Effect of Long-Acting Somatostatin Analog (Somatulin) on Renal Hyperfiltration in Patients With IDDM

MARLOES L. JACOBS, MD
FRANS H.M. DERKX, MD
THEO STIJNEN, PHD
STEVEN W.J. LAMBERTS, MD
ROB F.A. WEBER, MD

OBJECTIVE — To investigate whether long-acting somatostatin (SMS) can suppress renal hyperfiltration in patients with IDDM.

RESEARCH DESIGN AND METHODS — A double-blind, randomized treatment of nine patients with IDDM was used. Selection criteria were renal hyperfiltration (glomerular filtration rate [GFR] ≥129 ml · min^{-1} · 1.73 m^2) and absence of hypertension and macroalbuminuria. Treatment was either with a long-acting SMS analog (Somatulin, 30 mg) or with placebo, given by intramuscular injections every 10 days for 9 months. GFR, effective renal plasma flow (ERPF), IGF-I, and 24-h growth hormone (GH) profiles were used as evaluation parameters.

RESULTS — Five patients were randomized to Somatulin, four patients to placebo. One of the patients treated with Somatulin stopped after 3 months because of persistent abdominal discomfort after the injections. Somatulin treatment for 3 months lowered GFR and ERPF compared with placebo ($P < 0.05$). After 9 months, the differences were no longer significant. After 3 months, IGF-I concentrations were decreased in all Somatulin-treated patients. GH secretion tended to increase in the placebo group.

CONCLUSIONS — The administration of long-acting Somatulin to patients with IDDM and renal hyperfiltration leads to only a temporary reduction of ERPF/GFR.

Of patients with IDDM, ~30–40% develop diabetic nephropathy (DNP) (1). Renal hyperfiltration is considered to be the first abnormality in the diabetic kidney (2) and might be a risk factor for DNP (3–5). A role for growth hormone (GH) in hyperfiltration is suggested, based on the observation that the glomerular filtration rate (GFR) increases in patients with IDDM who received GH injections (6) and in healthy volunteers treated with IGF-I intravenously (7). Acromegalic patients also have increased renal function (8). Elevated GH concentrations have been found in patients with poorly and moderately controlled IDDM and are associated with renal hyperfiltration (9–11).

Treatment of these diabetes-associated abnormalities in the GH/IGF-I axis might offer an alternative treatment option to prevent DNP. Remission of DNP was seen after the onset of hypopituitarism (12). Subcutaneous injections of octreotide, a somatostatin (SMS) analog, led to a reduction in GFR in patients with acromegaly (8). In a short-term study, GFR was reduced by continuous subcutaneous infusion of SMS in patients with IDDM (13). We have investigated whether the administration of a long-acting SMS analog (Somatulin, BIM 23014), which has proven its efficacy to lower GH levels in patients with acromegaly (14), could achieve reduction of renal hyperfiltration.

From the Departments of Internal Medicine III (M.L.J., S.W.J.L., R.F.A.W.) and Internal Medicine I (F.H.M.D.), University Hospital Dijkzigt; and the Department of Biostatistics (T.S.), Erasmus University, Rotterdam, The Netherlands.

Address correspondence and reprint requests to Marloes L. Jacobs, MD, Department of Internal Medicine III, Room D435, University Hospital Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: weber@inw3.azr.nl.

Received for publication 20 August 1996 and accepted in revised form 19 November 1996.

CV, coefficient of variation; DNP, diabetic nephropathy; DRP, diabetic retinopathy; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; GH, growth hormone; HPLC, high-performance liquid chromatography; RIA, radioimmunoassay; SMS, somatostatin.

RESEARCH DESIGN AND METHODS

Patients and study design

Nine patients with IDDM and renal hyperfiltration (GFR ≥129 ml · min^{-1} · 1.73 m^2) participated in the study. They had no hypertension, macroalbuminuria, medication other than insulin, or oral contraceptives in women.

Five patients were allocated to treatment with the long-acting SMS analog Somatulin (30 mg) (14) and four patients to placebo therapy (both supplied by Ipsen Biotech, Paris, France) in a double-blind randomized fashion. Trial medication was administered by a study nurse, the patients themselves, or a spouse by intramuscular injections every 10 days. Compliance with the treatment was checked by examination of the empty vials. At baseline, 3, and 9 months, all patients were admitted to the ward for the assessment of serum GH concentrations every hour during 24 h, gallbladder ultrasound, and measurement of 24-h albumin excretion and renal function [GFR and effective renal plasma flow (ERPF)].

All patients were treated with insulin by the basal/prandial regimen with appropriate adjustments of insulin doses. The study was approved by the Medical Ethical Committee, and all patients gave written informed consent.

Laboratory techniques

Renal function was measured during normoglycemia after at least 8 h fasting. To maintain good hydration, a glucose 5% (wt/vol) infusion was given with an appropriate amount of insulin added. Blood glucose levels were measured at 30-min intervals and kept constant between 4 and 8 mmol/l. GFR and ERPF were measured simultaneously by the continuous infusion technique with ^{125}I-thalamate and ^{131}I-hippuran sulfate (15) and standardized to 1.73

m^2 body surface area. Normal GFR in our laboratory is 88–130 ml · min^{-1} · 1.73 m^2 (10).

Plasma GH was measured by a solid phase two-site immunoradiometric assay (CIS bio international, ORIS group, Gif-sur-Yvette, France; detection limit 0.04 μg/l; normal values are <10 μg/l; intra-assay and interassay coefficients of variation [CV] 3 and 4%, respectively). IGF-I was removed from its binding proteins by the acid-ethanol extraction method (16) and was measured by radioimmunoassay (RIA) (Medgenix, Fleurus, Belgium; reference range 9–64 nmol/l; intra-assay and interassay CV 7 and 10%, respectively). HbA_{1c} was determined by high-performance liquid chromatography (HPLC) (reference range 5.0–6.3%). Glucagon was measured after extraction by RIA (Eurodiagnostica; sensitivity 3 ng/l; normal values are <80 ng/l; CV 17–30%), serum creatinine by colorimetry (reference range 60–110 μmol/l), and albumin excretion by immunonephelometry. Microalbuminuria is defined as albumin excretion between 30 and 300 mg/24 h.

Dilated fundoscopy was performed by an experienced ophthalmologist and was graded as no diabetic retinopathy (DRP), background DRP, or proliferative DRP.

Table 1—*Baseline characteristics of the patients*

	Somatulin	Placebo
n	5	4
Sex (M/F)	3/2	3/1
Age (years)	25 (19–45)	28 (21–50)
Duration of diabetes (years)	14.0 (5–25)	15.5 (9–44)
BMI (kg/m^2)	28.2 (21.8–37.4)	22.5 (20.8–28.4)
Insulin dose (U/day)	72 (46–78)	65 (44–72)
DRP		
No	4	2
Background	1	1
Proliferative	—	1
DNP		
No	3	4
Microalbuminuria	2	—
HbA_{1c} (%)	8.8 (7.6–10.1)	7.7 (7.0–9.3)
Serum creatinine (μmol/l)	55.0 (50–73)	54.5 (45–65)
Glucagon (ng/l)	4 (3–56)	14 (3–47)
IGF-I (nmol/l)	24.7 (15.1–28.6)	23.1 (12.4–27.6)
Mean 24-h GH concentration (μg/l)	2.8 (1.0–3.5)	2.8 (1.2–8.3)
GH area under the curve (μg · l^{-1} · 24 h^{-1})	1,602 (536–2,087)	1,334 (703–4,032)
Albuminuria (mg/24 h)	22 (9–65)	10 (6–14)
GFR (ml · min^{-1} · 1.73 m^{-2})	144 (129–154)	142 (139–159)
ERPF (ml · min^{-1} · 1.73 m^{-2})	587 (540–598)	658 (553–687)
Gallbladder ultrasound		
Normal	5	3
Polyp	—	1

Data are median (range) or number (*n*) of patients.

Statistical analysis

Differences between the medians (ranges) in the Somatulin and placebo group were analyzed by the (exact) Mann-Whitney *U* test. Spearman rank correlation coefficients were calculated between individual variables. The two-sided level of significance was set at $P < 0.05$.

RESULTS — There were no statistically significant differences in baseline characteristics between the two groups (Table 1).

Side effects were reported both by Somatulin- and placebo-treated patients: abdominal discomfort and diarrhea for 1 to 2 days after the injection (temporary), painful induration at the injection site, and decreased blood glucose concentration in the evening or day after injection (recurrent). One patient in the Somatulin group stopped after 3 months because of persistent abdominal discomfort after each injection. No gallstones developed, but after 3 months asymptomatic gallbladder sludge was seen in one patient.

Individual data on GH area under the curve (GH-AUC), plasma IGF-I concentration, GFR, and ERPF are depicted in Fig. 1. Compared with baseline, GH-AUC had decreased in four of the five patients after 3 months treatment with Somatulin (Fig. 1*A*), whereas the four placebo-treated patients all had increased GH-AUC (Fig. 1*B*). IGF-I decreased in all patients treated with Somatulin (Fig. 1*C*). The changes from baseline in GH and IGF-I concentrations were not significantly different between the two treatment groups (Table 2).

GFR was decreased in four of the five Somatulin-treated patients at 3 months, but the decrease was sustained until 9 months only in patient 3 (Fig. 1*E*). The responding patient was one of the patients with microalbuminuria; reevaluation at 3 months after the last injection showed a return of his GFR to the level at baseline. There was a tendency to a further increase of hyperfiltration in the placebo group (Fig. 1*F*). Median change from baseline was significantly different in Somatulin compared with placebo-treated patients at 3 months (−3 vs. 12 ml · min^{-1} · 1.73 m^2; $P < 0.05$), but not at 9 months (Table 2).

As shown in Figs. 1*G* and *H*, ERPF was significantly different between the study groups at 3 and 9 months ($P < 0.05$). All patients treated with Somatulin had a decrease in ERPF from baseline to 3 months. At 9 months, values tended to return to pretreatment levels (Fig. 1*G*). Median ERPF in placebo-treated patients did not change (Fig. 1*H*). The change in ERPF from baseline was significantly different between Somatulin- and placebo-treated patients at 3 months only (Table 2).

Median insulin dose decreased during the study period, but not significantly differently in the Somatulin- versus placebo-treated patients (−12 vs. −16 U/day). At 3 months, the median change in HbA_{1c} was significantly different in Somatulin- versus placebo-treated patients (−0.8% vs. 0.5%; $P < 0.05$). The change in HbA_{1c} was significantly correlated with the change in ERPF ($r = 0.69$; $P < 0.05$). At 9 months there was no significant difference in HbA_{1c} between the two treatment groups. Blood pressure, body weight, albumin excretion, serum creatinine, and plasma glucagon concentration did not change in either group.

CONCLUSIONS — A role for GH in the development of diabetic renal hyperfiltration and eventually DNP has been suggested previously (6–8,10). In this study we demonstrate that patients with IDDM

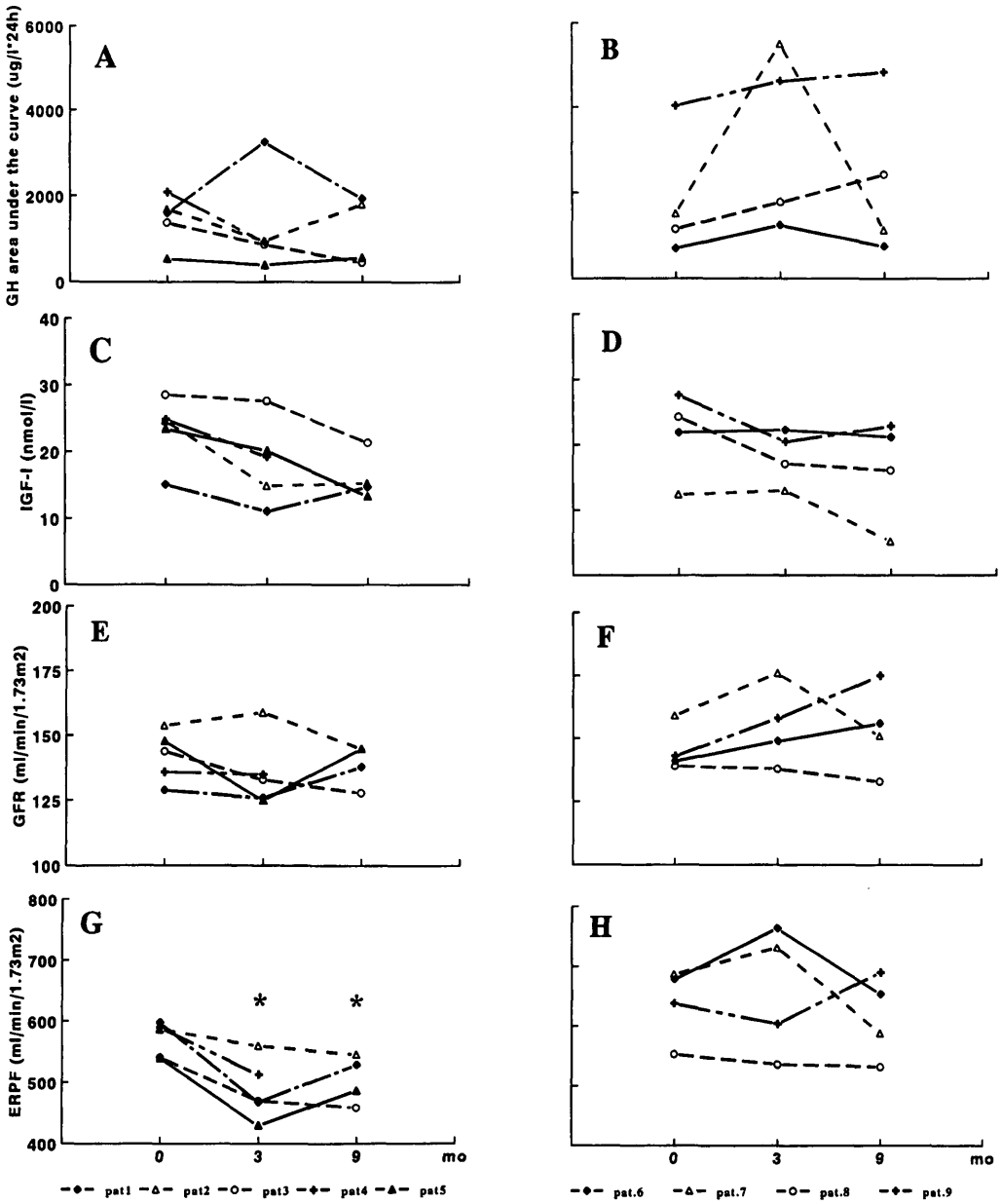

Figure 1—*Area under the 24-h GH curve, IGF-I concentrations, GFR, and ERPF of the individual patients before and during treatment with Somatulin (A, C, E, and G) or placebo (B, D, F, and H). *P < 0.05 versus placebo.*

and renal hyperfiltration show decreased GFR and ERPF after 3 months of treatment with Somatulin compared with placebo. The effect was lost after 9 months of Somatulin therapy in four of the five patients. Although our study population is small, our findings at 3 months are in accordance with other acute and short-term studies (17,13).

The mechanisms by which SMS reduces ERPF and/or GFR are not fully understood. Indirect effects of SMS on renal function can be assumed by suppression of GH/IGF-I and glucagon. GH suppression leads to a decrease in total body water (18), which might have caused a seeming decrease in ERPF. A reduced systemic and local IGF-I concentration leads to diminished renal vasodilation (7) and thereby to a reduction of ERPF, possibly by suppression of nitric oxide (19) or kinin (20) activity. The small and temporary suppression of GH in our study might have been sufficient to suppress IGF-I in the kidney and thereby hyperfiltration, although the changes in plasma IGF-I were only marginal. Reduction of plasma glucagon and insulin concentrations, other possible effects of SMS therapy with renal consequences, could not be demonstrated in our study. Somatulin led to a small improvement of glycemic control, which might have contributed to the reduction in GFR (9).

A direct effect of SMS on the kidney has been demonstrated in vitro, where SMS could relax cultured human mesangium cells by antagonizing the constricting effect of angiotensin II (21). This would induce an increase rather than a decrease in renal function, which might explain the return to high GFR after 3 months of Somatulin treatment.

Table 2—*Median changes from baseline in GH/IGF-I secretion and renal function tests*

	Somatulin	Placebo
After 3 months		
n	5	4
GH area under the curve (μg/l per 24 h)	−515 (−1,163 to 1,656)	602 (533 to 3,979)
Mean 24-h GH concentration (μg/l)	−1.0 (−1.9 to 2.6)	1.7 (1.0 to 6.4)
IGF-I (nmol/l)	−4 (−9.8 to −0.9)	−3.4 (−7.2 to 0.6)
GFR (ml · min^{-1} · 1.73 m^{-2})	−3 (−23 to 5)*	12 (−1 to 17)
ERPF (ml · min^{-1} · 1.73 m^{-2})	−77 (−130 to −27)*	14 (−34 to 85)
After 9 months		
n	4	4
GH area under the curve (μg · l^{-1} · 24 h^{-1})	68 (−931 to 340)	424 (−384 to 1,267)
Mean 24-h GH concentration (μg/l)	0.2 (−1.6 to 0.6)	0.1 (−1.0 to 1.7)
IGF-I (nmol/l)	−8.3 (−10.2 to −0.4)	−6.0 (−8.2 to −0.7)
GFR (ml · min^{-1} · 1.73 m^{-2})	−6 (−16 to 9)	5 (−8 to 32)
ERPF (ml · min^{-1} · 1.73 m^{-2})	−61 (−82 to −41)	−23 (−99 to 52)

Data are median (range) change from baseline. Differences were analyzed by the exact Mann-Whitney *U* test; *$P < 0.05$ versus placebo.

Because we could not reduce GFR in all patients, resistance to the GH suppressive effect of SMS is suspected (22,23). Increased doses of Somatulin might have overcome this problem, although acromegalic patients had persistent and effective GH reduction by less frequent administration of the same dose (14). Development of resistance to SMS by receptor adaptation (desensitization) (24,25) is supported by the lack of a long-term persistent beneficial effect in our study and in a study on diabetic retinopathy (26).

The increase of GH secretion and GFR at 3 months in the placebo-treated patients suggests that the maximum level of renal hyperfiltration has not yet been reached, even after a diabetes duration of at least 9 years. This increase was prevented by Somatulin treatment, but the effect was only temporary. However, due to the small number and clinical heterogeneity of patients, lack of statistical significance does not exclude a small real effect.

We conclude that administration of Somatulin does not seem suitable for long-term treatment of renal hyperfiltration in patients with IDDM. Persistent side effects and resistance to the GH suppressive effects are seen after treatment for more than 3 months. A larger long-term study, maybe with higher dosages of this or another analog, is needed to confirm our data.

Acknowledgments— Financial support for this study was provided by Novo Nordisk Farma B.V., The Netherlands, and Ipsen Biotech, France.

The authors thank the patients for their willing participation; Simone Mulder, Marjolein Gerrits-Boeye, and Nelleke Bos-Sonneveld for excellent technical assistance in performing the GFR/ERPF procedures; the nurses at the Clinical Research Unit for the organization of patient care; and Piet Uitterlinden for performing the GH and IGF-I assays.

References

1. Nathan DM: Long-term complications of diabetes mellitus. *N Engl J Med* 328:1676–1685, 1993
2. Selby JV, FitzSimmons SC, Newman JM, Katz PP, Sepe S, Showstack J: The natural history and epidemiology of diabetic nephropathy. *JAMA* 263:1954–1960, 1990
3. Mogensen CE: Early glomerular hyperfiltration in insulin-dependent diabetics and late nephropathy. *Scand J Clin Lab Invest* 46:201–206, 1986
4. Azevedo MJ, Gross JL: Follow-up of glomerular hyperfiltration in normoalbuminuric type I (insulin-dependent) diabetic patients (Letter). *Diabetologia* 34:611, 1991
5. Rudberg S, Persson B, Dahlquist G: Increased glomerular filtration rate as a predictor of diabetic nephropathy: an 8-year prospective study. *Kidney Int* 41:822–828, 1992
6. Christiansen JS, Gammelgaard J, Frandsen M, Ørskov H, Parving H-H: Kidney function and size in type I (insulin-dependent) diabetic patients before and during growth hormone administration for 1 week. *Diabetologia* 22:333–337, 1982
7. Guler H-P, Eckardt K-U, Zapf J, Bauer C, Froesch ER: Insulin-like growth factor I increases glomerular filtration rate and renal plasma flow in man. *Acta Endocrinol* 121:101–106, 1989
8. Dullaart RPF, Meijer S, Marbach P, Sluiter WJ: Effect of a somatostatin analogue, octreotide, on renal haemodynamics and albuminuria in acromegalic patients. *Eur J Clin Invest* 22:494–502, 1992
9. Christiansen JS: On the pathogenesis of the increased glomerular filtration rate in short-term insulin-dependent diabetes. *Dan Med Bull* 31:349–361, 1984
10. Blankestijn PJ, Derkx FHM, Birkenhäger JC, Lamberts SWJ, Mulder P, Verschoor L, Schalekamp MADH, Weber RFA: Glomerular hyperfiltration in insulin-dependent diabetes mellitus is correlated with enhanced growth hormone secretion. *J Clin Endocrinol Metab* 77:498–502, 1993
11. Jacobs ML, Nathoe HMW, Blankestijn PJ, Stijnen TH, Weber RFA: Growth hormone responses to growth hormone-releasing hormone and clonidine in patients with type I diabetes and in normal controls: effect of age, body mass index and sex. *Clin Endocrinol* 44:547–553, 1996
12. Plumb M, Nath K, Seaquist ER: Hypopituitarism stabilizes the renal and retinal complications of diabetes mellitus. *Am J Nephrol* 12:265–267, 1992
13. Serri O, Beauregard H, Brazeau P, Abribat T, Lambert J, Harris A, Vachon L: Somatostatin analogue, octreotide, reduces increased glomerular filtration rate and kidney size in insulin-dependent diabetes. *JAMA* 265:888–892, 1991
14. Heron I, Thomas F, Dero M, Gancel A, Ruiz JM, Schatz B, Kuhn JM: Pharmacokinetics and efficacy of a long-acting formulation of the new somatostatin analog BIM 23014 in patients with acromegaly. *J Clin Endocrinol Metab* 76:721–727, 1993
15. Zietse R, Blankestijn PJ, Pos B, Balk AHMM, Derkx FHM, Weimar W, Schalekamp MADH: Optimising glomerular filtration rate and effective renal plasma flow measurements using a simple pharmacokinetic model. *Clin Nephrol* 43:29–34, 1995
16. Daughaday WH, Mariz IK, Blethen SL: Inhibition of access of bound somatomedin to membrane receptor and immunobinding sites: a comparison of radioreceptor and radioimmunoassay of somatomedin in native and acid-ethanol-extracted serum. *J Clin Endocrinol Metab* 51:781–788, 1980
17. Vora J, Owens DR, Luzio S, Atiea J, Ryder R, Hayes TM: Renal response to intravenous somatostatin in insulin-dependent diabetic patients and normal subjects. *J Clin Endocrinol Metab* 64:975–979, 1987
18. Møller J: Effects of growth hormone on human fluid homeostasis. In *Growth Hormone in Adults*. Juul A, Jørgensen JOL, Eds. Cambridge Univ. Press, New York, 1996, p. 220–233
19. Hirschberg R, Brunori G, Kopple JD, Guler H-P: Effects of insulin-like growth factor I on renal function in normal men. *Kidney Int* 43:387–397, 1993

20. Jaffa AA, LeRoith D, Roberts CT, Rust PF, Mayfield RK: Insulin-like growth factor I produces renal hyperfiltration by a kinin-mediated mechanism. *Am J Physiol* 266: F102–F107, 1994
21. Díez-Marqués ML, García-Escribano C, Medina J, Boyano-Adanez MC, Arilla E, Torrecilla G, Rodríguez-Puyol D, Rodríguez-Puyol M: Effects of somatostatin on cultured human mesangial cells. *Endocrinology* 136: 3444–3451, 1995
22. Hyer SL, Sharp PS, Brooks RA, Burrin JM, Kohner EM: Continuous subcutaneous octreotide infusion markedly suppresses IGF-I levels whilst only partially suppressing GH secretion in diabetics with retinopathy. *Acta Endocrinol* 120:187–194, 1989
23. Cohen RM, Abplanalp WA: Resistance of growth hormone secretion to somatostatin in men with type I diabetes mellitus. *Diabetes* 40:1251–1258, 1991
24. Londong JE, Angerer M, Kutz K, Landgraf R, Londong V: Diminishing efficacy of octreotide (SMS 201-995) on gastric functions of healthy subjects during one-week administration. *Gastroenterology* 96:713–722, 1989
25. Lamberts SWJ, van der Lely A-J, de Herder WW, Hofland LJ: Octreotide. *N Engl J Med* 334:246–254, 1996
26. Mallet B, Vialettes B, Haroche S, Escoffier P, Gastaut P, Taubert J-P, Vague P: Stabilization of severe proliferative diabetic retinopathy by long-term treatment with SMS 201-995. *Diabetes Metab* 18:438–444, 1992