Pituitary tumors account for about 15% of primary intracranial neoplasms. Given the critical location of the gland, expanding tumors cause compressive symptoms. Furthermore, as pituitary cells secrete hormones, the proliferation of these cells may lead to a spectrum of endocrine symptoms. When tumors arise in pituitary somatotroph cells, aberrant secretion of growth hormone leads to the distinctive features of acromegaly. Understanding the development, function, and regulation of somatotroph cells provides insight into the cellular origin of this tumor, as well as approaches to the treatment of acromegaly. This review discusses advances in the understanding and treatment of acromegaly that have occurred since the topic was last reviewed in the Journal.

Phylogenetic Features of Somatotrophs

The pituitary gland integrates hormonal signals that control adrenal, thyroid, reproductive, growth, and metabolic functions. Distinct cellular compartments within the pituitary gland secrete highly specific trophic hormones in response to hypothalamic, intrapituitary, and peripheral hormonal and growth factor signals. Benign monoclonal adenomas can develop when specific types of pituitary cells proliferate and oversecrete their respective hormones. Acromegaly develops when somatotrophs (cells in the anterior pituitary gland that produce growth hormone) proliferate and oversecrete the hormone. A cascade of interacting transcription factors and genetic elements normally determines the ability of somatotroph cells to synthesize and secrete growth hormone (Fig. 1).

The development and proliferation of somatotrophs are largely determined by a gene called the Prophet of Pit-1 (PROP1), which controls the embryonic development of cells of the Pit-1 (POU1F1) transcription factor lineage, as well as gonadotroph hormone–secreting cells. Pit-1 binds to the growth hormone promoter within the cell nucleus, a step that leads to the development and proliferation of somatotrophs and growth hormone transcription. Once translated, growth hormone is secreted as a 191-amino-acid, 4-helix bundle protein and a less abundant 176-amino-acid form, entering the circulation in pulsatile fashion under dual hypothalamic control through hypothalamic-releasing and hypothalamic-inhibiting hormones that traverse the hypophysial portal system and impinge directly on specific somatotroph surface receptors (Fig. 1). Growth hormone–releasing hormone induces the synthesis and secretion of growth hormone, and somatostatin suppresses the secretion of growth hormone.

Growth hormone is also regulated by ghrelin, a growth hormone secretagogue–receptor ligand that is synthesized mainly in the gastrointestinal tract in response to the availability of nutrients. Studies to date suggest that ghrelin acts as a growth hormone–releasing hormone predominantly through hypothalamic mechanisms.
Control of the secretion of GH is achieved by hypothalamic GH-releasing hormone (GHRH) and somatostatin, which traverse the portal vein, somatotroph-specific transcription factors, and negative feedback control of insulin-like growth factor I (IGF-I). A list of activating and inactivating oncogenes and growth factors involved in the complex molecular pathogenesis of pituitary adenomas appears in Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org.) Accurate measurement of pulsatile secretion of GH requires ultrasensitive assays. POU1F1 denotes POU domain, class 1, transcription factor 1; Prop-1 Prophet of Pit-1; GHS growth hormone secretagogues (e.g., ghrelin); and SRIF somatostatin.
When growth hormone is measured in healthy persons with the use of standard assays, the level is usually undetectable (<0.2 μg per liter throughout most of the day), but there are approximately 10 intermittent pulses of growth hormone per 24 hours, most often at night, when the level can be as high as 30 μg per liter. These peaks may overlap with the range of elevated levels of growth hormone observed in patients with acromegaly. Fasting increases the secretion of growth hormone, whereas aging and obesity are associated with suppressed secretory bursts of the hormone.

The action of growth hormone is mediated by a growth hormone receptor, which is expressed mainly in the liver and in cartilage and is composed of preformed dimers that undergo conformational change when occupied by a growth hormone ligand, promoting signaling. Cleavage of the growth hormone receptor also yields a circulating growth hormone–binding protein, which prolongs the half-life and mediates the cellular transport of growth hormone. Growth hormone activates the growth hormone receptor, to which the intracellular Janus kinase 2 (JAK2) tyrosine kinase binds; both the receptor and JAK2 protein are phosphorylated, and signal transducers and activators of transcription (STAT) proteins bind to this complex. STAT proteins are then phosphorylated and translocated to the nucleus, which initiates transcription of growth hormone target proteins. Intracellular growth hormone signaling is suppressed by several proteins, especially the suppressors of cytokine signaling (SOCS).

Growth hormone induces the synthesis of peripheral insulin-like growth factor I (IGF-I), and both circulating (endocrine) and local (autocrine and paracrine) IGF-I induces cell proliferation and inhibits apoptosis. IGF-binding proteins and their proteases regulate the access of ligands to the IGF-I receptor, either enhancing or attenuating the action of IGF-I. Levels of IGF-I are highest during late adolescence and decline throughout adulthood; these levels are determined by sex and genetic factors and are elevated during pregnancy. The production of IGF-I is suppressed in malnourished patients, as well as in patients with liver disease, hypothyroidism, or poorly controlled diabetes. Although IGF-I levels usually reflect the integrated secretory activity of growth hormone, subtly elevated growth hormone levels may not uniformly induce high IGF-I levels.

SOMATOTROPH ADENOMAS

PATHOGENESIS

The molecular cascade underlying the formation of a growth hormone–secreting tumor is regulated by factors that influence the dynamic interaction of somatotroph-cell development, trophic status, and hormone secretion. Genetic changes in somatotroph adenoma cells develop on a background of chromosomal instability, epigenetic alterations, and mutations (Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Hypothalamic and paracrine growth hormone–releasing hormone and somatostatin, as well as growth factors, facilitate the expansion of the population of somatotroph tumor cells. For example, a mutation in the alpha-subunit of the stimulatory G protein confers constitutive activation of cyclic AMP (cAMP) in roughly 40% of somatotroph tumors. Patients with this variant do not have a distinct clinical phenotype. Expression of a proapoptotic factor, growth arrest and DNA damage–inducible (GADD) 45y protein, is lost in growth hormone–secreting adenomas, whereas the pituitary tumor–transforming gene protein (PTTG), a securin molecule that regulates sister chromatid separation, is overexpressed in growth hormone–secreting adenomas and correlates with tumor size. Pituitary-targeted transgenic overexpression of nuclear regulatory proteins results in the development of growth hormone–expressing pituitary tumors in mice. Thus, a broad spectrum of changes in growth factor levels can induce a cascade of genetic events, ultimately leading to pituitary-cell transformation and the genesis of adenomas.

CLINICAL AND PATHOLOGICAL FEATURES

More than 90% of patients with acromegaly have a benign monoclonal growth hormone–secreting pituitary adenoma surrounded by nonhyperplastic pituitary tissue (Fig. 2). Densely granulated somatotroph adenomas grow slowly, and patients presenting with these adenomas are usually older than 50 years of age. Younger patients usually present with more rapidly growing, sparsely granulated adenomas composed of growth hormone cells. About 25% of growth hormone adenomas cosecrete prolactin; these include dimorphous adenomas composed of growth hormone and prolactin cells, monomorphous somatotroph adenomas (which produce both prolactin and growth
hormone), and more primitive acidophil stem-cell adenomas. The third type are more commonly encountered in teenagers, often causing gigantism. Mixed single cellular or multicellular plurihormonal immunoreactivity is commonly reported by the pathologist, especially for the alpha-subunit of the glycoprotein hormones, and rarely for thyrotropin or corticotropin. Plurihormonal hypersecretion is rarely clinically apparent. Silent somatotroph adenomas have been described in patients with elevated levels of prolactin and IGF-I. More than 70% of somatotroph tumors are macroadenomas at diagnosis, but growth hormone–cell carcinoma is exceedingly rare and should be diagnosed only if extracranial metastases are demonstrated with the use of rigorous criteria. Extrapituitary ectopic hypersecretion of growth hormone has been reported in isolated cases of pancreatic islet-cell tumors or lymphoma. Familial acromegaly syndromes are rare (Fig. 2).

Excess production of growth hormone–releasing hormone can result in somatotroph hyperplasia and acromegaly. Both central hypothalamic tumors (usually gangliocytomas) and peripheral neuroendocrine tumors may secrete growth hormone–releasing hormone, which induces somatotroph proliferation (and very rarely, the formation of an adenoma), with resultant elevations in levels of growth hormone and IGF-I.

Figure 2. Causes of Acromegaly.
In most patients, acromegaly is caused by excessive production of growth hormone (GH) or GH-releasing hormone (GHRH). In rare cases, the disease is associated with familial syndromes, including multiple endocrine neoplasia type 1, the McCune–Albright syndrome, familial acromegaly, and Carney’s syndrome (see Table 2 in the Supplementary Appendix). GHS denotes growth hormone secretagogues, and PRL prolactin.
The clinical manifestations of acromegaly range from subtle signs of acral overgrowth, soft-tissue swelling, arthralgias, jaw prognathism, fasting hyperglycemia, and hyperhidrosis to florid osteoarthritis, frontal bone bossing, diabetes mellitus, hypertension, and respiratory and cardiac failure (Table 1). Growth hormone–secreting somatotroph adenomas arising in young patients before the closure of epiphyseal bone result in accelerated growth and gigantism.

### Table 1. Clinical Features of Acromegaly.

<table>
<thead>
<tr>
<th>Local tumor effects</th>
<th>Visceromegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary enlargement</td>
<td>Tongue</td>
</tr>
<tr>
<td>Visual-field defects</td>
<td>Thyroid gland</td>
</tr>
<tr>
<td>Cranial-nerve palsy</td>
<td>Salivary glands</td>
</tr>
<tr>
<td>Headache</td>
<td>Liver</td>
</tr>
<tr>
<td>Somatic systems</td>
<td>Spleen</td>
</tr>
<tr>
<td>Acral enlargement, including thickness</td>
<td>Kidney</td>
</tr>
<tr>
<td>of soft tissue of hands and feet</td>
<td>Prostate</td>
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<tr>
<td>Musculoskeletal system</td>
<td></td>
</tr>
<tr>
<td>Gigantism</td>
<td></td>
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<tr>
<td>Prognathism</td>
<td></td>
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<tr>
<td>Jaw malocclusion</td>
<td></td>
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<tr>
<td>Arthralgias and arthritis</td>
<td></td>
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<tr>
<td>Carpal tunnel syndrome</td>
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<tr>
<td>Acroparesthesia</td>
<td></td>
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<tr>
<td>Proximal myopathy</td>
<td></td>
</tr>
<tr>
<td>Hypertrophy of frontal bones</td>
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<tr>
<td>Skin and gastrointestinal system</td>
<td></td>
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<tr>
<td>Hyperhidrosis</td>
<td></td>
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<tr>
<td>Oily texture</td>
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<tr>
<td>Skin tags</td>
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<tr>
<td>Colon polyps</td>
<td></td>
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<tr>
<td>Cardiovascular system</td>
<td></td>
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<tr>
<td>Left ventricular hypertrophy</td>
<td></td>
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<tr>
<td>Asymmetric septal hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
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<tr>
<td>Congestive heart failure</td>
<td></td>
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<tr>
<td>Pulmonary system</td>
<td></td>
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<tr>
<td>Sleep disturbances</td>
<td></td>
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<tr>
<td>Sleep apnea (central and obstructive)</td>
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<tr>
<td>Narcolepsy</td>
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<tr>
<td>Endocrine and metabolic systems</td>
<td></td>
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<tr>
<td>Reproduction</td>
<td></td>
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<tr>
<td>Menstrual abnormalities</td>
<td></td>
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<tr>
<td>Galactorrhea</td>
<td></td>
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<tr>
<td>Decreased libido, impotence, low levels</td>
<td></td>
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<tr>
<td>of sex hormone–binding globulin</td>
<td></td>
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<tr>
<td>Multiple endocrine neoplasia type 1</td>
<td></td>
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<tr>
<td>Hyperparathyroidism</td>
<td></td>
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<tr>
<td>Pancreatic islet-cell tumors</td>
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<tr>
<td>Carbohydrate</td>
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<tr>
<td>Impaired glucose tolerance</td>
<td></td>
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<tr>
<td>Insulin resistance and hyperinsulinemia</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Lipid</td>
<td></td>
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<tr>
<td>Hypertriglyceridemia</td>
<td></td>
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<tr>
<td>Mineral</td>
<td></td>
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<tr>
<td>Hypercalciuria, increased levels of 25</td>
<td></td>
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<tr>
<td>hydroxyvitamin D₃</td>
<td></td>
</tr>
<tr>
<td>Urinary hydroxyproline</td>
<td></td>
</tr>
<tr>
<td>Electrolyte</td>
<td></td>
</tr>
<tr>
<td>Low renin levels</td>
<td></td>
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<tr>
<td>Increased aldosterone levels</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
</tr>
<tr>
<td>Low thyroxine-binding–globulin levels</td>
<td></td>
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<tr>
<td>Goiter</td>
<td></td>
</tr>
</tbody>
</table>

The incidence of acromegaly is approximately 3 cases per 1 million persons per year, and the prevalence is about 60 per million. Disease features develop insidiously over decades, often resulting in a delay of 7 to 10 years in diagnosis after the estimated onset of symptoms. About 40% of cases are initially diagnosed by an internist, and the rest are diagnosed when patients are seen by ophthalmologists for visual disturbances, by dental surgeons for bite disorders, by gynecologists for menstrual dysfunction and infertility, by rheumatologists for osteoarthritis, or by sleep-disorder specialists for obstructive sleep apnea.
COEXISTING ILLNESSES

Important factors determining the coexisting illnesses in a given patient include levels of growth hormone before and after treatment, IGF-I levels, the patient's age, the size of the tumor, the degree of tumor invasion, and the duration of symptoms before diagnosis. Skeletal disorders account for the most significant, functional disability and compromised quality of life in patients with acromegaly. Up to 70% of such patients have large-joint and axial arthropathy that includes thickened articular cartilage, periarticular calcifications, osteophyte overgrowth, and synovitis. Degenerative osteoarthritis, scoliosis, kyphosis, and vertebral fractures develop in patients whose disease is not brought under control.

Excessive levels of growth hormone and IGF-I can cause major structural and functional cardiac changes. By the time of diagnosis, arrhythmias, hypertension, and valvular heart disease are present in up to 60% of patients. With untreated, prolonged disease, concentric myocardial hypertrophy develops, and diastolic heart failure occurs. Unlike heart failure, aortic and mitral value regurgitation and hypertension are not reversible with octreotide treatment.

Respiratory dysfunction may be caused by soft-tissue swelling, nasal polyps, macroglossia, and pneumomegaly, with obstructive sleep apnea documented in more than 50% of patients. Soft-tissue edema and impaired exercise capacity are reversed once the hypersecretion of growth hormone is controlled. Centrally altered respiratory control may underlie the sleep apnea in acromegaly, which has been attributed to central effects of growth hormone itself.

Whether the relative risk of cancer in patients with acromegaly differs from that in the general population is controversial and has been extensively reviewed. In a retrospective cohort of 1362 patients with acromegaly, the overall incidence of cancer was lower than that in the general population; however, the rate of death from colon cancer was higher than expected (standardized mortality ratio, 2.47; 95% confidence interval, 1.31 to 4.22). Furthermore, prospective, controlled studies of colonoscopic screening indicate that the risk of colon cancer in patients with acromegaly is about twice that in the general population, which probably reflects a trophic IGF-I effect on the proliferation of epithelial cells. Screening colonoscopy should be performed when the diagnosis of acromegaly is made, with follow-up according to standard guidelines.

MORTALITY

The overall standardized mortality ratio of patients with acromegaly is 1.48. Factors contributing to increased mortality among persons with acromegaly include the higher prevalence of hypertension, hyperglycemia or overt diabetes, cardiomyopathy, and sleep apnea in this population. Among 419 patients followed in the West Midlands Pituitary Database, increased mortality was ascribed primarily to elevated levels of growth hormone (above 2 μg per liter) and to previous radiotherapy. Multivariate analysis of determinants of survival in long-term studies indicates that growth hormone levels of less than 2.5 μg per liter, a younger age, a shorter duration of disease, and the absence of hypertension independently predict longer survival. In some studies, increased IGF-I levels are associated with higher mortality. However, growth hormone levels seem to be more consistently independent predictors of mortality than are IGF-I levels. Most published studies examining mortality outcomes in relation to growth hormone levels measured the hormone with older, relatively insensitive assays. Prospective association studies using levels of growth hormone obtained with newer, ultrasensitive assays will be necessary to reassess this issue.

DIAGNOSIS

Most patients present with florid disease features. Biochemical diagnosis is made by assessing autonomous secretion of growth hormone (Fig. 3). This is done by measuring growth hormone levels during a 2-hour period after a standard 75-g oral glucose load (glucose-tolerance test), as well as by assessing the peripheral biologic effect of hypersecretion of growth hormone, as reflected by changes in IGF-I levels. In addition, clinical changes engendered by elevated levels of growth hormone and IGF-I should be assessed (Table 1). Several factors may make the biochemical diagnosis challenging, including the pulsatile nature of growth hormone secretion, the sensitivity of secretion of the hormone to sleep, and changes in the hormone according to the age and nutritional status of the patient. Measurements of
Clinical features of acromegaly

Measure IGF-I level

- Normal for age and sex
  - Active acromegaly ruled out

- Elevated
  - Perform oral glucose-tolerance test and measure GH level
  - Adequate GH suppression
  - Inadequate GH suppression

  Pituitary MRI

- Pituitary mass
  - GH-secreting pituitary adenoma
  - Assess likelihood of surgical success
  - Disease persistence
    - Surgery
    - SRL

- Normal, hyperplastic, or small pituitary gland
  - Extra-pituitary acromegaly
  - GHRH measurement
  - Chest and abdominal CT
  - Resect primary tumor

Disease persistence
- GH receptor antagonist with or without SRL
- SRL

Inadequate response or drug intolerance
- Repeated surgery or radiation therapy
growth hormone are also confounded by the lack of uniformity in reference standards and technical differences among assays, which contribute to poor reproducibility and wide interassay variation. Ideally, levels of growth hormone should be based on commonly accepted reference calibrations for recombinant human growth hormone and expressed in mass units, which would permit an accurate diagnosis of acromegaly, even in the context of subtle clinical features.

Measurement of the absolute nadir in levels of growth hormone after a glucose load is required both to confirm the diagnosis and to assess the efficacy of treatment, and the establishment of this level is assay-dependent. With the use of most commercial assays, nadir levels of less than 1 μg of growth hormone per liter rule out the diagnosis. However, with the use of ultrasensitive growth hormone assays (i.e., a detection threshold of 0.05 μg per liter), acromegaly may not be diagnosed in up to 25% of patients, if the criterion of a nadir level of less than 1 μg per liter is applied. For example, some patients with this nadir level of growth hormone may still have elevated IGF-I levels. Such patients should undergo magnetic resonance imaging (MRI) of the pituitary gland in order to settle the issue of whether they have acromegaly. With the use of some ultrasensitive assays, nadir levels of less than 0.3 μg per liter reliably distinguish patients without acromegaly and those with biochemically controlled disease from those with active disease. The production of growth hormone may not be suppressed in patients who have liver disease, renal insufficiency, uncontrolled diabetes, malnutrition, or anorexia or in those who are pregnant or are receiving estrogens. During late adolescence, growth hormone may also fail to be suppressed. Thus, IGF-I levels should ideally serve as a biomarker for growth hormone activity, but in some patients whose disease is controlled by therapy, levels of growth hormone and IGF-I are discrepant. Nadir levels of growth hormone should be evaluated along with IGF-I levels, since together these levels provide complementary evidence for establishing the biochemical diagnosis.

Pituitary MRI with the administration of contrast material is the most sensitive imaging study for determining the source of excess growth hormone. Adenomas that are more than 2 mm in diameter can be visualized, as can tumor dimensions, invasive features, and optic tract contiguity. At diagnosis, more than 75% of patients with acromegaly have a macroadenoma (>10 mm in diameter), which often extends laterally to the cavernous sinus or dorsally to the suprasellar region. In rare cases, when a nonpituitary cause of excess growth hormone or growth hormone–releasing hormone is suspected, abdominal and chest computed tomography, MRI, or both are indicated.
### Table 2. Results of Acromegaly Treatments

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Somatostatin Receptor Ligand†</th>
<th>Growth Hormone–Receptor Antagonist</th>
<th>Dopamine Agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of therapy or dose of drug</td>
<td>Transsphenoidal resection</td>
<td>Conventional or radiosurgery</td>
<td>Octreotide (50–400 μg every 8 hr); octreotide LAR (10–40 mg IM every 4 wk); lanreotide (30 mg IM every 10–14 days); lanreotide gel (60–120 mg deep SC every 4 wk)</td>
<td>Pegvisomant (10–40 mg SC daily)</td>
<td>Cabergoline (1–4 mg orally weekly)</td>
</tr>
<tr>
<td>Biochemical control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth hormone &lt;2.5 μg/liter</td>
<td>Macroadenomas, &lt;50%; microadenomas, &gt;80%</td>
<td>Approximately 35% in 10 yr</td>
<td>Approximately 70%</td>
<td>Level increased</td>
<td>&lt;15%</td>
</tr>
<tr>
<td>Normalization of IGF-I</td>
<td>Macroadenomas, &lt;50%; microadenomas, &gt;80%</td>
<td>&lt;30%</td>
<td>Approximately 70%</td>
<td>&gt;90%</td>
<td>&lt;15%</td>
</tr>
<tr>
<td>Onset of response</td>
<td>Rapid</td>
<td>Slow (years)</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Slow (weeks)</td>
</tr>
<tr>
<td>Compliance of patient</td>
<td>One-time consent</td>
<td>Good</td>
<td>Must be sustained</td>
<td>Must be sustained</td>
<td>Good</td>
</tr>
<tr>
<td>Tumor mass</td>
<td>Debulked or resected</td>
<td>Ablated</td>
<td>Growth constrained or tumor shrunk, about 50%</td>
<td>Unknown</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Disadvantages</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>One-time charge‡</td>
<td>One-time charge</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Approximately 10%</td>
<td>&gt;50%</td>
<td>None</td>
<td>Very low IGF-I level if overtreated</td>
<td>None</td>
</tr>
<tr>
<td>Other</td>
<td>Tumor persistence or recurrence, 6%; diabetes insipidus, 3%; local complications, 5%</td>
<td>Local nerve damage, second brain tumor, visual and CNS disorders, approximately 2%; cerebrovascular risk</td>
<td>Gallstones, 20%; nausea; diarrhea</td>
<td>Elevated liver enzymes</td>
<td>Nausea, approximately 30%; sinusitis; high dose required</td>
</tr>
</tbody>
</table>

* The goals of acromegaly management include the control of tumor growth and the secretion of growth hormone and IGF-I, the relief of any central compressive effects, the preservation or restoration of pituitary trophic hormone function, the treatment of coexisting illnesses, the prevention of death, and the prevention of biochemical recurrence. Percentages denote the proportion of patients who have the result after treatment. LAR denotes long-acting-release, IM intramuscular, SC subcutaneous, and CNS central nervous system.

† For details, see Table 3 of the Supplementary Appendix.

‡ There may be additional costs if the patient requires repeated surgery.
such as airway obstruction, severe glucose intolerance, hypertension, and heart failure should be addressed with appropriate medical management before surgery. Recent surgical advances that involve the use of imaging guidance, navigation and endoscopic approaches, and perioperative pharmacotherapy of the tumor have contributed to improved outcomes.

In experienced hands, surgery is generally effective. Although up to 10% of tumors recur, many recurrences probably represent persistent growth of residual nonresectable tumor tissue. In one study, pituitary damage leading to transient or permanent hypopituitarism was reported in up to 30% of patients who underwent surgery, and overall rates of complications correlate with the number of pituitary operations performed by the individual neurosurgeon.

**Radiotherapy**

Radiotherapy is generally reserved for tumors that have recurred or persisted after surgery in patients with resistance to or intolerance of medical treatment. Conventional external-beam radiotherapy is administered over a period of several weeks. Several centers now perform stereotactic radiosurgery with the use of the gamma knife, which delivers a single radiation fraction to a small tumor target. This technique requires precise delineation of the target mass and is limited by the vulnerability of adjacent soft-tissue structures, including the optic tracts. Advanced computerized imaging has permitted accurate targeting of the tumor mass, minimized radiation scatter to normal surrounding tissues, and reduced treatment times. Initial reports suggest the effectiveness of gamma-knife radiosurgery, with similar complication rates.

IGF-I levels attenuate very slowly after radiation therapy, and maximal control of the release of growth hormone may require more than 15 years. Within 10 years after radiation therapy, about 50% of patients have hypopituitarism involving one or more trophic axes. Rarely, local damage and cerebrovascular disorders, especially in patients with antecedent diabetes, are reported.

**Receptor Targets for Medical Therapy**

Somatostatin receptor ligands, such as octreotide and lanreotide, have been widely used to treat acromegaly during the past two decades. These compounds bind to somatostatin receptors, which, once stimulated, signal the pituitary to suppress the secretion of growth hormone and the proliferation of somatotroph cells and also act on the liver to block the synthesis of IGF-I (Fig. 4). Panselective, monoselective, and chimeric somatostatin receptor ligands are currently under investigation (Table 3 of the Supplementary Appendix). In addition, a growth hormone–receptor antagonist acts peripherally to block growth hormone signaling. Although somatotroph adenomas express dopamine D2 receptors, D2-receptor agonists are not as effective as other agents.

**Somatostatin Receptor Ligands**

Two biologically active, endogenous isoforms of somatostatin, SRIF-14 and SRIF-28, are expressed in neuroendocrine tissues and act on the brain, pituitary gland, pancreas, and gut. Somatostatin action is mediated by five specific receptor subtypes (SST1 through SST5) that are differentially expressed in a tissue-specific pattern, conferring both functional and therapeutic specificity of ligand action. Each of the subtypes activates distinct signaling mechanisms, and all inhibit adenylyl cyclase. Somatotroph cells express predominantly SST2 and SST5, which signal the pituitary to suppress growth hormone secretion. More than 90% of growth hormone–secreting tumors express SST2 and SST5, and because of their high expression levels, they present effective targets for drug application.

Octreotide and lanreotide are selective for SST2 and SST5 and are generally safe for treating patients with growth hormone–secreting adenomas, given the long half-lives and absence of insulin-suppressing effects of both drugs. Depot preparations — long-acting-release octreotide and a long-acting aqueous-gel preparation of lanreotide — allow for injections every 14 to 28 days yet maintain highly effective drug levels. Reports suggest that 80% of patients who were followed for up to 9 years during treatment with somatostatin receptor ligands had growth hormone levels of less than 2.5 μg per liter and normal IGF-I levels. Eugonadism was also restored in two thirds of patients who had acromegaly with hypogonadism. Determinants of the efficacy of somatostatin receptor ligands
include levels of growth hormone before treatment, presence or absence of abundant tumor SST2 and SST5 expression, drug dose, biochemical criteria used to assess status, and adherence to treatment by patients. Shrinkage of tumor mass occurs in approximately 50% of patients but generally reverses when treatment is discontinued. However, most of these findings are from uncontrolled, open-label studies.\textsuperscript{83,84} Surgical debulking of macroadenomas that are not amenable to total resection enhances the efficacy of subsequent octreotide treatment.\textsuperscript{85} More than 80% of patients receiving the drug report an improvement in symptoms, including headache and peripheral soft-tissue swelling.

Somatostatin analogues are indicated after surgery that has failed to effect biochemical control and after radiation therapy, during the period when growth hormone levels remain elevated. Although primary medical treatment is thought to be both efficacious and safe, several caveats should be considered in interpreting these studies, including the preselection of patients who were likely to have a response to octreotide, hormone evaluation at the time of study entry rather than at diagnosis, and the lack of data from randomized, controlled trials comparing primary medical therapy with surgery. Since equivalent biochemical responses to long-term drug administration are achieved regardless of whether patients have undergone surgery or irradiation, primary medical treatment can be offered to patients with large extracellular tumors who have no evidence of central compressive effects, those who are too frail to undergo surgery, and those who decline surgery.\textsuperscript{82,86,87}

Somatostatin analogues are costly, and prolonged monthly injections are required. Transient diarrhea, nausea, and abdominal discomfort may occur but typically resolve within 8 to 10 weeks, and blood glucose levels may rise in some patients. Gallbladder sludge or asymptomatic gallstones develop within 18 months in up to 20% of patients, and these conditions should be managed according to standard guidelines.

Selective activation of somatostatin receptors by specific somatostatin receptor ligands results in additive suppression of growth hormone.\textsuperscript{88} Pasireotide (SOM230), currently in clinical trials, suppresses levels of growth hormone in patients with resistance to octreotide.\textsuperscript{89} Chimeric molecules that recognize both the dopamine D2 receptor and somatostatin receptors may enhance receptor signaling and provide therapeutic synergy.\textsuperscript{90,91} These novel molecules, which have potent growth hormone-suppressing activity when tested in growth hormone-secreting tumor cells derived from patients resistant to octreotide, offer the potential for increased efficacy with lower monotherapy doses.

\begin{table}
\centering
\caption{Receptor Targets for the Treatment of Acromegaly.}
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Pituitary somatostatin receptor subtypes and D2 receptors and peripheral growth hormone (GH) receptors are targets for therapeutic ligands. Clinically approved and investigational drugs — with ligand affinities for human somatostatin receptors that are dually selective (octreotide and lanreotide), panselective, monoselective, or chimeric (for the D2 dopamine receptor) — are listed in Table 3 of the Supplementary Appendix. A somatostatin receptor ligand (SRL) suppresses levels of both GH and IGF-I, constrains tumor growth, and inhibits hepatic GH-receptor binding and action. GH-receptor antagonists prevent GH-receptor signaling, which attenuates peripheral IGF-I levels. Lanreotide compounds are not approved for use in the United States. SST denotes somatostatin receptor subtype, Gx, b, and G protein alpha, beta, and gamma subunits, P-L C phospholipase C, PTP protein tyrosine phosphatase, MAPK mitogen-activated protein kinase, IGFBP3 insulin-like growth factor–binding protein 3, ALS acid-labile subunit, STAT signal transducers and activators of transcription, JAK2 Janus kinase 2, P3K phosphoinositide 3 kinase, and IRS insulin receptor substrate.
\end{tabular}
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\textbf{Pegvisomant, a Growth Hormone–Receptor Antagonist}

Pegvisomant is a pegylated growth hormone analogue with eight amino acid substitutions in growth hormone–binding site 1 and the substitution of glycine for alanine at position 120, resulting in both enhanced affinity for the growth hormone receptor and prevention of functional growth hormone–receptor signaling.\textsuperscript{92} Pegvisomant is used in patients with resistance to or intolerance of somatostatin analogues.\textsuperscript{93} The drug should be used in patients who do not have central compressive symptoms and in those with resistant diabetes.\textsuperscript{94} Daily injection of 40 mg of pegvisomant blocks the growth hormone–mediated generation of IGF-I in approximately 90% of patients, which improves peripheral soft-tissue features.\textsuperscript{95,96} Combined administration of a somatostatin receptor ligand and a growth hormone–receptor antagonist has been reported as an additional treatment to suppress the production of...
IGF-I, improving glucose tolerance, and to permit the administration of lower doses of growth hormone–receptor antagonist. Pegvisomant requires daily injection and is costly. The drug acts on peripheral tissue and affects neither the pituitary tumor nor secretion of growth hormone. During therapy with this agent, growth hormone levels reportedly increase by as
much as 76% over baseline levels, which is probably caused by a loss of negative feedback by lowering IGF-I levels.96 Accordingly, IGF-I measurement is the biomarker for monitoring the success of treatment. Liver-function tests should be performed monthly for the first 6 months and then every 6 months, since elevated hepatic aminotransferase levels have been reported.98 MRI should be performed every 6 months to detect possible continued tumor growth.

Dopamine Receptor Agonists

Despite the poor efficacy of the first dopamine receptor agonists, agents such as cabergoline appear to be promising. In an uncontrolled study, high doses of cabergoline offered a partial benefit, especially in combination with somatostatin receptor ligands and in patients with tumors that also secreted prolactin. The addition of high doses of cabergoline to treatment with somatostatin receptor ligands may improve the responsiveness of growth hormone in patients who otherwise have resistance to maximal doses of somatostatin receptor ligands.99

MONITORING AND CLINICAL GOALS

Prolonged exposure to elevated endogenous levels of growth hormone and IGF-I results in both direct structural and functional tissue damage and the development of secondary systemic illnesses. Achievement of the criteria for cure during or after therapy is determined by assessing biochemical control, as evidenced by controlled levels of growth hormone and normalization of IGF-I levels, monitoring tumor size or remnant growth, assessing residual pituitary function, and monitoring coexisting illnesses58 (Fig. 3, and Table 4 of the Supplementary Appendix).

Despite the imprecision of assays for growth hormone and IGF-I, it is clear from epidemiologic studies that tight biochemical control is required to reduce complications and restore adverse rates of death to control levels.37 For biochemically and clinically inactive disease, patients should undergo annual biochemical testing and pituitary MRI, regardless of treatment used. Persistent subtle elevations of growth hormone levels in the presence of normalized IGF-I levels may predict recurrence, despite the remission of coexisting illnesses and normalized IGF-I levels.62 For patients with biochemically active and clinically inactive disease, the tumor mass should be monitored for growth by annual MRI, and treatment should be initiated; if patients are already being treated, the method of therapy should be altered. In symptomatic patients, treatment should be initiated or changed until the symptoms are controlled. Monitoring of endogenous pituitary reserve, cardiovascular function (including echocardiographic evaluation), pulmonary status, blood sugar control, and rheumatologic complications should be maintained. In patients whose disease is controlled, colonoscopy, mammography, and measurement of prostate-specific antigen should be performed according to guidelines for the general population.

Disease relapse is unlikely if nadir levels of growth hormone during an oral glucose-tolerance test remain under 1 μg per liter and IGF-I levels are normal. However, in a study of the use of a highly sensitive growth hormone radioimmunoassay to monitor treatment outcomes in 60 patients, 50% of those with elevated IGF-I levels had nadir growth hormone levels that were less than 1 μg per liter.100 Furthermore, another study demonstrated that high IGF-I levels, but not nadir levels of growth hormone, indicated relapse or lack of control.101 Nevertheless, complete normalization of IGF-I levels may not necessarily be required to prevent either progression or relapse.52

Clinical monitoring should include an awareness of the challenges that patients with acromegaly face, such as fertility issues, the need for cosmetic or functional maxillofacial surgery, and the repercussions of an altered self-image. Patients who are anxious about difficulties in interpreting laboratory data and making treatment decisions may benefit from counseling and educational materials; a support group with a professional facilitator can often be helpful in this process. More frequent follow-up visits may be needed for patients requiring assistance with the injection of medications, help in understanding abnormal laboratory test results, or treatment for anxiety (on the part of either the patient or a family member). The development of hyperglycemia or other medical problems will also require more frequent visits. The aim in treating patients with acromegaly should be to achieve clinically safe biochemical end points rather than a complete normalization of growth hormone axis measurements.102
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CORRECTION

Medical Progress: Acromegaly

Medical Progress: Acromegaly. In Figure 3 (page 2565), the text below the “Elevated” box should have read “Perform oral glucose-tolerance test and measure GH level,” not “Measure IGF-I level.” The figure has been corrected on the Journal’s Web site at www.nejm.org. We regret the error.