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Systemic Complications of Acromegaly: Epidemiology, Pathogenesis, and Management

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This review focuses on the systemic complications of acromegaly. Mortality in this disease is increased mostly because of cardiovascular and respiratory diseases, although currently neoplastic complications have been questioned as a relevant cause of increased risk of death. Biventricular hypertrophy, occurring independently of hypertension and metabolic complications, is the most frequent cardiac complication. Diastolic and systolic dysfunction develops along with disease duration; and other cardiac disorders, such as arrhythmias, valve disease, hypertension, atherosclerosis, and endothelial dysfunction, are also common in acromegaly. Control of acromegaly by surgery or pharmacotherapy, especially somatostatin analogs, improves cardiovascular morbidity. Respiratory disorders, sleep apnea, and ventilatory dysfunction are also important contributors in increasing mortality and are beneficially advantaged by controlling GH and IGF-I hypersecretion. An increased risk of colonic polyps, which more frequently recur in patients not controlled after treatment, has been reported by several independent investigations, although malignancies in other organs have also been described, but less convincingly than at the gastrointestinal level. Finally, the most important cause of morbidity and functional disability of the disease is arthropathy, which can be reversed at an initial stage, but not if the disease is left untreated for several years. (*Endocrine Reviews* 25: 102–152, 2004)

Abbreviations: ALS, Acid-labile subunit; ANP, atrial natriuretic peptide; Apo, apolipoprotein; CETP, cholesteryl ester transfer protein; DISH, diffuse idiopathic skeletal hyperostosis; ECG, electrocardiogram; ER, estrogen receptor; GH-R, GH receptor; HDL, high-density lipoprotein; IGFBP, IGF binding protein; IGF-IR, IGF type I receptor; IGT, impaired glucose tolerance; IMT, intima-media thickness; LAR, long-acting repeatable; LDL, low-density lipoprotein; Lp-a, lipoprotein-a; LPL, lipoprotein lipase; MRI, magnetic resonance imaging; PR, progesterone receptor; PRL, prolactin; PSA, prostate-specific antigen; SCLC, small cell lung cancer; SIR, standardized incidence ratio; TGHM, transgenic for the GH gene.

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I. Introduction

IN 1864, THE skull of a woman affected by *prosopectasia* (derived from the Greek words *prosopon*, face, and *ektasis*, stretching) was described by Verga (1) and added to the collection of the Anatomical Museum of Modena, Italy. During her lifetime, this patient suffered from typical somatic disfigurement, arrhythmias, and osteoarthropathy, although a postmortem examination revealed a giant pituitary (1). In 1881, Brigidi reported a description clinically consistent with acromegaly from the autopsy of the Italian actor Ghirlenzoni

(2). This man had visceromegaly and enlarged hypertrophic pituitary. However, both Verga and Brigidi misinterpreted the pathogenesis of the syndrome, which was attributed to early menopause in the former and to primary bone disease in the latter case. Five years after Brigidi's description, Pierre Marie (3) indicated with acromegaly his observation of two patients he had treated at the Salpetrière Hospital in Paris. At autopsy, Marie observed visceromegaly and enlarged pituitaries but was uncertain whether pituitary overgrowth was the cause etiology of such syndrome or whether it reflected the general process of organomegaly observed in these patients (3). Afterward, a progressively increasing number of similar descriptions were provided. Massalongo in 1892 and Benda in 1900 both indicated the cause of the disease as originating in the pituitary (2). However, it was only in 1909 that Harvey Cushing (4) reported the remission of clinical symptoms of acromegaly after partial hypophysectomy, thus indicating the etiology of the disease and its potential treatment as well. Acromegaly is known to be characterized by progressive somatic disfigurement and a wide range of systemic manifestations (5, 6). At diagnosis, patients generally exhibit coarsened facial features, exaggerated growth of hands and feet, and soft tissue hypertrophy (Table 1). Other characteristics may include hyperhidrosis, goiter, osteoarthritis, carpal tunnel syndrome, fatigue, visual abnormalities, increased number of skin tags, colon polyps, sleep apnea and daytime somnolence, reproductive disorders, and cardiovascular disease, which most commonly includes cardiac hypertrophy, hypertension, and moderate arrhythmias, although congestive heart failure occurs more rarely (5–7). Improvement of surgical procedures, radiotherapy tools, and the availability of pharmacological compounds active on somatotroph pituitary cells greatly changed the approach to this disease that is an extraordinary model to investigate the pathophysiology of GH and IGF-I actions on virtually all body organs and systems; several systemic consequences developing in the course of undiagnosed GH and IGF-I excess may remain undiagnosed for a long time.

The aim of this review is to focus on the systemic complications of acromegaly, their pathogenesis, and the potential reversibility after treatment of the primary disease. Because the disease is rare, prospective mortality data in patients undergoing modern therapies are still lacking. Nevertheless, both earlier and new data indicate that the increased mortality in acromegaly is mainly due to cardiovascular disease and respiratory impairment (see *Section I.A*). In this review, cardiovascular diseases, metabolic complications closely linked to the increased cardiovascular risk, respiratory abnormalities, and malignancies will by considered as the first and most relevant cause of mortality, whereas bone complications will be considered next as the most important cause of morbidity. A short introduction to the disease, its development, and management is provided to better present the specific analysis of single complications

TABLE 1. Clinical features of acromegaly

Direct effects of the tumor	
Headache visual impairment	Visual loss
	Temporal hemianopia of one or both eyes
	Quadrandopia
Hyperprolactinemia	Mixed tumoral secretion or pituitary stalk section
Hypopituitarism cavernous sinus syndrome	Hypothyroidism, hypogonadism, hypocorticism
Systemic effects of GH/IGF-I excess	
Soft tissue and skin changes	Acral enlargement
	Increased skin thickness and soft tissue hyperplasia
	Increased sweating
	Skin tags and acanthosis nigricans
Cardiovascular features	Biventricular hypertrophy
	Increased interventricular septum thickness (eccentric hypertrophy)
	Diastolic dysfunction at rest and/or systolic dysfunction on effort
	Diastolic heart failure
	Arrhythmias
	Hypertension
	Endothelial dysfunction and increased carotid IMT
Metabolic features	Impaired fasting glucose
	Impaired glucose tolerance
	Diabetes mellitus
	Insulin resistance
	Reduced total cholesterol and increased triglycerides
	Increased nitrogen retention
Respiratory features	Upper airway obstruction
	Macroglossia
	Sleep apnea
	Ventilatory dysfunction
Bone and joint features	Increased articular cartilage thickness
	Arthropathy/osteoarthritis
	Carpal tunnel syndrome
	Osteopenia
Other endocrine consequences	Multinodular thyroid goiter
	Thyrotoxicosis
	Hypercalciuria
	Hyperparathyroidism

and their epidemiology, pathogenesis, and partial or total reversibility after controlling GH and IGF-I hypersecretion.

A. Epidemiology and causes of mortality in acromegaly

Acromegaly has an estimated annual incidence of three to four cases per million population and a current estimated prevalence of 40 cases per million population, which can be reportedly as high as 90 cases per million population (8–10). In most cases, chronic GH hypersecretion is caused by a benign pituitary adenoma (5). Due to its indolent and insidious nature, the diagnosis of acromegaly is usually delayed for a variable number of years (7). Retrospective epidemiological studies showed that diagnosis can be preceded by approximately four to 10 or more years of active disease, and it is likely that today the diagnosis is made earlier than before because patients present much less with visual field defects (11). Analysis of determinants of mortality outcome indicates that approximately 60% of acromegalic patients die from cardiovascular disease, 25% from respiratory disease, and 15% from malignancies (12–19). The nadir GH value likely constitutes the most predictive survival index, regardless of the death cause (13, 15–18). There is compelling evidence indicating that control of GH levels and/or IGF-I levels normalized for age is associated with improvement of adverse mortality rates, independent of the type of associated complications (17). Suppression of GH below 5 mU/liter (<2.5 μg/liter) had been shown already to portend a favorable mortality outcome (19, 20). In fact, it has been suggested that overall mortality in patients with acromegaly is correlated with the degree of GH control (18); mortality rates for cancer can be stratified according to posttreatment GH levels (18); and, if GH secretion is controlled, mortality rates become similar to those recorded in the nonacromegalic population (13, 18). However, mortality in patients with cardiac disease at the time of diagnosis occurs within 15 yr in almost 100% of cases, and only 20% of patients with diabetes and acromegaly will survive 20 yr (16). High GH levels, hypertension, and heart disease constitute the major negative survival determinants in acromegaly (19), whereas symptoms duration and other factors, including uncontrolled diabetes and/or dyslipidemia and cancer, account less for mortality (Fig. 1). Thus, control of GH hypersecretion, hypertension, and heart disease is relevant to improve the ultimate mortality rates.

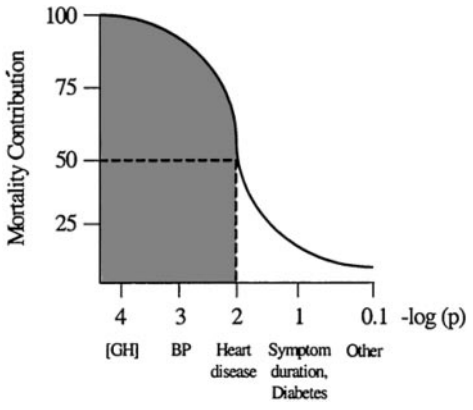

FIG. 1. Depiction of mortality determinants in patients with acromegaly. The x-axis reflects the *P* value (log) as calculated from published retrospective reports. [From S. Melmed: *J Clin Endocrinol Metab* 86:2929–2934, 2001 (19). Permission granted by The Endocrine Society.]

B. The clinical basis of increased mortality in acromegaly

As stated above, acromegaly is a disease developing slowly and insidiously, so that diagnosis is delayed by a number of years. Sleep apnea and daytime somnolence, reproductive disorders, and cardiovascular disease, which most commonly includes cardiac hypertrophy, hypertension, and moderate arrhythmias, are rather frequent, whereas congestive heart failure is rarer and occurs during the long-term exposure to high GH and IGF-I levels (5–7, 21). In particular, cardiovascular disease contributes significantly to mortality, and patients with hypertension and diabetes have the most severe alteration of cardiac function (22, 23); in a large cohort of 130 patients with acromegaly studied by echocardiography at diagnosis, we reported that patients with hypertension but without abnormalities of glucose tolerance had a higher prevalence of left ventricular hypertrophy and systolic and diastolic dysfunction than patients with uncomplicated disease (23). Conversely, the role of diabetes and other metabolic abnormalities in contributing to hypertension and cardiovascular disease in acromegaly is still not known. Patients with acromegaly are also at increased risk for arthritis, sleep apnea, and development of neoplastic lesions, particularly in the colon (19, 24). In the largest cohort study reported so far, however, cancer did not appear to act as a major cause of mortality (18). Possible genetic predisposing factors and enhanced family risk may be similarly relevant to the onset of and mortality from neoplastic complications, likely more than GH excess itself. Sleep apnea, both obstructive and central, is a significant cause of morbidity, closely linked to hypertension (25). Besides the negative effects of high circulating GH and IGF-I levels, the tumor mass itself may induce compression of the optic nerve tract or chiasm, cranial nerve palsies, headache, hydrocephalus, as well as various degrees of pituitary function insufficiency (5, 6). These mass-related complications are typical of pituitary tumor expansion and so are common to other tumor types and thus they will be not considered in this review.

C. The experimental basis for the GH/IGF-I effects at different body organs

Nearly one century after Verga's original documentation (1), Salmon and Daughaday's findings (26) set the basis for the somatomedin hypothesis with the identification of liver-derived serum factor-mediating GH actions on peripheral tissues. The same serum factor was sequentially termed sulfation factor, nonsuppressible insulin-like activity, multiplication-stimulation activity, and eventually IGF-I in independent investigations (reviewed in Refs. 27 and 28). The concept that GH operated on peripheral tissues through endocrine IGF-I was successively revised in the early 1980s, when IGF-I was shown to be expressed ubiquitously in several body tissues and its local expression could be modulated by exogenous GH administration to animals (27, 28). Subsequent studies in preadipocytes and chondrocytes at-

tempted at discriminating between GH and IGF-I effects in the periphery and demonstrated that GH promoted cellular differentiation, whereas IGF-I preferentially induced clonal expansion, thus introducing the dual effector theory (29). However, the congruity of the aforementioned theories has been recently questioned. GH has been found also to modulate the expression of various growth factors and their receptors in several tissues, in addition to IGF-I. GH can stimulate directly the proliferation of chondrocytes in the germinal zone of the growth plate (30), and it promotes the activation of immediate early gene (*i.e.*, transcription of early growth response factor-1) in 3T3-F442A preadipocytes (31). A demonstration that endocrine GH had local effects on cells originated from studies in mice carrying null mutations for the IGF-I gene that showed a normal proliferation of growth plate chondrocytes despite a 35% decrease in longitudinal bone growth (32). To explain this finding, the authors speculated that the lack of IGF-I stimulus had likely been replaced by endogenous GH or, alternatively, by local IGF-II (32). Recent investigations are now questioning whether liver IGF-I production actually plays an essential role in postnatal growth and development. Studies in conditional IGF-I knockout mouse models obtained with the Cre/loxP recombination system have, in fact, demonstrated that abrogation of liver IGF-I expression blunts 75% of endocrine IGF-I secretion, increases GH levels in serum likely due to feedback mechanisms, and preserves postnatal growth and development; as a result, autocrine/paracrine IGF-I production seems to be sufficient for normal growth and development, although a direct effect of GH on nonhepatic tissues cannot be excluded (33, 34).

GH action is achieved via its interaction on the cell surface with its receptor (GH-R) belonging to the family of the cytokine receptors (35), whereas IGF-I belongs to a system of proteins encompassing IGF-II, the type-I and -II IGF receptors (IGF-IR and -IIR), six IGF binding proteins (IGFBPs), three families of IGFBP proteases, and nine growth-mediating factors that share structural similarities in the N-terminus of the IGFBPs and have therefore also been termed IGFBP-related proteins (Fig. 2) (28). IGF-I circulates in serum bound to IGFBP-3 and the acid-labile subunit (ALS) in a 150-kDa ternary complex, which works both as a reservoir and regulator of IGF-I biodistribution to peripheral tissues/organs. Due to the molecular weight of ALS, IGF-I is unable to cross the endothelium unless it is released from the ternary complex after the proteolysis of IGFBP-3. IGFBP-3 proteolysis generates fragments with a lower IGF-I binding affinity, and this is key in the regulation of local IGF-I bioavailability. Studies in hypophysectomized rats have clearly demonstrated that all three peptides of the ternary complex are synthesized in the liver in a GH-dependent fashion, although a GH-responsive element has only been identified in the ALS promoter (36). In the liver, hepatocytes are the primary source for IGF-I and ALS production, whereas IGFBP-3 is synthesized preferentially in the portal venous and sinusoidal endothelium, as determined by the expression of mRNA by *in situ* hybridization histochemistry (37). Due to their GH dependence, the impairment of total and free IGF-I, IGFBP-3, and ALS secretion is used for diagnostic purposes in acromegaly and GH deficiency (38, 39). Although it has been shown that both IGF-I and IGFBP-3 elicit multiple cellular effects both dependently and independently of each other, ALS does not seem to possess intrinsic biological activity. The IGF-I cellular effects are achieved through the interaction of IGF-I with the IGF-IR, a heterotetrameric protein that is evolutionarily and structurally similar to the insulin receptor in its α- and β-subunits (40). The intracellular domains of the β-subunits of IGF-IR possess tyrosine kinase activity and tyrosine residues that are phosphorylated upon receptor activation. The consequence of receptor phosphorylation is the downstream recruitment of signaling proteins including the IRS and Shc families of proteins, which in turn activate the

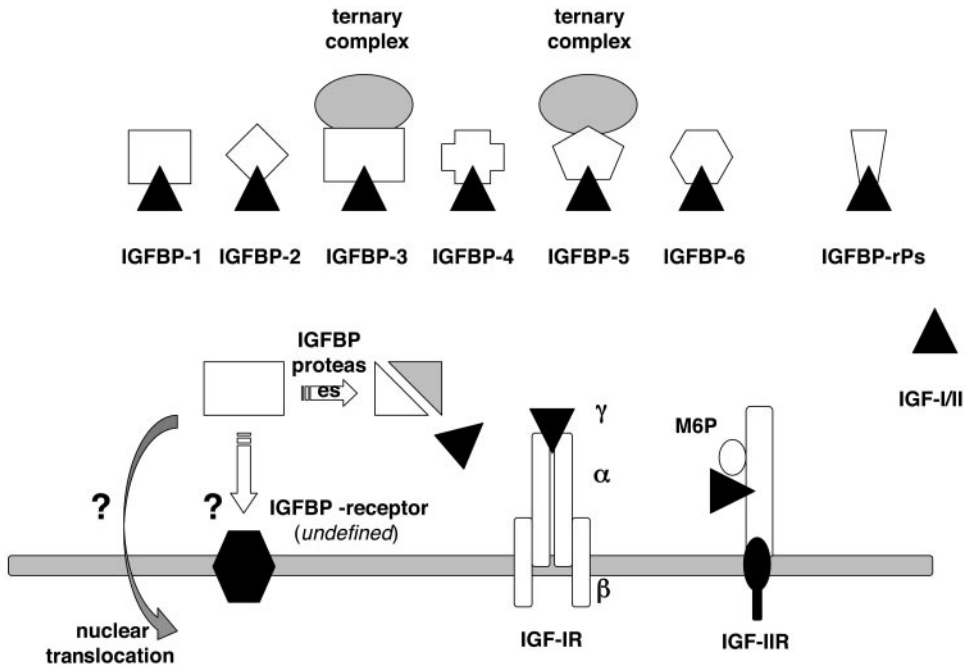

FIG. 2. Representation of the IGF system comprising IGFs, IGFBP-1 through 6, IGFBP-related proteins, IGF and IGFBP cell membrane receptors, and additional translocation mechanisms for IGFBP-3 to the nucleus.

MAPK and phosphatidylinositol 3-kinase pathways, as well as additional downstream signaling proteins leading to gene transcription (27). Depending on the preponderance of intracellular IRS or Shc proteins, IGF-I will promote either cellular proliferation/transformation or differentiation (41). Noteworthy, the primary role of IGF-I is the regulation of postnatal growth and the mediation of the growth-promoting effects of GH. The overexpression of bovine, murine, or rat GH stimulates body growth and increases IGF-I levels in transgenic mice (42). Similar body growth promoting effects are produced by human IGF-I overexpression in the mice liver (43). In contrast, IGF-I null mice suffer from impairment of fetal growth and development, whereas perinatal viability is markedly decreased (44). The physiological actions of IGF-I also encompass increased muscle protein synthesis (45), *in vivo* and *in vitro* stimulation of muscle cell differentiation (40), enhanced glucose uptake in peripheral tissues (45), bone growth and maturation (46), oligodendrocyte survival, and neuronal differentiation (47). These effects require a functionally active IGF-IR, which is essential for normal embryonic and fetal growth, modulation of cellular apoptosis, and the growth, proliferation, and migration of normal and tumoral cells (48).

Additionally, there is *in vitro* evidence to suggest that IGFBP-3 causes antiproliferative and apoptotic effects in breast, prostate, lung, and colorectal tumoral cell lines independent of the IGF axis (49). In addition, serum IGFBP-3 levels have been correlated negatively to cancer risk in human prostate, mammary, and gut neoplasms (50–52). Although uncertainty still exists on the clinical significance of these observations, demonstration of independent IGFBP-3 actions adds one more puzzling aspect to the dual effector theory and, more specifically, to the pathophysiology of acromegaly.

D. Management of acromegaly

An extensive discussion on the current approaches for an integrated and modern management of acromegaly lies beyond the scope of this review. However, because most of the subsequent parts will refer to the partial or total recovery of systemic complications of acromegaly after controlling GH/IGF-I hypersecretion, the most recent advances in the management of acromegaly will be summarized here.

The optimal treatment for acromegaly should be able to remove the tumor with resolution of its mass effects, preserve the normal residual pituitary function, prevent recurrences, restore normal GH and IGF-I secretion, relieve symptoms directly caused by GH excess, and, possibly, prevent progressive disfigurement, bone expansion, osteoarthritis, cardiomyopathy, hypertension, insulin resistance, diabetes mellitus, and lipid abnormalities, thus reversing the unfavorable long-term outcome (6). The treatment options currently available for such ambitious goals include surgery, irradiation, and pharmacological suppression of GH levels by somatostatin analogs or dopamine agonists, and/or by functional blockade of the GH-R by modified GH analog (53), which has provided promising results (54, 55). Cure criteria to evaluate the efficacy of all treatment approaches, except for the GH-antagonist, are mean integrated 24-h GH levels less than 2.5 μg/liter or no more than 1 μg/liter after glucose load, together with circulating IGF-I levels normalized for age and gender (20). Clearly, other pituitary hormone deficiencies that may be caused by the tumor and/or by its treatment must be treated as in other types of pituitary tumors.

Transsphenoidal adenomectomy remains a milestone treatment for GH-secreting tumors, but should be performed only in experienced centers. Moreover, it has been reported recently that the outcome of surgery when only one surgeon operates on patients is higher than that observed when more than one surgeon operates (56, 57). The outcome of surgery is successful in most microadenomas and enclosed macroadenomas, but it remains disappointing in larger adenomas and negligible in invasive tumors (6, 16, 56, 58). Among 224 consecutive patients, endocrine remission occurred in 72% of microadenomas, 50% of macroadenomas, and only 17% of giant adenomas (59). Normalized IGF-I levels with GH levels below 3 μg/liter (60), or 2.5 μg/liter (61), were achieved in 59% and 42% of unselected patients, respectively. In microadenomas, success of surgery was obtained in 61% of patients (61). Surgery relieves the compression on adjacent structures such as optic chiasm and ventricles, and it only rarely causes complications. In fact, in a study including questionnaires regarding 14 specific complications of transsphenoidal surgery mailed to 3172 neurosurgeons, it was reported that the mean operative mortality rate was low (0.9%), anterior pituitary insufficiency and diabetes insipidus were the most common complications (19.4% and 17.8%, respectively), whereas cerebrospinal fluid fistulas were found in a low number of cases (3.9%) and other complications, such as carotid artery injuries, hypothalamic injuries, loss of vision, and meningitis, occurred in 1–2% of cases (62). In another study (63), pituitary failure after surgery was confirmed to be the most frequent complication occurring in up to 30% of patients with macroadenomas. A controversy exists on the usefulness of a short preoperative drug treatment to improve surgical outcome (for review, see Refs. 6 and 64); we observed that a 6-month treatment with octreotide preoperatively improved metabolic and hemodynamic parameters and reduced the duration of hospital stay in acromegalic patients (65). Recently, to provide a technical refinement in pituitary surgery, a one-nostril endoscopic endonasal transsphenoidal procedure has been proposed to reduce the damage to nose and sphenoid sinus and to improve the management of the pituitary region (66). Interestingly, postsurgical complications using this technique are likely to be low compared with classical microscopical approach (67). In fact, among 146 consecutively treated patients who underwent an endoscopic endonasal transsphenoidal approach to the sellar region for resection of pituitary adenomas between January 1997 and July 2001, complications (divided into groups, *i.e.*, nasofacial, sphenoid sinus, sella turcica, supra or parasellar, and endocrine) were decreased in their incidence compared with large historical series of the traditional microsurgical transsphenoidal approach (67). The overview inside the anatomy facilitated by the endoscope and the consequent decreased surgical trauma can be taken as explanation for such positive findings.

Irradiation of GH-secreting pituitary tumor should be re-

served to patients in whom surgery is contraindicated or unsuccessful and medical treatment fails to control persistent hormone hypersecretion due to a remnant tumor (68). Multiple methods for delivery of radiation are currently used, including external radiation, proton beam, γ-particles, and interstitial radiotherapy. All seem to induce similar cure rates. The greatest fall in GH levels occurs within the first 2 yr, followed by a gradual decline thereafter for 10 yr (69). Earlier observations that pituitary irradiation normalized IGF-I concentrations only in a minority of patients (70, 71) have not been confirmed by later studies reporting higher cure rates (72, 73). Furthermore, the occurrence of severe complications, such as cranial nerve palsies, optic neuritis, impaired memory, lethargy, and tissue necrosis has decreased with modern techniques. However, damage of the normal hypothalamic-pituitary region results in hypopituitarism in more than half of patients within 10 yr (6, 63, 68, 69). Gamma-knife radiosurgery has been used as adjuvant treatment for pituitary adenomas in selected cases with promising results (74), but definitive data are still lacking.

Bromocriptine, the first and likely still the most widely used dopamine agonist in acromegaly, lowered GH levels below 10 μg/liter and 5 μg/liter in 50% and 10–20%, respectively, of over 500 patients with acromegaly included in a metaanalysis from 28 published series (75). It produced improvement of symptoms of acromegaly in up to 70% of the patients, but tumor shrinkage was rare; very high doses (10–20 mg/d) are generally required, and side effects are common (76). Variable results have been reported recently using cabergoline, a selective D_2 receptor agonist more potent than bromocriptine (77–79). Disease control is more likely achieved in patients with mixed prolactin (PRL)/GH-secreting adenomas than in the pure GH-secreting ones, and in patients with lower GH and IGF-I levels before treatment than in those with more aggressive disease (6).

Somatostatin analogs are, at present, the most widely used drugs to control acromegaly. Octreotide is an octapeptide, displaying a high affinity for somatostatin receptor subtypes 2 and 5 and a faint affinity for subtype 3, which has been largely used in acromegaly with excellent results (80). Octreotide given sc at a dose of 100–250 μg every 8 h for 6 months reduced GH levels below 5 μg/liter in 53% and normalized IGF-I levels in 68% of 115 patients enrolled in a multicenter placebo-controlled study (81). A metaanalysis of 466 patients treated worldwide showed that octreotide suppressed GH levels below 2.5 μg/liter in 29.2%, normalized IGF-I levels in 39.9%, and reduced tumor size (>20% of reduction in maximal diameter) in 38.6% of patients; the GH-lowering effect was related to initial GH values (6). Most clinical signs and symptoms of acromegaly, such as sweating, soft tissue swelling, fatigue, and headache, are generally relieved after the administration of the first doses of octreotide. Twenty percent of patients develop gallbladder abnormalities (biliary sediment/sludge, microlithiasis, or gallstones), but morbidity is negligible, and treatment with ursodehoxicolic acid can be performed in those patients with symptomatic gallstones (80). Lanreotide is another analog, showing a binding profile comparable to octreotide, and has a similar efficacy in suppressing GH and IGF-I levels (6, 68). Depot preparation of lanreotide and octreotide long-acting repeatable (LAR) have further improved the therapeutic success of sc octreotide (68). In particular, we showed tumor shrinkage, graded from mild to notable, in 80% of 15 newly diagnosed patients treated for 12 months with octreotide-LAR, suggesting its potential application as primary therapy in invasive adenomas (82). Our data have been subsequently confirmed by the results of a multicenter prospective study showing tumor shrinkage in all 27 newly diagnosed patients with acromegaly with median tumor volume reduction of 49% in microadenomas and 43% in macroadenomas (83). However, because a large variability in tumor shrinkage has been reported, it is still hard to estimate tumor size response to slow-release somatostatin analogs. Both depot formulations are well tolerated; the mild-to-moderate side effects experienced by up to 50% of the patients have short duration and often subside with treatment continuation (6, 68, 80).

As anticipated, the newest drug for treating acromegaly bases its efficacy on blocking the activity of the GH-R, thereby inhibiting the synthesis of IGF-I (53). In a placebo-controlled study, there was a significant dose-dependent fall in serum IGF-I in three groups treated with the GH-antagonist compared with placebo-treated patients, and 90% of patients treated with the highest dose (20 mg) achieved normal IGF-I levels for age (54). In line with IGF-I decrease, IGFBP-3 similarly decreased, and patients experienced an improvement of physical well-being and clinical signs. These results persisted until 24 months (55). Even if data on this new drug are still scant, the GH-antagonist seems to be well tolerated, except for rare cases of increased hepatic transaminase levels; two of 133 patients had increased tumor mass (54, 55), one of them being stabilized after a combined treatment with the GH-antagonist plus octreotide (84). Currently, the use of GH-antagonist is permitted in the United States and is still experimental in the rest of the world, but the drug should be available for treatment of acromegaly by the beginning of 2004.

II. The Complications at the Cardiovascular System

A. Epidemiology

GH and IGF-I elicit primary regulatory activities both in developing heart growth and in maintaining its structure (21). In the theoretical absence of other cardiac diseases, the involvement of the heart in acromegaly defines the acromegalic cardiomyopathy, which was first described at the end of the 19th century (85). Although the prevalence of the acromegalic cardiomyopathy has not been investigated in detail, its most common feature is considered to be a concentric biventricular hypertrophy (21, 86–90). Cardiac walls are generally thickened, but cardiac chambers are rarely enlarged due to the relative increase of cardiac myocyte width for the parallel assembling of new contractile-protein units (91). Aging and long duration of GH/IGF-I excess are main determinants of cardiac derangement; results collected *in vivo* and postmortem showed a prevalence of cardiac hypertrophy higher than 90% in patients with long disease duration (92, 93). However, more recent surveys demonstrated that structural changes of the heart can even occur in patients shortly exposed to GH hypersecretion (94–96), and

20% of normotensive patients younger than 30 yr develop cardiac hypertrophy (96). In particular, we recently reported that the left ventricular mass index was approximately 30% higher in 25 acromegalic patients below age 40 yr than in 25 age-matched control subjects (Fig. 3); 60% of the patients had clear-cut left ventricular hypertrophy (97). Characteristically, the cardiac hypertrophy of acromegaly occurs in the absence of hypertension that is present in approximately one third of patients (see *Section II.C*) and is further aggravated by hypertension and glucose abnormalities. In our analysis (22), 100% of patients with hypertension and diabetes had cardiac abnormalities at echocardiography (Fig. 4). The acromegalic cardiomyopathy develops after three steps: 1) in the early phase, and thus mainly in young patients with a short disease duration, there is initial cardiac hypertrophy, high heart rate, and increased systolic output altogether configuring the hyperkinetic syndrome (98); 2) in the middle phase, hypertrophy becomes more evident, signs of diastolic dysfunction appear, and insufficient systolic function on effort can be documented; and 3) in the end-stage of untreated disease, cardiac abnormalities may include systolic dysfunction at rest and heart failure with signs of dilative cardiomyopathy (21, 99). It should be considered, however, that longer acromegaly duration is generally accompanied by an older age, and it is well known that aging is accompanied by significant cardiovascular modifications, both structural and functional (100). In the nonacromegalic population, aging is associated with a slight degree of left ventricular hypertrophy and decrease, even modest, of resting heart rate and early filling rate, whereas end-diastolic and end-systolic dimensions,

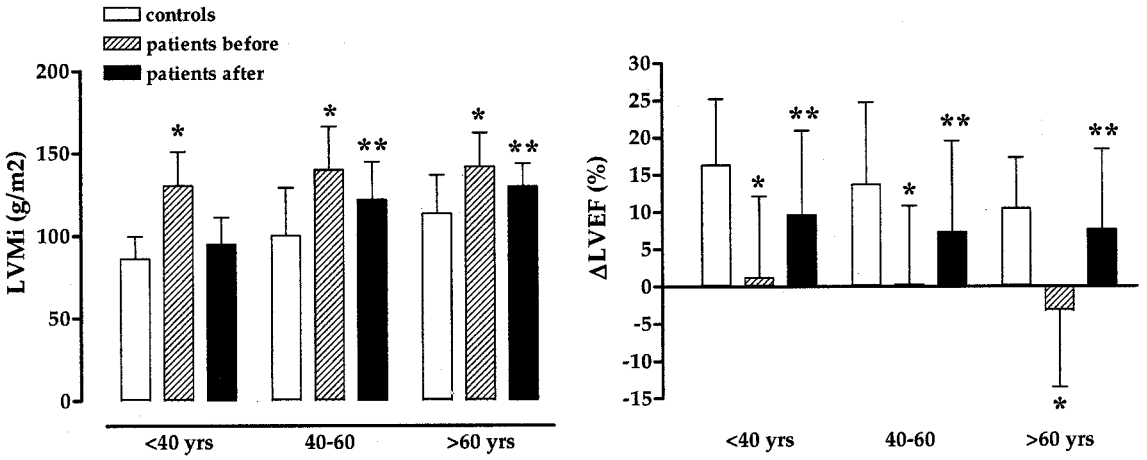

FIG. 3. Effect of age on the left ventricular mass index (LVMi, *left*) and response of left ejection fraction at peak exercise (ΔLVEF, *right*) in our series. Acromegalic patients and controls were grouped according to age [<40 yr (n = 32), 40–60 yr (n = 33), and >60 yr (n = 22)]. Data are derived from our own experience and include data reported in Refs. 97, 191, and 199. *, $P < 0.001$ *vs.* controls; **, $P < 0.001$ *vs.* before treatment that consisted of octreotide-LAR at a dose of 20–40 mg/month.

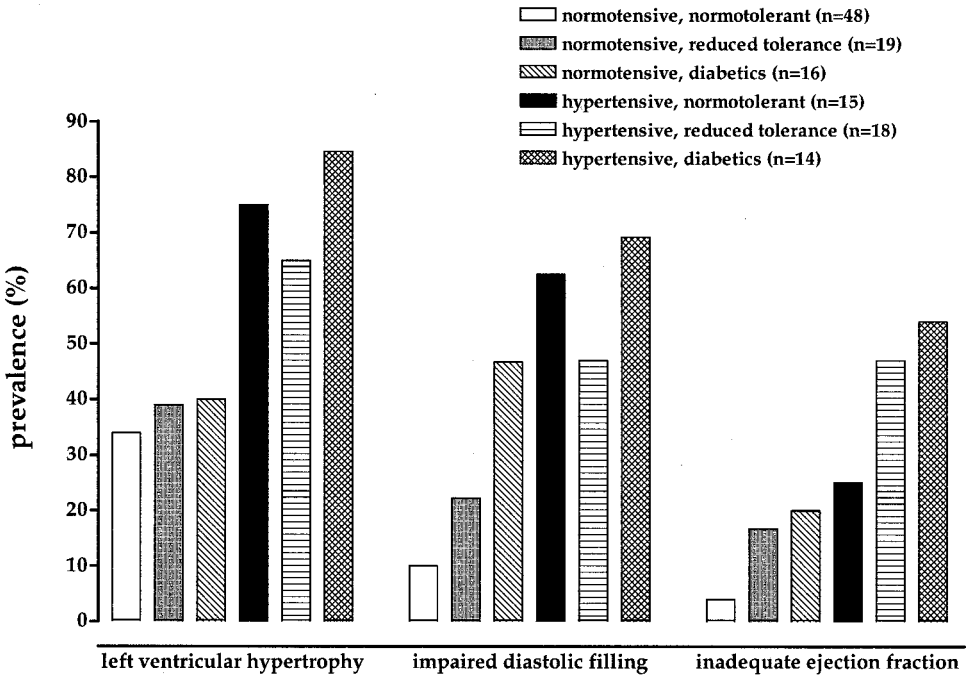

FIG. 4. Prevalence of left ventricular hypertrophy, impaired diastolic filling, and inadequate ejection fraction at rest in 130 patients with acromegaly studied at their diagnosis and grouped on the basis of the absence of hypertension and glucose tolerance abnormalities, absence of hypertension and IGT, absence of hypertension and diabetes mellitus, hypertension and glucose tolerance abnormalities, hypertension and IGT, hypertension and diabetes mellitus. [From A. Colao *et al.*: *J Clin Endocrinol Metab* 85:193–199, 2000 (23). Permission granted by The Endocrine Society.]

stroke volume, and ejection fraction are largely unchanged. It should be noted that in acromegaly the prevalence of left ventricular hypertrophy is predominant but, besides hypertrophy, the majority of the patients at diagnosis have a normal (55–78%) left ventricular ejection fraction in resting conditions (23).

Rhythm disturbances, such as ectopic beats, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, sick sinus syndrome, ventricular tachycardia, and bundle branch blocks, are also more frequently recorded than in controls mainly during physical exercise (101, 102). Up to 40% of patients can suffer from conduction disorders, and it is questioned whether recovery from acromegaly improves this rate (101). Cardiac valve disease is also underestimated; Lie and Grossman (93) found mitral and aortic abnormalities in 19% of their autopsy series. Only a few studies have reported increased prevalence of mitral and aortic valve regurgitation (103, 104). In a recent study, we demonstrated a high prevalence of both mitral and aortic valve dysfunction in patients with active acromegaly (105); in particular, compared with controls, the overall prevalence of valve abnormalities was increased both in the 42 active patients (86 *vs.* 24%; $P < 0.0001$) and in the 22 cured patients (73 *vs.* 9%; $P < 0.0001$). Cardiac valve abnormalities were associated with left ventricular hypertrophy both in the patients and in the controls, whereas among the subjects without left ventricular hypertrophy, mitral and aortic abnormalities were highly prevalent in the patients (75% of active and 54% of cured) and only minimally in the controls (3% of the active and none of the cured controls) (105). If acromegaly is not controlled, diastolic heart failure can develop as the most common end-stage feature of the acromegalic cardiomyopathy; this is typically seen in patients with hypertensive or valvular heart disease (both highly frequent in aged acromegalic patients) as well as in a variety of clinical disorders, especially tachycardia and ischemia, not so frequent in acromegaly (106).

B. Pathogenesis

The mechanisms of GH and IGF-I action on the heart have been reviewed recently (21, 107). The effects of GH, IGF, and their binding peptides on the cardiovascular system are both direct, via endocrine, autocrine, and paracrine mechanisms, and indirect because they cause increased cardiovascular risk and hypertension. GH and IGF-I receptors are expressed in cardiomyocytes (108, 109), and IGF-I mRNA is present in the epicardium and the coronary vessel of the human fetus (110). Neonatal rat ventricle tissue preferentially expresses IGF-II mRNA transcripts and contains both IGF-IR and IGR-IIR (111), although cardiac IGF-IR expression is partly blunted in the adult rat (109, 112). Interestingly, IGF-I immunoreactivity is reportedly increased in the inner layers of the left ventricle (113), where both tension and wall stress are high, and gradually decreases toward the epicardial surface (114). IGF-I expression accompanies the development of left ventricular hypertrophy (113, 115); in rat myocardium, IGF-I mRNA is increased after pressure overload secondary to banding of ascending aorta, aorto-caval shunt, myocardial infarction, experimental renal, or pulmonary hypertension (113, 116–118). However, the role of IGF-I in heart development during the prenatal life is still unclear. In fact, newborns of mice knocked-out for the IGF-I gene show a reduced body size compared with control littermates, but heart size is generally unaffected (119). Similarly, when the IGF-I synthesis in the liver is abolished by the Cre/loxP recombination system, no negative effect on the postnatal cardiac size is found (34). In the GH-R knockout mouse, there was no change in heart weight (120), although GH secretion rate has a prominent role in the postnatal cardiac development. Hypophysectomy in rats induces a decreased cardiac expression of IGF-I mRNA, which can be restored by exogenous GH administration (121). GH administration in hypophysectomized rats with moderate myocardial infarction does not improve ventricular function (122), whereas GH-secreting tumors implanted in rats determine cardiac hypertrophy, enhance the contractile performance, and produce the elongation of the action potential of cardiac fibers (91, 123). Exogenous GH and IGF-I administration in normal adult rats induces a hypertrophic response of the heart without developing significant fibrosis (124). Furthermore, IGF-I increases the intracellular calcium content and enhances the calcium sensitivity of myofilaments in cardiomyocytes (125). Cardiomyocyte stimulation induced by GH and IGF-I is associated with a low-energy conformational status, mediated by myosin phenoconversion from the isoform V3 to a low ATPase activity isoform (126). GH, either directly (127) or via IGF-I, increases myocardial hypertrophy (127) and increases myocardial contractility in animal models of chronic GH excess (128) and in cardiomyocytes from neonatal rats (129), likely via an increased calcium responsiveness of myofilaments (130).

C. The acromegalic cardiomyopathy

Although new sophisticated methods are currently available to study the acromegalic cardiomyopathy, echocardiography still remains the most used method (131). Clear-cut left ventricular hypertrophy is found in most patients at diagnosis, overall in those with long disease history (21), and interstitial fibrosis constitutes the main abnormality at histology (91, 93, 123). Subsequently, gradual impairment of heart architecture by increased extracellular collagen deposition, myofibrillar derangement, areas of monocyte necrosis, and lympho-mononuclear infiltration occurs, thus configuring a pattern of myocarditis (92, 93). Increase of apoptosis in cardiomyocytes and interstitial fibroblasts, inversely correlated to the output rate, was found in biopsied cardiac tissue obtained during heart catheterization in acromegalic patients (132). In a survey performed in our department including 200 patients undergoing echocardiography at diagnosis, left ventricular hypertrophy was found in 120 patients (60%); the left ventricular mass index significantly increased from young ($<$30 yr) to elderly ($>$60 yr) patients (Fig. 5). Accordingly, the prevalence of left ventricular hypertrophy was higher in patients older than 50 yr (74.3%) than in younger patients (57% in patients aged 31–50 yr and 35% in those aged $<$30 yr; our unpublished data). As already mentioned, left ventricular hypertrophy is not negligible in young patients with a presumed short duration of acromegaly, confirming previous data of other groups (95, 96) as well as from ours (97). This suggests that cardiac hypertrophy is an early event in

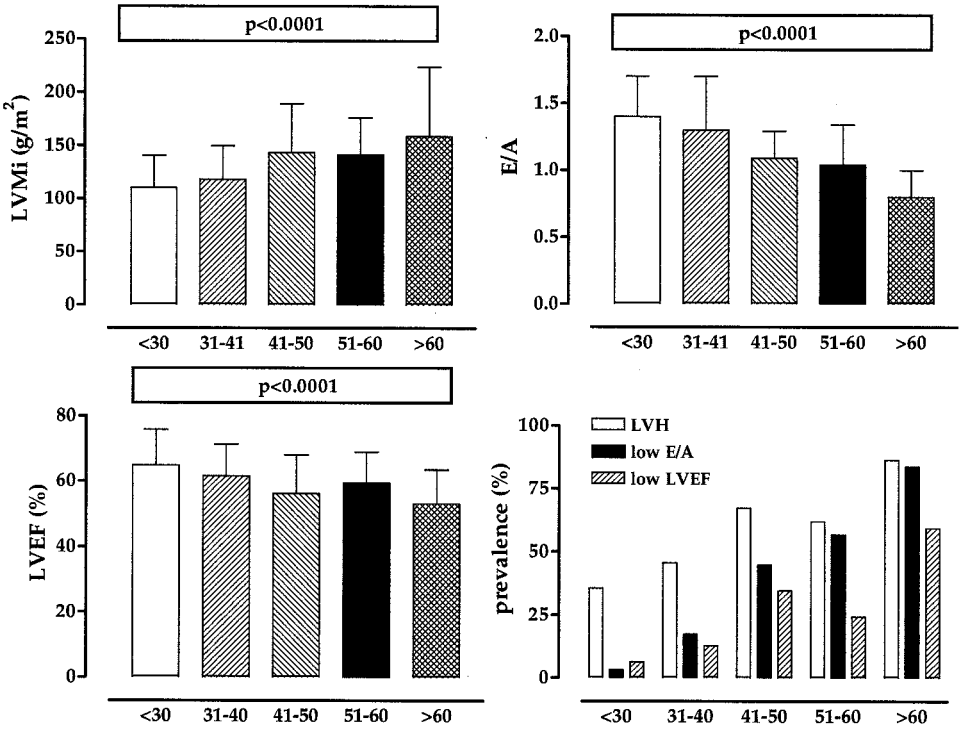

FIG. 5. Results of the echocardiography study performed at diagnosis in 200 patients with acromegaly studied at the Department of Molecular and Clinical Endocrinology and Oncology, University "Federico II" of Naples. Data are shown according with patients' age divided into decades. The left ventricular mass index (LVMi, *top left*) significantly increases with aging, whereas diastolic filling, measured as early to late mitral flow velocity (E/A, *top right*), and left ventricular ejection fraction at rest (LVEF, *bottom left*) significantly decrease with aging. As a consequence, the prevalence of left ventricular hypertrophy (LVH), inadequate diastolic filling, and systolic performance increases with aging.

acromegaly, which worsens proportionately with the duration of disease activity. It is known that arterial hypertension is likely the most important factor aggravating cardiac hypertrophy and has higher prevalence in aged patients (see *Section II.E*). In another study including a large series of patients (23), we observed that hypertension significantly increased the impact of cardiac hypertrophy, therein documented in 51% of cases. The prevalence of hypertrophy was higher in hypertensive patients (Fig. 4), and the multistep regression analysis showed that the diastolic blood pressure was the best predictive factor of cardiac hypertrophy (23). It should be mentioned that patients with hypertension and diabetes had an older age than those with uncomplicated acromegaly. Because aging in nonacromegalic subjects is characterized by a slight increase in left ventricular hypertrophy (100), it is likely that in acromegaly this phenomenon is emphasized. It should be stated, however, that it is currently unknown whether aging has independent negative effects on the heart in acromegaly, because there are no controlled studies in the elderly patients population. In our series, however, patients older than 60 yr had a significantly higher left ventricular mass than age- and sex-matched controls, who indeed had an increased mass compared with young controls (Fig. 3). It is also unknown whether there are gender differences in the prevalence and severity of the acromegalic cardiomyopathy. Gender difference is well known to occur in GH and IGF-I secretion both in healthy subjects (133) and in acromegaly (134, 135). Reviewing our experience in 200 patients with acromegaly, we did not find any difference in the prevalence of left ventricular hypertrophy between women (63.6%) and men (58%); similarly, the prevalence of hypertension and diabetes was similar in both sexes (our unpublished data). A minor but relevant complication that, similar to hypertension and diabetes, may further complicate acromegalic cardiomyopathy is thyrotoxicosis (136), which appeared to primarily affect systolic function.

Cardiac hypertrophy is associated with functional alterations. The most striking cardiac disorder of early acromegalic cardiomyopathy is represented by inadequate filling capacity. Doppler ultrasonography documented that both the diastolic filling wave and the early to late mitral and tricuspid velocity ratio are generally decreased, whereas a limited elasticity of myocardial fibers causes the elongation of the isovolumic relaxation time (21, 99). This disorder can remain asymptomatic for years before clinical and instrumental signs of cardiac involvement become overt. In the presence of diastolic impairment, the incomplete recovery of an adequate preload can affect systolic parameters during the physical effort (21, 99). In our cohort, inadequate diastolic filling (measured as an early to late mitral flow velocity ratio ≤ 1) was found in 41.5%, whereas inadequate left ventricular ejection fraction at rest ($\leq 50\%$) was found in 28% of 200 cases studied by echocardiography. As for the left ventricular hypertrophy, impairment of diastolic and systolic functions is more evident in older than in younger patients (Fig. 5). Radionuclide studies have provided a more accurate estimate of diastolic abnormalities and impaired ejection fraction on effort, revealing functional alterations in most patients (137). After excluding patients with hypertension and diabetes, in a smaller cohort of patients with uncomplicated disease compared with age-matched controls we observed a decline of the ejection fraction response to physical exercise according to age (Fig. 6), with abnormal results in 40% of young patients and 95% of middle-aged patients. In the same cohort, diastolic filling was inversely correlated with the estimated disease duration (Fig. 7). These findings strongly support the hypothesis that a long exposure to high GH and IGF-I levels has detrimental effects on cardiac performance even in the

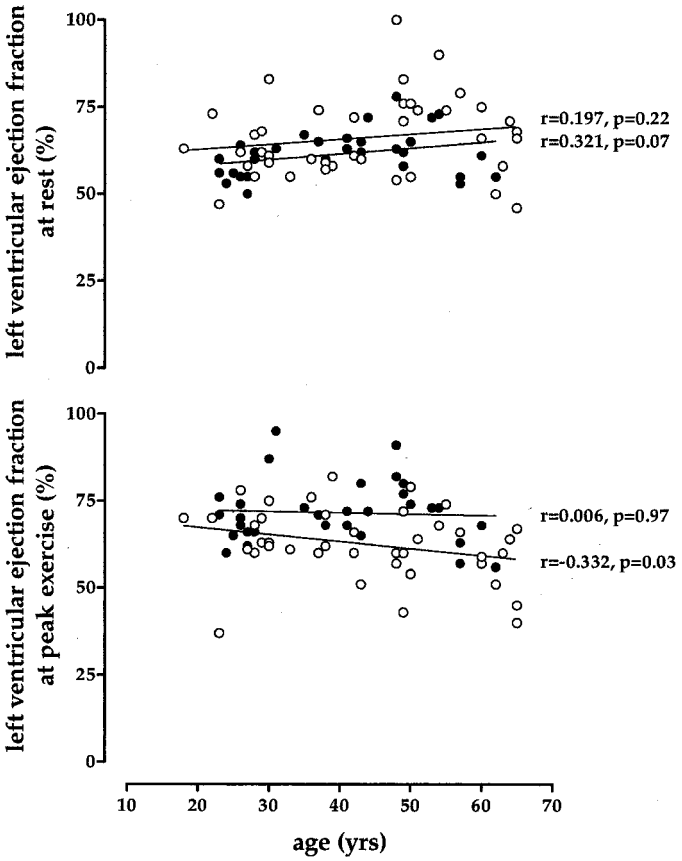

FIG. 6. Linear correlation analysis in patients (●) and controls (○) between age and left ventricular ejection fraction at rest (*top*) and at peak exercise (*bottom*). [From A. Colao *et al.*: *J Clin Endocrinol Metab* 84:1518–1523, 1999 (137). Permission granted by The Endocrine Society.]

absence of hypertension and diabetes, the most important complications of the disease. According to the results of the Framingham heart study (138), an increase in left ventricular mass predicts a higher incidence of clinical events, including death, attributable to cardiovascular disease. The relationship between left ventricular mass and cardiovascular events persisted after adjustment for age, diastolic blood pressure, pulse pressure, treatment for hypertension, cigarette smoking, diabetes, obesity, the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, and electrocardiographic evidence of left ventricular hypertrophy (138). Whether this relationship is also present in the acromegalic population, which presents a remarkably higher prevalence of left ventricular hypertrophy than the nonacromegalic one, is unknown. However, studies of the coronary artery disease in acromegaly are very scant. Hemodynamics of the coronary perfusion have not been studied extensively, and thus there is no general consensus as to the prevalence of coronary artery disease in acromegaly; it has been reported between 3% and 37% in different series (21). Postmortem and heart catheterization studies showed a prominent involvement of small vessels, and the thickening of the intramural vessels has been described in up to 22% of cases (92, 93, 123). Proximal arteries are generally normal, but they can be either enlarged and tortuous or, rarely, stenotic (93). Episodes of angina pectoris are rarely reported, but the presence of chronic myocardial ischemia cannot be excluded. On the other hand, systematic evaluation by myocardial perfusion scintigraphy has never been performed so far; in a previous study we detected coronary artery disease by myocardial perfusion in 20% of cases (139). The coexistence of additional risk factors may accelerate the progression of events leading to dysfunctional cardiomyopathy. Arterial hypertension, arrhythmias, and metabolic complications (see *Sections II, D and E, and III*), as well as common cardiovascular risk factors such as cigarette smoking, hereditary disorders, and elevated levels of lipoprotein-a (Lp-a), homocysteine, fibrinogen, and triglycerides have all been associated with increased cardiovascular morbidity (140). Untreated acromegaly is also exposed to elevated levels of triglycerides, apolipoprotein (Apo) A-I and Apo E, fibrinogen, plasminogen activator inhibitor activity, and tissue plasminogen activator (21). The role of this multifactorial mosaic should be considered to define the progression of cardiovascular complications and their potential reversibility in individual patients with acromegaly.

D. Arrhythmias

Electrocardiography studies and Holter recordings have documented abnormalities of cardiac rhythm. Supraventricular premature complexes do not seem to occur more frequently in acromegaly than in the normal population (141). Conversely, ectopic beats, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, sick sinus syndrome, ventricular tachycardia, and bundle branch blocks are frequently recorded in patients with acromegaly, mostly at peak physical exercise (101, 102). Forty percent of patients suffer from conduction disorders at the diagnosis of acromegaly. Both the prevalence and the severity of ventricular arrhythmia were found to be significantly higher in patients compared with controls (101). In particular, complex ventricular arrhythmias were found in 48% of acromegalic patients as compared with 12% of controls, and repetitive ventricular arrhythmias occurred in 31% of patients and 8% of controls (101). The frequency of ventricular premature complexes increased with the duration of acromegaly and, interestingly, the severity of ventricular arrhythmias correlated with left ventricular mass (101). In one case of sudden death (142), examination of the conduction tissue at autopsy revealed slight fibrolipomatosis and dispersion of the atrioventricular node, the right branch was prematurely intramural with sclerosis and lipomatosis, and the microscopic examination supported the hypothesis of electrical instability in the heart. Additionally, Herrmann *et al.* (143) investigated ventricular late potentials in active acromegaly to identify early markers of cardiac alteration. Late potentials, which are low-amplitude, high-frequency waves in the terminal tract of QRS-complexes at electrocardiogram (ECG), are considered as strong predictors of arrhythmic events in patients with previous myocardial infarction (144). Late potentials were found in 56% of patients with active acromegaly compared with 6% of patients with well-controlled acromegaly and none of controls (143). The detection of late potentials was independent of age, gender, disease duration, body mass index, and

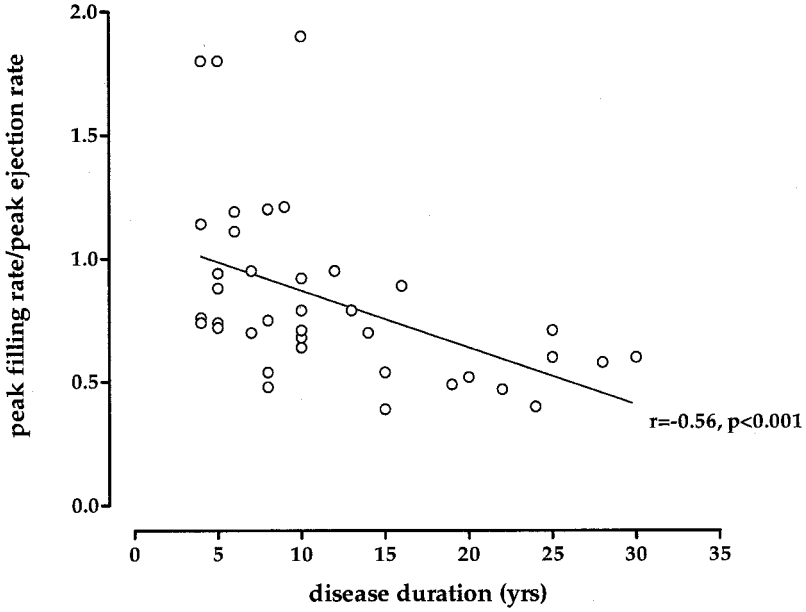

FIG. 7. Linear correlation analysis between the estimated disease duration and the diastolic filling, measured as the ratio between the peak filling rate and the peak ejection rate. [Data were modified from A. Colao *et al.*: *J Clin Endocrinol Metab* 84:1518–1523, 1999 (137). Permission granted by The Endocrine Society.]

left ventricular hypertrophy measured by echocardiography (143). Increased prevalence of late potential was confirmed in another study (145). However, to date no prospective data are currently available to infer the prognostic value of this measurement in acromegaly. Using Holter ECG, we have recently reported ventricular premature beats (>50 beats/24 h) in 33.3% of patients (146). Holter ECG analysis can be very informative before surgery, because severe arrhythmias can be a sudden cause of death in acromegaly.

E. Hypertension

Arterial hypertension is considered one of the most relevant negative prognostic factors for mortality in acromegaly. However, both epidemiology and pathophysiological mechanisms are far from totally clear. Hypertension is reported to affect approximately one third of patients with acromegaly, but only a few studies have estimated the prevalence of hypertension using the 24-h pressure Holter recording (147–150), and no control populations were included in these studies. The only study including a control group (151) revealed an increased prevalence of hypertension only in patients with familiarity for hypertension. In a survey study of 200 patients with acromegaly studied at diagnosis, we have found hypertension (based on a diastolic blood pressure > 90 mm Hg) in 40%, compared with 8% of controls; there was no gender difference in the patients or in controls (our unpublished data).

One mechanism likely contributing to inducing hypertension in acromegaly is represented by the increased plasma volume (152, 153). The evidence of an increase in the total exchangeable sodium pool in normotensive (154–157) and hypertensive acromegalic patients (151) further supports this hypothesis, because a direct relationship was demonstrated between total exchangeable sodium and blood pressure values (156, 157). Whether the sodium exchange pump is also involved is unclear, because either a reduction (158) or an increase (159) of its activity has been reported. Plasma volume and total exchangeable sodium were initially supposed to follow variations of aldosterone secretion. However, the levels of aldosterone, and its precursors corticosterone and 11-deoxy-corticosterone as well, were found to be normal in patients with acromegaly without (152, 157, 160, 161) or with (151) hypertension. Aldosterone levels were not correlated with disease activity unless overt heart failure was present (152). Similarly the aldosterone response to stimuli, such as posture or saline infusion, gave contradictory responses (152, 160, 162). Both the atrial natriuretic peptide (ANP) and the renin-angiotensin system have been claimed as potential causes to explain hypertension in acromegaly without success. In fact, basal ANP levels were found to be normal (160), not correlated with disease activity (152), not increased after saline infusion (160) or increased as in controls (152). Similarly, basal PRA was normal in most studies (152, 157, 160, 161), not correlated with disease activity (152) or hypertension (151), and reduced (155, 161) or inappropriately reduced to hypernatremia (155, 156); the response of the renin activity to stimuli was also unclear (152, 153, 157, 160, 161). The adrenergic system has also been investigated, but no clear evidence for its involvement emerged from different studies. Plasma epinephrine and/or norepinephrine levels were normal (157, 163, 164) or increased (165), and urinary catecholamines were also normal (157, 163, 166) or increased (167). Bondanelli *et al.* (162) reported that plasma catecholamines were normal but without the physiological circadian rhythm (Fig. 8) that reappeared after successful surgery (Fig. 8). No difference between patients with acromegaly and controls was found in catecholamine levels both basally and after hyperinsulinemic clamp (168). No change of catecholamine levels was found after bromocriptine or lysuride treatment (164), whereas norepinephrine levels were reduced in another study (167).

Insulin resistance and diabetes are also likely to play a relevant role in the onset of hypertension in acromegaly (169, 170). We found significantly higher blood pressure levels in

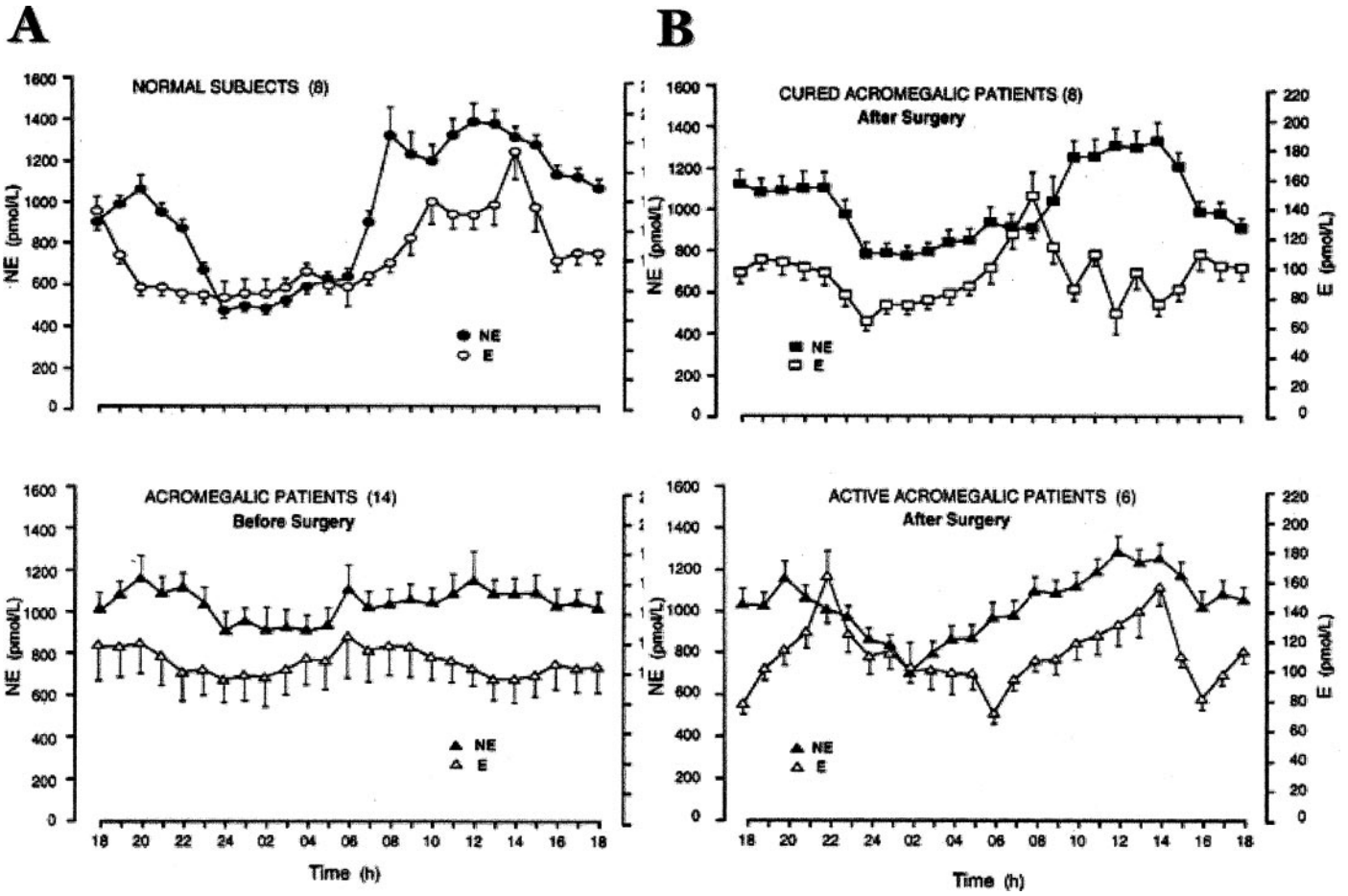

FIG. 8. Plasma norepinephrin (NE) and epinephrin (E) concentrations in blood obtained at 1-h intervals for 24 h from normal subjects and acromegalic patients before transsphenoidal surgery (A) and from acromegalic patients in remission or active disease after transsphenoidal surgery (B). [From M. Bondanelli *et al.*: *J Clin Endocrinol Metab* 84:2458–2467, 1999 (162). Permission granted by The Endocrine Society.]

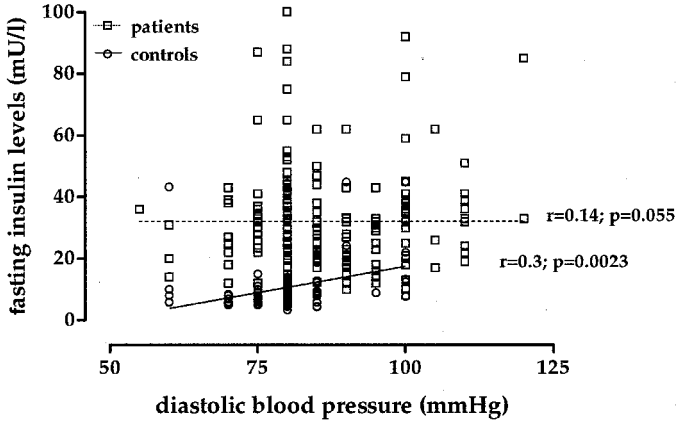

FIG. 9. Linear correlation analysis between fasting insulin levels and diastolic blood pressure in 200 patients with acromegaly (□) and 100 controls (○) studied at the Department of Molecular and Clinical Endocrinology and Oncology, University "Federico II" of Naples.

patients with acromegaly associated with reduced glucose tolerance or diabetes than in those with normal glucose tolerance (23). However, fasting insulin levels were significantly correlated with diastolic blood pressure in the control population but not in the acromegalic population included in our survey study (Fig. 9). Blood pressure was higher in subjects with diabetes than in those without diabetes either in the group with acromegaly or in controls (Table 2). To note, the age of diabetic patients was higher than that observed in nondiabetic patients, both in acromegaly and controls (Table 2). Glucose tolerance abnormalities independently influenced blood pressure measured by 24-h ambulatory blood pressure monitoring (150), and nondipping profile was associated with insulin resistance in both normotensive and hypertensive acromegalic patients (149).

Among several mechanisms hypothesized to explain hypertension in acromegaly, the evidence that both cardiac output and cardiac index are increased, while systemic vascular resistance is reduced (98, 99, 171), has been considered also. More recent studies, however, suggested that systemic vascular resistance could be conversely increased in some vascular districts due to specific morphofunctional alterations. In fact, Chanson *et al.* (172), measuring direct brachial artery hemodynamics, showed lower regional blood flow and increased local resistance in acromegalic patients compared with healthy controls, thus suggesting a heterogeneous distribution of cardiac output. Endothelial dysfunction and/or dysregulation of arterial tone may be responsible for these abnormalities (see *Section II.F*). According to

TABLE 2. Effect of diabetes on endocrine, metabolic, and hemodynamic parameters in 200 patients with acromegaly studied at their diagnosis at the Department of Molecular and Clinical Endocrinology and Oncology of the University "Federico II" of Naples

	No glucose alterations	Impaired fasting glycemia	Impaired glucose tolerance	Diabetes mellitus	*P*
No. of subjects	93	26	51	31	
Age (yr)	41.7 ± 13.5	49.8 ± 17.3	49.4 ± 12.9	55.3 ± 14.6	<0.0001
Median	40	50	50	50	
Range	17–76	22–76	26–77	26–76	
Estimated disease duration (yr)	10.5 ± 6.7	13.6 ± 7.1	12.3 ± 5.8	15.6 ± 9.8	0.005
Serum GH levels (μg/liter)	39.8 ± 25.8	53.6 ± 49.7	38.8 ± 26.8	30.5 ± 21.4	0.035
Serum IGF-I levels (μg/liter)	637.1 ± 209.7	776.8 ± 508.1	629.8 ± 208.7	632.6 ± 200.6	0.091
Systolic blood pressure (mm Hg)	130.4 ± 17.6	141.3 ± 19.2	138.2 ± 19.7	144.2 ± 18.2	<0.0001
Diastolic blood pressure (mm Hg)	83.8 ± 10.1	89.2 ± 12.4	87.6 ± 11.1	90.6 ± 11.7	0.008
Fasting glucose levels (mg/dl)	83.3 ± 7.1	119.5 ± 7.2	96.9 ± 9.3	150.5 ± 25.3	<0.0001
Fasting insulin levels (mU/liter)	22.8 ± 7.3	40.1 ± 15.2	32.8 ± 18.8	51.6 ± 21.3	<0.0001

Statistical analysis was performed by ANOVA followed by the Newman-Keuls test. Data are shown as mean ± SD unless otherwise specified.

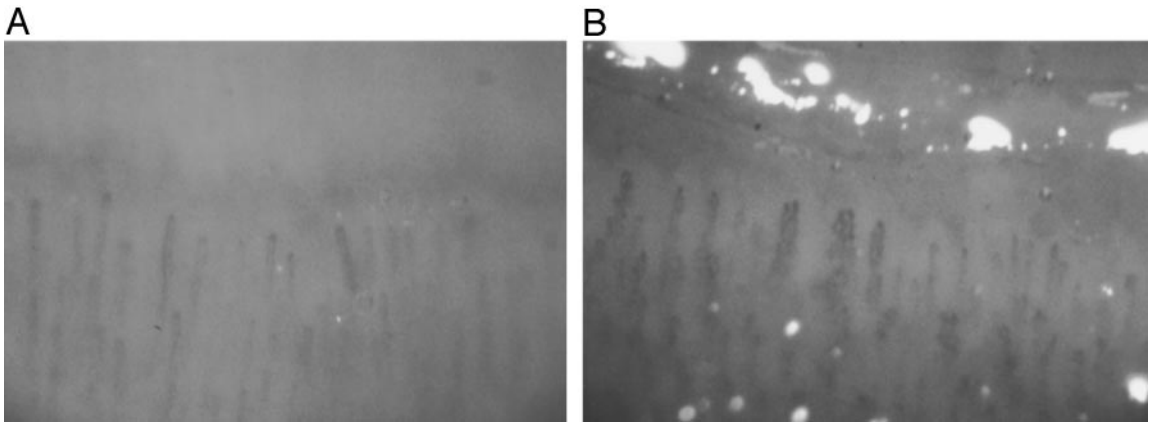

FIG. 10. Capillaroscopy in one control (A) and one patient with acromegaly (B). Note the remarkable meandering of several capillaries. [From F. Schiavon *et al.*: *J Clin Endocrinol Metab* 84:3151–3155, 1999 (175). Permission granted by The Endocrine Society.]

Folkow's hypothesis (173), the increased blood pressure in GH excess could directly originate from an increased thickness of wall resistance vessels. In mice transgenic for the GH gene (TGHM), Dilley and Schwartz (174) described an increase of wall mass without increase of blood pressure. Hypertensive vessels typically have an increased wall-to-lumen ratio, and in TGHM mice this was found only for the third branching order mesenteric vessels and not in thoracic aorta or carotid artery (174). Moreover, in the mesenteric network, the number of vessels was lower in TGHM mice than in their wild-type littermates. A reduction in the capillary density at the nailfold microcirculation also has been found in patients with acromegaly (Fig. 10) without any relationship to blood pressure (175). More recently, a salt-resistant form of hypertension has been described in transgenic mice overexpressing bovine GH (176); an impaired renal excretory capacity was ruled out by measuring the glomerular filtration rate. Moreover, in TGHM mice the increased blood pressure was accompanied by a significant structural narrowing of the resistance vasculature without changes in vascular reactivity or endothelial function, allowing the hypothesis that hypertension in these mice is due essentially to an increase of peripheral vascular resistance (176).

To conclude, the pathogenesis of hypertension in acromegaly is still to be elucidated. The coexistence of glucose abnormalities and insulin resistance increases the probability of having coexistence of hypertension that can also be due primarily to increased wall-to-lumen ratio in some vascular districts. The availability of an animal model of acromegaly developing hypertension will enable the study of the natural history of the disease, including abnormal endocrine reaction to increased plasma expansion, alteration of the renin/aldosterone system as well as ANP release, and negative cardiac and vascular effects aggravated by electrolytic and metabolic abnormalities.

F. Atherosclerosis and endothelial dysfunction

Few data are currently available on the vascular involvement in acromegaly. Cardiac output was shown to be heterogeneously distributed with lower regional brachial artery blood flow and increased local resistance (172). The study of the peripheral microcirculation (Fig. 10) showed a significantly lower capillary number and length and a significantly higher number of tortuous loops and meandering capillaries in patients with acromegaly than in controls (175). The capillaroscopic alterations were still observed in a smaller group of patients not bearing diabetes and hypertension (175). Increase of the carotid intima-media thickness (IMT) was observed in active as well as cured patients with acromegaly, but the prevalence of well-defined atherosclerotic plaques was not higher than in control subjects (177). It should be noted that in the group of cured acromegalic patients insulin, cholesterol, and fibrinogen levels were still slightly higher than in controls (177). The presence of still elevated insulin levels in patients cured from acromegaly can be the under-

lying factor able to maintain an increased IMT, because insulin levels are known to be directly correlated with IMT (178). In another series of patients with acromegaly, prospectively studied before and after 6 months of treatment with lanreotide, an increase of IMT at the level of common carotid arteries was similarly observed, and 29 of them had abnormal IMT levels (179). Only a mild increase of carotid IMT was conversely reported by Kasayama *et al.* (180); however, because plasma IGF-I concentration was significantly higher and the prevalence of hypertension was significantly lower in patients without than in those with atherosclerotic changes, the authors concluded that increased concentration of IGF-I might be involved in the lack of susceptibility to atherosclerosis in some acromegalic patients (180). We could not find, however, any correlation between IGF-I levels and carotid IMT (177, 179).

Laser Doppler flowmetry has also confirmed endothelial dysfunction at the hand cutaneous circulation. Vascular smooth cell ability to produce skin vasodilatation was normal, but endothelium-dependent vasodilatation was impaired and sympathetic-mediated vasoconstrictive response was increased in normotensive acromegalic patients (181). Very recently, we demonstrated that the increased IMT in patients with acromegaly mainly depends on concomitant risk factors, because there was no difference between patients with active or cured acromegaly and their controls matched for hypertension, diabetes, or dyslipidemia (182). Interestingly, the endothelium-dependent vasodilatation, measured at the brachial artery level, was impaired in patients with active acromegaly more than that expected on the basis of classical risk factors (Fig. 11); this allowed us to hypothesize a direct negative effect of GH and IGF-I hypersecretion on endothelial function (182). Clearly, the existence of other negative factors, such as glucose intolerance, dyslipidemia, and smoking habitus, further impairs vascular relaxation.

G. Effect of GH and IGF-I control on cardiovascular disease

A consistent number of investigations (Table 3) have suggested that normalizing GH and IGF-I levels can arrest the progression of cardiac disorders. This is confirmed by epidemiological data (13, 16, 17) showing that the therapeutic success is associated with a consistent reduction of both cardiovascular mortality and morbidity in acromegaly. Recently, adenomectomy has been reported to reduce the left ventricular mass and improve diastolic performance in patients achieving disease cure (183). A significant improvement of the left ventricular ejection fraction on effort was similarly documented in patients successfully cured by surgery at the 5-yr postsurgical follow-up (184). Radiotherapy presents some major limitations, such as partial and/or delayed effectiveness and high impact of pituitary deficiency that prevents further analysis of its beneficial effects on the cardiovascular risk. In addition, electrocardiograph and echocardiograph abnormalities have been reported to worsen during the long-term follow-up in irradiated patients (185). It should be noted, however, that cure criteria of acromegaly at the end of the 1980s were not strict enough to accept these conclusions. It is therefore possible that some patients in the series reported by Rodrigues *et al.* (102) and Baldwin *et al.* (185) were still in active acromegaly at the time of reevaluation. Improvement of cardiac hypertrophy has also been reported during long-term treatment with bromocriptine (186), but more extensive investigations are required to make any conclusive statement. On the other hand, treatment with somatostatin analogs has been reported to successfully improve cardiovascular parameters in a wide number of studies. A prompt reduction of cardiac mass occurs in patients treated with sc octreotide (187, 188), lanreotide (189, 190), and octreotide-LAR (191). The effect on the cardiac mass is even more significant after 6–12 months of treatment, which is also able to induce improvement of diastolic filling (192–196). Diastolic and systolic improvement is more evident in patients achieving disease control, whereas those not controlled by therapy had no response (184) or, even, further impaired their cardiac function (196). A positive response to octreotide has been reported also in acromegalic patients suffering from congestive heart failure, who achieved significant increase of the cardiac output (197). Similarly, the cardiopulmonary performance, impaired in acromegalic patients when compared with controls, was

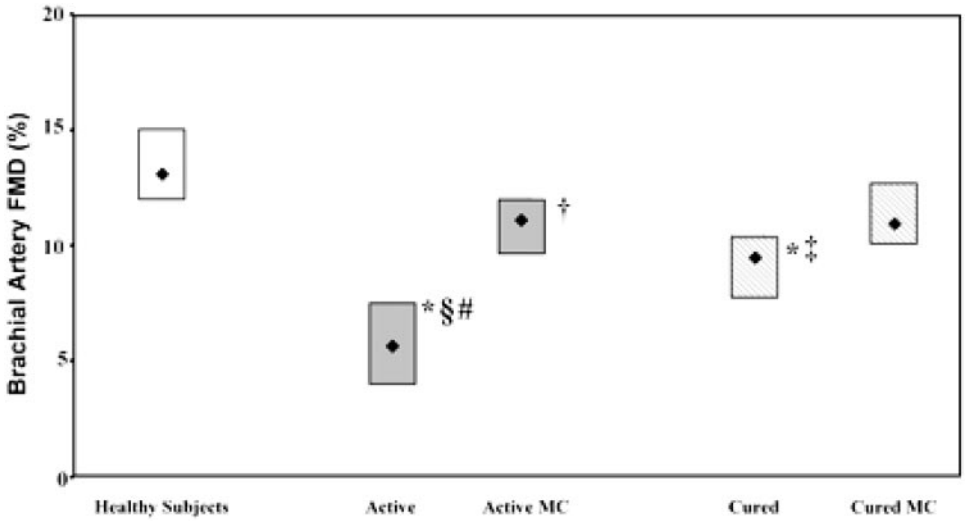

FIG. 11. *Boxes* showing median values (♦) and interquartile ranges of flow-mediated dilatation (FMD) in the study population. Active, Active acromegalics; Active MC, active acromegalic-matched controls; Cured, cured acromegalics; Cured MC, cured acromegalic-matched controls. *, Lower than in healthy subjects ($P < 0.01$); §, lower than in active MC ($P < 0.01$); #, lower than in cured ($P < 0.01$); †, lower than in healthy subjects ($P < 0.05$); ‡ lower than in cured MC ($P < 0.05$). [From G. Brevetti *et al.*: *J Clin Endocrinol Metab* 87:3174–3179, 2002 (182). Permission granted by The Endocrine Society.]

TABLE 3. Recovery from cardiac disease after treatment of acromegaly

Year	Ref.	No. of patients	Treatment	Follow-up	Methods	Results			
						LVH	Diastolic function	Systolic function	Others
1985	185	11	RT	3–17 yr	ECG, ECHO	n.a.	n.a.	n.a.	↑ Cardiovascular events
1989	192	9	OCT	12 months	ECHO	↓	n.a.	↔	↓ HR and BP
1991	193	5	OCT	6 months	ECHO	↓	↑	↔	No change in contractility
1992	188	16	OCT	2 months	ECHO	↓	n.a.	↓	Only in patients with hypertrophy
1993	194	11	OCT	6 months	ECG, ECHO	↓	↑	↔	↔ BP
1994	187	6	OCT	6 months	ECG, ECHO	↓	↑	↔	↑ Treadmill exercise, ↔ BP
1999	196	30	OCT	12 months	ERA	n.a.	↔	↑	↓ HR only in controlled patients
1999	189	13	LAN	12 months	ECHO	↓	↑	↔	↔ BP
1999	195	13	LAN	12 months	ECHO	↓	↑	↔	↔ BP
2000	191	15	OCT-LAR	6 months	ECHO, ERA	↓	↑	↔	Only in controlled patients, ↓ HR
2001	193	30	Surgery	6 months	ECHO	↓	↑	↔	↓ BP only in controlled patients
2001	184	18	Surgery/OCT	5 yr	ERA	n.a.	↔	↑	Only in controlled patients
2002	97	25	OCT-LAR	6 months	ECHO, ERA	↓	↑	↓	↓ HR, when disease duration <5 yr
2002	146	19	LAN	6 months	ECHO	↓	↑	↔	↓ Arrhythmias from 33.3 to 16.5%
2003	199	22	OCT-LAR	12 months	ECHO, ERA	↓	↑	↑	Mostly in young patients

n.a., Not assessed; RT, radiotherapy; OCT, octreotide; LAN, lanreotide; ECHO, echocardiogram; ERA, equilibrium radionuclide angiography; LVH, left ventricular hypertrophy; BP, blood pressure; HR, heart rate; ↓, decreased; ↑, increased; ↔, unchanged.

acutely improved by continuous infusion of sc octreotide for 24 h (198). Recovery from left ventricular hypertrophy or dysfunction appears to depend, however, not only on the strict biochemical control of acromegaly but also on patients' age and the duration of GH and IGF-I hypersecretion before intervention. In a recent study including 22 patients successfully controlled for 1 yr by octreotide-LAR, we observed the disappearance of left ventricular hypertrophy in 100% of patients aged below 40 yr and in only 50% of those aged above 40 yr (199). In addition, the left ventricular ejection fraction response at peak exercise significantly increased only in younger patients, being restored in 80% of young and in 50% of middle-aged patients (199). Similar results were recorded when capacity and duration of exercise were analyzed. Taken together, these observations suggest that acromegalic cardiomyopathy is more likely reversed in younger patients with short disease duration, whose disease activity is successfully controlled by 12-month treatment with octreotide-LAR. Indirectly, these results also indicate that early diagnosis and effective treatment are mandatory in acromegaly (199). When cardiac involvement in the early stage of acromegaly was investigated after 6 months of octreotide-LAR (97), we found that only patients aged below 40 yr and with disease duration no more than 5 yr achieved a significant decrease of total cholesterol and heart rate, both at rest and at peak exercise, and a significant increase of exercise-induced changes of left ventricular ejection fraction after treatment (97). Although the left ventricular mass index was significantly reduced in patients with both short (<5 yr) and long (>5 yr) disease duration, at the end of treatment it was still higher than controls; four patients with disease duration more than 5 yr still showed left ventricular hypertrophy (97). Supporting previous findings (99), we found that young patients with short disease duration had increased heart rate both at rest and at peak exercise and also increased exercise-induced changes of the left ventricular ejection fraction (97). Conversely, treatment reduced heart rate and ejection fraction to normal values (97). Interestingly, young patients had increased IMT of common carotids at baseline that significantly reduced after treatment, without any change in systolic and diastolic peak velocities (97). A less evident decrease of common carotid IMT was also observed in another series of patients with higher age treated for 6 months with lanreotide (179). Beneficial effects of somatostatin analog treatment were reported on heart rate (97, 195, 196) of peculiar relevance when the drug was given preoperatively (65). This effect can be due not only to the decrease of GH and IGF-I levels but also to a direct effect of octreotide, which was shown to have direct effects on the conduction system (200). Whether subtle alterations of vascular bed or of the renin/aldosterone system, which cannot be revealed by the commonly used detection systems, contribute to changing the hemodynamic parameters in acromegaly is still unknown. A remarkable effect of octreotide in reducing the number of ventricular premature complexes before surgery was also reported in a 59-yr-old patient (201). In a larger series of patients included in a recent Italian multicenter study, we found a significant reduction of mean 24-h heart rate (66.5 ± 11 *vs.* 71.5 ± 20 beats/min; $P < 0.05$) after lanreotide therapy (146). Ventricular premature beats (>50 beats/24 h) were found in 33.3% of patients before treatment and in only 16.5% after treatment (146). Improvement of metabolic alterations (see *Section III*) and hypertension (64, 184, 196, 197) have also been reported, but data are less convincing than those regarding recovery from left ventricular hypertrophy, improvement of diastolic filling, as well as improvement of systolic performance (Table 3). Very recently, we had the opportunity to investigate the effects of the GH-antagonist on the acromegalic cardiomyopathy. Although the study is still in progress and data are still unpublished, we observed that the left ventricular mass was significantly reduced in 15 patients treated with the GH-antagonist at a dose of 10–25 mg/d for 6 months (202). Of notable interest is the evidence that all but one of these patients had been shown to be resistant to somatostatin analogs and still showed abnormal echocardiographic findings (202).

By summarizing the wide number of data available on the acromegalic cardiomyopathy, we can conclude that it seems to be a frequent complication of the disease and shows a peculiar multisymptomatic aspect. If acromegaly is left un-

treated, cardiomyopathy can lead eventually to diastolic heart failure. Left ventricular hypertrophy is a characteristic of the acromegalic heart and is complicated by arrhythmias, which can be a cause of sudden death of these patients and should be carefully investigated. Treating acromegaly by combining surgery, radiotherapy, and pharmacotherapy enables the recovery from cardiomyopathy mostly in young patients who had had a presumably short exposure to GH and IGF-I excess. However, a substantial improvement of both morphological and functional alterations of the cardiovascular system has been observed in middle-aged patients, indicating that cardiovascular complications can be at least arrested by an adequate control of GH and IGF-I hypersecretion. In contrast, cardiac valve disease does not seem to be substantially changed by controlling hormone hypersecretion (105), but data on this issue are still scant. Because, as stated at the beginning of this review, acromegaly develops insidiously for several years before the diagnosis is made, more extensive data on prolonged follow-ups are required to satisfactorily respond to the question of whether the reversibility of cardiovascular complications after biochemical control of acromegaly is possible and whether this improvement is paralleled by the normalization of the risk of death for cardiovascular accidents.

III. The Metabolic Complications

A. Epidemiology

GH has long been known to be associated with changes in human metabolism. It is well established that GH counteracts the effects of insulin on glucose as well as on lipid metabolism, although it shares anabolic properties on protein metabolism with insulin. Moreover, GH modulates tissue response to insulin; indeed GH excess may cause insulin resistance, whereas GH deficiency may increase the sensitivity to insulin (203). GH exerts an overall lipolytic effect, inducing the hydrolysis of triglycerides to FFA and glycerol. However, the influence of GH on lipolysis has long been debated, and either direct or indirect effects on lipolysis have been described. Conversely, GH has been shown to elicit some degree of antilipolytic activity in different species depending strictly on other lipolytic factors. Moreover, there is clear evidence that GH can influence the sensitivity and or the responsiveness of adipose tissue to agents that influence lipolysis.

Impaired glucose tolerance (IGT) and overt diabetes mellitus are frequently associated with acromegaly (9, 63, 204, 205). Patients with acromegaly are insulin resistant either in the liver or in the periphery, displaying hyperinsulinemia and increased glucose turnover in the basal postabsorptive states (206). The prevalence of diabetes mellitus in acromegaly is unknown but ranges from 19–56% in different series (207). Alternatively, the most well-known intermediate form of altered glucose metabolism, referred to as IGT, has been assessed only recently in three different studies: the prevalence was 31% in a study by Biering *et al.* (208), 46% in the study by Kasayama *et al.* (209), and 16% in the analysis by Kreze *et al.* (207). Impaired fasting glycemia has recently been recognized as a second intermediate form of glucose intolerance (210). This intermediate disorder of glucose metabolism has not been detected in acromegaly in the only study where it has been investigated so far (207). Because impaired fasting glycemia occurs less frequently than IGT in the general population, the analysis of this entity appears to require a larger series of patients and alternative approaches. In fact, insulin sensitivity is reduced to a similar extent in acromegalic patients with normal glucose tolerance and those with IGT or diabetes, suggesting that a compensatory hyperfunction of pancreatic β-cells might counterbalance the reduced insulin sensitivity in the patients with normal glucose tolerance, but not in those with IGT or diabetes (207). The presence of impaired fasting glycemia was not assessed in this latter study. This new category warrants further investigation because it could predict the risk and/or the progression of developmental alterations of glucose metabolism in acromegaly.

As already mentioned, as well as suggested in even earlier investigations, the prevalence of overt diabetes mellitus in acromegaly largely differs among studies, likely due to different patient series and ethnicity (211). In the study by Nabarro (9), the analysis of risk factors promoting the development of glucose intolerance revealed that higher GH levels, higher age, and longer disease duration significantly predicted the tendency of developing symptomatic diabetes (9). In the study by Biering *et al.* (208), aging was the only variable that significantly predisposed patients to an increase in the severity of this complication. Results from a study by Kreze *et al.* (207), suggested that the development of glucose intolerance appeared to be associated with a family history of diabetes and with the concomitant presence of arterial hypertension. The importance of family history had already been suggested in previous analyses, although the supporting data was quantitatively insufficient. Systemic hypertension and IGT were also found to correlate independently to the severity of acromegalic cardiomyopathy in our patients (23). Compared with patients with uncomplicated acromegaly, those with hypertension but without abnormalities of glucose tolerance had an increased prevalence of left ventricular hypertrophy associated with impaired systolic and diastolic function, whereas patients with glucose tolerance abnormalities lacking hypertension had only an increased prevalence of impaired diastolic and systolic function (23). In our survey study, including 200 patients studied at their diagnosis, we found impaired fasting glycemia in 13%, IGT in 25.5%, and diabetes in 15.5% (Table 2), giving an overall prevalence of different alteration of glucose metabolism in 54% of the patients compared with 23% of controls, and in our series the prevalence was similar in men and women. Among other variables, the concomitance of hyperprolactinemia and pituitary tumor size are unlikely to predispose acromegalic patients to impairments of glucose metabolism. A positive association was found with female gender when the data of two studies were pooled, although in each single study the analysis was not significant (9, 207). It should be emphasized, however, that epidemiological data on the prevalence of glucose tolerance alterations in acromegaly should be reviewed after the currently accepted criteria for the diagnosis and classification of diabetes mellitus (210).

Besides the increased prevalence of glucose abnormalities,

acromegaly is also associated with abnormalities of lipid metabolism. Already in the early 1970s, patients with active acromegaly were shown to have lower cholesterol levels and higher triglyceride levels than in an age-matched control population. The incidence of hypercholesterolemia was similar to that in the general population, whereas the incidence of type IV hypertriglyceridemia was almost three times higher than in controls (212). Serum triglyceride levels were not related to relative body weight, basal serum GH, or insulin concentrations, nor did they correlate with glucose tolerance or with plasma insulin response to oral glucose load. However, patients with a higher insulin response had significantly higher serum triglycerides than the remaining acromegalic population. The endogenous serum triglycerides turnover rate was apparently unaltered, but the increased serum triglyceride levels were associated with an increase in production rate (212). In a small cohort of patients with active acromegaly, hyperlipidemia occurred in 63%, type V hyperlipoproteinemia in 13%, and type III hyperlipoproteinemia in 6% (213). In these latter cases, the activity of hepatic triglyceride lipase of lipoprotein lipase (LPL) was decreased (213). GH stimulates Apo E secretion, and Apo E as well as Apo A-I concentrations are significantly elevated in acromegalics (214); a correlation between GH, IGF-I, and changes in fibrinolysis has been observed in acromegalics, and disturbances in fibrinolysis may be a major cardiovascular risk factor for these patients. Plasma levels of Lp-a, Apo A-I, and Apo E are similarly increased, and 30% of patients have increased plasminogen activator inhibitor activity, whereas 66% have increased tissue plasminogen activator concentration levels compared with controls (214). A study of low-density lipoprotein (LDL) subfraction distribution in 24 patients with active acromegaly showed significantly higher LDL-III levels when compared with controls, with a concomitant reduction in the intermediate subfraction LDL-II (215). In this study, acromegalic patients were found to have lower hepatic lipase and LPL activities and higher plasma cholesteryl ester transfer protein (CETP) activity than controls (215). Univariate analyses showed that both GH and IGF-I correlated directly with LDL-III and inversely with LDL-II (215). Maffei *et al.* (216) reported an abnormal lipid pattern in 57% of 42 patients compared with 51% of controls; Lp-a was, however, the only parameter abnormal in 31% of patients and 7% of controls, whereas both triglyceride and cholesterol levels were closer to the upper limit of the normal range compared with controls. The prevalence of an altered lipoprotein pattern was addressed by Maldonado Castro *et al.* (217) in a relatively small series consisting of 20 patients (12 with active disease and eight cured); the highest Lp-a levels were observed in patients with active acromegaly, followed by patients with controlled acromegaly, whose Lp-a concentrations were still significantly higher than levels recorded in the normal subjects. There were no differences in other lipid and lipoprotein values among the groups. This study suggests that the currently used biochemical criteria for the cure of acromegaly may not be strict enough to cause the normalization of all the undesirable metabolic changes found in this disease. As an indirect consequence, the cardiovascular risk may persist significantly despite the successful treatment of acromegaly (217). Lower levels of HDL cholesterol and Apo A-I and higher Lp-a concentrations were confirmed by another study which demonstrated that patients with acromegaly have smaller and/or more dense LDL particles compared with controls (218); these alterations might contribute to the development of atherosclerosis, increasing the cardiovascular risk of these patients. Total cholesterol levels have been reported to be increased, normal, or even decreased in acromegaly (211, 212, 215). Lp-a, small dense LPL, and triglycerides were most likely to be increased (211, 212, 215–218), whereas HDL-cholesterol levels were unchanged or low (215, 219). Decreased levels of lecithin/cholesterol acyl transferase, CETP, phospholipid transfer protein activity levels, plasma cholesterol esterification, and cholesteryl ester transfer have also recently been reported compared with controls (220). At multistep regression analysis, plasma IGF-I was demonstrated to be negatively correlated with plasma lecithin/cholesterol acyl transferase, CETP, and phospholipid transfer protein activity (220). Postprandial lipoprotein remnant levels, which are commonly associated with premature atherosclerosis, have also been found to be significantly elevated at baseline and in the postprandial period in acromegalic patients (221). The altered postprandial response of lipoprotein remnant may increase the susceptibility for premature atherosclerosis, as observed in patients with acromegaly.

Abnormalities of protein metabolism in acromegaly have not been investigated as deeply as glucose and lipid metabolism thus far. GH increases muscle weight and nitrogen retention; these effects are partially indirect, via hepatic and locally produced IGF-I, and partially direct. However, most changes in protein metabolism are derived from the influence of GH and IGF-I on renal function. Glomerular hyperfiltration is a characteristic feature of acromegaly; overnight urinary albumin excretion rate and creatinine clearance are higher in patients than in controls, suggesting an influence of GH and IGF-I levels on albuminuria (222). This phenomenon is emphasized during submaximal exercise, where increased microalbuminuria is likely to be due to functional glomerular involvement (223).

B. Pathogenesis

1. Glucose metabolism. The mechanisms responsible for the GH action on carbohydrate metabolism have been investigated at different levels. Pharmacological doses of GH decrease glucose utilization; therefore, GH excess has been shown to induce insulin resistance by impairing the ability of insulin to suppress glucose production and stimulate glucose utilization. Numerous authors investigated how GH and IGF-I modulate insulin actions by altering insulin receptor binding or postreceptor events. Earlier studies suggested that impairment of glucose metabolism develops only in the so-called prediabetic patients, such as those with a decreased insulin response to hyperglycemia and thus unable to overcome the diabetogenic effect of GH by compensatory hyperinsulinism (224). In fact, the plasma insulin response to glucose is notably increased in patients with active acromegaly and with a normal glucose tolerance. Moreover, the insulin response to glucose is more pronounced in patients with highly active acromegaly than in those with mod-

erately active disease (224). Sonksen *et al.* (204) confirmed the presence of hyperinsulinism in a number of patients with acromegaly, delineating two intermediate stages in the development of diabetes in acromegaly: 1) a hyperinsulinemic stage, characterized by a normal or borderline glucose tolerance with a more rapid and higher insulin peak after glucose load, returning to normal later than controls; and 2) a stage characterized by a delayed insulin response to glucose in the presence of normal or slightly impaired glucose tolerance, which is likely reversible after adequate treatment. These authors (204) described an additional third stage characterized by a maximal pancreatic response in the fasting state with no further rise in insulin concentrations after glucose administration, which is likely irreversible after treatment. Therefore, GH excess is likely to induce a state of insulin resistance, initially manifested as a rise in fasting insulin concentration and an exaggerated insulin response to the glucose load. If GH excess remains untreated, fasting hyperglycemia may develop with a fall in fasting insulin, but a more dramatic loss of insulin response to the glucose load.

The number of insulin receptors, their affinity, and/or postreceptor defects may play a role in the development of glucose metabolism alterations in acromegaly as well. Muggeo *et al.* (225) demonstrated the abnormal binding of insulin to its receptor on circulating monocytes, which correlated with the severity of GH excess as well as with abnormal carbohydrate metabolism and insulin secretion. Moreover, in patients with euglycemia or hyperglycemia, the total receptor concentration per cell was decreased proportionately to hyperinsulinemia (226). In diseases involving the GH/IGF-I axis, the decrease in insulin sensitivity cannot be attributed exclusively to an alteration of insulin binding, but postreceptor defects must also be considered (227). In acromegaly, suppression of glucose production was impaired at insulin concentrations in the physiological but not in the supraphysiological range, whereas stimulation of glucose utilization was decreased at insulin concentrations in both the physiological and supraphysiological ranges (228). The decreased glucose utilization at supraphysiological insulin concentrations, together with normal monocyte and erythrocyte insulin binding, suggests that there is a postreceptor alteration in insulin action in acromegaly (228).

New insight in the pathogenesis of insulin resistance in acromegaly is derived from the prospective analysis of patients studied before and after cure. Cure is generally accompanied with the remission of diabetes and recovery of the normal pattern of insulin secretion, although this latter may be delayed. In fact, in a controlled study, acromegalic patients with normalized GH levels still had increased insulin secretion after glucose ingestion, suggesting either a persistently increased pancreatic islet β-cell mass or peripheral insulin resistance (229).

Insulin resistance in chronic GH excess might be accompanied by impaired muscle glucose uptake and nonoxidative glucose metabolism, which are considered early derangements, as observed in patients with normal glucose tolerance (230). Patients with acromegaly have indeed impaired peripheral muscle glucose uptake despite high insulin levels. Increased activity of the hepatic glucose-glucose 6-phosphate cycle is unlikely to contribute to the hepatic insulin resistance induced by GH, whereas changes in fatty acid metabolism may be partially responsible (231). On the other hand, in the early 1990s it was also demonstrated that lipids constitute the major fuel substrate in acromegalic patients (232). Subsequent data from glucose clamp studies showed definitively that the striated muscle is the primary site of peripheral insulin resistance (232). An improvement of the intermediate metabolism was reported after successful surgery (232). As already stated (see *Section II.E*), there is a close correlation between blood pressure values and plasma insulin levels in acromegaly. Recent studies have critically clarified that insulin sensitivity is clearly reduced to a similar extent in acromegalic patients with normal glucose tolerance as well as in those with IGT or diabetes (209). In patients with normal glucose tolerance, but not in those with impaired glucose metabolism, a compensatory hyperactivity of β-cells counteracts the reduced insulin sensitivity (209). Recently, two new actors entered the scene: glucose-dependent insulinotropic polypeptide and ghrelin. Hypersecretion of fasting and postprandial glucose-dependent insulinotropic polypeptide was recently found to be involved in determining the occurrence of hyperinsulinemia in acromegaly (233). Moreover, patients with active acromegaly show low levels of circulating ghrelin that did not change after the oral glucose tolerance test (234). This may depend on both GH-induced insulin resistance and the putative GH/IGF-I negative feedback control on ghrelin secretion. Further studies should investigate the potential role of ghrelin on metabolic pathways in acromegaly, because this recently discovered peptide has a wide range of metabolic functions. Insulin resistance in acromegaly involves protein metabolism as well, because both insulin and GH promote protein accretion. In fact, acromegalic patients recently have been shown to be severely insulin resistant for both glucose and protein metabolism (235). Although 6 months after successful surgery insulin resistance for glucose metabolism is completely reversed, a marked antagonism with the insulin effect on proteolysis and on leucine oxidation seems still to persist, demonstrating that the effects of GH on protein metabolism are not reversed by surgery, at least in the short term (235).

2. Lipid metabolisms. Alterations in lipid profile are more evident in patients with concomitant abnormalities in glucose metabolism, although the influence of genetic, dietary, ethnic as well as geographical aspects cannot be ruled out. Although the underlying mechanism of increased Lp-a concentrations in acromegalic patients is still poorly understood, the positive correlation between GH and Lp-a levels, as well as the decrease of Lp-a after either medical or surgical treatment, not only indicated a close link between these two parameters but also suggested that Lp-a synthesis may be GH-regulated (214, 236). However, it should be considered that other authors did not find any correlation between Lp-a and IGF-I (217, 237), suggesting that the GH stimulatory effect on Lp-a may be independent from IGF-I. Similarly, findings of increased HDL-cholesterol levels after treatment of acromegaly may be a consequence of GH decrease (214). GH excess can directly induce the reduction in LPL activity in acromegaly; a stimulatory GH effect on liver LDL-receptor expression has also been proven to be independent of IGF-I

levels (238, 239). The GH effect is probably displayed in the catabolism of LDL subfractions, because GH has been reported to induce hepatic LDL receptors, which will selectively lower LDL-II more than LDL-III (240).

Of particular interest is the recent data on LDL physical characteristics in acromegaly (205), because increased risk of vascular complications is associated with the presence of small and/or dense LDL particles in both diabetic and nondiabetic patients. In acromegaly, both hyperinsulinemia and reduced postheparin lipase activity, already known to influence the development of hyperlipidemia in these patients, are among the factors involved in modifying the LDL physical properties, which might also be modified by the hepatic lipase activity that is low in acromegaly (241). Therefore, small and/or dense LDL particles in acromegalic patients are likely due to factors other than hepatic lipase. Arosio *et al.* (218) found a correlation between Lp-a and GH, but not IGF-I. This confirms that GH and IGF-I have different, and probably contrasting, effects on Lp-a (242) and supports a major role for GH in the physiological regulation of Lp-a expression. Several abnormalities in HDL lipid composition in patients with acromegaly are consistent with an impaired plasma lecithin/cholesterol acyl transferase action and a decreased phospholipid transfer protein (220). Decreases in plasma cholesterol esterification and cholesteryl ester transfer and decreases in plasma phospholipid transfer protein activity in acromegaly may impair reverse cholesterol transport, thereby contributing to the increased cardiovascular risk. Finally, what remains to be clarified is the significance of changes in leptin release in acromegaly that are related to differences in body fat content and mass as well as insulin resistance (243). However, leptin in acromegaly does not seem to be influenced directly by GH or IGF-I secretion, because the acute effect of somatostatin analogs on leptin levels differs from the effect of a radical cure after pituitary surgery (243).

C. Effect of GH and IGF-I control on metabolic complications

Since the late 1960s, it was already recognized that surgical removal of GH-secreting pituitary tumors improved both glucose tolerance and diabetes (204). Successively, with the development of more accurate methods for assessing insulin immunoreactivity and glucose measurement, increased insulin secretion after glucose load failed to recover in some patients despite normalization of GH levels (229). Ongoing abnormalities were suggested to be due to persistently increased pancreatic islet β-cell mass and/or peripheral insulin resistance (229). However, it should be mentioned that cure criteria of acromegaly at that time were significantly different from those currently accepted. When stricter criteria for the control of the disease were considered, together with more sophisticated methods for assessing glucose and lipid metabolism, reversibility of metabolic abnormalities was demonstrated in a small series of patients that were surgically cured (232). Somatostatin analogs significantly improve GH and IGF-I control, especially in those patients in which surgery was unsuccessful, but they were initially suspected to aggravate glucose tolerance in acromegaly by suppressing plasma insulin concentrations (244). Later results, however, demonstrated that glucose tolerance and insulin resistance were only modestly altered by octreotide therapy (245). Additionally, improvement of insulin resistance by octreotide may likely counterbalance its inhibitory effect on insulin secretion (245). During octreotide treatment, the early insulin response to glucose load is reduced and is followed by a delayed normal increase. However, due to the concomitant GH suppression, peripheral insulin resistance is reduced, and glucose tolerance remains generally normal in most patients (246). Basically, both of the most widely used somatostatin analogs, octreotide and lanreotide, decrease insulin resistance in acromegalic patients. Interestingly, octreotide-LAR seems to be more detrimental to glucose metabolism than lanreotide SR, despite being more effective in reducing GH and IGF-I levels (247). The mechanism behind this phenomenon is still unclear. We observed, however, that the negative effect of somatostatin analogs on insulin levels appears to be more evident at the beginning of treatment, whereas glucose tolerance usually improves during long-term treatment with these drugs (68, 82). The newly discovered GH antagonist pegvisomant proved to be effective in improving insulin sensitivity and carbohydrate metabolism in acromegalics, an effect apparently independent of weight loss (248), and suggesting a potential role for this compound in the treatment of insulin-resistant states other than acromegaly (248).

The first study assessing changes in the altered lipid profile after treatment with octreotide in acromegaly reported a significant decrease in triglyceride levels despite reducing insulin levels, probably due to direct GH suppression (249). Several studies reported on the effectiveness of surgery and somatostatin analogs in lowering Lp-a levels in acromegaly (205, 206, 236, 249), but negative findings have also been described (217). Treatment with octreotide is associated with a general amelioration of lipid profile without any impact on small and/or dense LDL particles (218). In our cohort of patients, lipid profile abnormalities were also generally improved by treatment with somatostatin analogs, in either the short or the slow-acting formulation (64, 68, 97, 179).

Only limited data are currently available on lipid profile after GH-antagonist treatment. Very recently, van der Lely *et al.* (55) reported the results of a multicenter trial that confirmed the normalization of IGF-I levels previously shown. The majority of cases also showed a decrease of insulin and glucose levels without any change in cholesterol levels, which were elevated at study entry, nor were there changes of triglycerides and urea nitrogen. It should be noted that although 152 patients were included in the study, only data from 39 of them were available at the 18-month follow-up analysis (55). In another study including 48 patients receiving the GH-antagonist for 18 months, total cholesterol levels increased as well as the total/HDL-cholesterol ratio and triglyceride levels (250). Lp-a decreased, whereas glucose, insulin, homocysteine, and IL-6 did not change (250). Interestingly, C-reactive protein levels that were low at study entry significantly increased during treatment (250), leading the authors to hypothesize a direct GH effect on this cardiovascular risk parameter. Parkinson *et al.* (251) recently confirmed that successful treatment with pegvisomant in acro-

megaly increases low baseline serum total cholesterol and LDL levels, restoring the distribution of values to that of the general population and improving insulin resistance as well.

In conclusion, successful control of GH and IGF-I excess improves glucose and lipid metabolism, although at the beginning of treatment with somatostatin analogs an impairment of insulin secretion leading to further increase of glucose may be observed. Generally, this effect subsides with treatment continuation, but rarely, mostly in elderly patients, overt diabetes mellitus may develop, inducing treatment discontinuation. The effect of treatment of acromegaly on protein metabolism is largely unknown. As far as the new therapeutic approach to acromegaly is concerned, *i.e.*, the GH-antagonist, further data are required to establish its impact on metabolic parameters.

IV. The Complications at the Respiratory System

A. Epidemiology

Respiratory disorders constitute a relevant cause of illness and impaired physical performance in patients with acromegaly, contributing to 25% of all deaths recorded in this condition, where respiratory mortality appears to be threefold higher than in normal subjects (19). The pathophysiology and clinic of respiratory disorders occurring in acromegaly will be more extensively analyzed in the following two sections. Patients with acromegaly develop several respiratory alterations, as a consequence of anatomical changes affecting craniofacial bones and soft tissues, respiratory mucosa/cartilages, lung volumes, rib cage geometry, as well as activity of respiratory muscles (Table 4). This range of abnormalities results in two main respiratory dysfunctions, namely sleep apnea and impaired respiratory function. Sleep apnea, the phenomenon of recurrent cessation or decrease of airflow to the lungs during sleep, is a common cause of snoring and daytime sleepiness in acromegaly. It may affect as many as 60% of unselected acromegalic patients and 93% of patients with suspected sleep apnea (25), the vast majority of cases being due to anatomical narrowing of the upper respiratory airways causing obstructive sleep apnea (see *Sections IV.B and IV.C*). Impaired respiratory function is an alteration less frequently investigated in acromegaly and originates from multiple alterations involving the bone and muscle structure of the chest as well as the lung elasticity. Lung volumes become increased in as much as 81% of men and 56% of women with acromegaly (252–254), whereas up to 80% of patients may develop subclinical hypoxemia (255).

The impact of respiratory complications is high in acromegaly, and several epidemiology studies published since the early 1970s have documented an increased respiratory mortality in this condition. Wright *et al.* (12) showed that the rate of respiratory mortality was 3- to 7-fold higher in men and 3- to 5-fold higher in women with acromegaly aged 45–64 and 65–75 yr, compared with age-matched control populations of England and Wales. This finding was partly confirmed by the study of Alexander *et al.* (8), in which the death rate associated with respiratory disorders was significantly increased by 6-fold only in acromegalic men and nonsignificantly increased by 2-fold in women, whereas Nabarro (9) showed a faint increase in respiratory mortality among male patients, *i.e.*, three observed deaths *vs.* two expected. Despite the progressive improvement of treatment procedures and cure rates of acromegaly, enhanced rates of respiratory mortality have been subsequently recorded in surveys published in the early 1990s; respiratory disorders caused 25% of deaths reported in 1993 by Bates *et al.* (13), and nearly 12% of those reported in 1998 by Orme *et al.* (18). Peculiarly, this latter study showed that respiratory mortality was 85% higher than expected, independent of aging, an observation that may thus be suggestive of premature mortality among acromegalic patients. It is worth noting, how-

TABLE 4. Morphological and functional alteration of upper and lower respiratory airways, thoracic cage, and lungs in patients with acromegaly

Site	Pathological findings	Clinical disorder
Craniofacial region and upper respiratory tract		
Soft tissues and muscles	Macroglossia (283)	
	Swelling/lengthening of the soft palate (266, 267, 273–275, 277)	Impaired airflow transit
	Swelling/collapse of the pharyngeal walls (277)	Obstructive sleep apnea
	Thickening of true and false vocal cords (275, 278)	Nocturnal snoring
Bones	Overgrowth of mandible, maxilla and ioid (266, 267, 273, 277)	Fragmented sleep
	Mandible protrusion (266, 267, 273, 277)	Daytime somnolence
	Dorsocaudal rotation of the mandible (273)	Morning sleepiness
Organs	Thyroid overgrowth (283, 374, 375)	Morning headache
	Submandibular salivary gland hyperplasia (276)	
Neck/thoracic cage and lower respiratory tract		
Soft tissues and muscles	Small airway narrowing (253–255)	
	Derangement of respiratory muscles (286, 287)	Impaired airflow transit
Cartilages and bones	Enlargement/elongation of vertebral bodies (283)	Stiffened rib cage
	Thickened intervertebral discs of the neck (283)	Impaired breathing movements
	Thinned intervertebral discs of the thorax (283)	Respiratory muscle impairment
	Thoracic spine kyphoscoliosis (283)	Short inspiratory time
	Elongation and divergence of the ribs (283, 285)	Emphysema
Organs	Lung overgrowth (253–255, 288)	Bronchiectasis
	Increased lung volume (253–255)	
	Increased lung compliance (253–255)	

ever, that environmental/social factors, including smoking habits and industrialization rates, may have significantly influenced these results. Intriguingly, surveys conducted in acromegalic cohorts living in Sweden (10) or New Zealand (15) failed to record any significant increase in respiratory mortality.

B. Pathogenesis

Experimentally, the expression and the activity of GH and IGF-I have been investigated in several respiratory cell types. Both in rodents and humans, GH and IGF-I exert proliferative effects on lung and smooth muscle cells through interaction with their cognate receptors. This has been confirmed in Northern blot studies revealing the presence of GH-R mRNA in lung epithelium, smooth muscle cells, and pneumocytes of rodents (256), whereas the expression of mRNA transcripts for GH-R has been found subsequently in human fetal lung tissue by RT-PCR followed by Southern hybridization assays (257). Despite this observation, however, immunocytochemical analysis of GH-R failed to detect protein expression in human fetal lung tissue (258). Also, activated alveolar macrophages in human airway express gene transcripts encoding for GH and GH-R, IGF-I and IGF-IR, and several IGFBPs (259). On lung tissue, GH was shown to enhance the synthesis of type I collagen fibers and mucopolysaccharides (260) and to increase compensatory postpneumonectomy lung growth in rats (261). Similar effects have been subsequently shown for IGFs. In fact, IGF-I and IGF-II were shown to promote cell proliferation in cultured rabbit airway smooth muscle cells expressing IGF-IR and IGF-IIR (262). Inversely, IGF-I treatment was unable to induce the elastogenic response in rat pulmonary fibroblasts, as evaluated by expression of tropoelastin mRNA and soluble elastin levels (263).

C. The sleep apnea syndrome

Excessive nocturnal snoring and sleep apnea are disturbances about which acromegalic patients frequently complain. The first report of daytime sleepiness and obstructive apnea in patients with acromegaly appeared in 1896 (264, 265). It is now evident that between 20 and 80% of patients may suffer from sleep apnea (25, 266–268). In their detailed investigation, Grunstein *et al.* (25) reported the occurrence of sleep apnea in 60% of unselected patients and 81% of their entire series, encompassing patients preselected for sleep disorders. Weiss *et al.* (266) documented sleep apnea in 75% of patients, snoring in 78%, fragmented sleep in 60%, daytime somnolence in 51%, and morning sleepiness and morning headache in 16% of cases. Similar figures were reported by Dostalova *et al.* (267). As expected, these rates notably outnumber those observed in normal middle-aged men (2–4% prevalence) and women (1–2% prevalence) (269), where sleep apnea is a common cause of daytime sleepiness, impaired cognitive performance, and road traffic accidents. In the general population, sleep apnea also has been shown to predispose to ischemic heart disease, arrhythmias, arterial hypertension, and cerebrovascular accidents (269), which are also relevant sequelae of acromegaly. Sleep apnea, considered to be at least 10 (270) or at least five (271) episodes of apnea/hypopnea lasting at least 10 sec of every sleep hour, is classified as either central, due to cessation of respiratory movements, or obstructive, due to narrowing of upper respiratory airways. A combination of these two conditions leads to mixed sleep apnea. Central sleep apnea is known to depend on alterations of the nonbehavioral system controlling ventilation, as seen in several neurological and cardiovascular disorders. It is characterized by repeated apneic events occurring during the sleep without associated ventilatory effort. Grunstein *et al.* (25) noted that as many as one third of patients with acromegaly developed central sleep apnea in association with the obstructive type. This observation was speculatively related to direct effects on the breathing center exerted by either high GH/IGF-I levels or an enhanced somatostatin tone, because somatostatin is able to reduce animal breathing and decrease chemosensitivity to hypoxia in humans (25). In addition, acromegalic patients with central sleep apnea had a greater ventilatory response to hypercapnic hypoxia, compared with patients with obstructive sleep apnea (272). Despite this finding, however, acromegaly is predominantly associated with obstructive sleep apnea, a disorder ordinarily caused by anatomical abnormalities of the pharynx lumen. Under normal conditions, the pharyngeal potency depends on the balance between the negative intraluminal pressure on inspiration and the dilating activity of muscles acting on the tongue and the soft palate (*i.e.*, the genioglossus and the palatoglossus muscles) (269). As shown in Table 4, acromegaly causes several anatomical alterations, which may contribute to impairing the intrapharyngeal balance during inspiration and thus increase pharynx collapsibility during the sleep. By studying cephalometric geometry, Dostalova *et al.* (267) observed that acromegaly causes mandible protrusion, increases the mandibular length, and decreases the angle of sagittal maxillomandibular relations. The facial height of acromegalic patients is frequently elongated, and the mandible may undergo dorsocaudal rotation, thus causing a dolichofacial aspect (269). Compared with nonacromegalic patients suffering from sleep apnea, acromegalic patients with sleep breathing disorders have a narrower pharyngeal airway both at the level of the uvula tip and at the mandibular plane (267, 273). There is a similar degree of mandible/maxillary overgrowth and soft palate lengthening between patients with and without sleep apnea, but the uvular-tip plane is significantly narrower in those with sleep apnea (267). Other relevant pharyngeal abnormalities include swelling of soft tissues and mucosa hypertrophy. These alterations contribute to increasing the collapsibility of lateral/posterior hypopharyngeal walls on inspiration, which may then become invaginated into the laryngeal vestibule during sleep apneic episodes (274). Descriptions also exist of tongue hypertrophy causing fatal asphyxia (9), voluminous bilateral laryngocele (271), and increased volume of submandibular salivary glands (276). Remarkably, studies on static pharyngeal mechanics have identified the edge of the soft palate and the tongue base as the narrowest sites in the passive pharynx (277), whereas Morewood *et al.* (278) documented obstruction of the upper airways in 23% of their patients due to the thickening of both true and false vocal cords. Like ordinary

sleep apnea, however, the reduction of upper airway muscle activity at sleep onset appears to be an initial key event for the development of apnea in patients with acromegaly, because disordered breathing does not usually occur during active contraction of upper airway muscles in the awake state (277). Several studies have also reviewed the correlation between the severity of sleep apnea and both disease activity and GH/IGF-I levels. In a series of 11 patients, Perks *et al.* (279) diagnosed sleep apnea in five patients whose GH levels were significantly higher than in unaffected patients. Similarly, four of 10 acromegalic patients with active disease studied by Hart *et al.* (280) had obstructive sleep apnea, whereas none of 11 patients with inactive disease was affected. In the Grunstein *et al*. study (25), patients with central sleep apnea had higher GH and IGF-I levels than did patients with obstructive apnea. At variance with other reports, these authors failed to demonstrate any relationship between GH/IGF-I levels and either the severity or the frequency of apneas, whereas aging and disease duration were positively associated with the rate of apneic episodes (25). The role played by gender has been addressed by Pekkarinen *et al.* (281) using polysomnography; they reported a higher number of apneic episodes during non-rapid eye movement sleep in five of six active men and in none of five women. In the Weiss *et al*. study (266), the degree of sleep apnea was positively associated with male gender (3-fold higher prevalence compared with women), active disease (82% of active *vs.* 62% of inactive patients), and aging. Although the positive correlation between central sleep apnea and activity of acromegaly implies that control of disease activity may lead to the disappearance of central sleep apnea, previous studies reported the persistence of sleep apnea after pituitary surgery, presumably because of the persistence of obstructive causes. Pekkarinen *et al.* (281) recorded reversal of sleep apnea in only one of five patients treated with pituitary surgery, whereas Pelttari *et al.* (282) found persistence of periodic breathing in 10 of 11 patients previously treated by adenomectomy and/or radiotherapy, nine of whom were inactive at the time of the study.

D. The respiratory dysfunction

Acromegaly alters the structure, elasticity, and function of the entire respiratory apparatus (Table 4). Patients with acromegaly develop a barrel chest due to changes in vertebral and costal morphology. Vertebral bodies become enlarged and elongated due to periosteal bony apposition, whereas the intervertebral discs thicken at the cervical and lumbar levels and become thin in the thoracic region, thus resulting in development of kyphosis (283, 284). The epiphyses of the osteochondral junctions fail to close, and the ribs become elongated and diverged. The costochondral junctions may even become prominent and enlarged, thus giving a typical rosary-like aspect (285). These anatomical rearrangements alter the elastic chest mechanics and markedly impair the inspiratory muscle activation, which is further aggrieved by muscle weakness/wasting associated with acromegaly. In fact, muscle biopsy studies have shown segmental fiber degeneration, foci of small cell infiltration, thickening of capillary basement membranes, and variable derangement of type I or type II fibers (286). Both bone and muscle alterations may deteriorate the contraction of sternal intercostals, scalene, and diaphragm muscles and thus impair the physiological breathing act. Indirect proof of respiratory muscle dysfunction originates from the study by Iandelli *et al.* (287), showing that most patients with acromegaly achieve subnormal respiratory muscle force, during either inspiratory or expiratory breathing. The inspiratory time is usually shorter and, consequently, the breathing frequency may increase. As in several neuromuscular disorders, nonvagal afferent information originating from either weak respiratory muscles or stiffened rib cage may act centrally to terminate respiration and accelerate the respiratory pattern. The authors' observation of a normal chemoresponsiveness of respiratory muscles is consistent with the normal role of central factors and the prevalent effect of reduced muscle force in the setting of the respiratory responses observed (287). The relevance of lung volumes and ventilation/perfusion relationship is similarly crucial in the pathogenesis of respiratory disorders. Patients with acromegaly develop increased total lung capacity. This abnormality was originally observed by chest radiographs and subsequently confirmed in spirometry and pletismography studies. Brody *et al.* (288) found lung volume to be twice the normal in five of six men with acromegaly, and suggested that this increase was mostly due to hypertrophied interstitial tissue. Total lung capacity is increased in 81% of men and 56% of women, 36% have small airway narrowing, and 26% have upper airway narrowing (252–255). Eighty per cent of patients examined by Luboshitzky *et al.* (255) had subclinical hypoxemia; partial pressure of oxygen in arterial blood ranged between 58 and 90 mm Hg, whereas four of five patients subjected to lung perfusion scans showed defects in perfusion, indicative of ventilation-perfusion derangement. Increased vital capacity was reported in 34% of patients, upper airflow obstruction in 50%, and nocturnal hypoxemia in 23% of cases (255).

It has been shown that the increased lung volume is unrelated to hyperinflation or muscle strength. Rather, lung compliance is generally increased, whereas elastic recoil, diffusing capacity, and diffusing capacity per unit of alveolar volume are unchanged. Based on these evidences, many authors have attributed lung overgrowth to an increase in the size of alveoli (25, 252, 289). In line with these findings, studies of gas exchange across the alveolar capillary membrane failed to demonstrate ventilation/perfusion mismatching in patients with acromegaly. Donnelly *et al.* (290) reported values of pulmonary distensibility and diffusing capacity similar to those observed in control subjects. At significant variance with previous reports, however, they observed that the diffusing capacity per unit of alveolar volume was significantly lower than in controls, and thus interpreted these results as the consequence of an increased number of alveoli rather than their overgrowth (290). The role of disease duration and activity on lung disorders has been similarly analyzed. Lung volumes and the narrowing of intrathoracic and extrathoracic airways were correlated with the duration of acromegaly, and longer disease duration significantly increased the risk of developing respiratory abnormalities (252). Other authors failed to reproduce these correlations (254, 289).

For the aforementioned reasons, patients with acromegaly often achieve an inadequate response to ventilatory and skeletal muscle demand on effort. The workload at the cycloergometer is significantly reduced in acromegaly compared with controls, both at anaerobic threshold and at maximal exercise (97, 137, 198). Studies of aerobic fitness by self-paced walk test resulted in significantly higher heart rate and perceived fatigue in patients, whereas maximum oxygen uptake and ventilation threshold at the maximal exercise were significantly lower than the predicted values (291). Despite this body of evidence, however, the causes leading to respiratory deaths are still largely unknown. Nabarro (9) documented kyphoscoliosis in 13 cases, chronic bronchitis and emphysema in five, and bronchiectasis in three other patients out of a total of 256 cases reviewed. In this series, two patients with kyphoscoliosis and muscle weakness died from chest infections. In the largest series currently available, Orme *et al.* (18) identified 43 cases of cancer-independent respiratory deaths; the majority (31 cases) were caused by bronchopneumonia/pneumonia, which may have been smoking-related, whereas only a minority (11 cases) were attributable to smoking, chronic bronchitis, emphysema, and chronic airway obstruction. Despite these indications, however, more accurate ascertainment of specific mortality causes still awaits further clarification.

E. Effect of GH and IGF-I control on respiratory disease

Reports published in the early 1980s postulated that tracheostomy and/or tongue plasty needed to be included in the treatment plans for sleep apnea in acromegaly (274). Subsequent studies provided convincing evidence that control of acromegaly, either by pituitary surgery or somatostatin analogs, improved sleep breathing disorders in acromegaly. The likelihood of developing sleep apnea reportedly decreases to 25% in the case of posttreatment GH levels of 5 mU/liter or less ($\leq$2.5 μg/liter) (292). As previously mentioned, nocturnal breathing abnormalities may paradoxically persist several years after adenomectomy. Initial studies by Pekkarinen *et al.* (281) indicated that only one of five patients cured by pituitary adenomectomy achieved reversal of sleep apnea. Based on these findings, the authors hypothesized that anatomical abnormalities occurring in acromegaly were irreversible or, alternatively, took a longer follow-up time to improve significantly. Analysis of their results by modern cure criteria (20), however, revealed that only two of their patients achieved a reduction of GH levels into the therapeutic range. Pelttari *et al.* (282) studied the occurrence of periodic sleep breathing through analysis of body and respiratory movements in 11 patients previously treated by adenomectomy and/or radiotherapy, nine of whom were inactive at the time of the study. The authors found that periodic breathing persisted in 10 of their 11 acromegalic patients (282). Part of the occurrence of sleeping disturbances was explained by age and body mass index, but not by gender or by the duration of disease activity/inactivity (282). The introduction of somatostatin analogs in the clinical practice dramatically influenced the cure rate of sleep apnea. Chanson *et al.* (293) reported the significant improvement of sleep apnea in three patients treated with sc octreotide. Grunstein *et al.* (25) showed that octreotide treatment decreased the frequency of apneic and hypopneic episodes by 50% of baseline values, regardless of whether apnea was central or obstructive. Of note, these authors documented that patients with mixed or central sleep apnea achieved the predominant improvement of the central component of sleep breathing control. In the study by Ip *et al.* (268), the severity of obstructive apneas was significantly improved by octreotide-LAR treatment, whereas mixed and/or central sleep apnea was only modestly changed. In the case of persisting sleep breathing disorders, the use of continuous positive airway pressure devices should be recommended to prevent the long-term cardiovascular consequences of sleep apnea. GH and IGF-I suppression is also expected to produce similar beneficial effects on other ventilatory dysfunctions. Lung volumes and lung distensibility decrease after 3–11 months of octreotide treatment, whereas diffusion capacity remains unaltered (289). The change in lung elastic properties after therapy seems to suggest either changes in surface forces or increases in the strength of tissues tethering. Thus, changes in elasticity are reflected by a significantly improved response to physical exercise. Giustina *et al.* (198) observed that both workload and oxygen consumption at anaerobic threshold increased significantly after octreotide treatment, which abrogated the difference in exercise capacity recorded at baseline between acromegalics and controls. A 6-month treatment with octreotide-LAR did not determine a significant increase in the maximal oxygen uptake during a progressive treadmill test, but patients achieved an increase in ventilation threshold and in vigor score, as well as a decrease in perceived fatigue (291).

From the analysis of the above-mentioned studies, respiratory disorders of acromegaly appear to be complex in both their origin and development. The hypertrophic action of GH and IGF-I causes structural changes at the level of the upper as well as the lower airways. Thus, acromegaly leads potentially to several types of ventilatory dysfunction. In upper airways, remodeling of bones and soft tissues results in the impairment of the normal pharyngeal patency during sleep and is key to the onset of obstructive sleep apnea, the prominent type of sleep breathing disorder in acromegaly. Sleep apnea may affect as much as around 80% of patients and is apparently more frequent and severe in case of persistently active disease, elevated GH/IGF-I levels, and male gender. In up to one third of patients, obstructive sleep apnea can coexist with the central type likely due to concomitant neuronal stimuli to the respiratory center mediated by the somatostatin tone and triggered by an altered sensitivity threshold to carbon dioxide. Successful treatment of acromegaly dramatically improves sleep breathing disorders. However, the persistence of sleep apnea after surgical cure of acromegaly may be attributable to an irreversible process of remodeling of upper airways and should prompt the use of continuous positive airway pressure devices to prevent further cardiovascular complications associated with sleep apnea. In the lungs, the proliferation of pneumocytes and smooth muscle cells is reflected in the overgrowth of pulmonary epithelium and thickening of interstitial tissue. This alteration decreases pulmonary elasticity, whereas lung volumes are increased due to alveoli overgrowth. Clinically, this

process leads to respiratory dysfunction; the ventilatory response on effort is frequently inadequate in the face of a greater effort as well as the sense of physical exhaustion. Ventilatory dysfunctions are well correlated with both the activity and the duration of acromegaly, so that successful therapy of acromegaly improves significantly the ventilatory response to effort and the personal sense of weakness. From the studies reviewed, some questions remain: 1) can successful treatment of acromegaly also be reflected in a significant improvement of respiratory failure; 2) can respiratory dysfunctions consistently contribute to the impact/progression of cardiovascular complications in acromegaly; and 3) should researchers look into more specific causes to explain the enhanced respiratory mortality seen in this condition? Additional investigations are required to fully answer these questions.

V. The Neoplastic Complications

A. Epidemiology

Over the years, epidemiology studies have provided increasingly debated evidence that acromegaly may enhance the neoplastic risk, and that cancers constitute the third leading cause of mortality in this condition (8–10, 12–18). The recently identified relationship between the IGF system and human cancers has further persuaded many researchers that neoplasms of acromegaly may constitute an informative model to legitimize this link. From a teleological point of view, understanding of the GH/IGF-I role in tumorigenesis may depend upon reconciling this association with the neoplastic phenomena of acromegaly.

The first study exploring the cancer risk in acromegaly was performed in 1956 by Mustacchi and Shimkin (294) on 223 patients referred to 16 cooperating institutions, yielding 2981.5 person-years at risk. These authors found five patients with malignancy among 128 men, three of whom had developed lung carcinomas, and eight cancers among 95 women, two of whom had breast cancer and two had endometrial adenocarcinoma. No colon cancer was recorded, although a man with leukemia and a woman with sphenoidal angiosarcoma had received pituitary irradiation 15–20 yr earlier. Compared with the incidence rates recorded in North American metropolitan areas, they reported a nonsignificant increase in standardized incidence ratio (SIR) by 1.3 in the group as a whole (294) (Table 5). Data subsequently published by other groups added strength to the argument that acromegaly may increase both the cancer risk and cancer-related deaths. In 1982, Klein *et al.* (295) studied a group of 44 patients to explore the possible association between colon tumors and skin tags, an occurrence previously noted in the normal population. They reported four cases of colon adenocarcinoma among 26 acromegalic patients reviewed retrospectively, with no cancer among 17 patients consecutively studied by colonoscopy. Although the observed rates were not compared with those obtained in a control population, the authors speculated that acromegaly increased remarkably the risk of colon tumors. Two subsequent studies by Ituarte *et al.* (296) and Pines *et al.* (297) drew similar conclusions. The first investigation documented three cases of colon cancer among 12 patients, yielding a prevalence of 25% in the group as a whole and a 3-fold greater risk of colon cancer than in age-matched controls (296). In the second study on 48 patients, malignancies occurred in seven patients who all turned out to be Ashkenazic Jews, five of whom had gastrointestinal cancers and two had breast adenocarcinoma (297). Comparison with expected rates derived from age-sex-ethnic cancer rates yielded a SIR of 4.6 for gastrointestinal cancers and 3.5 for breast adenocarcinoma (297). In his personal series, Nabarro (9) reported evidence of malignancies in 26 of 256 cases, of whom nine were men and 17 were women. Cancer incidence rates were similar between men with acromegaly and men from the general population, whereas acromegalic women had 87% greater prevalence of cancer than the control population, mainly due to a greater prevalence of breast cancer (11 observed *vs.* 2.6 expected) (9). In 1991, Barzilay *et al.* (298) examined 120 clinical records of acromegalic patients; from an analysis of 87 of these charts, the authors found seven cases of cancer, which yielded a total standardized incidence rate of 2.45 compared with sex- and age-adjusted rates. Taken separately, the incidence rate in women with acromegaly was twice as high as in men (3.5 *vs.* 1.7). The existence of a causal link between acromegaly and cancer became even more suggestive after the publication of a 16-yr follow-up study by Ron *et al.* (299), who drew records on 1,041 acromegalic males hospitalized between 1969 and 1985 in United States Veterans Affairs (VA) hospitals, documenting a total of 116 cases of cancers. These included 27 digestive, 22 respiratory, and 15 genitourinary malignancies, as well as 27 cases of pituitary cancers. After a comparison with rates obtained from 3.7 million first admissions to VA hospitals among white and Afro-American nonacromegalic patients, acromegalic patients showed a 3-fold greater incidence of both esophageal and colon cancers and a 2.5-fold higher rate of gastric cancers. The overall standard incidence ratio calculated for cancers was 1.6 (299). Although remarkable, these latter results have raised a few criticisms: 1) inclusion of 27 cases of pituitary tumors may have originated from miscoded diagnoses of pituitary adenoma; 2) the prevalence of acromegaly emerging from the study outnumbers that observed in the general population (1 in 4000 *vs.* 4–6 per million population) (8); 3) because acromegaly is equally distributed between genders, results obtained in gender-restricted populations should be interpreted carefully; 4) inclusion of nonacromegalic hospital patients as control population may have led to ascertainment bias (19); and 5) analysis of databases collected in different centers may mask significant differences in management practice. Between then and 1998, two other studies have been published. The study by Rajasoorya *et al.* (15) analyzed the clinical determinants of acromegaly outcome from the medical records of 151 patients, followed up during a 26-yr period. These authors documented five cases of malignancies in their series, which caused overall 9% of the deaths recorded (15). Tumors were highly variable with regard to tumor type and gender distribution. A subsequent study by Cheung and Boyages (300) recorded seven malignant events in 50 patients; five cancers were diagnosed in women and contributed to a 4.3-fold higher cancer risk in this subgroup. Although breast and kidney cancers predominated in this series (two cases each),

TABLE 5. Prevalence and mortality rates of major cancers in acromegaly

Refs.	Year	Cancers/patients	Prevalence (%)	Lung	GEP (colorectal)	Thyroid	Breast	Prostate	LHP	FGT	Soft tissue	Skin
Retrospective studies focusing on cancer prevalence in acromegaly												
Mustacchi and Shimkin (294)	1957	13/223	14	3			2		1	2	1	3
Klein *et al.* (295)	1982	11/44	25		4 (4)	1	2			2		
Pines *et al.* (297)	1985	7/48	14.5		5 (3)		2					
Nabarro (9)	1987	26/256	10	3	2 (1)	1	11	1	2	2	1	
Barzilay *et al.* (298)	1991	7/87	8	1	1 (1)	2	1		1	1	1	
Ron *et al.* (299)	1991	89/1041[a]	8.5	22	27 (14)	1		15[b]	7		2	3
Cheung *et al.* (300)	1997	7/50	14		1 (1)		2	1				1
Orme *et al.* (18)	1998	79/1239	6.3	6	16 (16)	1	14					
Popovic *et al.* (301)	1998	23/220	10.4		4 (2)	3	4		3	5		2
Higuchi *et al.* (473)	2000	5/44	11.3		2 (1)	2						
Baris *et al.* (359)	2002	177/1634	10.8	14	59 (36)	3	20	13	9	9	2	13
Total		444/4886	10.9	49	121 (79)	14	58	30	23	21	7	22
Prevalence rates in acromegaly (%)				11	27.2 (17.8)	3.1	13	6.7	5.1	4.7	1.6	4.9
2002 Prevalence rate estimates in the U.S. population				13.1	19.5 (11.5)	1.6	15.9	14.7	8.3	21.7	0.6	4.5
Retrospective studies focusing on cancer mortality in acromegaly												
Wright *et al.* (12)	1970	10/55[a]	18	3	4 (2)	2					1	
Bengtsson *et al.* (10)	1988	15/62	24	2	1 (0)		3	1	3		1	1
Ritchie *et al.* (342)	1990	11/36	30.5	3	7 (4)		1					
Etxabe *et al.* (14)	1993	5/74	6.7	2	1 (0)			1			1	
Rajasoorya *et al.* (15)	1994	5/55	9	1	1 (1)		1					1
Total		46/282	16.3	11	14 (7)	2	4	2	3		3	2
Mortality rates in acromegaly (%)				23.9	30.4 (15.2)	4.3	10.8	4.3	6.5		6.5	4.3
2002 Mortality rates estimates in the U.S. population				27.9	23.8 (10.1)	0.23	7.2	5.4	10.5	10.3	0.7	0.4[c]

GEP, Gastroenteropancreatic cancers (colorectal in *parentheses*); LHP, lympho-hematopoietic neoplasms; FGT, female genital tract cancers; Skin, includes epidermal cancers and melanomas. Comparative prevalence and mortality rates are 2002 estimates in U.S. population based on rates collected in 1978–1998 (American Cancer Society, Atlanta, GA, 2002; published in NCI SEER Program 1979–1998.

[a] After excluding pituitary tumors.

[b] Includes male genitourinary cancers.

[c] Excludes basal/squamous cancers.

two other subjects developed dual malignancies (300). A deeper insight into this alleged acromegaly-cancer network has been provided by the key study published by Orme *et al.* (18), who investigated the incidence and mortality for cancer in a cohort of 1,239 patients, yielding 16,778 person-years at risk. Besides the study cohort, other strengths of this investigation resided in the exclusion of all malignancies prediagnosed with regard to the diagnosis of acromegaly and the cross-examination of reliable national cancer registers. The most striking finding of this study was the lack of difference in cancer incidence between acromegalic patients and the normal population (79 *vs.* 104 malignancies, respectively). Nevertheless, analysis of SIRs in acromegalic patients revealed a slight increase in colon cancers (SIR, 1.68) and a lower incidence of bronchial neoplasms (SIR, 0.33). Accordingly, this study partly confirmed previous reports of a higher incidence of colon cancers and a lower incidence of rectum and bronchial neoplasms (299), but it failed to record any significant increase in breast cancer incidence (9). One drawback emerging from the Orme *et al.* study (18) is the lack of a gender-related analysis, which would serve for comparative purposes with the prevalence rates reported in the other large study by Ron *et al.* (299). However, if we assume that acromegalic men constituted approximately one half of Orme's population, this study showed a lower prevalence of colon and, significantly, of bronchial cancers and a slight increase in the number of rectum cancers. In a successive study, Popovic *et al.* (301) observed a 3.4-fold higher rate of cancer incidence in patients with acromegaly, but the conclusions drawn by this study have been questioned (302).

On the other hand, mortality studies have shown that 15–24.5% of deaths in acromegaly are related to cancer-related complications. In the study by Wright *et al.* (12) performed on 194 patients living in the Newcastle region, 18% of all deaths were caused by malignancies. Lung and bowel cancers accounted for almost 70% of all neoplasms, whereas no death was attributable to breast cancer despite a significantly higher cancer mortality in women more than 65 yr of age (12). A successive study performed in the same geographical area by Alexander *et al.* (8) documented that cancers caused 15.5% of all deaths in acromegaly, cancer mortality being 4.6-fold higher in acromegalic men than in the normal male population. Other studies reported that malignant events caused 23% (9), 24.5% (10), and 9% (300) of all deaths recorded in acromegaly and that the risk of breast tumors was significantly increased (9, 10, 300). Remarkably, no significant enhancement of cancer mortality was found by Orme *et al.* (18) in the largest cohort of patients with acromegaly (83 deaths *vs.* 72 expected), although the death rate from colon cancer outnumbered significantly that recorded in the normal population (13 observed deaths *vs.* five expected). The standard mortality rate associated with cancer was increased in the case of posttreatment levels of GH above 10 μg/liter (standard mortality rate, 1.81; $P = 0.05$ at χ^2 test), but the occurrence of cancer was unrelated to either disease duration or age at the diagnosis of acromegaly (18).

B. Pathogenesis

The effect of GH and IGF-I on different cell systems has been discussed in more detail in *Section I.C*. The first evidence linking the GH/IGF system to cancer originates from experimental *in vitro* and *in vivo* studies. Although the effects produced by impure extracts of GH should be viewed with caution due to the potential action of natural contaminants, Moon *et al.* (303) recognized in 1950 that chronic high-dose treatment with extracted GH caused the development of tumors in lungs, adrenals, ovaries, and breast in female rats. Administration of bovine GH to Balb/c mice also induced lymphopoietic tumors, whereas hypophysectomy was found to modulate the growth of rat liver tumors induced by benzenic compounds and to decrease the growth of breast cancers xenografted in mice (304, 305). The role of GH in animal tumorigenesis was further confirmed in studies in which transgenic mice expressing human GH developed mammary tumors (306), although transgene expression of bovine GH did not appear to be carcinogenetic (307). GH was then found to stimulate the proliferation of several cancer cell lines *in vitro*, including human leukemic lymphocytes and murine erythroleukemic cells (308). Evidence for GH synthesis in a number of extrapituitary organs, including the lateral hypothalamus, lymphocytes, thymocytes, neutrophils, the placenta, and both normal and neoplastic mammary tissues, suggests that GH may have local paracrine/autocrine effects independent of or additional to endocrine-mediated IGF-I action (27). In mammary carcinoma cell lines, autocrine GH functions as a direct proliferative stimulus and decreases apoptotic activity, with marked synergism with trophic agents such as IGF-I (309). In prostate cancer cell lines, GH stimulation increases the rate of cell proliferation, and the coexpression of both pituitary and placental GH as well as GH-R mRNA isoforms has been shown in ALVA41, PC3, DU145, and LNCaP prostate cancer cells, where it can enable an autocrine-paracrine pathway to stimulate prostate growth (310). All of the effects of autocrine GH are mediated by GH-R. GH-R and its signal transductional mechanisms stimulate several genes involved with tumorigenesis, such as c-myc mRNA expression in liver and kidney (311). Nevertheless, the significance of GH-R activation in experimental animal models of tumorigenesis remains largely unknown.

Unlike GH, the IGF system modulates the tumorigenic process at different levels. Most human tumors develop by a multistep process in which cells acquire growth advantage by genetic damage, involving an accumulation of mutations. Gene mutations are usually prevented by host defense mechanisms including apoptosis, but several survival factors, such as IGF-I, may override these internal signals (312). Once quiescent cells are made competent, stimulation with IGF-I alone is sufficient to complete the cell cycle, promote cell proliferation, and arrest apoptosis, both in normal and cancer cell lines (48, 313). The efficiency of IGF-I stimulation requires an adequate density and functionality of the IGF-IR on the cell surface, and this prerequisite is also essential for the IGF-I-mediated proliferation of cells previously transformed by viral, cellular, and/or chemical oncogenes (48). IGF-I/IGF-IR involvement in cancer cell proliferation has been demonstrated in experiments where knockout of IGF-IR

gene, either by antisense oligodeoxynucleotides, dominant negative mutants, or triple-helix formation, was capable of decreasing cell proliferation and increasing apoptosis. The IGF-I/IGF-IR system appears to further influence cancer progression by promoting adhesion and migration of cells, as well as angiogenesis within tumoral tissues and in the surrounding areas (48, 314). Conversely, activation of tumor suppressor genes, such as p53, BRCA-1, or WT-1, results in a reduction of IGF-IR gene transcription and, hence, of cell proliferation (48). *In vitro*, IGF-I does not seem to promote cellular transformation, rather it stimulates proliferation of transformed cell clones and the growth of preexisting tumor tissues. These effects have been confirmed in studies on liver-specific IGF-I-deficient mice, in which chronic IGF-I treatment was able to promote growth and metastatic proliferation of colon adenocarcinomas transplanted on the caecum surface of the animals (315). In addition to its endocrine functions, IGF-I is widely synthesized locally and exerts autocrine/paracrine effects in a number of tissues and cell systems. Modulation of IGF-I gene transcription, usage of either of the two IGF-I promoters, alternative RNA splicing, and changes in RNA stability allow IGF-I gene expression to be cell- or tissue-specific, ontogeny-determined, or regulated by several factors (for review, see Refs. 49 and 316). Regulation of cancer growth through an IGF-I/IGF-IR-mediated autocrine/paracrine loop emerges from the demonstration of IGF-IR mRNA expression in colon carcinoma samples, which is significantly more abundant than IGF-I mRNA expression (317), and predominates in samples from colon tumor *vs.* the adjacent normal mucosa, a circumstance that is suggestive of paracrine and autocrine modulation of tumor growth (318). In breast cancer, IGF-I is expressed in the stromal cells and very rarely in the breast epithelium, as determined by *in situ* hybridization, whereas IGF-IR has been found on the surface of malignant breast epithelial cells, an event that suggests the existence of a paracrine interaction (for review, see Ref. 319). More recently, increasing attention has been paid to the biological activity of several IGFBPs, independently of their binding to IGF-I and/or IGF-II (44). IGFBP-3 has been extensively shown to promote apoptosis and arrest the proliferation of numerous tumoral cell lines, a process that involves intracellular modulation of cyclins and caspases (320). Initial studies demonstrated that mouse IGFBP-3 could inhibit the fibroblast growth factor-stimulated proliferation of mouse and chick embryo fibroblasts (321), whereas exogenous IGFBP-3 addition to HS578T human breast cancer cells inhibited proliferation, independently of IGF-I (322). In other investigations, transfection of IGFBP-3 cDNA in mouse embryo fibroblasts previously disrupted for the IGF-IR gene inhibited cell growth and promoted apoptosis (323, 324). Furthermore, IGFBP-3 mediates the antiproliferative activity of TGF-β, retinoic acid, vitamin D, TNF-α, tamoxifen, and histone deacetylase inhibitors (320). The biological activity of IGFBP-3 seems to be mediated by specific receptors present on the cell surface, although nuclear translocation mechanisms have been documented also.

The second clue relating the GH/IGF system to cancer originates from clinical studies performed in the normal population. In humans, it has been hypothesized that the pattern of IGF-I and IGFBP-3 secretion may predict cancer risk during the lifetime. IGF-I levels are significantly higher in women diagnosed with breast cancer (325) and in men harboring prostate tumors (326), compared with their normal counterparts. An 18-yr follow-up study found a positive association between the risk of developing malignant tumors and GH levels measured during an oral glucose tolerance test performed at the baseline visit (327), whereas an even tighter association emerged in large nested case-control studies between serum IGF-I levels and the risk of prostate, breast, and colon cancers (50–52). In a survey on 152 cases of prostate cancers, among nearly 15,000 men subjected to blood sampling for an average of 7 yr before diagnosis, Chan *et al.* (50) provided evidence of a 2.4-fold greater cancer risk associated with IGF-I levels in the upper quartile of the normal range, compared with patients whose IGF-I values were in the lower quartile. By inclusion of IGFBP-3 levels, the relative cancer risk lifted up to 4.3 and was nearly eight times above normal in men older than 60 yr. A similar study was conducted by Hankinson *et al.* (51) reporting that the relative risk of breast cancer in premenopausal women with IGF-I levels in the upper tertile of the normal range was 2.3 times higher than in patients with IGF-I in the lower tertile. In women below age 50 yr, the highest IGF-I tertile was associated with an increase in breast cancer risk to 4.6 and, after inclusion of IGFBP-3 levels in the multivariate analysis, to 7.3 (51). Ma *et al.* (52) analyzed IGF-I and IGFBP-3 levels in 193 men diagnosed with colorectal cancer over a 12-yr follow-up, and reported that the relative risk in men having IGF-I levels in the top quintile was 2.5 times greater than in those whose IGF-I was at the bottom quintile. Inversely, the relative risk calculated by IGFBP-3 quintiles was 0.28 for top *vs.* bottom quintile. In the Nurses' Health Study, IGF-I levels did not predict colon cancer risk unless a combination of high IGF-I and low IGFBP-3 tertiles was used; patients stratified by the highest IGF-I and the lowest IGFBP-3 had an increased risk of colon tumors (328). However, the relationship between IGF-I and cancer has been recently questioned (329).

The third corollary linking the GH/IGF system to human cancers arises from the demonstration that GHRH-antagonists, GH-antagonist, and somatostatin analogs elicit antineoplastic activity by altering the GH/IGF-I axis at the pituitary level or by inhibiting autocrine/paracrine activity of GHRH, GH, and IGFs. Ablative hypophysectomy has long been shown to reduce the neoplastic progression of disseminated breast and prostate cancers (330). Splicing variants of GHRH receptors have been found in many cancer cell lines, and GHRH-antagonists have proven to be able to inhibit tumor growth in mice xenografted with colorectal, prostate, breast, and lung cancers (331). Other studies have demonstrated that somatostatin analogs powerfully suppress tumor growth in experimental models of pancreatic, prostate, colorectal, breast, and lung carcinoma and elicit marked antineoplastic effects in several types of neuroendocrine tumors; however, their clinical efficacy in cases of prostate, breast, and lung cancers is largely disappointing (332, 333). Preliminary findings have indicated that the GH-antagonist decreased proliferation, stimulated apoptosis, and reduced metastatic spreading of MCF-7 breast cancer cells (309).

C. The gastrointestinal tract

Digestive tumors constitute the most frequent malignancies recorded in acromegaly (Table 5). Experimental studies have demonstrated that both normal and tumoral colorectal cell lines express large amounts of IGF-IR, and IGF-I induces the proliferation and antiapoptotic activity in colorectal cancer cells lines (330, 334). The role of serum IGF-I levels in stimulating tumor growth and metastasis has been further confirmed in mice carrying liver-specific deficiency of IGF-I, where both the growth and the metastatic spreading of adenocarcinomas transplanted on the caecum surface were significantly increased by a 6-wk ip treatment with IGF-I (315). In patients with acromegaly, the length of the colon and sigma is generally greater than in controls, and epithelial cells of sigmoid crypts present an enhanced pattern of proliferation, which is positively correlated with circulating IGF-I levels (335, 336). This finding is consistent with the observation of a decreased apoptotic activity, independent of Bcl-2 and Bcl-x_L proapoptotic proteins (337). It can thus be speculated that GH/IGF-I excess in acromegaly increases epithelial cell proliferation and decreases the apoptotic rate, which then may predispose to a greater accumulation of genetic defects leading to colon cancer. Many researchers have intriguingly claimed that one mechanism compensating for these growth-promoting effects of IGF-I on colon mucosa may depend upon the concomitant increase in IGFBP-3 levels, because IGFBP-3 has shown intrinsic antiproliferative effects *in vitro* and its serum levels are negatively correlated with cancer risk (50–52). IGFBP-3 may either promote apoptosis through specific receptors or bind IGF-I in small binary aggregates, thus inhibiting IGF-I activity. However, this unresolved issue awaits further clarification. Several other humoral and mechanical factors may play a crucial role in modulating colon cell proliferation in acromegaly. Abnormalities in lymphocyte subset pattern, consistent with a decrease in the number of B lymphocytes and Natural Killers and an increase in T lymphocytes, have been described by our group in the colon mucosa of acromegalic patients and appeared to be correlated with disease activity (338). The decrease in helper-inducer lymphocytes may imply an impairment of local Ig pattern and, hence, of immune surveillance mechanisms in the colon mucosa. Another potential tumor-promoting mechanism resides in the pattern of bile acid secretion. Unconjugated deoxycolic acids are able to stimulate the transformation and proliferation of colorectal cells *in vitro*, and it has been shown that in the general population subjects with higher levels of serum and intracolonic unconjugated deoxycolic acids are at increased risk of developing colorectal cancer (339). Patients with acromegaly harbor increased serum and intracolonic levels of secondary bile acids, especially if affected with colorectal cancer, and the coexistence of this event with a greater colon/sigmoid loop length and an increased colonic transit has been suggested to enhance the susceptibility to the development of colon tumors in acromegaly (340, 341).

The issue of whether acromegaly enhances the risk of colorectal cancer has attracted great attention, thus generating a heated debate. Cancers arising in the digestive tract constitute nearly 27% of all tumors developing in acromegaly, 18% of them being due to colorectal carcinomas (Table 5). The relative importance of esophageal and gastric cancers has been delineated in the study by Pines *et al.* (297) reporting a 7-fold higher risk of gastric cancer in their patient population. Upper digestive cancers constituted 60% of all gastrointestinal malignancies reported by Ron *et al.* (299), and the standard incidence ratios for esophagus, stomach, and small intestine cancers were 3.1, 2.5, and 6.2, respectively. As previously discussed in *Section IV.A*, however, many of the conclusions drawn by this study constitute a matter of concern. Remarkably, other studies failed to demonstrate similar data (10, 12, 342, 343). On the other hand, the past two decades have provided overwhelming evidence that acromegaly especially stimulates the development of colon adenomatous polyps. Colon adenomas are regarded as benign glandular dysplastic lesions carrying a high cellular proliferation rate, enlarged and hyperchromatic nuclei, and reduced cytoplasmic mucin (344). The cellular architecture identifies tubular, villous, or tubulovillous adenomas, with tubular and tubulovillous being the predominant types found in acromegaly. The existence of similarities between colon adenomas and carcinomas indicates a temporal link between these lesions; minute carcinomas are adenomatous in origin; adenomas and carcinomas share homologies in morphology, clonality, genetic mutations, and chromosomal deletions; familial adenomatous polyposis predisposes to colon cancer; adenomas and carcinomas often arise from the same area; and adenomas may swap into cancer within 10–15 yr of their onset (344). Mutation in tumor suppressor genes, such as adenomatous polyposis coli and p53, DDC (deleted in colon cancer), and DNA mismatch repair genes have been additionally isolated in colon adenomas and carcinomas (345). Very recently, a reduced expression of peroxisome proliferator-activated receptor-γ was found in the colonic mucosa of patients with active acromegaly (346); the expression of peroxisome proliferator-activated receptor-γ was inversely correlated with IGF-I levels, suggesting a direct role of this factor in the increased prevalence of colonic polyps. As in the general population, colon adenomas identify individuals at increased risk for colorectal cancer in patients with acromegaly. The first demonstration of an increased occurrence of premalignant colon polyps in acromegaly was provided almost two decades ago by Klein *et al.* (295), documenting nearly a 30% prevalence of colon adenomatous polyps in a prospective colonoscopy analysis in 17 patients with acromegaly. By retrospective review of this patient group as well as charts from 26 further patients, a total of four colon cancers were accounted (295). Several reports that followed have provided evidence that acromegalic patients are more prone to develop colon adenomas; on average, 24% of patients screened for colon disorders harbor colon adenomas (19). This estimate is representative of rates fluctuating between 9 and 38% across different studies, a wide range that may reflect dissimilarities in the selection of patients and/or controls, as well as in the gender prevalence, age, and adequate colon visualization. Terzolo *et al.* (347) studied 113 patients with acromegaly and compared colonoscopic results to those obtained in a control population undergoing colonoscopy because of hematochezia. Patients with acromegaly exhibited a greater prevalence of colon

adenomas (38% *vs.* 14%; $P < 0.001$), hyperplastic polyps (26% *vs.* 10%; $P < 0.001$), as well as multiple adenomas (57% *vs.* 29%). The difference between the two groups remained significant at ages below 50 yr (46% *vs.* 7% of controls; $P < 0.001$). GH/IGF-I levels as well as activity or duration of acromegaly appeared not to play any role in colonoscopic findings. Similar results were obtained by Delhougne *et al.* (348), recording a greater prevalence of adenomatous (22.3% *vs.* 8%; $P < 0.01$) and hyperplastic polyps (24.3% *vs.* 4.4%; $P < 0.001$) in acromegaly than in their control group. Like Terzolo's study, the finding of a higher prevalence of polyps in patients under the age of 55 yr (20% *vs.* 3% of controls) appeared to suggest an anticipated occurrence of adenomas in acromegaly, although both the duration and the activity of acromegaly did not influence the prevalence observed (348). In the Jenkins' series (349), tubulovillous adenomas were detected in 34 patients (29%), 53% of whom had multiple adenomas. Expectedly, aging predicted the occurrence of colon adenomas, because the proportion of patients with one or more adenomas increased with each decade, so that 39% of patients aged over 70 yr harbored at least one adenoma. Compared with a screening study on left-sided adenomas in asymptomatic subjects, the prevalence of left-sided adenomas reported by Jenkins *et al.* (349) was significantly higher in acromegalic patients at ages above 49 yr, providing an odds ratio of 4.2. A study performed by our group (338) located two thirds of adenomas in the proximal colon; the prevalence (22% *vs.* 5.7%; $P < 0.01$), synchronicity, and dysplasia of adenomas was significantly greater in acromegaly than in the control group, although the number of polyps was unrelated to disease duration and GH/IGF-I levels. The selection of our control group included subjects referred to colonoscopy because of irritable bowel syndrome. As in the studies of others in which control subjects were subjected to colonoscopy because of various bowel disturbances, the absence of a perfectly matched healthy population in our study may constitute a significant caveat in the interpretation of results. At variance with previous studies, the prevalence of colon adenomas reported by Renehan *et al.* (335) in their series of 115 patients recruited from two different centers was strikingly lower than in previous reports. The observed prevalence summed up to 9.5% and increased proportionately with patients' age; no adenoma was diagnosed under 40 yr (17 patients), whereas progressively increasing rates of 8, 12, 20, and 21% were recorded for decades of 40–49, 50–59, 60–69 and more than 70 yr. Five of 11 patients with adenomas (45% of this subgroup) had multiple polyps, whereas 18 subjects (16% of the whole series) had hyperplastic polyps. Interestingly, the significance of these findings was tested against a binary control model: eight autopsy studies encompassing 3559 exams of bowels from noncancerous patients, and four colonoscopy screening studies performed on 810 asymptomatic subjects with no family history of colorectal cancer (335). Such a comparison failed to demonstrate differences in adenoma prevalence between these control models and acromegaly, where adenomas exhibited a less advanced degree of dysplasia than in the control models. Of note, acromegalic patients with neoplasia were, on average, 10 yr older and had received colonoscopy 4 yr later than patients without neoplasia. Nevertheless, it has been noted that the observed 20% prevalence of adenomas reported by Renehan *et al.* (335) in patients older than 50 yr is similar to the rates reported in previous studies and outnumbers the generally accepted control prevalence of 9% (24). On the basis of the above-mentioned studies, indication emerges that acromegaly increases the risk of developing colon adenomas after the age of 50 yr and that colon adenomas developing in acromegaly share several clinical-pathological features: 1) although adenomatous polyps may virtually arise from any colon site, the involvement of ascending colon in acromegaly is variably predominant and is estimated to account for 5% (343), 21% (338, 349), 25% (347), 35% (348), 45% (350), and 68% (335) of cases; 2) polyp size is usually larger in acromegaly than in controls from a normal population: 3–15 mm *vs.* 4–10 mm (mean, 9 mm *vs.* 6 mm) in the study by Vasen *et al.* (350) and 7–28 mm *vs.* 5–14 mm (mean, 18.4 mm *vs.* 9 mm) in the study published by our group (338); in line with these observations, Jenkins *et al.* (349) reported evidence of polyps ranging from 5 to 35 mm in their series, whereas Renehan *et al.* (335) indicated a significantly higher prevalence ($P < 0.01$) of adenomas sized greater than 10 mm in acromegaly compared with control models; 3) colon adenomas in acromegaly occur more frequently after the age of 50 yr, and they predominate in males, in patients with disease duration longer than 5 yr, in those with three or more skin tags, as well as in the case of a family history of colon polyps; 4) conversely, disease activity, GH and IGF-I levels, years of exposure to high GH and IGF-I levels as well as familiarity for colon cancer do not predict the occurrence of colon adenomas (Table 5) (295–297, 335, 342, 343, 347–354).

The issue of whether the enhanced frequency of premalignant colon lesions implies a higher prevalence of colon cancers is, however, still a matter of debate, due to divergent conclusions reached in diverse epidemiology studies. The findings of a high cancer mortality in acromegaly reported in the retrospective studies published by Wright *et al.* in 1970 (12) and Alexander *et al.* in 1980 (8) were instrumental in the publication of four retrospective/prospective studies between 1982 and 1990, reporting 11 cases of colon cancer among 156 acromegalic patients (295–297, 352). This association was later supported by the findings of Ron *et al.* (299) of a 3-fold higher incidence of colon cancers in acromegalic men compared with in-hospital nonacromegalic patients. Despite its caveats, this latter study convinced many researchers of an enhanced colon cancer risk in acromegaly, thus endorsing further prospective research. Prospective series of colonoscopy screening studies in patients with acromegaly have revealed 25 cases of cancer out of 681 examinations (24), and colorectal cancers have been calculated to affect 2.5% to 3.7% of acromegalic patients (19, 24). In their series, Jenkins *et al.* (349) found six cases of colon adenocarcinomas in 129 patients, yielding a 5% prevalence in the group as a whole. Carcinomas were diagnosed at an average age of 66 yr and did not show any colon site preference, with two cancers located at the caecum, one at the splenic flexure, and the remaining three at the rectosigmoid area. None of the patients fulfilled criteria for either hereditary nonpolyposis colonic rectal cancer or familial adenomatous polyposis. By comparing multiple control models, the authors recorded a 13.5-fold greater prevalence of colon cancer compared with

a published series of 621 asymptomatic subjects and a rate 92.6-fold higher than age-matched Southeast England incidence rates (349). Such findings have been subsequently extended by the observation of four additional malignancies in a total of 155 patients, giving a combined prevalence of 6.5%. The results achieved in our concomitant prospective study (338) were somewhat in line with Jenkins' findings. Our observed prevalence rate of colon cancer in acromegaly was not significantly greater (2% *vs.* 1.2%) than that in our control population of subjects with irritable bowel syndrome (338), although another patient was diagnosed with a caecum adenocarcinoma soon after the publication of our study. More intriguing observations originated, however, from Renehan's study (335), which found three cases of colon cancer in 115 acromegalic patients, giving an overall prevalence of 2.6%. This rate proved to be similar to that recorded in autopsy (2.3%) and *in vivo* screening (0.9%) control models. Although adenomas tended to be right-sided, all neoplasms were detected in the recto-sigmoid area. Of note, two of three patients with carcinoma were 79 and 81 yr old, an age significantly older than the average age of 66 yr recorded in neoplastic patients by Jenkins *et al.* (349). On the basis of their findings, Renehan *et al.* (351) have indicated that acromegaly does not enhance the risk of colon malignancy and have thus questioned the policy of an aggressive diagnostic approach for colon disorders in acromegaly (Fig. 12). However, the control models used in this study by Renehan *et al.* have drawn a number of criticisms. Autopsy bowel examinations involve optimized visualization conditions, *i.e.*, detailed and magnified visualization of uncontaminated tissues, a circumstance that allows detection and excision of even minute lesions. Conversely, colonoscopy is associated with a significant miss rate for polyps sized less than 1 cm (355), and vigorous bowel preparation is additionally required in patients with acromegaly to compensate for the increased colon length (335). It is also significant that the control colonoscopy studies used in Renehan's study showed a nearly 3-fold greater prevalence of males, which may have overestimated the general cancer prevalence because colon adenomas/cancers are more frequent in males. A series of colonoscopy screening programs including nearly

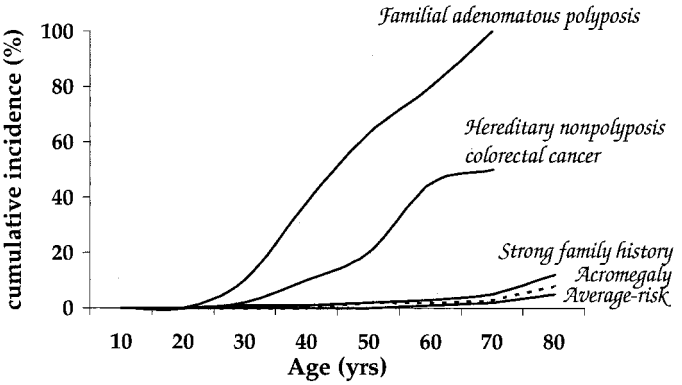

FIG. 12. Cumulative incidence of colorectal cancer by age in groups with hereditary predisposition and acromegaly compared with the general population. [Adapted from A. G. Renehan *et al.*: *Clin Endocrinol (Oxf)* 55:731–733, 2001 (351). Permission granted by Blackwell Science.]

6,000 asymptomatic subjects have reported colon cancer prevalence rates between 0.3 and 0.4% (356, 357) and 0.9% (358), but this latter study was biased by a tendency to select male subjects exposed to colon disorders and with a family history of colon cancer. Taking these circumstances into account, Renehan's results may be partly viewed in support of a positive association between acromegaly and colon cancer risk. In a recent retrospective study, Baris *et al.* (359) have collected 1634 cases of acromegaly in Sweden and Denmark and documented a value of SIR of digestive cancers 2.1-fold greater than in the control population. The incidence rate of colon and rectal cancers was 2.6- and 2.5-fold higher than normal, respectively, but risks were also enhanced for cancers of the brain, thyroid, kidney, and bones (standardized incidence rates equal to 2.7, 3.7, 3.2, and 13.8%, respectively). Another relevant issue is constituted by the influence of age and disease activity on colon cancer risk. Most prospective studies have indicated that colon carcinomas arise especially after the age of 50 yr, but up to one third of reported cancers have been diagnosed before age 55 yr (247, 296–298, 300, 301, 335, 352, 354). As noted by Atkin (360), colon cancer risk is highest just before the diagnosis of acromegaly, suggesting that the risk may increase in untreated disease. The Orme *et al.* study (18) showed that acromegaly quasi-significantly increased the incidence rates of colon cancer ($P > 0.06$ at one-sided Poisson probability). The finding of a 2.5-fold greater colon cancer mortality was speculatively attributed to the finding of higher posttreatment values of GH in patients with cancer (18). Consistent with this interpretation, colon cancer mortality was increased by three times in case of posttreatment GH levels between 2.5 and 9.9 μg/liter and by nearly five times for GH levels above 10 μg/liter. Renehan *et al.* (335) reported a nonsignificant increase in the prevalence of colonic lesions between active and inactive patients (18% *vs.* 6%), but they did not find any association between IGF-I or IGFBP-3 and the presence of adenomatous polyps. These findings would be in agreement with the observation that persistent elevation of GH/IGF-I levels increases the residual risk of developing colon tumors in the short term, as indicated in a follow-up study performed by Jenkins *et al.* (361). The authors recorded a recurrence of colon polyps in 14% of patients examined within 3–36 months after initial colonoscopy, and IGF-I was used as a surrogate to predict tumor recurrence rate: in fact, the relative risk of a new adenoma increased to 10.3 in case of elevated IGF-I levels (Fig. 13) (361). Colonoscopy studies have also provided information that carcinomas developing in acromegaly can potentially arise from any colon site and that patients can be asymptomatic for years; therefore, the finding of different degrees of colon wall infiltration, reportedly ranging from Dukes stage A through D at diagnosis, is not surprising (296, 335, 347, 354), although disseminated cancers are definitely rare (296, 352). Significantly, no information exists at the moment on clinical evolution and chemotherapeutic responsiveness of colon cancers in acromegaly.

Another unresolved issue is the screening age and, hence, the screening intervals in which patients should undergo colonoscopy. In the asymptomatic general population, colonoscopy at age 55, followed by adenoma excision, reduces the colon cancer risk (362, 363). The recurrence rate of

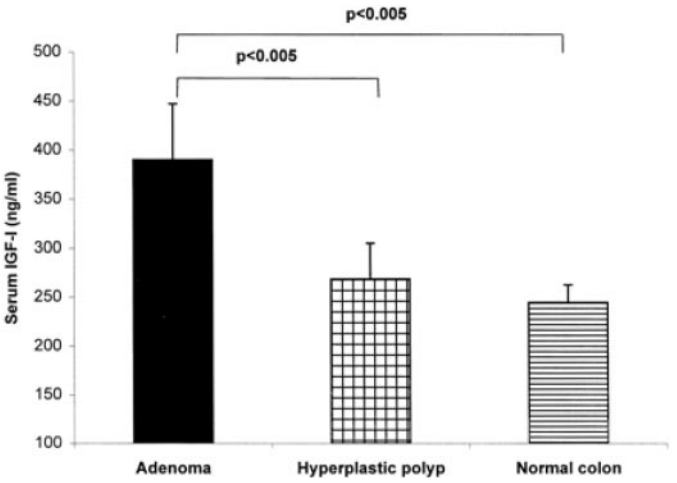

FIG. 13. The mean (±SEM) serum IGF-I at the second colonoscopy in 66 patients with acromegaly with colorectal adenomas, hyperplastic polyps, or normal colon. [From P. J. Jenkins *et al.*: *J Clin Endocrinol Metab* 85:3218–3221, 2000 (361). Permission granted by The Endocrine Society.]

adenomas is 37%, and the occurrence of newly diagnosed adenomas is 19% within 1–5 yr after the first exam (364). Patients with large and/or multiple adenomas at baseline screening colonoscopy are at a 2.6- to 4.5-fold risk for recurrence of adenomas (364). Compared with controls, the risk of developing adenomatous polyps in acromegaly is usually enhanced, anticipated, more frequently synchronous, and of larger size. Consistent with this evidence, Jenkins *et al.* (349) found it prudent to perform full-length colonoscopy at age 40 yr and, later, every 3 yr in case of adenoma/cancer or elevated IGF-I levels; if the first colonoscopy is negative, a 5-yr interval should be sufficient. However, Renehan *et al.* (351) indicated that patients with acromegaly are only exposed to a moderate risk of developing colon tumors and should be examined therefore according to the screening criteria approved for patients with hereditary polyposis syndromes (at very high risk), those with family history of colon cancer (at high risk), and the normal population (Fig. 12). These authors additionally calculated that 556 colonoscopy exams would be needed over a 10-yr period to prevent one colorectal cancer death. On these bases, they suggested that the first colonoscopy should be performed around age 50 yr (351). In her "independent view" report, Atkin (360) considered that a 2.5- to 3-fold increased risk of colorectal cancer strongly suggests that patients might benefit from a single sigmoidoscopy or colonoscopy at around age 55 yr. In our practice, we advise patients to undergo full-length colonoscopy at age 50 yr, independent of activity/duration of acromegaly as well as family history of colon disease, unless symptoms of bowel disorders occur earlier. Prerequisites for adequate colonoscopy are an accurate bowel preparation with efficacious enema, as well as examination being performed by an experienced operator, to overcome the enhanced difficulty that this type of exam implies in acromegaly. In case of colon cancer, patients should undergo exams yearly for the first 3 yr after surgical removal and then every third year. We also suggest performing colonoscopy every 3 yr when patients have been found with adenomas at first visit, especially if synchronous or larger than 10 mm, or if patients are scarcely responsive or resistant to acromegaly treatments. Conversely, we choose a 5-yr colonoscopy program if patients are negative for colon polyps.

D. Neck and lung tumors

1. Thyroid tumors. GH and IGF-I excess causes thyroid overgrowth, which is usually considered one typical aspect of the visceromegaly developing in acromegaly. Experimental work has demonstrated not only that IGF-I increases proliferation of porcine thyroid cells and FRTL-5 rat thyroid cells, but also that it potentiates TSH-mediated thyroid cell proliferation (365). Indirect evidence of a positive role for GH and IGF-I in thyroid growth is based on the antiproliferative effect exerted by hypophysectomy on TSH-mediated thyroid growth in rats (366) and, oppositely, by the stimulatory action elicited by incubation of FRTL-5 cells with serum from acromegalic patients (367). The existence of a local IGF-I-mediated autocrine loop is suggested by the detection of IGF-I production in follicular thyroid cells (368), papillary cell lines (369), and surgical thyroid specimens in which IGF-I synthesis is greater in tumoral than in normal tissue (370). Affinity cross-linking studies have shown the presence of IGF-I receptor in follicular and papillary cancer cells, as well as in tumoral tissue specimens.

Although benign thyroid overgrowth is a common phenomenon in acromegaly, the occurrence of thyroid tumors constitutes a relatively rare event in this condition (Table 5). Neck palpation and ultrasonography reveal goiter in 25–92% of cases, independent of TSH levels, whereas a positive relationship between GH/IGF-I levels and thyroid volume has been debatably documented (371–375). Multinodular goiter is detected in 65% of patients, and the chance of developing thyroid nodules increases with increasing disease duration (371, 374). Nodular goiter is toxic in 14% of patients (375), but the prevalence of hyperthyroidism reportedly ranges between 3.5 and 26% in unselected patients from different investigations (9, 136, 372, 375). In a study performed by our group, seven of eight patients who developed thyrotoxicosis were undergoing octreotide treatment at the time of onset of the disease (136). Unlike the general population, the influence of gender on the prevalence in thyroid disorders is seemingly null in acromegaly (375). Thyroid nodules are usually benign. At histology, colloidal, hyperplastic, or adenomatous aspects of thyroid tissue have been described (9, 295). In the study by Gasperi *et al.* (375) thyroid biopsy was performed in seven cases and showed histological patterns of microfollicular architecture (n = 2), Hurthle cells (n = 2), cellular dysplasia (n = 2), and papillary thyroid carcinoma in one patient, whereas two others were found to harbor papillary thyroid cancers. Overall, thyroid cancers constitute 3.1% of malignant events in acromegaly (9, 10, 297, 298, 376); the incidence of this cancer significantly increased by 3.3%-fold only in the study by Baris *et al.* (359). Thyroid tumors are predominantly papillary and occasionally aggressive, as confirmed by the rare occurrence of multifocal tumors (377) and by low mortality rates (9, 297, 298). The studies reviewed and our experience indicate that acromegaly enhances the risk of developing goiter, although the prevalence of thyroid can-

cers is not different from normal. Thyroid enlargement seems to occur independently of endemic, nutritional, and hereditary factors, but it is reportedly associated with aging, years of exposure to GH/IGF-I hypersecretion, as well as IGF-I levels. In the setting of a multinodular goiter, prudence should be used when starting thyroid suppressive therapy with L-T_4 due to an apparently enhanced risk of thyrotoxicosis. Because the rate of benign and malignant thyroid tumors appears to be similar to that recorded in the general population, acromegalic patients should undergo standard periodical examinations of thyroid morphology and function.

2. Lung tumors. The relationship between lung cancers and the IGF system has been suggested by experimental studies, demonstrating that IGF-IR expression occurs in small cell lung cancer (SCLC) and non-SCLC, as well as in normal and tumoral lung tissue (313). Autocrine IGF-I synthesis has been detected in lung cancer specimens and SCLC lines (378). IGI-I/IGF-IR stimulation and IGF-IR overexpression cause lung cancer cell proliferation and increase the metastatic activity of lung cancer cells; conversely, tumor growth progression is abolished by blockade of IGF-IR by αIR3 antibody (379, 380). An ongoing hospital-based case-control study detected a dose-dependent association between circulating IGF-I levels and lung cancer risk (odds ratio, 2.06) and a negative association with IGFBP-3 levels (381). The relationship between acromegaly and lung tumors emerged in the study of Mustacchi and Shimkin (294), where three cases of lung cancer were mentioned. In the study published by Wright *et al.* in 1970 (12), lung cancer mortality accounted for three of 10 cancer deaths. Similar records were obtained by Nabarro (9) and Bengtsson *et al.* (10), each reporting two deaths from this malignancy. In the general population, lung cancer affects the male gender more frequently, and the finding of 22 bronchial and seven oropharyngeal tumors in the Ron *et al*. study (299) on acromegalic men is, therefore, not surprising. These authors failed to record any significant difference in the lung cancer prevalence compared with nonacromegalic hospital controls. Similar observations were reported in the study by Orme *et al.* (18) in which both the incidence and the mortality from lung cancer were even lower than the expected rates.

E. Tumors of the reproductive system

1. Breast and female reproductive system. There is a tight link between the growth regulatory pathways of IGFs, and estrogen-receptor positive breast cancer cells in an *in vivo* study suggest a role of IGF-I and IGF-IR in breast cancer development (383). The relevance of GH/IGF-I involvement in breast tumors emerged in studies where extracted GH given chronically to female rats induced breast tumors over the long term (303). Mammary tissue expresses both GH-R and PRL-R, but only human GH is able to activate either receptor in primates and nonprimates, whereas nonprimate GH acts only through the GH-R and PRL acts only through the PRL-R (382). In mutant lit/lit mice carrying a mutation of the GHRH receptor, which thus blunts GH secretion, the growth of mammary tumor transplants is dramatically reduced (305), whereas mice transgenic for human GH were shown to develop pregnancy-independent metastatic mammary tumors through activation of the PRL-R (307). Experiments in other mammals appear to suggest that this tumor-promoting effect may be species-related. In fact, a 7-wk treatment with GH and/or IGF-I in rhesus monkeys caused the nontumoral proliferation of both stromal and epithelial mammary cells (384). Interestingly, GH-treated animals showed a greater rate of mammary lobule number and size than IGF-I-treated counterparts, suggesting a direct GH effect additional to that mediated by IGF-I. In humans, the GH-R is expressed in mammary tumors and cell lines, and although the expression of GH-R and PRL-R is primarily localized in epithelial cells, some expression is also evident in stromal cells (385). The additional finding of GH and PRL protein expression in mammary tumors as well as normal tissue appears to suggest a possible autocrine/paracrine role of these hormones on tumor development and growth (382). In line with this hypothesis, studies in MCF-7 mammary cancer cell lines have shown that blockade of GH-R by the specific GH-antagonist B2036 was capable of abrogating tyrosine phosphorylation of JAK2, cellular proliferation, and apoptosis mediated by autocrine GH (309). Similarly, the relevance of the IGF system in breast cancer has been suggested by studies demonstrating the existence of a polarized IGF-I/IGF-IR loop, where stromal cells can stimulate epithelial cells to grow via paracrine mechanisms. IGF-I is secreted in the conditioned medium of human breast cancer cell lines (386), whereas Rnase protection assays and *in situ* hybridization studies have identified the stromal tissue of breast cancer specimens as the source of IGF-I (387, 388). As in other cancer cell lines, exogenous addition of IGF-I to breast cancer cells promotes cell proliferation, and this effect can be prevented by stimulation with anti-IGF-IR antibody αIR3 (389). Conversely, IGF-IR mRNA is expressed on the surface of primary cultures of malignant breast epithelial cells (390) as well as in several estrogen-dependent and, at lower amounts, in estrogen-independent cell lines, where the expression of IGF-IR is positively correlated with that of estrogen (ER), progesterone (PR), and PRL receptors (391). The correlation between IGF-IR expression and the ER status in breast cancer specimens has been further confirmed in studies in which IGF-IR expression was significantly higher in specimens from ER/PR positive tumors at lower degree of risk than in ER/PR negative tumor at higher risk, thus suggesting a predictive role for IGF-IR as a good prognostic factor (392). From a clinical perspective, sex steroids can modulate the GH/IGF-I axis at many levels, including pituitary GH secretion, secretion of liver IGF-I as well as production of IGFBPs, which is ultimately reflected in IGF-I clearance rate (312). No consensus estrogen-responsive element has been identified in IGF-I promoters, but studies in chicken IGF-I gene P1 promoter have identified the AP-1 enhancer as a mediator of estrogen responsiveness, whereas time- and dose-dependent induction of IGF-I gene expression by estradiol treatment has been observed in human fetal osteoblasts (316). Because the concentrations of ovarian steroids are higher in the premenopausal stage, a greater effect of estrogen steroids on IGF-I levels may explain the results of studies exploring the relationship between IGF-I levels and breast cancer risk in pre-

menopausal women. As discussed above, breast cancer risk developing in premenopausal women has been suggested to be directly related to serum IGF-I and inversely related to serum IGFBP-3. Hankinson *et al.* (51) found that stratification of breast cancer-bearing patients by progressively increasing tertiles of IGF-I levels allowed them to identify a 2.6-fold greater risk of breast cancer in the group with the highest IGF-I levels; in premenopausal women less than 50 yr old, high IGF-I tertiles alone predicted a 4.6-fold higher risk and, in combination with low IGFBP-3, a 7.3-fold higher risk than in unaffected women. On the other hand, analysis of reports on breast cancers in acromegaly reveals an average prevalence of 1.7% for this type of tumor. As a whole, breast cancers represent 13% of all malignancies developing in acromegaly and cause nearly 11% of cancer-related deaths in acromegaly (Table 5). Despite these figures, reports focusing on mammary tumors are predominantly epidemiological and fail to provide an accurate insight into the problem. Nabarro's findings (9) attracted attention on a 4-fold higher incidence of breast cancer in acromegalic women, although the strong association between acromegaly and breast cancer was in apparent conflict with the low mortality from breast cancer observed in this study. Conversely, Orme *et al.* (18) did not find any increase in either the incidence or mortality from mammary tumors compared with the general rates, although the mortality from breast cancer was 60% higher than in normal women and increased by 3-fold in the case of post-treatment GH values above 10 μg/liter. Several studies have noted that a short interval (on average, 5 yr) generally separates the diagnosis of acromegaly from that of breast cancer, thus suggesting that risk may increase in the short term and/or in the presence of untreated disease (298, 301).

On the other hand, only a few reports have been published on the occurrence of cancers at the level of the female reproductive system, thus suggesting indirectly that uterine and ovarian tumors are much less common. Remarkably, a significant increase in the occurrence of uterine leiomyomata has been documented in nearly 80% of women in a small study (393). Oppositely, ovarian and uterine carcinomas are rare (Table 5); indirect evidence exists that uterine cancers may develop earlier in life and with shorter disease duration than ovarian carcinomas (9, 295, 298, 301, 352).

2. Prostate and the male reproductive system. As in breast tumors, the link between IGF-I and prostate tumorigenesis has experimental and clinical bases. Both normal and tumoral prostate cells express negligible amounts of IGF-I mRNA, which is increased in prostate tumors from transgenic adenocarcinoma of mouse prostate models, in which the severity of cancer progression seems to be directly correlated with IGF-I expression (394, 395). PC-3, DU-45, and LNCaP cancer cell lines do not produce IGF-I, whereas the elevated expression of IGF-IR mRNA constitutes a prerequisite for IGF-I to stimulate proliferation in these prostate cancer cell lines, which is, as a consequence, abrogated by transfection with antisense oligonucleotides complementary to IGF-IR mRNA (for review, see Refs. 313, 396, and 397). Conversely, the loss in IGF-IR mRNA expression documented in tumors from castrated transgenic adenocarcinoma of mouse prostate mice has been interpreted as a mechanism leading to dedifferentiation and greater tumorigenicity. Androgen sensitivity may similarly drive the proliferative response under IGF-I stimulation. In androgen-independent prostate cancer cells, such as PC-3 and DU-45, IGF-I causes cell proliferation regardless of the presence of androgens in culture media, whereas cultures of androgen-dependent cells, such as LNCaP, become responsive to IGF-I only in the presence of dihydrotestosterone (396). Transfection of rat PA-III prostate adenocarcinoma cells with an IGF-IR antisense construct reduced IGF-I mRNA levels in these cells, whereas injection with transfected PA-III cells induced tumors that were approximately 90% smaller than controls (398). One relevant phenomenon, which may explain some of the prostate alterations seen in acromegaly, is constituted by the observation that stromal cells derived from benign prostatic hyperplasia express IGF-IR mRNA and that IGF-I stimulation increases stromal cell density by 80%, an effect that is abrogated by coincubation with the IGF-IR-neutralizing antibody α IR3 (399). In humans, serum IGF-I levels appear to predict both risk and growth rate of prostate cancers, and the aforementioned study by Chan *et al.* (50) attributed to IGF-I the role of predictor of prostate cancer. In a subsequent nested case-control study on 530 patients with prostate cancer, IGF-I and IGFBP-3 levels appeared to predict the progression of advanced-stage prostate cancers, the relative risks being 5.1 for the highest *vs.* the lowest IGF-I quartiles and 0.2 for the highest *vs.* the lowest IGFBP-3 quartiles; combination of high IGF-I and low IGFBP-3 increased the relative risk to 9.5, whereas the combination of IGF-I and IGFBP-3 with values of prostate-specific antigen (PSA) increased the specificity from 91 to 93% but decreased sensitivity from 40 to 36% (400). The role of PSA remains, however, significantly more predictive than IGF-I in men with prostate cancers and elevated levels of PSA; the analysis of ratios of IGF-I, IGFBP-3, and free and total PSA does not seem to further improve the accuracy of PSA measurements alone (401, 402).

Acromegaly predisposes to benign prostate hypertrophy, the condition of stromal proliferation of the prostate. A pilot transrectal ultrasonography study revealed a marked increase of prostate volume and of the transitional zone in untreated acromegalic males, regardless of gonadal status and age of patients (403). In fact, all patients screened by transrectal ultrasonography study were found to be hypogonadal and were aged below 40 yr. In a larger series, including patients with active or cured acromegaly and postsurgical hypopituitarism, benign prostate enlargement (that is, volume exceeding 30 ml by ellipsoidal formula) occurred in 80% of active patients, 30% of cured acromegalic patients, none of the GH-deficient patients, and 26% of controls (404). At multiple regression analysis, prostate volume correlated significantly more with disease duration than with patients' age. Additional findings were represented by the development of calcifications in 61%, cysts in 26%, vesicle inflammation in 8%, and biopsy-proven benign nodules in 13% of acromegalic patients (404). On the other hand, and at variance with the indication that IGF-I links to prostate cancer risk in the normal population, acromegalic patients harbor a decreased risk of prostate cancers. This inference emerges mostly from epidemiology studies in which the number of prostate cancers constitutes a minority of malignancies and are signifi-

cantly less prevalent that in the normal population (Table 5). In 1970, Campbell and Harrison suggested that acromegaly did not predispose to prostate enlargement (405), and Krawitt's description, 3 yr later, of a 75-yr-old acromegalic man deceased after unsuccessful removal of a giant invasive prostate cancer remains anecdotal (406). In the largest study published on acromegalic men, 15 tumors arising from the genitourinary tract accounted for a 17% prevalence among all nonpituitary cancers, a rate nonsignificantly different from that recorded in the nonacromegalic control population enrolled in VA hospitals (299). Although unique among all epidemiology studies, however, the relevance of this observation is blunted by a pooled presentation of genitourinary tumors. Intriguingly, the absence of prostate cancers in any of the patients screened in our studies constitutes a relevant caveat in the theory linking IGF-I levels to prostate cancer in the general population. In this regard, Cohen *et al.* (407) have indicated a series of hypotheses to explain the observed relationship between IGF-I and prostate/breast cancer risk that are worth considering: 1) the observation may have originated from an ascertainment bias or a methodological error; 2) other cancer-controlling factors, such as nutrition, may have modulated IGF-I concentrations, which then act as a confounding factor rather than as cause of cancer; 3) tumors may work as a source of IGF-I, which can thus be considered as a tumor marker; 4) it is possible that autocrine IGF-I production is involved in the pathogenesis of a number of tumors, including those linked to increased circulating IGF-I levels; and 5) it is possible that IGF-I elevation reflects GH action on some types of cancer. It is interesting to note, however, that acromegaly also increases liver synthesis of IGFBP-3, which has shown IGF-independent proapoptotic and antitumoral effects at the local level, as discussed above. Although IGFBP-3 levels appear to predict a less aggressive behavior of breast, prostate, and colon cancers (50–52), it has been shown that a number of tumors are associated with increased IGFBP-3 proteolysis in the serum (49), which normally acts to release IGF-I locally. Because PSA also functions as a major IGFBP-3 protease, thus serum PSA elevation in prostate cancer-bearing patients may indirectly promote free IGF-I release locally. This possible mechanism is not applicable in acromegaly where IGFBP-3 proteolysis is not increased; speculatively, this circumstance may even protect acromegalic patients against the development of prostate cancers. However, this issue awaits further clarification. Of note, the return of GH and IGF-I levels to normal has beneficial effects on the prostate in acromegaly. Two years of treatment with lanreotide, together with a GH, IGF-I, and IGFBP-3 level decrease, induced a decrease of prostate volume in 16 patients well controlled by the treatment (408). Prostate volume decreased after treatment only in the eight controlled patients younger than 50 yr, but not in those controlled with age above 50 yr, despite a similar decrease in GH, IGF-I, and IGFBP3 levels. Taken together, these data appear to indicate that chronic elevation of GH and IGF-I levels constitutes a proliferative stimulus for stromal cells of the prostate independent of the androgen status. Thus, prostate epithelial cells appear not to be targeted by GH/IGF-I excess, although more extensive follow-ups are necessary to fully understand this observation.

F. Other tumors

At the level of the genitourinary tract, GH excess affects renal function and kidney size and increases glomerular filtration rate and renal plasma flow in GH-deficient as well as normal adults. IGF-I is implicated in compensatory renal hypertrophy, whereas markedly elevated serum GH levels accelerate glomerular sclerosis in rodents. Measurement of absolute glomerular size using a semiautomatic image analyzer revealed heavier kidneys in acromegalic patients than in controls (409). Histological comparison between acromegalic patients and subjects with single kidneys showed more global glomerulosclerosis and segmental lesions in single kidneys, a finding that likely implies different mechanisms for the renal enlargement seen in acromegaly. Functionally, submaximal exercise induces abnormal increases in microalbuminuria in patients with acromegaly, although α1-microglobulinuria levels, a marker of renal tubular damage, were normal both at rest and at peak exercise (410). Unlike these disorders, kidney cancers play an irrelevant role in tumoral phenomena of acromegaly (Table 5). Similarly, scattered reports have been published on brain tumors (299), meningiomas (410), osseous tumors (294, 411), ocular melanocytic nevi and melanoma (412), skin epidermoid cancers or melanomas (294, 299), as well as adrenal tumors (10). Description of lymphohematopoietic neoplasms includes lymphoma, multiple myeloma, chronic myelogenic or lymphocytic leukemia, and polycythemia vera (9, 294, 298, 299, 301, 352, 413). Among 106 patients treated for over 15 yr, Au *et al.* (414) found two cases of acute lymphoblastic leukemia and one patient with acute myeloid leukemia. Two of these patients had received radiotherapy as part of their treatment. At variance with other reports, the incidence of leukemia adjusted for age and follow-up years was significantly higher in this cohort than in the general population (414). The occurrence of lymphopoietic tumors in the late course of acromegaly suggests, however, that these two conditions are likely unrelated.

VI. The Complications at the Skeletal System

A. Epidemiology

As already stated, the osteoarticular manifestations feature the disease; symptoms or signs referable to articular joint disorders occur in the great majority of patients with acromegaly at their diagnosis (415–417). The delay between the estimated onset of acromegaly and the appearance of joint disease is approximately 10 yr, but the range is wide and oscillates between 0 and 27.5 yr, according to the report by Detenbeck *et al.* (418). Early signs of joint involvement were also noted in patients with short disease duration (419). The duration of acromegaly does not seem to be correlated with the presence and/or the severity of arthropathy (415, 420, 421), although the patients with arthropathy included in the study of Bluestone *et al.* (420) had severe and long-standing acromegaly. Articular manifestations include articular involvement and enthesopathy and are a leading cause of morbidity and functional disability in these patients (418, 420, 422). Crepitus on clinical examination is the most com-

mon sign (416, 418, 420, 423), whereas pain is the most common symptom, usually intermittent and exacerbated by activity (420).

The acromegalic arthropathy affects both axial and peripheral sites. The appendicular skeleton is involved in up to 74% of patients with moderate-to-severe involvement in one third of cases (9, 418, 420); neck or back pain is also common, occurring in more than half the patients, but abnormalities could be detected in 20–25% of cases (417, 421). The knee is the most commonly involved peripheral joint, followed by the shoulder, hip, ankle, elbow, and joints of the hand (417, 418, 420). Joint stiffness and swelling are also common; in 1952 Kellgren *et al.* (416) reported joint swelling in 52% and effusions in 40%, whereas prevalence rates reported 20 yr later by Bluestone *et al.* (420) accounted for 21% and 5% of patients, respectively. Acromegalic arthropathy is generally noninflammatory (418, 423), although features of osteoarthritis frequently develop in later stages of the disease (416, 418, 420, 422–424). Sinovial aspirates showed that effusions are degenerative without evidence of inflammation or crystal deposition (416, 418, 420). As noted by Lieberman *et al.* (425), the occurrence of hypermobility (15–30% of cases) or limitation of joint movement (16–27% of cases) likely depends on disease duration. The unusual bone disease that is occasionally associated with acromegaly, the McCune-Albright syndrome, has not been considered in this paper for its peculiar bone aspects.

B. Pathogenesis

The pathogenesis of arthropathy is complex, involving both GH/IGF-I excess and secondary degenerative changes. Most *in vitro* studies have focused on the effect of GH and IGF-I in chondrocytes derived from the epiphysial growth plate, which is metabolically active and whose function and degree of differentiation follow a topographical organization (425). However, the chondrocytes in adult articular cartilage are consistently less active than their epiphysial plate counterparts. These cells are found alone or in pairs in isolated lacunae within the cartilage matrix and rarely divide (426). They maintain the extracellular matrix through degradation and replacement of collagen proteoglycans, glycosaminoglycans, and other macromolecules (426), but their ability to repair damaged cartilage is very limited (427). Of historical note, the lack of *in vitro* response of cartilage to GH was the cause leading Salmon and Daughaday (26) to propose the existence of a secondary mediator later named IGF-I. Subsequent studies in suspension chondrocytes cultures demonstrated that GH preferentially stimulated growth and differentiation of prechondrocytes from the resting cell layers and increased their sensitivity to IGF-I (428, 429). Like other cells, chondrocytes are able to synthesize and release IGF-I locally (430). GH is an important stimulus for chondrocytes IGF-I mRNA and peptide expression. Other cytokines, such as TGF-β, basic fibroblast growth factor, and insulin, also stimulate chondrocyte growth (425). IGF-I binds specifically to chondrocytes with a greater binding affinity for proliferative than for resting zone cells (431). IGF-I stimulates DNA synthesis, cell replication, proteoglycan and glycosaminoglycan synthesis in chondrocytes or explants from a variety of animals and under a variety of culture conditions (425). IGF-I is a relevant regulator of collagen synthesis, because it can reverse the abnormalities in collagen synthesis based on experimental models of ascorbate deficiency (432). The role of GH and IGF-I in bone metabolism parallels their effects on the articular cartilage. Stimulation of DNA synthesis and cell proliferation by GH depends on the degree of cell differentiation (433), but GH also stimulates production of alkaline phosphatase (433) and collagen (434). As in the cartilage, GH effects on osteoblasts are likely to be mediated through paracrine IGF-I production, although circulating IGF-I also influences osteoblast metabolism (435). Additional effects of IGF-I include increased mRNA levels of α_1(I)-procollagen (435, 436), increased noncollagen protein mRNA and peptide synthesis (435–437), inhibition of protein degradation (438), and increased bone production in organ culture (437). However, in analogy with other body tissues, IGF-I action on the bone comprises interactions among IGF-I, IGF-I receptors, and IGFBPs. At least four distinct IGFBPs (IGFBP-1, -2, -3, and -4) are produced by various bone cells in culture, and distinct studies have intriguingly suggested that IGFBP-3 may enhance (439), whereas IGFBP-4 may inhibit, IGF-I action (440). Additionally, many osteotrophic factors including PTH, TGF-β, platelet-derived growth factor, estrogens, and cortisol, contribute in regulating GH and IGF-I production by osteoblasts (425). Although this complex system still needs to be fully elucidated, it seems conceivable that IGF-I may act to integrate multiple trophic signals controlling bone metabolism.

Based on experimental evidence, the pathophysiology of the acromegalic arthropathy may be hypothesized. At the initial stage, GH excess stimulates local production of IGF-I in cartilage which, combined with increased levels of circulating IGF-I, results in replication and hyperfunction of articular chondrocytes and increased matrix synthesis. The cartilage begins to thicken, leading to widening of the joint space, alteration of the normal geometry of the joint, and hypermobility of joints (Fig. 14). At radiology, widening of the joint spaces and periarticular soft tissue hypertrophy can be documented. GH also stimulates connective cell hyperfunction, resulting in growth of periarticular structures; sinovial hypertrophy further exacerbates the abnormal mechanical loading of the joint. At this stage arthropathy may be reversed by control of GH and IGF-I hypersecretion (see *Section VI.C*). Along with disease progression, fissures develop onto the cartilage surface and gradually enlarge, whereas regenerative fibrocartilage proliferates disproportionately more than in osteoarthritis, presumably as a result of GH stimulation (425, 432). The regenerative fibrocartilage frequently becomes calcified, resulting in osteophyte formation. In more advanced cases, fissures may extend to the subchondral bone, widen, and become undercut, producing ulceration of the articular cartilage. The underlying bone shows accelerated turnover, eburnation, and subchondral cyst formation. Ultimately, the articular cartilage becomes thinned with narrowing of the joint space, a process that shares many features with osteoarthritis. At this stage, the acromegalic arthropathy cannot be any further improved by GH and IGF-I suppression (Fig. 14).

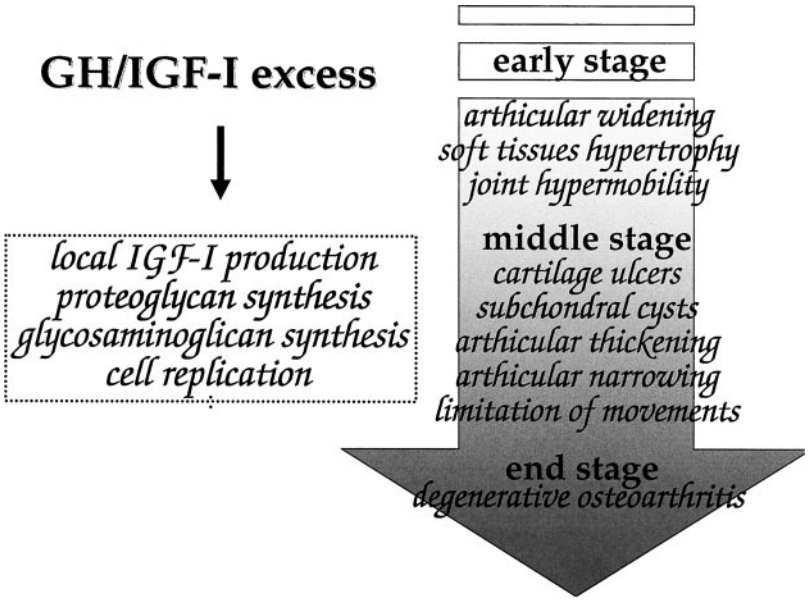

FIG. 14. Scheme of the potential progression of the acromegalic arthropathy during the different stages of the disease.

C. The acromegalic arthropathy

Arthropathy is the most frequent complaining symptom referred by patients with acromegaly at diagnosis, being the most frequent and severe cause of morbidity and inability in these patients. Radiological evidence of joint space widening occurs early, whereas long-standing disease is characterized by the narrowing of joint spaces, osteophytosis, and other features of osteoarthritis (425, 441). Radiographical changes in the peripheral joints are typically widespread. However, the presence of radiological abnormalities and clinical manifestations of arthropathy are not correlated, unless joints are severely affected, as in long-standing disease (425). In fact, joints of the hand are infrequently symptomatic but radiographic changes are found in more than 50% of patients (322). As already stated, changes include widened joint spaces, distal tufting of the phalanges (Fig. 15), osteophyte formation (especially of the base of the distal phalanges), enthesopathy (mineralization of ligamentous insertions) (Fig. 16), and calcification of the joint capsule (416–418, 420, 421). Eburnation and subchondral cyst formation, reflecting severe cartilage destruction, are less common. Abnormalities of radiograms at knees and hip are also found in more than 50% of patients; the knees show widening of the femorotibial and patellar joint spaces, osteophytosis, enthesopathy, capsular calcification, and occasionally chondrocalcinosis (415, 417, 418). In more severe cases, evidence of effusion, narrowing of joint space or angular deformity may occur (425). Joint space widening, osteophyte formation and enthesopathy are especially common in the hip and shoulder. Severe degenerative changes of the hip are less frequent and are frequently unilateral; this may occur in elderly patients with very long duration of exposure to high GH and IGF-I levels. In our series, five patients out of 45 aged above 60 yr (11%) had undergone surgical joint replacement at one femur head (our unpublished data). Detenbeck *et al.* (418) noted that cystic changes of the humeral head are a prominent feature. The spine also presents remarkable changes: widened intervertebral spaces, vertebral enlargement, and osteophyte formation, which are caused by endochondral, marginal, and subligamentous growth of vertebral bone (425). The lumbosacral region is very often affected, with symptoms occurring frequently in the cervical spine and rarely in the thoracic spine (417, 420, 421). The thoracic cage is also profoundly modified by GH and IGF-I excess as already mentioned (*Sections III.C* and *III.D*). Bluestone *et al.* (420) reported normal spinal mobility and increased total spine-plus-hip mobility for their patients compared with controls of a similar age. In a similar case-control study including 54 patients with acromegaly studied at diagnosis, we found that spinal mobility was reduced in 30 patients (55.6%) and 10 controls (18.5%; $P < 0.001$), whereas 39 patients (72.2%) and 16 controls (29.6%; $P < 0.0001$) complained of articular symptoms (pain and/or stiffness) attributable to spinal involvement; in particular, 27 patients (50%) and 10 controls (18.5%; $P < 0.0001$) suffered from frequent backache at the lumbosacral spine (our unpublished data). The presence of axial pain on objective examination was found in 32 patients (59.3%) and 15 controls (27.8%; $P = 0.002$). At radiographs, thoracic cage involvement was found in six patients (11.1%), alterations of the spinal profile were observed in 37 patients (68.5%) and in 15 controls (27.8%), and increased L2 vertebra diameters were observed in 34 patients (63%) and none of the controls (our unpublished data). The increased mobility was interpreted by Bluestone *et al.* (420) as being due to the thickening of intervertebral discs and lax paraspinal ligaments. Ossification of the anterior surface of the vertebral bodies is relatively common, and contributes to increasing their apparent anteroposterior diameter. In more severe cases, this ossification process can bridge the disc space resembling diffuse idiopathic skeletal hyperostosis (DISH) syndrome (420, 421, 442). DISH syndrome has been described in metabolic disorders such as diabetes mellitus, hyperinsulinemia, and gout (443, 444), but rarely in acromegaly (442). In our series, DISH features were recorded in 11 patients (20.4%) and none of the controls; we also found that DISH severity was correlated with basal and peak glucose levels after glucose load, sug-

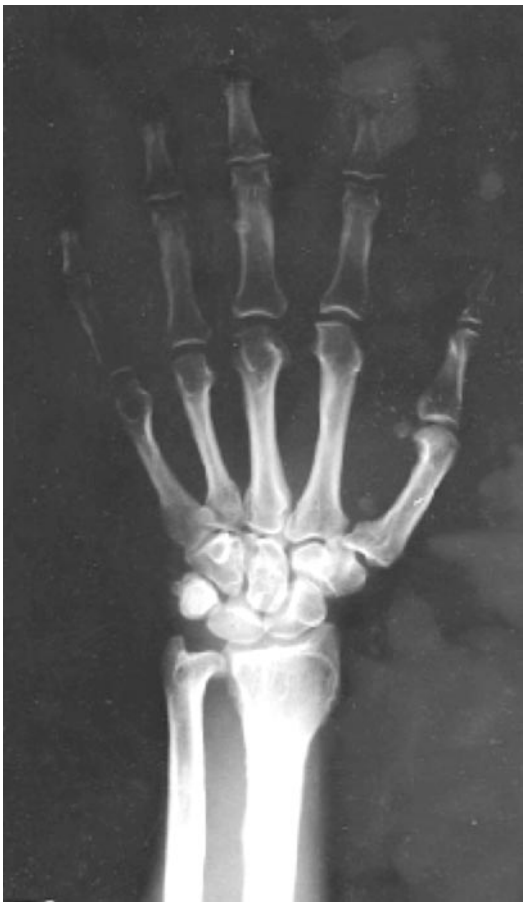

FIG. 15. Radiographic features of abnormalities of the hand and wrist in a female patient aged 48 yr with an estimated disease duration of 8–10 yr. At the hand, note at terminal phalanges the enlargement of tuft and bases. At metacarpophalangeal joints, it is worth noting the widening of some articular spaces, whereas at the proximal interphalangeal joints there is narrowing of others. Note the width of some proximal phalanges resembling the presence of "beak-like" osteophytes at the level of distal interphalangeal joints and at proximal interphalangeal joints. Periarticular calcific deposits are also present. At the wrist, note the enlargement of distal radius and ulna as well as at ulnar styloid. Lateral to the radius, some "beak-like" osteophytes can be appreciated.

gesting a close relationship between metabolic and bone complications (our unpublished data). Posterior scalloping of vertebral bodies is also frequently found, whereas facet joint hypertrophy is unusual (421). Periarticular soft tissue structures, such as joint capsules and tendons, especially in the presence of exudative processes, can be carefully investigated by ultrasonography. This technique revealed that the thickness of both weight-bearing (knees), and non-weight-bearing joints (shoulder and wrist) is significantly increased in patients with active acromegaly compared with controls (419). Joint thickness was found to be similarly increased in patients cured by surgery compared with controls (419), suggesting that even long-term normalization of GH and IGF-I levels is only partly effective in reversing advanced arthropathy of acromegaly. Particular mention merits the well-known prognathism, which is usually accompanied by the widening of the interdental spaces. In fact, several patients are referred for evaluation by dentists or oral surgeons.

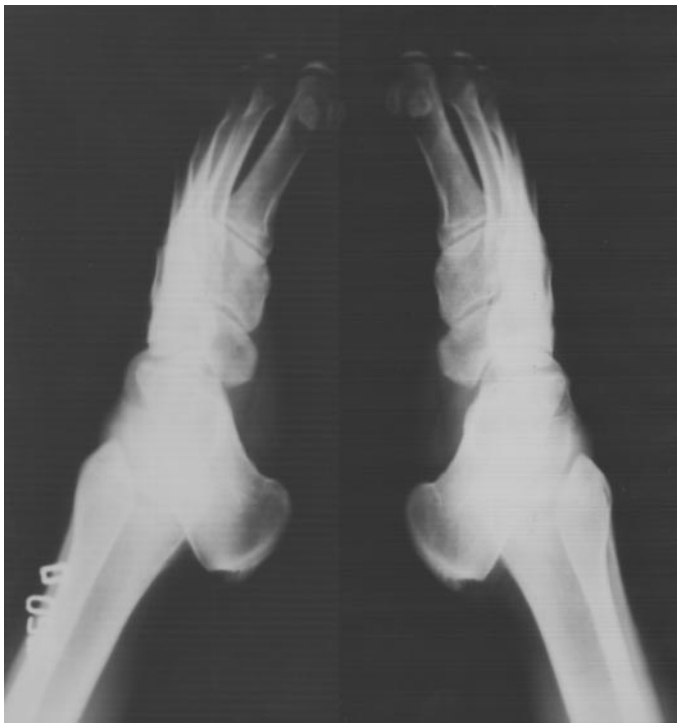

FIG. 16. Radiographic features of bone proliferation at sites of tendon and ligament attachment to bone (enthesopathy) in a female patient aged 48 yr with an estimated disease duration of 8–10 yr. Note the proliferation along the posterior margin of the calcaneus. This is a proliferative enthesopathy different from the common enthesopathy occurring in other rheumatic diseases. This latter spondyloarthopathy is characterized by a primary erosive, due to local release of cytokines, and a secondary proliferative process.

These changes often result in malocclusion and may lead to temporomandibular joint syndrome in up to 33% of patients with acromegaly (421). Less frequent rheumatological disorders include Raynaud's phenomenon, occurring in 24% of cases (420), and polymyalgia rheumatica, observed in 4% of patients (421).

D. The carpal tunnel syndrome

Symptomatic carpal tunnel syndrome is a common condition in acromegaly, with a prevalence from 20–52% (9, 415, 420, 421) up to 64% of patients at presentation (445). Nerve conduction studies have documented subclinical abnormalities in the vast majority of patients (446, 447). Jenkins *et al.* (448) showed by magnetic resonance imaging (MRI) that patients with symptoms of neuropathy had increased nerve size and signal intensity compared with asymptomatic patients, but the two groups did not differ in the volume of carpal tunnel contents. The predominant pathology of median neuropathy in acromegaly consisted of increased edema of the median nerve in the carpal tunnel, rather than extrinsic compression due to increased volume of the carpal tunnel contents (448). Clinical symptoms of median neuropathy likely originate from increased median nerve size within the carpal tunnel, consistent with swelling of nervous structures. This hypothesis is supported by the increased signal intensity recorded on T2-weighted images and the rapid reduction

in nerve size and resolution of symptoms after decrease of GH levels (448). The chronic impairment of nerve conduction suggests that edema may damage myelin sheathes (449, 450). In contrast with the MRI findings in idiopathic carpal tunnel syndrome, bowing of the flexor retinaculum did not change in acromegaly, indicating that the overall volume of the carpal tunnel contents is unaltered (448). Previous studies of median neuropathy in acromegaly proposed various pathogenic mechanisms, including an increase in connective tissue within the carpal tunnel (451), demyelination of Schwann cells (452), bony or synovial overgrowth of carpal bones (453), or an increase in extracellular fluid within the tunnel itself (454). There is no correlation between GH and IGF-I levels or the duration of acromegaly and the presence of carpal tunnel syndrome (445–447, 455). Similarly, Jenkins *et al.* (448) did not find any correlation between GH or IGF-I levels and both radiological and electrophysiological measurements, either before or after treatment. Additionally, hormone levels were equally elevated both in symptomatic and asymptomatic patients. It should be noted, however, that nerve swelling decreases after reduction of GH and IGF-I hypersecretion, therefore suggesting that control of hormone levels is a prerequisite for regression of nerve abnormalities (445, 447, 453).

E. Bone mass alterations

Until the end of the 1960s, acromegaly was considered as a relevant cause of secondary osteoporosis (456), a theory that paradoxically contradicts the observed stimulatory effect of GH and IGF-I on osteoblast function. In the 1970s, several studies contributed to changing this inference by indicating a potential anabolic effect of GH, at least on the cortical bone (457, 458). Successively, Seeman *et al.* (459) demonstrated that osteoporosis occurs rarely in acromegaly and thus hypothesized that it could be a consequence of hypogonadism in a variable number of patients. Characteristically, acromegaly causes an increase in both bone apposition and resorption (460), but data on bone mass are controversial (457, 459, 461–468). This discordance of results depends mainly on differences in skeletal sites investigated, diagnostic equipment used, and grouping of patients regardless of gender and gonadal status. Data on cortical bone generally show a normal or even increased bone mineral density (regardless of the gonadal status), although discrepant data are available on the trabecular bone (460). Riggs *et al.* (457) first reported increased cortical bone density in the forearm at a distal site, which is almost entirely composed of cortical tissue. Increased cortical, but not trabecular, bone density in the forearm was also reported by Diamond *et al.* (461). At the spine and femur, both cortical and trabecular bone density has been reported to be increased in series including both hypogonadal and eugonadal patients (464), as well as only eugonadal patients (468). Differently, bone density at the spine levels was reported to be normal in other series including either eugonadal patients (461, 463) or hypo- and eugonadal patients (461, 465). Indeed, the impact of hypogonadism should be considered of the utmost importance in patients with acromegaly when evaluating bone density. Scillitani *et al.* (466) reported normal bone density in the forearm regardless of the gonadal status of patients, while bone density was increased in the femur in their entire series of patients. The authors also documented an increased trabecular bone mass in the spine, but not in the femur or the forearm, in the series as a whole as well as in the subset of eugonadal patients. In contrast, at each site examined, hypogonadal patients had values of trabecular bone mass similar to those detected in the matched controls (466). Altogether, these data suggest that GH and IGF-I excess induces an increase of the cortical bone density, independently of gonadal function, whereas hypogonadism seems to counteract the anabolic effect of GH on the trabecular bone.

F. Effect of GH and IGF-I control on the skeletal system

Whether acromegalic arthropathy can be reversed by controlling GH and IGF-I levels is still questioned. The extensive structural changes occurring at the joints and the limited reparative ability of chondrocytes appear to prevent the significant improvement of acromegalic arthropathy. However, surgery or treatment with somatostatin analogs was shown to be associated with improved symptoms and signs of acromegalic arthropathy (6, 417, 441, 469, 470). Mild to moderate improvement in pain, crepitus, and range of motion has been reported in the majority of patients treated with octreotide (6). The possibility exists that some of the milder early changes, such as cartilage thickening and joint space widening, may resolve with successful early treatment. Nonetheless, several reports indicate that symptomatic and functional improvement may occur, although the arthropathic process itself is irreversible. Podgorski *et al.* (421) noted that arthropathy was milder in patients responder than in nonresponder to octreotide, and Layton *et al.* (417) reported improvement of symptoms after octreotide treatment, but objective improvement was observed only in one of nine patients. Conversely, Dons *et al.* (415) reported decreased joint pain in 12 patients and pain worsening in 29 of 47 patients 5 yr after radiotherapy. We recently demonstrated that cartilage thickness measured by ultrasonography at the shoulder, wrist, and left knee was significantly decreased after 6 months of octreotide treatment in a small group of previously untreated acromegalic patients (419). However, in neither patients cured for acromegaly nor those receiving octreotide treatment did cartilage thickness return to values comparable to healthy subjects (419). In a subsequent study, we found that thickening of shoulder, wrist, and knee cartilages and of heel tendons significantly decreased in all patients after 12 months of treatment with lanreotide (471). We also found that the reduction of right shoulder cartilage thickness by 37% was significantly greater than that observed at the level of right and left knee cartilages and heel tendons, ranging in these sites from 14 to 19% (471). More recently, in a prospective evaluation of joint thickness after 12 months of octreotide-LAR treatment, we demonstrated that there was a decrease in the thickness of the shoulder (15.1 $\pm$ 3.2%), wrist (20.5 $\pm$ 3.1%), right (22.2 $\pm$ 3.4%) and left knee (18.2 $\pm$ 2.8%) in all patients; however, the reduction in joint thickness at all sites was significantly greater in the patients with controlled disease after octreotide-LAR treatment than in the uncontrolled ones (Fig. 17) (472). Moreover, values com-

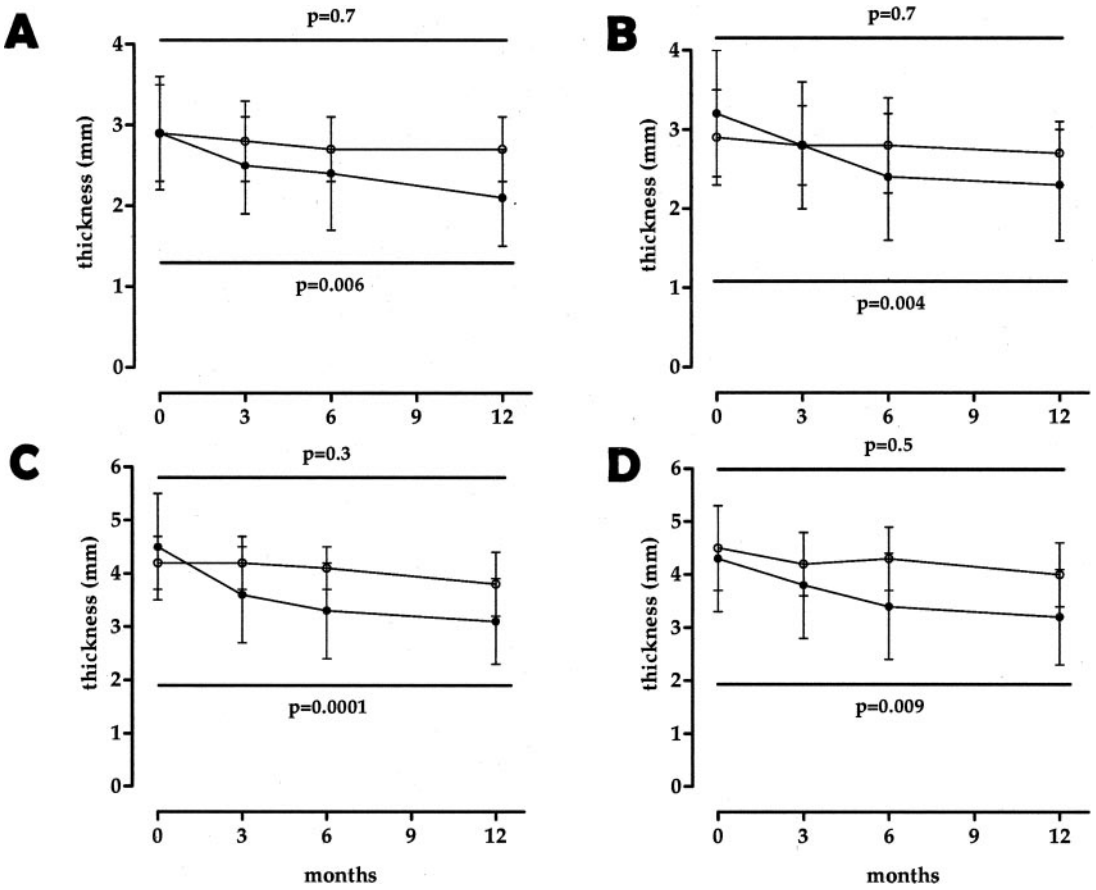

FIG. 17. Ultrasonographic evaluation of joint thickness before and during octreotide-LAR therapy for 12 months in 30 *de novo* patients with active acromegaly. A, Left shoulder; B, left wrist; C, right knee; D, left knee. ●, Patients with controlled disease; ○, patients with uncontrolled disease. Data were modified by Ref. 272. Data are shown as mean ± SD and were analyzed by the two-way ANOVA.

pared with controls of shoulder and right knee thickening were found in as high as 61% and 89%, respectively, in well-controlled patients (472). We did not find any gender difference (472). Carpal tunnel syndrome is also significantly improved in most patients after control of GH and IGF-I level hypersecretion (186, 445, 447, 453), but the underlying pathogenic mechanisms are unknown (452, 454). Jenkins *et al.* (448) showed that the increased nerve size and signal intensity at MRI improved with treatment of acromegaly in symptomatic patients, whereas asymptomatic patients experienced no change or worsening. Because the prevalent pathological mechanism of median neuropathy in acromegaly is edema of the perineural sheathes, rather than increased volume of the carpal tunnel contents, the rapid resolution of edema after suppression of GH and IGF-I levels is associated with resolution of neuropathic symptoms (448). However, when all findings on acromegalic arthropathy are considered together, it appears that some early alterations, such as joint thickness or osteopenia, can be reversed by suppressing GH and IGF-I levels, whereas later bone complications, such as osteoarthritis and bone deformities, should be considered definitive features of the disease.

VII. Summary

Acromegaly is a very peculiar and interesting disease that engenders intense interest from a wide variety of spheres. Since its initial definition over 100 yr ago, extraordinary efforts have been made to control GH levels and the pituitary tumor in the vast majority of patients. Criteria of cure have been evolving constantly, and all previous statements should be revised according with modern criteria of disease control. It is well accepted that mortality in acromegaly is increased mostly because of cardiovascular and respiratory diseases. Whether neoplastic complications may also increase death rates in acromegaly, as it was formerly theorized, has been questioned by more recent epidemiological studies. Among different cardiovascular complications, the most frequent is biventricular hypertrophy, which occurs independently of hypertension and metabolic complications but is, in turn, aggravated by these disorders. Diastolic and systolic dysfunction develops in a variable number of patients, depending on age and disease duration. Other cardiac disorders, such as arrhythmias, valve disease, hypertension, atherosclerosis, and endothelial dysfunction, have been less characterized, but all appear to be present in acromegaly, depicting the so-called "acromegalic cardiomyopathy." Control of acromegaly by surgery or pharmacotherapy, especially somatostatin analogs, improves cardiovascular morbidity. The beneficial effects on the new pharmacotherapy of acromegaly using a GH-antagonist are still largely unknown. Besides direct negative effects of GH/IGF-I excess on heart and vessels, there are other negative effects on glucose and

lipid metabolism, which also ultimately lead to an increased cardiovascular risk. The metabolic complications seem to be more directly due to GH than to IGF-I excess. They affect virtually all patients with acromegaly, even if glucose and lipid changes developing at an early stage may not be clinically significant. Although somatostatin analogs were initially suspected to cause an impairment of glucose tolerance, the majority of the studies indicate that the control of acromegaly improves glucose and lipid alterations. Respiratory disorders are also important contributors in increasing mortality; the best-characterized respiratory disease is sleep apnea, which is beneficially advantaged by controlling GH and IGF-I hypersecretion. Ventilatory dysfunction, a less studied cause of respiratory disorders, recognizes bony changes of thoracic cage and lung overgrowth as relevant pathogenetic factors. Improvement after therapy seems hardly achieved. Earlier evidence that patients with acromegaly have an increased risk of developing malignancies has become more realistic in recent years. Most studies have reported an increased risk of colonic polyps, which more frequently recur in patients not controlled after treatment. Malignancies in other organs have also been described, but less convincingly than at the gastrointestinal level. Hypertrophy is also common at different body sites, such as thyroid and prostate. At the beginning of the disease, hypertrophic changes are likely to be reversed, whereas patients with long-standing disease are more prone to develop degenerative changes, such as nodules and calcifications, which prevent the recovery to the predisease state. Arthropathy is undoubtedly the most important cause of morbidity, and functional disability and bone alterations are highly characteristic of this syndrome. They involve theoretically all bones and, particularly, the appendicular and the axial skeleton. Radiographic changes at different joint sites are more common than symptoms related to their involvement. As previously stated, there is a progression in the acromegalic arthropathy resembling that described for the acromegalic cardiomyopathy or for the acromegalic features at other organs such as thyroid, breast, and prostate. At an early stage, cartilage hypertrophy predominates, and then degenerative changes start until osteoarthritis features occur. Arthropathy can be reversed at this stage, but not if the disease is left untreated.

VIII. Conclusions

Early and modern studies agree on identifying cardiovascular and respiratory complications as the most relevant causes of the increased risk of mortality in acromegaly. Doubts have been raised on the relevance of neoplastic complications, and future elucidation of local IGF-I and IGFBP-3 action will contribute to clarifying this issue more adequately. There is enough good evidence to infer that acromegaly is currently diagnosed earlier than, for instance, in the 1930s because patients only rarely present visual field defects. Indeed, early detection prevents the development of irreversible complications of the disease, including cardiomyopathy, respiratory dysfunction, and arthropathy. Clear evidence also exists that, in the early stage, all of these disorders can be totally reversed. Whether improvement in morbidity will correspond to a similar improvement in mortality, although highly likely, still awaits further demonstration by large prospective studies.

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