Endocrine, *vol. 30, no. 1, 145–149, August 2006* 0969–711X/06/30:145–149/$30.00
ENDO (Online) ISSN 1559-0100

CASE

Acromegaly Presenting with Diabetic Ketoacidosis, Associated with Retinitis Pigmentosa and Octreotide-Induced Bradycardia

A Case Report and A Review of the Literature

Cihangir Erem,[1] Halil Önder Ersöz,[1] Kubilay Ukinç,[1]
Avni Murat Avunduk,[2] Arif Hacihasanoglu,[1] and Mustafa Koçak[1]

[1]Department of Internal Medicine, Division of Endocrinology and Metabolism, and [2]Department of Ophthalmatology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey

Carbohyrate intolerance is a common feature of acromegaly. Frank diabetes mellitus is seen in about 10–20% of patients. There is no report of acromegaly presenting with diabetic ketoacidosis (DKA), associated with retinitis pigmentosa (RP), in the literature. We report the occurrence of DKA and RP in a patient with acromegaly. A 39-year-old Turkish man was admitted to the emergency ward with a 1-mo history of thirst, polyuria, weight loss of 10 kg, and loss of consciousness for 2 d. Physical examination revealed findings suggestive of acromegaly, including coarse facial features and enlargement of his hands and feet. At ophthalmological examination, funduscopy showed RP. Laboratory studies confirmed the diagnoses of DKA and acromegaly. Magnetic resonance imaging disclosed the presence of a pituitary adenoma. During the medical treatment with octreotide, symptomatic sinusoidal bradycardia was developed (pulse rate 45 bpm, and blood pressure 70/40 mmHg). Octreotide therapy was stopped. Pituitary adenoma was removed surgically. For treatment of DKA, insulin need was very high in the first days after the onset of ketoacidosis, but decreased after initiation of treatment with octreotide and after successful operation. Insulin was stopped 7 d after surgery. Follow-up showed normalization of growth hormone levels and plasma glucose levels. Only six other cases of DKA associated with acromegaly and only three other cases of RP associated with acromegaly were found in the medical literature. In conclusion, to our knowledge, the present case is a first report of DKA and RP in patient with acromegaly.

Received June 14, 2006; Revised July 13, 2006; Accepted July 14, 2006.
Author to whom all correspondence and reprint requests should be addressed: Prof. Dr. Cihangir Erem, K.T.Ü. Tip Fakültesi, Iç Hastaliklari Anabilim Dali, 61080, Trabzon, Turkey. E-mail: cihangirerem@hotmail.com and cihangirerem@netscape.net

Key Words: Acromegaly; diabetic ketoacidosis; retinitis pigmentosa; octreotide; bradycardia.

Introduction

Acromegaly is an uncommon disorder with an annual estimated incidence of 3 to 4 cases per 1 million people. It is characterized by hypersecretion of growth hormone (GH) *(1)*. Altered glucose metabolism is a common feature of acromegaly and the severity of this disturbance correlates with the level of GH *(2)*. Impaired glucose tolerance (IGT) and overt diabetes mellitus (DM) are frequently associated with acromegaly *(3)*. IGT is present in approximately half of the cases with acromegaly *(2,3)*. The prevalence of DM in acromegaly ranges from 19% to 56% in different series *(4)*. Usually, altered glucose metabolism improves after adequate treatment of acromegaly.

Conventionally, diabetic ketoacidosis (DKA) is regarded as the hallmark of type 1 diabetes and indicates pancreatic beta-cell failure. Although being uncommon, DKA may also occur in type 2 diabetes and insulin resistant states such as acromegaly. Six cases of DKA have been described in acromegalic patients *(2,5–9)*. The underlying pathophysiology for DKA in such cases is not very well understood. Usually, these episodes were triggered by serious pathological conditions such as an acute infections.

On the other hand, only three cases of retinitis pigmentosa (RP) in association with acromegaly had been reported in the literature *(10,11)*. To our knowledge, there is no report of acromegaly presenting with DKA, associated with RP, in the literature. Here, we describe a first case of acromegaly presenting with DKA and RP.

Case Report

A 39-yr-old Turkish man was admitted to the emergency ward with a 1-mo history of thirst, polyuria, weight loss of 10 kg, and loss of consciousness for 2 d. He had no known

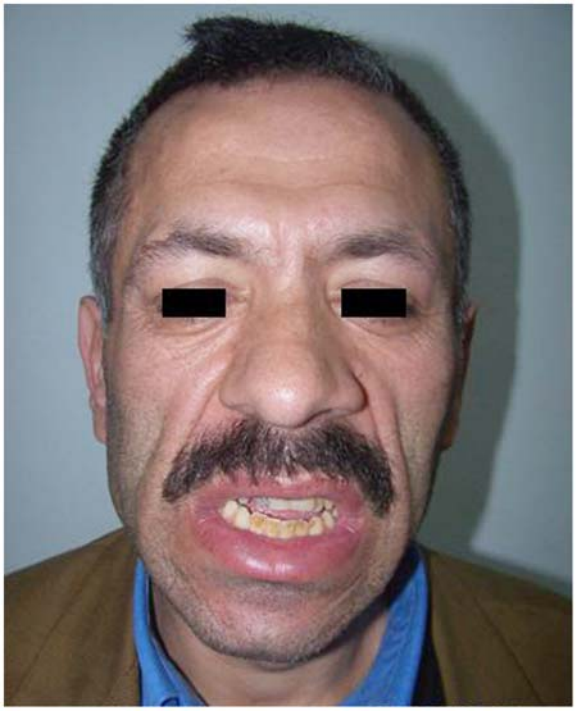

Fig. 1. General coarsening of features, frontal bossing, mandibular growth, prognathism, thickened lips, sweating, and wide nasal bridge (with permission of patient).

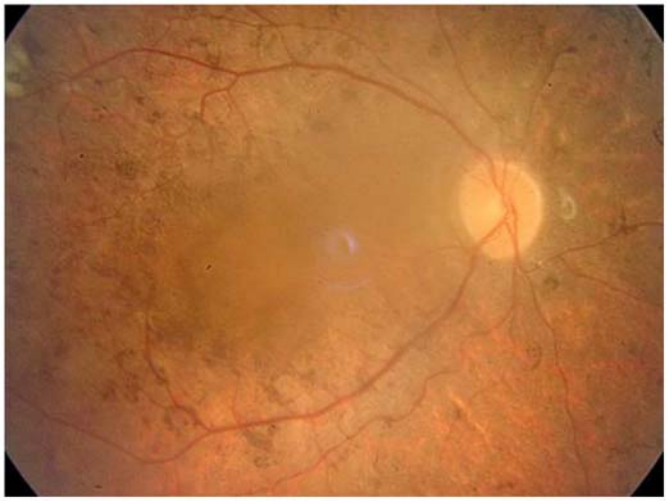

Fig. 2. Fundus appearance of the right eye, showing retinitis pigmentosa, especially in the periphery with a normal optic disc.

disease history and there was no history of diabetes or retinitis pigmentosa in his first and second degree relatives. Three days prior, he could not recognize his relatives and became lethargic. He complained of headache for 4 yr, which became more severe over the prior month. He also had swelling of the hands and feet, excessive perspiration, physical weakness, and increased shoe size. On admission, his blood pressure was 100/50 mmHg. He had a clearly acromegalic appearance, was severely dehydrated, and exhibited Kussmaul's respiration. He had large and spade-like hands and feet, swelling of cutaneous tissue, frontal bossing, coarse facial features, wide nasal bridge, thick lips, macroglossia, mandibular growth with widely spaced teeth (Fig. 1). Also, acanthosis nigricans was found at the neck region. There was no motor and sensory deficit on neurological examination. But, on ophthalmologic examination, the patient's sight was significantly decreased. He could not see objects farther than 3 m. A visual field examination could not be done because of RP (Fig. 2). In initial laboratory tests obtained in the emergency room; serum glucose 1700 mg/dL (N: 70–110), basal insulin 3 mIU/mL (N: 5–25), C-peptide level 0.9 ng/mL (N: 1.1–5.0), blood urea nitrogen 64 mg/dL (N: 7–21), creatinine 3.1 mg/dL (N: 0.3–1.5), sodium 144 mmol/L, potassium 5.4 mmol/L (N: 3.6–5.0), chloride 98 mmol/L (95–110), calcium 8.9 mg/dL, phosphorus 5.6 mg/dL (N: 2.5–4.5), and HbA1c 12.8% (N: 4.8–6%). There was metabolic acidosis: pH: 7.17, bicarbonate 7.5 mmol/L (N: 22–26), pCO_2: 23 mmHg (N: 35–45). Urinary ketone level was 80 mg/dL. Endocrinological evaluation showed elevated levels of GH (124 ng/mL, normal values < 5 ng/mL) and insulin-like growth factor-1 (IGF-1, 776 ng/mL, normal range for males aged 30–39 yr is 114–492 ng/mL). GH rhythm was obtained. Diurnal rhythm of GH secretion was lost associated with increased amplitude. Serum GH levels (ng/mL) were 141 at h 8.00, 171 at 12.00, 202 at 16.00, 193 at 20.00, 107 at 24.00, and 137 at 4.00. Because of the presence of very high glycemia in the patient, we did not perform an oral glucose load test for the diagnosis of acromegaly. There was evidence of hypogonadotropic hypogonadism. Luteinizing hormone 1.79 IU/L (N: 5–20), follicle-stimulating hormone 2.46 IU/L (N: 5–20), testosterone 0.44 ng/mL (N: 2.8–8.0). The remaining anterior pituitary functions were found to be normal. Radiological examination revealed soft tissue swelling on heel, enlargement of sella turcica and sinuses, bone overgrowth on skull. Heel-pad thickness was 28 mm. Magnetic resonance imaging of the pituitary showed an intrasellar mass of 16 × 21 × 22 mm with suprasellar extension (Fig. 3). Adenoma infiltrated into bilateral cavernous sinuses. According to physical examination and laboratory results, DKA in a patient with acromegaly and accompanying RP was diagnosed. The treatment was immediately initiated in the emergency room. He was treated with fluid replacement therapy and intravenous insulin infusion. His clinical condition improved rapidly. After DKA treatment, basal-bolus insulin therapy was initiated. Type 1 diabetes was ruled out because of negative antiglutamic acid decarboxylase and islet cell autoantibodies. Plasma glucose levels remained in the desired ranges with insulin basal-bolus treatment at a dose of 1.5 U/kg/d. Pituitary surgery was planned for the treatment of acromegaly. Before the surgery, medical treatment was initiated because of the large tumor size and in order to improve biochemical control. For this purpose, octreotide treatment was initiated at dose of 150 μg, divided into three doses a day via the subcuta-

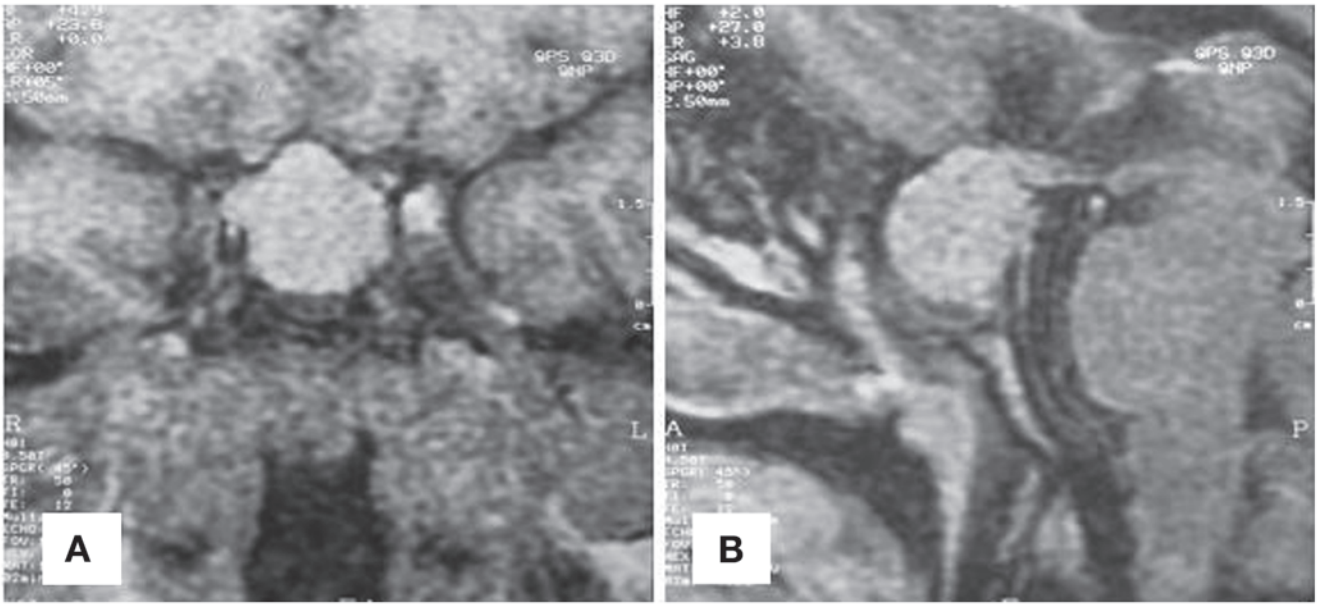

Fig. 3. (**A**) T1-weighted coronal MR image, and (**B**) T1-weighted saggital MR image. All images show an intrasellar mass of 16 × 21 × 22 mm with supra and parasellar extension.

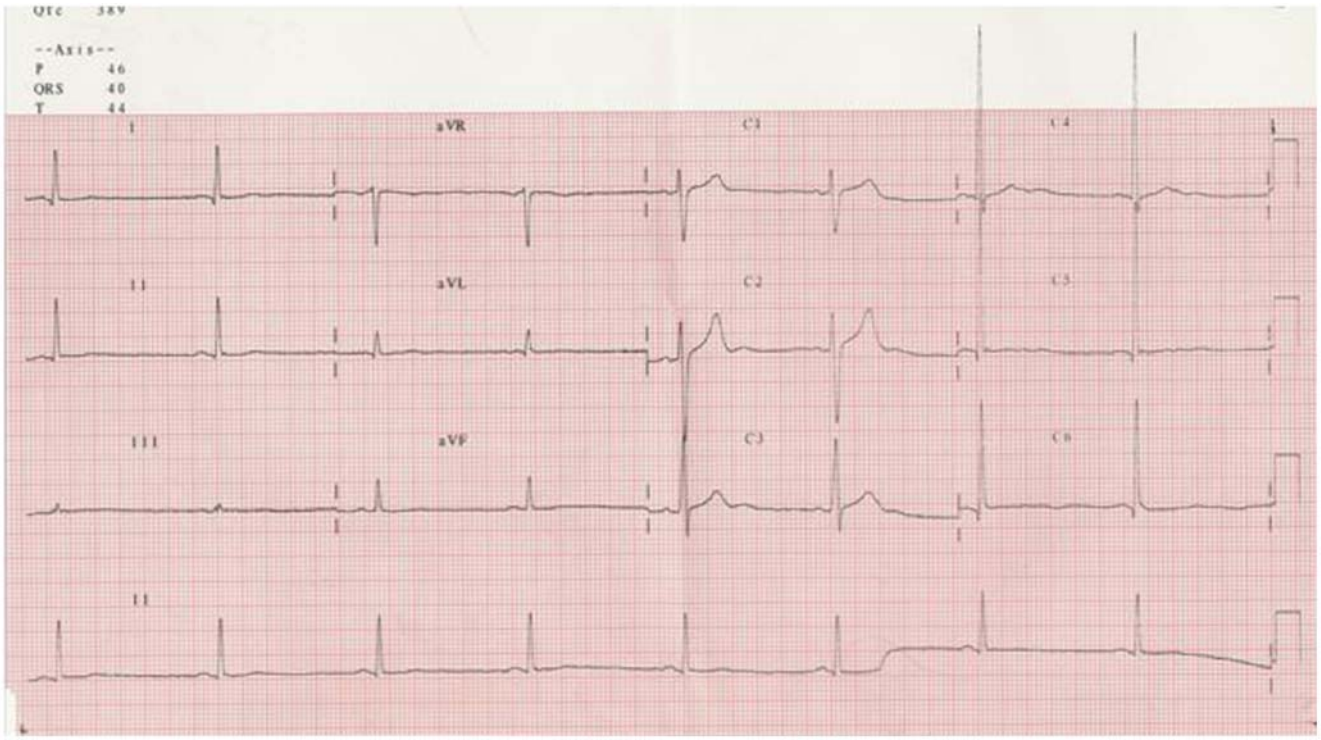

Fig. 4. EKG reveals sinus bradycardia (45 bpm).

neous route. On the fourth day of the octreotide treatment, the dose was increased to 300 μg, divided three doses a day. On the fifth day of the octreotide treatment, insulin dose was reduced to 0.7 U/kg/d and metabolic control of the glucose regulation could be easily done. But symptomatic bradycardia developed (blood pressure 70/40 mmHg) at the seventh day of the octreotide treatment. Pulse rate decreased to 45/min (Fig. 4). After this side effect, octreotide dose was decreased to 150 μg/d. Unfortunately, bradycardia persisted and medical treatment was stopped. Then the patient was referred to surgery. Transsphenoidal surgery was carried out 12 wk after initial presentation. Histological examination showed an eosinophilic adenoma, which stained positively for GH. Insulin was stopped 7 d after surgery. After 6 wk, postoperatively, the basal GH level was 0.08 ng/mL and IGF-1 was 31.6 ng/mL. Postoperative

panhypopituitarism developed. He was treated with full replacement therapy with L-thyroxine, prednisone, and testosterone, and his clinical condition was good. No medication for DM is needed and control of glycemia was maintained with medical nutrition therapy. Two months later, pituitary MRI was normal.

Discussion

In the present case the diagnosis of DM secondary to acromegaly has been established. GH excess is known to be associated with changes in glucose metabolism. GH counteracts the effects of insulin on glucose metabolism. The mechanisms responsible for the GH action on carbohydrate metabolism have been investigated at different levels. 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 *(12)*. In our patient, exact duration of diabetes and acromegaly was unknown. But this was approx 4 yr for acromegaly. A subgroup of patients with acromegaly exhibits severe hyperglycemia and requires insulin therapy; these patients usually have low endogenous insulin levels and markedly impaired insulin secretion. It has been suggested that these patients are really true diabetics independent from their acromegaly *(2)*.

DKA is a rare but recognized finding in acromegaly. There are a few reports of initial presentation of an acromegalic patient with DKA (total four cases) *(5,7–9)*. This severe metabolic derangement develops in the situation of absolute or relative deficiency of insulin and excess of counterregulatory hormones (cortisol, glucagon, catecholamines, and GH) *(8)*. DKA in the presence of normal circulating levels of insulin has been described previously *(13)*, but a normal insulin level is inappropriately low in the presence of hyperglycemia. It has been suggested that elevated levels of counterregulatory hormones lead to the development of DKA in these patients *(13,14)*. In our case serum glucose level was very high in initial laboratory evaluation (1700 mg/dL). This was not appropriate to DKA but this condition might be due to late admission to hospital (after 2 d of loss of consciousness) and severe dehydration. Presence of acanthosis nigricans, very low insulin and C-peptide levels, high daily insulin requirement (1.5 U/kg/d) shows a very high peripheral insulin resistance and very low insulin secreting capability of the β-cells that would lead to DKA in our patient. Suppressing the GH level (but not to normal levels) with octreotide treatment improved insulin resistance, and insulin dose could be decreased to 0.7 U/kg/d. The unusual feature in our case is, despite presenting with DKA initially, he became non-insulin dependent after his GH excess was controlled with operation and was adequately controlled on diet alone. Previous case reports of DKA in acromegalic patients were associated with significant reduction of insulin secretion and, in some cases, complete discontinuation of insulin therapy could be possible after normalization of GH levels *(2,8,9)*.

Octreotide therapy can improve glycemic control and insulin resistance *(15,16)*. Also, a rapid reduction of insulin requirement in insulin-dependent diabetic patients who were successfully treated for acromegaly has been observed *(12,17)*. Common adverse effects of octreotide treatment include nausea, abdominal cramps, diarrhea, malabsorption of fat, and flatulence *(1,3)*. These symptoms start within hours after the first injection of the drug, severity is dose-dependent, and usually subside spontaneously in 10–14 d, despite continued treatment. Cardiac complications are reported in acromegalic patients taking octreotide; for example, sinus bradycardia (<50 bpm) developed in 25%, conduction abnormalities in 10%, and arrhythmias in 9% *(18)*. Other electrocardiographic changes include QT prolongation, axis shifts, early repolarization, low voltage, R-S transition, and early R wave progression *(18)*. Dilger et al. reported that an intravenous bolus of octreotide resulted in hemodynamically significant bradycardia, Mobitz type II atrioventricular block, and complete heart block in an anesthetized patient undergoing carcinoid tumor surgery *(19)*. Herrington et al. described a nonacromegalic patient who was receiving octreotide subcutaneously and who developed bradycardia (38 bpm) without heart block *(20)*. In several other reports, octreotide administration did not consistently demonstrate a reduction of heart rate *(21,22)*. The mechanisms by which octreotide can cause bradycardia are numerous, and it is still not known if these effects are mediated indirectly through its effects on systemic circulation *(23)* or directly through ionic mechanisms at the level of the heart *(24)*. Octreotide increases systemic vascular resistance, and bradycardia may be a baroreceptor-induced reflexive response to increase in the systemic blood pressure *(13,25)*. Also, octreotide suppresses the secretion of vasoactive intestinal peptide (VIP) *(26)*, which can increase the heart rate even more so than norepinephrine *(27)*. Therefore, by blocking VIP, octreotide may cause bradycardia. The most plausible explanation for bradycardia after octreotide is through its direct effects on the heart. Intravenous infusions of somatostatin slow the sinus rate and depress atrioventricular conduction *(24)*.

RP occurs sporadically or in an autosomal recessive, dominant, or X-linked pattern. It is characterized by development of night blindness and loss of peripheral vision. Optic atrophy, narrowing of the arterioles, and peripheral pigmentation are hallmarks of the disease. Retinal abnormalities, unrelated to visual pathway compression, in acromegalic patients were originally described by Smail in 1972 *(11)*. He illustrated a case of primary pigmentary degeneration of the retina occurring in a patient with a chromophobe adenoma of the pituitary gland. Then, Cosemans et al. described two male patients with RP in association with acromegaly *(10)*. As the prevalence of acromegaly is 40–50 per

10^6 people *(28)* and that of RP is 1 in 4000 *(29)*, we calculated that the chance of having a combination of the above disorders would be approx one in a billion. The exact mechanism that explains this association is not yet clear. Smail suggested that melanocyte-stimulating hormone, a hormone secreted by the intermediate lobe of the pituitary gland, could be the missing link, but further investigation to prove the effect of MSH on the retinal pigment epithelium is warranted *(11)*. However, RP most likely has no connection with acromegaly. It also may be a coincidence.

In summary, we presented a patient of acromegaly presenting with DKA. This case demonsrates both a rare presentation of acromegaly and an unusually rapid cure of diabetes following surgical resection of the pituitary tumor.

References

1. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice For The Diagnosis and Treatment of Acromegaly. AACE Acromegaly Guidelines Task Force. (2004). *Endocr. Pract.* **10,** 213–225.
2. Kopff, B., Mucha, S., Wolffenbuttel, B. H. R., and Drzewoski, J. (2001). *Med. Sci. Monit.* **7**, 142–147.
3. Colao, A., Ferone, D., Marzullo, P., and Lombardi, G. (2004). *Endocr. Rev.* **25,** 102–152.
4. Kreze, A., Kreze-Spirova, E., and Mikulecky, M. (2001). *Braz. J. Med. Biol. Res.* **34,** 1429–1433.
5. Vidal Cordata, J., Conget Donlo, J. I., Navarro Tellez, M. P., Halperin Rabinovic, I., and Vilardell Latorre, E. (1995). *Ann. Med. Interna.* **12,** 76–78.
6. Abramson, M. J. (1990). *Lancet* **336,** 318–319.
7. Szeto, C. C., Li, K. Y., Chow, C. C., Yeung, V. T., Chan, J. C., and Cockram, C. S. (1997). *Int. J. Clin. Pract.* **51,** 476–477.
8. Katz, J. R., Edwards, R., Khan, M., and Conway, G. S. (1996). *Postgrad. Med. J.* **72,** 682–683.
9. Westphal, S. A. (2000). *Endocr. Pract.* **6,** 450–452.
10. Cosemans, I., Demaerel, P., Wets, B., De Hauwere, B., and Spileers, W. (1999). *Doc. Ophthalmol.* **98,** 175–181.
11. Smail, J. M. (1972). *Br. J. Ophthalmol.* **56,** 25–31.
12. Nabarro, J. D. (1987). *Clin. Endocrinol.* **26,** 481–512.
13. Schade, D. S. and Eaton, R. P. (1979). *Diabetes Care* **2,** 296–306.
14. Marshall, S. M., Walker, M., and Alberti, K. G. M. (1992). In: *International textbook of diabetes mellitus*. Alberti, K. G. M. M. (ed.). John Wiley: Chichester, pp. 1151–1164.
15. Hirose, T., Kuroda, T., Otsuki, M., et al. (1997). *Intern. Med.* **36,** 345–350.
16. Colao, A., Ferone, D., Cappabianca, P., et al. (1997). *J. Clin. Endocrinol. Metab.* **82,** 3308–3314.
17. Sato, K., Takamatsu, K., and Hashimoto, K. (1995). *Endocr. J.* **42,** 739–745.
18. Sandoz Pharmaceuticals. (1996). Sandostatin product information. East Hanover, NJ.
19. Dilger, J. A., Rho, E. H., Que, F. G., and Sprung, J. (2004). *Anesth. Analg.* **98,** 318–320.
20. Herrington, A. M., George, K. W., and Moulds, C. C. (1998). *Pharmacotherapy* **18,** 413–416.
21. Erbas, T., Usman, A., Erbas, B., Varoglu, E., Aras, T., and Bekdik, C. (1993). *J. Endocrinol. Invest.* **16,** 857–861.
22. Sabat, M., Guarner, C., Soriano, G., et al. (1998). *Dig. Dig. Sci.* **43,** 2184–2189.
23. Gaudin, C., Moreau, R., Champigneulle, B., Soubrane, O., Kleber, G., and Lebrec, D. (1995). *Liver* **15,** 236–241.
24. Day, S. M., Gu, J., Polak, J. M., and Bloom, S. R. (1985). *Br. Heart J.* **53,** 153–157.
25. McCormick, P. A., Chin, J., Greenslade, L., et al. (1995). *Hepatology* **21,** 1255–1260.
26. Katz, M. D. and Erstad, B. L. (1989). *Clin. Pharm.* **8,** 255–273.
27. Henning, R. J. and Sawmiller, D. R. (2001). *Cardiovasc. Res.* **49,** 27–37.
28. Baumann, G. (2001). In: *Principles and practice of endocrinology and metabolism.* 3rd ed. Becker, K. L. (ed.). Lippincott Williams and Wilkins: Philadelphia, PA, pp. 129–145.
29. Scanelli, G., Dattola, L., and Padovani, F. (1996). *J. Endocrinol. Invest.* **19,** 647–648.