I level in a patient with the appropriate clinical picture establishes the diagnosis with 100% certainty. It is especially useful in rare patients whose plasma GH is only minimally elevated. One should be careful, however, in interpreting elevated IGF-I levels in pubertal children and in pregnant women, since IGF-I may be physiologically high in these circumstances. In patients with acromegaly, plasma IGF-I levels increase almost linearly following increase in mean plasma GH levels from normal up to ~20 µg/L, and plateau thereafter (Barkan 1989). This explains the well-known fact that clinical severity of acromegaly does not correlate well with the magnitude of GH hypersecretion. Therapy should be aimed at lowering plasma GH to <2 µg/L to normalize IGF-I levels and provide meaningful clinical improvement.

GH responses to a variety of provocative stimuli are abnormal in patients with acromegaly. Of these, two carry clinical importance: a paradoxical fall to dopamine agonists is employed as a rationale for therapy (bromocriptine); and a paradoxical rise to TRH, seen in 60%–80% of patients, is helpful in detecting even minimally abnormal GH secretion after surgery. Unfortunately, the mechanism(s) of the GH rise to TRH in acromegaly is uncertain, and may relate either to the presence of the tumor or to GHRH excess. Recently, measurement of plasma GHRH has become available. Even though the diagnostic yield will be low, this assay should be performed in every newly diagnosed patient because it is the single best test to exclude the "ectopic GHRH syndrome." GH responses to a variety of dynamic maneuvers (TRH, L-DOPA, glucose load, and GHRH) cannot differentiate between this condition and a simple pituitary tumor. The distinction, however, is crucial because pituitary surgery in patients with ectopic GHRH secretion is of no value (any remnant of pituitary tissue will undergo additional hyperplasia and GH hyperse-

cretion will not abate), and unnecessary hypopituitarism is almost inevitable. Removal of the GHRH-producing tumor, on the other hand, is curative.

Pituitary computed tomography or magnetic resonance imaging scan is necessary to delineate the size of the tumor and the degree of invasiveness. Most somatotropinomas are large by the time of diagnosis, measuring 2–3 cm in diameter and expanding into the cavernous sinuses, sphenoid sinus, or above the sella, abutting on the optic chiasm. In these patients, residual pituitary function is frequently compromised.

Therapy

Surgery is the best treatment for almost all patients with newly diagnosed disease. Only rarely would one prefer nonsurgical treatment, that is, in an elderly patient with mild disease or in one whose general medical condition precludes anesthesia. The operation should be carried out by an experienced pituitary neurosurgeon, because the first operation is often the last one, and repeat operation is rarely successful because of distorted anatomy and intrasellar scarring. Most surgical series report an ~75% cure rate in patients with enclosed microadenomas and a 20%–30% cure rate in patients with large tumors (Ross and Wilson 1988). One should appreciate, however, that these data were generated from remarkably liberal criteria for cure, such as single GH <5 µg/L with or without glucose load. Most of these patients have persistently high plasma IGF-I, indicating active disease, and will require further therapy. Most often, radiation is administered in an attempt to destroy the residual pituitary tumor tissue. External pituitary radiation, proton beam, α particle, interstitial radiation, or stereotactic ^{60}Co beam ("γ-knife") (Thorén et al. 1991) have been employed and none of these offers even marginal long-term advantage over the other. GH declines by ~50% within the first 2 years after radiation, and by 10%–20% per year thereafter. Thus, the initial GH level is the crucial determinant of the final result, and patients with preradiation GH levels of >20 µg/L are unlikely to benefit from the procedure for at least 5–10 years. Hypopituitarism develops in 50% of patients within 5 years after radiation, but true normalization of the GH secretory rate is seen in

<20%. Many endocrinologists are still reluctant to recommend radiation therapy for fear of side effects. However, modern techniques have practically eliminated systemic side effects, and damage to distant brain structures is virtually never seen. The fear of decreased cognitive function appears to be unfounded because of the small radiation dose to cerebral hemispheres and the maturity of brain tissue in adult acromegalics. Furthermore, the balance between the minute theoretical possibility of brain dysfunction and the real dangers of persistent GH hypersecretion is clearly tilted toward the latter. Dopamine agonists, of which bromocriptine is the most popular, have beneficial effect in some patients. Unfortunately, even though they decrease plasma GH in half of the patients, only in 20%–25% of the cases does plasma GH decline to <5 µg/L, and plasma IGF-I becomes normal in no more than 10%–15% of the patients (Barkan 1989).

Somatostatin analogue SMS 201-995 (Sandostatin or octreotide) represents the most powerful nonsurgical therapeutic modality (Barkan 1989). It is usually administered as 3–4 daily injections of 50–500 µg each or as a continuous subcutaneous infusion. The latter appears to be more effective. Approximately 90% of patients respond to this treatment and plasma GH and IGF-I can be normalized in 60%–70% of cases. The acute side effects (abdominal cramps or diarrhea) are usually self-limited, but there is a high incidence of gallstone formation with long-term therapy. Normalization of GH secretion relieves arthropathy and cardiomyopathy of acromegaly. Interestingly, headaches disappear within minutes after the injection, well before there is an effect on GH hypersecretion. Octreotide is the only effective therapy for a surgically incurable ectopic GHRH secretion by a carcinoid tumor.

Preoperative therapy with octreotide in patients with GH-producing macroadenomas appears to shrink and soften the tumor in the majority of patients (Barkan et al. 1988). Preliminary data have suggested that this may result in a more favorable surgical outcome, and additional studies of this nature are needed. High doses of octreotide are probably necessary for this effect in patients with macroadenomas, because

the morphologic effects of the drug are likely to parallel its ability to normalize GH hypersecretion. Pretreated tumors exhibit smaller cell size, perivascular fibrosis, and dense granularity. The drug is not tumoricidal, since cessation of therapy is followed by restoration of GH hypersecretion and by the reexpansion of the tumor.

The year 1992 marks the 100th anniversary of the first attempt to treat a patient with a GH-producing tumor (Caton and Paul 1893). This century brought remarkable advances in our ability to diagnose and to treat acromegaly, but crucial questions of the etiology and the physiologic and molecular mechanisms involved remain unanswered. Recent advances in molecular biology and development of novel physiologic paradigms will enable a better understanding of the physiopathology of this disease and more effective therapy.

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