0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 82, No. 9
Printed in U.S.A.

EXTENSIVE PERSONAL EXPERIENCE

Acromegaly

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Acromegaly is a rare pituitary disorder with an estimated incidence of three to four cases per million population per year (1). Because it is a chronic and slowly developing disease, clinically progressive disfigurements or disabilities go unnoticed, and the diagnosis can be delayed. It is a severe systemic disease, because the GH/insulin-like growth factor I (IGF-I) excess causes impairment of cardiac and respiratory functions that contribute to the increased mortality and morbidity (1).

This report refers to our clinical experience in the diagnosis and management of acromegaly over a period of two decades, focusing on specific clinical problems, such as cardiac morphology and function, follow-up of pregnancy, and different approaches to therapy. During these years we cared for 168 patients for a mean period of 8 yr (range 1–18 yr). Although approximately half of them were lost at follow-up after 5–10 yr, and 11 died from different causes, the large number of patients studied gave us the opportunity to draw a number of preliminary conclusions.

Cardiac features of acromegaly

Because atherosclerosis, cardiovascular and cerebrovascular diseases, and respiratory diseases double the death rate compared with the healthy population, especially after the age of 45, additional testing should be performed after the diagnosis of acromegaly is made. In particular, we have developed a careful cardiological assessment strategy, including standard and 24-h Holter electrocardiogram (ECG), echocardiography, and equilibrium radionuclide scintigraphy. In acromegaly, cardiac enlargement is a consistent finding and seems to be disproportionate as compared with the increase in size of other internal body organs (2). An increased frequency of cardiovascular diseases, such as systemic hypertension, premature coronary disease, arrhythmias, especially ventricular premature beats and intraventricular conduction defects, and congestive heart failure have been described (2). Most studies of acromegalic cardiopathy have focused on structural and anatomical abnormalities of the heart (like ventricular wall hypertrophy and/or ventricular dilatation). Particularly, myocardial hypertrophy with interstitial fibrosis, lymphomononuclear infiltration, and areas of monocyte necrosis resembling myocarditis often resulting in increased left ventricular mass (LVM) and concentric hypertrophy have been described (2). Similar alterations have been observed for the right ventricle. Conversely, little information is available on the diastolic function in acromegaly, although it is known that diastolic abnormalities may precede systolic dysfunction and may represent a distinct cause of impaired cardiac function. Using Doppler echocardiography and equilibrium radionuclide scintigraphy we have shown that abnormal diastolic filling patterns of transmitral, transtricuspid, and superior vena cava flowmetry are frequently present in acromegalic patients, indicating an impaired relaxation associated with an increased left and right ventricular mass (2). Moreover, cardiac performance was significantly impaired in uncomplicated acromegaly as evidenced by the significantly reduced ejection fraction during physical exercise as compared with controls. This has been documented for both left ($61 \pm 11\%$ *vs.* $75 \pm 8\%$, $P < 0.001$) and right ventricle (45 ± 13 *vs.* $58 \pm 11\%$, $P < 0.002$). In 73% of our patients, the left ventricular ejection fraction during exercise increased by less than 5% compared with basal values, thereby fulfilling the criteria for impaired cardiac performance (2). These findings could indicate the presence of a specific acromegalic cardiomyopathy, which seems to be correlated with the duration of disease rather than with circulating GH and/or IGF-I levels. Thus, acromegalics may be asymptomatic for many years before showing clinical and/or echocardiographic features of cardiac impairment. In the early stages of the disease, some patients may even present with a hyperkinetic syndrome, characterized by increased heart rate and cardiac output and decreased vascular resistance. Frequently, left ventricular hypertrophy occurs first, often leading to slow deterioration of diastolic function. Congestive heart failure may develop when the disease is untreated or unsuccessfully treated. Of 168 patients admitted to our Department for acromegaly, only 3 developed heart failure as their initial symptom. Two were elderly (65 and 67 yr old), whereas the third, a 37-yr-old male, presented with an end-stage cardiac failure. Initial signs of cardiac hypertrophy can also be recorded in young

Received July 31, 1996. Revision received March 14, 1997. Re-revision received May 29, 1997. Accepted June 10, 1997.

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acromegalic patients (<40 yr old) with disease duration shorter than 5 yr. With the aid of monodimensional and pulsed Doppler echocardiography, we recently found a significant increase of the LVM and the LVM indexed for body surface area in 20 normotensive, untreated young acromegalics (Fig. 1). In these patients both end-systolic and end-diastolic dimensions, as well as the isovolumic relaxation time, were significantly higher than controls (Fig. 1) in the absence of signs of cardiac impairment. In fact, the ejection fraction was similar between patients and age- and sex-matched controls (67.6 ± 2.5% *vs.* 66.6 ± 1.8%). These findings suggest an early involvement of the cardiac muscle in young acromegalics as well. The treatment with octreotide (OCT) lead to an improvement of cardiac parameters. A significant decrease of LVM, interventricular septum thickness, and right posterior wall thickness was found after 6 months of OCT treatment (3), although hemodynamic parameters remained unchanged after 12 months of treatment (4). Suppression of GH/IGF-I levels for 24 months was not paralleled by a significant change in the ejection fraction, either at rest or after exercise, in 11 acromegalics treated with OCT (4). This indicates that a longer period of treatment may be needed to normalize cardiac performance. It could be argued that, during standard sc treatment with OCT, incomplete suppression of the GH/IGF-I levels throughout the day might have contributed to the failure to improve cardiac function. In agreement with this hypothesis are our preliminary results in 3 patients treated for 18 months with the long-lasting im formulation of OCT, at the dose of 20 mg/month (Sandostatin LAR, Sandoz, Basel, Switzerland), showing a significant decrease of the LVM and a significant increase of the ejection fraction (in the 2 normotensive patients) after only 6 months of treatment.

Follow-up of pregnancy in acromegalic women

Pregnancy is a rather rare event in acromegalic women because fertility is often reduced during the disease. Thus, only a few pregnancies in acromegalic women have been reported in the literature. We followed up on ten pregnancies in six patients with active acromegaly (Table 1). One pregnancy spontaneously ended after 3 months, and the last one was ongoing at the time of this report. In four women, acromegaly was first diagnosed during pregnancy, and all patients delivered naturally healthy newborns whose height and weight were on or over the 97th percentile. All infants were breast-fed and in good health. Three women became pregnant 1–3 yr after surgery, and in two of them, pregnancy occurred when GH and IGF-I levels were still slightly elevated. In two other cases pregnancy occurred during chronic OCT treatment. OCT withdrawal was recommended to these patients when pregnancy was confirmed. However, one patient refused to discontinue OCT treatment (no.5, Table 1) because of persistent and analgesic-resistant headache; she continued therapy at high doses (900–1200 μg/day divided in multiple administrations) during the whole period of pregnancy. In four women, serum GH and plasma IGF-I levels were assessed every month, while assessment of the GH secretory profile, with sampling every hour from 0800 to 1600 h, was carried out every 3 months. Circulating GH and IGF-I levels were only suppressed in the patient who continued OCT therapy. The patient who stopped OCT treatment gave birth to an overweight girl (4.5 kg), while the patient who continued OCT treatment had a girl whose weight was normal (3.2 kg). Against our recommendations, the latter patient breast-fed her baby for 4 months with no apparent problem. No growth of pituitary adenoma in the six patients was shown by computed tomography (CT) or mag-

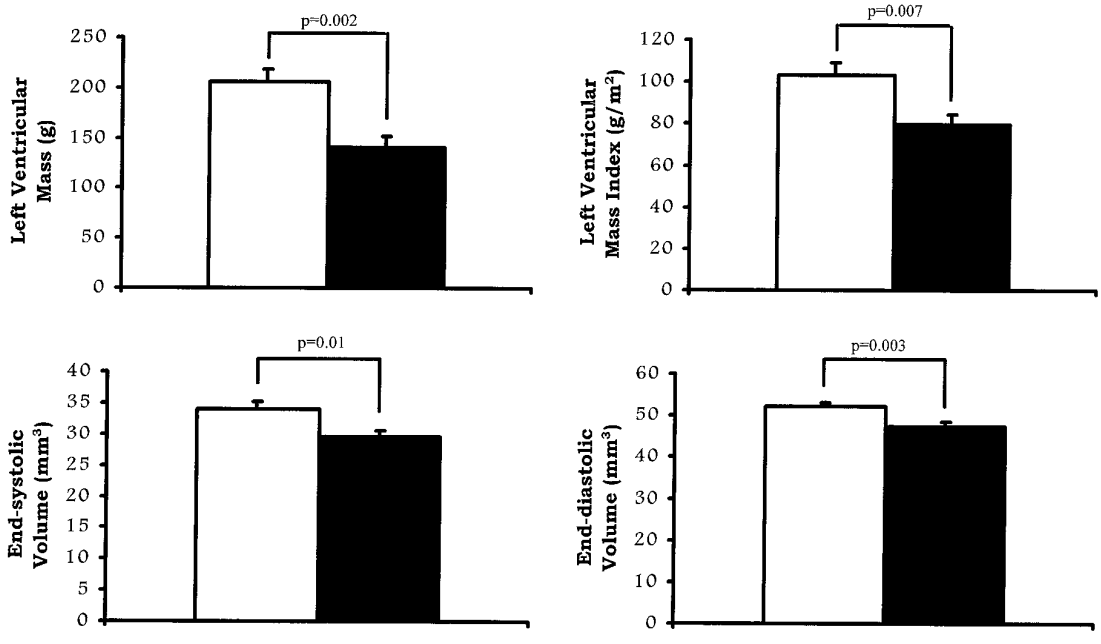

FIG. 1. Echocardiographic findings of cardiac structure and function in 20 young (aged 20–39 yr) normotensive acromegalics with a presumed duration of the disease ranging from 3–5 yr, and 14 sex- and age-matched healthy subjects. □, patients; ■, controls.

TABLE 1. Summary of the follow-up of pregnancies in acromegalic women

Patient no. (age, yr)/ no. of pregnancies	Pregnancy	Newborn sex/weight (Kg)	Newborn sex/ height (cm)	Previous treatments	Concomitant treatments	GH levels (μg/L) during pregnancy	IGF-I levels (μg/L) during pregnancy	Notes
1 (23)/3[a]	1st	F/4.2	F/57	none	none	n.d.	n.d.	Acromegaly developed
2 (25)/2	1st	M/5	M/60	none	none	n.d.	n.d.	Acromegaly developed
	2nd	F/4.5	F/58	S, OCT	OCT	22	780	OCT withdrawal during pregnancy
3 (26)/2	1st	M/4.8	M/59	none	none	n.d.	n.d.	Acromegaly developed
	2nd	F/4.5	F/58	S, OCT	none	8.5	552	2 yr after surgery
4 (28)/1	1st	M/5	M/61	none	none	n.d.	n.d.	Acromegaly developed This boy was studied at the age of 6 yr for gigantism[b]
5 (29)/1	2nd	F/3.2	F/52	S, RT, OCT	OCT	2	210	OCT during pregnancy
6 (38)/1	4th	M/4.1	M/60	S, OCT	OCT	13	623	1 yr after surgery

F, female; M, male; S, surgery; RT, radiotherapy; OCT, octreotide; n.d., not done.

[a] One of three ended in miscarriage after 3 months, and the third one occurred 3 yr after surgery and was ongoing at time of this report.

[b] This boy is presently followed in our Department. His height is still at the 97th percentile, with growth velocity on the 50th percentile. At the last biochemical control, circulating GH and IGF-I were in the normal range for age and sex.

netic resonance imaging (MRI) studies performed after delivery. Visual field studies performed during pregnancy failed to reveal any defect. The two patients with mildly elevated GH/IGF-I levels before pregnancy (nos. 3 and 6, Table 1) reported an improvement of signs and symptoms during pregnancy.

Treatment of acromegaly

The treatment of acromegaly is aimed at removing the source of GH hypersecretion or at suppressing its activity. The effectiveness of therapy is documented by the suppression of GH to levels below 2 μg/L after glucose load and the normalization of IGF-I levels (5). Surgery is considered the first choice of treatment, followed by radiotherapy and/or medical therapy, on the basis of the presence and invasiveness of tumor remnant (6). Among the 168 patients admitted to our Department for acromegaly, 145 were treated by surgery. In 5 out of these 145, a second operation was performed after 5–10 yr because of tumor regrowth, as documented by CT and/or MRI. Because the cut-off levels of serum GH to indicate cure has significantly changed during the years from 10 to 2.5 μg/L, and because presently the normalization of plasma IGF-I should also be considered, the number of patients cured by surgery decreased progressively, with a total success rate of 40%. Moreover, radiotherapy was used in 33 patients of our series, more frequently in the past for the inadequacy of medical treatment. Surgery together with radiotherapy caused the cure of the disease in 19 out of 33 patients. It should be pointed out that the majority of these 19 patients have demonstrated GH deficiency at recent follow-ups. Taking into account the evidence that GH deficiency in adult age is associated with metabolic and body composition alterations and with impairment of cardiovascular function (8), this finding may be clinically relevant. Table 2 summarizes the results of different therapeutic approaches in our acromegalic patients during these last 20 years.

Medical treatment has greatly improved in the last decade with the introduction in the clinical practice of somatostatin analogs, such as octreotide (OCT) and lanreotide, and new dopamine agonists, such as quinagolide (CV 205–502) and cabergoline. Most studies indicate that somatostatin analogs are more effective than dopamine agonists (1, 2, 7). We have recently shown that the treatment with quinagolide, at the dose 0.3–0.6 mg/day for 6 months, normalized circulating GH and IGF-I levels in only 43.8% of patients (9). The long-lasting im formulations of bromocriptine and cabergoline were even less effective (9). OCT is the most widely used drug, but because it must be administered at least three times daily sc, the frequency of injections has been reported to cause poor compliance and/or early side effects, sometimes leading to therapy withdrawal (10). To test for tolerability and to predict chronic responsiveness to treatment, the acute test with 50–100 μg OCT is commonly used (10). However, in our experience the acute OCT administration did not prove to be a reliable pretreatment screening test because of

TABLE 2. Summary of treatment results in our 168 patients

	Total number of patients	Number of cured patients	Cure rate (%)
First option			
Surgery	86	39	45.3
Radiotherapy	3	0	0
Somatostatin analogs	54	43	79.6
Dopamine agonists	25	2	8
Second option			
Surgery	59	19	32.2
Radiotherapy	30	19	63.3
Somatostatin analogs ↕	41	28	68.2
Dopamine agonists	21	9	42.8
Third option			
Second surgery	5	0	0
Combined treatment with somatostatin analogs and dopamine agonists	13	2	15.3

The *double arrow* indicates that either somatostatin analogs or dopamine agonists were given separately in order to suppress GH/IGF-I levels. In patients who did not achieve GH/IGF-I normalization, a switch to the other class of compounds was carried out before moving to the third option.

a sensitivity of 71% and a specificity of 55% (11). The recent availability of lanreotide prompted us to test its effectiveness in acromegalic patients and to compare it with the effectiveness of OCT. In the first 15 patients treated with either one of the drugs, both drugs strongly suppressed the GH/IGF-I hypersecretion (Fig. 2). However, patients' compliance was markedly better during lanreotide treatment than during OCT treatment. In these patients, OCT caused a significantly greater suppression of GH levels than lanreotide (89.3 ± 3% *vs.* 77 ± 3.9%, $P < 0.001$, Fig. 2). Three patients showing a poor response to OCT showed a poor response to lanreotide treatment as well.

Although it is current opinion that pharmacotherapy should be instituted after unsuccessful surgery (5, 6), OCT therapy before surgery has been reported to improve the surgical outcome. In fact, the treatment with OCT has been shown to improve glucose tolerance or diabetes mellitus (5, 6, 9), cardiovascular parameters (2–4), and to cause tumor shrinkage. Clearly, the achievement of improved metabolic conditions is favorable for the anesthesiological procedure, while the reduction of tumor mass can facilitate the neurosurgical excision. Based on these observations, we administered OCT for 3–6 months before surgery in a group of 22 acromegalics. OCT pretreatment caused a significant decrease of serum GH in these 22 patients. GH and IGF-I normalized in 12 OCT-pretreated patients (54.5%), between 10–15 days after surgery. GH and IGF-I normalized in only 11 of 37 patients who did not receive OCT pretreatment (29.7%). The surgical outcome was significantly improved in OCT-pretreated patients ($P < 0.005$, χ^2 test). In 3 out of 7 diabetic acromegalics receiving OCT, glucose lowering drugs could be withdrawn because blood glucose normalized on a low carbohydrate diet alone. In 2 diabetic acromegalics, insulin could be replaced by oral glucose lowering drugs, while in the remaining 2 patients the insulin dose could be reduced. In OCT-treated patients the average blood glucose levels before surgery were significantly lower than in untreated patients, and the levels remained low at the first follow-up after surgery (Fig. 3). Similarly, both circulating total cholesterol and triglycerides levels were significantly higher in untreated than in OCT-treated patients either before or after surgery (Fig. 3). In addition, both systolic and diastolic blood pressures decreased in 5 patients, and ECG recording normalized in 7 of 11 OCT-treated patients. A significant tumor shrinkage was documented with CT and/or MRI in 5 out of 22 OCT-treated patients and in none of the untreated patients. Macroscopically, no difference was found between untreated and OCT-pretreated adenomas. The tumor could be easily removed in most cases (83.2% *vs.* 81.8%), and tumor invasion of perisellar tissues was noticeable in 27% and 22.7% of untreated *vs.* OCT-pretreated adenomas, respectively. Pathology showed a significant increase of cellular atypia in OCT-pretreated *vs.* untreated adenomas (31.6% *vs.* 19.2%, $P < 0.05$). Finally, from the analysis of the results of this retrospective study it appeared that the time needed to recover from surgery was significantly shorter in patients who were pretreated with OCT than in untreated patients (5.6 ± 0.5 *vs.* 8.6 ± 0.7 days; $P < 0.002$). In conclusion, a short-term treatment with OCT before surgery might improve cardiac and metabolic conditions in acromegalics, reducing the generic anesthesiological risk while also improving the clinical recovery after surgery.

When OCT alone is ineffective in normalizing GH and/or IGF-I concentrations, a combined treatment with dopamine

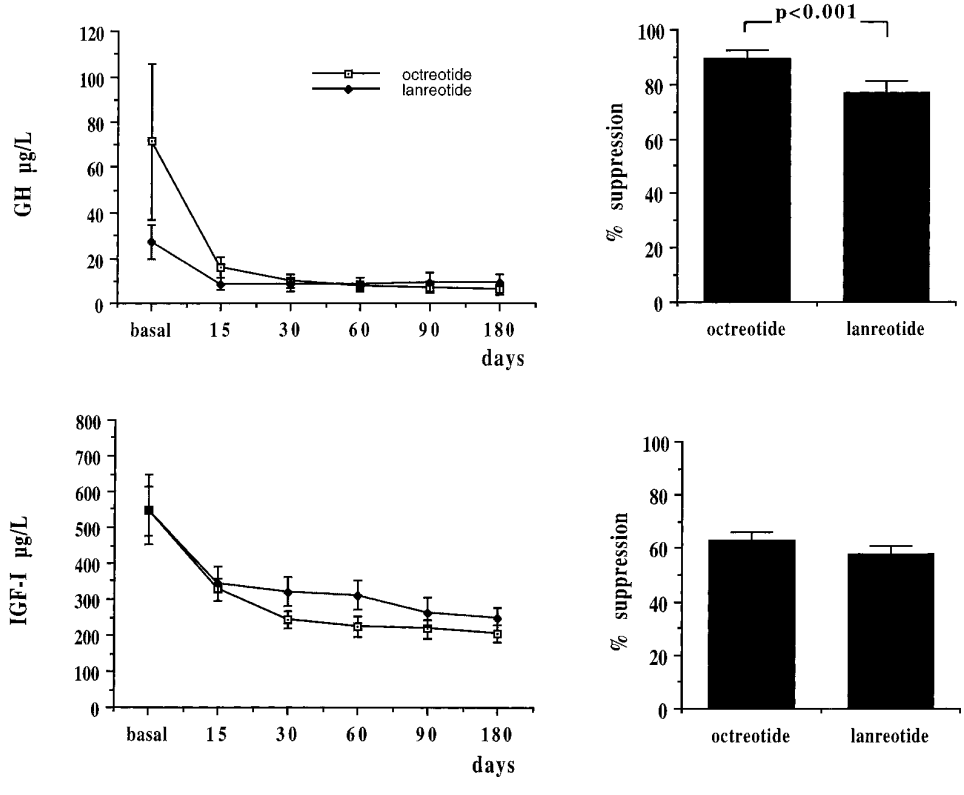

FIG. 2. Serum GH (*top*) and IGF-I (*bottom*) levels during octreotide and lanreotide treatment in 15 patients (*left*) and corresponding percent hormone suppression (*right*). All 15 patients were treated first with OCT at a dose of 0.3–0.6 mg/day, in three daily doses for 6 months and subsequently, after 7–15 day withdrawal, with LAN, at the dose of 60–90 mg/month for 6 months.

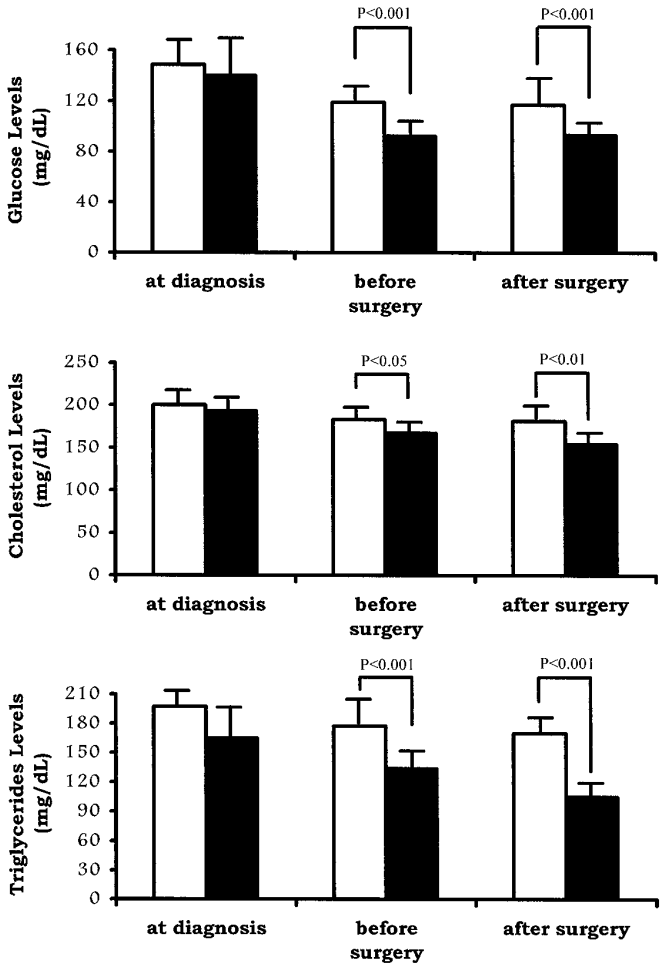

FIG. 3. Blood glucose (*top*), cholesterol (*middle*), and triglycerides (*bottom*) levels in 22 patients treated before surgery with octreotide at a dose of 0.3–0.6 mg/day for 3–6 months compared with 37 untreated patients. □, untreated patients; ■, OCT-treated patients.

agonists can be considered, because the combined administration of these compounds has been reported to be more effective in lowering GH levels compared with either drug given alone. We have demonstrated that the combined treatment with OCT plus quinagolide was effective in a few therapy-resistant acromegalics (12). This effect is likely the result of an increased bioavailability of dopamine agonists, as shown for bromocriptine (13), caused by the combined administration with OCT.

Conclusions

Our Department serves an area of about 4 million people. Therefore, the number of patients we have observed in the last 10 years fits with the expected frequency of 3–4 cases/million population/year. Of the 168 patients followed by our Department, 58 were cured by surgery, 19 were cured after surgery and radiotherapy, and 91 had their GH/IGF-I suppressed by medical treatment. Our studies on cardiac function led us to conclude that the cardiovascular system can be involved in the early stage of the disease. Successful treatment with long-acting somatostatin analogs can prevent the occurrence of cardiac disorders and can ameliorate cardiac function parameters as well. It is noteworthy that pregnancy in acromegalic women does not seem to significantly influence GH/IGF-I levels or tumor size. Apparently, treatment had no adverse effect on the outcome of pregnancy, but further studies are needed to firmly establish whether pregnant acromegalic women need to be treated or not. Chronic administration of somatostatin analogs represents the milestone of medical treatment of acromegaly. We have also shown that a short-term course of OCT before surgery can improve the surgical outcome. Clearly, the new long-acting formulations represent a further advancement in GH suppression activity as well as patients' compliance. It is expected that in future years, new more effective, and safer drugs will be available. By analogy with the effectiveness of medical treatment of prolactinomas, it is hoped that these drugs might become the treatment of choice for acromegaly.

Acknowledgments

This paper is dedicated to the memory of Marco Minozzi, Chief of the Endocrine Unit at the "Federico II" University of Naples, from 1973 to 1981.

We are greatly indebted to Paolo Marzullo for his skillful contribution in taking care of our patients and to Sandro Loche for kindly revising the manuscript.

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