Regular Review

Somatostatin

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Somatostatin, a peptide, was isolated first from the hypothalamus of the pig and shown to inhibit the release of growth hormone from the pituitary.¹ It contained 14 amino acids bridged by a sulphur sulphur bond, and other mammalian somatostatins were later shown to have identical amino acid sequences; indeed, somatostatin like peptides from early vertebrates are also closely similar.^{2,3} This suggests that spontaneous mutations, which are common over millions of years, have always proved fatal, and implies that this peptide is important in vertebrate physiology.

A widespread peptide

Somatostatin was identified first as a product of specific hypothalamic neurones⁴ but was later shown to be the secretory product of the δ cell of the islets of Langerhans.⁵ Considerable quantities of somatostatin were also extracted from the gut; most of it was synthesised in a mucosal endocrine cell found in highest density in the antrum,⁵ although a little was produced in a particular type of neurone in the myenteric and submucous neural plexus.⁷ Nerve fibres that produce somatostatin have now been found in the genitourinary system, heart, eye, thyroid, thymus, and skin.⁸ They are also common in the central nervous system.⁹

Actions of somatostatin

As well as inhibiting the release of growth hormone somatostatin was soon found to inhibit the release of insulin and glucagon from the pancreas¹⁰⁻¹³ and of gastrin from the stomach.¹⁴ There is now a long list of regulatory peptides whose release is inhibited by somatostatin, leading to the nickname "endocrine cyanide."¹⁵⁻¹⁷ This is not quite fair, however, as the release of many peptides—for example, luteinising hormone and follicle stimulating hormone—is not physiologically affected.

Somatostatin not only inhibits peptide hormone release but also often inhibits the target tissue. Thus somatostatin blocks the release of gastrin and, independently, secretion of gastric acid.¹⁴ These inhibitory effects are powerful—for example, in man somatostatin can prevent the release of insulin in response to every known stimulus, rendering the patient a temporary insulin dependent diabetic.

Specific receptors for somatostatin are easily identified in many sites¹⁷⁻²⁸ but the intracellular mechanism of action is unknown. It may have to do with regulating calcium flux, suppressing production of intracellular cyclic adenosine monophosphate, and stimulating potassium permeability.²⁹⁻³²

The physiological jobs of this ubiquitous and powerful

inhibitory peptide clearly vary from tissue to tissue and are highly diverse. It circulates in the blood and rises after a meal.³³⁻³⁶ Infusing exogenous somatostatin to mimic this rise reduces insulin and gastric acid secretion by about a third.³⁷⁻³⁹ Depletion of somatostatin by the agent cysteamine causes peptic ulcers and high acid secretion.⁴⁰⁻⁴³ Somatostatin is found in hypothalamic-pituitary portal plasma in sufficient concentrations to inhibit powerfully growth hormone release from the pituitary.⁴⁴⁻⁴⁵ Intracerebroventricular injection of somatostatin inhibits adrenocorticotrophin secretion and adrenal adrenaline output and prevents hyperglycaemia in response to certain stimuli.⁴⁶⁻⁴⁸ Somatostatin also appears to play a part in the sensory nervous system.⁴⁹⁻⁵⁴

Importance in disease

Is somatostatin important in human disease? Cortical concentrations of somatostatin are dramatically reduced in Alzheimer's disease,⁵⁵⁻⁵⁸ but the cause and consequence of this reduction are unknown.

Somatostatin is secreted by certain endocrine tumours (somatostatinomas), including medullary carcinoma of the thyroid, small cell carcinoma of the lung, and pancreatic endocrine tumours.⁵⁹⁻⁶⁶ A somatostatinoma syndrome has been described comprising weight loss, malabsorption, diabetes, gall stones, and hypochlorhydria. Yet despite the widespread and dramatic effects of somatostatin the tumours present late and are large. This is presumably because concentrations of somatostatin have been rising slowly for years (as these tumours are usually slow growing), leading to adaptive changes and diminished clinical consequences.

Speculation that deficiency of gastric somatostatin may cause peptic ulcer and deficiency of pancreatic somatostatin may cause hypoglycaemic syndromes lacks biochemical proof.

Disappointing therapeutic effects

The therapeutic use of somatostatin has been restricted by its half life in the circulation being only a few minutes and by its not being absorbed orally. Scientists in drug companies have, however, produced long acting peptides,⁶⁷⁻⁶⁸ and the Sandoz octapeptide analogue, octreotide (SMS 201-995, Sandostatin), has been widely tested clinically.

Somatostatin reduces coeliac axis blood flow⁶⁹⁻⁷⁴ and inhibits gastric acid secretion and has therefore been given to patients to stop upper gastrointestinal bleeding.⁷⁴⁻⁸¹ The initial reports were good but have not been confirmed, and the long acting analogue is of doubtful usefulness in treating either bleeding peptic ulcer or bleeding varices.

Several aspects of diabetes mellitus appear to be potentially

treatable with somatostatin. Diabetic retinopathy is arrested when growth hormone is removed by pituitary ablation,⁸² but unfortunately complete inhibition of growth hormone secretion is required and seems not to be possible with reasonable doses of the somatostatin analogue (E M Kohner, personal communication).

The insulin dependent diabetic often has considerable swings in plasma glucose concentration throughout the day and a steady rise during the night with highest concentrations just before the morning insulin.^{83,84} These swings and the overnight rise may be caused partly by "counterregulatory hormones"—that is, growth hormone and glucagon—and their suppression might therefore have improved diabetic control. Somatostatin and the long acting analogue do, indeed, suppress growth hormone and glucagon and thereby reduce daily insulin requirements appreciably, but they do not seem to improve the glucose swings.⁸⁴⁻⁸⁸ Even the long acting analogue given last thing at night would probably not be sufficiently active in the early morning to prevent the release of growth hormone completely; yet it does increase the incidence of insulin induced hypoglycaemia in the early night.

It was hoped that in the obese patient with mild maturity onset diabetes, who has good insulin secretion but appreciable insulin resistance, somatostatin or its analogues, which also delay carbohydrate absorption from the gut,⁸⁹ might improve insulin sensitivity more than they inhibit its release. It appears a close run thing as the Sandoz somatostatin analogue does not cause much deterioration in glucose tolerance despite considerable inhibition of insulin secretion. But overall there is no improvement.⁹⁰

Dramatic results with tumours

Finally, this "endocrine cyanide" might be used to inhibit hormone production by tumours—and this has proved dramatically successful. Patients with metastatic vasoactive intestinal polypeptide tumours (vipomas) terminally ill from uncontrollable diarrhoea (due to excessive intestinal secretions caused by the vasoactive intestinal peptide) were

rescued from death.⁹¹⁻⁹⁶ Although the injection is transiently uncomfortable, patients can give themselves the new somatostatin analogue subcutaneously. The treatment has no important side effects, and patients can return to work. As well as inhibiting hormone output somatostatin probably inhibits secretion directly.⁹³ These tumours are naturally slow growing, and growth may be temporarily halted by the treatment.⁹⁴⁻⁹⁹

Diarrhoea caused by the carcinoid syndrome and glucagonomas has also been treated successfully with somatostatin.¹⁰⁰⁻¹⁰³ Other tumour syndromes—for example, the hypoglycaemia associated with malignant insulinoma^{104,105}—are sometimes responsive to somatostatin, and since the treatment is harmless (providing a low starting dose is used) it is always worth considering.

Pituitary tumours associated with acromegaly are usually large and resistant to surgical or radiation treatment in up to half the cases. The patients have appreciable morbidity, and the mortality is roughly doubled in untreated patients.¹⁰⁶ The only effective medical treatment has been bromocriptine, which usually fails to reduce growth hormone release sufficiently. In contrast, the somatostatin analogue octreotide is both effective and well tolerated.¹⁰⁷⁻¹¹² Headache is dramatically reduced, suggesting a mechanism independent of the inhibition of growth hormone.¹¹³ Glucose tolerance does not usually deteriorate appreciably, and the mild steatorrhoea produced causes few problems. Octreotide is resistant to enzymic degradation, even by gastrointestinal juices, and was therefore tested orally and found to be active.^{114,115} Improved formulations are being produced, and the drug will now probably be available orally.

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- 1 Brazeau P, Vale W, Burgus R, et al. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. *Science* 1983;179:77-9.
- 2 Benoit R, Böhlen P, Brazeau P, Ling N, Guillemin R. Isolation and characterization of rat pancreatic somatostatin. *Endocrinology* 1980;107:2127-9.
- 3 Spiess J, Rivier JE, Rodkey JA, Bennett CD, Vale W. Isolation and characterization of somatostatin from pigeon pancreas. *Proc Natl Acad Sci USA* 1979;76:2974-8.
- 4 Elder RP, Parsons JA. Immunocytochemical localisation of somatostatin in cell bodies of the rat hypothalamus. *Am J Anat* 1975;144:541-8.
- 5 Polak JM, Pearse AGE, Grimelius L, Bloom SR, Arimura A. Growth hormone release-inhibiting hormone in gastrointestinal and pancreatic D cells. *Lancet* 1975;ii:1220-5.
- 6 Arimura A, Sato H, Dupont A, Nishi N, Schally AV. Somatostatin: abundance of immunoreactive hormone in rat stomach and pancreas. *Science* 1975;189:1007-9.
- 7 Keast JR, Furness JB, Costa M. Somatostatin in human enteric nerves. *Cell Tissue Res* 1984;237:299-308.
- 8 Polak JM, Bloom SR. Somatostatin localization in tissues. *Scand J Gastroenterol* 1986;119:11-21.
- 9 Patel YC, Reichlin S. Somatostatin in hypothalamus: extra hypothalamic brain and peripheral tissues of the rat. *Endocrinology* 1978;102:523-30.
- 10 Mortimer CH, Carr D, Lind T, et al. Growth hormone release-inhibiting hormone: effects on circulating glucagon, insulin and growth hormone in normal, diabetic, acromegalic and hypopituitary patients. *Lancet* 1974;ii:697-701.
- 11 Alford FP, Bloom SR, Nabarro JDN, et al. Glucagon control of fasting glucose in man. *Lancet* 1974;ii:974-6.
- 12 Alberti KGMM, Christensen SE, Iversen J, et al. Inhibition of insulin secretion by somatostatin. *Lancet* 1973;ii:1299-301.
- 13 Gerich JE, Lorenzi M, Schneider V, et al. Inhibition of pancreatic glucagon response to arginine by somatostatin in normal man and in insulin-dependent diabetics. *Diabetes* 1974;23:876-80.
- 14 Bloom SR, Mortimer CH, Thorner MO, et al. Inhibition of gastrin and gastric-acid secretion by growth hormone release-inhibiting hormones. *Lancet* 1974;ii:1106-9.
- 15 Lucey MR. Progress report. Endogenous somatostatin and the gut. *Gut* 1986;27:457-67.
- 16 Reichlin S. Somatostatin (second of two parts). *N Engl J Med* 1983;309:1556-63.
- 17 Reichlin S. Somatostatin (first of two parts). *N Engl J Med* 1983;309:1495-501.
- 18 Steiner C, Dahl R, Sherman N, et al. Somatostatin receptors are biologically active before they are inserted into the plasma membrane. *Endocrinology* 1986;118:766-72.
- 19 Beal MF, Tran VT, Mazurek MF, Chattha G, Martin JB. Somatostatin binding sites in human and monkey brain: localisation and characterization. *J Neurochem* 1986;46:359-65.
- 20 Colas B, Arilla E, Prieto JC. Characterization of somatostatin binding sites in cytosolic fraction of pig retina. *Neurosci Lett* 1986;65:193-8.
- 21 Srikant CB, Patel YC. Somatostatin receptors on rat pancreatic acinar cells. *J Biol Chem* 1986;261:7690-6.
- 22 Reubi JC, Maurer R, Klijn JGM, et al. High incidence of somatostatin receptors in human meningiomas: biochemical characterization. *J Clin Endocrinol Metab* 1986;63:433-8.
- 23 Reubi JC, Maurer R. Different ionic requirements for somatostatin receptor subpopulations in the brain. *Regul Pept* 1986;14:301-11.
- 24 Cotroneo P, Marie JC, Manto A, et al. Molecular characterization of somatostatin-28 receptors subunits of B cell membranes by cross-linking procedure. *Diabetologia* 1986;29:530A.
- 25 Reubi JC. New specific radioligand for one subpopulation of brain somatostatin receptors. *Clin Sci* 1985;36:1829-36.
- 26 Weightman DR, Whitford C, Snell CR, Hirst BH, Brundish DE, Kendall-Taylor P. H-somatostatin: two high affinity binding sites in rat brain. The effect of Ca, Mg and GIP on binding. *J Endocrinol* 1985;104:112.
- 27 Srikant CB, Patel YC. Somatostatin receptors in the rat adrenal cortex: characterization and comparison with brain and pituitary receptors. *Endocrinology* 1985;116:1717-23.
- 28 Tran VT, Beal MF, Martin JB. Two types of somatostatin receptors differentiated by cyclic somatostatin analogs. *Science* 1985;228:492-5.
- 29 Beal MF, Mazurek MF, Tran VT, Chattha G, Bird ED, Martin JB. Reduced numbers of somatostatin receptors in the cerebral cortex in Alzheimer's disease. *Science* 1985;229:289-91.
- 30 Draznin B, Sherman N, Sussman K, Dahl RA, Vatter A. Internalization and cellular processing of somatostatin in primary culture of rat anterior pituitary cells. *Endocrinology* 1985;117:960-6.
- 31 Reisine T. Somatostatin desensitization: loss of the ability of somatostatin to inhibit cyclic AMP accumulation and adrenocorticotropin hormone release. *J Pharmacol Exp Ther* 1984;229:14-20.
- 32 Koch BD, Schonbrunn A. The somatostatin receptor is directly coupled to adenylate cyclase in GH C pituitary cell membranes. *Endocrinology* 1984;114:1784-90.
- 33 Lucey MR. Progress report. Endogenous somatostatin and the gut. *Gut* 1986;27:457-67.
- 34 Webb SM, Wass JAH, Penman E, et al. Circulating immunoreactive somatostatin in man. Effect of age, pregnancy, growth hormone of deficiency and achlorhydria. *Acta Endocrinol (Copenh)* 1985;110:145-51.

- 35 Burhol PG, Lygren I, Jenssen TG, Florholmen J, Jorde R. Somatostatin release and plasma molecular somatostatin components in man. *Acta Physiol Scand* 1984;121:223-8.
- 36 Coltrui TJ, Unger RH, Feldman M. Role of circulating somatostatin in regulation of gastric acid secretion, gastrin release, and islet cell function. Studies in healthy subjects and duodenal ulcer subjects. *J Clin Invest* 1984;74:417-23.
- 37 O'Shaughnessy DJ, Long RG, Adrian TE, et al. Somatostatin-14 modulates postprandial glucose levels and release of gastrointestinal and pancreatic hormones. *Digestion* 1985;31:234-42.
- 38 Loud FB, Holst JJ, Egense E, Petersen B, Christiansen R. Is somatostatin a humoral regulator of the endocrine pancreas and gastric acid secretion in man? *Gut* 1985;26:445-9.
- 39 Schudziarra V, Laweck J, Ditschuneit HH, Lukas B, Maier V, Pfeiffer EF. Effect of low-dose somatostatin infusion on pancreatic and gastric endocrine function in lean and obese nondiabetic human subjects. *Diabetes* 1985;34:595-601.
- 40 McIntosh C, Bakich V, Trotter T, et al. Effect of cysteamine on secretion of gastrin and somatostatin from the rat stomach. *Gastroenterology* 1984;86:834-8.
- 41 Brown MR, Fisher LA, Sawchenki PE, Swanson LW, Vale WW. Biological effects of cysteamine: relationship to somatostatin depletion. *Regul Pept* 1983;5:163-79.
- 42 Seiler M, Szabo S, Ourieff S, McComb DJ, Kovacs K, Reichlin S. The effect of the duodenal ulcerogen cysteamine on somatostatin and gastrin cells in the rat. *Exp Mol Pathol* 1983;39:207-18.
- 43 Szabo S, Reichlin S. Somatostatin in rat tissues is depleted by cysteamine administration. *Endocrinology* 1981;109:2255-7.
- 44 Patel YC, Srikant CB. Somatostatin mediation of adenohypophyseal secretion. *Ann Rev Physiol* 1986;48:551-67.
- 45 Plotsky PM, Vale W. Patterns of growth hormone-releasing factor and somatostatin secretion into the hypophyseal-portal circulation of the rat. *Science* 1985;230:461-3.
- 46 Brown MR, Fisher LA. Brain peptide regulation of adrenal epinephrine secretion. *Am J Physiol* 1984;247:41-6.
- 47 Brown MR, Rivier C, Vale W. Central nervous system regulation of adrenocorticotropin secretion: role of somatostatins. *Endocrinology* 1984;114:1546-9.
- 48 Brown MR. Central nervous system sites of action of bombesin and somatostatin to influence plasma mepinephrine levels. *Brain Res* 1983;276:253-7.
- 49 Krukoff TL, Ciriello J, Calaresu FR. Somatostatin-like immunoreactivity in neurons, nerve terminals, and fibers of the cat spinal cord. *J Comp Neurol* 1986;243:13-22.
- 50 Polak JM, Bloom SR. Somatostatin localization in tissues. *Scand J Gastroenterol* 1986;119:11-21.
- 51 Tessler A, Himes BT, Gruber-Bollinger J, Reichlin S. Characterization of forms of immunoreactive somatostatin in sensory neuron and normal and deafferented spinal cord. *Brain Res* 1986;370:232-40.
- 52 Wiesendfeld-Hallin Z. Substance P and somatostatin modulate spinal cord excitability via physiologically different sensory pathways. *Brain Res* 1986;372:172-5.
- 53 Kuraishi Y, Hirota N, Sato Y, Hino Y, Satoh M, Takagi H. Evidence that substance P and somatostatin transmit separate information related to pain in the spinal dorsal horn. *Brain Res* 1985;325:294-8.
- 54 Tuchscherer MM, Seybold VS. Immunohistochemical studies of substance P, cholecystokinin-octapeptide and somatostatin in dorsal root ganglia of the rat. *Neuroscience* 1985;14:593-605.
- 55 Fine A. Peptides and Alzheimer's disease. *Nature* 1986;319:537-8.
- 56 Price DL, Whitehouse PJ, Struble RG. Cellular pathology in Alzheimer's and Parkinson's diseases. *Trends in Neurological Sciences* 1986;9:29-33.
- 57 Harrison PJ. Pathogenesis of Alzheimer's disease—beyond the cholinergic hypothesis: discussion paper. *J R Soc Med* 1986;79:347-52.
- 58 Davies P, Katzman R, Terry RD. Reduced somatostatin-like reactivity in cerebral cortex from cases of Alzheimer disease and Alzheimer senile dementia. *Nature* 1980;288:279-80.
- 59 Ch'ng JLC, Polak JM, Bloom SR. Endocrine syndromes. In: Polak JM, Bloom SR, eds. *Endocrine tumours: pathobiology of regulatory peptide-producing tumours*. Edinburgh: Churchill Livingstone, 1985:264-80.
- 60 Impicciatore M, Hansen DG, Rachmilewitz D, Maitra SK, Lugaro G, Grossman MI. Comparison of human urine gastric inhibitor (HUGI) and bacterial endotoxin as inhibitors of acid secretion. *Eur J Pharmacol* 1980;65:365-8.
- 61 Szabo M, Berelowitz M, Pettengill OS, Sorenson GD, Forthman LA. Ectopic production of somatostatin-like immuno- and bioactivity by cultured human pulmonary small cell carcinoma. *J Clin Endocrinol Metab* 1980;51:978-87.
- 62 Roos BA, Lindall AW, Ellis J, Elde R, Lambert PW, Birnbaum RS. Increased plasma and tumor somatostatin-like immunoreactivity in medullary thyroid carcinoma and small cell lung cancer. *J Clin Endocrinol Metab* 1981;52:187-94.
- 63 Lundqvist M, Wilander E. Somatostatin-like immunoreactivity in mid-gut carcinoids. *Acta Pathologica Microbiologica Scandinavica* 1981;89:335-7.
- 64 Friesen SR. Tumors of the endocrine pancreas. *N Engl J Med* 1982;306:580-90.
- 65 Stacopole PW, Kasselberg AG, Berelowitz M, Chey WY. Somatostatinoma syndrome: does a clinical entity exist? *Acta Endocrinol (Copenh)* 1983;102:80-7.
- 66 Pipeleers D, Couturier E, Gepts W, Reynders J, Somers G. Five cases of somatostatinoma: clinical heterogeneity and diagnostic usefulness of basal and tolbutamide-induced hyper-somatostatinemia. *J Clin Endocrinol Metab* 1983;56:1236-42.
- 67 Bauer W, Briner U, Doepfner W, et al. SMS 201-995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. *Life Sci* 1982;31:1133-40.
- 68 Veber DF. Design of a highly active cyclic hexapeptide analog of somatostatin. In: Rich DH, Gross E, eds. *Peptides, synthesis, structure and function*. Rockford, Illinois: Pierce Chemical Co, 1981:685-94.
- 69 Samnegard H, Thulin L, Andreen M, Tyd NG, Hallberg D, Efendic S. Circulatory effects of somatostatin in anaesthetized dogs. *Acta Chir Scand* 1979;145:209-12.
- 70 Hagopian W, Lever EG, Cohen D, et al. Predominance of renal and absence of hepatic metabolism of pancreatic polypeptide in the dog. *Am J Physiol* 1983;8:171-7.
- 71 Price BA, Jaffe BM, Zinner MJ. Effect of exogenous somatostatin infusion on gastrointestinal blood flow and hormones in the conscious dog. *Gastroenterology* 1985;88:80-5.
- 72 Merkel C, Gatta A, Zuin R, Finucci GF, Nosadini R, Ruol A. Effect of somatostatin on splanchnic hemodynamics in patients with liver cirrhosis and portal hypertension. *Digestion* 1985;32:92-8.
- 73 Bosch J, Kravetz D, Rodes J. Effects of somatostatin on hepatic and systemic hemodynamics in patients with cirrhosis of the liver: comparison with vasopressin. *Gastroenterology* 1981;80:518-24.
- 74 Tyd G, Samnegard H, Thulin L, Efendic S. Somatostatin and bleeding esophageal varices. *N Engl J Med* 1979;301:46.
- 75 Kayasseh L, Gyr K, Keller U, Stalder GA, Wall M. Somatostatin and cimetidine in peptic-ulcer haemorrhage. *Lancet* 1980;i:844-6.
- 76 Somerville KW, Henry DA, Davies JG, Hine KR, Hawkey CJ, Langman MJS. Somatostatin in treatment of haematemesis and melaena. *Lancet* 1985;ii:130-2.
- 77 Magnusson I, Ihre T, Johansson C, Seligson U, Torngren S, s-Moberg KU. Randomised double blind trial of somatostatin in the treatment of massive upper gastrointestinal haemorrhage. *Gut* 1985;26:221-6.
- 78 Langman MJS. Upper gastrointestinal bleeding: the trials of trials. *Gut* 1985;26:217-20.
- 79 Gyr K, Kayasseh L, Stalder GA, Prestele H. Somatostatin: budget buster only, or effective anti-bleeding drug? *Lancet* 1985;iii:155-6.
- 80 Christiansen J, Yotis A. The role of somatostatin and a long-acting analogue, SMS 201-995, in acute bleeding due to peptic ulceration. *Scand J Gastroenterol* 1986;21:109-14.
- 81 Jenkins SA, Baxter JN, Corbett WA, Shields R. Effects of a somatostatin analogue SMS 201-995 on hepatic haemodynamics in the pig and on intravascular pressure in man. *Br J Surg* 1985;72:1009-12.
- 82 Christensen NJ, Hansen AP, Lundback K. Metabolic and hormonal factors in diabetic retinopathy. *Int Ophthalmol Clin* 1978;18:55-66.
- 83 Schmidt MI, Hadji-Georgopoulos A, Rendell M, Margolis S, Kowarski A. The dawn phenomenon, an early morning rise: implications for diabetic intraday blood glucose variation. *Diabetes Care* 1981;4:579-85.
- 84 Pickup JC. Improved control of brittle diabetes by continuous subcutaneous infusion of insulin. In: Pickup JC, ed. *Brittle diabetes*. Oxford: Blackwell Scientific Publications, 1985:214-31.
- 85 Nolken G, Plewe G, Kustner E, Krause U, del Pozo E, Beyer J. Reduction of insulin requirement and growth hormone secretion by the long-acting somatostatin analogue SMS 201-995 in type I diabetics with retinopathy. *Aktuelle Endokrinologie und Stoffwechsel* 1984;5:111.
- 86 Davies RR, Turner SJ, Orskov H, Alberti KGM, Johnston DG. The response of patients with type 1 (insulin-dependent) diabetes to a single night time injection of SMS 201-995. *Diabetologia* 1986;29:532A.
- 87 Spinas GA, Bock A, Keller U. Reduced postprandial hyperglycemia after subcutaneous injection of a somatostatin-analogue (SMS 201-995) in insulin-dependent diabetes mellitus. *Diabetes Care* 1985;8:429-35.
- 88 Plewe G, Nolken G, Krause U, del Pozo E, Beyer J. Somatostatin analogue SMS 201-995 in type I diabetes mellitus. *Scand J Gastroenterol* 1986;21:166-9.
- 89 Long RG, Christofides ND, Fitzpatrick ML, O'Shaughnessy DJ, Bloom SR. Effects of intravenous somatostatin and motilin on the blood glucose and hormonal response to oral glucose. *Europ J Clin Invest* 1982;12:331-6.
- 90 Williams G, Fuessl HS, Burrin JM, Chilvers E, Bloom SR. Post-prandial effects of the long-acting somatostatin analogue, SMS 201-995, in non-insulin dependent diabetes mellitus (NIDDM). *Clin Sci* 1987;72:14p.
- 91 Ch'ng JLC, Anderson JV, Williams SJ, Carr DH, Bloom SR. Remission of symptoms during long term treatment of metastatic pancreatic endocrine tumours with long acting somatostatin analogue. *Br Med J* 1986;292:981-2.
- 92 Santangelo WC, Strickland AJ, Ducore JM, Krejs GJ. Long-term treatment of a child with pancreatic cholera syndrome with somatostatin analog (SMS 201-995). *Can J Physiol Pharmacol* 1986;64:66-7.
- 93 Maton PN, O'Dorisio TM, O'Dorisio MS, et al. Successful therapy of pancreatic cholera with the long-acting somatostatin analogue SMS 201-995. *Scand J Gastroenterol* 1986;21:181-6.
- 94 Williams NS, Copper JC, Axon AT, King RF, Barker M. Use of a long-acting somatostatin analogue in controlling life-threatening ileostomy diarrhoea. *Br Med J* 1984;289:1027-8.
- 95 Kraenzlin ME, Ch'ng JLC, Wood SM, Carr DH, Bloom SR. Long-term treatment of a VIPoma with somatostatin analogue resulting in remission of symptoms and possible shrinkage of metastases. *Gastroenterology* 1984;88:185-7.
- 96 Wilson DM, Hoffman AR. Reduction of pituitary size in a patient with a GRF secreting islet cell tumor by continuous subcutaneous infusion of a somatostatin analog. *Endocrinology* 1985;116:39.
- 97 Sagman U, Fine S. Demonstration of tumour regression with somatostatin analogue (SMS 201-995) in a patient with pancreatic cholera. *Can J Physiol Pharmacol* 1986;64:66.
- 98 Shepherd JJ, Senator GB. Regression of liver metastases in patient with gastrin-secreting tumour treated with SMS 201-995. *Lancet* 1986;ii:574.
- 99 Clements D, Elias E. Regression of metastatic VIPoma with somatostatin analogue SMS 201-995. *Lancet* 1985;ii:874-5.
- 100 Oberg K, Norheim I, Lundqvist G, Wide L. Treatment of the carcinoid syndrome with SMS 201-995, a somatostatin analogue. *Scand J Gastroenterol* 1986;21:191-2.
- 101 Richter G, Stockmann F, Lembecke B, Conlon JM, Creutzfeldt W. Short-term administration of the somatostatin analogue SMS 201-995 in patients with carcinoid tumours. *Scand J Gastroenterol* 1986;21:193-8.
- 102 Buchanan KD, Shaw C, O'Hare MM, Dalzell G. Evaluation of SMS 201-995 in gastrointestinal APUomas. *Scand J Gastroenterol* 1986;21:199-205.
- 103 Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, Hahn RG. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *N Engl J Med* 1986;315:663-6.
- 104 Verschoor L, Uitterlinden P, Lamberts SW, Del Pozo E. Prevention of hypoglycemia in patients with insulinoma. *Diabetes* 1985;34:13A.
- 105 Osei K, O'Dorisio TM. Malignant insulinoma: effects of a somatostatin analog (compound 201-995) on serum glucose, growth, and gastro-entopancreatic hormones. *Ann Intern Med* 1985;103:223-5.
- 106 Wright AD, Hill DM, Lowy C, Fraser TR. Mortality in acromegaly. *Q J Med* 1970;39:1-16.
- 107 Ch'ng JLC, Sandler LM, Kraenzlin ME, Burrin JM, Joplin GF, Bloom SR. Long term treatment of acromegaly with a long acting analogue of somatostatin. *Br Med J* 1985;290:284-5.
- 108 Magee S, Manni A, Boucher A, O'Dorisio T, Demers L. Treatment of refractory acromegaly with large doses of the somatostatin analog SMS 201-995. *Clin Res* 1986;34:428A.
- 109 Plewe G, Nolken G, Schrezenmeir J, Krause U, Beyer J. Long-term treatment of acromegaly with the somatostatin analogue SMS 201-995. *N Engl J Med* 1986;314:1390-1.
- 110 Kingsnorth AN, Moss JG, Small WP. Rapid improvement in sleep apnoea of acromegaly after short-term treatment with somatostatin analogues SMS 201-995. *Lancet* 1986;ii:1270-1.
- 111 Lamberts SWJ, Zweens M, Verschoor L, Del Pozo E. A comparison among the growth hormone-lowering effects in acromegaly of the somatostatin analog SMS 201-995, bromocriptine, and the combination of both drugs. *J Clin Endocrinol Metab* 1986;63:16-9.
- 112 Daughaday WH. A new treatment for an old disease. *N Engl J Med* 1985;313:1604-5.
- 113 Panconesi A, Pietrinin U, Marabini S. Powerful vasospastic activity in man of an analogue of somatostatin (SMS 201-995), a potential symptomatic agent in cluster headache. *Cephalalgia* 1985;5:36-7.
- 114 Fuessl HS, Domin J, Bloom SR. Oral absorption of somatostatin analogue SMS 201-995: theoretical and practical implications. *Clin Sci* 1987;72:255-7.
- 115 Williams G, Ball JA, Burrin JM, Joplin GF, Bloom SR. Effective and lasting growth-hormone suppression in active acromegaly with oral administration of somatostatin analogue SMS 201-995. *Lancet* 1986;ii:774-7.