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# The Effect of Long Acting Somatostatin Analogue SMS 201-995 in Acromegaly

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*Somatostatin is a potent inhibitor of the growth hormone (GH) secretion. However, the short half-life as well as the rebound phenomenon have rendered it impractical for therapeutic use. SMS 201-995, a long acting somatostatin analogue, has been shown to have a long acting inhibitor effect on GH secretion. To observe its suppressive effect on GH secretion and to determine whether it has a diabetogenic effect and whether it can suppress the paradoxical response of GH, we administered 50 μg of SMS 201-995 subcutaneously to five acromegalic patients before breakfast. Serum GH was reduced 85% from the basal concentration four hours after the administration of SMS 201-995 and remained below the basal level for up to eight hours without a rebound phenomenon. The pattern of glucose intolerance was observed in 4 out of 5 patients but not in the normal controls; it seemed to be caused by exessive GH. Also SMS 201-995 did not suppress postprandial insulin and glucagon secretion. In addition, we observed that SMS 201-995 suppressed the paradoxical release of GH to TRH in two of three patients who showed a paradoxical response. Unexpectedly one patient who had no paradoxical response before the administration of SMS 201-995 showed a paradoxical response. In conclusion, we suggest that more than 50 μg of SMS 201-995 should be given at least 3 times a day for adequate adjunctive therapy of acromegaly. The SMS 201-995 has no diabetogenic effect.*

**Key Words:** *SMS 201-995, Acromegaly, Growth hormone*

## INTRODUCTION

Somatostatin is a potent inhibitor of secretion of the GH in patietns with acromegaly[1~8]. However, the short half-life of somatostatin as well as the rebound hypersecretion of growth hormone that occurs after its infusion, have rendered the native tetradecapeptide impractical for therapeutic use[2].

Efforts have been directed toward developing somatostin analogues with a longer and more specific effect[9~10]. Bauer et al[11] finally found an octapeptide which they called selective minisomatostatin (SMS 201-995; Sandoz, Bases, Switzerland). The subcutaneous administration of a single 50 μg dose of SMS 201-995 to patients with acromegaly has been shown to have a long-acting inhibitor effect on plasma growth hormone without producting rebound hypersecretion[12~13]. Thereafter SMS 201-995 has been reported to be an useful adjunctive therapeutic drug in acromegalic patients[14], but the adequate dosage and frequency of administration were variable.

A possible adverse effect of SMS 201-995 is the suppression of insulin and glucagon secretion. Several reports demonstrated no diabetogenic effect of SMS 201-995[15~17].

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Most of acromegalic patients shows a paradoxical response to TRH or LRH. Somatostatin suppressed the response in some of them[18] although the mechanism has not been known. However, the effect of SMS 201-995 on the paradoxical response has not been demonstrated so far. Therefore, we have tested the effectiveness and the duration of action of SMS 201-995 as a suppressor of serum GH. Also, we have tested the effects on blood glucose, secretion of insulin and glucagon, and the paradoxical response.

## METHODS

### 1. Subjects

Five patients with acromegaly, one male and four females, were studied. All the patients had clinical manifestations, such as acral enlargement of extremities, excessive perspiration, and radiologic evidence of a pituitary tumor. The duration of symptoms was in the range of 4-13 years. One patient (patient 1) had undergone a transsphenoidal adenomectomy followed by bromocriptine. Two patients (patient 2, 4) had had radiation followed by bromocriptine, and one patient (patient 3) had received only bromocriptine. One patient was a new case who had not received any treatment prior to the study (Table 1).

### 2. Study Design

All patients discontinued medication at least two weeks before the present study. On the first morning, 200 $\mu$g of thyrotropin releasing hormone (TRH) was administered intravenously to observe the paradoxical response of GH. Venous blood was obtained every thirty minutes via inserted antecubital cannula.

During the second day, all the patients were injected subcutaneously with 0.5 ml of normal saline as a placebo thirty minutes before breakfast, then their diurnal variation of GH secretion was measured every two hours for up to twenty-four hours in order to use those data as a reference.

On the third day, all the patients were injected the 50 $\mu$g of SMS 201-995 with the same method and measured the GH concentration at the same time. In addition, the levels of glucose, insulin, and glucagon were measured every hour for up to four hours after the injection of SMS 201-995 which were compared to those of the control group consisting of four healthy young men.

On the last day, four patients were injected the 50 $\mu$g of SMS 201-995 one hour before TRH injection in order to determine the influence of SMS 201-995 on the paradoxical response to TRH.

### 3. Materials and Laboratory Method

Plasma levels of growth hormone, insulin and glucagon were determined by radioimmunoassay kit purchased from Radioassay System Laboratories, INC., Dinabbot Co. and Daiichi Co. respectively.

SMS 201-995 was kindly suppled by the Sandoz pharmaceutical, Inc. in Seoul, Korea. TRH was purchased from Hoechst pharmaceuticals.

## RESULTS

The absence of diurnal variation after injection of normal saline as a placebo was shown in all patients (Fig. 1).

A single dose of 50 $\mu$g SMS 201-995 could suppress the GH level maximally by 85% on average which was noticed at about 4 hours after administration. The suppressive effect gradually decreased thereafter and the GH level returned to that of preinjection period at 8 to 10 hours after injection without rebound phenomenon (Fig. 2).

The figure 3 shows the changes in glucose levels during the 4 hours period after the injection of SMS 201-995. The glucose levels of four healthy males reached a maximum 2 hours after breakfast

**Table 1. Clinical Profile of the Subjects**

| Patients | Sex | Age | Duration of history (yr) | Surgery | Bromocriptine | Radiotherapy | Result |
|---|---|---|---|---|---|---|---|
| 1 | F | 40 | 13 | + | + | – | Not improved |
| 2 | F | 51 | 4 | – | + | + | Not improved |
| 3 | F | 43 | 5 | – | + | – | Not improved |
| 4 | M | 35 | 5 | – | + | + | Not improved |
| 5 | F | 31 | 5 | – | – | – | None |

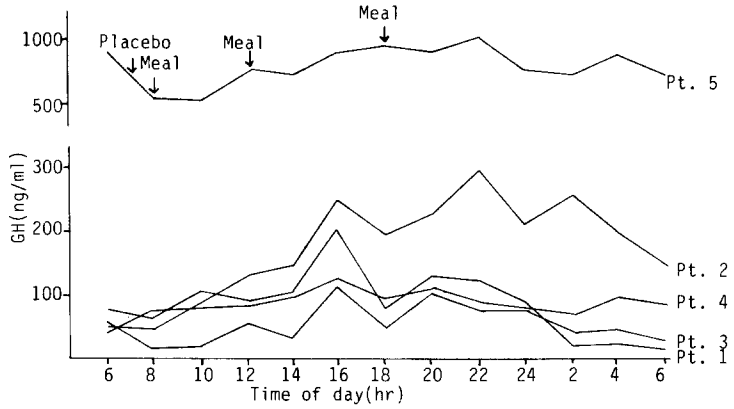
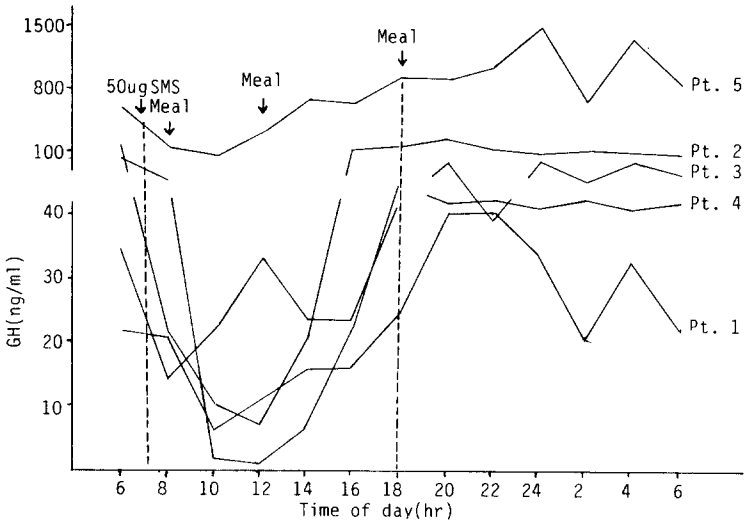



**Fig. 1.** *GH response to placebo.*




**Fig, 2.** *GH response to SMS 201–995.*

and decreased thereafter shown in the shaded area; however, the glucose levels of four patients (patient 1, 2, 3, 4) continued to increase even after three hours after breakfast.

The changes of serum insulin concentration after administration of SMS 201-995 are shown in Fig. 4. The insulin levels of healthy males reached their peak at 2 hours after breakfast and declined thereafter according to the changes of blood glucose level. However, the insulin levels of the patients continued to increase for up to 4 hours after breakfast showing a delayed response similar to the changes of blood glucose levels.

Only one patient (patient 5) among four patients who had their glucagon levels measured showed an adequate decrease in accord with the change of blood glucose after breakfast, and the other three patients showed no definite declining pattern. In general, the changes of glucagon level did not show any significant difference compared with those of healthy males (Fig. 5).

The paradoxical responses of the GH to TRH were apparent in patients 1, 2, and 4 (Fig. 6). However, the paradoxical responses disappeared in two (patients 2 and 4) of them with SMS 201-995 injected one hour before TRH stimulation.

The two patients (2, 4) whose paradoxical response had been more prominent showed more marked suppression of the response with SMS 201 -995 (Fig. 7).

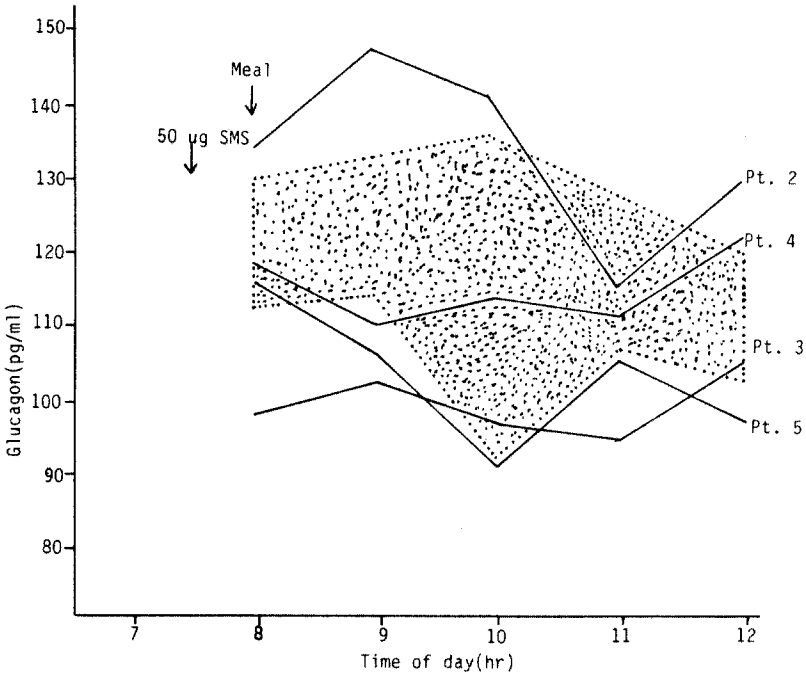



**Fig. 3.** *Glucose response to SMS 201–995.*

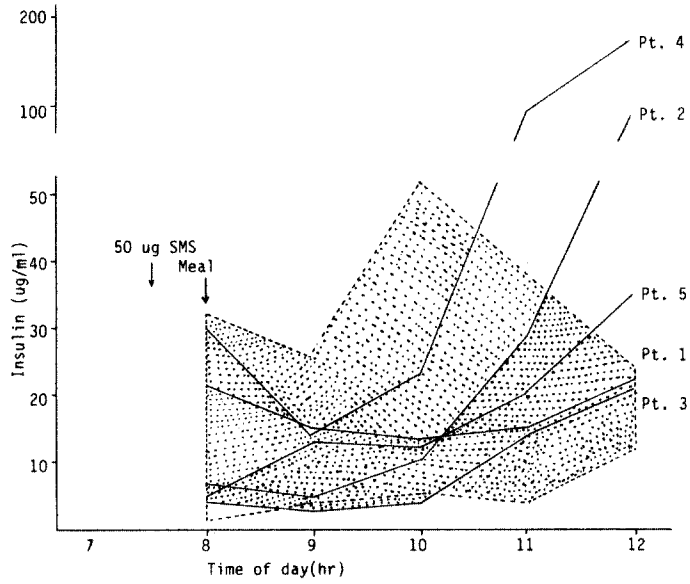



**Fig. 4.** *Insulin response to SMS 201–995.*

## DISCUSSION

Somatostatin is produced by processing a larger precursor molecule and exists in both the 28- and 14-amino acid forms. 28-amino acid somatostatin has a longer half-life and is a more potent inhibitor of GH and insulin secretion. It is found in

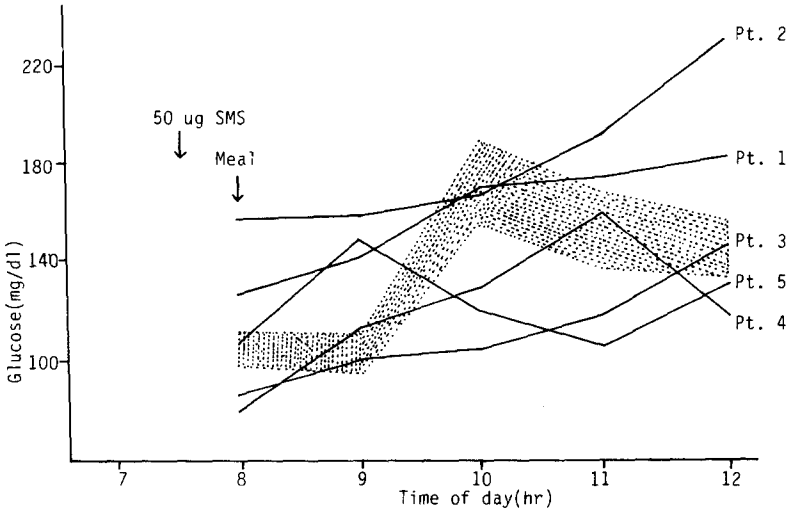



**Fig. 5.** *Glucagon response to SMS 201–995.*

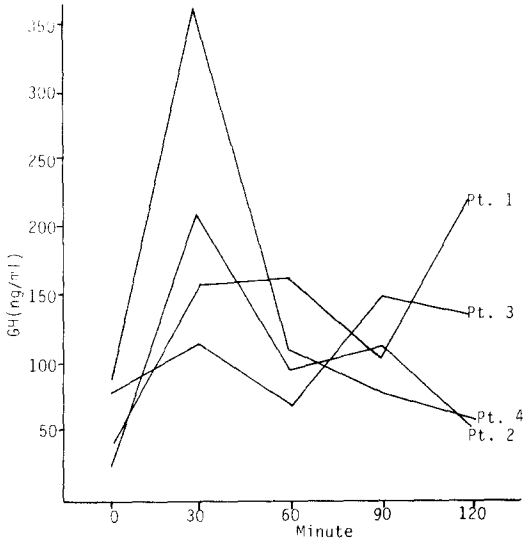



**Fig. 6.** *Paradoxical response to TRH.*

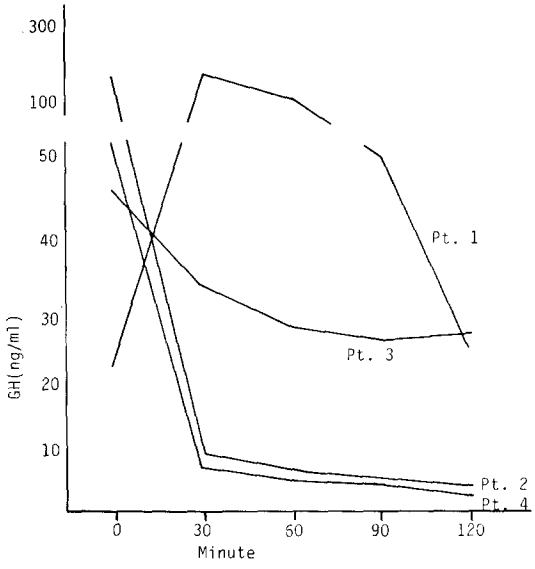



**Fig. 7.** *Effect of SMS 201–995 on paradoxical response to TRH.*

man and seems particulary prevalent in the gastrointestinal tract.

Somatostatin-14 has a greater affinity for hypothalamic and cortical receptors and is more potent in the inhibition of glucagon release. When pharmacological doses of somatostatin 14 are infused, the effects include inhibition of endocrine secretions (growth hormone, thyroid-stimulating hormone, insulin, glucagon, and all the gut hormones), exocrine secretions (gastric acid, pancreatic bicarbonate, and enzymes), small bowel absorption, and depression of splanchnic blood flow.

Somatostatin-14 has two main drawbacks as a potential drug. First, its actions are non-specific and its long-term use is likely to result in adverse effects such as intestinal malabsorption and glucose intolerance. Trials have therefore been made to synthesize analogues that are more specific for individual effects. The second drawback of

somatostatin-14 is its short plasma half-life; this means that it must be given continuously by intravenous infusion. Rebound effects, such as severe flushing in patients with carcinoid syndrom, are sometimes seen a few minutes after the infusion has stopped.

Some somatostatin analogues have a selective effect on GH secretion[15~17] and others have a prolonged action[19~20], but the effect of SMS 201-995 on serum GH is selective and lasts for up to 9 hours.

The intravenously administered natural somatostatin has a half-life of 2 to 3 minutes whereas the SMS 201-995 has an elimination half-life of 41 to 58 minutes. In addition, SMS 201-995 has been shown to be 45 times more potent than natural somatostatin in suppressing growth hormone release[21].

Preliminary clinical trials have confirmed the pharmacological profile of this analogue. Plewe et al[12] reported decrease in plasma growth hormone concentrations to normal or nearly normal levels that lasted for 9 hours in a group of subjects with acromegaly who received a single subcutaneous injection of 50 $\mu$g of SMS 201-995.

In this study, we observed the effect of a single subcutaneous injection of 50 $\mu$g SMS 201-995 on five resistant acromegalic patients. Plasma GH level decreased maximally by 85% but the GH levels were not reduced to the normal range. It suggested that more than 50 $\mu$g of SMS 201-995 as one dose should be necessary for sufficient suppression of GH.

The duration of the suppressive effect was about 8 hours, which was comparable to those of others. It indicated that SMS 201-995 should be administered every 8 hours subcutaneously in order to maintain the continuous suppression of growth hormone secretion.

Unlike natural somatostatin, SMS 201-995 had only a slight and short-lasting inhibition effect on insulin secretion. In normal subjects, the administration of 10 to 20 $\mu$g of SMS 201-995 per hour intravenously and 50 to 100 $\mu$g subcutaneously was found to inhibit growth hormone, glucagon, and insulin elevations induced by an arginine infusion[22]. However, when an arginine infusion was done three hours after the injection of SMS 201-995; growth hormone did not increase markedly above basal levels, although the normal rise in insulin levels did occur. Steven WJ et al[14] found that the diabetogenic effect of SMS 201-995 decreased toward the end of the long-term treatment period. This would have been caused by a diminished inhibition effect on insulin secretion during long-term treatment with the drug, but it also might have been due to the beneficial effect on carbonhydrate tolerance by the reduction of plasma growth hormone level.

We also tried to determine whether SMS 201-995 had diabetogenic effect in this study.

Serum levels of glucose increased to reach their peak at about two hours after meal in healthy male controls acompanied by the simultaneous increase of serum insulin levels. In four acromegalc patients, a delayed increase of serum glucose occurred with delayed increased serum insulin. This delayed increase of serum glucose intolerance is believed to be caused by growth hormone excess in acromegaly rather than the suppressive effect of insulin by SMS 201-995[23,24]. In fact, many reports proposed postreceptor defect caused by growth hormone excess as a possible pathogenetic mechanism for the glucose intolerance in acromegaly. If SMS 201-995 suppressed the insulin secretion, the serum glucose would have been increased markedly above normal range at about two hours after meal. Furthermore, the fact that serum insulin level increased in accord with the increase of glucose level under the condition which GH was suppressed maximally suggests that SMS 201-995 has no significant suppressive effect on insulin secreation. Because our results cannot exclude the diabetogenic of SMS 201-995 when it is administered in more high dosage or for a longer duration, long-term follow-up study should be needed in the future.

SMS 201-995 also seems to have no significant suppressive effect on the glucagon secretion in small dosage and short term administration. The paradoxical responses of GH to TRH or LHRH are frequently observed in acromegalic patients. However, the mechnism is unknown. To our knowledge, there have been no reports which observed the paradoxical response of GH to TRH or LHRH after SMS 201-995 injection. In this study, two of three patients who had paradoxical response showed the disappearance of the response after administration of SMS 201-995, but the fact that the paradoxical response to TRH and the suppression of GH secretion by somatostatin occur via the adenylate cyclase system[25] might explain the mechanism for the suppression of paradoxical response. The paradoxical responses had been more prominent in the two patients (patient 2, 4) whose responses were more markedly suppressed by SMS 201-995 compared to patient 1. This sug-

gests the possibility that the patients might have a deficiency of somatostatinergic activity which caused the paradoxical response. Nevertheless, more studies are mandatory concerning the mechanism of paradoxical response and the effect of SMS 201-995 on the response.

In conclusion, the somatostatin analogue SMS 201-995 can be a candidate for the adjunctive therapy to the medical management of acromegaly. Its long duration of action at relatively low doses without rebound phenomenon are suitable for clinical use, but our data suggests that more than 50 $\mu$g SMS 201-995 should be required at least 3 times a day for the adequate suppression of GH. SMS 201-995 does not suppress the insulin and glucagon secretion in low dosage and short term treatment. Further evaluation should be needed for the suppressive effect on the paradoxical response.

## REFERENCES


1. Lamberts SWJ, Verleun T, Oosterom R: *The interrelationship between the effects of somatostatin and human pancreatic growth hormone-releasing factor on growth hormone release by cultured pituitary tumor cells from patients with acromegaly. J Clin Endocrinol Metab 58:2500, 1984*
2. Besser GM, Mortimer CH, Carr D, Schally AV, Coy DH, Evered D, Kastin AJ, Turnbridge WMG, Thorner MO, Hall R: *Growth hormone release inhibiting hormone in acromegaly. Br Med J 1:352, 1974*
3. Yen SSC, Siler TM, Devane GW: *Effect of somatostatin in patients with acromegaly. N Engl J Med 290:935, 1974*
4. Dunn PJ, Donald RA, Espiner EA: *A comparison of the effect of levodopa and somatostatin on the plasma levels of growth hormone, insulin, glucagon and prolactin in acromegaly. Clin Endocrinol (Oxf) 5:167, 1976*
5. Hanew K, Kokubun M, Sasaki A, Nouri T, Yoshinaga K: *The spectrum of pituitary growth hormone responses to pharmacological stimuli in acromegaly. J Clin Endocrinol Metab 5:282, 1980*
6. Oppizzi G, Botalla L, Verde G, Cozzi R, Liuzzi A, Chiodini P: *Homogeneity in growth hormone lowering effects of dopamine and somatostatin in acromegaly. J Clin Endocrinol Metab 51:616, 1980*
7. Pieters GFFM, Romeijn JE, Smals AGH, Kloppenborg PWC: *Somatostatin sensitivity and growth hormone response to releasing hormones and bromocriptine in acromegaly. J Clin Endocrinol Metab 54:942, 1982*
8. Besser GM, Mortimer CH, McNeilly AS, Thorner MO, Bastistoni GA, Bloom SR, Kastrup KW, Hanssen KF, Hall R, Coy DH, Kastin AJ, Schally AV: *Longterm infusion of growth hormone release inhibiting hormone in acromegaly: effects on pituitary and pancreatic hormones. Br Med J 1: 622, 1974*
9. Brown M, Rivier J, Vale W: *Somatostatin; analogues with selected biological activities. Science 196:1467, 1977*
10. Schally AV, Meyers CA: *Somatostatin, basic and clinical studies. A review. Mater Med Pol 12:28, 1980*
11. Bauer W, Briner U, Doepfner W, Haller R, Huguenin R, Marbach P, Petcher TU, Pless J: *SMS 201-995: A very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 31:1133, 1982*
12. Plewe G, Beyer J, Krause U, Neufeld M, Del Pozo E: *Long-acting and selective suppression of growth hormone secretion by somatostatin analogue SMS 201-995 in acromegaly. Lancet 2:782, 1984*
13. Lamberts SWJ, Oosterom R, Neufeld M, Del Pozo E: *The somatostatin analog SMS 201-995 induces long-acting inhibition of growth hormone secretion without rebound hypersecretion in acromegalic patients. J Clin Endocrinol Metab 60:1161, 1985*
14. Steven WJ, Lamberts, Piet Uitterlinden, Louis Verschoor, Krijn J, Van Dongen, Emilio Del Pozo: *Long-term treatment of acromegaly with the somatastatin analogue SMS 201-995. N Engl J Med 313:1576, 1985*
15. Meyers CA, Arimura A, Gordin A, Fernando-Durango R, Coy DH, Schally AV, Drouin J, Ferland L, Beaulieu M, Labrie F: *Somatostatin analogues which inhibit glucagon and growth hormone more than insulin release. Biochem Biophys Res Commun 74:630, 1977*
16. Gordin A, Meyers C, Arimura A, Coy DH, Schally AV: *An in vivo model for testing inhibition of arginine-induced insulin and glucagon release by somatostatin analog. Acta Endocrinol 86:833, 1977*
17. Waichenberg BJ, Cesar FP, Leme CE, Borghi VC, Souza ITT, Neto DG, Germeck OA, Coy DH, Comaru-Schally AM, Schally AV: *Dissociated effects of somatostatin analogs on arginine-induced insulin, glucagon and growth hormone release in acromegalic patients. Horm Metabol Res 15:471, 1983*
18. Belanger A, Labrie F, Borgeat P, Savary M, Cote J: *Inhibition of growth hormone and thyrotropin*

*release by growth hormone release inhibiting hormone. Mol Cell Endocrinol 1:329, 1974*

19. Sarantakis D, Teichman J, Lien EL, Fenichel RL: *A novel cyclic undecapeptide, WY-40, 770, with prolonged growth hormone release inhibiting activity. Biochem Biophys Res Commun 73:336, 1976*
20. Long RG, Barnes AJ, Adrian TE, Mallinson CN, Brown MR, Vale W, Rivier JE, Christofides ND, Bloom SR: *Suppression of pancreatic endocrine tumor secretion by long-acting somatostatin analogue. Lancet 11:764, 1979*
21. Investigators brochure. East Hanover, NJ: *Research Department, Sandoz, Inc 1983*
22. del Pozo E, Schlüter K, Neufeld M: *Endocrine profile and pharmacokinetics of the new somatostatin analogue SMS 201-995. Acta Endocrinol (Copenh) (in press)*
23. Sönksen PH, Greenwood FC, Ellis JP, Lowy C, Rutherford A, Naburro JDN: *Changes of carbohydrate tolerance in acromegaly with progress of the disease and in response to treatment. J Clin Endo Metabl 27:1418, 1967*
24. Trimble ER, Atkinson AR, Buchanan KD, Hadden DR: *Plasma glucagon and insulin concentrations in acromegaly. J Clin Endo Metabl 51:626, 1980*
25. Matsukura S, Kakita T, Hirata Y, Yoshimi H, Fukase M, Iwasaki Y, Koto Y, Imura H: *Adenylate cyclase of GH and ACTH producing tumors of human: Activation by non-specific hormones and other bioactive substances. J Clin Endo Meta 44:392, 1977*