Sonography of Gallbladder Abnormalities in Acromegaly Patients following Octreotide and Ursodiol Therapy: Incidence and Time Course

Nilo A. Avila, MD,[1] Thomas H. Shawker, MD,[1] Paris Roach, MD,[2] Mary H. Bradford, RT, RDMS,[1] Monica C. Skarulis, MD,[3] Richard Eastman, MD[4]

[1] Diagnostic Radiology Department, Warren Grant Magnuson Clinical Center, National Institutes of Health, Building 10, Room 1C660, 10 Center Drive, MSC 1182, Bethesda, Maryland 20892-1182
[2] Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285
[3] Division of Intramural Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Center Drive, Bethesda, Maryland 20892
[4] Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Center Drive, Bethesda, Maryland 20892

Received 18 June 1997; accepted 16 December 1997

ABSTRACT: *Purpose.* We studied the effects of octreotide and ursodiol on the gallbladders of patients with acromegaly.

Methods. We performed gallbladder sonography in patients with acromegaly at various intervals during treatment. Group I (18 patients) was treated with subcutaneous injections of the somatostatin analogue octreotide. Group II (10 patients) was treated with ursodiol while receiving octreotide therapy.

Results. Seventy-eight percent of patients receiving octreotide developed gallbladder abnormalities: sludge in 72% (13/18) and calculi in 39% (7/18). Ursodiol reversed the gallbladder abnormalities in 7 of 10 patients.

Conclusions. A majority of patients receiving octreotide develop gallbladder abnormalities. Ursodiol appears to reverse the abnormalities in most cases. © 1998 John Wiley & Sons, Inc.* *J Clin Ultrasound* **26**:289–294, 1998.

Keywords: gallbladder; ultrasonography; acromegaly; octreotide; ursodiol

Acromegaly is a disfiguring and life-threatening disorder caused by excessive secretion of growth hormone (GH), usually owing to a pituitary adenoma. The therapeutic efficacy of surgery and radiotherapy is high over the long term. However, in 10–20% of patients, the GH levels remain elevated even 15 or more years after therapy.[1] In recent years, the somatostatin analogues have become available for clinical use, and the results of many studies of their long-term use in acromegaly have been positive.[2] Most patients display marked improvement in signs and symptoms, and 30–90% have significant suppression of both serum GH and insulin-like growth factor I (IGF-I) levels. Shrinkage of the pituitary tumor, usually to a moderate degree, has been reported in 30–50% of patients.[3–7] However, somatostatin analogues have been associated with an increased incidence of gallbladder calculi.[1,8]

Ursodiol is an agent intended for the dissolution of radiolucent gallstones. It is a naturally occurring bile acid that inhibits the hepatic synthesis and secretion of cholesterol as well as the absorption of cholesterol in the intestine. Ursodiol causes the bile of patients with gallstones to change from cholesterol-precipitating to cholesterol-solubilizing, thus resulting in bile conducive to cholesterol stone dissolution.[9]

Correspondence to: N. A. Avila
 CCC 0091-2751/98/060289-06

We studied the incidence of sonographically detectable gallbladder abnormalities associated with long-term therapy with the somatostatin analogue octreotide and evaluated the effect of ursodiol on these abnormalities.

PATIENTS AND METHODS

Sonographic examinations of the gallbladder were performed as part of a protocol studying the effects of octreotide in patients with acromegaly and GH excess after noncurative pituitary surgery. Informed consent was obtained from all patients. After 8 hours of fasting, patients were scanned in the supine and right anterior oblique positions by a technologist and by a radiologist. Sagittal and transverse gray-scale images were obtained using 3.5- and 5.0-MHz sector transducers with Acuson 128 and 128XP ultrasound scanners (Acuson, Mountain View, CA). The greatest length, width, and height of the gallbladder were recorded, and the gallbladder volume (GBV) was calculated according to the following formula: GBV = $\pi/6 \times$ length $\times$ width $\times$ height.[10,11] The following parameters were also recorded: presence of sludge (fluid layering within the gallbladder lumen that may or may not contain particulate floating material, eg, cholesterol crystals); presence of calculi; thickness of the gallbladder wall; diameter of the common hepatic duct; sonographic Murphy's sign; and presence of pericholecystic fluid.

Group I consisted of 18 patients with acromegaly: 7 men and 11 women ranging in age from 25 to 58 years (mean, 38 years). The dose of octreotide was adjusted to attain maximum suppression of GH and IGF-I levels. The ultrasound examinations were performed 1 week prior to starting octreotide and at various times thereafter. The scanning parameters and the patient's fasting state were reproduced for all examinations. We plotted the observed fraction of patients developing sludge and calculi (Figure 1). Because the follow-up period varied among the patients, we obtained estimates of the probability of developing sludge and calculi using an actuarial (Kaplan-Meier) method (Figures 2 and 3).

Group II consisted of 10 of the 18 patients in Group I. While receiving octreotide, these patients, in response to the detection of gallbladder abnormalities, were also given ursodiol, 300–900 mg/day (10 mg/kg/day), for 8–50 months (mean, 27 months). Serial sonographic examinations of the gallbladder were performed over a period of 1–30 months (mean, 4 months) after beginning therapy with ursodiol, and the findings were recorded as outlined above.

RESULTS

Group I

All patients had normal findings on gallbladder sonograms obtained before the initiation of

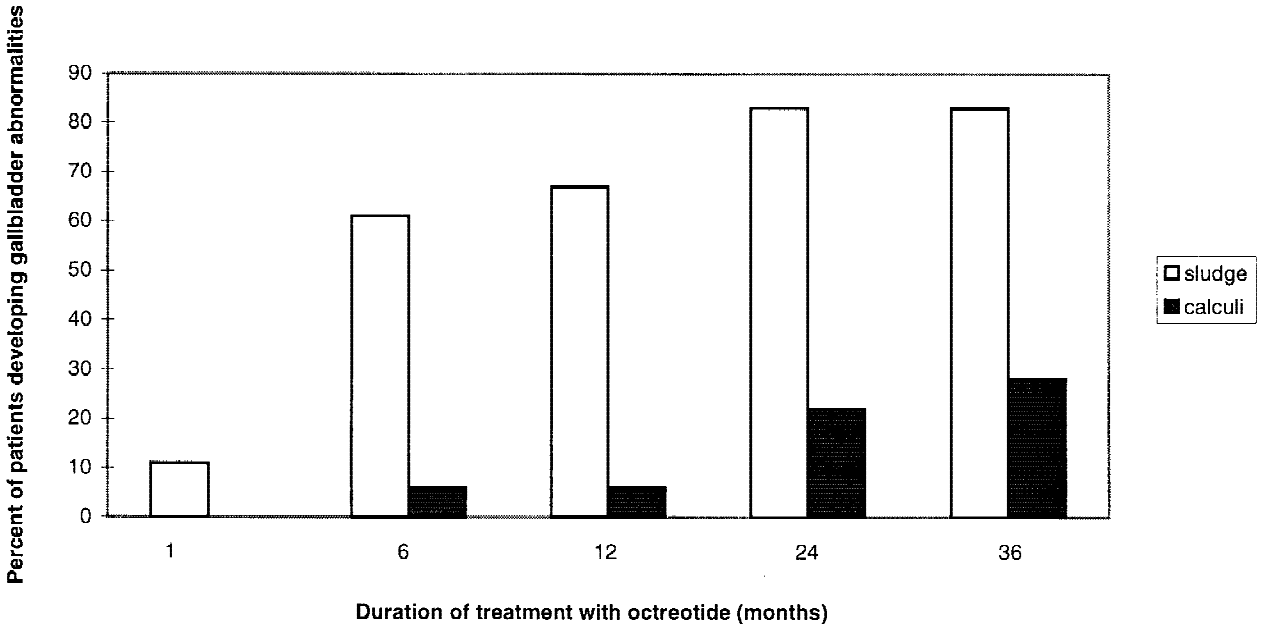

FIGURE 1. Observed fraction of patients receiving octreotide who developed sludge or calculi as a function of months of treatment.

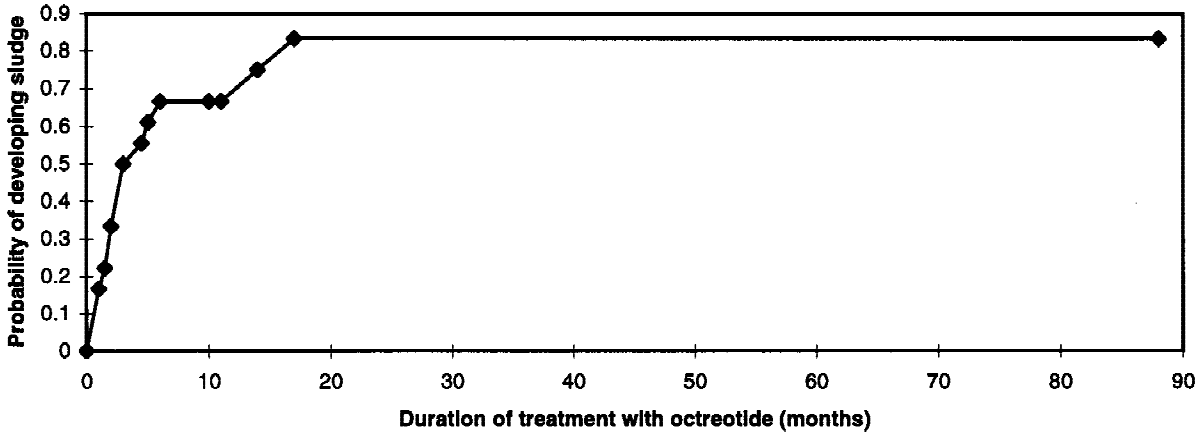

FIGURE 2. Probability of developing sludge during treatment with octreotide (Kaplan-Meier method).

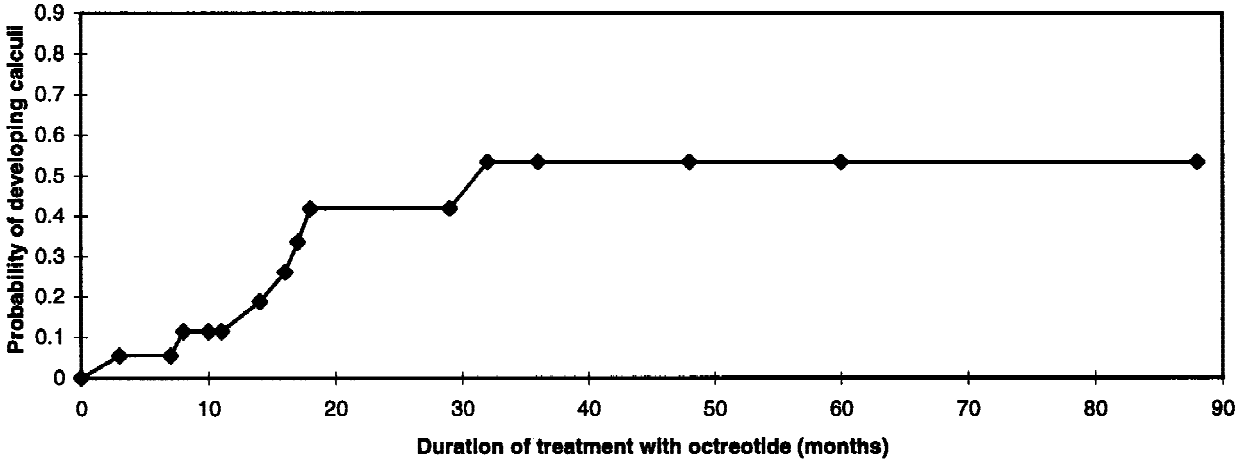

FIGURE 3. Probability of developing calculi during treatment with octreotide (Kaplan-Meier method).

therapy. In 4 (22%) of 18 patients, the gallbladder remained normal during therapy with octreotide (8–88 months). Fourteen patients (78%) developed various abnormalities after the initiation of therapy with octreotide: 13 (72%) developed sludge (150–400 μg/day octreotide for 1–17 months), and 7 (39%) developed gallbladder calculi (150–900 μg/day octreotide for 3–32 months) (Table 1). None of the patients developed pericholecystic fluid, dilatation of the common hepatic duct, or sonographic Murphy's sign. None of the patients developed any symptoms that were clinically consistent with gallbladder disease.

The observed fractions of patients developing sludge and calculi are plotted in Figure 1. The actuarial (Kaplan-Meier) probabilities of developing sludge and calculi are plotted in Figures 2 and 3, respectively. These data suggest a transition from sludge to gallstones as the time of exposure to octreotide increases. In general, the patients receiving higher doses of octreotide (≥ 300 μg/day) developed gallbladder sludge sooner (mean, 3.6 months) than did the patients receiving lower doses (< 300 μg/day) (mean, 14 months) (Table 1).

The gallbladders of 2 patients who developed abnormalities while receiving octreotide returned to normal (without intervention) during octreotide therapy. Patient 5 developed sludge 2 months after the initiation of octreotide (300 μg/day); the gallbladder was normal 2 months later, while the patient was still receiving octreotide. Patient 7 developed sludge 6 months after the initiation of octreotide (300 μg/day); the gallbladder returned to normal at 15 months, while the patient was still receiving octreotide. The gallbladder again developed sludge at 34 months, became normal at 41 months, and remained normal for an additional 9 months.

Group II

Ten patients who developed gallbladder abnormalities while receiving octreotide were given ur-

TABLE 1
Summary of Sonographic Findings in Patients Treated with Octreotide with or without Ursodiol

Patient No.	Age/Sex	Duration of Therapy in Patients who Remained Normal during Octreotide	Average Dose and Duration of Therapy		Ursodiol Dose	Follow-up after Initiation of Ursodiol Therapy
			Developed Sludge during Octreotide	Developed Calculi during Octreotide		
1	39/F	88 months	—	—	—	—
2	38/M	8 months	—	—	—	—
3	33/F	11 months	—	—	—	—
4	25/F	17 months	—	—	—	—
5	58/F	—	300 μg/day 2 months	—	—	—
6	29/M	—	300 μg/day 1.5 months	—	—	—
7	35/F	—	300 μg/day 6 months	—	—	—
8	31/M	—	300 μg/day 17 months	300 μg/day 17 months	— —	— —
9	38/F	—	300 μg/day 3 months	—	600 mg/day	Remained abnormal with sludge after 28 months
10	31/F	—	300 μg/day 1 month	—	300 mg/day	Normal after 24 months
11	32/M	—	300 μg/day 1 month	—	900 mg/day	Normal after 5 months
12	42/F	—	300 μg/day 4.5 months	—	600 mg/day	Normal after 11 months
13	52/M	—	300 μg/day 5 months	300 μg/day 16 months	900 mg/day	Normal after 13 months
14	37/M	—	300 μg/day 2 months	300 μg/day 18 months	900 mg/day	Normal after 18 months
15	42/F	—	150 μg/day 14 months	150 μg/day 14 months	600 mg/day	Normal after 13 months
16	34/F	—	300 μg/day 3 months	300 μg/day 8 months	600 mg/day	Normal after 10 months
17	31/F	—	400 μg/day 1 month	400 μg/day 3 months	900 mg/day	Remained abnormal with sludge and calculi after 24 months
18	48/M	—	300 μg/day 3 months	900 μg/day 32 months	600 mg/day	Remained abnormal with sludge and calculi after 27 months

sodiol at various times after the initiation of octreotide. Follow-up sonograms showed that the gallbladders of 7 patients (all 7 had sludge, and 4 also had calculi) returned to normal after 5–18 months of treatment with ursodiol (Figure 4). The gallbladders of 3 patients remained abnormal 24–28 months after therapy with ursodiol was initiated (all 3 had sludge, and 2 also had calculi) (Table 1).

DISCUSSION

In our series, we showed that the gallbladders of some patients receiving octreotide remained normal for as long as 88 months of treatment but that 78% developed abnormalities. None of our patients had any history of liver or biliary tract diseases, and their gallbladder sonograms were normal before therapy. We also demonstrated an increased probability of developing gallbladder abnormalities with increasing duration of octreotide therapy. Five of 7 patients with gallbladder calculi had sludge before the appearance of calculi; in 2 of 7, calculi and sludge appeared on the same examination. These data suggest a transition from sludge to gallstones as the time of exposure to octreotide increases (Figures 1–3).

Gallbladder abnormalities developed with doses of octreotide as low as 150 μg/day and as high as 900 μg/day. The 1 patient in our series who received 150 μg/day octreotide developed sludge and calculi 14 months after initiation of therapy. On average, the patients receiving higher doses of octreotide who developed gallbladder sludge did so earlier during therapy (mean, 3.6 months). Thus, the rate of development of gallbladder abnormalities seems to be related to the dose of octreotide.

Meal-stimulated cholecystokinin release and gallbladder contraction following a fatty meal are significantly lower than normal in patients with acromegaly treated with somatostatin ana-

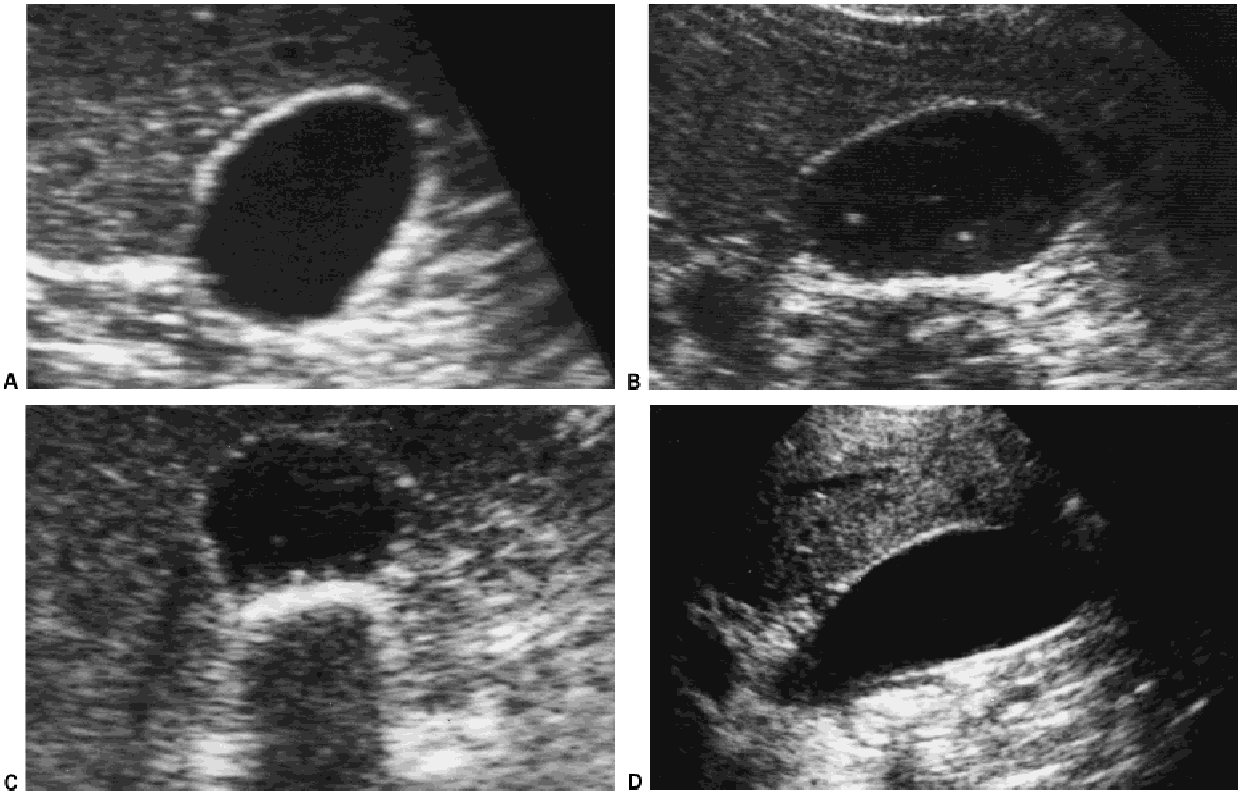

FIGURE 4. Sonograms of gallbladder in a 37-year-old acromegaly patient (patient 14). **(A)** Normal transverse sonogram of the gallbladder prior to octreotide therapy. **(B)** Transverse sonogram through the gallbladder after 15 months of octreotide therapy. Note sludge in the gallbladder. **(C)** Transverse sonogram through the gallbladder after 18 months of octreotide therapy. Note echogenic calculi layering posteriorly, producing acoustic shadowing. **(D)** Sagittal sonogram of the gallbladder 52 months after initiation of octreotide and 18 months after initiation of ursodiol therapy. Note normal gallbladder.

logues.[12] Somatostatin analogue doses as low as 5 μg/day have an immediate inhibitory action on the gallbladder in healthy adults. Therefore, gallbladder paresis does not seem avoidable by reducing the dose of somatostatin analogue while maintaining the agent's suppressive effect on GH secretion.[1,13] The sequence of development of gallbladder disorders following somatostatin analogue therapy seems to be as follows: suppression of gallbladder contractility, cholestasis, development of sludge, and, finally, gallstone formation.[1] Indeed, all of our patients who developed gallstones did so simultaneously with or after the development of sludge.

In the majority of cases, sludge and gallstones induced by somatostatin analogues are rich in cholesterol and thus amenable to dissolution with oral bile acid therapy.[8] In our series, however, the gallbladders of 3 of the 10 patients receiving long-term treatment with ursodiol (24–28 months) remained abnormal: all 3 had sediments and sludge, and 2 had calculi. One patient (patient 18) developed gallstones while receiving octreotide and ursodiol. In theory, resistance to ursodiol treatment as a result of concurrent somatostatin analogue therapy is possible. However, ursodiol dissolved the sludge and calculi in 7 of 10 patients while they were receiving octreotide, suggesting that octreotide does not affect ursodiol efficacy adversely in all patients. The efficacy of ursodiol in this setting may also be affected by the fact that some of the calculi associated with somatostatin analogue therapy contain varying degrees of calcium, which is not dissolved by ursodiol.[9]

Somatostatin analogues are currently being used in the treatment of acromegaly, metastatic carcinoid, and vasoactive intestinal peptide–secreting tumors. Prior studies have reported an increased incidence of gallstones in patients treated with somatostatin analogues; however, to our knowledge, there has been no prior report of somatostatin-induced gallstones in the imaging literature. Radiologists should be aware of our finding that a majority (78%) of patients treated with somatostatin analogues developed gallbladder abnormalities. Gallbladder sludge may spontaneously resolve in a minority of patients while they are receiving somatostatin analogues. In our

limited study population, ursodiol appeared to reverse the formation of sludge and gallstones in a majority of patients.

REFERENCES

1. Eastman RC, Gorden P, Glatstein E, et al: Radiation therapy of acromegaly. *Endocrinol Metab Clin North Am* 1992;21:693.
2. Shi Y-F, Zhu X-F, Harris AG, et al: Prospective study of the long-term effects of somatostatin analog (octreotide) on gallbladder function and gallstone formation in Chinese acromegalic patients. *J Clin Endocrinol Metab* 1993;76:32.
3. Lamberts SWJ, Uitterlinden P, Vrschoor L, et al: Long-term treatment of acromegaly with the somatostain analogue SMS 201-995. *N Engl J Med* 1985;313:1576.
4. Barkan AL, Kelch RP, Hopwood NJ, et al: Treatment of acromegaly with the long acting somatostatin analogue SMS 201-995. *J Clin Endocrinol Metab* 1988;66:16.
5. Sassolas G, Harris AG, James-Deidier A: The French SMS 201-995 Acromegaly Study Group. Long term effect of incremental doses of the somatostatin analog SMS 201-995 in 58 acromegalic patients. *J Clin Endocrinol Metab* 1977;71:391.
6. Barkan AL, Lloyd RV, Chandler WF, et al: Preoperative treatment of acromegaly with long-acting somatostatin analog SMS 201-995: shrinkage of invasive pituitary microadenomas and improved surgical remission rate. *J Clin Endocrinol Metab* 1988;67:1040.
7. Ho KY, Weissberger AJ, Marbach P, et al: Therapeutic efficacy of the somatostatin analogue SMS 201-005 (octreotide) in acromegaly. *Ann Intern Med* 1990;112:173.
8. Eastman RC, Arakaki RF, Shawker TS, et al: A prospective examination of octreotide-induced gallbladder changes in acromegaly. *Clin Endocrinol (Oxf)* 1992;36:265.
9. Hussaini SH, Pereira SP, Murphy GM, et al: Composition of gallbladder stones associated with octreotide: response to oral ursodeoxycholic acid. *Gut* 1995;36:126.
10. Everson GT, Braverman DZ, Johnson ML, et al: A critical evaluation of real time ultrasonography for the study of gallbladder volume and contraction. *Gastroenterology* 1980;79:40.
11. Dodds WJ, Groh WJ, Darweesh RM, et al: Sonographic measurement of gallbladder volume. *AJR Am J Roentgenol* 1985;145:1009.
12. Van Liessum PA, Hopman WPM, Pieters FGGM, et al: Postprandial gallbladder motility during long term treatment with the long-acting somatostatin analog SMS 201-995 in acromegaly. *J Clin Endocrinol Metab* 1989;69:557.
13. Zhu XF, Shi YF, Dai Q, et al: Effect of small doses of a somatostatin analogue, octreotide, on gallbladder contractility in normal Chinese adults. *Dig Dis Sci* 1992;37:105.